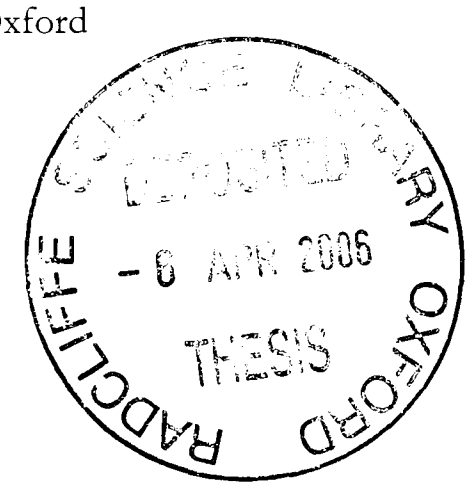
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Human Frontal Eye Fields and Visual Search

Jacinta O'Shea

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Oxford

Magdalen College



Trinity Term 2005

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Short Abstract

This thesis tested whether the human frontal eye fields (FEFs) have visuospatial functions that are dissociable from FEF oculomotor functions. Functional magnetic resonance imaging (fMRI) was used to localize the FEFs, and transcranial magnetic stimulation (TMS) was applied in a series of experiments to transiently disrupt information processing in the FEFs.

It was shown that TMS applied over the right FEFs degrades subjects' performance on a visual conjunction search task in which eye movements were not required and were not made. A TMS timing protocol subsequently showed that computations in the FEFs that occur between 40 and 80ms after the onset of a visual search array are critical for accurate performance. This suggests that, as in the monkey, the human FEFs may accumulate and use visual evidence from extrastriate cortex, which forms the basis for accurate visuospatial discrimination.

A training protocol showed that the right FEFs are no longer critical for accurate visuospatial discrimination performance once a search task has been extensively practised. This study further suggested that the FEFs may have a previously unknown role in the perception of left-right rotated shapes.

A study on feature and spatial priming indicated that these two phenomena have distinct causal mechanisms. The left FEFs appear to access a spatial memory signal during the process of saccade programming. When TMS is applied during this period, the spatial priming benefit is abolished.

Altogether, this thesis presents evidence that visuospatial and oculomotor functions can be dissociated in the human FEFs. The data on timing and the effects of learning correspond well with results reported in monkeys. The priming experiment offers the first evidence that the left FEFs are crucial for spatial priming, while the learning study suggests the novel hypothesis that the FEFs are crucial for left-right rotated shape perception.

This thesis contains approximately 50,000 words.

Publications arising from work in this thesis

O'Shea, J., N. G. Muggleton, et al. (2004). "Timing of Target Discrimination in Human Frontal Eye Fields." Journal of Cognitive Neuroscience **16**(6): 1060-1067.

O'Shea, J., Muggleton, N.M., Cowey, A. & Walsh, V. "On the roles of the human frontal eye fields and parietal cortex in visual search", Visual Cognition **(in press).**

O'Shea, J. and V. Walsh (2004). "Visual Awareness: The Eye Fields Have It?" Current Biology **14**(7): R279-R281.

O'Shea, J., Muggleton, N.M., Cowey, A. & Walsh, V. (2004). "Human Frontal Eye Fields and Mirror Symmetry". Society for Neuroscience Abstracts Program No. 481.4 Washington, D.C.: Society for Neuroscience.

O'Shea, J., Muggleton, N.M., Cowey, A. & Walsh, V. (2005). "The Left Frontal Eye Fields are critical for spatial priming of pop-out". European Conference on Visual Perception, Abstract.

Acknowledgements

I am grateful to the volunteers who participated in these experiments in both Oxford and London – particularly to those who came back time and time again.

Thanks are owed to all members of the Walsh/Cowey laboratories for generously offering me their time and expertise on an ad hoc and daily basis throughout the course of my doctoral degree. I would like particularly to thank Otto Bjoertomt and James Hung.

I owe a huge debt to Neil Muggleton for his generosity and technical wizardry - in ways too numerable to mention. Thank you.

I am grateful to Paul Taylor for his help with the TMS FEF localization task and more generally for useful discussions about the frontal eye fields. Hawkan Lau and Joe Devlin guided me through all steps of the fMRI experiment and without their help it would have been much more difficult and time-consuming.

The Wellcome Trust provided me with personal and research funding.

I was fortunate to have had two great supervisors in Vincent Walsh and Alan Cowey. Thank you both for encouraging me to stand on my own two feet. I am especially indebted to Vincent for being enough of a friend to remind me that "there are more important things in life than coloured lines on a screen".

Thank you to my parents for having always given me the freedom to follow my own course in life, even when its trajectory appeared rather dubious. My apologies that you continue to field enquiries about when I'm going to "leave school and get a proper job". I am doubtful that this thesis will help you with that task.

Finally, thank you to Tal for bearing the worst excesses of thesis blues and for being the happy core of my daily life.

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Long Abstract

This aim of the work described in this thesis was to test the hypothesis that the human frontal eye fields (FEFs) engage in visuospatial processing, and that this is independent of their role in oculomotor programming. This hypothesis was generated from neurophysiological studies in the monkey brain, which show that perceptual and oculomotor processes can be dissociated in the FEFs. The experiments reported here used functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) to test this hypothesis. Chapters 1 and 2 are introductory, chapters 3-6 present experimental data. Chapter 7 summarizes the experimental findings and suggests future research directions.

Chapter 1 reviews the anatomy, physiology and behavioural functions of the FEFs in the monkey and human brains. The functioning of the FEFs as a structure that transforms visual input into oculomotor response output is described. The evidence for distinct perceptual and oculomotor functions of the monkey FEFs is then presented. Finally, the current state of evidence for a similar dissociation in the human brain is reviewed.

Chapter 2 describes the physical principles and biological mechanisms underlying functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS). Methodological principles guiding the appropriate use of these techniques for localizing (fMRI) and transiently disrupting (TMS) brain activity are discussed.

Chapter 3 presents data from a fMRI experiment which was carried out to localize the FEFs for TMS. Activations related to fixation were subtracted from those

related to executing saccades. The resultant FEF activations were clustered around the junction of the superior frontal sulcus and precentral sulcus, at coordinates that correspond with previous published reports on the probabilistic location of the human FEFs. Data are also presented from a follow-up experiment, which attempted to validate a TMS protocol for FEF localization by applying stimulation over the coordinates determined by fMRI. The results did not show the predicted TMS effect. Based on this, and on a review of previous work that has used this method, it was concluded that the reliability and robustness of the TMS localization protocol remains to be demonstrated.

Chapter 4 presents data from two experiments during which TMS was applied while subjects carried out visual conjunction search. The first experiment showed that repetitive-pulse TMS applied over the right FEFs disrupts target discrimination accuracy (d') when eye movements are not required. By moving the window of repetitive stimulation, the results suggested that interference was maximal when TMS was applied early during search performance. A second experiment tested this hypothesis further by applying dual pulses of TMS over the right FEFs at a number of different times during search. Dual pulses applied at 40 and 80ms after search array onset disrupted performance. There was no effect in any other time bin. It was argued that TMS during this period had interfered with the accumulation of visual evidence in the FEFs, upon which discrimination of the search target is based.

Chapter 4 presented evidence that the right FEFs are critical for accurate visual search performance. Chapter 5 aimed to test whether this was still the case after a search task had been extensively practised. Two groups of subjects were tested with TMS on two different search arrays – before and after training, and again upon transfer to a previously unseen array. The results for one of the groups indicate that the FEFs are no

longer critical for search performance once a task has been learned. The results for the other group suggest that the FEFs may have a previously unknown critical role in discriminating between symmetric shapes that are rotated to the left or right.

Chapter 6 presents four experiments that were carried out to test whether the FEFs or the posterior parietal cortex (PPC) play a crucial role in feature or spatial priming of pop-out. The results indicate that spatial and feature priming have distinct causal mechanisms. They also suggest a critical role for the left FEFs in reading-out a short-term spatial memory signal during the process of saccade programming. This process appears to form the basis of spatial priming, in which saccades to a repeated location are facilitated.

Finally, Chapter 7 summarizes the findings reported in this thesis and makes suggestions for future research. These include TMS designs to test temporal interactions between the FEFs and extrastriate cortex while subjects carry out visuospatial discrimination tasks.

CHAPTER 1: Introduction

Abstract

The aim of this thesis is to address a gap in our current understanding of the frontal eye fields (FEFs) by providing evidence that the human FEFs engage in visuospatial processing, and that this can be independent of their oculomotor functions. To set the context for this aim, this chapter reviews the known anatomy, physiology and functional roles of the FEFs in humans and macaque monkeys. For ease of exposition, FEF visuospatial and oculomotor functions are treated separately and, consistent with the aims of the thesis, the discussion is weighted towards visuospatial processing. This section first describes the gross anatomy of the FEFs, and then considers their connectivity with respect to oculomotor circuitry and cortical visual areas. Evidence is presented that questions the current position of the FEFs in models of the visual cortical hierarchy. The next section establishes a view of the FEFs as a visuomotor integrative structure, which takes visual information as input and transforms this into oculomotor response output. In the following section, the Premotor Theory of Attention is discussed and questioned, based on evidence that visuospatial and oculomotor processes can be successfully dissociated within the monkey FEFs. This is followed by a review of the few studies that have argued for a similar functional dissociation with respect to the human FEFs. In the next section, the similarities between the FEFs and posterior parietal cortex (PPC) are briefly described in order to justify and promote an assessment of their relative contributions to visual search behaviour. That section concludes with an account of TMS studies of the PPC during visual search, which establish the comparative context for the experiments presented in this thesis. Since experiments in this thesis were analysed using signal detection theory, that framework is briefly explained. In the final section, the aims of the thesis are summarized in the statement of four hypotheses about the visuospatial functions of the human FEFs.

1. Anatomy of the Frontal Eye Fields

1.1. Gross Anatomy and Cytoarchitecture

1.1.1.Monkeys

The frontal eye fields (FEFs) were first identified by David Ferrier (Ferrier, 1875), whose electrical stimulation studies of exposed monkey brains showed that eye movements

could be elicited from broad regions of frontal, temporal and parietal cortex, as well as from the superior colliculus and cerebellum. In pre-frontal cortex, Ferrier evoked contraversive saccades from a broad region extending from the arcuate sulcus to the midline, a finding later replicated in a number of ape and monkey species (Beevor & Horsley, 1888, 1890; Gruenbaum & Sherrington, 1903; Leyton & Sherrington, 1917). More recent work has distinguished the supplementary eye fields (SEFs) on the dorso-medial surface from the frontal eye fields (FEFs) on the lateral surface of the frontal lobes, based on both anatomical and physiological criteria (Woolsey et al., 1952; Woolsey, 1958; Schlag & Schlag-Rey, 1985). The FEFs have been physiologically defined as that region of lateral frontal cortex from which saccades can be evoked with currents of less than 50 $_{\mu}$A (Bruce et al., 1985a). This region lies within the rostral bank of the arcuate sulcus, extending anteriorly "...a few mms onto the surface of the prearcuate gyrus" (Bruce & Goldberg, 1985bb, pg. 723) and posteriorly encroaching a few millimeters into the caudal bank (Segraves & Goldberg, 1987; Gottlieb et al., 1993; Gottlieb et al., 1994); the region extends about 10mm medio-laterally in either direction from the junction of the inferior and superior rami of the arcuate sulcus (Tehovnik et al., 2000) (see Figure 1.1(a)).

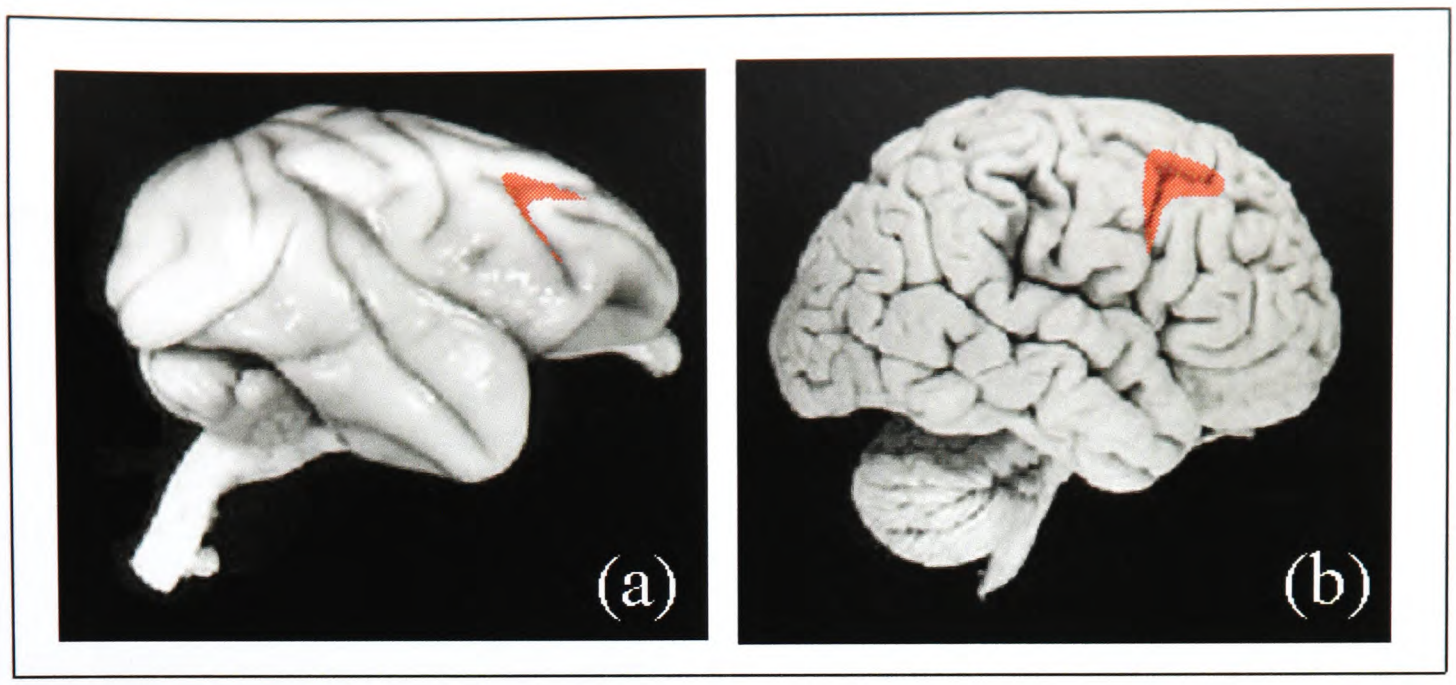


Figure 1.1. Gross anatomical location of the monkey and human FEFs. (a) The frontal eye fields (FEF) in the macaque monkey brain are located in the rostral arch of the arcuate sulcus. **(b)** The putative human homologue of FEF (based on neuroimaging studies) is located at the junction of the superior frontal sulcus and the precentral sulcus. These areas are rendered on the cortical surface for display purposes but they are actually buried within the sulci.

Cytoarchitecturally, the FEFs are characterized by a high concentration of large layer V pyramidal cells in the rostral bank of the arcuate sulcus (Stanton et al., 1989). Their areal designation, however, is less clear. A number of cytoarchitectural schemes have split the cortex comprising the FEFs into various sub-fields (Brodmann, 1909; Vogt & Vogt, 1919; Walker, 1940; von Bonin & Bailey, 1947; Preuss & Goldman-Rakic, 1991; Petrides & Pandya, 1994), but none of these correspond exactly with the electrically-defined FEFs, which overlap Brodmann's Areas 8 and 6 (BA 8/6), occupying a cytoarchitectural transition zone between granular (BA 8) and agranular (BA 6) cortex (see Figure 1.2 (b)). In the rostro-caudal transition from the lip of the arcuate sulcus to the fundus, a moderately thick, granular layer IV tapers off, such that it is hardly visible in the posterior bank (Tehovnik et al., 2000). From medial to lateral, layer III pyramidal cells get bigger, and the distinct radial and horizontal myelination patterns in medial FEF become more diffuse (Preuss & Goldman-Rakic, 1991).

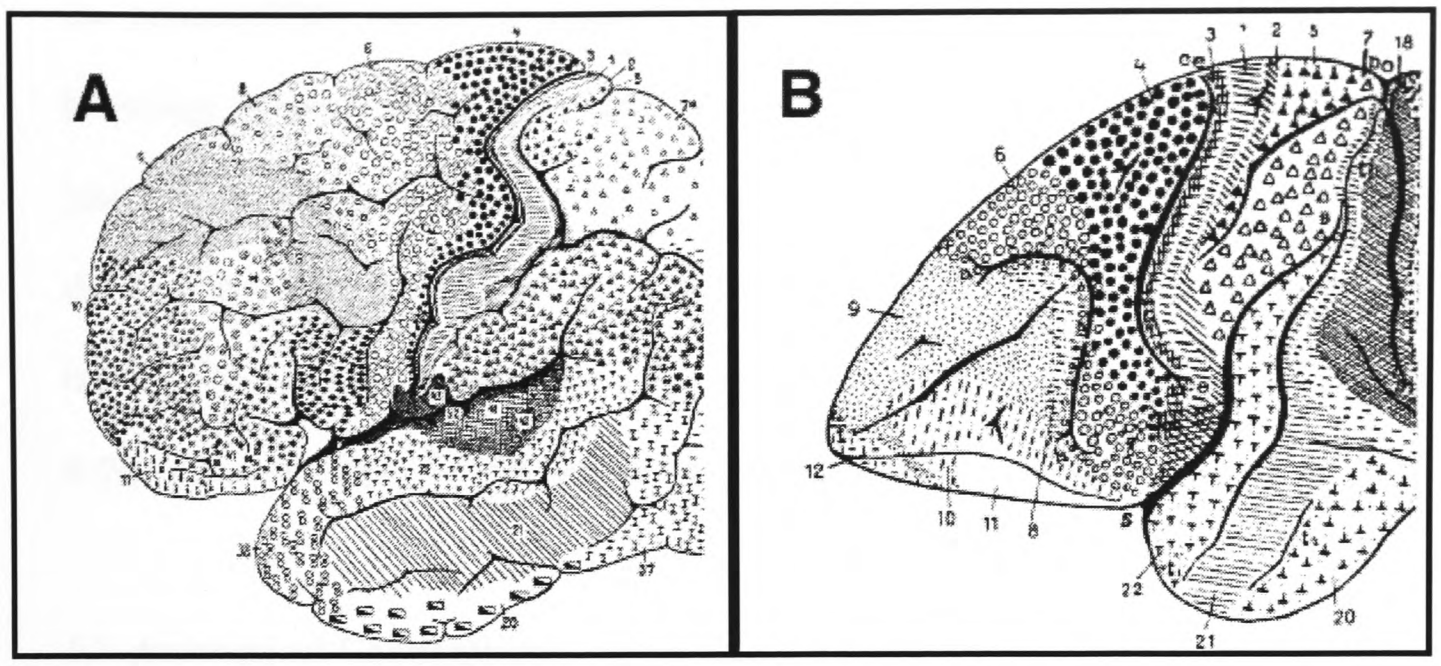


Figure 1.2. Cytoarchitecture of the monkey & human FEFs according to Brodmann (1909). (A) The human FEFs at the junction of the superior frontal sulcus and the precentral sulcus appear to be located entirely in BA 6. The boundary between BA 6 and BA 8 is located anteriorly in the middle frontal gyrus. **(B)** The monkey FEFs occupy a cytoarchitectonic border between BA 6 and BA 8.

1.1.2. Humans

Foerster was the first to evoke saccades by electrical stimulation of a region of lateral frontal cortex in the human brain (Foerster, 1931a, 1936). This was subsequently replicated by Penfield and colleagues (Penfield & Rasmussen, 1950; Penfield & Jasper, 1954). However, human electrical stimulation studies are rare and, owing to intra-operative constraints, there exists no minimum voltage criterion analogous to that defined for the monkey FEFs. Human FEFs are typically localized by neuroimaging and they are robustly activated in a wide range of eye movement tasks (eg: Fox et al., 1985; Petit et al., 1993; Petit et al., 1997; Grosbras et al., 2001). Imaging studies have consistently localized the human FEFs to the junction of the precentral sulcus (PCS) and the superior frontal sulcus (SFS), the same region from which electrical stimulation evokes saccades (Lobel et al., 2001), and which has been proposed to constitute the human homologue of the monkey arcuate sulcus (Rizzolatti et al., 1998) (see Figure

1.1(b)). A degree of controversy has surrounded this localization, since it appears to place the human FEFs entirely in agranular cortex (BA 6), implying a significant lack of homology between the two species (Luna et al., 1998) (Chapter 3 reviews this debate) (see Figure 1.2(a)). However, recent cytoarchitectural and imaging studies that have directly compared the two species reassuringly indicate that, like the monkey FEFs, human FEFs occupy an agranular-to-granular transition zone overlapping BA 6 and BA 8 (Petrides & Pandya, 1999; Rosano et al., 2003; Koyama et al., 2004).

1.2. Anatomical Connectivity

1.2.1. Oculomotor Circuitry

The eye is moved and held in position by six extra-ocular muscles, arranged in opposing pairs. Vertical, horizontal and torsional eye movements are controlled by inputs from the brainstem motor nuclei (oculomotor, trochlear, abducens), which innervate the eye muscles. Conjugate eye movements are brought about when impulses in the oculomotor nerves move the eye muscles, whilst a maintained force holds the eye in the new position (Robinson, 1964). Neuronal inputs to the oculomotor nuclei occupy an extensive region in the brainstem reticular formation. Populations of medium- and long-lead burst cells in the paramedian pontine reticular formation (PPRF) and the medullary reticular formation (MDRF) coordinate phasic bursting of agonist motor neurons and inhibition of antagonist motor neurons to induce conjugate eye movements. Medium-lead burst cells are directionally-tuned and their discharge parameters correlate well with saccade metrics: discharge/saccade amplitude and duration correlate and peak firing rate determines saccadic velocity (Schall, 1991a). This 'where' system is supplemented by a 'when' system of omnipause neurons, which are continuously active except during saccades, so may be described as active fixation cells (van Gisbergen et al., 1981). Microstimulation of

omnipause neurons prevents saccades from being executed (Keller, 1974). Models of the brainstem oculomotor circuit require two descending inputs – a trigger signal and a signal specifying target location (van Gisbergen & Van Opstal, 1990). A saccade is initiated when a trigger signal is carried in the descending projection from the deep oculomotor layers of the superior colliculus. This inhibits omnipause neuronal firing, thus triggering an eye movement by releasing fixation (Raybourn & Keller, 1977). The superior colliculus receives inputs from a wide range of oculomotor and cortical visual structures and its descending projection to the brainstem is believed to constitute the major route by which cortical inputs influence the generation of eye movements (eg: Hanes & Wurtz, 2001). The outcome of cortical visual processing is a decision where to move the eyes (Schiller & Tehovnik, 2001). Visual sampling, achieved through cycles of saccades and fixation, relies on balanced coordination of the range of cortical and subcortical inputs to the brainstem 'when' and 'where' systems.

FEF: Oculomotor Connectivity

The FEFs can influence the brainstem through a number of projections and terminations (see Figure 1.3). Layer V pyramidal cells in the FEFs project directly to the deep oculomotor layers of the superior colliculus and to both mesencephalic and pontine oculomotor regions (Huerta et al., 1986a). These projections are reciprocated via a disynaptic pathway relayed through the thalamus (Lynch et al., 1994). The FEFs are reciprocally and heavily connected with the lateral sector of the mediodorsal nucleus of the thalamus (Barbas et al., 1991), which undergoes retrograde degeneration following removal of the FEFs, and to a lesser extent with a number of thalamic regions lateral and anterior to this (Giguere & Goldman-Rakic, 1988). They also send a prominent topographic projection to the striatum (Parthasarathy et al., 1992), and this terminates in an area in which visuomotor units have been recorded (eg: Hikosaka et al., 1989).

Reciprocal projections are relayed in a polysynaptic loop via the substantia nigra and the thalamus back to the FEFs (Alexander et al., 1986). The FEFs share profuse reciprocal connections with the supplementary eye fields (SEFs) and the parietal eye fields (PEFs) in the lateral intraparietal sulcus (LIP) (Huerta et al., 1987) and receive afferents from cingulate cortex (Wang et al., 2004). They also connect with a number of skeletomotor regions in post-arcuate premotor cortex, which may provide a structural basis for coordination of eye, head and body movements (van der Steen et al., 1986). Of course these connections do not of themselves indicate anything about functional roles, but they become more informative when considered in relation to electrophysiological recordings (see Introduction Section 3).



Figure 1.3. FEF Oculomotor Circuitry. Principal areas in the cortex, basal ganglia, brainstem and cerebellum involved in oculomotor control. For clarity, ascending pathways are not shown. Arrows do not always correspond to direct anatomical connections. FEF = frontal eye field, SEF = supplementary eye field, LIP = lateral intraparietal area, MT/MST = middle temporal/middle superior temporal areas, CN = caudate nucleus, SNr = substantia nigra pars reticulata, SC = superior colliculus, PMN = brain stem premotor nuclei, PON = pre-cerebellar pontine nuclei, Verm = oculomotor vermis (cerebellum), VN = vestibular nuclei, VPF = ventral paraflocculus. From Krauzlis (2005).

1.2.2. Visual Circuitry

Retinal inputs are relayed to cortex by two major routes (together with a minor projection via the inferior pulvinar). The smaller retino-tectal projection (comprising ca. 10% of retinal ganglion cells) innervates the superficial (visual) layers of the superior colliculus, which also receive afferents from striate and extrastriate cortex (Finlay et al., 1976) and the frontal eye fields (Huerta et al., 1986b). The primary retino-geniculate projection routes principally through the dorsal lateral geniculate nucleus (dLGN) of the thalamus, carrying visual information in three cellular assemblies (magno-, parvo- and koni-cellular pathways) to striate cortex (V1) (Dacey, 2000). Magnocellular (M) neurons respond rapidly and transiently with high contrast gain to low spatial frequency signals, making them suitable for signalling sudden visual changes (Lennie, 1993). Parvocellular (P) neurons respond tonically to colour and a range of spatial frequency stimuli, depending on retinal eccentricity, appropriate for signalling detailed information about visual form (Kaplan et al., 1990). Konicellular (K) neurons constitute 90% of the retino-tectal projection, but the nature of koniocellular information processing is less well understood (Irvin et al., 1986; Dacey, 2000). Visual neuronal onset latencies to flashed stimuli have been shown to occur 10-20ms faster in the M than P layers of the dLGN, and those cortical areas innervated by M inputs appear to be activated earlier than those receiving P input (Schmolesky et al., 1998). However, it has been suggested that multiple sites of convergence between the different processing streams in cortex may be sufficient to cancel out the implied behavioural consequences of faster M cell inputs (Maunsell et al., 1999). Hypercolumns in primary visual cortex (V1) process orientation information (in orientation columns), and colour information (in 'blobs') from both eyes (in ocular dominance columns) in a retinotopic fashion. This is then relayed via pyramidal neurons through a series of cortical visual areas (Zeki, 1993). Cortical visual processing is frequently hierarchical, reflected in the increasing size and complexity of neuronal

receptive fields across each synaptic relay (Maunsell & Newsome, 1987). Visual information appears to be processed through cortex in two largely parallel streams (Baizer et al., 1991). Based on neuropsychological dissociations, a simplifying functional framework has been proposed, according to which occipito-parietal dorsal stream areas are specialized for visuospatial processing (or 'perception for action' (Goodale & Milner, 1992)), while occipito-temporal stream areas are specialized for visual object recognition (see Figure 1.4). It has been claimed that magno- and parvo-cellular inputs preferentially innervate these two respective streams (Livingstone & Hubel, 1987), but there is now evidence for cellular (Merigan & Maunsell, 1993), anatomical (Morel & Bullier, 1990) and functional convergence in several areas of cortex (Claeys et al., 2004).



Figure 1.4. Schematic representation of the two cortical visual pathways. The dorsal stream (blue) projects from V1 to posterior parietal cortex. Parietal cortex also receives visual input from the superior colliculus via the pulvinar. The ventral stream (red) projects from V1 to regions in occipito-temporal cortex. Both routes feature a series of complex inter-connections. From Goodale & Westwood (2004).

FEF: Visual Connectivity

The FEFs receive massive converging input from a wide range of extrastriate areas in both the dorsal and ventral visual streams (Baizer et al., 1991). They share reciprocal, topographically-organised connections with extrastriate visual areas V2, V3, V4, V5,

MST, but not with V1, as well as with areas TE, TEO and peri-principal prefrontal cortex (Huerta et al., 1987; Barbas, 1988; Petrides & Pandya, 1988; Stanton et al., 1995). The medial and lateral parts of FEF appear to have distinct patterns of dorsal/ventral stream connectivity (Schall et al., 1995b) (see Figure 1.5). Medial FEF, from where electrical stimulation evokes large-amplitude saccades (Robinson & Fuchs, 1969) and in which FEF visual cells have large receptive fields (Suzuki & Azuma, 1983), is preferentially connected with peripheral visual field representations in the dorsal stream. Lateral FEF, from where electrical stimulation evokes small-amplitude saccades and where FEF visual cells have small receptive fields, is preferentially connected to foveal/macular representations in the ventral stream (Bullier et al., 1996). Dorsal and ventral stream inputs converge in lateral but not medial FEF. Although human imaging studies frequently report distinct medial and lateral FEF activation clusters, these remain to be functionally dissociated. The available evidence for saccadic amplitude-based mapping indicates that, if anything, the lateral-small/medial-large saccade organisation of the monkey FEFs is reversed in the human brain (Paus, 1996).



Figure 1.5. Summary of the major connections of FEF with visual cortical areas. The distinct connectivity patterns of lateral (area 45) and medial (8Ac) FEF are indicated on this lateral view of the macaque monkey brain. Solid lines indicate major projections to medial FEF; dotted lines indicate major projections to lateral FEF. The figure also shows that large amplitude saccades are evoked by microstimulation of medial FEF, while small amplitude saccades are evoked from lateral FEF. From Schall, et al. (1995b).

Position of the FEFs in the Cortical Visual Hierarchy

The information processing hierarchy is structurally underpinned by a hierarchical ordering of anatomical projection patterns. 'Feedforward' projections originate predominantly in supragranular layers (2 and 3) of cortex and terminate in layer 4 of the recipient zone; 'feedback' (sometimes called recurrent) projections tend to originate in infra-granular layers (5 and 6) and terminate outside layer 4 (Rockland & Pandya, 1979). So-called horizontal, intracortical, connections originate in supra- and infra-granular layers and terminate in all four layers. Laminar organisation has proved a useful tool for classifying cortico-cortical projection patterns (Barbas & Rempel-Clower, 1997; Rempel-Clower & Barbas, 2000). By applying these principles to the known anatomy of about 30 visual areas, Van Essen and colleagues (Maunsell & van Essen, 1983; Felleman & Van Essen, 1991) generated the first hierarchical model of the visual cortex (see Figure 1.6). This structural model corresponded well with physiological studies, which had suggested an orderly progression of increasingly complex information processing from areas V1, V2, V3 and onward to prefrontal cortex.

Subsequent mathematical modelling of this connectivity database, however, showed that the hierarchy was under-determined, partly because there was no clear indication of the distance separating successive levels (Hilgetag et al., 1996). A recent attempt to tackle this issue has demonstrated a correlation between hierarchical level and the proportion of cells originating in supragranular layers (%SLN) (Barone et al., 2000). By applying this graded parameter to classify connections, the authors showed that the classical hierarchy was governed by a distance rule. Feedforward projections exhibited high %SLN values, which increased with hierarchical distance from the afferent zone. Estimates of %SLN values in efferent zones labelled by injections in V1 and V4 largely confirmed the rank ordering of the classical model.

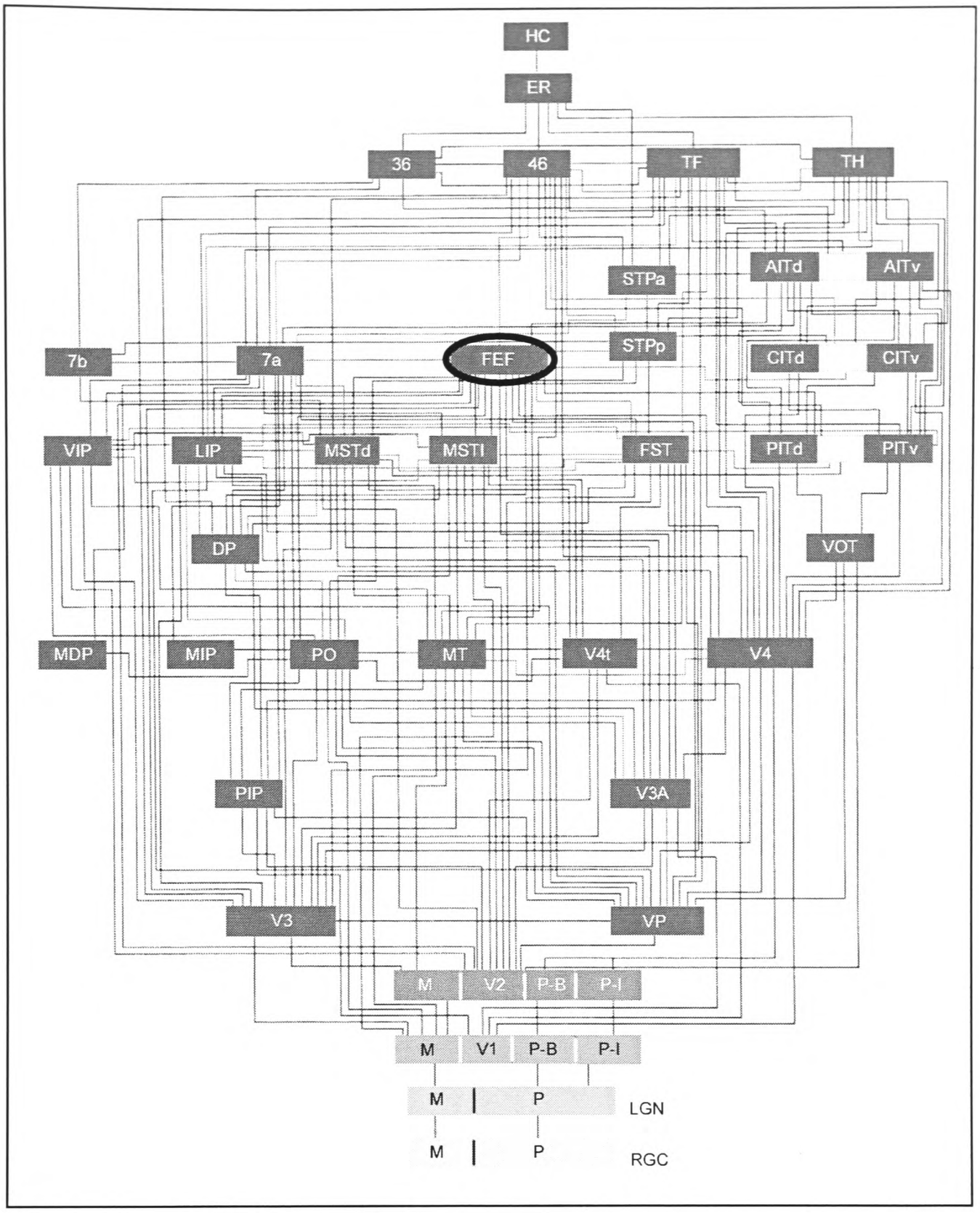


Figure 1.6. Anatomical hierarchical model of the visual system according to Felleman & Van Essen (1991). Lines indicate inter-areal projections. The model is organised into 12 hierarchical levels including V1 (level 1). The FEFs are encircled for emphasis. In this model the FEFs are located on level 8, above extrastriate areas MT, MST, V3 and V4. Dorsal stream areas are located in the left half of the diagram; ventral stream areas are on the right.

There was one notable exception - the FEFs, which exhibited a feedforward relationship with area V4 (Figure 1.7). Ongoing work in this group argues in favour of a higher rank for lateral than medial FEF. Preliminary analyses suggest that while areas LIP and FST send feedback projections to medial FEF, they are horizontally connected (in terms of

hierarchical level) to lateral FEF. Prefrontal cortex feeds back to both areas, but is nearer to lateral FEF in terms of hierarchical distance. The authors suggest that lateral FEF occupies a central position within the visual hierarchy (Vezoli et al., 2004), at the junction of the dorsal and ventral streams. This fits with the observed discrepancy that the FEFs, alone of visual areas, violate the principle of preferential connectivity with neighbouring areas, instead sending long-range projections throughout visual cortex (Bullier, 2001a). An alternative approach to the anatomical hierarchy uses non-parametric cluster analysis to rank order anatomical connections (Hilgetag et al., 2000). This computational modelling approach has led to the development of a variety of possible hierarchical arrangements that depart significantly from the classical framework.

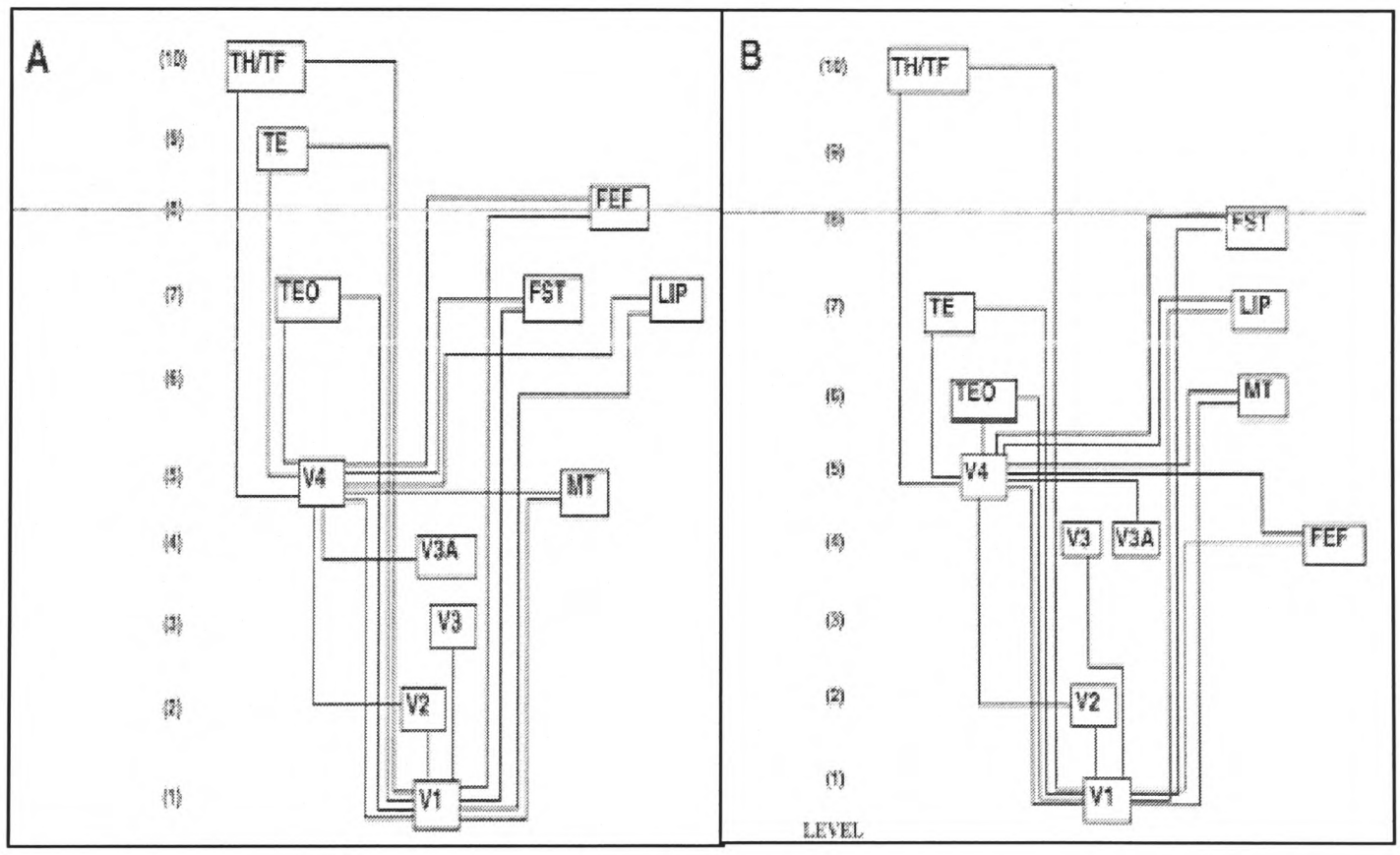


Figure 1.7. (A) Model of the visual hierarchy according to Felleman & Van Essen (1991). **(B)** Modified version of model A derived from %SLN graded parameter (Barone, et al. 2000). Note the change in hierarchical position of the FEFs. Numbers on the left denote hierarchical level.

If the anatomical model approximates the hierarchical order of visual information processing, then rank order should predict the timing of activation of visual areas (Schmolesky et al., 1998). In a review of studies of neural onset latencies throughout the visual system, Bullier and colleagues concluded that the structural model provided a reasonable fit for most visual areas, with the notable exception of the FEFs (Nowak & Bullier, 1997). However, in a follow-up study measuring neuronal latencies to flashed stimulation in several visual areas within the same subjects, they showed that, after V1 neurons, V3, MT, MST and FEF neurons produced the fastest response to flashed stimulation, discharging as early as 35-40ms after stimulus onset, with a mean response latency of 60-70ms (Schmolesky et al., 1998). The mean response latency in these areas was only 6-9ms slower than the mean response latency in V1. By contrast, mean responses in areas V2 and V4 were slower (82/104ms) and more broadly distributed (Figure 1.8). Thus, neural response latencies are inconsistent with the ordinal arrangement of these cortical areas in classical anatomical hierarchical models. For instance, it is difficult to account for the early response latencies of FEF neurons unless it is assumed that multiple tiers in the hierarchy are by-passed during the initial transfer of information from V1. Thus, connectivity-based hierarchical models must be revised to incorporate neuronal latency data if they are to plausibly reflect the structural organisation of visual information processing.



Figure 1.8. Cumulative distribution of visually evoked onset latencies of neurons in various visual areas. The percentile of cells that have begun to respond is plotted as a function of time from visual stimulus presentation. MLGN = magnocellular lateral geniculate nucleus, PLGN = parvocellular lateral geniculate nucleus. The V4 range extends to 159ms. From Schmolesky, et al. (1998).

The early response profile of FEF visual neurons (which discharge in the same latency range as V3, V5, MST) raises the question of functional significance. Whilst it makes intuitive sense that an oculomotor area should receive inputs from across the visual system, the early response latency and nodal anatomical position of the FEFs in the visual hierarchy (Vezoli et al., 2004) raises the relatively neglected possibility that the FEFs may contribute directly to perceptual processing, like other rapidly-activated extrastriate areas of the dorsal stream (Bullier, 2001b).

2. The FEFs Integrate Visual Input into Oculomotor Commands

The connectional architecture of the FEFs, with afferent projections from the dorsal and ventral visual streams, and efferent connections with the superior colliculus and brainstem, implies a functional role in integrating visual information with eye movement commands. This is further supported by the variety of response properties that exists in the FEFs, ranging from purely sensory to purely motor (Bruce & Goldberg, 1985b).

Despite these indicators, it has only been recently demonstrated that the FEFs operate as a visuomotor integrative circuit, taking visual signals as input and producing saccade commands as output (Tehovnik et al., 2000). Using ortho- and anti-dromic stimulation techniques, it was shown that signals carried in the descending projections from the FEFs to the superior colliculus, the pons and to brainstem oculomotor structures are driven by FEF movement cells and by only those FEF visual cells with foveal receptive fields ('fixation cells') (Segraves & Goldberg, 1987; Segraves, 1992). Conversely, all of the FEF units that were activated orthodromically by stimulation of the superficial visual layers of the superior colliculus (presumably via a tecto-thalamo-cortical route (Lynch et al., 1994)) exhibited visual responses, with half of those showing a visuo-movement profile (Sommer & Wurtz, 1998).

Much more is understood about the output end of this visuomotor circuit than the input end (eg: Brown et al., 2004). This emphasis probably derives historically from observations that FEF lesions disrupt eye movements (Bianchi, 1895; Kennard, 1939), and more recently from work indicating that cortical inputs to the brainstem oculomotor circuit comprise two parallel pathways, one dependent on the superior colliculus and the other on the FEFs (reviewed by Schiller, 1985; but see Keating & Gooley, 1988; Hanes & Wurtz, 2001). Whereas lesions of either the superior colliculus or the FEFs temporarily disrupt eye movements, combined lesions of both structures produce a permanent deficit (Schiller et al., 1979a). The close functional coupling of the FEFs and the colliculus in programming oculomotor output can be demonstrated by simultaneous electrical stimulation of both structures. Evoked saccades have an amplitude and direction that constitute the vector sum of those evoked by stimulation of either site alone (Schiller et al., 1979b).

Recent approaches to visuomotor integration conceptualize the process as one in which featural input from extrastriate areas (visual evidence) is further processed in visuomotor structures and, in relation to some perceptual decision threshold, guides the motor response output (eg: Gold & Shadlen, 2001). Much of this work derives from experiments using random-dot motion displays in which various proportions of dots move coherently to the left or right (Britten et al., 1992). In a forced-choice direction discrimination task, the model claims that the probability of making a correct decision is based on computing the relative magnitude of sensory evidence supporting each alternative decision (Roitman & Shadlen, 2002). When perceptual discrimination is difficult, because the sensory evidence (proportion of motion coherence) is weak, the build-up of signal in visuomotor structures accumulates more slowly and the firing rate at threshold is lower. The speed with which evidence accumulates, and the maximal firing rate achieved, is proposed to correlate with the respective speed and certainty of the decisional response. Evidence for this model supports the existence of a sensory integration process in the dorso-lateral prefrontal cortex, including the FEFs (Kim & Shadlen, 1999; Gold & Shadlen, 2000), as well as in the superior colliculus (Horwitz & Newsome, 1999; Horwitz & Newsome, 2001) and LIP (Shadlen & Newsome, 2001). Precisely how perceptual evidence that reaches a decision criterion is translated into a motor command remains opaque.

In what follows, I will review evidence consistent with this conception of the FEFs as a structure that integrates visuospatial input towards a decision threshold. The well-established role of the FEFs in oculomotor programming will be briefly summarized, followed by more detailed discussion of those aspects of oculomotor function that bear on visuospatial selection. A visual/oculomotor dichotomy will be relied upon for ease of exposition. Its artificiality is emphasized, and is already presaged by the review of

anatomical connectivity, since many of the same structures (eg: superior colliculus, striatum) participate in both kinds of functional assembly.

Before proceeding, a clarification of terminology is in order. The aim of this thesis is to assess visuospatial function in the human FEFs. Terms such as target detection, discrimination, selection or visual attention will be used (often interchangeably) to refer to visuospatial computations ascribed to the FEFs based on the demands imposed by the tasks used in their assessment. In all cases, these terms are intended to describe a perceptual process by which a visual stimulus is chosen from among competing distractors. These terms are explicitly intended to distinguish FEF visuospatial processes from oculomotor processes by which a saccade is programmed or executed to a particular location.

3. FEF Visuospatial and Oculomotor Processes are Distinct

3.1. FEF Neurons exhibit Visuospatial and Oculomotor Responses

FEF neurons show a continuum of responses, from purely sensory to purely motor, and have been classified into three main categories: visual, movement and visuo-movement (Bruce & Goldberg, 1985ba). The receptive/movement fields of all cell types emphasize the contralateral hemifield. About half of FEF neurons have visual responses, discharging phasically when a visual stimulus is present in the cell's receptive field (Mohler et al., 1973a). In 50% of these, the visual response is enhanced if the stimulus is a target for a saccade (Goldberg & Bushnell, 1981). Cell discharge is not necessarily linked to the presence of a visual stimulus. Some cells show a tonic level of discharge after the offset of a stimulus until a saccade is executed. Others discharge when a saccade

brings the location of a previously flashed (but no longer visible) stimulus into the receptive field – in which case no visual stimulus has ever appeared in the cell's receptive field (Umeno & Goldberg, 1997). Thus FEF visual cells appear able to encode a short-term memory signal for a visual stimulus in oculocentric (ie: saccade vector needed to acquire the target) rather than in retinal coordinates (Goldberg & Bruce, 1990). Visual response latencies can occur as early as 35-40ms after stimulus onset (mean: 70ms) (Thompson et al., 1996; Schmolesky et al., 1998) and peak activation is reached after a further 45-50ms.

FEF movement cells discharge before, during and after saccades (Bizzi, 1968; Bizzi & Schiller, 1970; Schall, 1991b). Some cells also respond during active fixation (Suzuki et al., 1979). The pre-saccadic discharge is greater during intentional than reflexive saccades (Burman & Segraves, 1994), while the post-saccadic burst may reflect corollary discharge (Goldberg & Bruce, 1990). FEF movement neurons typically begin to discharge about 150ms prior to a saccade, with activity peaking 13ms before saccade initiation (Segraves & Park, 1993).

Both FEF visual and movement cell populations are topographically organised, with the maps of visual receptive fields and evoked saccades in broad spatial register (Schall, 1991ab). Visual FEF cells with large receptive fields representing peripheral locations are found within medial FEF, while smaller, more central receptive fields are located ventro-laterally. Microstimulation evokes large amplitude saccades from medial FEF, while small amplitude saccades are elicited ventro-laterally (Robinson & Fuchs, 1969).

Visuomovement cells typically exhibit a double-burst profile, discharging both to visual targets and before purposive saccades. Like tonic visual FEF cells, a subset show

sustained activation during the delay period in tasks that feature a separation between the visual stimulus and the response cue (Funahashi et al., 1989). Many visuomovement cells exhibit combined double-burst and sustained activation.

Subpopulations of FEF cells have been discovered that are activated by pursuit and vergence eye movements (MacAvoy et al., 1991; Gamlin, 2002). These are outside the scope of this thesis, and so will not be discussed, which is not to say that they are irrelevant.

3.2. Oculomotor Aspects of FEF Function

Microstimulation of FEF movement neurons evokes saccades whose amplitude and direction vary not with gaze angle but with topographic location in the FEFs (as described in the previous section). That saccades can be evoked with low current thresholds (> 50 $_{\mu}$A) and short stimulation train durations (< 70ms), and are less resistant to behavioural modulations, indicates that, of the three cortical eye fields, the FEFs are most closely coupled to the brainstem oculomotor generator (Tehovnik & Sommer, 1997; Mushiake et al., 1999; Tehovnik et al., 1999). Pre-saccadic FEF movement cell activity has been shown to accumulate over time to reach a threshold level of activation, after which a saccade is initiated (Hanes & Schall, 1996). The response characteristics of FEF movement neurons during tasks in which monkeys are alternately required to initiate or inhibit intentional saccades (eg: Hanes & Schall, 1995) provide a good fit with computational models of the mechanisms underlying saccadic reaction time (Carpenter & Williams, 1995; Hanes & Carpenter, 1999; Ratcliff et al., 1999). In addition to pre-saccadic burst activity, the level of preparatory or anticipatory activity in FEF neurons prior to visual target onset (Schall, 1991b) has been shown to predict both

saccade direction and latency in monkeys and humans (Everling & Munoz, 2000; Coe et al., 2002; Connolly et al., 2004).

Unilateral FEF damage induces a transient ipsilesional deviation of the eyes, impaired fixation and a reduction in contralateral saccades, which show reduced gain and increased latencies (Latto & Cowey, 1972). Damage can also induce neglect and extinction (Kennard & Ectors, 1938; Rizzolatti et al., 1983). Both monkeys and patients can recover from visually-guided saccade deficits in a matter of months, but sequential and memory-guided saccade deficits are more severe and long-lasting (Dias & Segraves, 1999; Gaymard et al., 1999; Schiller & Chou, 2000a). Recovery of exploratory oculomotor capacities appears to be mediated by a compensatory strategy of moving the foveas by means of head movements instead (Russell, 1982; van der Steen et al., 1986). A similar strategy has been shown to occur in a human patient with a congenital inability to make eye movements (Gilchrist et al., 1997; Gilchrist et al., 1998). Various lines of evidence indicate that the FEFs make a critical contribution to the generation of intentional but not reflexive saccades, which appears to rely more on parietal cortex (eg: Schiller & Tehovnik, 2001). Patients with frontal lobe damage often exhibit deficits in inhibiting reflexive saccades to salient targets (Guitton et al., 1985), but whether the FEFs are critical for reflexive saccade inhibition is disputed (eg: Gaymard et al., 1999). Pharmacological evidence indicates that FEF GABA-ergic inhibitory circuits play a critical role in eye movement generation (eg: Schiller & Tehovnik, 2003). Microstimulation of the foveal representation within the FEFs delays saccade release, which also results from subthreshold stimulation of sites whose movement fields do not contain the saccade target (Burman & Bruce, 1997). Transient disruption of anti-saccades (Muri et al., 1991), saccade triggering (Wipfli et al., 2001; Nyffeler et al., 2004), double-

step saccades (Tobler & Muri, 2002), and inhibition of return (Ro et al., 2003) can be induced by applying TMS over the FEFs.

3.3. The Premotor Theory of Attention: Is Visual Selection a Saccade Command?

Although the existence of three cell classes in the FEFs suggests a physiological basis for visual-to-motor transformation (Bruce & Goldberg, 1985aa), accounts of visual cell function are typically cast in the service of saccades: visual response enhancement occurs only when a stimulus is the target for a saccade; sustained memory signals constitute the saccade vectors needed to acquire a target. There is a convincing body of human behavioural evidence arguing for a close link between visual target selection (attention) and saccades (Hoffman & Subramanian, 1995; Kowler et al., 1995; Deubel & Schneider, 1996). These data indicate that when a saccade is programmed to a particular location, there is an obligatory (covert) shift of visual attention to that location which precedes the orienting response. Various accounts of the link between attention and saccades have been proposed, ranging from complete independence (Klein, 1980; Klein & Pontefract, 1994) to sequential deployment (Henderson, 1992) to identity (Rizzolatti et al., 1987; Rizzolatti et al., 1994; Sheliga et al., 1997).

Rizzolatti's 'premotor theory of attention' has had a significant impact on the interpretation of FEF activations in imaging studies. This theory holds that, in the normal case (eg: blindsight exception as mentioned above), the act of programming a saccade to an object or location *constitutes* attention to that location. A robust finding is that covert selection and orienting activate overlapping fronto-parietal networks with shared activation clusters in the frontal eye fields and parietal cortex (eg: Corbetta et al., 1998) (see Figure 1.9). Yet, while parietal activations during covert selection are usually

ascribed to visuospatial processes (coordinate transformation, search, binding, 'top-down control', distractor filtering, etc.) (Corbetta et al., 1995; Shulman et al., 2002), FEF activations are typically identified with saccade programs (Buchel et al., 1998; Gitelman et al., 1999). According to a commonly invoked explanatory scheme (Mesulam, 1981, 1990), parietal cortex integrates information from feature-selective extrastriate areas to select targets that are behaviourally relevant. This information is then relayed to the FEFs, where saccades are programmed to these targets in an obligatory manner. Inhibition prevents these programs being executed during covert tasks. This asymmetric scheme is clearly under-determined. The challenge is to specify the mechanisms underlying the bi-directional relationship in which visual selection processes direct saccades, and visual processing is gated by the probability that a saccade will be made to a particular location. Hence, as an identity account, the premotor theory has been something of a conceptual impediment to understanding the human FEFs as a centre for visuomotor integration. That the bulk of imaging studies fail to report modulations of FEF activity by perceptual factors may reflect a lack of sensitivity in the design, or more commonly, a reliance on recursive explanation in which all FEF activations are eye movement ones. In the few studies in which factors like perceptual difficulty have been varied parametrically, FEF activity has been modulated accordingly (Donner et al., 2000; Donner et al., 2002; Marois et al., 2004).



Figure 1.9. Overlapping patterns of fronto-parietal activation elicited by covert and overt orienting. Activations elicited by saccadic eye movements are on the right; activations associated with covert attention are on the left. The FEFs are located at the junction of the precentral sulcus (precs) and the superior frontal sulcus (sfs). SEF = supplementary eye fields, IPS = intra-parietal sulcus, IPS-POCS = intra-parietal and post-central sulci. From Corbetta & Shulman (1998).

There have been a number of demonstrations that oculomotor signals affect visual processing before, during and after saccades (eg: Duhamel et al., 1992a; Moore et al., 1998). Evidence that saccade commands in the FEFs causally affect visual sensitivity at the saccade target location derives from microstimulation in awake behaving monkeys (Moore & Fallah, 2001; Moore & Armstrong, 2003; Moore & Fallah, 2004). Moore and colleagues showed that stimulation of an FEF movement neuron below the threshold needed to evoke a saccade enhanced sensitivity to a visual target in the neuron's response field. Stimulation lowered the monkeys' luminance change detection thresholds and reduced false alarms. In a follow-up study, the authors applied sub-threshold FEF stimulation whilst recording from a V4 neuron whose receptive field overlapped with the FEF neuron's movement field. The FEF stimulation increased the gain of the V4 neuron's response to a stable oriented bar stimulus. This modulation depended on the presence and strength of visual stimulation. It was enhanced when the stimulus matched the cell's tuning preference and was further enhanced by the presence of distractors. The size and nature of the effects was very similar to those obtained by attentional

manipulations in V4 unit recording studies (McAdams & Maunsell, 1999). It appears unlikely that these effects issue from selective activation of FEF movement cells. Despite a lack of detailed knowledge about synaptic circuitry, FEF movement and visual cells are topographically aligned, with overlapping activation time-courses, and they normally operate in a functionally integrated fashion. Nevertheless, this work has elegantly demonstrated that, for a given area of the FEF, stimulation-induced biases in saccade programming initiate spatially corresponding biases in the gain of visual representations.

Other work has shown that FEF damage can induce a long-lasting impairment in visual sensitivity even after oculomotor deficits have recovered (Latto & Cowey, 1971). After unilateral FEF lesions, monkeys showed raised detection thresholds for flashed luminance stimuli presented in the contralesional field. This field defect persisted, despite recovery of exploratory eye movements. It is noteworthy (O'Shea & Walsh, 2004) that while their oculomotor deficits are well-characterized, human FEF patients are rarely tested for visual field defects that involve assessing detection thresholds (eg: Rivaud et al., 1994; Ploner et al., 1999).

Thus there is physiological evidence for distinct, but interacting perceptual and oculomotor processes within the monkey FEFs. Within the past ten years, single-unit studies have begun to dissociate these processes. This work has shown that these two processes map to discrete populations of FEF visual (and visuomovement) and movement neurons, respectively. This demonstration argues for a re-focussing of research effort away from the traditional debate, according to which the content of attentional signals in visuomotor structures is *either* a boosted representation of a salient target /location *or* a motor plan for action upon that target (Mountcastle et al., 1975; Robinson et al., 1978). Rather, having established the existence of both kinds of

representation within the same neural structure, the challenge is to understand how visual representations become transformed into motor ones.

3.4. Dissociating Perceptual Processes from Oculomotor Response Preparation in the FEFs during Visual Search

3.4.1. FEF Visual Cells

In a series of studies, monkeys carried out feature (eg: Schall & Hanes, 1993) and conjunction (eg: Bichot et al., 2001a) visual search tasks while recordings were made from FEF visual, visuomovement or movement cells (see Figure 1.10). During a typical search trial, FEF visual (and visuomovement) units began to discharge with a minimum latency of 35-40ms and an average latency of 70ms after search array onset (Thompson et al., 1996). This initial visual response was non-selective, but typically by 120-150ms after search array onset, the neuron's response had evolved to distinguish a target from a distractor in its receptive field (Bichot et al., 2001b). Discrimination correlated with a reduction in the activity of neurons with a distractor in their receptive field, and sustained activation of those neurons with a target in their receptive field (Schall et al., 1995a). Thus, the outcome of the discrimination process was a signal representing the spatial location of the search target (see Figure 1.11(a)). In a detection paradigm combined with backward masking, it was shown that, during the period of visual signal build-up, small differences in the amplitude of visual FEF signal correlated reliably with monkeys' subsequent perceptual reports on hit, miss, false alarm and correct rejection trials (Thompson & Schall, 1999). FEF neurons are not selective for colour, shape or motion direction (Mohler et al., 1973b), and yet this discrimination process has been observed during search of arrays defined by these features (eg: Sato et al., 2003). This implies that performance accuracy and discriminative signal build-up in FEF visual neurons must rely

on input from cells in extrastriate cortex that are selective for colour, shape or motion (Schall, 2002).



Figure 1.10. Visual search task used to investigate FEF neuronal responses. (a) A simple visual detection task used to map FEF visual neuron receptive fields. Monkeys had to maintain fixation while a target stimulus was flashed in one of four locations in the visual field. **(b)** A sample visual conjunction search task. The monkeys' task was to make a saccade to the target that had been defined in the earlier detection trials. The responses of FEF visual, visuomovement and movement cells were recorded while monkeys carried out the search task. From Bichot & Schall (1999).

3.4.2. FEF Movement Cells

Whereas FEF visual cell activity reflects the evolving process of target selection, activity of FEF movement cells reflects the programming of a saccadic response that signals the outcome of this selection process. FEF movement neurons exhibit little or no visual activity, but they show strong discharge prior to the initiation of a saccade into a cell's movement field (Thompson et al., 1996) (see Figure 1.11(b)). They do not show a fixed onset latency with respect to visual stimulation (Thompson & Schall, 2000), but their activation typically increases steadily 100-150ms prior to saccade initiation (Schall, 1991b). During visual search, this activation has been shown to rise sharply from the

time of visual target discrimination (Bichot et al., 2001a). FEF movement cell responses do not differ when targets are presented alone or with distractors, nor as a function of the accuracy of the perceptual decision guiding the saccadic response (Hanes et al., 1995; Thompson & Schall, 2000). Thus, FEF movement cell activity reflects saccade metrics, rather than the visual context in which a saccade is produced. Consistent with this, descending projections to oculomotor circuitry in the brainstem and superior colliculus derive from FEF movement cells (Segraves & Goldberg, 1987; Segraves, 1992).



Figure 1.11. Responses of FEF visual (a) and movement (b) neurons during the visual search task outlined in Figure 10. (a) The upper panel shows the average spike density function of a population of FEF visual neurons during visual conjunction search performance. The bold line indicates the neurons' response to the target. The initial response is non-selective (ca. 50ms after visual stimulus onset), but by ca. 100ms the amplitude of signal distinguishes the target from distractors. The three grey lines represent the average FEF visual neuron response to distractors of varying degrees of similarity to the target. Note the sharp divergence in signal between target and distractor distributions after 100ms. **(b)** The lower panel shows the average spike density function of a sample of FEF movement neurons during search performance. Note how pre-saccadic activity builds in the period following the target discrimination process. From Bichot & Schall (1999a,b).

3.4.3. Visual Target Discrimination and Saccade Programming are Distinct

A number of manipulations have shown that target discrimination processes are dissociable from oculomotor processes in the FEFs. On a given feature-search trial, the time of target discrimination does not account for the variability of saccadic reaction time, which instead correlates with the duration of activity in the interval between target discrimination and saccade initiation (Thompson et al., 1996). The magnitude and time-course of the target discrimination signal has been shown not to differ between standard search trials and 'no-go' trials in which the saccadic response is inhibited (Thompson et al., 1997). Thus, target discrimination does not depend on saccade production. This has also been shown in a 'search-step' task, in which an odd-man-out feature search target switched from its initial position to a different location during a trial (see Figure 1.12(i)). On some trials, monkeys were able to alter their saccades mid-flight, so that they correctly acquired the new target location. On others, they made errors, executing a saccade to the initial location. On both kinds of trials, whereas FEF movement cells signalled the executed saccade trajectory (correct or erroneous), FEF visual cells signalled the actual target location (Murthy et al., 2001) (see Figure 1.12(ii)). When target discrimination difficulty was manipulated, by increasing target/distractor similarity (Sato et al., 2001) or by using conjunction rather than feature targets (Bichot et al., 2001b), the timing of discrimination was delayed, and this induced a corresponding delay in saccadic reaction time. However, stimulus-response incompatibility, achieved either by means of the 'search step' manipulation (Sato et al., 2001), or by randomly cueing pro- or anti-saccade responses (Sato & Schall, 2003), delayed saccadic reaction time, but target discrimination continued to occupy a fixed mean interval from the onset of the visual display. Strong evidence that the accumulation of sensory evidence is distinct from response preparation comes from a FEF microstimulation study (Gold & Shadlen, 2003). When saccade trajectories are re-plotted, the start- and end-points of a saccade are

typically linked, not by a straight-line, but rather by a curved trajectory. Gold & Shadlen measured changes in the curvature of FEF stimulation-evoked saccades evoked to probe the evolving perceptual decision signal in the FEFs during a motion direction discrimination task. When the direction of motion and the direction of the saccadic response were spatially congruent, saccade curvature reflected the strength of the motion direction signal (sensory evidence). When the task required a response saccade to be made to a spatially incongruent location, evoked saccades were unaffected by the perceptual context. A similar effect has been demonstrated using microstimulation during visual search with interleaved pro- and anti-saccade responses (Juan et al., 2004).



Figure 1.12(i). FEF visual and movement responses are dissociable. (a) Odd-man-out search task in which monkeys had to make a saccade to the odd-coloured target. The right-most figure shows the eye position trace. **(b) Search-step manipulation.** On a proportion of trials the target switched location unpredictably after a short delay. Monkeys either made a compensatory eye movement to acquire the new target location (upper eye trace) or they failed to compensate (lower eye trace). From Murthy, et al. (2001).

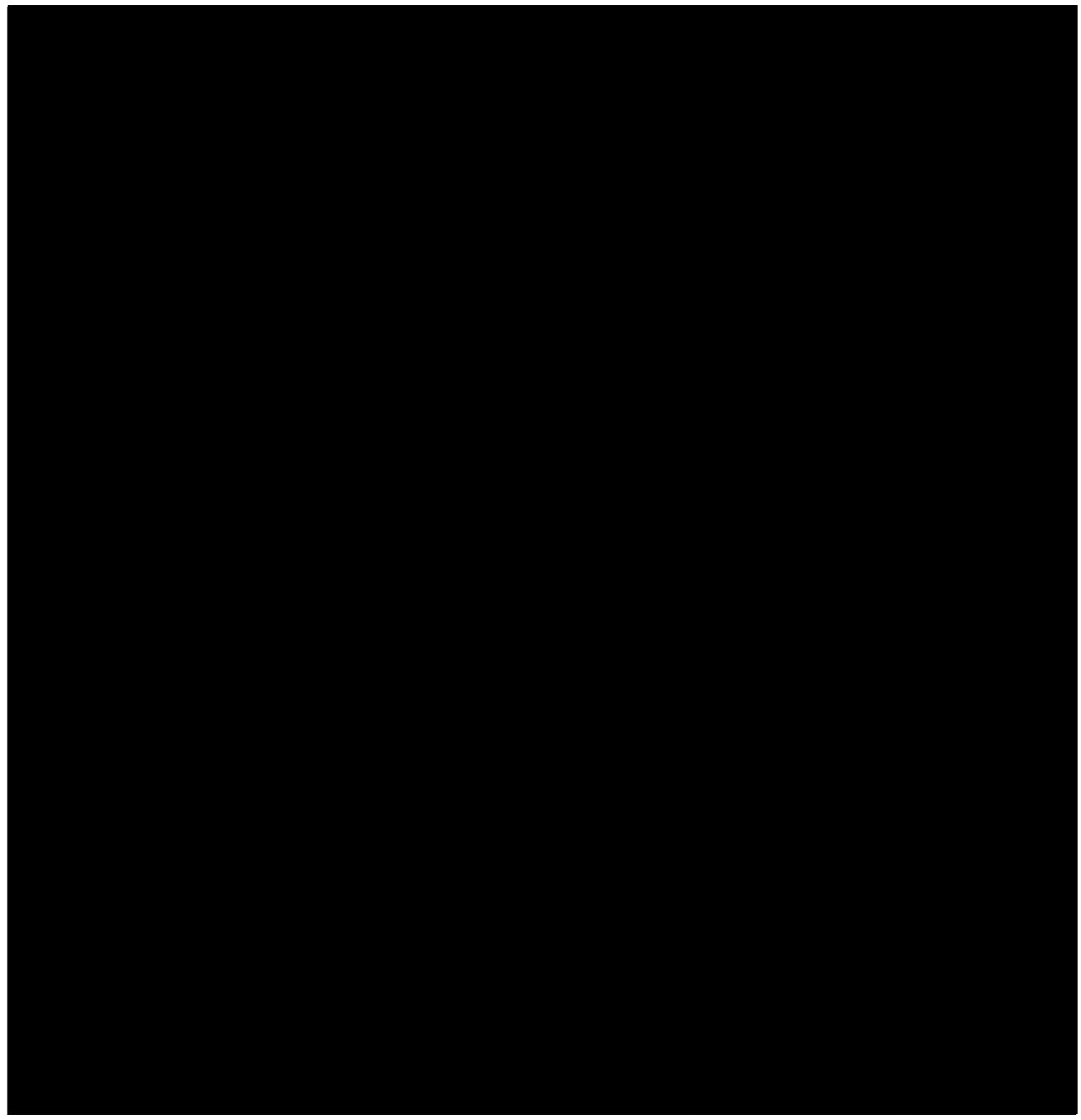


Figure 1.12(ii). Responses of FEF visual neurons. (a) The typical target/distractor discrimination response function of a FEF visual neuron during performance of an odd-man-out search task. The arc indicates the location of this neuron's receptive field (lower right quadrant). The dark line represents the response when the target fell in the neuron's receptive field. The grey line represents the response to the distractor. **(b) Averaged FEF visual neuron activity on search-step trials.** The dark line represents responses on compensated trials when the distractor in the receptive field unexpectedly became the target. The dotted line represents non-compensated trials, and the thin line represents the response when the distractor remained in the receptive field. Note that the visual response is the same on both compensated and non-compensated trials: FEF visual neuronal responses discriminate the target irrespective of whether an eye movement is made to the target location. From Murthy, et al. (2001).

3.4.4. Factors that modulate Target Selection in the FEFs

Target discrimination in FEF visual neurons is influenced by long-term visual experience (Bichot et al., 1996), short-term visual priming (Bichot & Schall, 2002) and visual feature similarity between targets and distractors (Bichot & Schall, 1999a). Although the initial FEF visual response is normally non-selective, after repeated training on a constant target/distractor colour pop-out configuration, 50% of FEF visual neurons became

colour-selective, signalling within 50ms of array onset whether a target or distractor was in the receptive field (Bichot et al., 1996). Effects of target/distractor similarity and the history of target feature properties have been observed in the degree of FEF visual and movement neuron activation in the post-selection period between target discrimination and saccade initiation. During a conjunction search task, the level of distractor-related activity in FEF visual (Bichot & Schall, 1999aa) and movement neurons (Bichot et al., 2001a) during this period was greater when the distractor shared a feature with the target (colour/shape) (see Figure 1.11(a)). This suggests that, at least for learned stimulus-response associations, during the process of visuomotor integration, FEF visual neurons continuously send input to FEF movement neurons, which represents the evolving perceptual decision (cf. Gold & Shadlen, 2000, 2003). Visual FEF neurons were also affected by the history of target properties across successive days of testing. Behaviourally, this effect was manifested in the tendency of monkeys to make errant saccades to distractors that shared a feature with the target of a previous day's testing session (Bichot & Schall, 1999bb). Neurally, this corresponded with greater activity during the post-selection period when such a distractor fell in a visual FEF neuron's receptive field (Bichot & Schall, 1999aa). In a feature search priming study, the timing of target discrimination, and the degree of separation between target- and distractor-related activity in the post-selection period, were correlated positively and respectively with behavioural improvements in saccadic reaction time and accuracy (Bichot & Schall, 2002).

3.4.5. FEF as a Visual Saliency Map

The response profile of FEF visual neurons during visual search may be characterized as a process of accumulating perceptual evidence about the presence or absence (Sato et al.,

2003) and location of a visual target until a decision threshold is reached, the outcome of which (usually) determines the oculomotor response. Alternatively, target discrimination may be described as a visual saliency map (Cave & Wolfe, 1990; Thompson & Bichot, 1999), a process by which the population response of FEF visual neurons represents the location of conspicuous or behaviourally-relevant stimuli in retinotopically-mapped space (Cave & Wolfe, 1990; Thompson & Bichot, 1999). Saliency maps have been described in a number of visual and oculomotor structures (eg: Chelazzi et al., 1993; Luck et al., 1997; Basso & Wurtz, 1998; Gottlieb et al., 1998; McPeek & Keller, 2002a). This apparent redundancy sets a challenge for future work to distinguish saliency representations that are task-critical (eg: McPeek & Keller, 2004) from those that are downstream 'echoes' of maps computed elsewhere. That the FEF target discrimination process observed during visual search is task-critical is suggested by the effect of FEF lesions, which impair search performance in monkeys (Latto, 1978) and humans (Teuber et al., 1949). Lesions also induce visuospatial discrimination deficits (Collin et al., 1982) and perceptual neglect and extinction (Silberpfennig, 1941). Neglect has both visual and motor aspects (Kennard & Ectors, 1938; Kennard, 1939). However, while FEF lesions or ablation induce only mild or transient deficits in saccade latency, accuracy or velocity (Sommer & Tehovnik, 1997; Schiller & Chou, 1998; Dias & Segraves, 1999), visual target detection (Latto & Cowey, 1971), selection (Schiller & Chou, 2000b; Schiller & Kendall, 2004) and spatial memory (Gaymard et al., 1999; Mannan et al., 2005) processes show more severe and long-lasting impairments.

Whilst the concept of a saliency map in movement cells implies a motoric commitment to a single saccade target, the concept of a visual saliency map implies no obligatory link between representing a visual stimulus and foveating it. Although salient visual stimuli will typically constitute saccade targets, the neurophysiology just reviewed demonstrates

that the link is not obligatory. The main aim of this thesis is to furnish evidence that the human FEFs engage in visuospatial selection, and that this process is distinct from oculomotor commands. The next section reviews the existing evidence in favour of this claim.

3.5. Visuospatial Processing in the Human FEFs

Evidence for visuospatial processing in the human FEFs is scarce. One study using intra-cranial recordings showed that contralateral visual stimuli modulated visual evoked potentials recorded from the FEFs. Electrical stimulation at the same site evoked contraversive saccades (Blanke et al., 1999). Only a small number of neuroimaging studies have interpreted FEF activations during detection and discrimination tasks in terms of visuospatial processes (eg: Donner et al., 2000), rather than in terms of a covert orienting (premotor) account (Shulman et al., 2001; Claeys et al., 2004). Such studies have shown that FEF activations are modulated by the difficulty of perceptual discrimination in search (Donner et al., 2002) and non-search tasks (Marois et al., 2004). Against a covert orienting account, a few studies have shown that the FEFs are not modulated by the 'number of attentional shifts', as measured by the slope of reaction time search functions (Muller et al., 2003; Nobre et al., 2003). A common finding is that the FEFs are activated in the delay periods of cueing tasks, which is often attributed to covert orienting, but sometimes to a spatial 'top-down control' signal, which is proposed to gate visual processing in extrastriate areas (Kastner et al., 1999).

Three recent studies have begun to assess visuospatial function in the human FEFs using transcranial magnetic stimulation (TMS). In a Posner paradigm, single-pulse TMS applied during the cue-target period speeded subjects' manual reaction times. When TMS was

applied over left FEF, this effect occurred for validly, invalidly and neutrally-cued trials, but only when the target was in the contralateral hemifield. TMS over right FEF facilitated reaction time to targets in either hemifield on all but invalidly cued trials (Grosbras & Paus, 2002). The authors concluded that TMS had enhanced target detection processes in the FEFs on the trials specified above, except on the invalidly cued trials when TMS over right FEF disrupted spatial attentional re-orienting.

In a follow-up study, the authors tested the detection interpretation using a backward masking paradigm (Grosbras & Paus, 2003). Single-pulse TMS applied 40-100ms prior to the onset of a single target (that was subsequently masked) lowered subjects' luminance detection thresholds. The hemifield asymmetry was replicated: TMS over right FEF improved detection in both hemifields; TMS over left FEF facilitated detection of only contralateral targets. This asymmetry concurs with patient, imaging and TMS studies claiming a right hemisphere bias in the fronto-parietal network subserving visuospatial attention (Mesulam, 1981; Kim et al., 1999; Walsh et al., 1999).

Grosbras & Paus interpreted these results by analogy with the detection and backward masking study of Thompson & Schall (2000) and the microstimulation studies of Moore and colleagues (2003; , 2004). Thompson & Schall reported that higher levels of activity in FEF visual neurons during the period of visual signal build-up towards threshold correlated with hit and false alarm responses, rather than misses and correct rejections. Accordingly, Grosbras and Paus concluded that detection sensitivity had improved because TMS had 'pre-activated' FEF neurons, raising their baseline activation level such that incoming stimulation could reach the detection threshold more easily. However, TMS should affect both the signal and noise distributions in FEF, making it difficult to see how a selective enhancement could occur. The key factor may be the presence of a

single stimulus – if TMS increases neural activity in an area carrying a single visual representation, then it is conceivable that this signal could be enhanced. The addition of a distractor, making the task one of luminance discrimination rather than detection, would predict a disruptive effect of TMS.

A visual discrimination deficit has been demonstrated by Muggleton, et al. (2003), who applied repetitive-pulse TMS (10Hz, 500ms) over the right FEFs during visual search of cluttered arrays. TMS degraded performance (d') during conjunction, but not feature search. An interleaved feature search paradigm, where the target/distractor combination alternated across trials, produced a trend towards impaired performance. Since eye movements were not permitted, the authors interpreted these effects in terms of a selective effect on target discrimination processes computed by visual FEF neurons. The graded pattern of interference effects, from no effect on feature search, to a trend in the interleaved paradigm and significant disruption on the conjunction search task, may issue from decreasing magnitudes of difference between target and distractor signals in the period of accumulating evidence towards threshold, as well as in the post-selection period (Bichot et al., 2001a). If TMS interferes with both target and distractor signals, stimulation should reduce the proportional difference between these signals, making discrimination more difficult.

4. The Roles of Posterior Parietal Cortex and the FEFs in Visual Search

The parietal eye fields (in lateral intra-parietal cortex, LIP) and the FEFs, share dense reciprocal connectivity (Cavada & Goldman-Rakic, 1989). Whereas all visual areas preferentially connect with either medial or lateral FEF, LIP afferents and efferents

connect with both aspects (Schall et al., 1995b; Stanton et al., 1995). Whether these patterns of innervation are organised with respect to saccadic amplitudes (as per medial/lateral FEF) remains to be clarified (Schall et al., 1995b). Microstimulation of LIP evokes saccades, and there appears to be a rough columnar organisation with respect to saccade direction.

Like the FEFs, LIP neurons show a continuum of responses from visual to motor, together with sustained delay-period activity, on tasks requiring oculomotor responses or (covert) spatial attention (Lynch et al., 1977; Robinson et al., 1978; Colby et al., 1995, 1996; Bisley & Goldberg, 2003). Significant research effort has been expended on attempts to dissociate visual from oculomotor preparatory activity in LIP (Colby & Goldberg, 1999; Andersen & Buneo, 2002). Although the response profile of LIP neurons is perhaps most accurately characterized as a process of transforming behaviourally-relevant visual stimuli into saccade commands (Zhang & Barash, 2000), it has been argued that LIP signals more closely reflect the visuospatial processing stage (Bisley & Goldberg, 2003) or the response preparation stage along the integration continuum (Platt & Glimcher, 1997).

FEF and LIP show close temporal and presumably functional coupling during tasks requiring visual target selection, retention of target location across a delay, and saccade programming (eg: Chafee & Goldman-Rakic, 1998, 2000). Both sets of neurons exhibit a pre-target preparatory shift in their baseline activation levels when a saccade is being planned to a particular location (Coe et al., 2002). By analogy with the FEFs, LIP lesions reduce the frequency and increase the latency of contralateral saccades, and disrupt fixation and pursuit (Lynch & McLaren, 1983, 1989). Reversible inactivation does not impair saccade accuracy or latency, but reduces the frequency of contralateral saccades

when distractors are present; increases the time required to find the target during visual search; and significantly impairs the accuracy of memory-guided saccades (Sommer & Tehovnik, 1997; Li et al., 1999; Wardak et al., 2002; Wardak et al., 2004).

Neither LIP nor FEF neurons are colour-selective, though this can be induced by training (Bichot et al., 1996; Toth & Assad, 2002). Like FEF neurons, the average visual response latency of LIP neurons is around 75ms, and the pre-saccadic discharge begins 100-150ms before saccade initiation (Barash et al., 1991). A recent study has reported mean visual response latencies as early as 45ms after stimulus onset, raising a similar question about the visual hierarchical position of LIP neurons as that which has been raised for the FEFs (Bisley et al., 2004). Like FEF, the responses of LIP neurons are consistent with the formation of a perceptual saliency map (Gottlieb et al., 1998), and the integration of sensory evidence towards a perceptual decision threshold (Shadlen & Newsome, 2001).



Figure 1.13. Visual areas in the parietal lobe. A recent parcellation of parietal visual areas based on diverse criteria (cytoarchitecture, connections, physiological recordings). Area 7a is located on the postero-lateral aspect of the inferior parietal lobule. LIP is located within the intra-parietal sulcus (IPS). From Cavada (2001).

Although the homology of monkey and human parietal areas remains somewhat controversial, there is an emerging consensus that monkey parietal area 7a, on the postero-lateral aspect of the inferior parietal lobule, and one of its subdivisions, area LIP (on the lateral bank of the intra-parietal sulcus), correspond to the angular gyrus/lateral intra-parietal sulcus in the human brain (Passingham, 1998; Bremmer et al., 2001; Rushworth et al., 2001a; Rushworth et al., 2001c). For brevity, these areas in the human brain will be referred to throughout this thesis as the 'posterior parietal cortex' (PPC) (Figure 1.13).

In both species, the PPC is implicated in gaze control. Together with the FEFs, various parietal areas are typically activated in neuroimaging studies of saccades and spatial attention (eg: Nobre et al., 2000), as well as spatial working memory (Corbetta et al., 2002), and have been characterized as important nodes in a fronto-parietal network that controls voluntary overt and covert orienting (Corbetta & Shulman, 2002). Both the FEFs and the PPC have also been shown to be modulated by perceptual difficulty in visual detection tasks (Shulman et al., 2001).

Patients with parietal damage typically present with a range of visuomotor (Pierrot-Deseilligny et al., 1986; Mattingley et al., 1998) and visuospatial deficits (especially after right hemisphere damage) including neglect, extinction, visuo-spatial distortion, and spatial memory impairments (Critchley, 1953; Mesulam, 1981). Although the neuroanatomy of neglect remains a matter of debate (Karnath et al., 2001; Mort et al., 2003), deficits most commonly result when damage compromises the angular gyrus and/or the intra-parietal sulcus (Vallar, 1993; Mannan et al., 2005). The neglect- and extinction-like deficits incurred by parietal damage have been modelled successfully using TMS (Pascual-Leone et al., 1994; Hilgetag et al., 2001; Bjoertomt et al., 2002). TMS has

also been applied over the PPC to transiently disrupt performance on visually-guided (Yang & Kapoula, 2004), memory-guided (Muri et al., 2000) and double-step saccade tasks (van Donkelaar & Muri, 2002). Parietal patients have difficulty filtering out distractors during visual discrimination tasks, a deficit exacerbated by increasing distractor salience (Friedman-Hill et al., 2003). During visual search, they frequently re-fixate previously inspected locations, implying impaired memory for searched locations across saccades (Husain et al., 2001). On conjunction search tasks, they make frequent false positive errors, which has been ascribed to a failure to correctly bind object features into a unified percept (Arguin et al., 1994; Friedman-Hill et al., 1995). Parietal patients have had a significant influence on accounts of parietal cortex as a locus for visuospatial perception (Ungerleider & Mishkin, 1982) and visuomotor integration (Goodale & Milner, 1992). Patients and monkeys with damage that includes the FEFs often present with similar symptoms (Eglin et al., 1991; Schiller & Chou, 1998; Maguire & Ogden, 2002; Mannan et al., 2005; Peers et al., 2005), but a focus on oculomotor deficits and the tendency to group FEF damage with other frontal patients has led to these similarities being neglected.

An important comparative context for the experiments presented in this thesis is a body of TMS studies that have been carried out on the PPC (angular gyrus) during visual search. By analogy with patient studies, these experiments have shown that performance can be disrupted when TMS is applied over the right angular gyrus during conjunction visual search. The timing of interference appeared to be yoked to the subjects' manual reaction times: disruption occurred with a single-pulse of TMS at a stimulus onset asynchrony (SOA) of 100ms on target present and 160ms on target absent trials (Ashbridge et al., 1997). After training on the task, TMS no longer disrupted performance, but a deficit re-emerged upon transfer to a novel search array. The

interference effect also re-emerged during search of the trained array when the target/distractor features were inverted (Walsh et al., 1998a). As TMS ceased to be disruptive after only a small amount of training (ca. 250 trials) (Walsh et al., 1999), the authors concluded that the critical role of the right angular gyrus in search may be that of learning the association between a novel visual target and the requisite manual response (Ellison et al., 2003). The authors rejected an interpretation based on visual feature binding (Treisman, 1996) because TMS disrupted performance on trials when there was no target with features to bind, and because when subjects had foreknowledge of the location of a conjunction target, TMS did not disrupt performance. These effects on search were obtained by TMS applied over the dorsal aspect of the angular gyrus. Human LIP, in the intra-parietal sulcus, is not directly or selectively accessible to TMS. However, it is possible that the search effects reported here may in part derive from spread of stimulation to that region.

The similar functional profile of areas FEF and PPC in visuospatial processing raises the question of the relative causal roles of these distinct nodes within 'the fronto-parietal attention network'. A major aim of this thesis is to motivate the need for a comparative assessment (O'Shea & Walsh, in press). The issue of similarities and differences between the FEFs and the PPC is not addressed experimentally in this thesis (except in Chapter 5). However, the TMS studies reviewed above provide an important basis for qualitative comparison with the frontal eye field TMS data presented here. Although this comparison is qualitative, rather than quantitative, a guiding aim of this thesis was to compare the effects of TMS over each of these regions on search behaviour, as tested by broadly similar paradigms. Specifically, one of the aims was to determine whether a visuospatial role in search behaviour could be attributed to the FEFs, as distinct from the visuomotor role ascribed to the angular gyrus by previous TMS studies.

5. Visual Search and Signal Detection Theory

The experiments reported in this thesis assessed visuospatial function in the FEFs by using similar visual search tasks and TMS protocols to those reviewed in the previous section. The interpretation of the results was largely guided by single-unit evidence, and no attempt was made to evaluate the results with respect to psychological theories of visual search and attention (Treisman & Gelade, 1980; Duncan & Humphreys, 1989; Wolfe et al., 1989; Treisman & Sato, 1990; Wolfe, 1994). Nor were the results couched in terms of biased competition (Bundesen, 1990; Desimone & Duncan, 1995), which offers a good account of neural indices of visual selection, including enhanced gain effects (Tootell et al., 1998; McAdams & Maunsell, 1999); heightened baseline firing (Luck et al., 1997; Chawla et al., 1999) and suppressed activity in response to distractors (Moran & Desimone, 1985; Kastner et al., 1998).

Instead, signal detection theory (SDT) (Green & Swets, 1966) was used to analyse the TMS data in two out of three of the studies presented here. SDT offers an attractive framework for interpreting TMS effects, since it makes no assumptions about psychological or neural mechanisms, and yet has been shown to provide a good explanatory account of many aspects of visual search behaviour (Palmer et al., 2000; Verghese, 2001).

Under SDT, visual search for a target amongst distractors is conceptualized as a problem of detecting a signal (S) amongst noise (N), with performance weighted by the observer's decision criterion (C) (see Figure 1.14). Under this framework, stimuli in a visual search array are represented as noisy, random variables. The neurons selective for the features

of the search target or a distractor will discharge when that stimulus falls within the receptive field, but the probability that a given neuron's discharge will be of a particular strength is distributed in a normal fashion (Newsome et al., 1989). Those neurons preferentially tuned for a particular feature (say a line oriented at 45 degrees, which happens to be the search target) will also discharge in response to similar orientations (eg: a line oriented at 30 degrees, which is a distractor), but on average less strongly. Hence, the evidence that a stimulus in the neuron's receptive field is a target or a distractor may be reasonably construed as based on which stimulus evokes a greater neuronal response. When the target and distractor differ markedly in their orientations, the target will almost always generate a greater neuronal response. Hence, the sensory evidence will be strong and so the discrimination task will be easy. However, when the orientation difference is reduced, the response distributions for the target and distractor will overlap, the sensory evidence will be weaker, and the discrimination task will be more difficult. Within the region of overlap between the signal and noise distributions, the neural response to a distractor can exceed that to a target, resulting in an erroneous basis for the observer's discrimination decision.

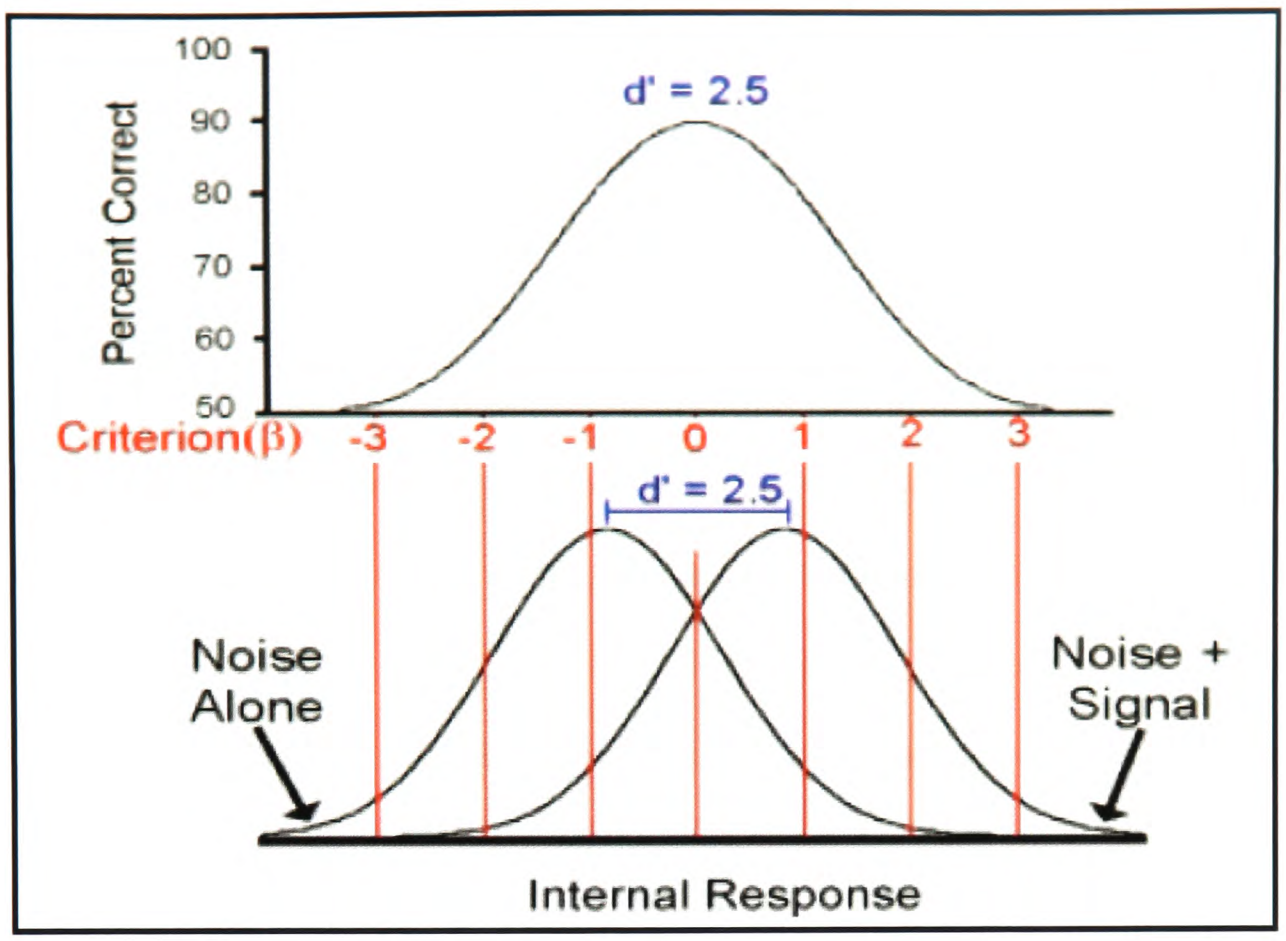


Figure 14. Schematic of key concepts in Signal Detection Theory. The lower graph (notionally) represents distributions of stimulus intensity in the brain. Noise is represented by the distribution on the left, the signal distribution is on the right. Both signal and noise are assumed to be normally distributed. The area of overlap between the two distributions represents a range of detection uncertainty in which stimulus intensity derives from both signal and noise. The greater the separation between the means of the two distributions (d'), the smaller the area of overlap, and the easier it is to make an accurate detection decision. An important feature of signal detection theory is that observers' response bias (tendency to say 'yes/no' when uncertain) can be measured independently and does not co-vary with perceptual sensitivity (d'). This is illustrated in the upper-most graph.

Thus, the accuracy with which a target is discriminated from a distractor (d') depends on the degree of separation between the means of the target (S) and distractor (N) firing rate distributions, as well as on the variability of these distributions. The SDT assumption that both the signal and noise distributions are normally distributed is supported by data indicating that the variability of neural spike rates is typically proportional to the mean discharge rate (Bradley et al., 1987).

SDT makes quantitative predictions about search accuracy based on discriminability. This relationship is represented by the following equation, which was used to calculate d' throughout this thesis:

$$d' = [Z(H) - Z(F)]$$

This equation states that an observer's performance accuracy (d'), assessed over a number of trials, derives from the probability that an observer will correctly detect the target (Z(H) = hit rate) minus the probability that the observer will incorrectly judge the target to be present (Z(F) = false alarm rate). The hit and false alarm rates are calculated as the proportions of each response type on trials in which a target was present (hits) or absent (false alarms).

The accuracy of discrimination performance can be affected by response bias - an observer's tendency to respond either 'yes' or 'no' when s/he is uncertain. An advantage of SDT analysis is that independent measures can be obtained of an observer's perceptual sensitivity (d') and his/her response bias or criterion (C). There are a number of different measures of bias (eg: beta, log beta, C'), but C is the only measure of response bias that is independent of d' (Gescheider, 1997, pg 123). The following equation was used to calculate response bias throughout this thesis:

$$C = -0.5 * [Z(H) + Z(F)]$$

6. Thesis Aims

This chapter reviewed evidence that the FEFs transform visual information into eye movement commands. While the output end of this function is well-understood, significantly less is understood about the visuospatial aspects of FEF function and their

importance for vision. By contrast with accruing evidence from monkey neurophysiology, there is a paucity of evidence for visuospatial processing in the human FEFs. This gap in the literature is one of the things that this thesis aims to redress.

Sufficient data exist on FEF neurophysiology during visual search performance to generate testable predictions for human FEF function. In the experiments reported here, an interference technique, transcranial magnetic stimulation (TMS), was used to demonstrate that the human FEFs have a *causal* role in visuospatial processing that is independent of generating eye movement commands. It is hoped that this chapter, which has attempted to present a more nuanced view of visuomotor integration, has dispensed with the need to temper my rhetorical approach, which emphasizes visuospatial processes and attempts to exclude eye movement ones. Visual search tasks were combined with TMS and manual and saccadic responses to test the following hypotheses:

1) The human FEFs are critical for normal visual search performance even when eye movements are not required.

2) The timing of this contribution occurs early during visual processing, as predicted by the response latencies of FEF visual neurons.

3) The FEFs are not required when visual search performance is highly practiced.

4) The FEFs play a causal role in spatial and feature priming.

CHAPTER 2: Methods for Assessing Frontal Eye Field Function

Abstract

This section reviews the neural recording and interference techniques used to assess frontal eye field (FEF) function in this thesis. Functional magnetic resonance imaging (fMRI) was used in one experiment to localize the FEFs for Transcranial Magnetic Stimulation (TMS). TMS was applied in all subsequent experiments to temporarily disrupt neural activity in the FEFs. The two techniques are reviewed with respect to their physical and biological mechanisms of action, as well as the methodological principles that govern their effective use as tools for measuring (fMRI) and transiently disrupting (TMS) information processing in the human brain.

1. Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is an interference technique that temporarily disrupts neural processing in the cortical area over which it is targeted. By analogy with animal lesion and neuropsychological patient studies, it can be used to test causal hypotheses about the contribution of a given brain area to behavioural performance. Unlike those approaches, with TMS the experimenter can control, to some extent, the severity and time-course of the transient 'lesion', and make functional inferences about cortical areas without the complications of plastic neural reorganisation in response to injury.

1.1. What is TMS?

The first successful attempt to stimulate human cortex in a non-invasive, painless and reversible way using magnetic stimulation was by Barker (1985), who applied TMS over the motor cortex and measured induced muscle twitches using motor evoked potentials (MEPs). TMS is based on Farraday's principle of electromagnetic induction. Faraday (1831) showed that electric current passing through a wire generates a time-varying

magnetic field that in turn induces electrical current in a second wire. In TMS, a large, rapidly-changing electric current is passed through a coil which generates a magnetic field perpendicular to the angle of orientation of the coil. When the coil is positioned on the scalp, the magnetic field passes through the skull and induces an electrical field in the underlying cortex. The size of the induced current depends on the amplitude and rate of change of the current passing through the TMS coil. In TMS, the inducing current is large (typically ca. 8 kA), with a very rapid rise time (ca. 200 microseconds) and an overall duration of about 1ms (see Figure 2.1). The induced current alters the electrical state of the cellular environment both inside and outside nerve axons (Nagarajan et al., 1993). When the voltage differs across the cell membrane (see Figure 2.2), cells can become depolarized or hyperpolarized. Thus, the application of a TMS pulse to a cortical area can raise the resting membrane potential of some neurons, whilst causing others to discharge. The extent to which TMS alters neural processing in a cortical area depends critically on both the orientation of the coil and the orientation of the underlying nerve fibres (Amassian et al., 1992). The experiments reported in this thesis were carried out using a small-diameter (50mm) figure-of-eight TMS coil, which induces more focal neural stimulation than a circular coil. Current flows through a figure-of-eight coil in opposite directions around each of the windings, converging at the centre-point of the coil where the electrical currents summate. The resultant magnetic field induces focal neural stimulation with a maximal effect on the cortex located directly under the centre-point of the coil. The stimulation effects dissipate gradually with distance from this maximum (see Figure 2.3).

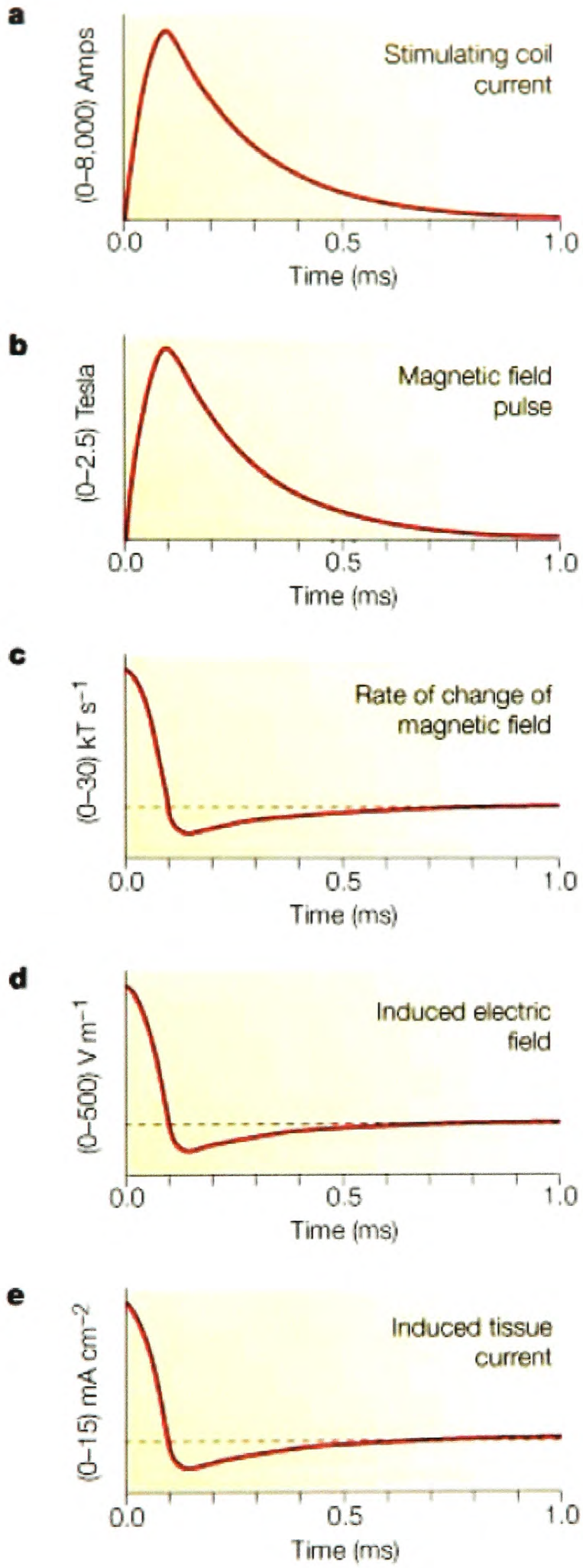


Figure 2.1. Sequence of events that occurs with a single TMS pulse. A rapidly changing electrical current is passed through a coil (a), which induces a magnetic field perpendicular to the angle of orientation of the coil (b). The magnetic field has a steep rate of change (c) and so generates an electrical current (d) that induces current flow in the underlying neural tissue (e). From Magstim Company Guide to Magnetic Stimulation.



Figure 2.2. How TMS-induced current may activate neurons. (a) current flow in a uniform electrical field runs parallel to the neuron and so does not cause any change in transmembrane current. **(b)** a non-uniform electrical field along the axon produces an activation gradient, which causes transmembrane potentials, resulting in action potentials. **(c)** here the change in transmembrane current is due to spatial variation (bending) of the nerve fibre, rather than inhomogeneities in the electrical field. **(d)** depolarization is caused by transverse activation of the neuron by the induced electrical field **(e)** changes in the activation of the axon terminal. D and H denote regions of depolarization and hyperpolarization, respectively. From Ruohonen & Ilmoniemi (1999).



Figure 2.3. TMS-induced electrical fields produced by circular and figure-of-eight shaped coils. With a circular coil the induced electrical field is maximal under the winding. With a figure-of-eight shaped coil the field is maximal at the intersection of the two windings. The intensity of induced current dissipates with radial distance from this maximum. From Magstim Company Guide to Magnetic Stimulation.

1.2. Neural Effects of TMS

Although TMS is known to induce neuronal depolarizations and hyperpolarizations and to affect neurotransmitter release (eg: Strafella et al., 2003), the mechanisms by which TMS exerts its neural effects remain to be fully clarified. For instance, it is not known to what cortical depth TMS penetrates; which neural sub-populations it stimulates; and to what extent brain areas connected to a stimulation site are affected. Current evidence indicates that effects on the stimulation site are confined to the superficial layers of cortex (Epstein et al., 1990; Rudiak & Marg, 1994), and most likely issue from neurons that are oriented perpendicular to the cortical surface (Tofts, 1990; Jahanshahi & Rothwell, 2000). The neural and behavioural efficacy of TMS varies as a function of the frequency, intensity, duration and inter-trial interval of the stimulation, which interact with the effects of coil and nerve fibre orientation (Kammer et al., 2001a; Kammer et al., 2001b). Individual subjects show differences in cortical excitability (Maeda et al., 2000a), which may be partly a function of differences in cortical folding. Given that this level of detail about individual subject anatomy is not available (each neuron's orientation, resting potential, type, etc.), in practice, the interpretation of TMS effects cannot usually avail of distinctions between neural excitation and inhibition or ortho-/anti-dromic influences (but see Heinen et al., 1998).

Nevertheless, there is general consensus that low-frequency (eg: 1Hz) stimulation decreases cortical excitability (eg: Chen et al., 1997a) and metabolic activity in the targeted cortical area (eg: Pascual-Leone et al., 1998). Low-frequency TMS effects on behaviour also tend to be inhibitory. Low-frequency stimulation (1-3Hz) has been shown to inhibit learning when applied over primary motor cortex during a motor sequencing task (Pascual-Leone et al., 1996b), and over V5 during a visual motion discrimination

task (Stewart et al., 1999). When combined with PET (positron-emission tomography), high-frequency TMS (eg: 10Hz) has been shown to increase regional cerebral blood flow (Pascual-Leone et al., 1998). Yet, it is somewhat less well-established that high-frequency TMS (eg: 10Hz) increases cortical excitability (Maeda et al., 2000b). The behavioural effects of high-frequency stimulation also appear to be more complex and variable (eg: Pascual-Leone et al., 1996b).

1.3. Spatial Resolution

The issue of spatial resolution relates not to the magnitude of the magnetic field (which is theoretically infinite), nor to the size of the induced electrical field, which induces a local spread of activation beyond the stimulation focus. Rather, spatial resolution concerns the minimum volume of cortex that can be effectively stimulated to produce behavioural effects. While stimulation effects are maximal under the centre-point of the coil, there is a dissipating local spread of effect as distance from the centre-point increases (see Figure 2.3). Indirect estimates, from computational models of induced electrical fields, indicate that the effective stimulation volume is significantly smaller than the induced current volume (eg: Thielscher & Kammer, 2002). Effective spatial resolution, and the behavioural efficacy of 'leaky spread' of activation, can be estimated by measuring how a stimulation-induced behavioural effect diminishes as the coil position is moved gradually away from the effective stimulation site. This technique has been applied to measurements of motor-evoked potentials (MEPs) and muscle twitches induced by TMS of primary motor cortex (M1), and to phosphenes evoked by TMS of primary visual cortex (V1). TMS over M1 evoked muscle twitches from the fingers, hand, arm, face, trunk and leg in a manner that matches the gross organisation of the motor homunculus (Wassermann et al., 1992; Singh et al., 1997). Stimulation applied at scalp sites spaced between 0.5 and 1cm apart was sufficient to selectively activate each of these

different muscles (Brasil-Neto et al., 1992). A similar effective spatial resolution of less than 1cm has been demonstrated in primary visual cortex (Cowey & Walsh, 2000), where stimulation-induced phosphenes exhibit a spatial distribution that corresponds with the retinotopic organisation of V1 (Kammer, 1999). Outside primary sensory and motor areas, effective spatial resolution cannot be measured by observable output, and instead needs to be inferred from diminishing effects on cognitive tasks (changes in errors/RTs) as the coil position is gradually moved away from an effective stimulation site (eg: Ashbridge et al., 1997). In practice, effective spatial resolution in association cortex appears to concur with a 1cm estimate. Studies that have combined TMS with imaging modalities (eg: PET, fMRI) have shown good correspondence between the spatial extent of a TMS-defined functional region and that defined by other measurement techniques (Ruohonen et al., 1996; Siebner et al., 1998; Terao et al., 1998).

In addition to local spread of activation, TMS activates connected neural regions through trans-synaptic transmission. This has been visualized by combining TMS with PET, EEG and fMRI (Ilmoniemi et al., 1997; Paus et al., 1997; Bohning et al., 1999). The strength of activation of distal sites appears to depend on connectional strength: those regions more densely connected with the stimulation site undergo greater modulation (Valero-Cabre et al., 2005). Connectional spread complicates the interpretation of TMS effects. A useful strategy is to stimulate connected regions as a control for the experimental site. The homologous region in the opposite hemisphere (eg: right and left FEF) is a good candidate control for connectional spread, since reciprocal connectivity is strong. If TMS effects obtained at the stimulation site are not replicated by stimulation at a connected site, then this justifies constraining the interpretation to the functions of the stimulated region. Although parsimonious, this approach can encourage a homuncular fallacy. As progress is made in understanding the physiological implications of

connectional spread, it will become easier to assess whether TMS effects derive from disrupted local computations in the stimulated region, or interruption of task-relevant signals that route through that area. At present, most studies most remain agnostic on this front (eg: Grosbras & Paus, 2003). An alternative to controlling for connectional spread is to actively harness it in the service of probing the time-course of functional interactions between connected sites (Pascual-Leone & Walsh, 2001; Silvanto et al., 2005a).

1.4. Temporal Resolution

The total duration of a single TMS pulse is about 1ms, but the effects on neural tissue can out-last this to an extent that can be manipulated by the stimulation parameters. Unfortunately, few studies have measured the duration of effect of a TMS pulse at the single-cell level. Moliadze, et al. (2003) reported that a high-intensity (< 50% stimulator output) single TMS pulse applied to V1 neurons in an anaesthetized cat preparation produced an initial suppression of neuronal excitability (lasting ca. 100-200ms), followed by a period of rebound excitation. A similar 100ms time window of interference has been suggested by a combined TMS/EEG study that measured the effect of a single TMS pulse applied to V1 on visual-evoked responses to a chequerboard stimulus (Thut et al., , in press). Ilmoniemi, et al. (1997) used combined TMS/EEG to assess the temporal profile of local-area and connectional spread effects. A single TMS pulse applied over M1 or V1 exerted an immediate effect on the cortex underlying the coil. This effect had spread to adjacent visual/motor areas within 5-10ms and had activated homotopic regions of the opposite hemisphere within 20ms.

In practice, as with spatial resolution, the temporal resolution of TMS is assessed with respect to the behavioural effect being modulated. The usual first step in a TMS study is

to apply repetitive-pulse stimulation to demonstrate that an area makes a critical contribution to the performance of a given task. However, trains of repetitive-pulse TMS affect very long periods of time in information processing terms, and they likely induce cumulative effects on neural tissue, which may out-last the duration of the TMS train. To disrupt function with improved temporal resolution, and to establish the critical timing of an area's contribution to a task, a single- or double-pulse TMS protocol can be used. Studies that have used this approach have tended to report temporal windows of interference (eg: Amassian et al., 1989), rather than effects restricted to discrete time-points. Studies of the behavioural effects of TMS applied to V1 (Corthout et al., 1999), dorsal premotor cortex (Schluter et al., 1999) and the angular gyrus (Ashbridge et al., 1997) have reported effective temporal resolution in the order of 40ms. These temporal windows of TMS interference often correlate quite well with the times at which single-unit responses can first be recorded from homologous regions of the monkey brain (Walsh & Cowey, 1998; Schluter et al., 1999).

Single-pulse and double-pulse protocols can be used effectively to establish the relative temporal order with which connected regions make their critical processing contributions to a behavioural task (Leff et al., 2001), or to explore ongoing temporal interactions between connected sites (Pascual-Leone & Walsh, 2001; Silvanto et al., 2005a). By contrast with restricting the duration of interference, long trains of low-frequency stimulation can be used to induce long-lasting suppression of cortical excitability (Kosslyn et al., 1999). Typically, this suppression, and its concommitant behavioural effects, persists for at least half the duration of the total period of stimulation (Thut et al., 2003; Thut et al., 2004). This kind of temporal protocol may be particularly useful in studies of cognitive processes that have an extended temporal profile (eg: short-term memory)(Mottaghy et al., 2002).

TMS is currently being explored as a therapeutic intervention to ameliorate depression. In these studies, long trains of high-frequency stimulation are used (eg: 20 trains at 10Hz for 10secs each at 90% of stimulator output, repeated over 25 consecutive days, Pascual-Leone et al., 1996a). Studies of dorso-lateral prefrontal cortex suggest that these kinds of TMS protocols can induce mood and affect changes which can persist for days or weeks (eg: George et al., 1996). This temporal scale of effects exceeds that germane to cognitive studies, which are interested in millisecond resolution, and which adopt stimulation parameters that restrict TMS effects to this temporal scale.

1.5. Safety Issues

The principal safety concern in TMS studies is the risk of inducing a seizure. There is a consensus that single-pulse TMS carries no such risk if used in neurologically normal subjects. Repetitive-pulse TMS can induce seizures in individuals with epileptic susceptibility. In individuals with no known susceptibility, factors such as alcohol withdrawal, caffeine and insufficient sleep can temporarily lower seizure thresholds. Hence, screening procedures must be used to eliminate potential subjects with any of these contraindications. Published guidelines exist that prescribe appropriate limits on stimulation parameters for the safe use of repetitive-pulse TMS (Pascual-Leone et al., 1993; Wassermann, 1998; Bernabeu et al., 2004). These advise on TMS frequency, intensity and duration and on appropriate inter-trial intervals between stimulation trains (eg: Chen et al., 1997b). As used in cognitive studies, TMS has been shown not to induce side-effects on hormone levels (Pascual-Leone et al., 1993), on tests of cognitive function or on EEG measures (Bridgers, 1991).

The experiments reported in this thesis were approved by local ethical review (Oxford Research Ethics Committee and the Institute of Neurology, University College London). Subjects were recruited after screening, based on informed consent, and experimental design was guided by the safety considerations reviewed above.

1.6. Functional Resolution

As intimated by the methods used to determine the effective spatial and temporal resolution of TMS, the critical dimension along which TMS must be assessed is in terms of its capacity to effectively probe cognitive function ("functional resolution", Walsh & Rushworth, 1999). TMS is a safe, non-invasive, interference technique, which can be used in normal volunteers to transiently disrupt neural and information processing with the kind of spatial and temporal resolution appropriate to assess cognitive function.

Along with animal lesion and human patient studies, TMS allows for causal inferences to be drawn about the functional roles of a given cortical area. Its chief advantage over these methods is that TMS interference is transient, and so functional inferences can be drawn without the complicating effects of plastic neural re-organisation in response to injury. In addition, it offers temporal information that is not possible with lesions, and disrupts cortical function with a spatial resolution that is vanishingly rare in brain-damaged populations. Its use in normal volunteers also offers a useful complement to animal studies using pharmacological or cooling inactivation procedures. Since TMS and lesion studies share a similar logic of inference, it is often claimed that TMS can tell you whether processing in a given area is *necessary* (even if not sufficient) for performance of a particular task. Against the backdrop of compensatory strategies and plastic reorganisation documented after brain damage in humans and animals, this claim needs

to be tempered. A more sober re-statement of this claim would be that TMS allows one to interfere with the functioning of information-processing circuits that normally underlie the performance of a given task.

An effective TMS protocol adds 'noise' to information processing. Although the effect of the magnetic field is to induce neural depolarizations and hyperpolarizations, which are in fact 'signals', these changes are effectively random with respect to the structured configuration of neural firing in the targeted region that affords task-critical information processing. Thus, TMS-induced changes in neuronal excitability reduce the fidelity of signals in the stimulated region on which accurate task performance depends. This explains why the effect of TMS on behavioural performance is usually deleterious. The process by which TMS over V1 induces phosphenes, or TMS over M1 evokes muscle twitches, is no different. This is made clear by the demonstration that lower-intensity TMS over V1 can induce a visual scotoma at the same site from which higher-intensity stimulation induces a phosphene (Amassian et al., 1989; Maccabee et al., 1991; Kammer & Nusseck, 1998; Kammer, 1999). In the case of M1, evoking a finger muscle twitch is to add noise to the baseline (hand-resting) state, in the same way that TMS applied during a hand movement disrupts movement metrics (eg: Glover et al., 2005). In all cases, the behavioural, perceptual or motor effects of TMS are manifestations of 'noise' being added to the baseline information state of the targeted cortical area.

TMS-induced behavioural facilitations, rather than deficits, are infrequently reported (Seyal et al., 1995; Walsh et al., 1998b; Oliveri et al., 1999). For instance, whereas TMS over the right angular gyrus typically slows reaction time during visual search, TMS over the left angular gyrus can speed response time (Walsh et al., 1999). The predominant framework for interpreting facilitations is in terms of altered patterns of competitive

interaction between connected cortical regions (Kinsbourne, 1977). For example, a commonly-held view is that the right parietal cortex has a dominant role (over the left) in tasks requiring visuospatial processing (Mesulam, 1981). By disrupting processing with TMS in the (dominant) right hemisphere, task performance should get worse, while disrupting processing in the left parietal cortex will reduce a source of competitive inhibition on the right, thus facilitating reaction time. Interpretations based on dysregulation of competitive inhibition have their counterpart in the animal and patient literature on 'paradoxical lesion effects' (eg: Sprague, 1966; Kapur et al., 1986; Hilgetag et al., 1999).

It is parsimonious to interpret TMS effects in terms of disrupted processing in the cortical area directly underneath the coil, as this is where stimulation effects are maximal. The use of TMS site, task and timing controls helps to further justify this. However, the account of facilitations just offered makes it clear that the issue of proximal versus distal effects can be constrained, but not eliminated, by appropriate controls. In fact, it has been argued that, without full knowledge of the information processing network within which an area functions, it is not possible to correctly interpret the neural basis of lesion effects (Young et al., 2000). In the context of this thesis, TMS effects are ascribed to disrupted functions of the frontal eye fields, an approach justified on grounds of parsimony and the use of appropriate controls.

2. Functional Magnetic Resonance Imaging

Functional Magnetic Resonance Imaging (fMRI) is a technique for indirectly measuring neural activity by means of changes in blood oxygenation in the brain areas that are activated by an experimental task. fMRI was used in one experiment in this thesis to

localize the frontal eye fields for TMS application in subsequent experiments. This section describes the physical and physiological principles underlie fMRI and the data analysis methods used in this thesis.

2.1. Physical Principles

Sub-atomic particles (protons) possess a property known as 'spin', which causes them to move about their own axis. This movement generates an electric current and hence a magnetic field. Each proton is therefore slightly magnetic and so when placed in a stable magnetic field (as in a MRI scanner) the nuclear spins align parallel or anti-parallel to the axis of the magnetic field. The majority of protons align parallel to the field, as this is the lower energy state (see Figure 2.4). Once aligned, the protons oscillate (or 'precess') around the axis of the magnetic field with a frequency ('Larmor frequency') that is determined by the strength of the magnetic field and the gyromagnetic ratio of the proton, which is fixed for a given nucleus. In fMRI, the typical nuclei of interest are those of hydrogen atoms in water (H_2O). Different tissues in the brain possess different quantities of water molecules and hence experience different degrees of magnetization.

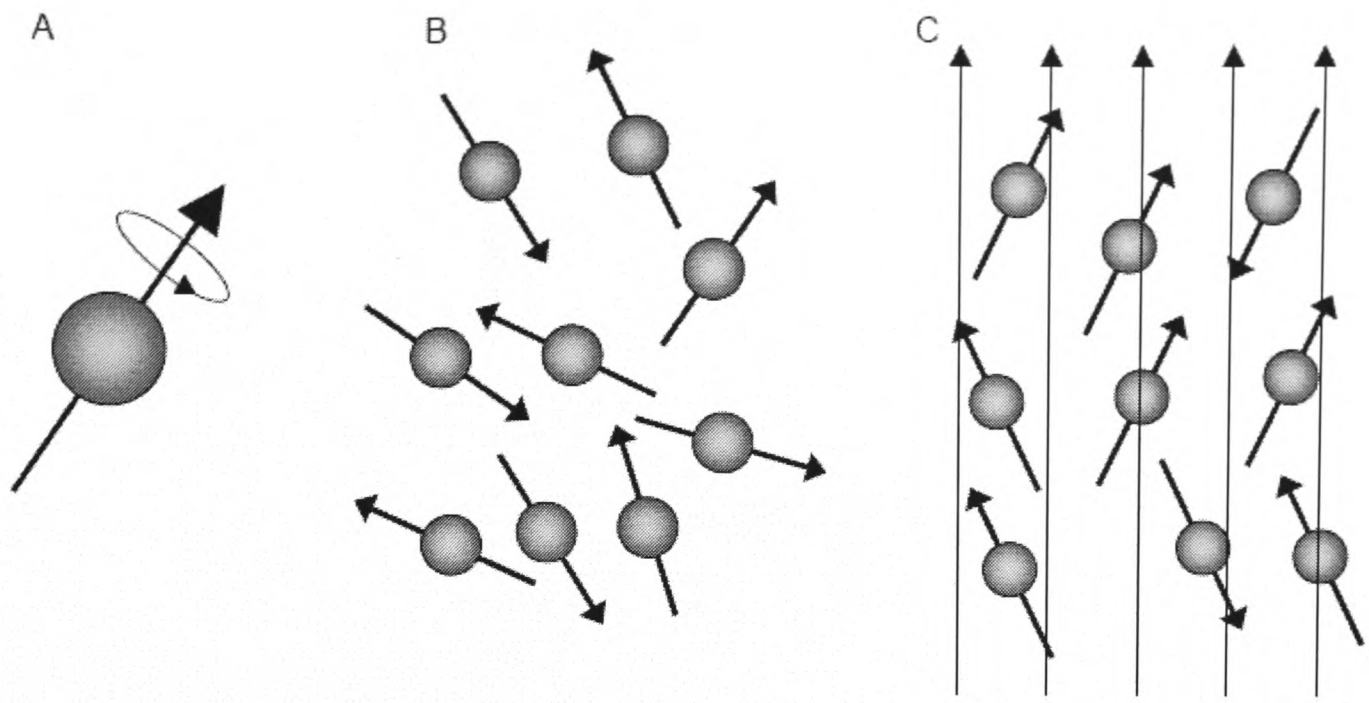


Figure 2.4. A. A proton with a magnetic moment precessing about its own axis. **B.** Randomly aligned protons in the absence of an external magnetic field. **C.** Protons aligning parallel to a stable magnetic field.

When a person is lying supine in a MRI scanner, hydrogen protons precess around the axis of the external, static magnetic field and align parallel to it (z direction). A radiofrequency (RF) pulse is then emitted from the surrounding transmitter coil. If the frequency of this pulse matches the Larmor frequency, resonance occurs (ie: energy is transferred to the nuclear spins). This results in protons being 'flipped away' from the axis of the static magnetic field. The angle by which the protons are flipped depends on the strength and duration of the RF pulse. For example, a 90 degree pulse will flip the net magnetization vector into a plane perpendicular to that of the static field (x-y direction) (see Figure 2.5). As the protons then precess around this x-y axis, a transverse component to the net magnetization results and it is this that is detected (as electrical signal) in the surrounding receiver coil.

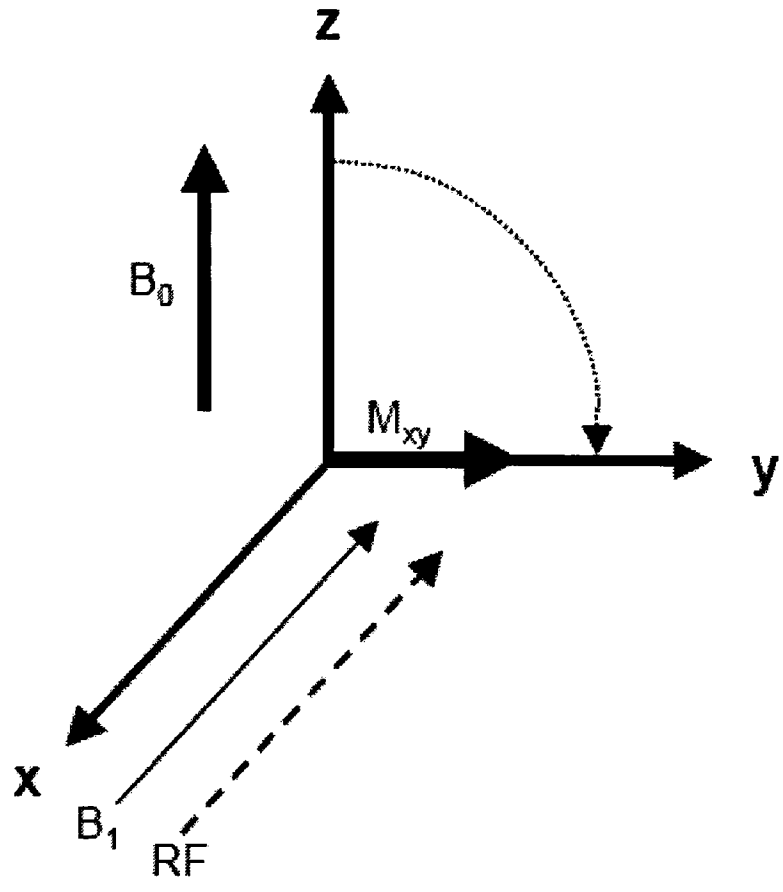


Figure 2.5. A RF pulse 'flips' the proton spins away from the axis (z) of the stable magnetic field (B0). In this example the spins are flipped by 90 degrees, into the x-y plane. B1 refers to the horizontal magnetization vector that results.

Variations in the water content of different substances (eg: bone, brain, cerebrospinal fluid) imply different proton densities, and this can be exploited to produce MR image contrast. In order that proton density can be accurately measured, a number of factors need to be considered. First, the MR signal is maximal when acquired immediately after the RF pulse, as at this time the maximum number of nuclear spins will have magnetization in the x-y plane (the plane in which they can be detected). Second, sufficient time needs to elapse between successive RF pulses to allow the magnetized spins to return to a low-energy state in which they are aligned parallel to the static external field (z direction). The time taken for the spins to re-align parallel to the magnetic field is known as 'T1 relaxation time' and it is fixed for a given nucleus. T1 time ensures that the maximum number of spins are available to be 'flipped' by the next RF pulse. The process by which net magnetization in the x-y plane decays over time is known as T2 ('transverse relaxation time'). T2 occurs faster than T1. Both T1 and T2

provide sources of image contrast, since each of these times differs across tissue types, and so RF pulse parameters can be manipulated to emphasize difference tissue properties in the image. If you vary the scan repeat time (TR) and the time between applying a RF pulse and measuring the MR signal (TE), the measured contrasts between different tissue types will be altered accordingly (see Figure 2.6). A third source of contrast is T2*, which also characterizes the decay of horizontal magnetization, but it takes account of local inhomogeneities in the magnetic field. Protons are influenced by small magnetic fields from neighbouring nuclei that are unevenly distributed. This, combined with field inhomogeneities, results in protons having different precession frequencies such that once the RF pulse is turned off protons are soon out of phase.

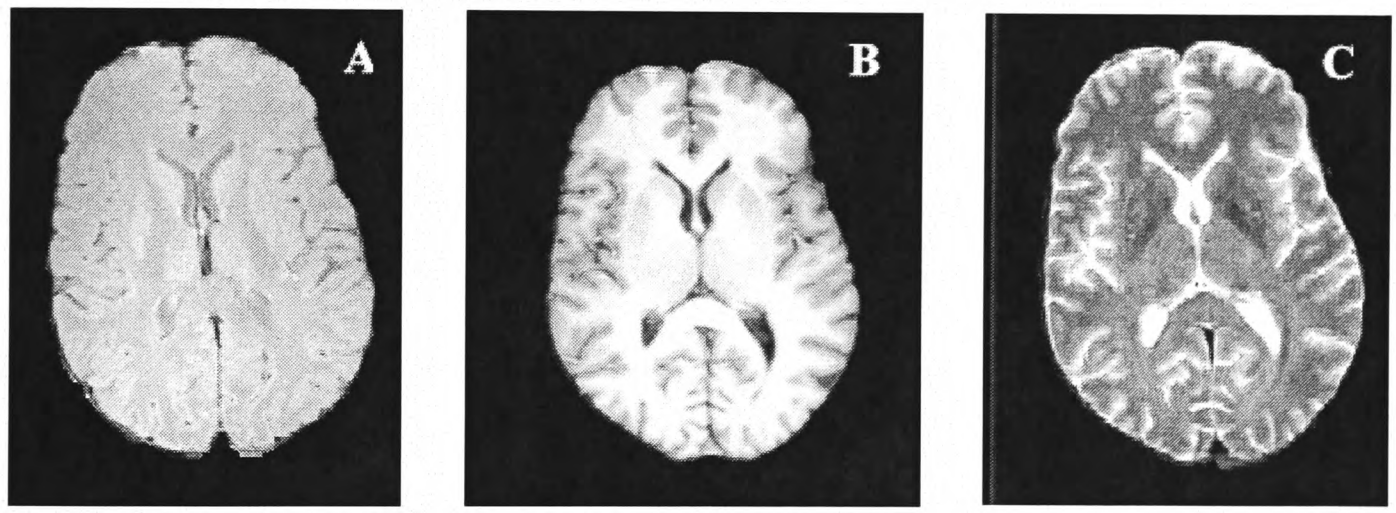


Figure 2.6. (A) Proton density MR image. **(B)** T1- weighted image. **(C)** T2-weighted image.

2.2. Physiological Principles

Functional MR imaging takes advantage of T2* to generate image contrast that varies as a function of local changes in blood oxygenation (Ogawa et al., 1990). The contrast is not based directly on blood oxygenation, but on the distribution of haemoglobin, an iron-containing molecule in blood. When oxygen binds to haemoglobin, it changes from being in a paramagnetic state (having a magnetic effect on its environment) to being

diamagnetic (having little effect). So, changes in blood oxygenation induce distortions in the magnetic field and thus changes in local MR image contrast. Changes in neural firing incur changes in local blood oxygenation. Neural depolarizations require energy, derived from oxidative metabolism, and this process is supplied by an increase in local blood flow (velocity) that delivers oxygen to the brain area where it is required. The increased blood flow exceeds the increase in oxygen consumption, which results in a transient increase in the ratio of oxyhaemoglobin : deoxyhaemoglobin. The reduction in paramagnetic deoxyhaemoglobin results in reduced magnetic susceptibility around local blood vessels and higher MR signal – thus 'blood oxygenation level dependent' (BOLD) contrast (see Figure 2.7). Optical imaging studies (Malonek & Grinvald, 1996) have reported a transient initial increase in deoxyhaemoglobin that occurs prior to the oxygenation increase, and this may correspond to the initial dip in the BOLD signal that has been reported in some fMRI studies (eg: Menon et al., 1995).

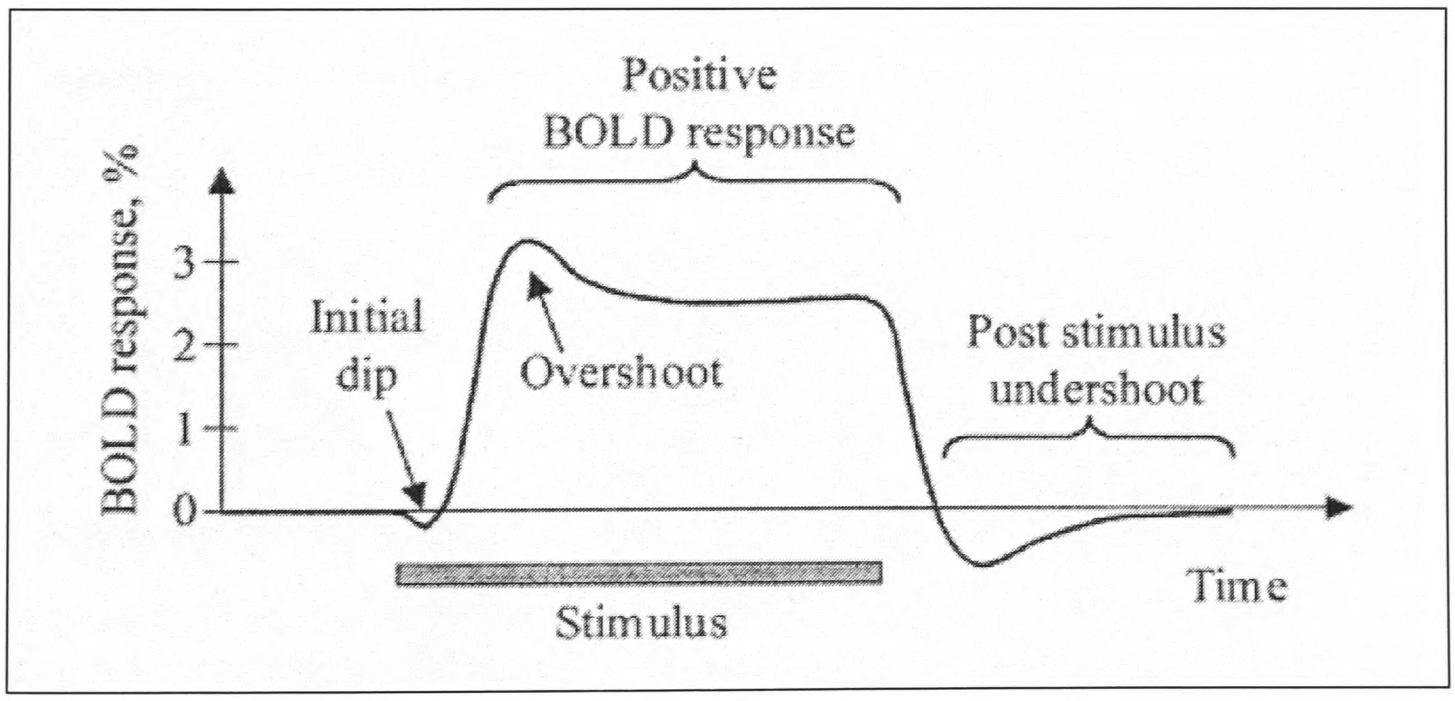


Figure 2.7. The BOLD Signal. After stimulus presentation, the level of blood oxygenation gradually increases to a peak over the course of 2-4 seconds. Within 12-18 seconds the signal has returned to baseline.

The BOLD response is an indirect measure of neural activity. It is typically considered to reflect excitatory neural activity, and increases in blood flow have been shown to be proportional to increases in neural activity (Raichle, 1998). However, BOLD may also reflect inhibitory neural activity, subthreshold activity, and modulatory influences in addition to spike rates (Heeger & Ress, 2002). Recent work, in which BOLD signal measurements and electrophysiological recordings were carried out simultaneously (Logothetis et al., 2001), suggests that the BOLD signal more accurately reflects the input signals and local computations carried out within a brain area than its spiking output. This conclusion was based on the observation that local field potentials (which reflect spiking activity and subthreshold neural activity) were a better predictor of the BOLD response than single- or multi-unit recordings, which reflect only spiking activity.

2.3. Spatial Resolution

The spatial resolution of fMRI depends on both the spatial resolution of the scanning parameters and on the spatial resolution of the BOLD signal itself. Since a typical image voxel (volume element) will reflect the activity of many thousands of neurons and synapses (Menon, 2001), BOLD signal measures the activity of large populations of neurons. BOLD signal changes are greater in larger blood vessels than in smaller ones, and so the presence of large draining vessels near a brain region of interest can skew the localization of signal changes away from the site of neural activity (Lai et al., 1999). More generally, changes in blood flow and oxygen metabolism are not restricted to the site of neural activity, a phenomenon that has been characterized as 'watering the garden for the sake of a single flower'. Maximal spatial resolution can be achieved by designs that optimize signal-to-noise ratio. For instance, (Menon et al., 1997) resolved ocular dominance columns in primary visual cortex by comparing the relative strength of

BOLD signal in response to left or right eye stimulation in overlapping areas of activation. Spatial resolution of between 0.5 and 1.5mm, depending on magnetic field strength, has been estimated for fMRI (Menon & Goodyear, 1999). In the fMRI experiment reported in this thesis, slices were acquired at an image resolution of 3 × 4 × 5 mm.

2.4.Temporal Resolution

Temporal resolution on a second and sub-second time scale can be achieved with fMRI (Menon & Kim, 1999). There is typically a lag of about 3-4 seconds between the onset of an experimental stimulus and the peak of the haemodynamic response function (HRF)(BOLD signal). The total time between initial changes in the BOLD signal and the return to baseline is 12-18 seconds (Matthews, 2001). However, so long as the shape of the HRF can be accurately estimated, then the initial lag need not limit the temporal resolution, as the expected time course can be convolved with the HRF (see Figure 2.8).



Figure 2.8. Stimulation parameters convolved with the expected time-course of the BOLD response. The figure shows a boxcar design matrix of the type used in the <Saccades – Fixation> blocked fMRI experiment reported in this thesis. The square waveform describes the on/off timing of successive block of experimental stimulation (saccades vs fixation). The curved waveform represents the input stimulation after it has been convolved with the HRF. From Smith (2001).

Lag times have been shown to vary across brain areas (Miezin et al., 2000), tasks (Rajapakse et al., 1998) and individual subjects (Aguirre et al., 1998), and it is this variability, rather than the latency itself, which limits the temporal resolution (Bandettini, 1999). Temporal resolution also depends on the scan repetition time (TR), which should be longer than T1 (eg: 1-1.5 secs) to allow for the recovery of horizontal magnetization, and hence for maximum MR signal to be detected. In the fMRI experiment reported in this thesis, a block design was used to localize the FEFs by comparing averaged activations from 30-trial blocks of saccades with averaged activations from blocks of fixation. Temporal resolution is less important in block designs, which assume that the BOLD signal remains constant across a whole block. Hence, strategies for optimizing temporal resolution, of importance to event-related designs, will not be discussed here.

2.5. Safety

There are no known side effects of MR imaging. However, subjects must be screened for metal implants or items such as heart pacemakers, which could be disrupted by magnetic fields. The scanner environment can be claustrophobic and is also very noisy, so earplugs and headphones should be used for subject comfort. The fMRI experiment presented in this thesis was approved by local ethical review (Oxford Research Ethics Committee). Subjects were recruited based on informed consent after fMRI safety screening procedures devised by the Department of Clinical Neurology, Oxford University.

2.6. Image Analysis

Whole-head fMRI image volumes are acquired as a series of two-dimensional slices. The slices are then co-registered to produce a single volume, which consists of many small

image volume elements (voxels). The aim of fMRI analysis is to determine whether the level of BOLD signal in each voxel's time series can be explained by the experimental stimulation conditions, rather than by noise. The fMRI experiment reported in this thesis used Statistical Parametric Mapping (SPM) (Friston et al., 1995a) for image pre-processing, first-level general linear model (GLM) analysis, registration of fMRI data to structural image space, and for group image analysis.

2.7. Image Pre-Processing

Prior to statistical analysis, fMRI data undergo various pre-processing steps to reduce artefacts. 'Slice-timing correction' is the first procedure, which is used to re-align each of the individual image slices in time by co-registration with the first scan in the sequence. In this thesis, a 'rigid body transformation' procedure was used to align all the scans in a single subject's fMRI time series with the mean image by re-sampling the data. This procedure assumes that whilst the head can change in position and size, it cannot change in shape. Motion correction ('unwarping') was carried out during re-alignment. This is required to compensate for movements of the head and for breathing-related artefacts, and is critical to ensure that a single voxel corresponds to the same brain area throughout the course of an experiment. A 'B0 field map' correction was then applied to correct for the static geometric distortion brought about by the difference between functional and structural image spaces (R. Cusack, Medical Research Council, U.K.). The data were then spatially smoothed to increase the signal-to-noise ratio using a Gaussian kernel of 6 x 6 x 6 mm at full-width half maximum. This procedure assumes that noise varies randomly across voxels, and that (physiologically relevant) activation which is larger than the size of the smoothing kernel will not be cancelled out to the same extent as will noise. Smoothing is also required to better satisfy the assumptions of Gaussian random field theory, which is used for statistical analysis. The data then underwent 'intensity

normalization', a procedure designed to correct for drifts in signal intensity over time, whereby all voxels in a time series are re-scaled to have the same mean intensity. Finally, the data underwent 'temporal smoothing'. High-pass filters were used to remove low-frequency noise (eg: scanner-related drifts, cardio-respiratory effects). Temporal auto-correlations (an artefact of temporal smoothing which increases the similarity of signal across successive scans) were estimated and corrected for.

2.8. Single-Subject Analysis

In the block design experiment presented in this thesis, the time series of each individual voxel was compared to the boxcar design matrix convolved with the HRF (see Figure 2.8). A univariate (general linear model, GLM) approach was used, according to which each individual voxel is analysed separately at the model-fitting stage. The boxcar model used in this thesis consisted of two regressors (explanatory variables – EVs) that specified the timing of the two experimental blocks (saccades, fixation). For each EV, the GLM takes the form:

$$y = \beta 1(x_1) + \beta 2(x_2) + \varepsilon$$

where y is the data (over time) from a voxel, x_1 is the model (ie: EV) of the fixation trials, x_2 is the model of the saccade trials, β is the parameter estimate (ie: height of signal resp for that voxel) and ε is the error in model fitting. Parameter estimates predict the amplitude of BOLD response in a given condition, and these can be converted into useful statistics (eg: t) by dividing β by the standard error (SE) of the parameter estimate. The degree of activation for different experimental conditions can be compared by performing contrasts of parameter estimates. For instance, in the experiment presented in this thesis, to determine whether the activation in the <Saccades> condition was

greater than that in the <Fixation> condition, the β value for <Fixation> was subtracted from that for <Saccades> and was then divided by the SE of the resulting estimate. Once a statistical parameter (eg: t) has been calculated for each voxel, it needs to be determined whether the activation is statistically significant. To circumvent the problem of multiple comparisons generated by the sheer volume of voxels in a whole brain volume, Gaussian random-field theory is used to estimate the spatial smoothness of the statistical parametric map and to adjust for the number of spatially independent tests performed. Finally, each individual subject's fMRI data is co-registered to their structural MRI so that activations can be viewed with respect to gyral and sulcal detail that is absent from the statistical parametric map.

2.9. Group Analysis

Owing to variations in individual neuroanatomy and in the spatial extent of fMRI activations, individual subject image data must be normalized into a common standard image space before group analysis can take place. The mean image generated during the 'slice-timing correction' pre-processing procedure was used to determine the parameters for transforming the single-subject data into standard image space. In this thesis, each individual subject's fMRI data were normalized against the Montreal Neurological Institute template (Evans et al., 1994) derived from the mean of 152 individual subject's structural scans. Other templates are available, and like the MNI-152 template, many use the Talairach coordinate reference frame (Talairach & Tournoux, 1988). For the group statistical analysis, each normalized contrast image was smoothed using a 8mm (at full-width half maximum) Gaussian filter. The smoothed and normalized contrast images were then entered into a random effects analysis. By contrast with fixed effects analyses, random effects analysis incorporates inter-subject variance, and so can be used to generalize results to the population as a whole. Group data are presented in this thesis,

but the main aim of the fMRI experiment was to localize the FEFs in each individual subject's brain, and to compare the coordinates generated by haemodynamic mapping with the anatomical coordinates used to guide TMS coil placement.

CHAPTER 3: Localizing the Human Frontal Eye Fields with fMRI and TMS

Abstract

The precise location and extent of the human FEFs has been somewhat controversial. This chapter reviews the available evidence and argues that the anatomical criteria used to guide TMS coil positioning throughout this thesis are appropriate and reliable. In the monkey, the FEFs are localized by both anatomical and physiological criteria. Hence, the major aim of this chapter is to demonstrate that the anatomically-targeted areas exhibit a physiological profile consistent with the human FEFs. To achieve this, subjects performed saccade tasks during fMRI scanning and TMS application. The aim was to show that the anatomically-targeted areas were activated when subjects made saccades and that activity in these areas was disrupted by TMS. Since the aim of the thesis as a whole is to explore non-oculomotor functions for the human FEFs, it is important to show that the effects reported in this thesis result from interference with the functioning of an area normally involved in programming saccades.

1. Introduction

The frontal eye fields (FEFs) in the macaque monkey are located in the rostral arch of the arcuate sulcus, extending a few millimeters posteriorly into the caudal bank (Segraves & Goldberg, 1987; Gottlieb et al., 1993; Gottlieb et al., 1994) and a few millimeters anteriorly onto the prearcuate gyrus (Bruce et al., 1985). Neuroimaging (PET/fMRI) studies have localized the human homologue to the junction of the precentral sulcus (PCS) and superior frontal sulcus (SFS) (Anderson et al., 1994; Petit et al., 1996; Corbetta et al., 1998; Berman et al., 1999), but there is uncertainty about the areal extent of the human FEFs. There have been varying reports of activation being confined within the precentral sulcus (Luna et al., 1998), centred more posteriorly on the precentral gyrus (Paus, 1996), or more anteriorly on the caudal middle frontal gyrus (Kawashima et al., 1998; Tehovnik et al., 2000). A meta-analysis (Paus, 1996) further reported substantial variability in the medio-lateral plane. Since the aim of this thesis is to explore FEF function, it is important to ensure that the area targeted for TMS fits with the best currently available location estimate.

Controversy about FEF location has focussed on the rostro-caudal axis. The majority of imaging studies have localized human FEFs within or attached to the precentral motor strip in agranular cortex (BA6) (Brodmann, 1909; Braak, 1980), substantially posterior to the Brodmann's area 6/8 (BA6/8) agranular-to-granular transition zone, where the monkey FEFs are located (see Figure 3.1).

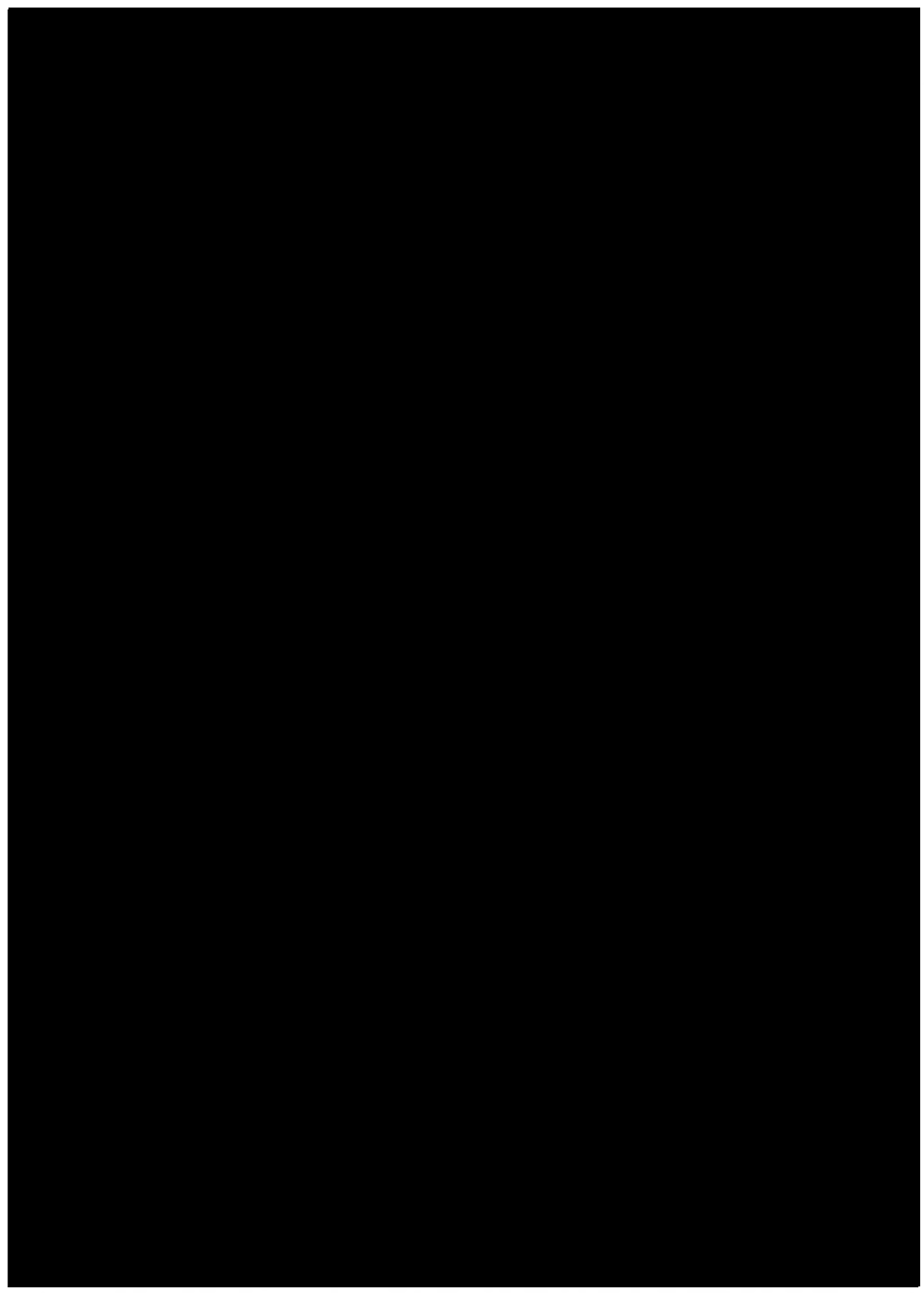


Figure 3.1. Cytoarchitecture of and thalamic projections to the human FEFs. Ellipses show the approximate location of human FEF according to imaging studies. **(A)** Cytoarchitecture of frontal lobe. Region 1 anterior of the central sulcus (CS) is agranular frontal cortex. Region 2 is the extent of granular cortex. **(B)** Thalamo-cortical projections. The "regio frontalis" is connected primarily with the mediodorsal (MD) nucleus of the thalamus; the region caudal to that is connected primarily with the ventrolateral (VL) thalamic nucleus. Figure from Tehovnik, et al. (2000).

It is perhaps unsurprising that human FEFs may have been shifted caudally during phylogenetic development to accommodate an expanded range of functional capacities in frontal cortex (Courtney et al., 1998). However, this apparent caudal shift implies a significant lack of homology between the two species (Tehovnik et al., 2000). Whilst monkey FEFs receive their principal thalamic input from the medio-dorsal nucleus, BA6 receives projections from the ventrolateral nucleus (Giguere & Goldman-Rakic, 1988; Stanton et al., 1988; Barbas et al., 1991), implying substantially altered patterns of thalamo-cortical connectivity across the two species. Attempts to circumvent this conclusion have appealed to methodological factors, reviewed as follows.

1.1. Functional Imaging

In imaging studies, differential blink rates between experimental (saccade) and control (fixation) blocks (Tehovnik et al., 2000); spatial blurring due to smoothing and normalization (Luna et al., 1998), and artefacts from group data averaging (Swallow et al., 2003) have all been cited to explain the apparent (and presumed erroneous) caudal displacement of the human FEFs. However, the spatial error incurred by image processing artefacts is in the order of millimeters, and so seems insufficient to bridge the distance from BA6 to the BA6/8 boundary zone in the middle frontal gyrus. Nor do these factors explain why displacement should chiefly affect the rostro-caudal plane. A related issue is that imaging may over-estimate the areal extent because of activations that are not subtracted out. There are a number of regions around the SFS/PCS junction that display saccade- and eyeblink-related modulation (Bodis-Wollner et al., 1999; Ramnani et al., 2000). In the monkey, intra-cortical microstimulation (ICM) studies have uncovered an "eyeblink field" in the face area of the motor strip and a "motor strip eye field" medial to that (Beevor & Horsley, 1890; Leyton & Sherrington, 1917), together with saccade-related regions in dorsal and ventral premotor cortex (Fujii et al., 1998, 2000). Hence, in a

subtractive activation map of <Saccades vs. Fixation>, premotor areas modulated by eye movements are likely to be included. A fMRI study (Koyama et al., 2004) of monkeys and humans performing identical saccade tasks showed that the activation-defined monkey FEFs are caudally shifted. In that study, BOLD signal extended from the arcuate sulcus into BA6, likely reflecting premotor saccadic activity. Thus, the reported foci and borders of (human or monkey) FEFs seem to depend inherently on the mapping technique.

1.2. Electrical Stimulation

Early classic stimulation studies in patients (Rasmussen & Penfield, 1948) uncovered a broad region anterior and posterior to the PCS from which saccades could be evoked. This is also the case in the monkey (Wagman et al., 1961), and so the FEFs have been electrically defined as that region of cortex from which contraversive saccades can be evoked with currents below 50 μV (Bruce & Goldberg, 1985b). Owing to intra-operative constraints, no such criterion exists for the human FEFs, although two recent studies in awake patients have begun to refine voltage parameters. Godoy, et al. (1990) used chronically implanted subdural electrodes to evoke contraversive saccades anterior to the motor arm and face representations, confirming previous work. Blanke, et al. (2000) replicated this, but specified effective stimulation sites with respect to sulcal landmarks, Talairach space and functionally-defined adjacent areas. Using low current thresholds (mean 4.3 mA), saccades were elicited from only a restricted area of the caudal middle frontal gyrus, replicating the findings of Foerster (1931, 1936) (see Figure 3.2). The authors further showed that visually-evoked potentials could be recorded from the same sites at which stimulation evoked saccades (Blanke et al., 1999). Blanke, et al.'s work represents the most precise demarcation yet of human FEFs by electrical means and, significantly, places the human FEFs in BA8, not BA6 as ascribed by imaging.



Figure 3.2. Areal borders of the human FEFs according to microstimulation and functional imaging. Horizontal lines indicate areas from which Rasmussen & Penfield evoked saccades with ICM (all frontal gyri and precentral gyrus). Vertical lines indicate the caudal end of the middle frontal gyrus, the only area from which Foerster (1936) could elicit saccades. The grey patchy area centred mostly on the precentral gyrus represents the FEF as localized by imaging studies (Petit, et al., 1999). PCG = precentral gyrus, SFG = superior frontal gyrus, MFG = middle frontal gyrus, IFG = inferior frontal gyrus. From Blanke, et al. (2000).

1.3. Chemoarchitecture

Traditional cytoarchitectonic maps were derived using Nissl staining (Brodmann, 1909; von Economo & Koskinas, 1925; Sarkissov et al., 1955), and place the border of human BA6/8 in the middle frontal gyrus. This placement has been questioned (Luna et al., 1998) and recently re-assessed. Rosano, et al. (2003) used a range of neurochemical markers that have been applied reliably to parcellate the monkey prearcuate cortex (Hof & Morrison, 1995). They sectioned and stained the PCS/SFS junction, and uncovered an agranular-to-granular transition in layer IV from the posterior to anterior wall of the PCS. This work suggests that classic cytoarchitectonic maps of the human brain have mislocalized the BA6/8 boundary, placing it too anterior, thus generating the apparent inhomology between the two species.

1.4. Medio-Lateral Axis

Block-design human imaging studies have consistently identified at least two distinct activation clusters along the PCS comprising "FEF complex": a superior cluster at the PCS/SFS junction, and an inferior cluster located around the caudal end of the inferior frontal gyrus (eg: Culham et al., 1998; Lobel et al., 2001). It has been suggested that a constellation of clusters along the PCS might constitute functionally heterogeneous fields (eg: Corbetta et al., 1998; Petit & Haxby, 1999), although this remains to be systematically explored. Kato, et al. (2003) found that whilst the superior cluster was activated during blinking and saccade trials, the inferior cluster was only activated during blinking. Other work has suggested that "superior FEF" is preferentially activated by saccades, while smooth pursuit tends to activate "inferior FEF" (Petit et al., 1997; Petit & Haxby, 1999). Paus, et al. (1996) has suggested that small amplitude saccades activate "superior FEF" whilst large saccades activate "inferior FEF", the reverse pattern to that found in the monkey (Robinson & Fuchs, 1969). Event-related designs have shown stronger functional coupling with the intra-parietal sulcus (Shulman et al., 1999) and greater direction-selectivity during covert orienting (Corbetta et al., 2002) in superior versus inferior FEF. Electrical stimulation of the fMRI-defined FEFs has also shown that saccades are more easily elicited from superior rather than inferior FEF (Lobel et al., 2001). Hence, current evidence suggests that superior FEF constitutes "FEF proper", whilst "inferior FEF" may be properly designated the "eye-and-head fields", which are activated when larger gaze shifts recruit neck and head musculature.

1.5. TMS Coil Placement

The emerging consensus from imaging, ICM & immunochemical mapping is that the human FEFs lies in the PCS/SFS junction, in an agranular-to-granular transition zone (BA6/BA8) extending some (unspecified) distance into the caudal middle frontal gyrus.

The differential caudal (imaging, BA6) versus rostral (ICM, BA8) emphasis in published spatial coordinates likely reflects sampling biases that are inherent to the different (vascular/electrical) measuring techniques. As TMS is an electrical stimulation technique, coil placement in the rostro-caudal plane throughout this thesis was guided by ICM estimates and corresponds with the electrically-defined FEFs (Foerster, 1931b, 1936; Blanke et al., 2000) (see Figure 3.2). Since the experiments in this thesis required fixation or the execution of small amplitude saccades (< 12 DVA), the superior rather than inferior FEFs were targeted. On this basis, TMS was applied at the PCS/SFS junction, at the caudal-most end of the middle frontal gyrus.

Since sulcal landmarks were used to localize the FEFs, it is important to demonstrate that these anatomically-targeted areas exhibit classically accepted functional characteristics of the human FEFs. To establish this, two experiments were conducted. Both were attempts to replicate protocols that have been proposed as functional localizers for the human FEFs. The fMRI experiment (Luna et al., 1998) subtracted activations during fixation from those during visually-guided saccades, and compared the location of the activation peaks with the coordinates at which TMS was applied. The TMS experiment (Ro et al., 1997) measured saccade latencies and durations to test whether stimulation disrupted saccades. Each experiment used a case study approach to test for these physiological indicators at anatomically-defined FEF locations. Group data are reported, but the main focus was on each single-subject case.

2. Methods

Subjects

Eight subjects (1 female) participated in the fMRI experiment and five of these (1 female) also took part in the TMS experiment. The data from one subject (C.W.) in the TMS experiment had to be discarded since, despite two testing attempts, the data were contaminated by blinks and could not be analysed. Of the eight subjects, six had participated in all of the experiments presented in this thesis. The other two had taken part in at least one other experiment. All subjects had normal vision and did not report any psychiatric or neurological contraindications. They each gave written informed consent and underwent MRI and TMS safety screening before the experiments. All procedures were approved by the Oxford Research Ethics Committee (OxREC).

Behavioural Tasks

1. Endogenous Orienting (TMS) Task

This experiment replicated the procedures of Ro, et al. (1997). Visual stimuli were presented on a 17" VDU (Iyama) running at 75 Hz. Stimulus presentation, triggering of the TMS machine and registration of subject keyboard presses were controlled by a PC (Celeron) running Presentation software (Psychology Software Tools, Inc.). All stimuli were white on a black background (see Figure 3.3). Subjects were seated in a dimly-lit room at a distance of 100cm from the display and triggered the onset of a trial by pressing the keyboard space bar. Each trial began with a central fixation cross and two unfilled squares, one each presented at approximately 10 degrees to the right and left of fixation. After a variable interval (300 – 700 ms), a directional cue (central arrowhead pointing left or right) was presented for 100ms and was then removed from the screen. Subjects were instructed to saccade as quickly and accurately as possible towards the

lower outer corner of the relevant target square. Left and right target locations were equiprobable. The inter-trial interval varied between 1800 and 2100ms. At the start of the experiment, subjects ran two practice blocks of 40 trials each to help stabilize reaction times. Subjects were instructed to suppress eyeblinks during trials and were encouraged to blink during the inter-trial interval.

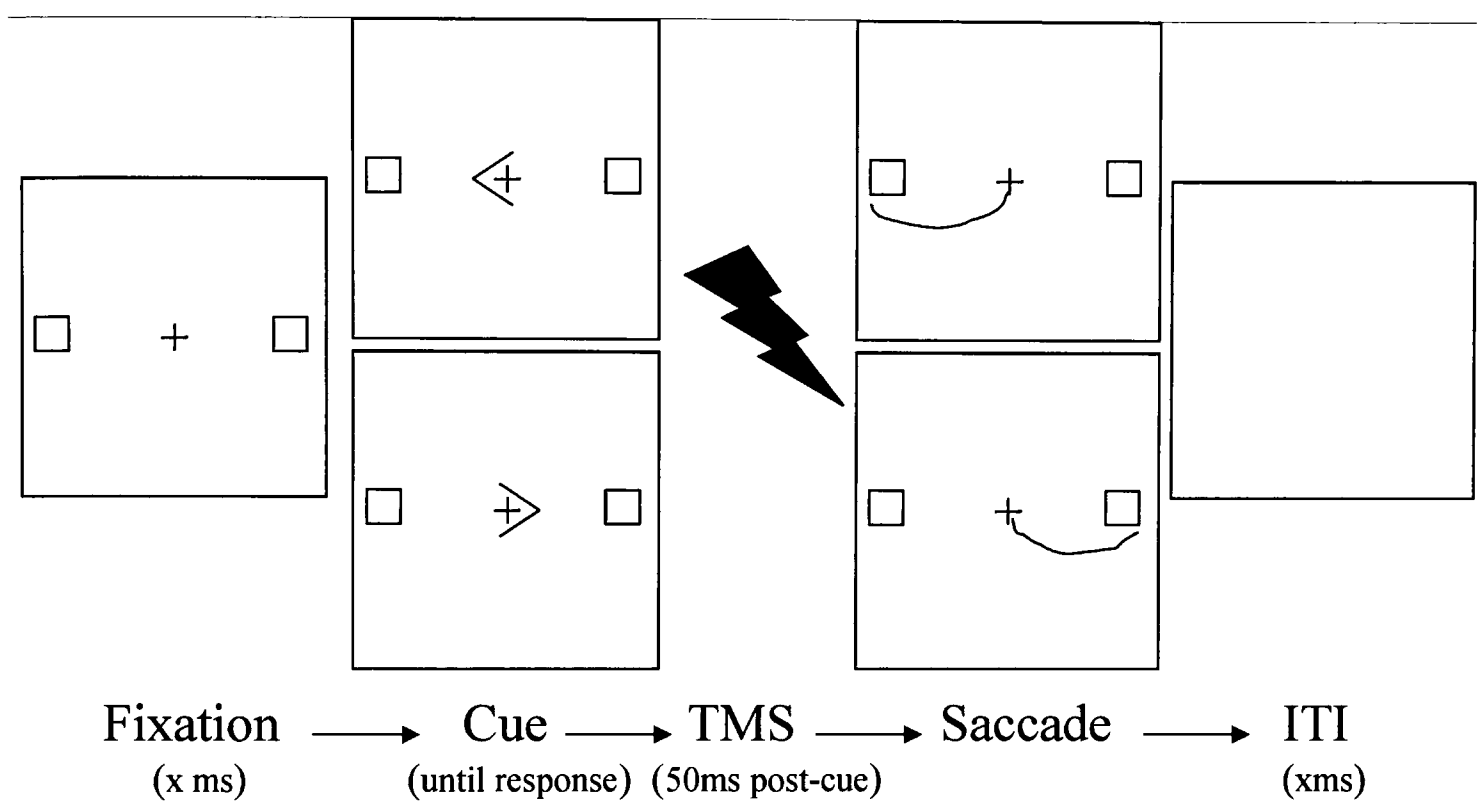


Figure 3.3. Stimuli and sequence of events in the endogenous orienting TMS task. A trial began with a central fixation cross and two square landmarks ca. 10 degrees to the right and left. After a variable interval, a central arrowhead cue instructed subjects to saccade to the right or left square as quickly as possible. 10Hz TMS (500ms) was applied on 50% of trials starting 50ms after the onset of the cue.

2. Visually-Guided Saccades (fMRI) Task

Subjects performed a visually-guided sequential saccade task in the scanner which replicated the procedures used by Luna, et al. (1998). Subjects performed twelve continuous blocks of the task, with each block consisting of 30 secs of fixation, followed by 30 secs of visually-guided saccades (see Figure 3.4). The saccade target was a white circle and the fixation target was a white cross-hair on a black background. Saccade targets were presented at central fixation and also at approximately 3, 6 and 9 DVA to

the left and right of the centre along the horizontal plane. The target moved with a 0.5 probability to the left or right every 0.75 secs in a 3 degree step from its previous position, except at the 9 degree location when the next step was always back to the centre of the screen. Thus the location of upcoming saccades had a low level of spatial predictability. Visual stimuli were presented using Presentation software (Psychology Software Tools Inc) and were back-projected onto a screen which subjects viewed through inverting mirror spectacles. Subjects were instructed to suppress blinks during fixation and saccade blocks and encouraged to blink during the interval between blocks, which lasted for 2 scanner pulses (ie: 6 secs). As in the original study by Luna, et. al (1998), eye movements were not recorded in the scanner. However, given that the task was so simple, and that participants were experienced psychophysical subjects, it is reasonable to assume that the task was carried out as instructed by volunteers.

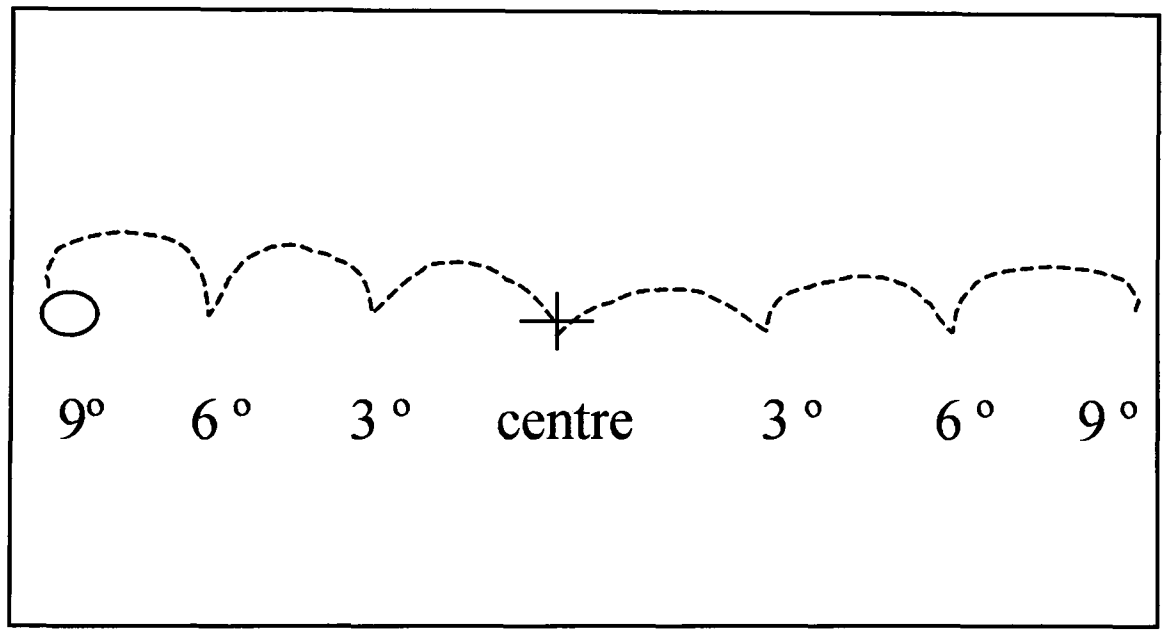


Figure 3.4. Stimuli and sequence of events in the visually-guided saccades fMRI task. The fMRI visually-guided saccade task alternated between 30 sec blocks of fixation and saccades. The target moved in 3 degree steps every 0.75 seconds, occupying positions 3, 6 and 9 degrees from fixation. Target movements to the left or right were equiprobable. Subjects were instructed to saccade or fixate in line with the movements of the visual target.

Eye Movement Recording and Analysis (TMS Experiment)

Eye movements were recorded using an ISCAN® infra-red eye-tracking system (ISCAN Inc., Burlington, Mass., U.S.A) sampling at 250Hz. Head movements were restricted by use of a head and chin rest and by verbal instruction to subjects to remain as still as possible. Recordings were made from the right eye and the eye tracker was calibrated using a five-point procedure at the beginning of each block. Eye movement data were analysed off-line using Spike 2 software (Cambridge Electronic Design, Cambridge, U.K.). An average saccade wave-form was calculated for each block separately. These wave-forms were then inspected by eye to determine the onset and end-point of the saccade. The latency, duration, start- and end-point of each saccade was recorded by hand. To compare wave-form averages in the TMS versus no TMS conditions, an equal amplitude criterion was chosen. Since TMS often increased the duration and reduced the slope of the saccade, the saccade endpoints in TMS conditions tended to be more ambiguous. However, since saccades were always directed to targets at the same horizontal displacement from the centre, the time-point at which the saccade amplitude in the TMS condition matched that in the no TMS condition was chosen as the saccade end-point.

Cortical Site Localization (fMRI & TMS Experiments)

FEF was localized for TMS using the Brainsight frameless stereotaxy system (Version 1.5; Rogue Research, Montreal, Canada). The stimulation site was identified on each subject's T_1-weighted MRI scan and was then co-registered with scalp coordinates over which TMS was applied. The probabilistic locations of each subject's FEFs were determined according to anatomical landmarks. Stimulation was applied over the posterior middle frontal gyrus, just rostral of the junction of the precentral sulcus and the superior frontal sulcus (Blanke, et al., 2000)(see Figure 3.5). This area constituted the *a*

priori defined FEF region-of-interest in each hemisphere for the fMRI experiment. The site of stimulation was also referenced to each subject's motor hand area, defined as the most anterior scalp point from which a visible hand twitch could be elicited (Yousry, et al., 1997; Ro, et al., 1999). Using this method, on average, TMS was applied 5cm lateral of the saggital midline and 3 - 4cm rostral of each subject's motor hand area. This site corresponds well with scalp coordinates used in other TMS studies of FEF (Muri, et al., 1991; Leff, et al., 2001; Wipfli, et al., 2001).

The Brainsight system was also used to check the anatomically-derived FEF coordinates from the TMS experiment against the FEF coordinates derived from the fMRI experiment. Using SPM2 (2003) software (Wellcome Department of Cognitive Neurology, London, UK), the <Saccades – Fixation> contrast map for each subject was co-registered and resliced to match that subject's high-resolution ($1 \times 1 \times 1$) structural scan. The statistical map was then superimposed on the anatomical image using the "overlay" function in Brainsight. Anatomically-derived coordinates were then checked for correspondence with activation clusters in the functional overlay.

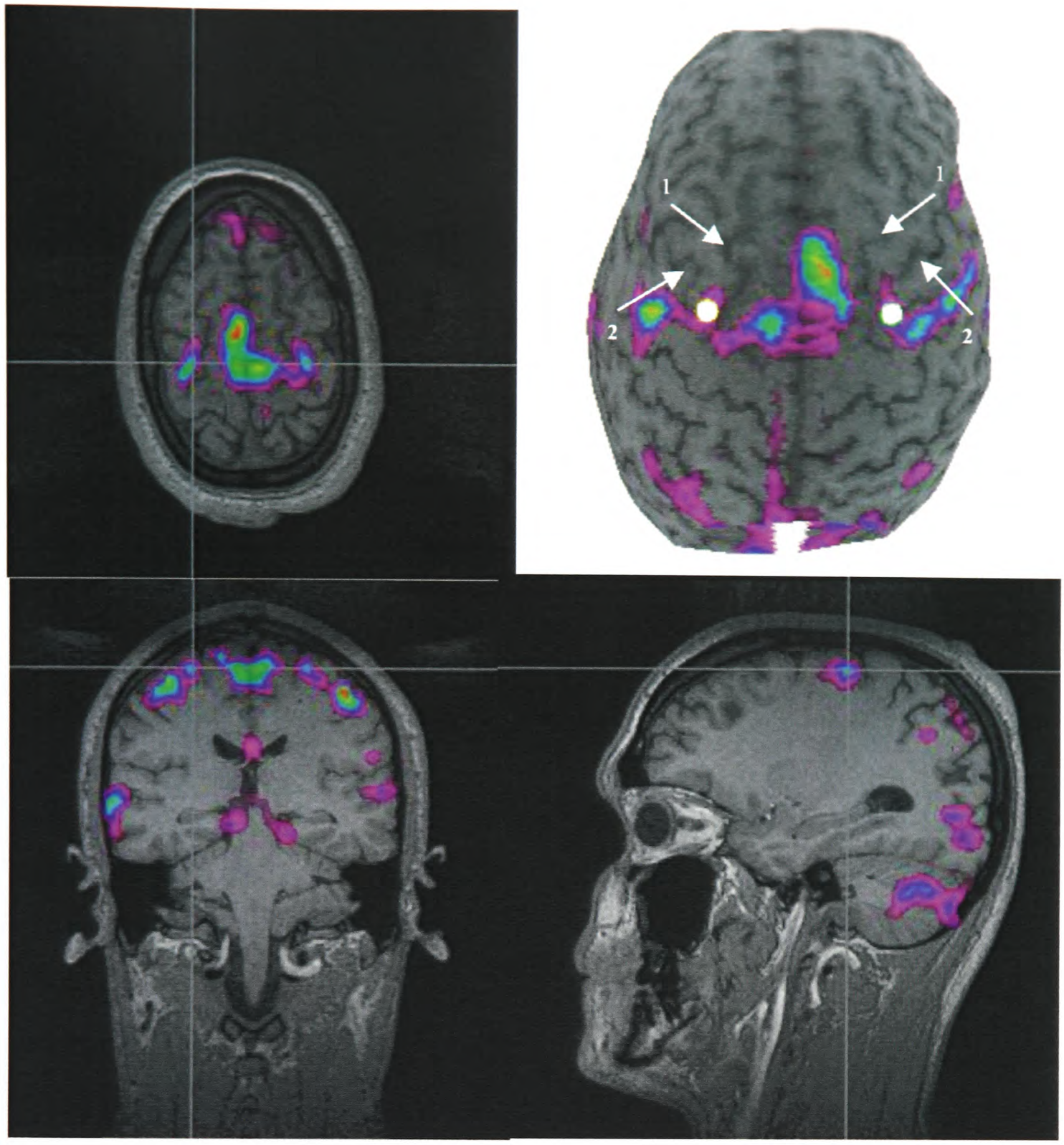


Figure 3.5. Localization of frontal eye fields using anatomical landmarks and Brainsight frameless stereotaxy. The anatomical landmarks used to localize the FEFs are shown on subject K.T's high-resolution (1 × 1 × 1) T1-weighted anatomical MRI. The cross-hairs indicate the anatomically-defined right FEFs at the caudal end of the middle frontal gyrus, at the junction of the superior frontal sulcus **(1)** and the pre-central sulcus **(2)**. The centre-points of magnetic stimulation are marked on the 3D rendered brain by the white circles. This subject's statistical parametric map for the <Saccades – Fixation> contrast from the fMRI experiment is superimposed on the structural scan, confirming good correspondence between the anatomically- and fMRI-defined FEFs.

Magnetic Stimulation

A Magstim Super Rapid machine (Magstim Company, Dyfed, U.K.) was used to deliver repetitive-pulse TMS at 65% of stimulator output through a small diameter (50 mm) figure-of-eight coil. Each coil handle was oriented parallel to the floor with the induced

current running in a posterior-anterior direction and was clamped in position using a mechanical arm. The coil size, orientation and stimulation intensity (65% maximum) were the same in every experiment reported in this thesis.

Each block in the endogenous orienting task consisted of 40 trials with half left and half right targets. On 50% of trials (pseudo-randomly chosen), 10Hz TMS lasting 500ms was triggered 50ms after the onset of the directional cue. This TMS protocol adapted the single-pulse protocols used by Ro, et al. (1997) and Grosbras & Paus (2002), so that more pulses were applied during the cue-target interval shown to be most effective in these studies. Subjects ran a total of two blocks at each TMS location. This yielded 20 trials in each TMS condition (RFEF/LFEF TMS * right/left target) and a corresponding 20 trials without TMS for each condition. One subject (J.O'S.) did not show saccade disruption with TMS applied over the anatomically-defined FEFs, so the coil was re-positioned over the nearest local peak voxels using the Brainsight functional overlay (see Cortical Site Localization (TMS Task)). Thus, the coil was centred over the precentral gyrus and a further two blocks were run for each hemisphere. However, TMS at these locations caused significant blinking, such that the waveform averages for this subject at this site could not be analysed.

Functional Image Acquisition

The fMRI data were acquired in a Varian-Inova 3T whole-body scanner (Siemens, Erlangen, Germany) at the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB). A quadrature birdcage head coil was used and head movements were restrained with foam pads. For each subject, 244 T2*-weighted echo-planar images (EPI) were acquired continuously with a repetition time (TR) of 3s and at an image resolution of 3 × 4 × 5 mm. The echo time (TE) and flip angle were 30ms and 90°,

respectively. Slices were acquired in axial orientation parallel to the anterior commissure–posterior commissure (AC–PC) line, and they covered the entire brain volume. After the behavioural task a b0 field map and a high-resolution (1 × 1 × 1) T1-weighted structural image were acquired.

fMRI Data Processing and Analysis

The fMRI data were analyzed with statistical parametric mapping (Friston et al., 1995b) using SPM2 (2003) software (Wellcome Department of Cognitive Neurology, London, UK). The first four scans of an EPI series were excluded from the analysis to minimize T1 relaxation artifacts. A mean image of all scan volumes was created, to which individual volumes were spatially realigned by rigid body transformation. Unwarping was performed during realignment to correct for motion-distortion interaction artefacts. Static geometric distortions were then corrected using the B0 field map and the Field-Map Undistortion Toolbox (R. Cusack, Medical Research Council, U.K.). The high-resolution structural image was co-registered with the mean image of the EPI series. A Gaussian filter of 6-mm full width at half maximum (FWHM) was then applied to smooth the data spatially and thus reduce noise. The time series data at each voxel were further processed using a high-pass filter with a cutoff of 128 seconds to remove low frequency drifts. Short-term serial correlations in the data were modeled by an auto-regressive process with white noise. For each scan, the data at each voxel were computed separately and scaled according to the global mean intensity of the image. The individual subject-level and group statistical analyses were performed using the general linear model (GLM). Vectors containing the onsets and duration of events in both conditions (fixate, saccade) were convolved with the canonical hemodynamic response function (HRF) to form the main regressors in the boxcar design matrix. For each subject statistical parametric maps from the comparison of <Saccades – Fixation> were generated using a

false-discovery rate (FDR) threshold of $P < 0.05$ with an extent threshold of ten voxels. In two subjects (P.T. & O.B.), an uncorrected threshold ($P < 0.05$) had to be applied to reveal bilateral activation in the FEFs. The final t-statistic map was superimposed on the high-resolution T1-weighted structural image of each subject.

The FEFs were identified *a priori* as regions of interest using sulcal landmarks. By transforming coordinates from Brainsight space into SPM space, the SPM marker cross-hairs in each individual subject's MRI were placed at coordinates just rostral of the PCS/SFS junction, at the caudal end of the middle frontal gyrus. Given that the aim of the study was to determine the spatial relation of the anatomically- and activation-defined FEFs, a spherical small volume correction (SVC) of radius 5mm was applied at these coordinates to assess whether the area stimulated by TMS was activated by the fMRI task. Statistical analysis was performed on the raw images, but the coordinates of the TMS site and of the peak local voxel were transformed into MNI coordinates for reporting purposes using the image-to-MNI conversion algorithm in the FMRIB Software Library (Oxford Centre for Functional MRI of the Brain).

For the group analysis, each individual subject's anatomical scan was normalized to the Montreal Neurological Institute (MNI) 152-mean brain T1 template. The mean image for each subject generated by the realignment procedure was used to determine the parameters for transforming the subject's < Saccades – Fixation > contrast image into MNI EPI space. Each normalized contrast image was then smoothed using a 8mm (at full-width half maximum) Gaussian filter. The smoothed and normalized contrast images were then entered into a random effects analysis using a one-sample t-test. Activations were determined in the group <Saccades – Fixation> contrast map using an uncorrected threshold ($p < 0.01$) since the aim was to test the anatomical hypothesis that the *a priori*

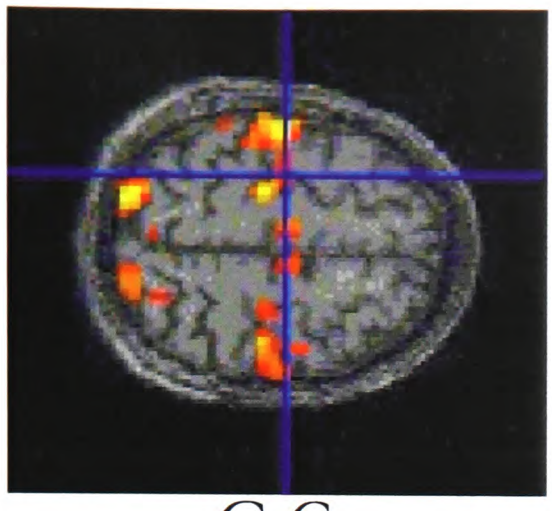
anatomically-defined FEFs would be significantly activated in this task. The group t-statistic map was superimposed on the MNI-normalized mean structural scan of all eight subjects.

3. Results

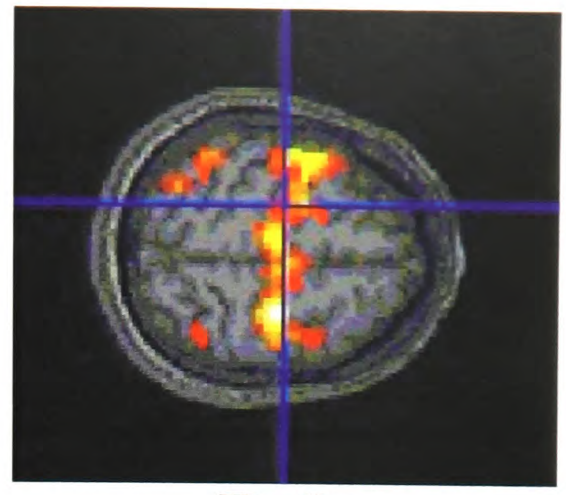
fMRI Experiment

The spatial relationship between the anatomically- and fMRI-defined FEFs are plotted for each individual subject and each hemisphere (Figure 3.6. Upper panel (pg. 99) = LFEF, Lower panel (pg. 100) = RFEF). In all but two subjects (J.O'S. & O.B.), BOLD activations extended from the precentral sulcus onto the caudal aspect of the middle frontal gyrus where the TMS coil was targeted. The cross-hairs in the figure are centred on the anatomical coordinates at which TMS was applied. In six out of eight subjects in each hemisphere, these coordinates fell within a significantly activated cluster.

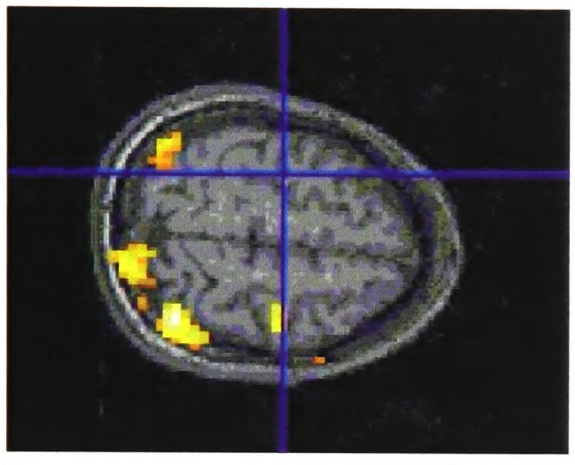
Figure 3.6. BOLD t-statistic maps for the subtraction of < Saccades – Fixation > in each of the 8 individual subjects. See next 2 pages: The first panel shows LFEF location for each subject; second panel shows RFEF. For all subjects (except J.O'S. LFEF), BOLD activation clusters extended from the precentral sulcus into the caudal end of the middle frontal gyrus where the TMS coil was targeted (this is not apparent for all subjects at the z coordinate pictured). The cross-hairs in the figure are centred on the anatomically-defined FEFs, showing that, for 6 out of 8 subjects in each hemisphere, the anatomically-defined FEFs were located within significantly activated voxel clusters. For the two subjects in each hemisphere for whom this was not the case (J.O'S. & O.B. - LFEF; G.C. & C.W. - RFEF), the nearest local peak voxel was located medial and posterior to the centre-point of the anatomically-defined FEFs.



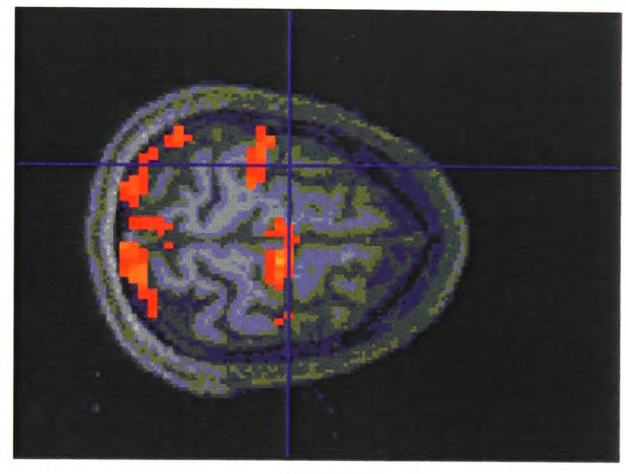
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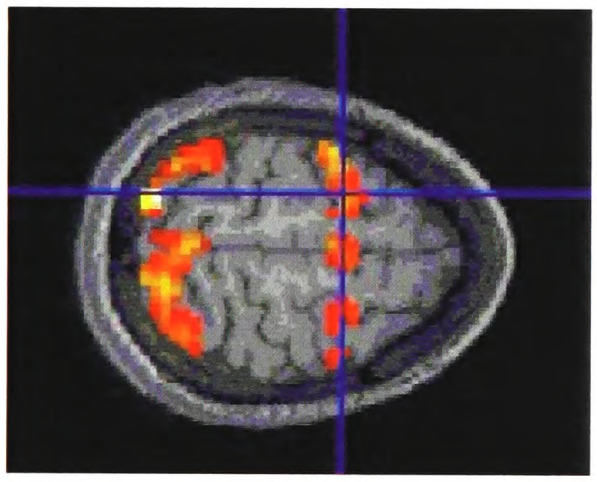
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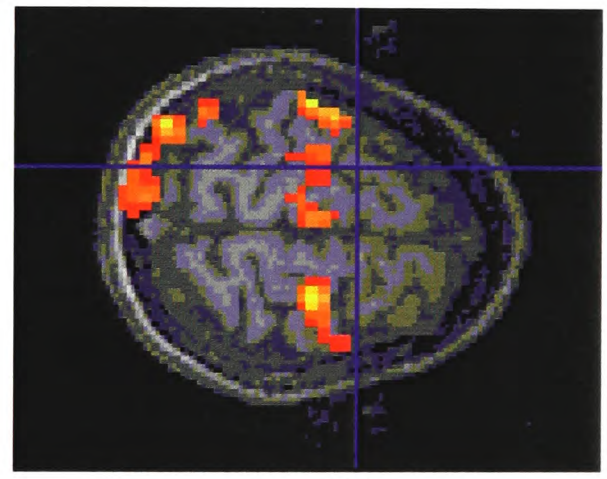
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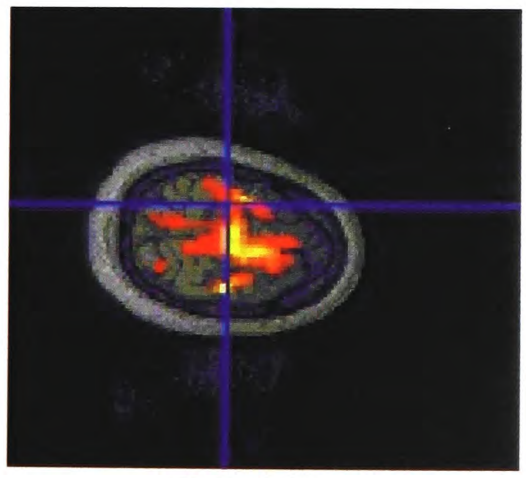
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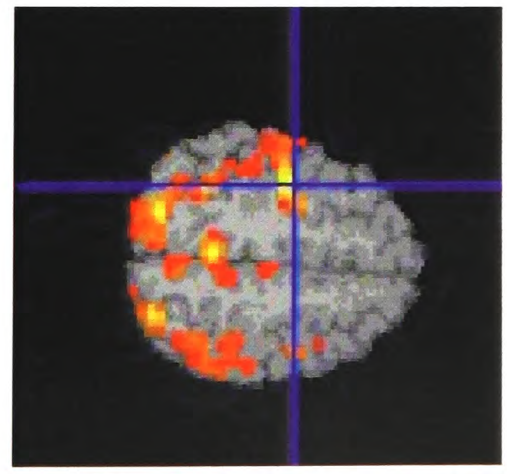
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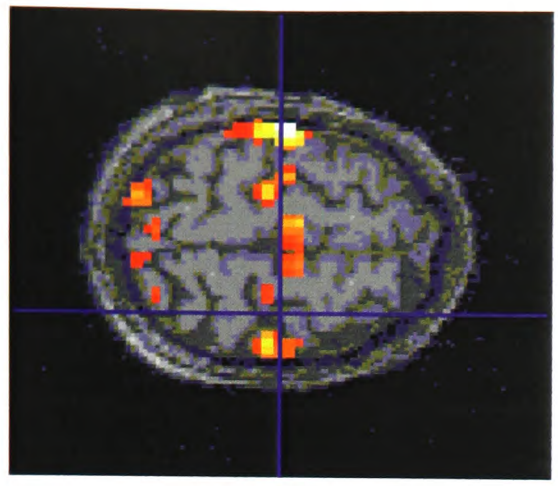
J.O'S.



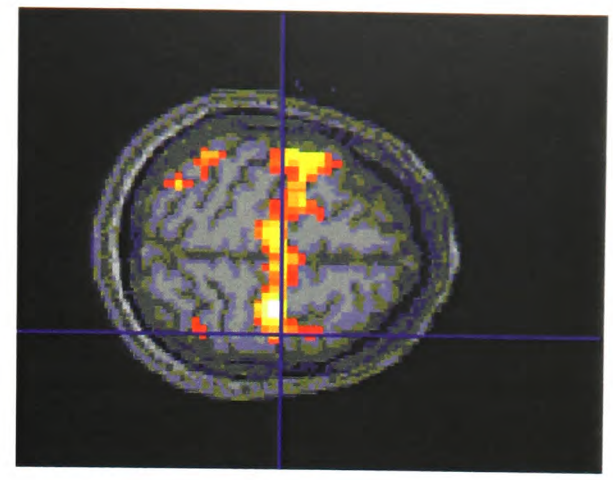
N.M.



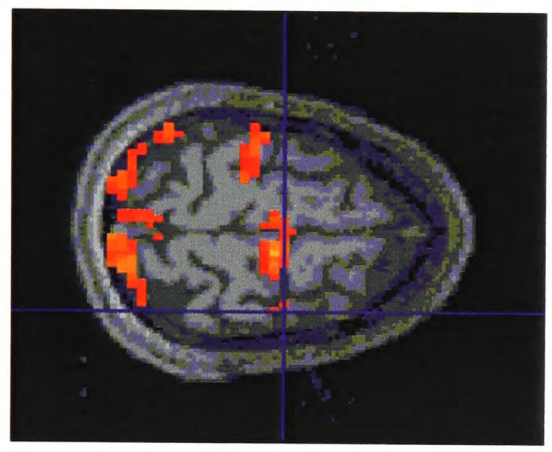
P.T.



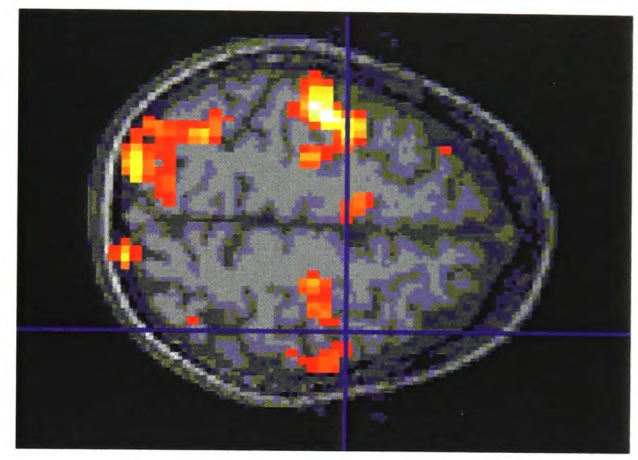
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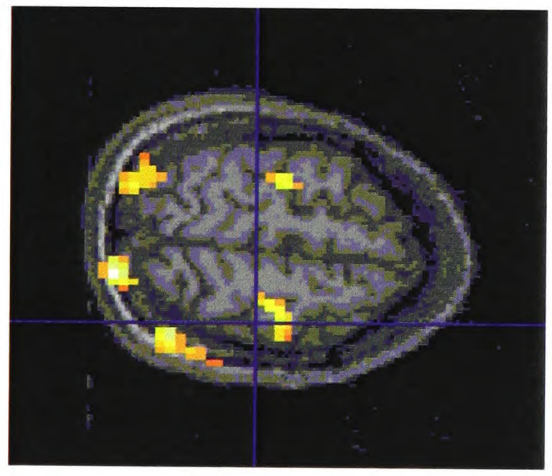
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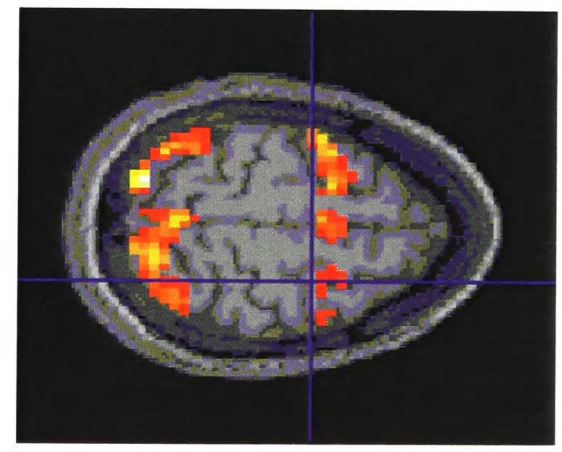
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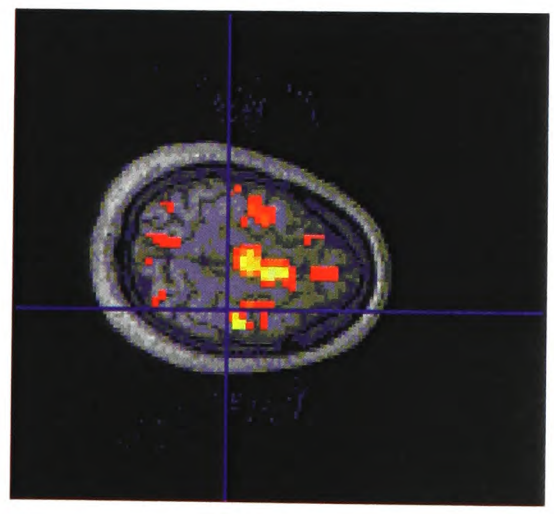
J.O'S.



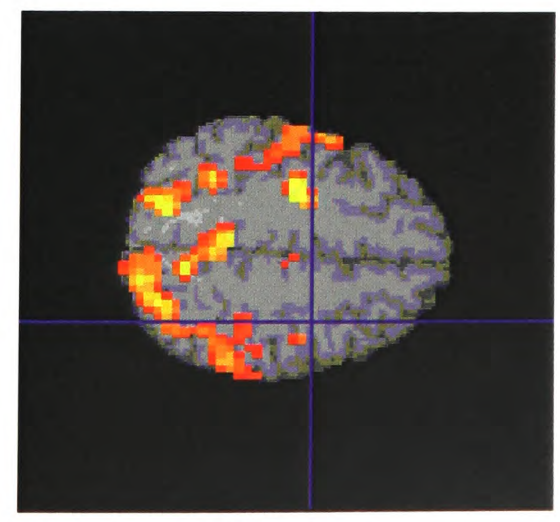
C.W.



N.M.



K.T.



P.T.

Statistical results for significantly activated voxels at the anatomical sites are listed for each subject in Table 3.1, which contains coordinate conversions from image to MNI space generated using the FSL matrix transform. Where a set of coordinates was not significantly activated, the coordinates of the nearest local peak voxel were identified and these are also listed. In all four cases where the anatomical coordinates were not significantly activated, the coil was positioned somewhat lateral and anterior of that subject's peak local voxel. In the left hemisphere subjects, the anatomical coordinates were 2mm lateral and 13mm anterior (J.O'S.), and 5.5mm lateral and 11.5mm anterior (O.B.). In the right hemisphere subjects, the anatomical coordinates were 7mm lateral and 4mm anterior (C.W.), and 9mm lateral and 6mm anterior (G.C.). Mean coordinates derived from each individual subject's anatomically-defined right FEFs and converted from image to MNI space were: x = 31, y = -1, z = 61 (Talairach: x = 30, y = 2, z = 56) and left FEFs were: x = -30, y = 0, z = 60 (Talairach: x = -30, y = 2, z = 55). Mean coordinates derived from each individual subject's activation-defined right FEFs and converted from image to MNI space were: x = 30, y = -2, z = 60 (Talairach: x = 30, y = 1, z = 55) and left FEFs were: x = -30, y = -4, z = 60 (Talairach: x = -30, y = -1, z = 55). The group average activation map is shown in Figure 3.7.

Table 3.1. Relationship between the anatomically- and fMRI-defined FEFs revealed by the subtraction of < Saccades – Fixation >. See next page: The left panel (TMS Site) shows the centre-point in MNI coordinates of the anatomically-defined FEFs. These coordinates mark the centre-point at which magnetic stimulation was applied for each individual subject in the right (a) and left (b) hemispheres. The right panel (Peak Voxel) shows MNI coordinates for the nearest local peak voxel with respect to the site of TMS application. SPM(Z) is the Z score of significantly activated voxels at these locations ("Inf" indicates Z > 8.2). Z scores at the TMS site were generated using a spherical small-volume correction (SVC) of radius 5mm. The extents (k) (in $3 \times 4 \times 5$ mm^3 units are shown for a false-discovery rate (FDR)-corrected height threshold of $p < 0.001$. Data for subjects P.T. and O.B. are uncorrected thresholds of $p < 0.05$.

RFEF TMS Site					
	x	**y**	**z**	**SPM(Z)**	**Extent**
CW	32.21	-2.49	65.41	N.S.	
PT	30.89	0.53	52.66	3.01	1
DC	32.56	0.68	60.08	5.9	6
GC	27.05	1.74	59.51	N.S.	
JOS	35.13	-3.02	59.76	2.77	1
KT	27.6	-5.51	68.13	Inf	4
OB	36.08	1.76	66.15	1.83	2
NM	24.89	-0.26	57.9	3.8	3
Mean	***30.80***	***-0.82***	***61.2***		
SD	3.981236	2.597281	5.074547		
SE	1.40758	0.918278	1.794123		
RFEF Peak Voxel					
	x	**y**	**z**	**SPM(Z)**	**Extent**
CW	25.62	-6.36	50.12	5.97	82
PT	36.57	-1.92	51.13	5.79	8
DC	34.05	1.36	61.68	7.72	10
GC	17.98	-4.02	63.92	3.81	26
JOS	35.19	-3.15	58.1	4.07	140
KT	29.34	-7.3	67.09	Inf	6
OB	33.32	1.31	67.2	3.23	8
NM	29.3	3.79	60.47	Inf	43
Mean	***30.17***	***-2.04***	***59.96***		
SD	6.116508	3.932796	6.550993		
SE	2.162512	1.390453	2.316126		
LFEF TMS Site					
	x	**y**	**z**	**SPM(Z)**	**Extent**
CW	-33.73	1.55	54.23	4.62	2
PT	-36.61	-5.46	54.8	3.64	21
DC	-25.62	-1.5	56.95	6.24	9
GC	-33.04	0.01	51.4	5.75	7
JOS	-28.58	-1.43	68.16	N.S.	
KT	-27.52	-4.02	66.79	7.49	10
OB	-33.37	4.03	64.57	N.S.	
NM	-25.48	4.52	62.5	6.01	3
Mean	***-30.49***	***-0.29***	***59.92***		
SD	4.209425	3.559285	6.362558		
SE	1.488256	1.258397	2.249504		
LFEF Peak Voxel					
	x	**y**	**z**	**SPM(Z)**	**Extent**
CW	-34.33	0.37	53.72	4.99	19
PT	-38.35	-6.35	60.43	6.11	491
DC	-26.04	-3.09	57.64	7.41	10
GC	-33.09	0.33	52.39	5.75	168
JOS	-26.75	-11.81	62.43	6.29	275
KT	-27.68	-2.49	69.92	7.49	10
OB	-27.85	-7.52	56.88	2.86	8
NM	-25.19	-1.44	62.99	3.67	155
Mean	***-29.91***	***-4***	***59.55***		
SD	4.741004	4.249649	5.662796		
SE	1.676198	1.502478	2.002101		

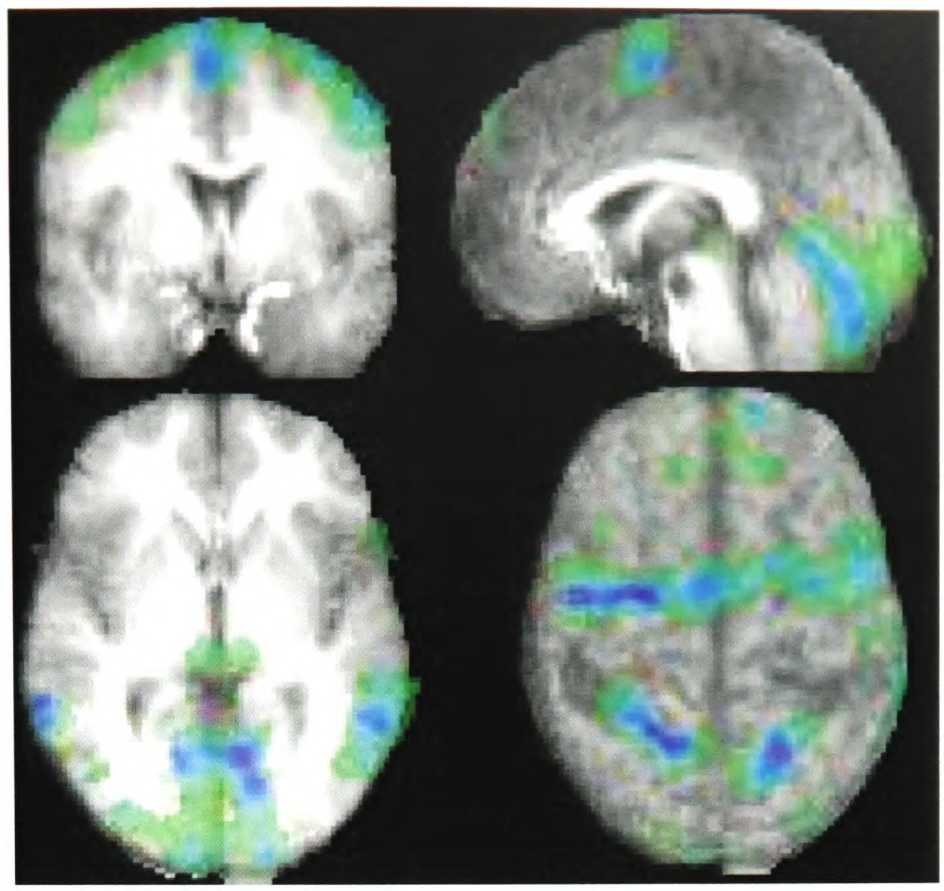


Figure 3.7. Group BOLD t-statistic maps for the subtraction of < Saccades – Fixation >. Group-level activations displayed on the mean structural MRI of the eight subjects.

TMS Experiment

Individual Subject Data:

Saccade latencies (top panel) and durations (middle panel) derived from average waveforms are reported for each of the four subjects in each condition in Table 3.2. Each data-point is derived from an average waveform for each condition composed of 20 saccade trials. Saccade amplitudes (bottom panel) are also cited to demonstrate the comparability of saccade sizes across conditions. All subjects showed a baseline hemifield bias in saccade reaction times (SRTs) and/or durations. The precise pattern of effects differed across subjects, but for 3 out of 4 subjects TMS over either of the FEFs consistently reduced baseline biases. All subjects had faster baseline SRTs to right targets. TMS over either of the FEFs slowed SRTs to right targets for subjects O.B. and N.M. and speeded SRTs to left targets for subject P.T. There was no clear effect for subject

J.O'S. All subjects (except J.O'S.) showed shorter baseline saccade durations to left targets. TMS increased the duration of leftward saccades for all subjects.

Saccade Direction	RFEF Block				LFEF Block			
	LEFT		RIGHT		LEFT		RIGHT	
Latencies	*No TMS*	*RFEF*	*No TMS*	*RFEF*	*No TMS*	*LFEF*	*No TMS*	*LFEF*
P.T.	257	241	244	257	263	238	254	245
O.B.	238	246	214	261	251	257	208	281
N.M.	244	252	240	253	251	251	218	249
J.O'S.	282	289	273	273	290	293	276	265
Mean	***255.25***	***257***	***242.75***	***261***	***263.75***	***259.75***	***239***	***260***
SD	19.51709	21.80214	24.15747	8.640988	18.39157	23.54251	31.60169	16.45195
SE	9.758543	10.90107	12.07873	4.320494	9.195787	11.77126	15.80084	8.225975
Durations								
P.T.	55	75	118	107	52	73	64	73
O.B.	107	125	142	138	90	133	140	108
N.M.	88	107	113	133	91	97	132	105
J.O'S.	62	74	69	95	75	84	66	66
Mean	***78***	***95.25***	***110.5***	***118.25***	***77***	***96.75***	***100.5***	***88***
SD	23.98611	25.06492	30.42477	20.61351	18.20256	26.0816	41.12988	21.58703
SE	11.99305	12.53246	15.21239	10.30675	9.101282	13.0408	20.56494	10.79352
Amplitudes								
P.T.	12.6	11.65	11	11	12.4	12.4	11	11
O.B.	20	20	16	17	17.25	16.4	14.6	15.2
N.M.	9.8	9.8	10.8	10.8	10.4	10.4	10.4	10.6
J.O'S.	7.8	7.8	8	7.8	11	11	10	10
Mean	***12.55***	***12.3125***	***11.45***	***11.65***	***12.7625***	***12.55***	***11.5***	***11.7***
SD	5.342596	5.360717	3.328163	3.855299	3.106814	2.7	2.107131	2.369247
SE	2.671298	2.680359	1.664081	1.92765	1.553407	1.35	1.053565	1.184624

Table 3.2. Saccade latencies and durations for each individual subject in each TMS condition. RFEF data are on the left; LFEF data are on the right. Data in each cell are based on 20 trials. Saccade amplitudes are cited to show the comparability of saccade sizes across blocks.

Group Data:

Latency and duration data from the non-TMS trials were analysed first to test for baseline biases (Figure 3.8). A repeated-measures ANOVA (Block (RFEF/LFEF) * Hemifield) revealed a significant hemifield effect on saccade latency ($F(1,3) = 12.607$, $p = 0.038$). S.R.T.s were faster to right targets (mean difference: 18.62ms; 95% C.I. -35.31,

-1.93). There was also a trend towards longer saccade durations to right targets (F(1,3) =8.065, p = 0.066)(mean difference: 28ms; 95% C.I. –3.37, 59.37).

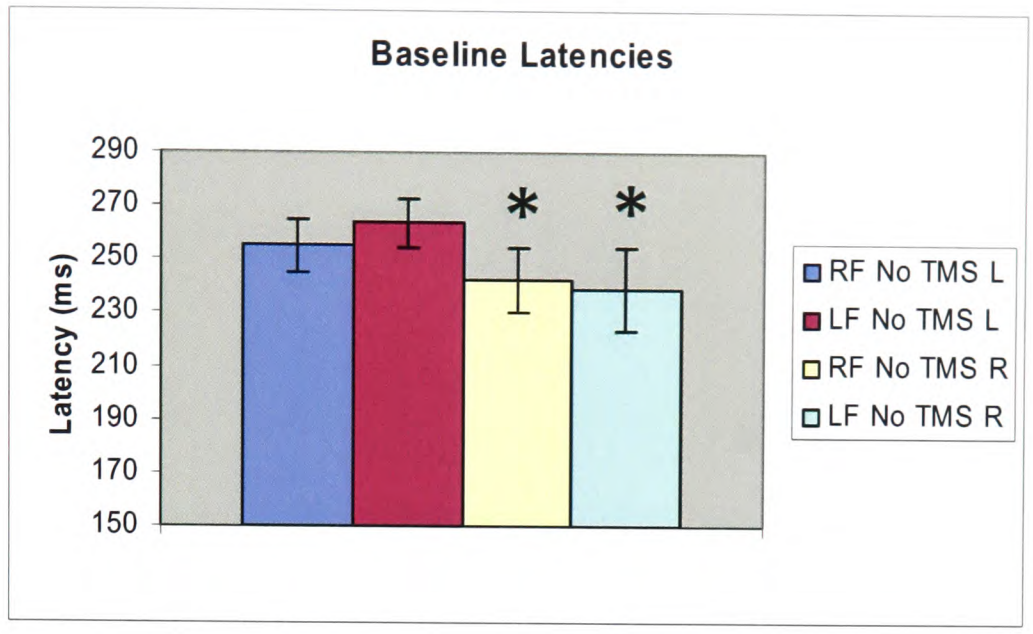
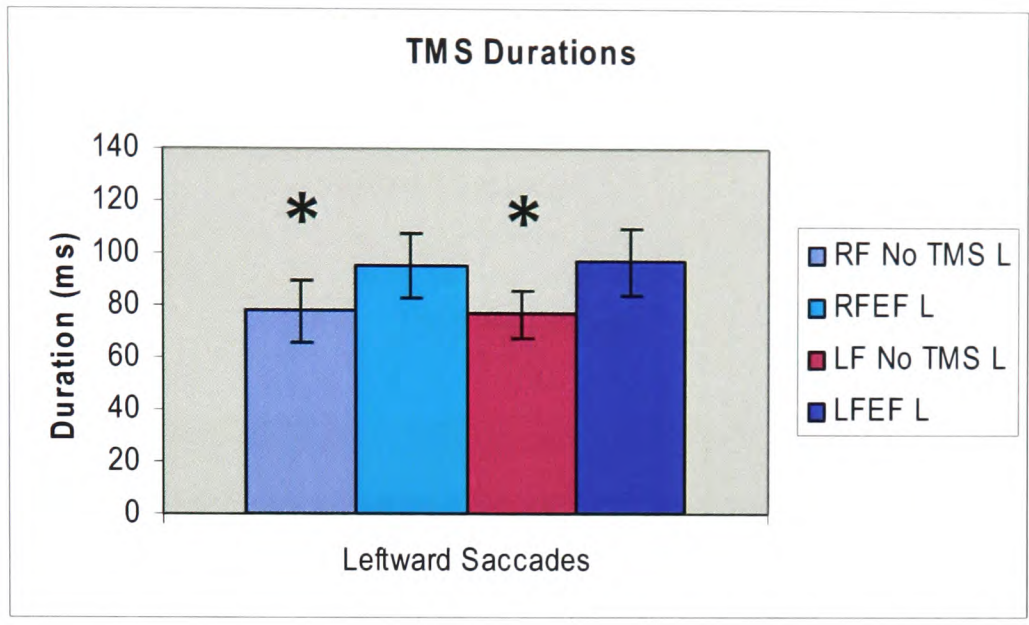


Figure 3.8. Baseline saccadic latencies and durations in the TMS FEF localizer experiment (n = 4). There was a significant hemifield bias in saccade latencies: subjects made faster saccades to right targets. There was a trend towards longer saccade durations to right targets.

Given the directional bias in the baseline data, the TMS latency and duration data for right and left hemifield targets were analysed separately. A repeated measures ANOVA (Block (RFEF/LFEF) * Condition (TMS/No TMS)) revealed a significant effect of TMS on saccade durations to left targets (F(1,3) = 16.56, p = 0.027)(Figure 3.9). TMS

increased saccade durations by 19.3% (from 77/78 ms to ca. 95/97 ms), bringing the data closer to the duration of baseline saccades to right hemifield targets (101/110 ms). No other analyses were significant (Figure 3.10).



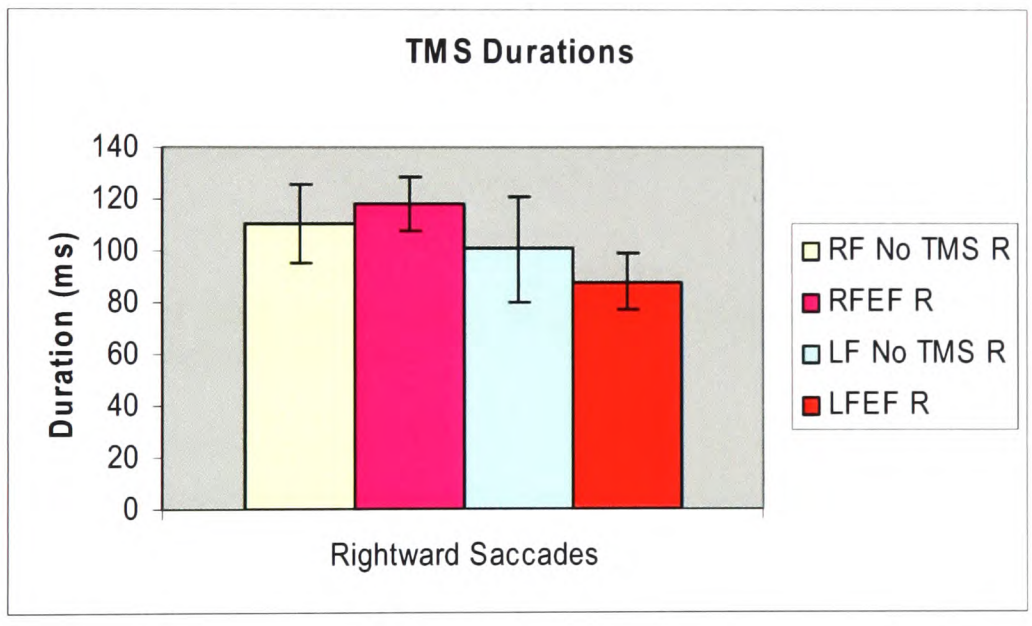


Figure 3.9. Effect of TMS on saccade durations. TMS over right or left FEF increased the duration of leftward saccades, eliminating the baseline trend towards shorter leftward than rightward saccades.

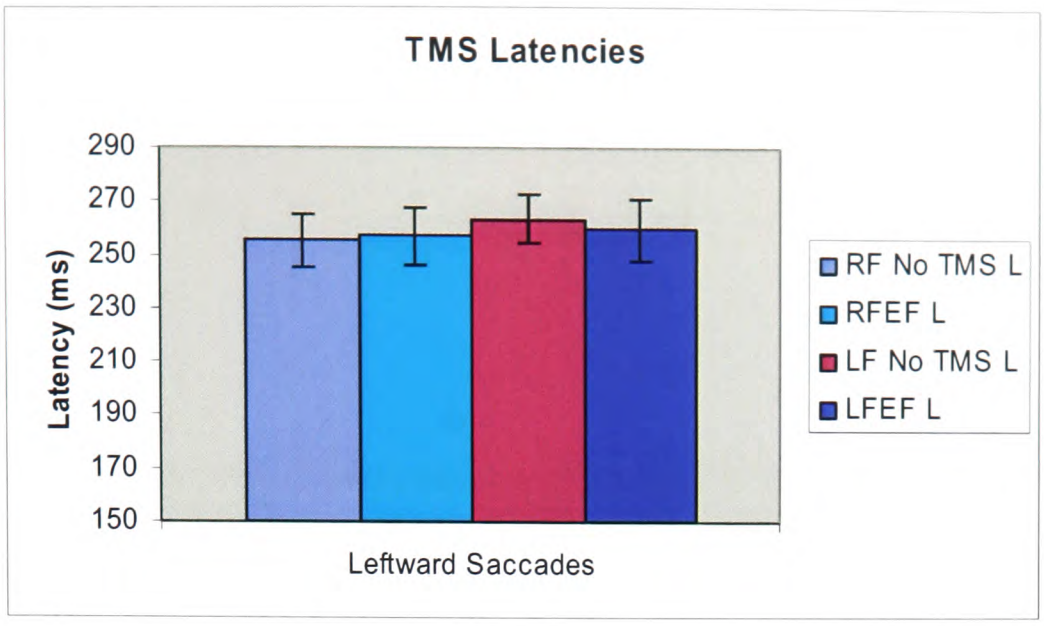


Figure 3.10. Effect of TMS on saccade latencies. There was no effect of TMS over right or left FEF on saccade latencies.

4. Discussion

The aim of this chapter was to demonstrate that the areas targeted for TMS in this thesis play a role in saccade programming. The fMRI experiment showed that these areas are activated when subjects make saccades, whilst TMS over these areas increased saccade duration. The coordinates at which TMS was applied show good correspondence with published imaging coordinates of the location of the FEFs. Taken together, the results suggest that the areas stimulated are in fact the human frontal eye fields. Further, the good correspondence between the anatomical coordinates and physiological effects

(activation and disruption) validates the anatomical localization protocol used throughout this thesis.

4.1. fMRI Data

In 14 out of 16 cases (8 Ss, 2 hemispheres; exceptions: J.O'S. & O.B.), the fMRI-defined FEFs extended rostrally from the PCS/SFS junction into the caudal middle frontal gyrus where the TMS coil was targeted. In 6 out of 8 subjects in each hemisphere, the anatomical coordinates fell within significantly activated voxel clusters. In all four cases where this was not the case, the coil was targeted anterior and lateral of that subject's peak local voxel. Overall, however, there was good correspondence between the anatomically- and haemodynamically-defined FEFs. The group fMRI data show good correspondence with published mean coordinates for the location of the FEFs. Average Talairach coordinates for the RFEFs and LFEFs were: x = 30, y = -1, z = 55. These coordinates correspond well with the average Talairach coordinates reported in a meta-analysis of FEF imaging studies (Paus, 1996): x = +/- 24 to 40mm, y = -6 to 1mm, z = 44 to 51mm.

As might be expected, there was individual variability in the location, morphology and extent of the FEF activation clusters. In the medio-lateral plane, some subjects showed distinct superior and inferior FEF clusters (eg: N.M., J.O'S., G.C. RFEF), whilst in others there was a continuous band of activation linking the two, sometimes extending to include the supplementary eye fields (SEFs) (eg: D.C.) The boundary between the FEFs and SEFs is frequently unclear in imaging studies. In the present study, lowering the activation threshold for this subject (D.C.) did not succeed in separating out distinct FEF and SEF activation clusters. In the rostro-caudal plane, the locations of FEF clusters in subjects O.B. and J.O'S. were more posterior than in other subjects. For O.B., the

clusters were located at the caudal junction of the PCS/SFS, in line with other subjects, but they did not extend anteriorly beyond the PCS. For J.O'S., both clusters were distinctly medial and posterior to those of other subjects, and were centred on the superior branch of each PCS (Ono et al., 1990), medial to the PCS/SFS junction. For J.O'S., only the more lateral "inferior FEFs" extended into the frontal gyri. The anatomical coordinates for O.B. and J.O'S. fell within significantly activated voxels in the right hemisphere. Unlike for O.B., for subject J.O'S., the spherical small-volume-correction showed this to be a function of proximity to the more lateral "inferior FEF" rather than the superior cluster.

The single-subject data reveal some individual variability in the location and extent of the human FEFs, which suggests that the spatial smearing of FEF clusters in imaging studies is not solely a product of processing artefacts. Unlike previous studies, the group data for this study were not caudally displaced to the precentral gyrus. This presumably reflects the fact that individual subject activations extended rostrally into the middle frontal gyrus

4.2. TMS Data

At the single-subject level, for 3 out of 4 subjects, TMS over the left or right FEFs disrupted both the latency and duration of saccades. The precise pattern of effects differed across subjects but seemed to be consistent with respect to subjects' baseline hemifield biases. For each of the three subjects, the effect of TMS was to reduce the baseline difference between rightward and leftward saccades. The group data mirrored this pattern, although only the duration data were significant. There was a baseline trend towards shorter saccade durations to left targets. TMS increased leftward durations by ca. 19%, substantially reducing the baseline difference. Although a tentative conclusion, in view of the small sample and single-subject approach, the pattern of results suggests that

the effect of TMS was to modulate subjects' inherent spatial biases between left and right space.

One subject (J.O'S.) did not show this effect. However, the fMRI data showed that this subject's FEFs were medio-caudally displaced with respect to the anatomical site at which TMS was applied. Although subject J.O'S' anatomically-defined RFEF was significantly activated, this activation originated in the inferior rather than superior FEF cluster. Further, J.O'S. showed only a very small baseline difference in left versus right saccades. Hence, it is unclear whether the lack of a TMS effect for J.O'S. was due to ineffectively targeted stimulation, or the absence of a baseline spatial bias, or both.

4.3. TMS as a Localization Tool

The TMS study reported here attempted to replicate studies which have proposed a delay in contralateral saccadic reaction time as a functional marker for the human FEFs (Ro et al., 1997; Ro et al., 1999; Grosbras & Paus, 2002; Ro et al., 2002; Grosbras & Paus, 2003). There are a number of factors which likely account for the discrepancy between present results and previous work.

In their first paper, Ro, et al. (1997) used a large (90mm diameter) circular coil placed "slightly anterior" to the cortex 5cm anterior of the motor hand area. Such a coil is likely to have stimulated a large volume of frontal cortex, as evidenced by the fact that hand twitches were observed in a number of subjects. As the authors themselves note, the TMS effects reported are likely to have resulted from stimulation of a number of saccade regions, including the dorso-lateral prefrontal cortex, supplementary eye fields and the frontal eye fields. In their second paper, Ro, et al. (1999) used more focal stimulation (90mm diameter figure-of-eight coil) combined with anatomical MRIs to confirm

selective stimulation of the FEFs. They reported that TMS over a number of sites around the FEFs delayed contralateral relative to ipsilateral saccades. Inspection of the means, however, shows that at only 3 out of the 14 "significant" sites was the mean contralateral S.R.T. longer than the baseline S.R.T. without TMS (RFEF subject baseline left S.R.T. = 284.2ms, TMS = 285.3; LFEF subject baseline right S.R.T. = 233.3, TMS = 236.9 and 237.1). Hence, since TMS did not increase saccade latencies relative to baseline, it is difficult to interpret what longer contra- versus ipsi-lateral latencies might mean. This is exacerbated by the fact that single pulse TMS was applied 50ms *before* the cue signalling the required saccade direction. Ro, et al. (2002) replicated these findings with TMS over RFEF in 7 out of 10 subjects. However, in that experiment baseline data without TMS were collected for only two subjects – neither of whom had shown the delay effect. One of these had a hemifield bias, prompting the authors to comment: "In one of these subjects there may be a natural tendency to execute faster leftward saccades making delays in contralateral leftward saccades with TMS more difficult to measure". However, baseline hemifield biases in spatial and saccadic behaviour have been shown to be common and robust (eg: Jewell & McCourt, 2000; Honda, 2002). The failure to analyse TMS data against control saccades implies that the reported contralateral TMS delays may in fact be spurious effects of baseline spatial biases. In accord with this, the remaining 3 subjects produced faster contralateral saccades, which Ro, et al. re-described thus: "we may have been stimulating too early or too late with respect to the eye movement go-signal causing the effects on eye movements to be facilitatory rather than inhibitory". In a further report (Ro et al., 2003), the authors claimed to have replicated this contralateral delay effect again. However, inspection of mean SRTs shows that the ipsi/contra-lateral difference in the FEF stimulation condition matched a baseline contralateral SRT bias in the No TMS condition. Moreover, SRTs in the FEF condition were all shorter than baseline saccade latencies.

Grosbras & Paus (2002) used a similar paradigm to functionally localize the FEFs. They applied single-pulse TMS 50ms prior to subjects' expected saccade onset (Priori et al., 1993) and predicted saccade delays, particularly in the contralateral direction (Thickbroom et al., 1996). TMS over either of the FEFs increased saccade latencies, but the effect was equivalent for ipsi- and contra-lateral directions (11.25% ipsi- and 10.9% contra-lateral mean increase). On an individual subject basis, TMS over LFEF increased only ipsilateral saccades for two subjects, only contralateral saccades for three subjects and both for three subjects. RFEF stimulation increased only ipsilateral latencies for one subject, only contralateral latencies for three subjects and both for three subjects. Despite targeting TMS for each individual subject with frameless stereotaxy and confirming that this location matched published Talairach coordinates for FEF location (Paus, 1996), the authors regarded only those subjects showing contralateral saccade delays as having been successfully targeted with TMS.

In summary, published data proposing contralateral saccade delays as a functional marker for the FEFs seem unreliable. The data reported here instead suggest that TMS over either of the FEFs modulates subjects' baseline spatial biases in saccadic latency and/or duration.

The aim of this chapter was to demonstrate that the areas targeted for TMS throughout this thesis show physiological effects consistent with the frontal eye fields. The imaging data showed good correspondence with the anatomical coordinates over which TMS was applied, validating the anatomical localization protocol. Given the caveats expressed regarding the proposed TMS localizer, the remaining experiments in this thesis used

anatomical landmarks to localize the FEFs for TMS. These were transformed into Talairach space to confirm concordance with the imaging-defined FEFs.

Chapter 4: Timing of Target Discrimination in Human Frontal Eye Fields

Abstract

Neurons in the frontal eye fields (FEFs) discharge in response to behaviourally relevant stimuli that are potential targets for saccades. Distinct perceptual and oculomotor processes have been dissociated in the FEFs of macaque monkeys, but little is known about the perceptual processing capacity of the human FEFs. To test whether the human FEFs make a critical perceptual contribution to visual search performance, two experiments were carried out. In the first, repetitive-pulse transcranial magnetic stimulation (TMS) was applied in three timing windows. This experiment suggested that the earlier the timing of TMS application, the greater the interference effect. In a second experiment, double-pulse TMS was applied to sample discrete windows within the first 200ms of search array processing. Dual TMS pulses separated by 40ms were applied over right FEF and Vertex in five different timing conditions. TMS impaired search performance, reflected in reduced d'. This effect was limited to a time window between 40 and 80ms after search array onset. These timing parameters correspond with single-cell activity in FEF that predicts monkeys' behavioural reports on hit, miss, false alarm and correct rejection trials. The data demonstrate that the human FEFs make a critical early contribution to visual search performance. It is argued that this reflects the operation of target discrimination processes within the FEFs, and that these are distinct from saccade programs.

4.1. Introduction

The frontal eye fields (FEFs), in the rostral arch of the arcuate sulcus in the macaque monkey (BA8/6) (Bruce & Goldberg, 1985b), have an important role in converting the outcome of visual processing into eye movement commands. In classical anatomical models of the hierarchical organisation of cortical visual areas (Maunsell & van Essen, 1983; Felleman & Van Essen, 1991; Young, 1992; DeYoe et al., 1994), the FEFs are situated in the upper reaches of the visual hierarchy, several levels above sensory visual areas. This comports well with the classical segmentation of visual processing into perceptual and motor components, associated with posterior visual and anterior motor/visuomotor cortical areas, respectively (Mesulam, 1981; Posner & Petersen, 1990; Banich et al., 2000a). However, recent findings have challenged the characterization of

FEF function solely in terms of oculomotor control (for reviews see Schall & Bichot, 1998; Schall & Thompson, 1999).

FEF neurons exhibit response latencies in the same range as early sensory visual areas V3, MT and MST, with the earliest responses discharging 35-40ms after visual stimulus onset and the mean response latency being 60-70ms (Nowak & Bullier, 1997; Schmolesky et al., 1998). This early response latency, combined with the discovery of feed-forward connectivity between FEF and V4 suggests that the position of the FEFs within the visual processing hierarchy should be re-defined (Barone et al., 2000). Monkey lesion work has shown that FEF damage induces a visual field defect which can remain evident in raised detection thresholds after oculomotor deficits have recovered (Latto & Cowey, 1971). In addition, single unit data have demonstrated that FEF neurons play a *perceptual* role in visual processing, that is independent of issuing saccade commands (Thompson et al., 1997).

Using feature (Thompson et al., 1996) and conjunction (Bichot et al., 2001aa) search tasks, Schall and colleagues have dissociated two processing operations in FEF: target selection by FEF visual neurons and saccade programming by FEF movement neurons. FEF visual neurons do not respond selectively to particular physical visual attributes (Mohler et al., 1973b; Goldberg & Segraves, 1989). Instead, they respond to behaviourally relevant stimuli, and have been described as computing a saliency map which encodes targets for potential saccades (Schall & Bichot, 1998). The initial visual response (ca. 50ms post-stimulus) is non-selective, but typically within 120-150ms after search array onset the activity of FEF visual neurons distinguishes whether there is a target or a distractor in the receptive field (Bichot et al., 2001bb). Distractor-related activity decreases, while target-related activity is sustained, signalling the spatial location

of the stimulus (Schall, 1995). FEF movement neurons do not respond to visual stimulation, but fire before saccades, signalling whether and when to make a saccade (Hanes & Schall, 1995). Target discrimination occurs independently of saccade programming. The timing of the discrimination process does not predict the variability of saccadic reaction times and target discrimination occurs whether or not monkeys proceed to saccade to the target (eg: Murthy et al., 2001).

In human imaging studies, the FEFs are commonly activated in orienting paradigms whether or not an eye movement is required. In the latter case, this activity is commonly interpreted in terms of the premotor theory of attention (Rizzolatti et al., 1987). FEF activation is attributed to the generation of saccade programs that are not overtly executed, rather than to visual analytic processes in the FEFs (but see Donner et al., 2000). To date, only a small number of studies have directly addressed the perceptual role of the human FEFs independently of eye movements using TMS. These studies have reported roles for the FEFs in contralateral visual stimulus analysis (Blanke et al., 1999), preparatory vision (Grosbras & Paus, 2002, 2003), and target discrimination in conjunction visual search (Muggleton et al., 2003). These studies have argued that the human FEFs engage in perceptual processing that is not reducible to oculomotor commands. This case would be strengthened if it could be shown that the human FEFs make a critical contribution to perceptual processing within a similar time-range to that of sensory visual areas.

The experiments reported in this chapter exploited the temporal resolution of TMS to test the hypothesis that, as in the macaque brain, target discrimination processes occur early in the human FEFs. To de-couple perceptual from oculomotor processes, a conjunction search task was used in which eye movements were not required. Search

arrays were presented briefly enough to ensure subjects could not saccade to elements in the search array and fixation was monitored. A staircase procedure determined array duration for each subject, supporting performance at 75% accuracy. In the first experiment, repetitive-pulse (r)TMS was applied to gather preliminary evidence for an early profile of TMS interference. Based on those results, double-pulse (d)TMS was applied in a second experiment to probe discrete temporal windows throughout the first 200ms of stimulus processing. The effect of TMS on search performance was quantified using a measure of perceptual sensitivity (d').

4.2. Methods

Subjects

Eight subjects (7 male, 1 female) participated in Experiment 1 (mean age = 27.6 + 4.3). Nine subjects (8 male, 1 female) participated in Experiment 2 (mean age = 27.7 + 3.6). Of these, four had participated in Experiment 1. Data from a further four subjects were discarded for reasons given below (see Task Design). All subjects were right-handed and had normal or corrected-to-normal vision. All gave informed written consent and reported an absence of any neurological condition in their known family history. All procedures were approved by the Oxford Research Ethics Committee (OxREC) and the Institute of Neurology, University College London.

Visual Stimuli

Visual search arrays (see Figure 4.1) were displayed on a 16" VDU with 100 Hz vertical refresh rate, controlled by a Pentium 4 (1.7 GHz) microcomputer. E-Prime software (Psychology Software Tools, Pittsburgh) controlled presentation of the search stimuli, triggering of the TMS machine and the eye tracker and also recorded subjects' responses on a keyboard. Subjects sat in a dark room 57cm in front of the screen and were restricted by a forehead and chin rest. Each search array subtended 2 x 2 degrees of visual angle around a central fixation cross. Each array contained 12 stimuli. In Experiment 1, these consisted of luminance-matched (22 cd/m^2) purple vertical (CIE: x = 0.217, y = 0.130) and green horizontal (CIE: x =0.282, y =0.589) lines, each subtending ca. 0.23 degrees of visual angle. The target was a purple horizontal and was present on 50% of trials. In Experiment 2, stimuli were luminance-matched (23.3 cd/m^2) pink (CIE: x = 0.288, y = 0.149) and purple (CIE: x = 0.233, y = 0.203) diagonal lines in opposite orientations. Each line subtended ca. 0.18 degrees of visual angle. The target was a purple diagonal sharing the same orientation as the pink diagonals and was present on 50% of trials. Stimulus colour pairings and orientations were different in the two experiments to avoid potential learning confounds for subjects who had already participated in Experiment 1. The background luminance of both arrays was uniform grey (35.8cd/m^2). In both experiments, the stimulus mask subtended 2 x 2 degrees of visual angle and was composed of patches of the two stimulus colours used in that experiment.

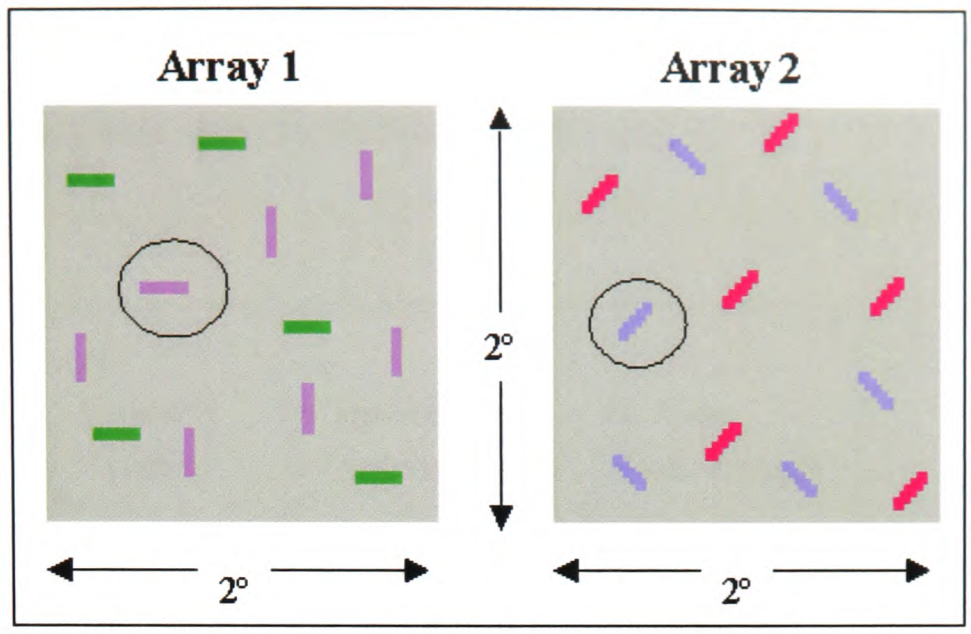


Figure 4.1. Visual Search Arrays. (1) Sample search array of purple vertical and green horizontal lines from Experiment 1. **(2)** Sample search array of pink and purple diagonal lines from Experiment 2. Targets are encircled.

Task Design

The task procedure replicated that used by Muggleton, et al. (2003)(see Figure 4.2(a)). A trial began with a central fixation cross displayed for 500ms, followed by a briefly presented search array, which was then masked until the subject made a response. Subjects had to decide whether the target was present or absent and signalled their decision using a key press. Accuracy was emphasized over speed of response. The inter-trial interval was 2000ms. Stimulus duration was determined for each subject individually, based on a staircase procedure which varied presentation time by one screen refresh (10ms) until subjects performed at a 75% accuracy level. Subjects had to perform exactly six out of 8 trials correctly on two consecutive blocks of eight trials to establish their stimulus thresholds. They then performed a block of 60 trials (Experiment 1) or two blocks of 40 trials (Experiment 2) to determine the validity of this threshold value. When subjects scored $d' > 1.0$, they began formal trials. Performance yielding a d' score greater than or equal to 1.0 indicates reliable perceptual sensitivity (Green & Swets, 1966). If subjects failed to achieve the d' criterion, the stimulus duration was increased by the

experimenter until the criterion was reached. Block order was counterbalanced and all the above procedures were identical in both experiments.

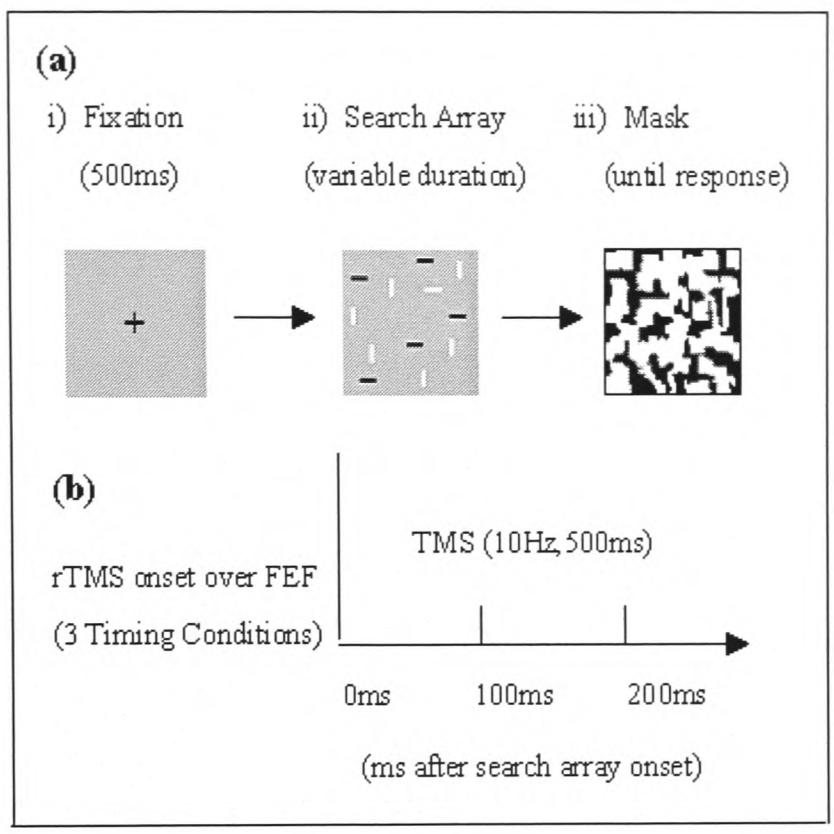


Figure 4.2. (a) Stimuli and Sequence of Events in a Single Trial. A trial began with central fixation (i), followed by the search array, for a duration determined individually for each subject (ii). The array was then masked until the subject signalled whether the target was present or absent (iii). Array is in black and white to represent arrays from either of the two experiments.
(b) Timing of rTMS application in Experiment 1. rTMS (10Hz, 500ms) was applied over the right FEFs in three timing conditions: (1) simultaneous with the onset of the search array (0ms), (2) beginning 100ms after search array onset (100ms), (3) beginning 200ms after search array onset.

In Experiment 1, subjects performed five blocks of 60 trials, one for each TMS condition: Vertex, V5, $FEF_{(0)}$, $FEF_{(100)}$ and $FEF_{(200)}$. In the first three conditions (Vertex, V5 and $FEF_{(0)}$), TMS was applied for 500ms beginning at visual stimulus onset (see Figure 4.2(b)). These data were then analysed to test for a selective effect of frontal eye field TMS on search performance. In the latter two conditions, TMS was applied for 500ms beginning 100ms ($FEF_{(100)}$) or 200ms ($FEF_{(200)}$) after visual stimulus onset. By comparing these two conditions and the $FEF_{(0)}$ condition against Vertex, the aim was to isolate different periods of FEF activity and to test the relative effect of TMS in each

time window: during the first 100ms of visual processing ($FEF_{(0)}$); during visual processing, but after the first 100ms ($FEF_{(100)}$); and after visual processing, when subjects were no longer viewing the search array ($FEF_{(200)}$). Hence, a second analysis compared the data from the three FEF conditions against Vertex to test for an effect of TMS pulse timing.

In Experiment 2, subjects performed two blocks of 40 trials in each of five timing conditions (0/40ms; 40/80ms; 80/120ms; "pre-threshold" and "post-threshold") at each TMS site (Vertex and right FEF). In the first three timing conditions, dual TMS pulses were applied at: 0/40ms; 40/80ms and 80/120ms after stimulus onset; in the last two conditions, dual pulses were applied during the last 40ms below each subject's visual threshold ("pre-threshold") and during the first 40ms above threshold ("post-threshold"). For example, if a subject's threshold was 150ms, dual pulses were applied at 100/140, and at 160/200ms, respectively (Figure 4.3). The 0/40ms and "post-threshold" conditions were chosen as temporal limit controls to bracket the earliest and latest arrivals of retinal input to the FEF: the 0/40ms stimulation precedes the earliest onset latencies of FEF neurons (Schmolesky, et al., 1998), while the "post-threshold" condition allows 40ms after the end of retinal stimulation. Interspersed among these experimental blocks, subjects performed four blocks in which TMS was not applied. If a subject's d' scores on each of these baseline blocks did not exceed 1.0, testing did not continue and the subject was excluded from the experiment. Four subjects were discounted on these grounds.

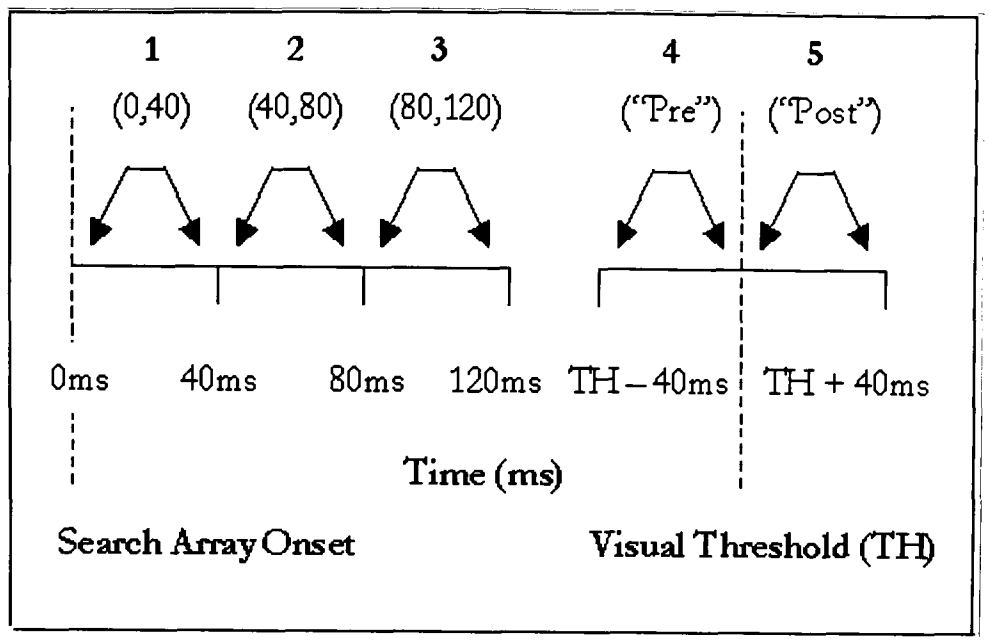


Figure 4.3. Timing of Double-Pulse TMS in Experiment 2. The figure shows the timing of first and second TMS pulses applied in five experimental conditions. The timing of the first three conditions was determined relative to the onset of the search array, and these were identical for each subject. The last two conditions were determined relative to each individual's visual threshold and differed across subjects.

Eye Movement Recording

To detect potential saccades or eye blinks during search trials, fixation was monitored using infrared light transducers in the Skalar IRIS 6500 system attached to the forehead rest. Signals were sampled at a rate of 1000 Hz by an analogue to digital converter card (Type PCM-DAS 16d/12, Computerboards, Pittsburgh) and recorded using DASYlab 5 software on an IBM compatible PC. Eye position traces were recorded for the duration of search array presentation on every trial and the equipment was re-calibrated between blocks.

Cortical site localization

Based on the results of a previously published pilot experiment (Muggleton et al., 2003), which reported RT costs on visual search when TMS was applied over right but not left FEF, right FEF was chosen as the site of an expected TMS effect. Right FEF was localized for TMS using the Brainsight frameless stereotaxy system (Rogue Research, Montreal, Canada). The stimulation site was identified on each subject's T_1-weighted

MRI scan and was then co-registered with scalp coordinates over which TMS was applied. The probabilistic location of each subject's right FEF was determined according to anatomical landmarks. Stimulation was applied over the posterior middle frontal gyrus, just rostral of the junction of the precentral sulcus and the superior frontal sulcus (Blanke et al., 2000). The site of stimulation was also referenced to each subject's motor hand area (Yousry et al., 1997; Ro et al., 1999). Using this method, on average, TMS was applied 5cm lateral of the saggital midline and 3 - 4cm rostral of each subject's motor hand area. This site corresponds well with scalp coordinates used in other TMS studies of FEF (Muri et al., 1991; Leff et al., 2001; Wipfli et al., 2001). After registration of the MRI images to the Montreal Neurological Institute series average (Evans et al., 1996), mean MNI coordinates for the site stimulated were 32, -2, 61 (standard error: 1.34, 6.09, 1.55). These coordinates correspond well with mean Talairach coordinates (Talairach & Tournoux, 1988) for FEF derived from a review of PET imaging studies (Paus, 1996). Vertex was chosen as the principal control site for the non-specific effects of TMS, such as somatosensory and acoustic artefacts. V5 was chosen as an additional control to demonstrate that any effects of frontal eye field TMS on visual search were specific and not a general consequence of interference with the visual system. Vertex stimulation was applied at electrode site "Cz" according to the 10-20 International Electrode System. V5 was functionally localized using the established method of moving phosphene elicitation (Stewart et al., 1999; Battelli et al., 2002).

Transcranial Magnetic Stimulation

A Magstim Super Rapid machine (Magstim Company, Dyfed, U.K.) was used to deliver repetitive- and double-pulse TMS. A small-diameter (50mm) figure-of-eight TMS coil was used to apply stimulation over the cortical sites of interest. Each coil was cooled on ice before use to prevent over-heating during a block and was replaced at the end of each

block. Over FEF and Vertex, the coil was oriented parallel to the floor with the handle running in an anterior-posterior direction and was clamped in position using a mechanical arm. Over V5, the coil was oriented at a right angle with the floor. In the rTMS experiment, 10Hz TMS (500ms) was applied at 65% of stimulator output over Vertex and FEF. Over V5, TMS was applied at 110% of each subject's phosphene threshold (Stewart et al., 2001). In the dTMS experiment, stimulation was applied at 65% of maximum stimulator output. Subjects wore ear plugs to attenuate the sound of the coil discharge (Pascual-Leone et al., 1993).

4.3. Results

Eye Movement Data

Subjects typically made a small saccade on the first trial of each new experimental block, likely to improve the accuracy of fixation. Additional blinks and saccades occurred rarely (total on average = fewer than 3% of trials) and did not differ across conditions in either experiment. Since neither blink nor saccade rates differed between conditions, none of the trials were excluded from the d' analysis (Figure 4.4).

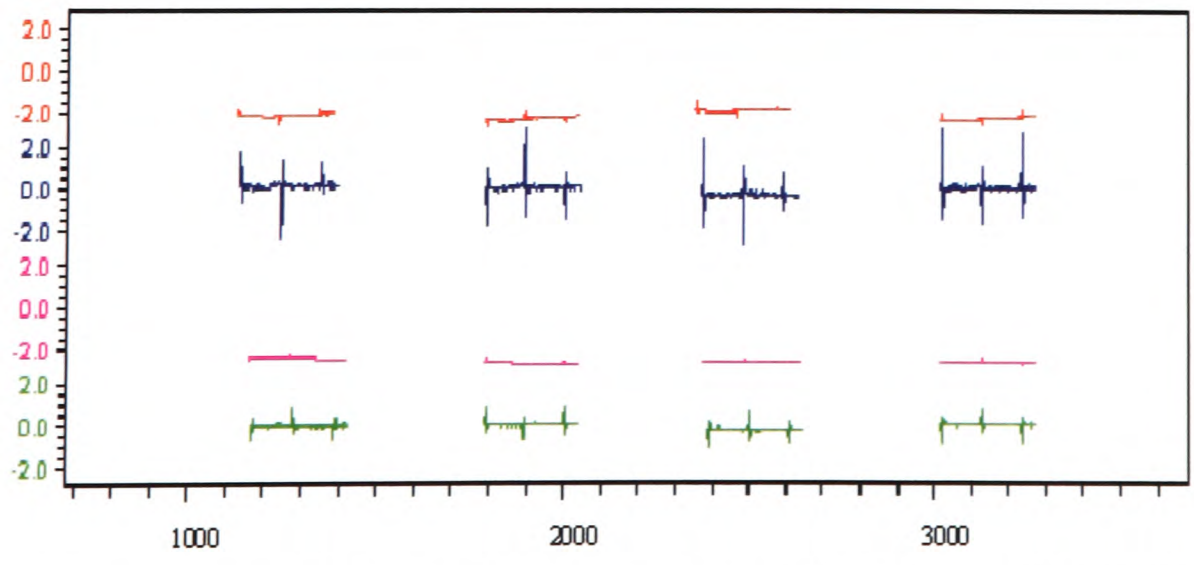


Figure 4.4. Sample eye trace from a single subject. A four-trial sample eye movement recording taken from a single subject. This subject had a visual threshold of 250ms, so TMS artefacts are visible at 0, 100 and 200ms after search array onset on every trial. Time (ms) is represented on the x axis. The inter-trial interval has been reduced for illustrative purposes. The y axis represents eye position and velocity. The upper pair of lines represents the left eye and the lower pair represents the right eye. Velocity information is on top and eye position information is on the bottom for both eye traces.

Experiment 1: Repetitive-Pulse TMS

The d' data for all eight subjects in three of the five experimental conditions (Vertex, V5, $FEF_{(0)}$) were submitted to a one-way repeated measures ANOVA to test whether TMS over the FEF degraded search performance. There was a main effect of TMS Site ($F(2,14) = 5.844$, $p = 0.014$). Planned comparisons revealed a significant difference between Vertex and $FEF_{(0)}$ ($F(1,7) = 7.930$, $p = 0.026$) but no significant difference between the two control sites, Vertex and V5 ($F(1,7) = 1.525$, $p = 0.257$) (Figure 4.5). Subjects' d' scores were degraded on the $FEF_{(0)}$ block relative to the Vertex block (mean $FEF_{(0)} = 1.124$, SE = 0.263; mean Vertex = 1.754, SE = 0.184). Hence, TMS over the right FEF significantly reduced perceptual sensitivity (d'), replicating the findings of Muggleton, et al. (2003). To test whether TMS selectively affected the hit or false alarm rate, the d' scores were decomposed by response type and subjected to a two-way repeated measures ANOVA (TMS Site * Response Type (hits, false alarms)). The interaction was not significant ($F(6,42) = 1.984$, $p = 0.09$). Analysis of subjects' bias scores (C) showed a tendency towards "target absent" responses in all conditions, but TMS had no effect on this response bias ($F(2,14) = 0.512$, $p = 0.610$; mean C values: Vertex = 0.16 (SE = 0.2), $FEF_{(0)} = 0.356$ (SE = 0.183), V5 = 0.417 (SE = 0.132)).

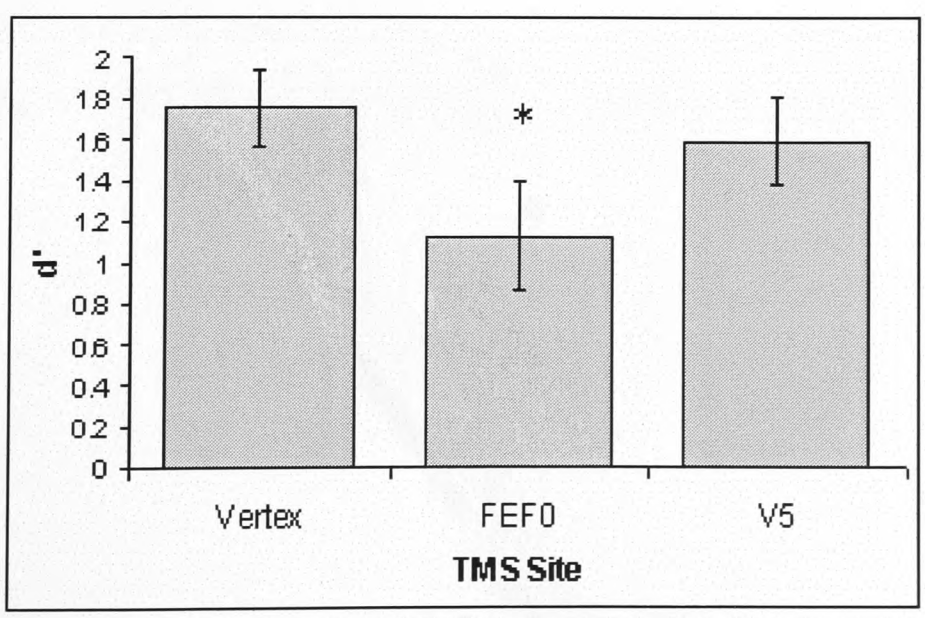


Figure 4.5. Effect of rTMS over right FEF on Search Performance (Experiment 1). Search performance was impaired when TMS was applied over right FEF, but not over V5 or Vertex. TMS significantly reduced d' (* refers to planned comparison with Vertex, $p < 0.05$)(n = 8).

To test the hypothesis that earlier TMS application would produce greater interference effects, d' data from the $FEF_{(0)}$, $FEF_{(100)}$ and $FEF_{(200)}$ conditions were compared against Vertex. The $FEF_{(200)}$ condition was intended as a control: it was expected that all subjects would have visual thresholds below 200ms and so TMS would be applied only after subjects had finished viewing the stimulus. However, two subjects had visual thresholds of 230 and 250ms (mean: 150ms). Hence, unlike all others in the $FEF_{(200)}$ condition, these two subjects received TMS while they were viewing the search array. For this reason, these two subjects were excluded from the timing analysis and only the data from the other six subjects were analysed. A repeated-measures ANOVA showed that there was no main effect of TMS Condition (Vertex, $FEF_{(0)}$, $FEF_{(100)}$ and $FEF_{(200)}$)($F(3,15) = 2.249$, $p = 0.125$). However, planned contrasts comparing each FEF timing condition against Vertex revealed a significant reduction in d' only in the $FEF_{(0)}$ condition: ($F(1,5) = 25.019$, $p = 0.004$) (mean $FEF_{(0)} = 1.152$, SE = 0.238; mean Vertex = 1.585, SE = 0.198). There was a trend in the $FEF_{(100)}$ condition ($F(1,5) = 4.904$, $p = 0.078$), while the $FEF_{(200)}$ condition did not approach significance ($F(1,5) = 1.513$, $p = 0.273$). These results suggest that the earlier that TMS was applied, the greater was the effect on d'. Inspection of the graphs (see Figure 4.6) supports this impression. Analysis of subjects' bias scores (C) showed a tendency towards "target absent" responses in all conditions. TMS did not affect this response bias ($F(3,15) = 2.017$, $p = 0.215$; mean C values: Vertex = 0.376 (SE = 0.125), $FEF_{(0)}$ = 0.278 (SE = 0.199), $FEF_{(100)}$ = 0.296 (SE = .138), $FEF_{(200)}$ = 0.176 (SE = .214)).

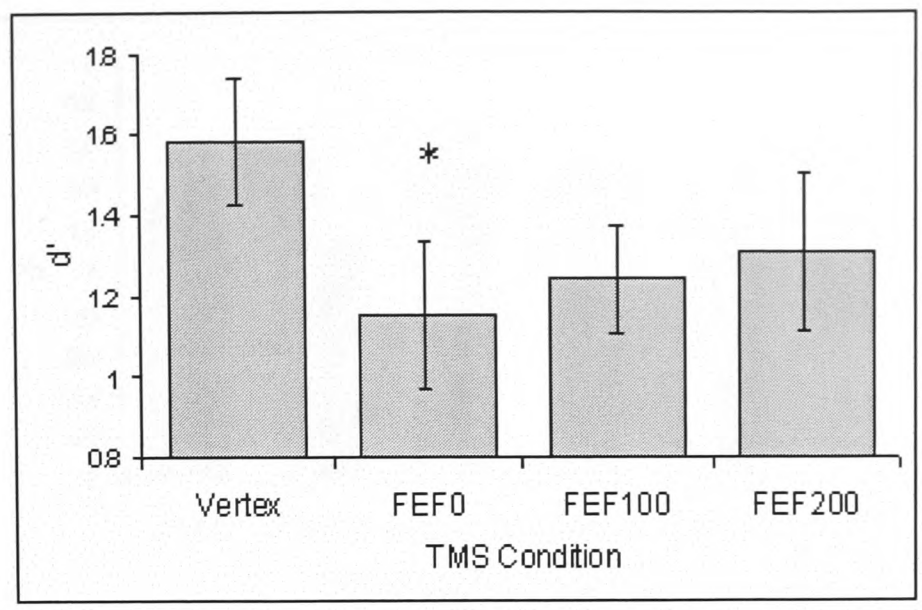


Figure 4.6. Effect of rTMS Timing over the right FEFs. Search performance (d') was impaired when TMS was applied over right FEF simultaneous with the onset of the search array (* refers to planned comparison with Vertex, $p < 0.05$) ($n = 6$).

Experiment 2: Double-Pulse TMS

The results of Experiment 1 suggested that the earlier the timing of frontal eye field TMS, the greater the disruption of search performance. Based on this, Experiment 2 was designed to sample discrete sub-sets of the first 200ms of stimulus processing. All nine subjects' d' data were subjected to a MANOVA analysis to test whether TMS over the FEF differed significantly from control TMS (Vertex) in any of the five timing conditions (0/40, 40/80, 80/120, 'Pre-Threshold', 'Post-Threshold'). There was a significant effect in the 40/80ms condition only ($F(1,16) = 4.762$, $p = 0.044$). TMS applied over FEF at 40/80ms significantly reduced subjects' perceptual sensitivity (FEF 40/80 mean d' = 1.132, SE = 0.133; Vertex 40/80 mean d' = 1.543, SE = 0.133) (Figure 4.7). A follow-up MANOVA on trials classified as hits, misses, false alarms and correct rejections revealed no significant effects. Analysis of C bias measures showed that subjects had a baseline tendency towards "target absent" responses. TMS had no effect on this response bias.

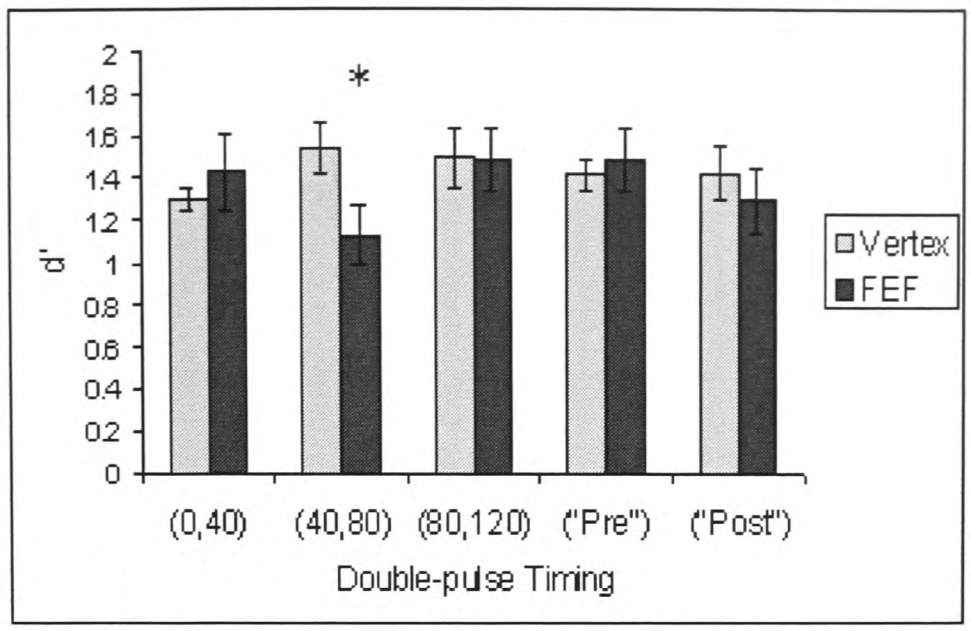


Figure 4.7. Effect of rTMS Timing over the right FEFs. Search performance (d') was impaired when TMS was applied over right FEF simultaneous with the onset of the search array (* refers to planned comparison with Vertex, $p < 0.05$) ($n = 6$).

4.4. Discussion

The aim of the experiments reported in this chapter was to test whether the human FEFs make a critical early contribution to visual search performance. In Experiment 1, repetitive-pulse TMS applied over the right FEF degraded subjects' perceptual sensitivity (d'), compared to control stimulation over Vertex or V5. Perceptual processing was de-coupled from saccade programming by using brief displays to prevent saccades and by monitoring fixation. The finding of reduced stimulus discriminability in the absence of measurable eye movements indicates that the human FEFs are critical for normal conjunction search performance when eye movements are not required. These data replicate the findings of Muggleton, et al (2003). Experiment 1 further suggested that the earlier the timing of TMS application, the greater the disruptive effect. Using double-pulse TMS, Experiment 2 isolated this disruptive effect of TMS to a short time window within 40-80ms after search array onset. This temporal profile of interference coincides with neurophysiological data. In a visual detection study using backward masking,

Thompson & Schall (1999) showed that, after the initial non-selective visual response, small differences in the amplitude of signal in FEF neurons during the period of sustained signal build-up predicted monkeys' subsequent perceptual reports on hit, miss, false alarm and correct rejection trials. The early and discrete effect of TMS suggests that TMS disrupted target discrimination processes within the FEF rather than saccade programming.

Under normal circumstances, visual scenes are inspected by cycles of stimulus fixation and analysis, followed by saccades that direct gaze to subsequent targets in the visual scene. Minimum estimates of the time required to perform these operations suggest that perceptual processing requires approximately 100ms (Salthouse et al., 1981), while saccade programming requires 100-150ms (Lisberger et al., 1975; Becker & Jurgens, 1979). The contention that early TMS interference reflects disruption of target discrimination, rather than saccade programming, seems to imply that there are temporally discrete stages of perceptual and oculomotor processing. However, there is evidence that perceptual processing and saccade programming proceed in parallel (McPeek & Keller, 2002b; McPeek et al., 2003). Moreover, it has been shown that FEF movement-related neurons are modulated by visual stimulus properties, suggesting a model of continuous information transfer between FEF visual and motor neurons (Gold & Shadlen, 2000; Bichot et al., 2001ab). Accordingly, disruption of visual analytic processes in FEF should produce a concomitant build-up of error in the signal that shapes the oculomotor response. Hence, despite the absence of measurable eye movements in these experiments, it could be argued that the TMS effects stem from disruption of *latent* saccade programming.

In the rTMS experiment, TMS over FEF reduced d'. Planned comparisons showed that this effect was significant in the $FEF_{(0)}$ condition only. This effect was attributed to disruption of target discrimination processes in FEF occurring during the first 100ms. However, in the $FEF_{(0)}$ condition, TMS was applied continuously throughout a 500ms period, such that the effect may have reflected disruption of *both* perceptual and oculomotor response preparation activity in the FEFs. It is beyond the scope of the rTMS design (Experiment 1) to evaluate this possibility. By contrast, the double-pulse design (Experiment 2) showed a discrete effect of TMS that corresponds with target discrimination processes in macaque FEF. The effective time of dTMS interference was early (40-80ms), about 100ms earlier than the mean visual threshold (178ms). Since the effect of a TMS pulse on neural firing is immediate, if the effects were due to disruption of latent saccade programs then one would expect interference to occur later, closer to the time of saccade evolution (eg: in the 80/120 or 120/160 time bin). Significantly, however, there was no effect of dTMS in any of the later time bins. Moreover, although it is clear that disrupting visual discrimination should affect saccade programming, it is difficult to explain how disrupting saccade programming should affect visual discrimination (d'). In light of this, the argument that TMS disrupted target discrimination is more parsimonious than an account based on latent saccade programs.

Although the timing of interference is close to the timing data reported for FEF single units, the correspondence is not exact. Typically, target discrimination in FEF neurons evolves within 120-150ms after onset of the visual search array (Thompson et al., 1996). Further, the timing of target discrimination has been shown to occur later as task difficulty is increased (eg: Sato et al., 2001). Hence, target discrimination tends to occur earlier during feature than conjunction search (Bichot et al., 2001ab). The combination of a conjunction search paradigm and an early disruptive effect thus seems to pose an

interpretative problem. The following observations are offered in an attempt to address this. First, Bichot, et. al (2001b, Figure 2, page 716) provided evidence that FEF neurons can exhibit target discrimination activity during conjunction search that is as early as that typically recorded during feature search. Second, it is important to note that the search paradigms used in the work on monkeys and in this TMS study were different. The present search displays were foveal, whereas the monkey displays were peripheral, a factor which might contribute to the early timing of the present effect. Third, the repetition of the same target/distractor combination likely induced feature priming across the ten blocks of eighty trials in the present experiment (Maljkovic & Nakayama, 1994). Such priming has been shown to produce earlier target discrimination peaks in the monkey FEFs (Bichot & Schall, 2002). Finally, species differences, including brain sizes, should not be dismissed in considering the lack of precise concordance between the timing of TMS interference and the timings reported for the monkey FEFs.

Based on the close temporal correspondence between the present TMS results and single-unit data (Nowak & Bullier, 1997; Thompson & Schall, 1999; for a discussion of TMS and single-unit timing correspondence see Walsh & Pascual-Leone, 2003), I have argued that the TMS effects reflect disruption of target discrimination processes computed within the FEFs. However, since FEF neurons are not colour-selective (Mohler et al., 1973b), the target selection process manifested in FEF is likely to to be closely related to selection processes observed in extrastriate areas such as V4 (Chelazzi et al., 1993; Luck et al., 1997; Schall, 2002). FEF sends extensive feedback projections to extrastriate cortex (Schall et al., 1995b; Stanton et al., 1995), and has been proposed to exert "top-down control" on these areas, such as modulating the gain of visually driven signals (Moore & Fallah, 2001; Moore & Armstrong, 2003). Feedback mechanisms are often proposed to explain effects that are delayed in time relative to the response onset

of the cell (eg: Lamme, 1995). However, a number of studies have shown that feedback connections are matched in conduction speed to feedforward connections (Nowak & Bullier, 1997; Girard et al., 2001b; Hupe et al., 2001), consistent with the notion that feedback modulation by FEF may occur simultaneous with feedforward driving input. Hence, it could be argued that the early timing of the TMS effect does not arbitrate between a feedforward (VanRullen & Koch, 2003) or feedback (Bullier, 2001b) interpretation. Based on neurophysiological data, I have argued that TMS disrupts the activation state of FEF neurons during the earliest period of the initial visual response, and that this disrupts target/distractor discrimination by altering FEF activity during the period when the first influx of feature information into the FEFs enters from extrastriate cortex. A competing account in terms of an early feedback signal would need to specify what the functional role of such a signal might be. Bullier (2001) has argued that rapidly activated visual areas (such as FEF, MT, MST) might perform a first-pass, global 'gist' interpretation of a visual scene, and might then feed this information back to slower-responding extrastriate areas receiving parvocellular inputs, such that more detailed visual analysis is guided by this global interpretation. In the context of the current study, it is not clear how such a coarse signal could facilitate performance on a task that depends on fine-grained colour and shape discrimination in a small, cluttered display. It seems more plausible to argue that the FEFs may send 'top-down' signals to extrastriate cortex in the post-selection period, after discrimination has occurred, when a target location signal would be available to facilitate detailed visual analysis such as target 'feature checking' at that location (Thompson & Schall, 2000).

The computational role of human FEF in vision remains to be established. Current functional sketches ascribe roles for FEF in covert orienting, visual search, saliency map formation and oculomotor responses (Schall & Thompson, 1999; Corbetta & Shulman,

2002). Similar functions have been ascribed to posterior parietal cortex (PPC) (Colby & Goldberg, 1999; Andersen & Buneo, 2002). FEF and PPC share strong reciprocal interconnections (Cavada & Goldman-Rakic, 1989) and are both consistently activated nodes in the fronto-parietal networks associated with these functions (eg: Donner et al., 2002). Despite these similar profiles, human imaging data are most commonly interpreted in terms of relative specialization of FEF for overt motor-exploratory and PPC for the perceptual-representational aspects of attentional tasks (Mesulam, 1981; Gitelman et al., 1999). A widely held view is that PPC neurons perform feature binding that enables target selection in conjunction search (Treisman, 1996). PPC damage is believed to impair binding mechanisms, causing patients to report illusory conjunctions - a kind of error in which features of distinct stimuli are reported as features of a single stimulus (Arguin et al., 1994; Friedman-Hill et al., 1995). However, other work has shown that the PPC also plays a role on trials in which there is no target present to bind (Ashbridge et al., 1997), and that it is not necessary when subjects have some degree of familiarity with the task (Walsh et al., 1998a). A previous timing study applying single TMS pulses over the angular gyrus during search found that TMS interference times were yoked to subjects' response times: reaction time costs were induced 100ms after array onset on target present trials and at 160ms on target absent trials (Ashbridge et al., 1997). Taken together, these results suggest that the critical contribution of the FEFs to search performance may occur earlier than that of the PPC. However, since the search paradigms used in the two experiments were not identical, caution is necessary. In summary, the present findings emphasize the need for future work to distinguish the relative contributions of the FEF and PPC to visual target selection.

CHAPTER 5: Human Frontal Eye Fields and Learning in Visual Search

Abstract

Most everyday searches are for familiar objects in familiar environments. Despite this, neurocognitive models of search behaviour are largely derived from performance on novel, unpractised laboratory search tasks. As experience can induce significant changes in neural activity, it is important to establish how search networks change as a function of expertise. This chapter presents a TMS study designed to test whether the frontal eye fields remain critical for search performance as expertise develops. Two groups of subjects were tested for TMS effects before and after training on one of two search arrays. After training, they transferred to the opposite array and were re-tested with TMS. For one of the subject groups, the results replicated the findings of previous work on the angular gyrus (Walsh et al., 1998a), suggesting that the FEFs no longer make a critical contribution to well-practised search. The second group showed a different pattern of results: TMS over the FEFs disrupted performance in the case of both novel and expert search. This unexpected pattern of results is proposed to result from the greater perceptual difficulty of discriminating left-right versus up-down inverted stimuli. The data suggest a new hypothesis: that the FEFs make a critical contribution to left-right mirror image discrimination.

5.1. Introduction

Inefficient visual search can become efficient with practice. In both feature (Sireteanu & Rettenbach, 1995) and conjunction (Ellison & Walsh, 1998) domains, learning improves target detectability and reduces the reaction time cost of distractors: the target "pops out" and search slopes become flat. The specificity of training benefits has been proposed as an indirect behavioural marker of the neural level at which plastic change occurs (Ahissar & Hochstein, 1997). If, for a given task, learning is supported by changes in neurons with small receptive fields, then training benefits will remain specific to the features for which those neurons are tuned. If neurons with larger receptive fields are implicated, then performance improvements may transfer across stimulus changes in orientation, size or position. Most studies of relatively low-level detection and discrimination tasks, like vernier acuity (Saarinen & Levi, 1995), texture (Karni & Sagi, 1993) and spatial frequency discrimination (Fiorentini & Berardi, 1981), have concluded

that perceptual learning is highly specific (eg: Fahle, 1994). Accordingly, sensory visual areas have been implicated as the chief substrates of change (Fahle & Skrandies, 1994; Gilbert et al., 2000). This interpretation has received more direct support from neuroimaging (Schwartz et al., 2002), electro-physiological (Skrandies & Fahle, 1994) and neuro-physiological studies (Li et al., 2004).

The usefulness of specificity to diagnose search plasticity is less clear. Specificities have been demonstrated for orientation, size and position (Treisman, 1992; Treisman et al., 1992; Ahissar & Hochstein, 1993, 1996; Campana & Casco, 2003), but others have shown task-specific (Ellison & Walsh, 1998) or entirely non-specific transfer of search learning to new arrays and stimulus locations (Sireteanu & Rettenbach, 2000), and from the trained to the untrained eye (Sireteanu & Rettenbach, 1995; Schoups & Orban, 1996). Lobley & Walsh (1998), for instance, reported transfer from one colour/orientation conjunction task to another when either the colour or orientation remained constant across tasks. Learning did not transfer when both features were changed, but performance was intermediate between pre- and post-training levels, suggesting some transfer of task-specific skill. This lack of consensus is perhaps unsurprising. Visual search is a relatively complex task, engaging many computations and cortical areas. As such, training is likely to have different effects throughout the network, rendering transfer specificity too crude an inference tool.

On a cellular level, training may sharpen the tuning curves of behaviourally relevant neurons, such that they fire faster, with higher gain and more selectively (eg: Zohary et al., 1994). Receptive fields may increase in size (Gilbert & Wiesel, 1992) or change position (Pons et al., 1991). Learning might also improve population coding efficiency by reducing the number of neurons that discharge to an effective stimulus; alternatively, it

could increase the cortical resources devoted to a task (Recanzone et al., 1993). Strengthening of effective connectivity between different cortical circuits has been documented as a function of learning (Buchel et al., 1999; Toni et al., 2002). Another possibility is that training could change the composition of the network, such that computations required for inefficient search performance are no longer necessary for expert search (Walsh et al., 1998a). Computationally, training might improve search performance by reducing external noise (Dosher & Lu, 2000), enhancing sensitivity to targets (Gold et al., 1999), or strengthening stimulus-response associations (Ellison et al., 2003).

Most neural studies have cast search efficiency in terms of target type, exploring how network configurations differ between feature (efficient) versus conjunction (inefficient) search (eg: Leonards et al., 2003). Differential activations by target type have been uncovered (eg: Donner et al., 2000), but most fMRI studies have shown substantial overlap in feature and conjunction search networks (eg: Corbetta et al., 1995; Leonards et al., 2000; Nobre et al., 2003). Despite this, TMS (Ashbridge et al., 1997; Muggleton et al., 2003) and neuropsychological data (Eglin et al., 1991; Arguin et al., 1994; Friedman-Hill et al., 1995) imply functional inequivalence, since the same nodes (angular gyrus, FEFs) have been shown to be task-critical for conjunction but not feature search.

Evidence for a continuum of search slopes that cuts across the putative feature vs. conjunction dichotomy suggests that task difficulty (search slope in ms/item) is orthogonal to target type (Wolfe et al., 1989; Verghese & Nakayama, 1994). By comparing difficulty-matched feature versus conjunction search (Donner et al., 2002), overlapping fMRI activations have been found in parietal cortex and the FEFs. The FEFs and IPTO (intra-parietal transverse occipital) junction were modulated by both

efficiency and target type, showing higher signal amplitude for conjunction and difficult (conjunction or feature) search. The anterior intra-parietal sulcus showed greater activation for feature search, whilst the posterior intra-parietal sulcus showed an effect of efficiency only. Another study that manipulated target type and task difficulty independently (Nobre et al., 2003) replicated the efficiency effect in the intra-parietal sulcus together with the superior parietal lobule, and a conjunction analysis showed tight correspondence between these activations and the slope of the reaction time search function. Parietal modulations have also been replicated when efficiency was manipulated by varying distractor similarity (eg: Wilkinson et al., 2002). There are fewer published data on efficiency effects in the FEFs. Both Leonards, et al. (2000) and Donner, et al. (2002) reported bilateral FEF activations modulated by search efficiency. Nobre, et al. (2003) replicated this, and showed that the magnitude of these activations correlated with the intercept (but not slope) of the reaction time search function. Two of these studies (Leonards et al., 2000; Nobre et al., 2003) further suggested a right hemisphere dominance in efficiency-driven FEF activations. In combination, these data suggest the hypothesis that as inefficient search becomes efficient with training, the FEFs may no longer make a critical contribution to performance.

Despite factor analytic techniques designed to measure efficiency and target type effects independently, all of these imaging studies are limited by having combined both factors during stimulus processing. To my knowledge, only one neural study has avoided stimulus confounds by keeping the search array constant throughout training-induced changes in processing efficiency. Walsh, et al. (1998) applied TMS over the right angular gyrus, which increased reaction times on a conjunction search task. Subjects then trained on the task until their initially steep search slopes became flat (criterion: < 10ms/per item). Once trained, TMS no longer disrupted performance. When subjects transferred

to a new conjunction array (eliciting inefficient search), the TMS effect re-appeared, demonstrating the specificity of both the training and the interference effect. The authors concluded that whilst the angular gyrus was critical for a novel conjunction (inefficient) search, its contribution was no longer required once a search task had been learned.

The authors argued that the role of the angular gyrus was to form new associations between search targets and the requisite motor response (Ellison et al., 2003). While this association is being learned, TMS disrupts performance, whereas training removes this susceptibility. They also considered that training could strengthen visual representations in infero-temporal (IT) cortex, causing conjunction targets that were previously difficult to detect to "pop out". Consistent with this, evidence suggests that some neurons in TEO and caudal TE are selective for conjunctions of elementary features such as colour and shape (Tanaka et al., 1991; Komatsu & Ideura, 1993). The two scenarios likely co-occur. The developing target-response association in parietal cortex may help bias relevant feature representations in extrastriate cortex, which input then modifies salience maps of behavioural relevance in FEF and elsewhere.

Single-unit studies have shown that perceptual learning does indeed modify salience representations in the FEFs (as well as in V4 (Ghose et al., 2002) and IT (Jagadeesh et al., 2001)). Bichot & Schall (1996) trained monkeys on a feature search task in which the target/distractor colours remained constant across trials. Extended task practice dramatically altered the target discrimination profile computed by FEF visual neurons. In half of these neurons, training abolished the normal pattern of target/distractor discriminative signal build-up such that the neurons' *initial* visual response selected the trained target colour. This acquired colour selectivity correlated with monkeys' behaviour on transfer to a new array in which target/distractor colours were inverted. Instead of

selecting the odd-coloured target, the monkeys shifted their gaze to distractors of the trained target colour. Similar experience-induced colour selectivity was observed during conjunction search (Bichot & Schall, 1999a) (and has also been reported in LIP neurons using a non-search paradigm (Assad, 2003)). In Bichot & Schall's study, a new conjunction search target was presented at each daily training session and remained constant throughout. Distractors varied according to whether or not they shared the colour or shape of the target from the previous day's training session. Significantly more errant saccades were made to distractors that did share prior target features. There was a significant correlation between these errors and the amplitude of distractor signals in visual FEF neurons: the amplitude of distractor activity in the post-discrimination phase was enhanced for distractors that shared features with the previous day's target. In a feature search paradigm, this "long-term priming" of (previous target) distractors has also been shown to influence FEF movement-related neurons (Bichot et al., 2001a). On correct trials, when a (prior target) distractor fell in an FEF neuron's movement field, that neuron's pre-saccadic response was enhanced, even though a saccade was not executed into its movement field. Thus search learning has been shown to affect both the perceptual and motor components of FEF function, although Schall and colleagues have argued that these are dissociable. With respect to search efficiency, changes in the timing of the FEF target discrimination peak have been shown to correlate with improved selection behaviour (Sato & Schall, 2003). The effect of search efficiency seems to be to decrease the duration and increase the slope of visual discriminative signal build-up in the FEFs.

The major aim of this chapter was to use a similar TMS protocol to Walsh, et al. (1998) to investigate the effect of training on the FEFs during search. The combined data from fMRI and single unit studies predicts the same pattern of TMS effects for the FEFs as

that found for the angular gyrus. If human FEFs compute a target discrimination function, then one might expect training to abolish discriminative signal build-up, as it does in the monkey. If (as argued in Chapter 4), TMS interferes with this signal build-up, then once abolished by training, TMS over the FEFs should no longer disrupt search. To test this, two conjunction search arrays were presented in a similar behavioural paradigm to that used in Chapter 4 (see Figure 5.1). Half the subjects trained on Array 1 and transferred to Array 2; half did the reverse. A thresholding algorithm was used to determine array duration for each subject individually, in order to maintain subjects at a comparable level of performance across the tasks and stages in the experiment. Repetitive-pulse (r)TMS was applied over the right and left frontal eye fields (FEFs) before and after training, and during transfer to the untrained search array. The hypothesis was that the initial effect of right FEF TMS on search performance would be abolished by task learning, but would re-emerge when subjects transferred to a new search array on which they had not trained.

5.2. Methods

Subjects

Twelve subjects (3 female) participated in the experiment (mean age = 27.8 $\pm$ 3.4). A further eight subjects were excluded for reasons given below (see Task Design – Exclusion Criteria). All subjects were right-handed and had normal or corrected-to-normal vision. All gave informed written consent and completed a TMS screening questionnaire. All reported an absence of any neurological condition in their known family history. All procedures were approved by the Oxford Research Ethics Committee (OxREC) and the Institute of Neurology, University College London.

Visual Stimuli

Two visual search arrays (see Figure 5.1), each containing 12 stimuli, were used to test the effect of TMS on search. Search efficiency was assessed by using the same stimuli in arrays of three different set sizes (4, 8 and 12 stimuli). Search Array 1 consisted of luminance-matched (48 cd/m^2) green rightward-facing (CIE: x = .299, y = .591) and orange leftward-facing (CIE: x = .612, y = .350) square letter Cs. The target was always a green left-facing C. Each stimulus subtended 0.18 degrees of visual angle vertically and horizontally. Search Array 2 consisted of luminance-matched (51 cd/m^2) blue upright Vs (CIE: x = .205, y = .292) and pink inverted Vs (CIE: x =.300, y =.160). The target was always a blue inverted V. Each stimulus subtended 0.18 degrees of visual angle vertically and horizontally. Each search array subtended 2 x 2 degrees of visual angle around a central fixation cross and the target was present on 50% of trials. The search array was divided into 36 equally-sized boxes which were not visible, forming a 6 x 6 virtual grid. The twelve search stimuli were pseudo-randomly located within this grid on a trial-by-trial basis by the experimental program, written using E-Prime software (Psychology Software Tools, Pittsburgh). The luminance of the background was uniform grey (x = .295, y = .330; 35 cd/m^2). The stimulus mask (2 x 2 degrees) was composed of patches of the stimulus colour pair used in that search array. The search arrays were displayed on a 16" VDU with 100 Hz vertical refresh rate, controlled by a Pentium 4 (1.7 GHz) microcomputer. E-Prime software controlled presentation of the search stimuli and triggering of the TMS machine and also recorded subjects' responses on a keyboard. Subjects sat in a dimly lit room 57cm in front of the screen and were restrained by a forehead and chin rest.

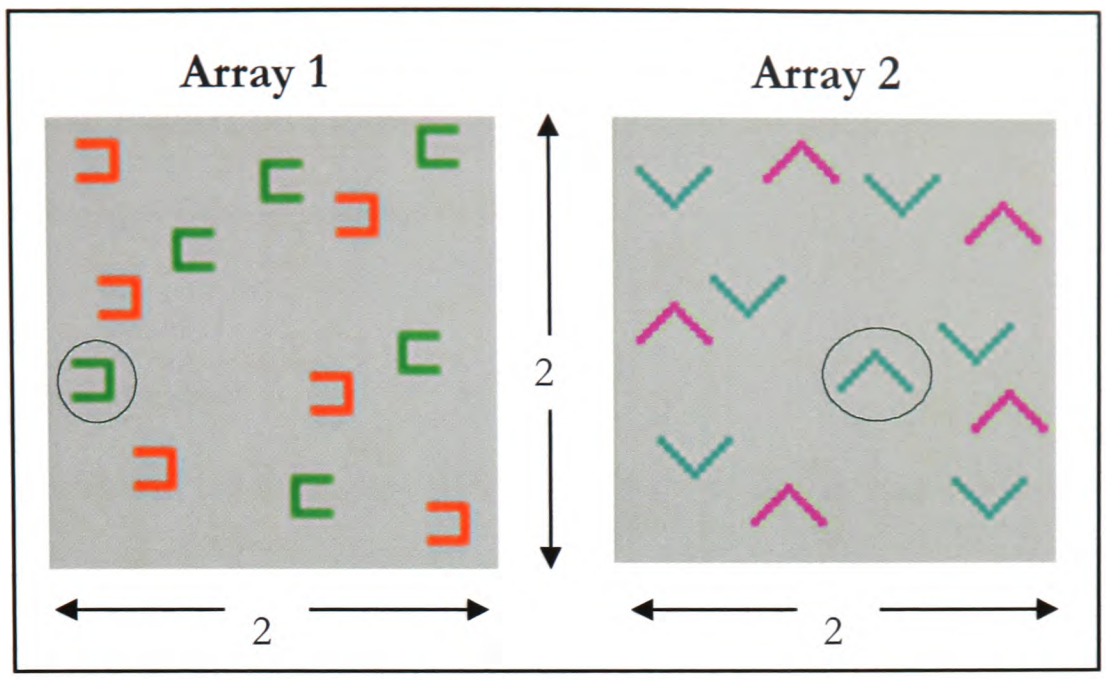


Figure 5.1. The Two Visual Search Arrays. (1) Array of right-facing and left-facing square "C" stimuli. The target was always a green left-facing C. (2) Array of upright and inverted Vs. The target was always a blue inverted V. Targets are encircled. Arrays were 2 X 2 degrees of visual angle.

Task Design

Baseline Search Behaviour:

To assess baseline search efficiency, subjects performed 120 trials of each search array with set sizes of 4, 8 and 12 stimuli (40 trials per set size). The arrays were not masked and reaction times from speeded manual present/absent responses were analysed. Subjects whose "target present" slope for each array exceeded 10ms/item proceeded to the main experiment. This slope criterion was chosen as the lower bound for searches described as "difficult" (or "conjunction" or "serial"), primarily to maintain consistency with a number of previous studies (for a discussion of issues in setting this criterion see Lobley & Walsh, 1998, pg. 1247; Wolfe, 1998).

Stage One – Pre Training:

Subjects then performed the main experiment (see Procedure) in which they were tested for an effect of TMS over FEF on search. Subjects were randomly assigned such that

half were tested on array 1 (Group A) and half on array 2 (Group B) (see Figure 5.2). Only those subjects who showed an effect of TMS on search performance progressed to the next stage of the experiment.

Stage Two - Training:

Subjects trained for three days (1000 trials/session) on the search array (1 or 2) tested in Stage One. Their slopes were then re-tested. If a subject's slope on target present trials was 10ms/item or lower, s/he proceeded to Stage Three. Otherwise, subjects carried out additional days of training until they reached criterion. Two out of six subjects in Group B (Array 2) had reached criterion after three days of training. The remaining four subjects needed five training sessions. In Group A (Array 1), three out of six subjects needed six training sessions, while the remaining three subjects needed five.

Stage Three – Post Training:

Subjects were then tested as in Stage One to see whether TMS disrupted search of the trained array.

Stage Four - Transfer:

Subjects then transferred to the array on which they had not trained. Slopes were re-tested to assess whether training benefits had transferred to the second array. Subjects were then tested for an effect of TMS on the transfer array, exactly as in Stages One and Three.

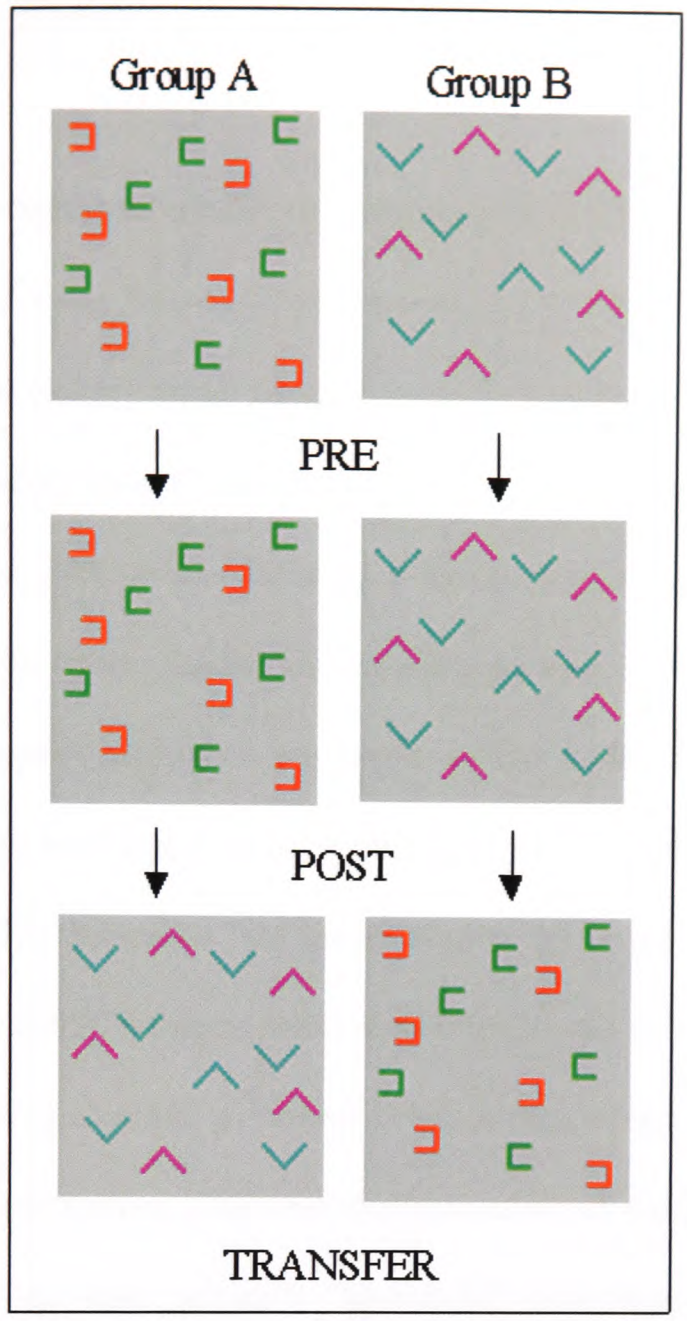


Figure 5.2. Experimental Design. Half of the subjects (Group A) were tested with TMS on Array 1 and half (Group B) on Array 2 at the pre-training stage. Each group then trained on that array for five days and were re-tested with TMS post-training. They then transferred to the array on which they had not trained and were tested with TMS again.

Exclusion Criteria:

Two subjects were excluded at the outset for having search slopes below criterion (<10ms/item) on at least one of the arrays. Four subjects were excluded for not showing an effect of TMS in Stage One. Two subjects were excluded for being unable to maintain performance above criterion (d' > 1.0) on the baseline blocks during Stage One (see Procedure).

Procedure

The behavioural paradigm was similar to that reported in Chapter One (see Figure 5.3). A trial began with a central fixation cross presented for 500ms, followed by the search array, which was then masked until the subject made a response. Subjects made manual keyboard "target present/absent" responses. Accuracy was emphasized over speed. The inter-trial interval was 2000 msec. Stimulus duration was determined for each subject individually, using a Bayesian adaptive thresholding procedure devised by Kontsevich & Tyler (1999). The adaptive algorithm was implemented using the E-Basic programming language (Psychology Software Tools, Pittsburgh). Using this procedure, threshold estimation within 23% precision has been shown to require fewer than 30 trials (Kontsevich & Tyler, 1999). Subjects performed three blocks of 40 trials of the threshold procedure. They then performed a 40-trial block at the lowest of the three threshold estimates to check their d' score. The array duration at which subjects scored d' > 1.0 but < 2.0, was chosen as that subject's "threshold" and was used throughout the experimental blocks. Performance yielding a d' score greater than or equal to 1.0 indicates reliable perceptual sensitivity (Green & Swets, 1966). Block order was counterbalanced within and across subjects. Subjects performed two blocks of 40 trials in each of four TMS conditions: TMS over right FEF, TMS over left FEF, right sham FEF and left sham FEF. If a subject's d' score on each of the baseline (sham) blocks did not exceed 1.0, testing did not continue and the subject was excluded from the experiment.

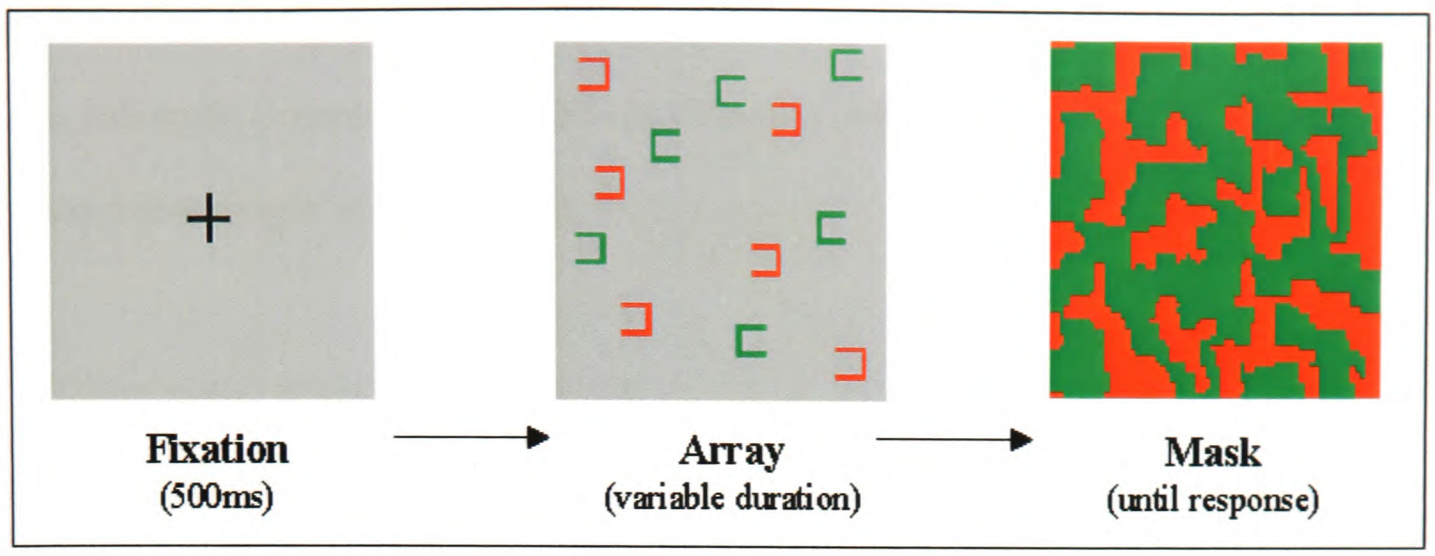


Figure 5.3. Time-course of an experimental trial. Each trial began with central fixation for 500ms, followed by the search array. Array duration was determined for each individual subject using a thresholding algorithm. Arrays were masked until the subject responded. The inter-trial interval was 2 seconds.

Eye Movement Recording

To monitor fixation and blinks during search trials, horizontal eye movements were recorded using infrared light transducers in the Skalar IRIS 6500 system attached to the forehead rest. Signals were sampled at a rate of 1000 Hz by an analogue to digital converter card (Type PCM-DAS 16d/12, Computerboards, Pittsburgh) and recorded using DASYlab 5 software on an IBM compatible PC. Eye traces were recorded for the duration of the visual stimulus and the equipment was re-calibrated between blocks.

Cortical site localization

The right and left FEFs were targeted for TMS using the Brainsight frameless stereotaxy system (Rogue Research, Montreal, Canada) and anatomical landmarks as described in Chapter 3. The anatomical coordinates were transformed into MNI space (Montreal Neurological Institute 152-mean brain T1 template) to check correspondence with published mean and range coordinates for FEF location. Mean FEF MNI coordinates for the twelve subjects in this study were: $x = 24$, $y = 0$, $z = 61$, which corresponds well with published FEF coordinates from imaging studies (Paus, 1996). Five of the subjects

in this study (3 from Group A, 2 from Group B) participated in the fMRI FEF localizer experiment reported in Chapter 3.

Transcranial Magnetic Stimulation

A Magstim Super Rapid machine (Magstim Company, Dyfed, U.K.) was used to deliver repetitive-pulse TMS through a small diameter (50mm) figure-of-eight TMS coil. Each coil was replaced at the end of a block and was air-cooled to prevent over-heating. In the FEF conditions, the coil handle was oriented parallel to the floor, resulting in an anterior-posterior direction of induced current flow. During the sham blocks, the coil was placed over the FEFs but oriented perpendicular to the floor, such that the magnetic field was orthogonal to the subjects' skull. 10Hz TMS (500ms) was applied at 65% of stimulator output.

5.3. Results

Behavioural Data:

1. Search Slopes

All subjects underwent behavioural testing to measure their slopes on both search arrays at the start of the experiment. Search slopes were calculated for every subject based on raw median RTs. Subjects were then randomly assigned to Group A (Array 1) or Group B (Array 2). To test whether there was any initial difference in slope between the groups or the arrays, a mixed model ANOVA (Group (A/B) * Array (1/2) * Target (Present/Absent)) was carried out on the means of the median search slopes (see Figure 5.4). There was an effect of Target Present/Absent ($F(1,10) = 6.992$, $p = 0.025$), with

mean target absent slopes being higher than present slopes (mean difference: 12.25, 95% C.I.s: 1.928, 22.572). There were no other effects, interactions or trends.

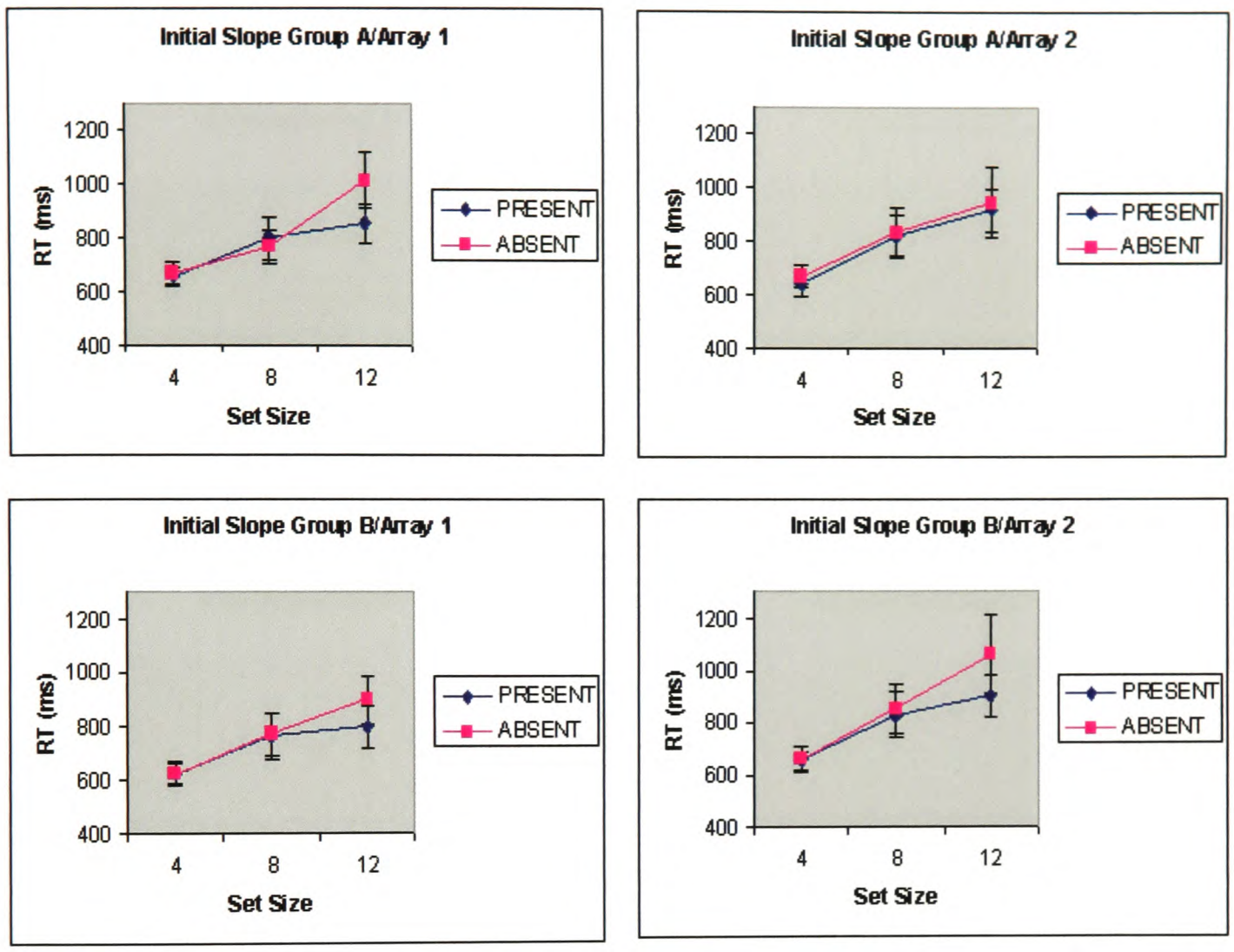


Figure 5.4. Baseline Search Slopes. Analysis of initial search slopes revealed no significant difference between the groups or the arrays at the outset of the experiment. The graphs show the baseline search slopes of Group A on Array 1 (upper left) and Array 2 (upper right) and of Group B on Array 1 (lower left) and Array 2 (lower right). Error bars = 1 SEM.

A three-way mixed-model ANOVA (Group * Stage * Target Present/Absent) was conducted to test whether the groups differed in slope across the stages of the experiment. There was no effect of Group ($F(1,10) = 0.150$, $p = 0.707$). "Target Present" slopes were significantly lower than "Target Absent" slopes throughout the experiment ($F(1,10) = 14.946$, $p = 0.003$). There was a significant effect of Stage ($F(2,20) = 15.819$, $p = 0.001$ (Greenhouse-Geisser corrected)), with slopes being highest at the "Pre" stage, lowest at the "Post" stage and intermediate at the "Transfer" stage (see Figure 5.5).

There was a trend towards an interaction of Stage * Target Present/Absent ($F(2,20) = 3.602$, $p = 0.074$ (Greenhouse-Geisser corrected)), reflecting a reduction in the target present/absent ratio at the transfer stage.

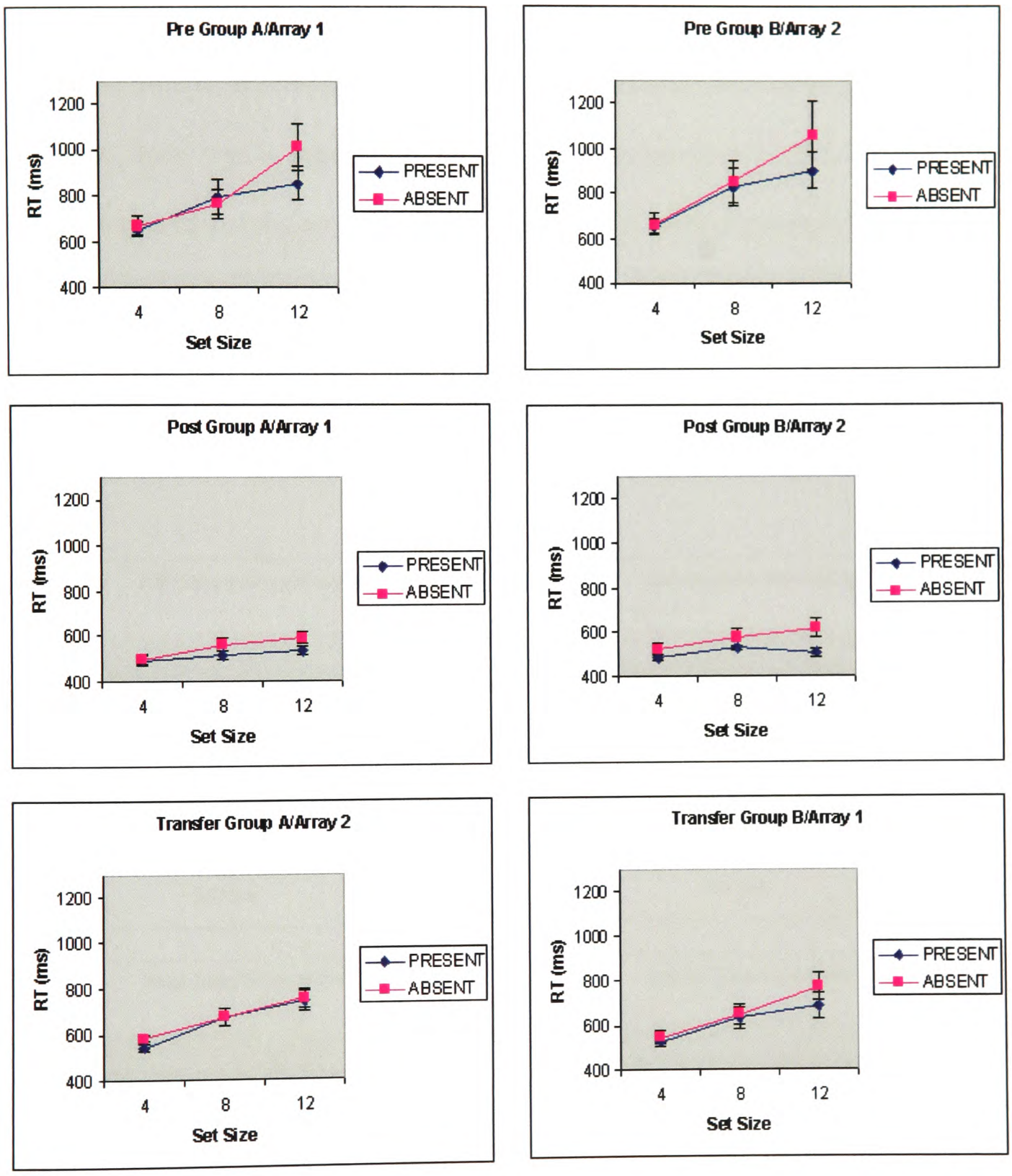


Figure 5.5. Group Search Slopes at the Pre, Post and Transfer Stages of the Experiment. Slopes were highest at the Pre, Lowest at the Post and intermediate at the Transfer stage. There was no difference between the groups. Plots show mean of median search slopes. Data for Group A are on the left; Group B are on the right. Error bars = 1 SEM.

To test for possible training benefits on the transfer array, a mixed model ANOVA (Group * Stage * Target Present/Absent) compared slopes at the "Pre" and "Transfer" stages on the untrained task (ie: slopes on Array 2 for Group A and Array 1 for Group B). Figure 5.6 plots the baseline and "Transfer" stage slopes for both groups on the transfer array. There was no effect of Stage ($F(1,11) = 2.604$, $p = 0.138$) or Group ($F(1,10) = 84.502$, $p = 0.729$) or Target Present/Absent ($F(1,10) = 2.547$, $p = 0.142$). However, there was a significant Group * Present interaction ($F(1,10) = 5.914$, $p = 0.035$). Inspection of the means revealed that whilst the target present slope (20.77, SD = 5.28) was lower than the target absent slope (31.74, SD = 5.922) for Group B (Array 1), the opposite was the case for Group A (Array 2) (mean present slope: 30.04, SD = 5.28; mean absent slope: 27.77, SD = 5.92).

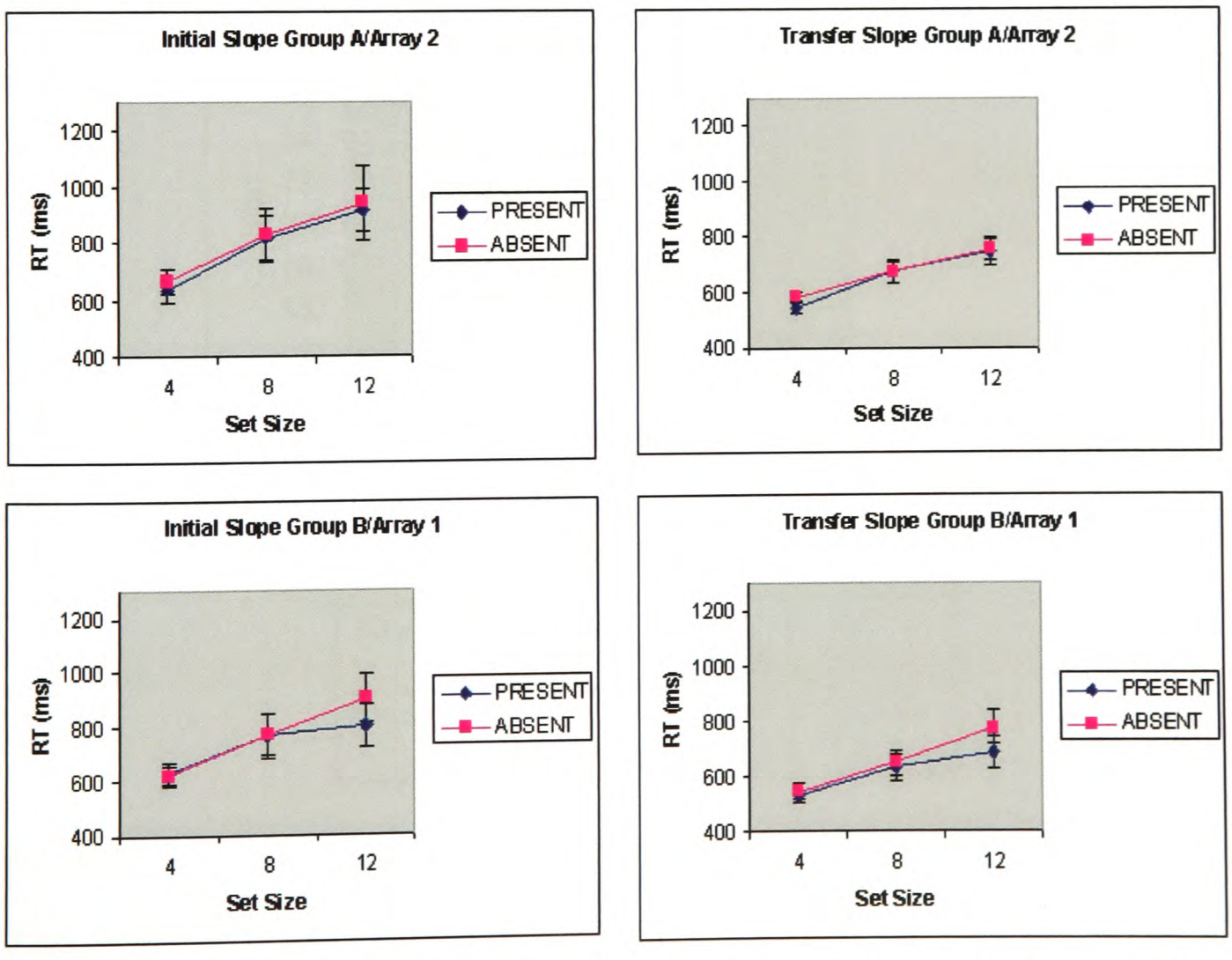
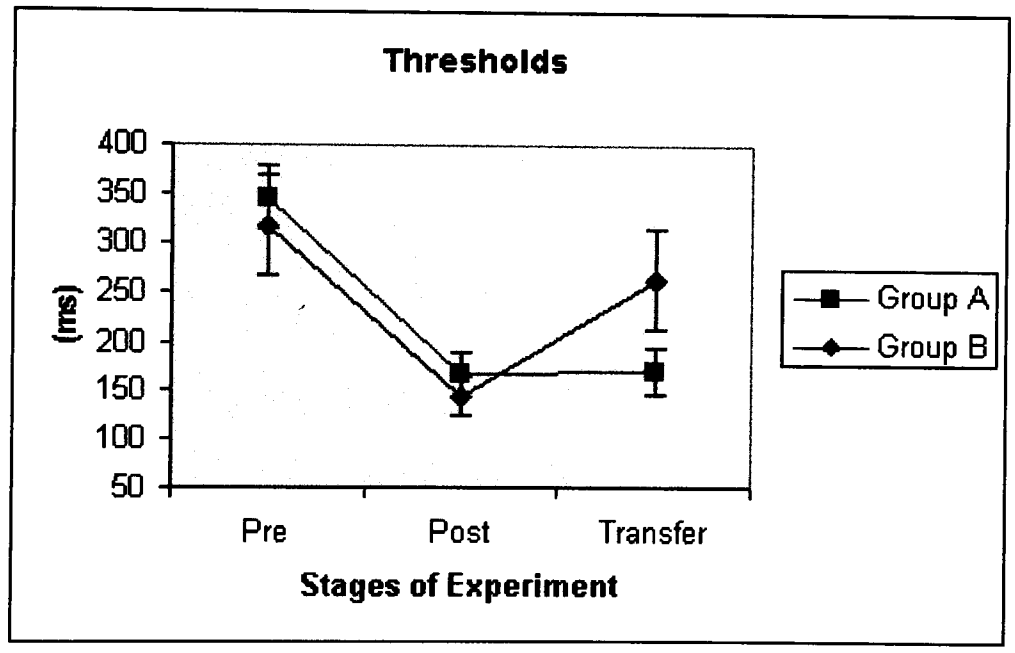


Figure 5.6. Group Search Slopes at the Pre, Post and Transfer Stages of the Experiment. Slopes were highest at the Pre, Lowest at the Post and intermediate at the Transfer stage. There was no difference between the groups. Plots show mean of median search slopes. Data for Group A are on the left; Group B are on the right. Error bars = 1 SEM.

2. Thresholds

Mean threshold values were analysed in a 2-way mixed model ANOVA (Group * Stage). There was no effect of Group ($F(1,10) = 0.113$, $p = 0.743$), but there was an effect of Stage ($F(2,20) = 38.601$, $p < 0.001$). Inspection of the means (see Figure 5.7) revealed a similar overall trend to the slope data with threshold values longest at the "Pre" stage, shortest at the "Post" stage and intermediate at the "Transfer" stage. Thresholds for Array 1 were longer than Array 2 at every stage of the experiment. There was also a significant Group * Stage interaction ($F(2) = 5.660$, $p = 0.011$). Thresholds for the two groups differed at the "Transfer" stage. Thresholds for group A, but not B, were the same at the "Post" stage (Array 2) as at the "Transfer" stage (Array 1).



	Pre	Post	Transfer
Group A	346.66 (78.66)	165 (53.57)	168.33 (57.07)
Group B	318.33 (125.61)	143.33 (50.86)	263.33 (123.56)

Figure 5.7. Array Viewing Durations (Thresholds). Mean thresholds are plotted for each group at each stage of the experiment. Group A searched Array 1 at the "Pre" and "Post" stages and Array 2 at the "Transfer" stage. Group B searched Array 2 at the "Pre" and "Post" stages and Array 1 at the "Transfer" stage. The table cites means (ms) and standard deviations (in brackets). Error bars = 1 SEM.

3. Eye Movements

Owing to slight head movements and the absence of a head-movement compensation system, complete eye movement recordings could not be collected for all subjects, blocks and stages of the experiment. However, based on the traces that were recorded, blinks and small amplitude saccades occurred on fewer than 4% of trials. Importantly, there was no difference in the rate of blinks and saccades between TMS and non-TMS blocks.

TMS Data:

A 4-way mixed model ANOVA (Group * Stage * TMS Site (FEF/Sham) * Side (Right/Left)) was carried out on subjects' d' scores. There was a main effect of TMS Site ($F(1, 10) = 11.544$, $p = 0.007$), reflecting a significant reduction in d' with TMS over the FEFs relative to sham TMS. There were two three-way interactions: Group * Stage * TMS Site ($F(2) = 19.074$, $p < 0.001$) and Stage * Site * Side (($F(2, 20) = 8.984$, $p = 0.002$).

*3-way Interaction of Group * Stage * TMS Site:*

To further explore this, two 2-way ANOVAs (Stage * TMS Site) were conducted on the data decomposed by Group.

For Group A (Array 1, transfer to Array 2), there was a significant main effect of TMS Site ($F(1, 5) = 7.474$, $p = 0.041$) and a significant Stage * Site interaction ($F(2, 10) = 11.206$, $p = 0.003$). Post-hoc paired-samples t-tests revealed that TMS over the FEFs significantly reduced d' relative to sham TMS in the "Pre" ($t(5) = 6.811$, $p = 0.001$) and "Post" ($t(5) = 3.156$, $p = 0.025$) stages of the experiment. There was no effect of TMS at the "Transfer" stage when subjects were tested on Array 2 ($t(5) = -1.378$, $p = 0.227$) (see Figure 5.8(a)).

For Group B (Array 2, transfer to Array 1), there was no main effect of TMS Site ($F(1, 5) = 4.614$, $p = 0.084$) or Stage ($F(2, 10) = 2.744$, $p = 0.112$), but the interaction was significant ($F(2, 10) = 11.006$, $p = 0.003$). Post-hoc paired-samples t-tests showed a trend towards a reduction in d' with TMS over the FEFs at the "Pre" stage ($t(5) = 2.232$, $p = 0.076$), no effect of TMS at the "Post" stage ($t(5) = -2.66$, $p = 0.801$) and a significant reduction in d' at the "Transfer" stage when subjects were tested on Array 1 ($t(5) = 4.433$, $p = 0.007$) (see Figure 5.8(b)).

*3-way Interaction of Stage * TMS Site * Side:*

To further explore this, three 2-way ANOVAs (TMS Site * Side) were carried out on the d' data decomposed by Stage.

At the "Pre" stage, there was a significant effect of TMS Site ($F(1, 11) = 25.701$, $p < 0.001$) and Side ($F(1, 10) = 10.685$, $p = 0.007$) and an interaction ($F(1, 11) = 15.758$, $p = 0.002$). Inspection of the means showed that TMS over the right FEFs reduced d' compared with all other conditions (right sham mean = 1.89 (SD = 0.55), left sham mean = 1.82 (SD = 0.39), right FEFs mean = 1.28 (SD = 0.49), left FEFs mean = 1.81 (SD = 0.50). No other analyses were significant.

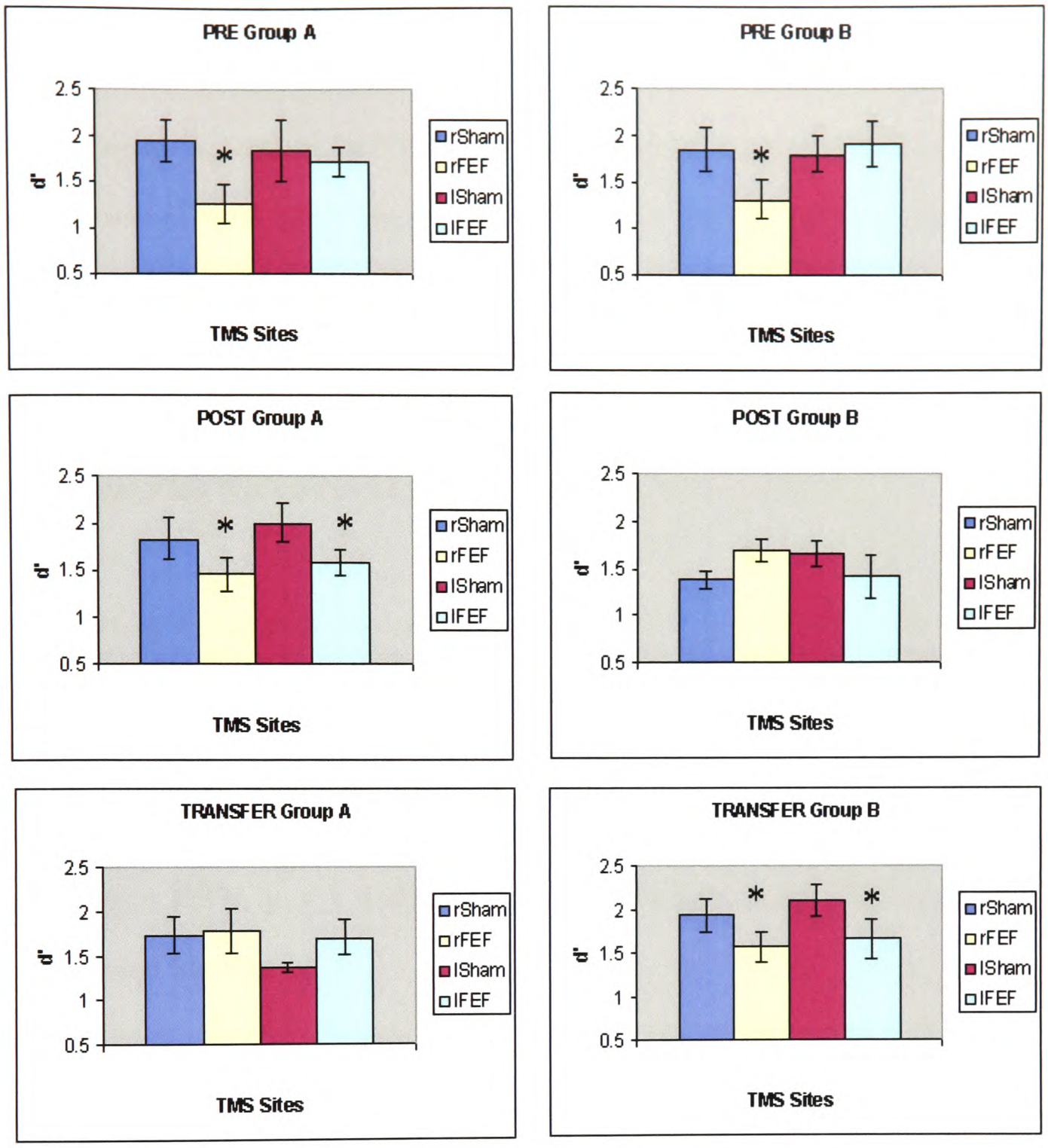


Figure 5.8. TMS Results. d' data for both groups in all three stages of the experiment. **(a)** For Group A, TMS over right FEF reduced d' at the "Pre" stage; TMS over right or left FEF reduced d' at the "Post" stage and there was no effect of TMS on d' at the "Transfer" stage. **(b)** For Group B, TMS over right FEF reduced d' at the "Pre" stage; there was no effect of TMS on d' at the "Post" stage and TMS over right or left FEF reduced d' at the "Transfer" stage. Labels refer to left and right FEFs (lFEF, rFEF) and control conditions featuring sham TMS over the right and left FEFs (rSham, lSham). Error bars = 1 SEM.

Response Type Analysis:

To investigate whether the changes in d' reflected a selective effect on the hit or false alarm rate, analyses were conducted on the data decomposed by response type (hits, misses, false alarms, correct rejections).

For Group A, analysis of "Pre" stage responses revealed a significant three-way interaction of Site * Side * Response Type ($F(3,15) = 5.924$, $p = 0.007$). Examination of the means (see Table 5.1) showed that TMS over the right FEFs selectively increased false alarms. At the "Post" stage, the two-way interaction of Site * Response Type ($F(3,15) = 9.148$, $p = 0.013$ (Greenhouse-Geisser corrected)) was significant. TMS over the right or left FEFs increased false alarms and reduced the hit rate.

For Group B, the three-way interaction (Site * Side * Response Type) for "Pre" stage responses was not significant ($F(3,15) = 2.594$, $p = 0.091$). Inspection of the means showed that TMS over the right FEFs increased false alarms and reduced the hit rate. At the "Transfer" stage (Array 1), the Site * Response Type interaction was significant ($F(3,15) = 12.775$, $p = < 0.001$) and TMS over the right or left FEFs increased both misses and false alarms.

Group A					Group B				
PRE	**H**	**M**	**F**	**C**	**PRE**	**H**	**M**	**F**	**C**
rSham	32	8	7.5	32.5	rSham	31	9	6.66	33.33
rFEF	30.16	9.83	11.8	28.16	rFEF	28.33	11.66	9.8	30.2
lSham	30.83	9.16	6.5	33.5	lSham	31	8.8	7.3	32.6
lFEF	28	10.33	6.66	33.33	lFEF	30.6	9.3	5.8	34.2
POST					**POST**				
rSham	31.66	8.33	7.33	32.66	rSham	28.83	11.17	10.33	29.66
rFEF	29.33	10.66	9.2	30.8	rFEF	30.33	9.66	7.5	30.83
lSham	32.8	7.2	6.66	33.33	lSham	30.5	9.5	9.17	30.83
lFEF	29.66	10.33	8.5	31.83	lFEF	28.5	11.5	10	30
TRANSFER					**TRANSFER**				
rSham	28	12	5.33	34.66	rSham	29	11	4.83	35.17
rFEF	29.33	10.66	5.66	32.66	rFEF	27.17	12.83	6.83	32.83
lSham	27.66	12.33	7.8	32.2	lSham	30.5	9.5	4.83	35.17
lFEF	28.66	11.33	5.8	34.2	lFEF	27.33	12.66	6.83	33.83

Table 5.1. Mean response types per experimental condition. H refers to hit trials, M to misses, F to false alarms and C to correct rejections.

Response Bias (C) Analysis:

A 4-way mixed model ANOVA (Group * Stage * TMS Site (FEF/Sham) * Side (Right/Left)) was conducted on a measure of subjects' response bias (C). There was a main effect of Stage ($F(2,20) = 5.035$, $p = 0.017$). Subjects had a baseline tendency towards 'target absent' responses throughout the experiment. This bias was highest at the 'Transfer' stage (mean C: 0.283, SE = 0.104), lowest at the 'Post' stage (mean C: 0.059, SE = 0.123) and intermediate at the 'Pre' stage (mean C: 0.109, SE = 0.096). There were no other effects, interactions or trends.

5.4. Discussion

The results of this experiment suggest the unexpected conclusion that the two search arrays were processed differentially by the FEFs. Analysis of search slopes revealed no difference between the two groups across the three stages of the experiment. Slopes on both tasks were steep at the "Pre" stage, flat at the "Post" stage and intermediate at the "Transfer" stage. Hence, according to this standard measure of search efficiency, there was no difference in the search demands imposed by the two tasks. Despite this, the pattern of TMS effects diverged. Whereas performance on Array 2 was only disrupted at the "Pre" stage, when search was novel, performance on Array 1 was disrupted at the "Pre", "Post" and "Transfer" stages (ie: irrespective of subjects' training state).

Analysis of threshold measures provides a clue to the source of this difference. The aim of the thresholding procedure was to equate subjects' baseline performance across all stages of the experiment. On average, baseline performance was between d' of 1.5 - 2.0 (73% - 83% correct) throughout, allowing meaningful comparisons to be made across the different stages. The overall pattern of thresholds matched that of slopes, being

longest at the "Pre", shortest at the "Post" and intermediate at the "Transfer" stage. However, the threshold data suggest a difference between the two arrays not evident in the slope measures. At all stages, mean thresholds were longer for Array 1 than Array 2 – by ca. 28ms at the "Pre" stage, 22ms at the "Post" stage and 95ms at the "Transfer" stage. This suggests that processing of Array 1 was in fact more difficult than Array 2, since, irrespective of training state, subjects always needed to view Array 1 for longer in order to reach criterion. This claim is further supported by the training data. Whereas two out of six subjects in Group B (Array 2) needed only three training sessions to reach criterion, three out of six subjects in Group A (Array 1) needed six sessions.

The difference in array viewing time suggests one possible interpretation of the divergent pattern of TMS effects. Viewing time and susceptibility to TMS interference seem to correlate. Array 1 is viewed for longer and is subject to TMS interference at every stage of the experiment. By contrast, search of Array 2 is only disrupted at the "Pre" stage, the longest viewing time for that array. It might be that longer thresholds imply more eye movements, and the disruptive effects of TMS reflect disruption of eye movement programs. However, mean thresholds for Group A at the "Post" (165ms) and "Transfer" (168.3ms) stages argue against this interpretation. Although viewing times for Array 1 ("Post") and Array 2 ("Transfer") were virtually the same, TMS disrupted performance of Array 1 but not of Array 2. Since these data were from the same subjects viewing the two arrays for the same duration, this argues against a simple saccade/duration account of the divergent pattern of TMS effects.

Taken together, the longer viewing requirement of Array 1, and the fact that TMS disrupts search of Array 1 irrespective of subjects' training state, suggests that Array 1 imposes additional computational demands over Array 2. Since search efficiency (slopes)

does not distinguish the arrays, it can be argued that this extra computational load is not related to search *per se*. Additional support for this claim comes from the fact that one subject in Group B showed efficient search (target present slope = 5.25) at the "Transfer" stage (Array 1), and yet showed a d' decrement of 0.6 with TMS over the right FEFs. Before going on to consider what the source of this processing difference might be, it is worth examining the findings for each array separately.

Group B:

As predicted, the overall pattern of results matched that reported for TMS of the angular gyrus (Walsh et al., 1998a). At the "Pre" stage, when subjects were new to the search task, TMS over the right FEFs disrupted performance (d'). After training, this effect disappeared. When subjects transferred to a new array (Array 1), TMS interference re-appeared, demonstrating the specificity of the training (and TMS) effects. Search efficiency, measured by RT slope (ms/item), correlated with TMS interference, which was effective only when slopes were steep (> 10ms/item) (at the "Pre" and "Transfer" stages), but not when they were flat (<10ms/item) (at the "Post" stage). One limitation of these data is that subjects transferred to Array 1. Since subjects in Group A were impaired on Array 1 even after many days of training, it is unsurprising that performance was disrupted for Group B at the transfer stage. For this reason, the discussion of results for Group B will focus only on the change in TMS effects between "Pre"/naïve and "Post"/expert search.

Single-unit work has shown that training changes the nature of the target discrimination function computed by the monkey FEFs. In the case of novel search, neuronal activity reliably distinguishes targets from distractors only after a period of signal evolution lasting ca. 60-80ms after the initial response (Thompson et al., 1996). With search

expertise, in 50% of the visual FEF neuronal population, this period of build-up disappears and the initial response becomes selective (Bichot et al., 1996). It was argued in Chapter 4, based on the timing of interference, that search decrements induced by TMS reflect disruption of an evolving discrimination signal in human FEFs. The results for Group B bolster this claim. If, as shown in the monkey, training removes discriminative signal build-up in the FEFs, then the absence of TMS effects at the "Post" stage suggests that it is this evolving signal window that is susceptible to TMS.

Taken in isolation, the data for Group B confirm initial predictions about the effect of learning on the FEFs during search. Training-induced search efficiency removed susceptibility to TMS interference. This suggests that the FEFs, like the angular gyrus, no longer make critical contributions to efficient search performance.

Group A:

Search performance on Array 1 was disrupted at all stages of the experiment, irrespective of subjects' training state. At the "Pre" stage, only TMS over the right FEFs disrupted search, whereas at the "Post" and "Transfer" stages, TMS over either of the FEFs disrupted performance. This bilateral effect was unexpected and contrasts with Array 2 ("Pre") where only right stimulation disrupted search.

Although the effect of TMS over lFEF on d' was not tested in Chapter 4, reaction time data from Muggleton, et al. (2003) showed that TMS over lFEF did not disrupt search. Although RT and d' measures need not correlate, a previous TMS study on the angular gyrus showed a right hemisphere bias in TMS disruption of d' (Muggleton, et al., in preparation), as is the case for RTs (Ashbridge et al., 1997; Walsh et al., 1999). Other TMS work has shown a right hemisphere bias for target detection in the FEFs (Grosbras

& Paus, 2002, 2003), and a number of imaging (Kim et al., 1999), lesion (Mesulam, 1981) and TMS (Muri et al., 2002) studies have suggested that the fronto-parietal network supporting search is right-lateralized. Nobre, et al. (2003), for instance, subtracted saccade-related activations from those elicited by inefficient search, which revealed right-lateralized activity in the FEF and the IPS. Hence, the unexpected bilateral pattern of d' deficits at the "Post" (and "Transfer") stage on Array 1 raises two questions: 1) why does rFEF remain susceptible to TMS interference after search has become efficient? 2) what is the nature of the lFEF deficit?

The fact that rFEF deficits persist and lFEF disruption emerges after training raises the question of whether the FEFs provide a memory storage site for search learning. Specifying the kind of memory trace laid down by training, however, is difficult and evidence suggests that search learning is best thought of as developing a spatial skill (Chun & Jiang, 1998; Chun, 2000; Chun & Jiang, 2003). One possible mechanism by which expertise could proceed is by development of a "guided search" strategy (Wolfe et al., 1989; Treisman & Sato, 1990) where subjects learn to ignore distractor colours such that the task becomes one of searching for a unique shape in the relevant colour subset. Guided search has been shown to be preferentially lateralized to the left hemisphere, with search of displays that cross the midline (as here) reliant on cross-callosal transfer (Kingstone et al., 1995). Might bilateral "Post" stage FEF effects reflect disruption of a guided search strategy? Imaging studies of spatial (eg: LaBar et al., 1999) and object (Makino et al., 2004) working memory have reported significant overlap with nodes in the fronto-parietal search network (including the FEFs). The evidence is inconsistent as to whether this network is right (Smith & Jonides, 1999; Zarahn et al., 1999) or left lateralized (eg: Grosbras et al., 2001; Corbetta et al., 2002), or whether it activates both hemispheres (and the FEFs) equivalently (Brown et al., 2003). The problem with either a

memory or guided search interpretation, however, is that both predict significant "Post" stage disruption on Array 2, which did not occur. Hence, since the pattern of TMS effects for Group A cannot be explained by the behavioural data (slopes) or neural literature on search efficiency, alternative factors need to be considered.

The performance of Group A at the "Transfer" stage (Array 2), however, is likely explained by search slope. Contrary to expectations, Group A showed no effect of TMS on transfer to the new array. The analysis of slopes at the "Pre" versus "Transfer" stages showed that Group A differed from Group B. Instead of the usual conjunction search present : absent slope ratio (typically approaching 2 : 1), Group A showed a small search speed advantage for target absent trials (mean present slope: 30.04, SD = 5.28; mean absent slope: 27.77, SD = 5.92). This was not an effect of training. From the outset, Group A had an unusual slope pattern with respect to Array 2 (see Figure 4(b)). That search of Array 2 was atypical is further supported by the "Transfer" stage threshold being the same as the "Post" stage threshold (Array 1). This diverged from the actual and expected overall pattern of slopes and thresholds (longest at the "Pre", shortest at the "Post" and intermediate at the "Transfer" stage). How TMS effects vary as a function of search slope has not been systematically addressed. It has been reported, however, that TMS over the right angular gyrus did not disrupt inefficient search on a motion/form conjunction task among subjects who had trained on other arrays (Walsh et al., 1999). As search slope (steep vs. flat) *was* predictive of TMS effect on Array 2 at the "Pre" and "Post" stages, the absence of an effect for Group A at transfer is likely some function of the non-standard search behaviour evidenced here.

Both search arrays featured rotated stimuli of the same size, number and density, and only the stimuli themselves differed. The most striking difference between the two

stimulus sets was plane of rotation. Array 1 consisted of horizontally rotated square C stimuli (left or right), whereas Array 2 contained vertically rotated V stimuli (up or down). A large body of research has shown that mirror symmetric stimuli (such as these) are difficult to discriminate, but that left/right inversions are significantly more difficult than up/down (for reviews see: Gross & Bornstein, 1978; Walsh & Butler, 1996). A well-known example is the tendency to confuse the letters 'b' and 'd' more often than 'b' and 'p', particularly among children who are learning to read. Whilst it has been argued that the tendency to treat left/right inversions of mirror symmetric stimuli equivalently is adaptive (Gross & Bornstein, 1978), the fact that we can learn to discriminate them testifies to a neural basis for this discriminative ability, the nature of which is not well understood. It has been known for a long time (Ades & Raab, 1949; Riopelle & Ades, 1953) that lesions of infero-temporal cortex (IT) disrupt the discrimination of different shapes, with the exception of lateral mirror images (Cowey & Gross, 1970; Gross et al., 1971). More recently, unit recordings in IT, where neurons are selective for shapes and their orientations (Desimone et al., 1984), have revealed that whilst these neurons can discriminate up/down rotated stimuli, they respond similarly to left/right inversions (Tanaka et al., 1991; Rollenhagen & Olson, 2000). The ability to discriminate left/right inversions seems to depend on the spatial capacities of parietal cortex (Eacott & Gaffan, 1991), in combination with feature-selective prestriate cortex (Walsh et al., 1992). The bilateral pattern of TMS deficits on Array 1, which consists of left/right inverted stimuli, raises the possibility that the FEFs, like parietal cortex, may be critically involved in resolving left/right mirror image confusions.

To my knowledge, only two published studies (and one abstract) have presented data on FEF activations during mirror image discrimination (Goebel et al., 1998; Dong et al., 1999; Kassubek et al., 2001). In two other studies on mirror reading, the scanning

parameters were such that only volumes posterior (1998) or inferior (2001) to the FEFs were acquired (Poldrack et al., 1998; Poldrack & Gabrieli, 2001). Although none of the studies compared left/right versus up/down discriminations, they each indicate a role for the FEFs in performing visual spatial transformations. Goebel, et al. (1998) reported task-dependent BOLD signal increases in the FEFs during the spatial transformation of words and letter strings. The authors attributed this to "covert shifts of attention" because "a BOLD signal increase of the same scale was observed in the oculomotor control task". However, a between-subjects design was used, making valid comparisons between the two tasks difficult. Further, whilst the saccade task activated the right and left FEFs equivalently, all 10 subjects in the mirror reading task had robust left activations, with only four showing activations in the right FEFs. Activation specific to the left FEFs was also reported by Dong, et al. (1999). Kassubek, et al. (2001) scanned subjects reading normal and mirror-reversed words. In 8 out of 10 subjects, the amplitude of BOLD signal in bilateral FEFs was significantly higher during mirror-reversed compared with normal reading. After training, these activations were significantly reduced. To test whether a saccadic interpretation could explain the data, four subjects performed an oculomotor control task during the pre- and post-training sessions. The saccade task elicited equivalent activation of the right and left FEFs and neither saccade frequency nor BOLD signal changed between the pre- and post-training sessions. By contrast, although mirror reading elicited stronger activations than normal reading, subjects made more saccades during normal reading. Crucially, though there was no change in saccade frequency after training on mirror reading, BOLD signal was significantly reduced (see Figure 5.9). Given the independence of the activations from saccades, the authors interpreted the FEF findings in terms of higher demands on the precision and maintenance of gaze fixation during mirror than normal reading. In combination with the data presented here, however, I would argue that Kassubek et al's

study strongly suggests a role for bilateral FEFs in visuospatial transformations, which may decrease as a task is learned. Importantly, in combination, the two data sets argue that this role is not reducible to eye movements.

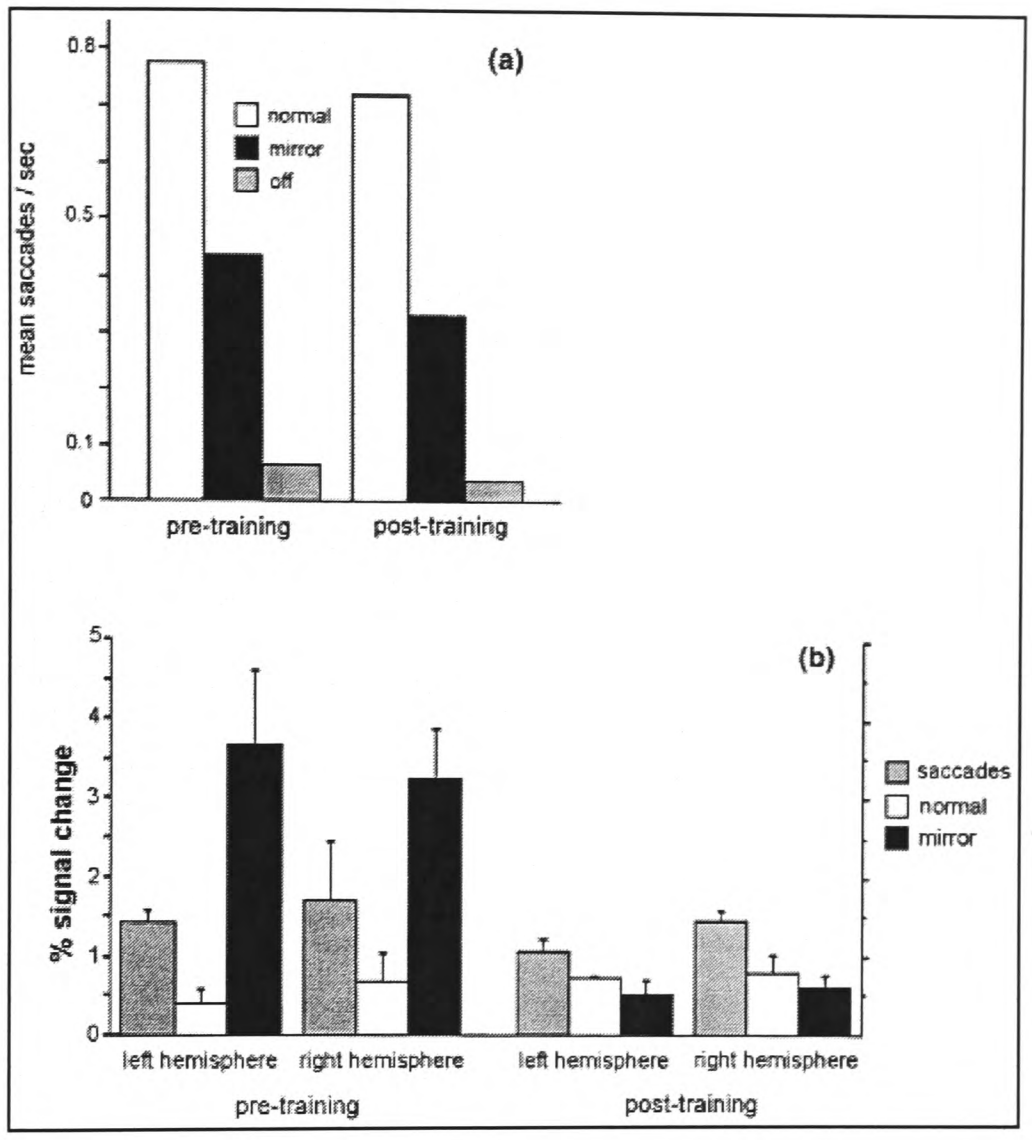


Figure 5.9. Saccade Frequency and % BOLD signal change across conditions in the mirror reading study of Kassubek, et al. (2001). Figure (a) shows saccadic activity (amplitude x frequency of saccades in ◦/sec) during normal text reading (white), mirror reading (black) and fixation ('off', grey). Subjects made significantly more saccades during normal compared to mirror reading. Saccadic activity did not change significantly between the pre- and post-training fMRI sessions. Figure (b) shows BOLD signal amplitudes (% change) during normal text reading (white), mirror reading (black) and during an oculomotor control experiment (grey) in the left and right FEFs. BOLD signals were higher during mirror reading than normal reading and decreased markedly after training. Note the higher activations during mirror reading compared to normal reading (b, pre-training), in contrast with the higher number of saccades (a) during normal versus mirror reading.

The longer thresholds required for Array 1 at every stage of the experiment, together with the fact that 50% of the subjects in Group A needed an extra day of training to

reach criterion, supports the claim that search of Array 1 was more difficult. If the source of this difficulty was the requirement to resolve left/right symmetry in addition to visual search, then the effects of this extra computational load should be detectable in the size of the TMS effects. At the "Pre" stage, TMS over rFEF (relative to rSham) produced a d' deficit of 0.68 on Array 1 compared to 0.53 on Array 2. In addition, subjects needed an additional 28ms of viewing time for Array 1 to perform at the same level of baseline accuracy as Array 2. Consistent with the claim that the d' deficits for Array 1 at the "Pre" stage were a compound effect of search and symmetry resolution, at the "Post" stage the d' deficits were smaller: 0.37 with TMS over rFEF and 0.43 with TMS over lFEF. The "Transfer" stage deficits for Group B were almost identical (rFEF: 0.37, lFEF: 0.44), but subjects needed an additional 98ms of viewing time to achieve the baseline accuracy criterion compared to the post-training threshold of Group A. The fact that FEF effects were unilateral at the "Pre" stage but bilateral at the "Post" and "Transfer" stages perhaps reflects some kind of strategy change in task performance as a function of practice. Alternatively, since three individual subjects had lFEF deficits at the "Pre" stage (Array 1) (and no subject had lFEF deficits at the "Pre" stage on Array 2), bilateral recruitment of the FEFs for left/right symmetry discrimination may occur as standard.

Conclusions:

The unexpected pattern of TMS effects reported here cannot be explained by search efficiency (slopes), and instead most likely results from symmetry processing differences between the two arrays. Both arrays were matched with respect to stimulus size, number and density, and subjects' behavioural performance was equated by a thresholding procedure across all stages of the experiment. Hence, the greater viewing and training requirements of Array 1 together with its larger d' decrement at the "Pre" stage support the claim that Array 1 exerted additional computational demands over Array 2. Plane of

symmetric rotation was the most striking difference between the stimuli in the two arrays, and so it is suggested that the FEFs may make a critical contribution to left/right symmetry judgements. Resolving left/right orientations would fit with the known role of the FEFs in spatial processing, whilst the bilateral recruitment may depend on an array that crosses the meridian, reflecting the need to carry out this computation in both hemifields simultaneously. Further work is needed to test this hypothesis directly, but in a different paradigm not contaminated by the potentially multiplicative interactions of search, learning and symmetry resolution demands.

Considering Array 2 in isolation, the data for Group B ("Pre" and "Post") confirmed initial predictions and extend findings from the angular gyrus, suggesting that the contribution of the FEFs to search performance is no longer task-critical once the search task has been learned. The failure of Group A to show an effect of TMS at transfer highlights the need for future experiments to systematically explore how search slope and TMS effects may correlate.

CHAPTER 6: The Role of the Frontal Eye Fields in the Priming of Pop-Out

Abstract

Priming of pop-out is a form of implicit memory which is believed to promote efficient search by facilitating saccades to targets that have been recently inspected. Repetition of a target's defining feature or its spatial position improves target detection speed. Pop-out priming has been well-characterized psychophysically, but little is known about its neurophysiological basis. The aim of the current chapter was to investigate a potential role for the frontal eye fields in pop-out priming. To test the hypothesis that the FEFs play a role in short-term memory storage, TMS was applied during the inter-trial interval. To test whether the FEFs are critical when a saccade is being programmed to a repeated target colour or location, TMS was applied during stimulus processing. There was no effect of TMS in the inter-trial interval on either spatial or feature priming. TMS applied over the left FEFs during stimulus processing abolished spatial priming, but had no effect on feature priming. The data implicate a selective role for the left FEFs in the read-out, but not the storage, of a spatial memory signal that facilitates saccades to a repeated location.

6.1. Introduction

Memory mechanisms play a significant role in most theories of visual search (eg: Schneider & Shiffrin, 1977; Treisman & Gelade, 1980; Duncan & Humphreys, 1989; Treisman & Sato, 1990; Wolfe, 1994). Proposed cognitive components of the search process for which mnemonic functions have been invoked include: prospective memory for a pre-defined search target; working memory for that target template to guide search; within-trial tagging to prevent re-inspection of previously fixated items; implicit memory for previously seen search array configurations, and perceptual learning effects with task practice. For many of these proposed functions, clarifying what constitutes a mnemonic process as distinct from a mechanism of search *per se* remains both conceptually and empirically opaque. Accordingly, imaging studies have shown there is substantial overlap between the fronto-parietal search network and that activated by both spatial (LaBar et al., 1999; Corbetta et al., 2002) and feature/object working memory tasks (Linden et al., 2003; Makino et al., 2004). In light of the conceptual and neural overlap between search

and memory mechanisms, implicit memory paradigms are an attractive research tool. Implicit memory appears to be passive, automatic and unaffected by prior knowledge, expectations or conscious control (Maljkovic & Nakayama, 1994; Goolsby & Suzuki, 2001), meaning that task strategy complications are eliminated (Glabus et al., 2003). The aim of this chapter was to test the impact of implicit memory on search-related computations in the frontal eye fields (FEFs) and the angular gyri (AGs).

Priming of pop-out refers to the behavioural (reaction time (RT)/accuracy) advantage that is conferred when observers search repeatedly across trials for the same odd target (eg: red) among the same distractors (eg: green), compared with the cost incurred when the target/distractor combinations change across trials. That is, if the current trial target has the same features or is in the same location as the target on the previous trial, then the observer's detection response is faster. Manual RT benefits in the order of 20-50ms have been demonstrated when either the feature or the spatial location of the target is repeated (Maljkovic & Nakayama, 1994, 1996). The priming effect has been shown to last over five to eight consecutive trials (ca. 30 seconds) and is cumulative: RT benefits were largest on the first trial after a location or feature repeat and gradually decayed over the next eight trials[1]. The authors attributed this effect to the operation of "a decaying memory trace of the attention-focussing feature that is laid down with each trial". Observers were unable to wilfully overcome priming, indicating it is an automatic process. Feature and spatial priming operated independently, and were feature- or object- rather than space-based, thus implicating 'higher' visual cortex where retinotopy is not preserved and where the coordinate reference frame is more abstract (Maljkovic & Nakayama, 1996; Kristjansson et al., 2001) (but see Bar & Biederman, 1999).

[1] This was not quite the case for spatial priming. The RT benefit was greatest on the second trial after a location repeat rather than the first.

The authors proposed that priming plays an important functional role in naturalistic vision. In particular, they argued that rapid and efficient re-orienting of gaze is critical for chaining together complex action sequences, and that priming may facilitate this. In support of this, priming has been shown to facilitate saccadic reaction times to repeated targets in both humans (McPeek et al., 1999) and monkeys (McPeek & Keller, 2001). Given the proposed functional coupling of priming and eye movements, its non-retinotopic reference frame, and the claim that priming may account for search effects previously attributed to 'top-down control' (Kristjansson et al., 2002), this chapter aimed to test a potential role for the frontal eye fields (FEFs) or the angular gyri (AGs) in keeping track of features or spatial locations across saccades.

There have been very few neural studies of pop-out priming. To my knowledge, only two imaging studies (conference posters) have been published (Yoshida et al., 2003; Kristjansson et al., 2004), both of which reported activation of the fronto-parietal search network. Kristjansson, et al. found that target feature or location repetition induced bilateral suppression of the BOLD signal in the frontal eye fields and parietal cortex (SPL, IPL, IPS), as well as in the middle frontal gyrus and extrastriate cortex. Feature priming induced additional suppression in infero-temporal areas involved in colour processing. Repetition suppression of the haemodynamic response has been reported for priming in domains other than search (eg: Kourtzi & Kanwisher, 2000), and has a potential cellular basis in a reduced firing rate of neurons on repeated stimulus presentation (Desimone, 1996; Wiggs & Martin, 1998). The 'cortical sharpening theory' of priming proposes that repeated stimulus presentation reduces the firing of neurons that are not necessary for stimulus processing. This reduced population firing rate is then reflected in a decreased haemodynamic response and sparser stimulus representation, which yields more efficient stimulus processing and behavioural priming effects (Henson

et al., 2000; Henson & Rugg, 2003). Hence, repetition suppression implicates the fronto-parietal network as a neural correlate of pop-out priming.

However, this does not establish whether fronto-parietal repetition suppression is task-critical. A large body of psychophysical and neurophysiological evidence supports a conceptual scheme according to which those areas of visual cortex that are selective for a particular visual feature (eg: colour) also support short-term perceptual memory for that feature (Tulving & Schacter, 1990). Such studies have shown that memory for basic visual attributes (eg: colour, motion, orientation, contrast, spatial frequency) is subserved by low-level mechanisms of perception, located beyond V1 but prior to regions involved in visual object perception (eg: Magnussen & Greenlee, 1999; Bisley & Pasternak, 2000; Magnussen, 2000). In the case of feature priming, Campana, et al. (2002) showed that TMS applied over V5 but not right parietal cortex abolished visual motion priming. TMS over either of these sites had no effect on colour priming. By contrast, three interference studies have implicated colour-selective V4 as a crucial substrate of colour priming (Walsh et al., 2000; Girard et al., 2001a; Rossi et al., 2001). Walsh, et al. trained monkeys on a colour pop-out task and then lesioned V4 or TEO bilaterally. Post-operative testing showed that whilst colour discrimination was unaffected, lesions of V4 abolished colour priming in all three animals. TEO lesions had a similar but diminished effect. Girard, et al. reported the same effect with reversible inactivation of V4 using cortical cooling. Following complete unilateral removal of prefrontal cortex, the corpus callosum and the anterior commissure, Rossi, et al. reported that colour priming remained intact in the contralesional hemifield. Such data imply that neural adaptation in colour-selective cortex is critical for colour priming. This suggests that fronto-parietal suppression may simply reflect downstream effects of sensory adaptation in extrastriate cortex.

Since neither the FEFs nor the AGs are colour-selective (but see Bichot et al., 1996; Toth & Assad, 2002), haemodynamic repetition suppression likely reflects efficiency changes in target discrimination and visuomotor integration that result from sensory adaptation in colour-selective cortex. Partial support for this claim comes from single-unit recordings in the FEFs during priming of pop-out. Bichot & Schall (2002) found that feature (colour) repetition produced earlier target discrimination in FEF visual neurons and greater separation between target and distractor activity in the post-selection period. These neural changes correlated with faster saccadic reaction times (SRTs) and improved accuracy, respectively. Importantly, there was no change in FEF neurons' baseline firing rate, as might be expected of a sensory adaptation effect. If fronto-parietal repetition suppression affects similar target discrimination processes in the human brain, then interference should potentially disrupt these processes on every trial, but have no effect on the relative reaction time difference between feature-repeat versus feature-switch trials. That is, TMS over the FEFs or AGs should not disrupt feature priming.

In their study of pop-out priming, Bichot & Schall (2002) found that changes in FEF target discrimination time correlated with monkeys' saccadic reaction times in both feature and spatial priming tasks. When the target location was repeated, the monkeys showed inhibition of return (IOR) (ie: slower SRTs), rather than facilitation, and this correlated with later target discrimination in the FEFs. While changes in target discrimination time can be envisioned as changes in target salience, spatial but not feature priming can also be conceptualized as maintaining or switching task set (Rogers & Monsell, 1995; Fecteau & Munoz, 2003). On location repeat trials, the same saccade program is re-executed, facilitating reaction time. This benefit can be thought of as a 'motor memory' or 'preparatory set' effect: it is easier to perform the task when the same saccade program must be executed ('stay' trials) than when a new saccade vector must be

programmed ('switch' trials). Such 'stay' trials have been shown to increase the baseline activation of neurons in the superior colliculus, which lowers the threshold for saccade initiation, facilitating SRT. Threshold activity is reduced on switch trials and the correlation is significant on a trial-by-trial basis (Dorris et al., 2000; Gore et al., 2002). The reaction time cost of location switching has also been ascribed to competing oculomotor programs within the superior colliculus (McPeek & Keller, 2002b; McPeek et al., 2003), an effect that could account for switch deficits during feature or spatial priming tasks. However, the RT benefit on 'stay' trials when target features repeat but location does not cannot be explained in terms of 'motor memory', and is more appropriately conceived of as a visual memory effect. This juxtaposed characterization of feature/sensory priming and spatial/motor priming fits with the behavioural evidence suggesting that these two effects operate independently (Maljkovic & Nakayama, 1996). It also suggests the hypothesis that feature and spatial priming may be neurophysiologically dissociated within the FEFs or the AGs (see for example Rushworth et al., 2001c).

There are reasons to expect that, contra the predictions for feature priming, spatial priming may engage a critical contribution from either the FEFs or the AGs. Sustained activity associated with various forms of spatial memory has been observed in a number of regions within the pre-frontal (Levy & Goldman-Rakic, 2000) and parietal cortices (Snyder, 2000). Imaging studies have reported greater activation of a fronto-parietal network during memory-guided versus visually-guided saccades (Sweeney et al., 1996; Brown et al., 2003), and FEF, LIP and parietal 7a neuronal recording studies have shown that these neurons exhibit elevated discharge rates during the delay period (Bruce & Goldberg, 1985b; Andersen et al., 1990; Constantinidis & Steinmetz, 1996). Fronto-parietal activation patterns appear to be coordinated, suggesting that parietal and FEF

neurons are closely functionally coupled during spatial memory tasks (Chafee & Goldman-Rakic, 1998, 2000). Lesions (Latto & Cowey, 1971; Schiller & Sandell, 1983) or reversible inactivation of the FEFs (Sommer & Tehovnik, 1997; Dias & Segraves, 1999) induce targeting errors and increase memory-guided saccade latencies, which is exacerbated by increasing the delay. This effect has also been replicated in patients with FEF damage (Rivaud et al., 1994; Gaymard et al., 1999; Ploner et al., 1999). During visual search, right parietal patients with (Pisella et al., 2004) and without neglect (Husain et al., 2001) frequently return to previously inspected items and show no awareness of having done so. This 're-visting' behaviour has been argued to depend on damage to the angular gyrus and/or the intra-parietal sulcus (Mannan et al., 2005), although patients with frontal damage that includes the FEFs, and monkeys with FEF (but not superior colliculus lesions) show similar impairments (Collin et al., 1982). This 're-visiting' behaviour has been interpreted as a failure to maintain and update searched locations across saccades, and may also explain why parietal patients do not benefit from the preview effect in search (Shimozaki et al., 2003). Impaired performance on the double-step saccade task after parietal damage has similarly been interpreted as a deficit in trans-saccadic memory or in mechanisms of spatial re-mapping across saccades (Duhamel et al., 1992b; Heide & Kompf, 1998). Finally, a number of imaging, patient and unit recording studies indicate that the frontal eye fields and parietal areas play an important role in preparatory set (Banich et al., 2000b; Everling & Munoz, 2000; Rushworth et al., 2001c; Connolly et al., 2002; Cornelissen et al., 2002; DeSouza et al., 2003; Konishi et al., 2003; Sakai & Passingham, 2003; Aron et al., 2004; Connolly et al., 2004).

The proposal that areas that are specialized for spatial selection may also subserve short-term memory for those selected locations is a natural extension of the sensory memory hypothesis to visuomotor cortex (Awh & Jonides, 2001). It also amounts to a re-

statement of the hypothesis that the patterns of fMRI and FEF single unit activity common to both spatial and feature priming may obscure different causal bases. Suggestive evidence for a potential feature/spatial dissociation comes from the only published study (to my knowledge) to have tested parietal patients on pop-out priming (Kristjansson et al., 2005). All four right parietal patients with neglect and extinction showed intact feature and spatial priming, irrespective of target hemifield location. In a follow-up manipulation with briefly presented targets, the patients had to indicate whether the target was on the left (neglected hemifield), the right, or absent. Feature priming remained unimpaired, but spatial priming for left targets occurred only when patients had correctly detected the target on the previous trial. Using a consecutive colour prime-and-probe paradigm, Marangolo et al. (1998) reported that unilateral parietal patients had deficits in feature priming when the probes were presented in the contralesional hemifield. However, these patients also had impaired spatial priming and it has been argued, on grounds of parsimony, that the feature priming deficits likely derive from the spatial priming impairments (Campana et al., 2002). It is not clear what accounts for the conflicting findings of Marangolo, et al. and Kristjansson, et al., but it is possible that performance on the orienting task used by Marangolo may have depended on additional parietal mechanisms that were compromised by damage (Posner et al., 1984; Posner et al., 1987; Posner & Petersen, 1990).

The aim of the study reported in this chapter was to use TMS to test whether the frontal eye fields and/or the angular gyri make critical contributions to feature or spatial priming. The experiments combined the priming of colour pop-out paradigm with saccadic responses (McPeek et al., 1999) and a TMS protocol previously shown to disrupt visual motion priming (Campana et al., 2002). The imaging and single-unit evidence reviewed above indicated that both feature and spatial priming modify FEF

activity in a similar way. However, I have proposed that these modulations may be task-critical in the case of spatial but not feature priming. To test this hypothesis, four experiments were carried out. TMS was applied over the right and left FEFs and AGs in two different priming paradigms (feature versus spatial) and with two different TMS timing protocols. To test whether these cortical areas are involved in primed memory storage across trials, TMS was applied in the inter-trial interval. To test whether these areas are important when a repeated saccade is made to a primed feature or location, TMS was applied simultaneous with the onset of the visual search array.

6.2. Methods

Subjects

In Experiment 1 (Feature Priming/TMS in ITI) thirteen subjects were tested. Of these, five (1 female) showed a baseline behavioural priming effect. In Experiment 2 (Feature Priming/TMS at stimulus onset) eleven subjects were tested and five (1 female) showed baseline priming. In Experiment 3 (Spatial Priming/TMS in ITI) twelve subjects were tested and five showed baseline priming (2 females). In Experiment 4 (Spatial Priming/TMS at stimulus onset) ten subjects were tested and five (2 females) showed baseline priming. One additional subject showed baseline inhibition of return. In all four experiments, only the data from subjects who showed a baseline behavioural priming effect were analysed to test for an effect of TMS. Two subjects participated in three of the four experiments. A further four participated in two of them – one feature and one spatial priming experiment. All subjects were right-handed and had normal or corrected-to-normal vision. All gave informed written consent and reported an absence of any neurological condition in their known family history. All procedures were approved by

the Oxford Research Ethics Committee (OxREC) and the Institute of Neurology, University College London.

Visual Stimuli

Two varieties of odd-man-out search arrays, each containing three stimuli (1.4 x 1.4 DVA), were used in the feature and spatial priming experiments (see Figure 6.1). An array with two distractors was chosen as the fewer distractors, the more difficult it is to select the odd-man-out target (Bravo & Nakayama, 1992; McPeek et al., 1999). Stimuli in the feature priming arrays consisted of luminance-matched (12.5cd/m^2) green (CIE: x = .287, y = .581) and mauve (CIE: x = .459, y = .252) diamond shapes. The centre of each diamond contained a small white square. On half the trials, the target was green and the distractors were mauve, otherwise target/distractor colour pairings were inverted. Stimuli in the spatial priming arrays consisted of X-shaped stimuli of three different luminance-matched (71cd/ m^2) colour pairings: blue (CIE: x = .209, y = .311) and orange (CIE: x = .480, y = .384); green (CIE: x = .285, y = .590) and brown (CIE: x = .338, y = .319); and pink (CIE: x = .295, y = .185) and purple (CIE: x = .249, y = .195). The centre-point of each X stimulus was coloured black. On half the trials, the target location was repeated on consecutive trials, otherwise it switched. Both feature and priming stimuli were displayed on a background of uniform white (177cd/m^2) on a 16" screen running at 100Hz. The stimuli were arranged on an imaginary ellipse subtending 14.8 DVA horizontally and 11.7 DVA vertically. The stimuli were positioned on each trial at one of six possible locations, corresponding to 1, 3, 5, 7, 9 and 11 O' Clock. All three stimuli were positioned equidistant from one another.

In the feature priming experiments, target colour and location were randomized across trials with the constraint that target location was never repeated on consecutive trials.

Hence, target colour had a 0.5 switch probability, but target location switched on every trial. In the spatial priming experiments, target colour and location were randomized with the constraint that target colour never repeated on consecutive trials. Hence, target location had a 0.5 switch probability, but target colour always switched on every trial.

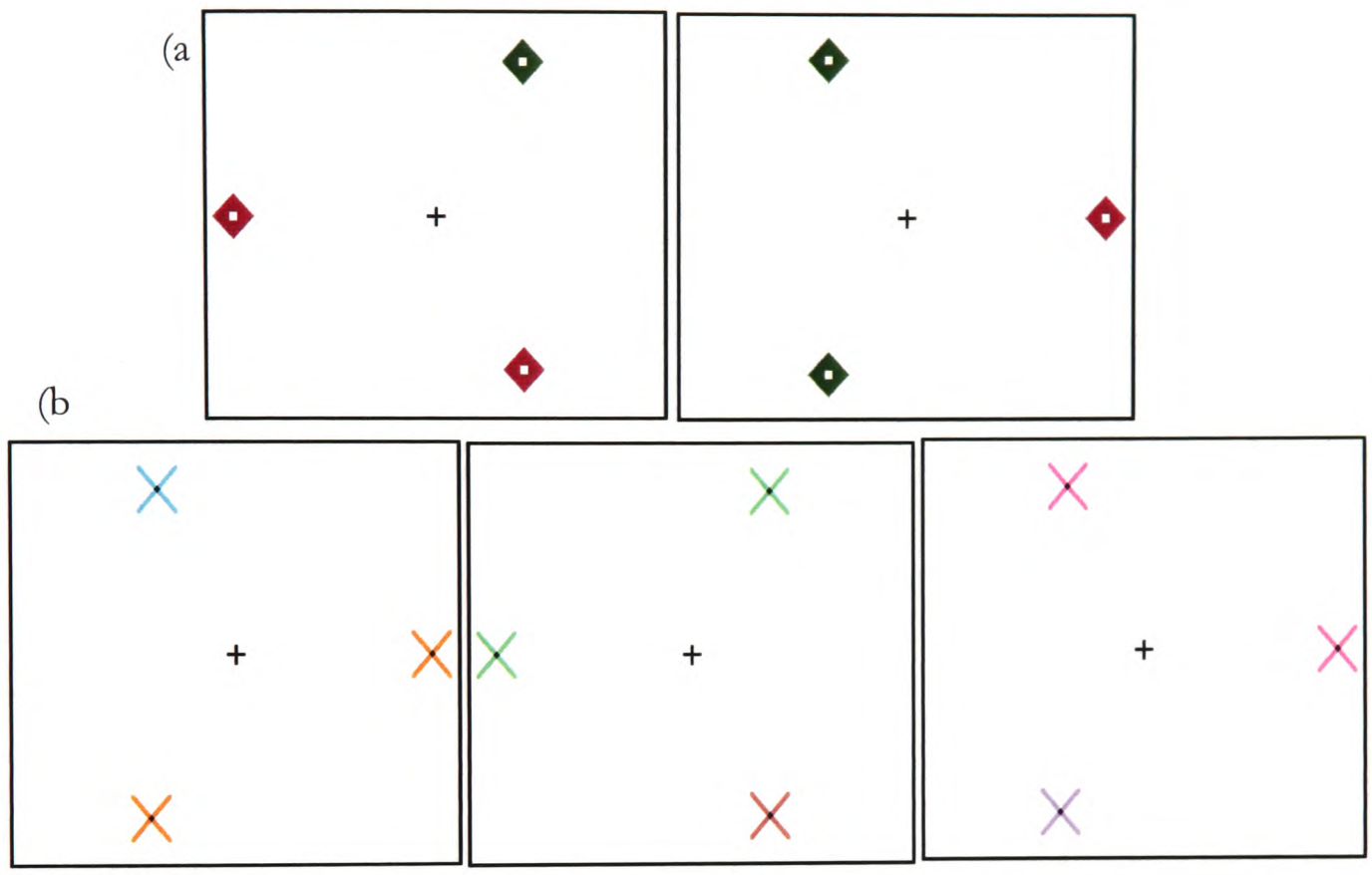


Figure 6.1. Visual Search Arrays. (a) Feature Priming Arrays: the target and distractors were green and mauve coloured diamonds with a 0.5 colour switch probability. In the sample arrays shown a green target is at 1 O'Clock in the left array (trial n) and a mauve target is at 3 O'Clock in the right array (trial n+1). Trial n+1 represents a switch trial. **(b)** Spatial Priming Arrays: the target and distractors were X-shaped stimuli of three different colour pairs. The left-most array shows a blue target at 11 O'Clock among orange distractors (trial n). The middle array shows a brown target at 5 O'Clock among green distractors (trial n+1). The right-most array shows a purple target at 7 O'Clock among pink distractors (trial n+1). Trial n+1 represents a switch trial and trial n+2 represents a stay trial.

Procedure

Four experiments were run. Two tested the effect of TMS on feature priming and two on spatial priming. Apart from the visual stimulus differences between the spatial and feature priming experiments, the only other difference was the timing of TMS application. In two experiments, TMS was applied during the inter-trial interval ("TMS in ITI"); in the other two experiments, TMS was triggered by the search array onset ("TMS at onset"). The experimental procedure was adapted from McPeek, et al. (1999). Subjects

sat in a dimly lit room 57cm in front of the screen. The experiment started with an eye movement calibration procedure that was repeated at the start of each new experimental block. At the start of the experiment, subjects performed two practice blocks (40 trials each) to stabilize saccadic reaction times. Each experimental block began with five practice trials, followed by 40 trials, the data from which were subjected to statistical analysis. At the start of each trial a fixation circle appeared (see Figure 6.2). Subjects initiated the trial by pressing a key on the keyboard. A fixation cross (variable duration 300-500ms) then appeared, after which the search array was drawn to the screen. During the "TMS at onset" experiments, 10 Hz TMS (500ms) was triggered by the onset of the visual search array. Subjects were instructed to make a saccade to the odd target as quickly and accurately as possible. The array was removed once a saccade was initiated. Following the response, there was a 1500ms inter-trial interval (ITI). During the "TMS in ITI" experiments, 10 Hz TMS lasting 500ms was applied during the middle 500ms period. This TMS protocol replicated that used by Campana, et al. (2002) in a study of motion priming. After the ITI the fixation circle re-appeared signalling the start of the next trial. Subjects performed a total of twelve experimental and two practice blocks. There were six experimental conditions, comprising a total of 80 trials per condition: TMS over the right FEFs (RFEF), left FEFs (LFEF), right angular gyrus (RAG), left angular gyrus (LAG) and sham TMS over the right FEFs (Rsham) and left FEFs (Lsham).

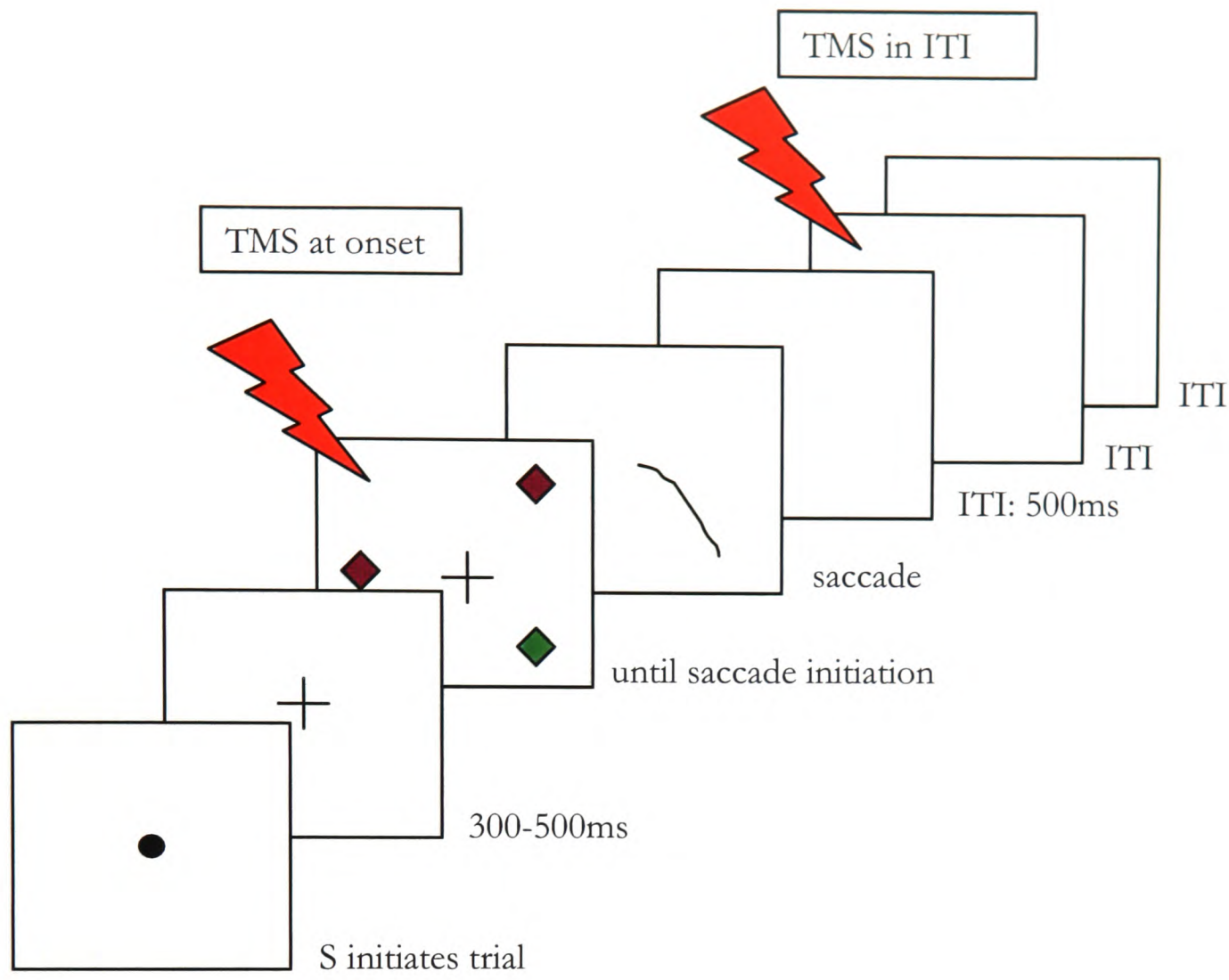


Figure 6.2. Time-line of an experimental trial. Subjects pressed a key to start a trial. A fixation cross was presented for a variable duration (300 - 500ms) followed by the search array, which terminated when a saccade was initiated. Following the saccade, there was an ITI (1500ms). In the "TMS at onset" experiment, 10 Hz TMS (500ms) was applied during the array. In the "TMS in ITI" experiment, TMS was applied in the middle 500ms period of the ITI.

Eye Movement Recording and Analysis

Eye movements were recorded using the Eyelink I System (SR Research, Ontario, Canada) using corneal reflection to define pupil position. The head movement compensation system was removed to enable TMS application and the eye tracker was bolted to a chinrest. Head movement was restricted by a forehead and chin rest and was compensated for by an automated drift correction procedure carried out at the start of each trial. During calibration, subjects made a saccade to a white circle on a black background presented sequentially at each of nine points on a square array. Eye

movements were recorded at a sampling rate of 250Hz. Saccades were detected by means of an automated algorithm using minimum velocity and acceleration criteria of 35°/sec and 9,500°/sec, respectively. Eye position data were analysed off-line. Trials in which subjects blinked or broke fixation were automatically terminated and the search array was removed from the screen.

Saccadic reaction times from correct trials only were admitted to statistical analysis if they fulfilled latency and amplitude criteria. Saccades were considered to be in the correct direction when the amplitude in that direction was greater than 1 DVA. Saccades with latencies below 80ms or above 1000ms were excluded. On average, 5% of trials were rejected in each condition of each experiment owing to blinks and breaks of fixation. There was no difference in blink rates across conditions.

Magnetic Stimulation Protocol

The right and left FEFs were targeted for TMS using the Brainsight frameless stereotaxy system (Rogue Research, Montreal, Canada) and anatomical landmarks as described in Chapter 3. The anatomical coordinates were transformed into MNI space (Montreal Neurological Institute 152-mean brain T1 template) to check correspondence with published mean and range coordinates for FEF location. Mean FEF MNI coordinates for the subjects in this study were: x = 23, y = 1, z = 60, which corresponds well with published FEF coordinates from imaging studies (Paus, 1996). Three of the subjects in this study participated in the fMRI FEF localizer experiment reported in Chapter 3. One of these participated in three of the priming experiments; two participated in two of them – one feature and one spatial priming experiment.

The right and left angular gyri (RAG, LAG) in each hemisphere were localized using group average Talairach coordinates from a study that reported TMS interference on a visual search and visuospatial orienting task (Rushworth et al., 2001a). Each subject's anatomical MRI scan was normalized against the MNI 152-mean brain T1 template and the Talairach coordinates were then translated into that individual subject's normalized image space. These coordinates were then converted into non-normalized image space and plotted within Brainsight. The locations marked by this method were confirmed against anatomical landmarks for the angular gyrus. By combining these two methods, the area stimulated by TMS was located inferior to the intra-parietal sulcus and superior to the posterior end of the superior temporal sulcus, which bisects the angular gryus (mean MNI coordinates: x = 39, y = 68, z = 5)(see Figure 6.3).

A Magstim Super Rapid machine (Magstim Company, Dyfed, U.K.) was used to deliver repetitive-pulse TMS through a small diameter (50mm) figure-of-eight TMS coil. Coils were replaced at the end of each block and air-cooled to prevent over-heating. In the FEF conditions, the coil handle was oriented parallel to the floor, resulting in an anterior-posterior direction of induced current flow. Over the angular gyrus, the coil was held tangential to the skull, oriented at approximately 45 degrees to the spinal cord. During the sham blocks, the coil was placed over the FEFs but oriented perpendicular to the floor, such that the magnetic field was orthogonal to the subjects' skull. 10Hz TMS (500ms) was applied at 65% of stimulator output. During the "TMS at onset" experiments, stimulation was triggered by the onset of the visual search array. During the "TMS in ITI" experiments, TMS was applied during the middle 500ms of the 1500ms ITI.

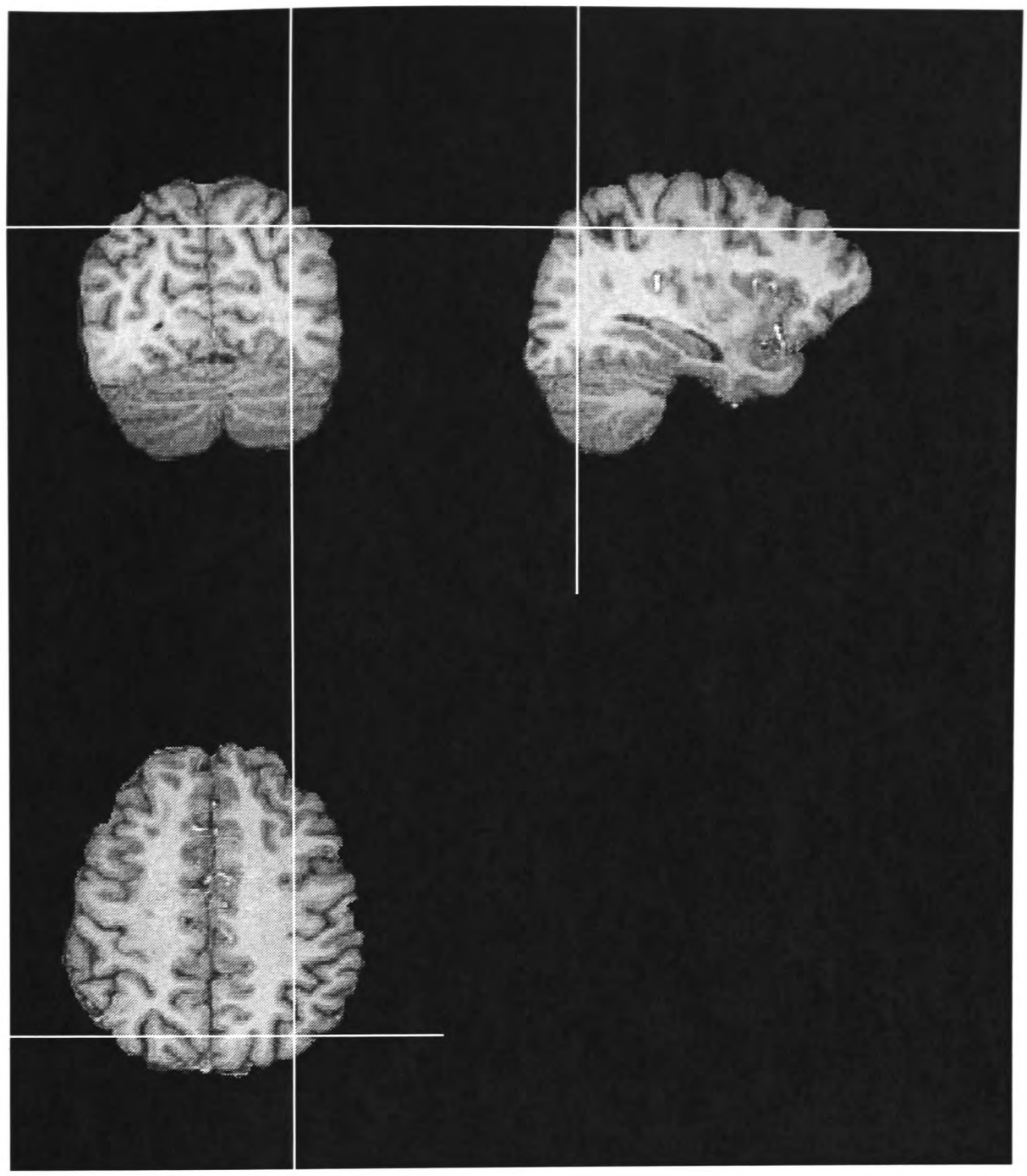


Figure 6.3. Sample MRI from single subject showing angular gyrus localization.

6.3. Results

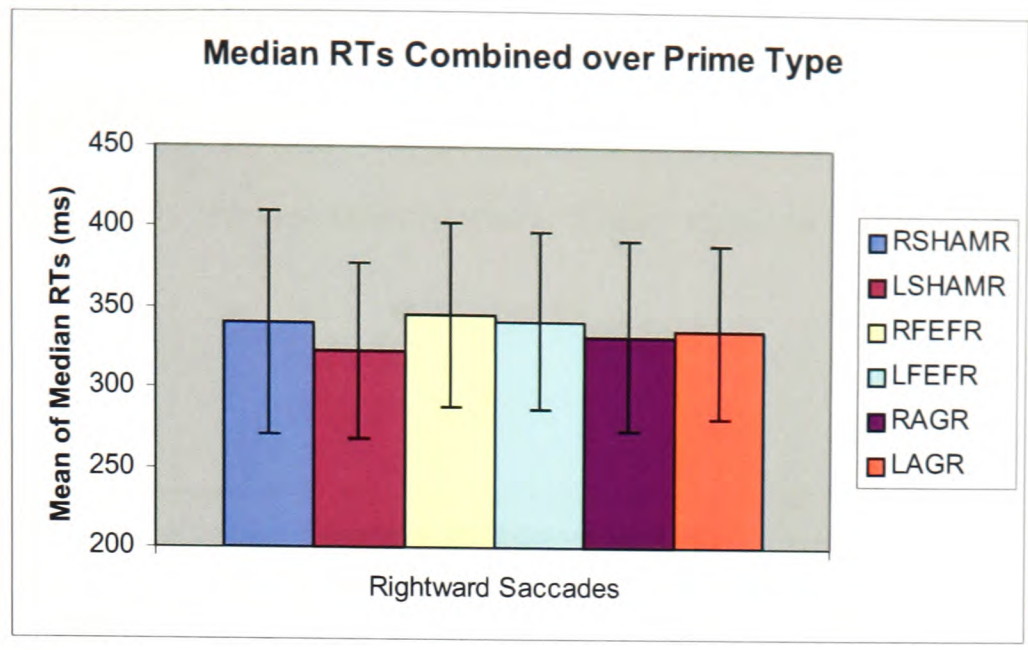
Each trial was classified according to the target on the preceding trial. On "stay" trials, the target on the previous trial was either the same colour (Feature Priming) or had been at the same location (Spatial Priming) as the current trial target. If the previous trial target differed, the trial was classified as a "switch" trial. Trials were sorted into "stay" or "switch" categories and median saccadic reaction times (SRTs) were calculated for each category and experimental condition. Only those subjects with a median switch trial SRT that was a minimum of 10ms slower than the median stay trial SRT in both sham

conditions were regarded as showing a baseline priming effect. Only data from subjects who fulfilled this criterion were analysed for an effect of TMS.

To investigate potential TMS effects on the distribution of saccadic reaction times, cumulative frequency curves of stay versus switch trial latencies were generated for each subject in each condition. Each stay trial curve was then subtracted from the corresponding switch trial curve to yield a difference curve, which represented the size of the priming effect (proportionate stay/switch SRT difference) for each subject in each time bin. A group mean difference curve was then calculated for each condition. The data for the right and left sham conditions were combined to yield a baseline priming curve composed of 160 trials. Each priming curve for a TMS condition consisted of 80 trials. Priming curves were plotted with 95% confidence intervals (C.I.s).

Generalized Effect of TMS on Saccadic Reaction Time:

To assess whether TMS induced a generalized delay in contralateral saccades (Ro et al., 1997), the data were pooled over stay and switch trials and separated by target hemifield. There was no difference in saccade latencies to either hemifield when TMS was applied in the inter-trial interval or at stimulus onset in either the feature or spatial priming experiments (Figure 6.4).



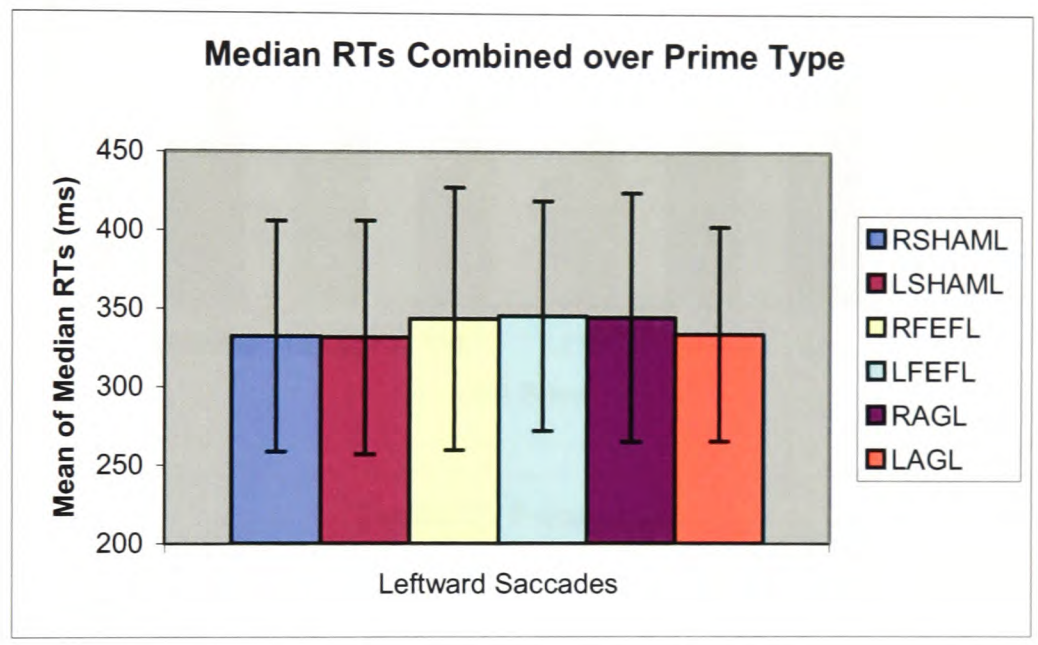


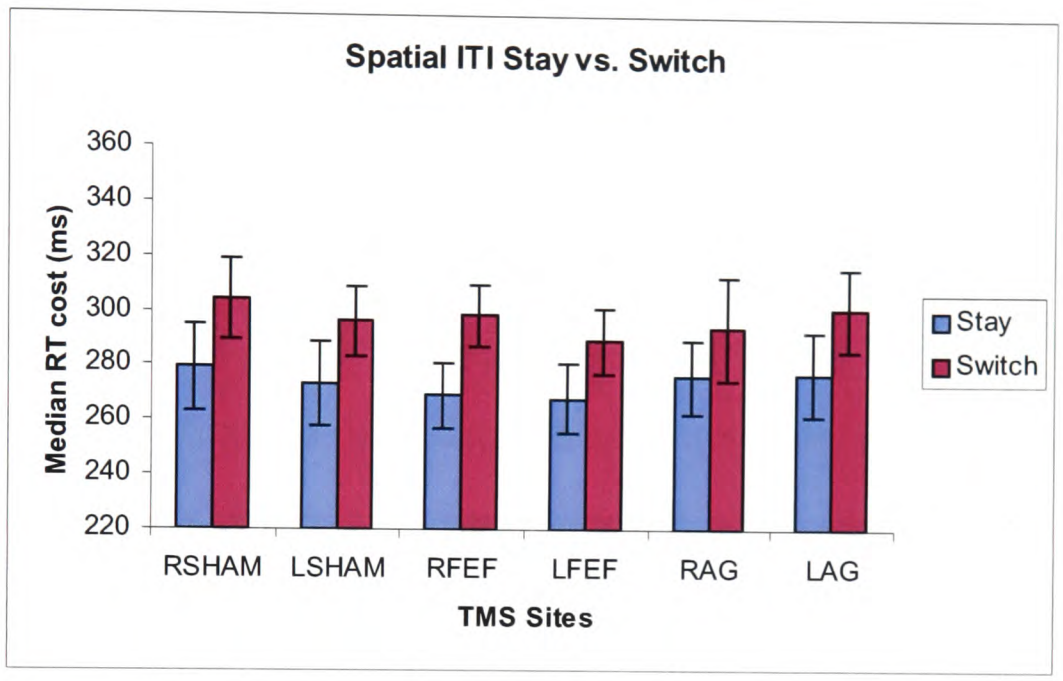
Figure 6.4. Median saccade latencies to targets in each hemifield. TMS did not increase contralateral saccade latencies in any condition (error bars = 1SEM).

Spatial Priming:

Expt 1 (Spatial Priming - TMS in ITI):

Median SRTs from the five subjects showing baseline priming were entered into a three-way repeated measures ANOVA (TMS Site (Sham/FEF/AG) * Side (Left/Right) * Prime (Stay/Switch)). There was a significant effect of Prime ($F(1,4) = 40.202$, $p = 0.003$) with median switch latencies being significantly longer than stay latencies (mean

difference: 23.3 ms, 95% C.I.s: 13.09, 33.50). There were no other effects, trends or interactions (see Figure 6.5). The pattern of errors matched that of SRTs (see Table 6.1). There was a significant effect of Prime ($F(1,4) = 176.942$, $p < 0.001$), with greater accuracy on stay trials versus switch trials. There were no other effects, trends or interactions.



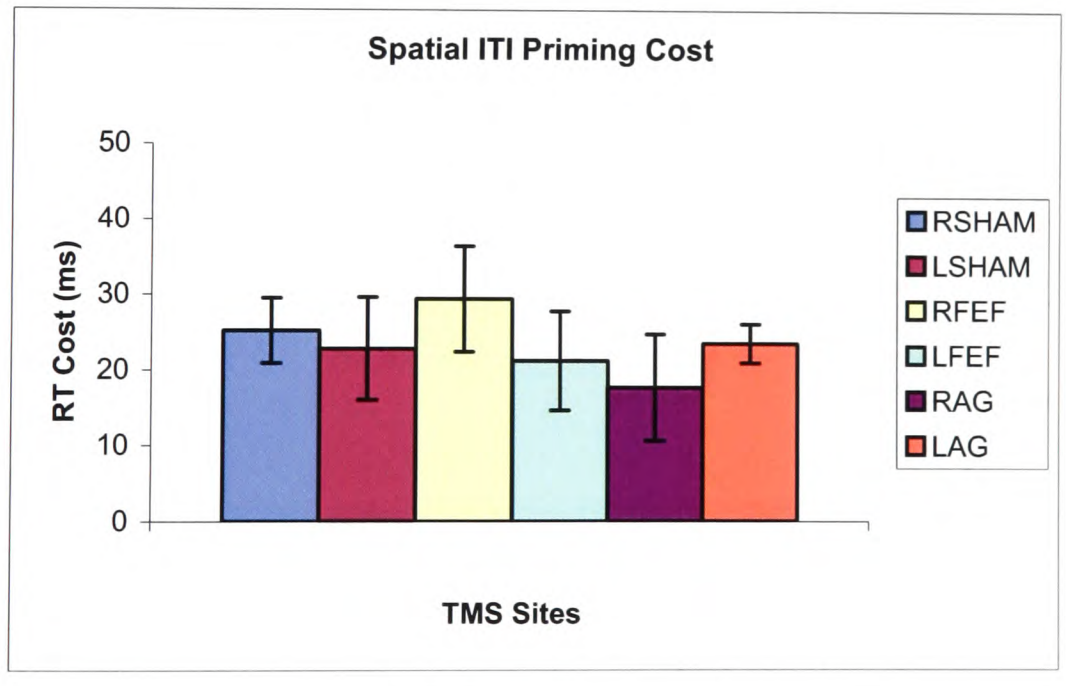


Figure 6.5. Spatial Priming Median Data ("TMS in ITI"). The upper graph shows median saccadic reaction times (SRTs) (ms) in all conditions for the trials in which the target location repeated ("Stay") or changed ("Switch"). The lower graph plots the mean stay/switch difference (cost), indicating the size of the priming effect (error bars in both graphs = 1SEM). TMS had no effect on baseline priming.

Mean % Correct	RSham	LSham	RFEF	LFEF	RAG	LAG
Stay	47.5	53.75	45	48.75	40	37.5
	(7.2)	*(7.75)*	*(7.84)*	*(6.9)*	*(5.4)*	*(9.99)*
Switch	42.5	28.75	38.75	32.5	32.5	31.25
	(9.12)	*(7.16)*	*(7.98)*	*(8.36)*	*(5.05)*	*(7.32)*
Total	90	82.5	83.75	81.25	72.5	68.75
	(15.1)	*(14.21)*	*(13.79)*	*(14.37)*	*(9.94)*	*(16.78)*

Table 6.1. Spatial Priming Accuracy Data ("TMS in ITI"). Table shows mean performance accuracy in each of the experimental conditions. SD in brackets.

The baseline priming window was short (see Figure 6.6) – extending between 250ms and 325ms (ca. 75ms duration) and the average proportionate stay/switch difference within this period was 0.16. There was significant priming in each of the TMS conditions, which tended to be longer in duration and larger in size than the baseline. Since the TMS conditions did not differ significantly, the data were pooled over TMS site and a TMS priming curve was plotted against the baseline. There was a close fit between the shapes of the baseline and combined TMS priming curves (see Figure 6.6(b)).

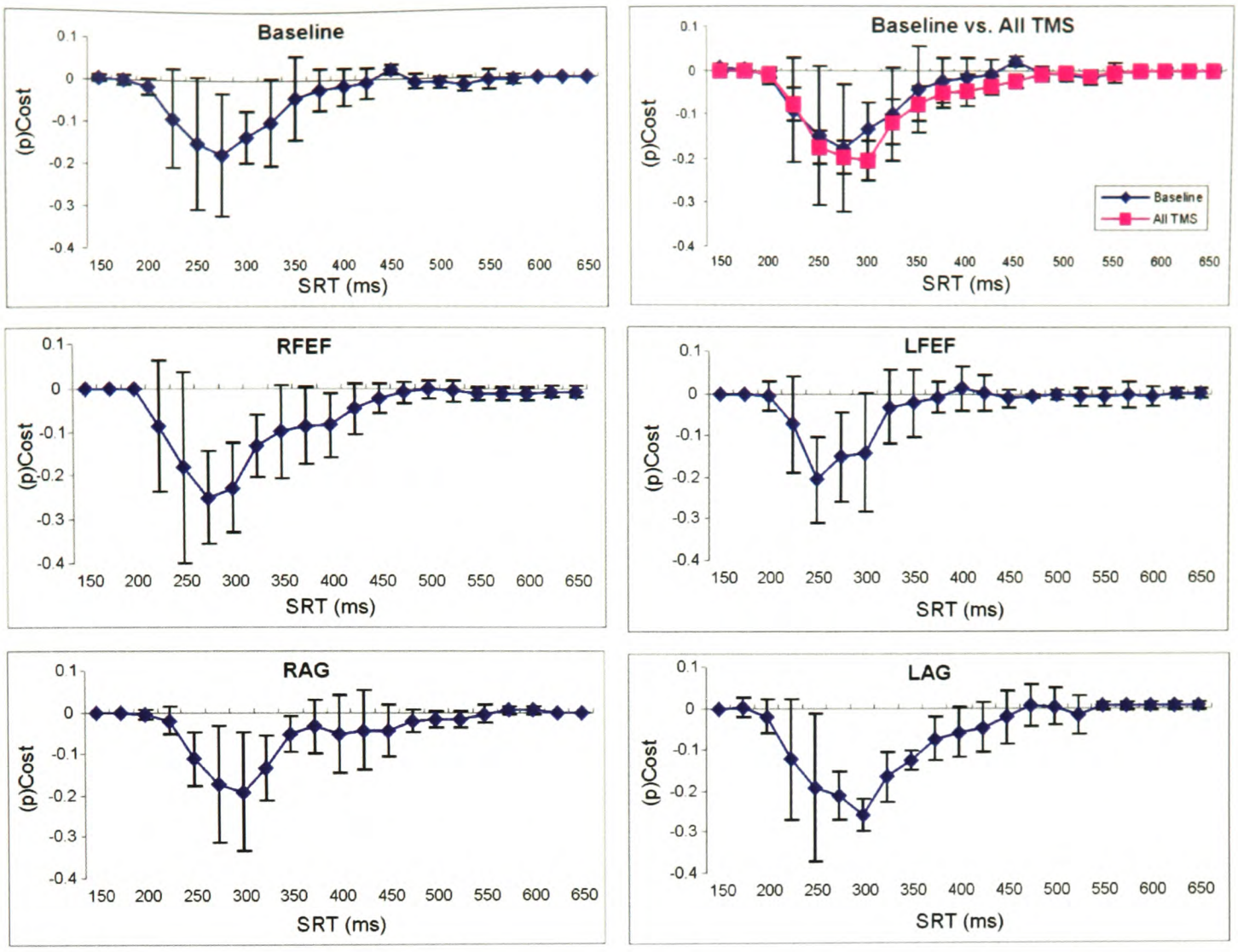


Figure 6.6. Priming distributions for Spatial Priming ("TMS in ITI") Experiment. Each graph plots the proportionate difference ((p)cost) between switch and stay trial saccadic reaction times (SRT, y axis), indicating the size of the priming effect at each time interval. The baseline sample consisted of 160 trials. Each TMS condition sampled 80 trials. Error bars = 95% C.I.s. **From top left: (a)** baseline priming curve **(b)** priming curve for all TMS conditions combined against baseline **(c)** RFEF priming curve **(d)** LFEF priming curve **(e)** RAG priming curve **(f)** LAG priming curve.

Expt 2 (Spatial Priming - TMS at stimulus onset):

Median SRTs from the five subjects showing baseline priming were submitted to a three-way repeated measures ANOVA (TMS Site (Sham/FEF/AG) * Side (Left/Right) * Prime (Stay/Switch)). There was a main effect of Prime ($F(1,4) = 15.589$, $p = 0.017$). Median switch latencies were significantly longer than stay latencies (mean difference: 22.83 ms, 95% C.I.s.: 38.89, 6.77). There was also an effect of TMS Site ($F(2,8) = 7.575$, $p = 0.014$), with planned contrasts showing that FEF latencies were significantly longer

than baseline sham TMS latencies ($F(1,4) = 33.378$, $p = 0.004$; mean difference: 15.4 ms, 95% C.I.s: 22.80, 7.99). Angular gyrus latencies did not differ significantly from baseline ($F(1,4) = 2.608$, $p = 0.182$). There was a two-way interaction of Site * Prime ($F(2,8) = 4.654$, $p = 0.046$) and a three-way interaction of Site * Side * Prime ($F(2,8) = 10.419$, $p = 0.006$).

These interactions were explored further by decomposing the data according to Side. A two-way ANOVA on the right hemisphere TMS sites (TMS Site (Rsham/RFEF/RAG) * Prime) revealed an effect of Prime ($F(1,4) = 40.049$, $p = 0.003$) but no other effects, trends or interactions. A two-way ANOVA on the left hemisphere sites (TMS Site (Lsham/LFEF/LAG) * Prime) showed that the priming effect was not significant ($F(1,4) = 5.794$, $p = 0.074$). There was no effect of TMS Site ($F(2,8) = 3.349$, $p = 0.088$), but there was a significant Site * Prime interaction ($F(2,8) = 13.174$, $p = 0.003$). Inspection of the means showed there was no difference between switch latencies in the Lsham, LFEF and LAG conditions, but that stay trial latencies were reduced in the LAG and LFEF conditions. The stay/switch difference was abolished with LFEF TMS (see Figure 6.7). Two paired-samples t-tests compared the means of the median stay trial latencies of LFEF and LAG against the Lsham baseline. The LAG latencies did not differ significantly from baseline ($t(4) = -2.459$, $p = 0.07$), but the LFEF latencies did ($t(4) = -3.083$, $p = 0.04$). TMS over the LFEFs significantly increased stay trial latencies (mean difference: 41ms, 95% C.I.s: 3.08, 78.91).

Analysis of the error data revealed a significant effect of Prime ($F(1,4) = 23.870$, $p = 0.008$), with greater accuracy on stay versus switch trials, but no other effects, trends or interactions (Table 6.2). This indicates that the effect of TMS over the LFEF on priming was not the result of a speed/accuracy trade-off. To test for a possible hemifield bias, the

data were analysed according to whether the target was in the right or left hemifield. The data tended to correspond with the overall analysis, showing an effect of TMS over LFEF. There was significant priming in both hemifields ($F(1,4) = 29.680$, $p = 0.006$), and a main effect of TMS Site ($F(1,8) = 8.227$, $p = 0.044$ (Greenhouse-Geisser corrected)). There was a trend towards a Site * Prime interaction ($F(2,8) = 4.066$, $p = 0.06$) and Site * Side * Prime interaction ($F(2,8) = 3.442$, $p = 0.083$), but there was no effect of hemifield nor any hemifield interaction.

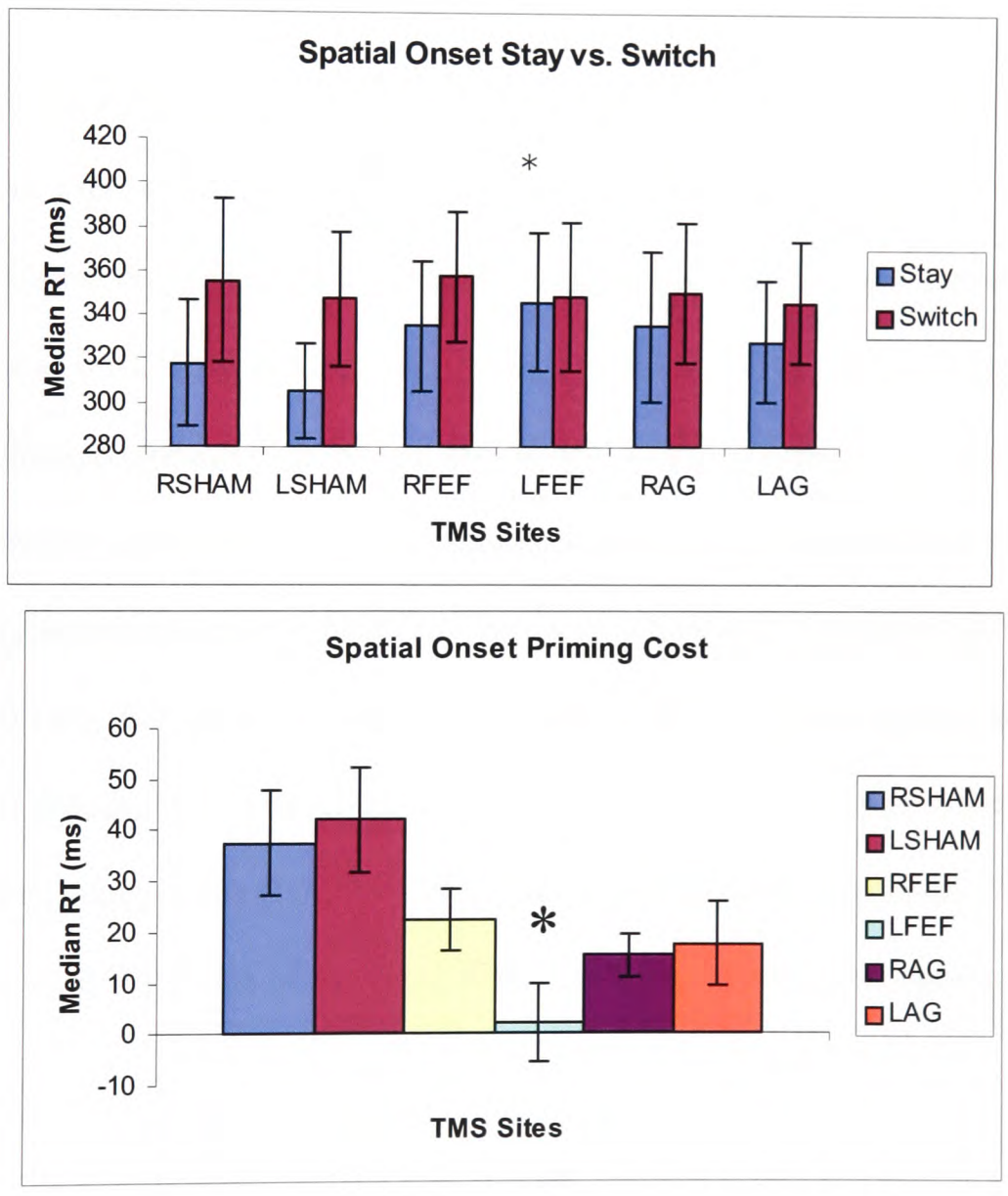


Figure 6.7. Spatial Priming Median Data ("TMS at stimulus onset"). The upper graph shows median saccadic reaction times (SRTs) (ms) in all conditions for the trials in which the target location repeated ("Stay") or changed ("Switch"). The lower graph plots the mean stay/switch difference (cost), indicating the size of the priming effect (error bars in both graphs = 1SEM). TMS over LFEF significantly reduced baseline priming by increasing saccadic latencies on stay trials.

Mean % Correct	RSham	LSham	RFEF	LFEF	RAG	LAG
Stay	48.25 (20.48)	47.25 (19.37)	44.75 (20.08)	43.25 (18.51)	44 (18.3)	44.5 (18.44)
Switch	34 (11.85)	33.5 (12.15)	34.75 (12.23)	33.5 (12)	36.5 (13.6)	32.75 (12.49)
Total	82.25 (6.24)	80.75 (6.85)	79.5 (3.29)	76.75 (4.72)	79.75 (9.92)	77.25 (7.39)

Table 6.2. Spatial Priming Accuracy Data ("TMS at stimulus onset"). Table shows mean performance accuracy in each of the experimental conditions. SD in brackets.

Priming curves for the baseline and for the combined TMS conditions (excluding LFEF) are plotted in Figure 6.8. The baseline priming window extended between 250ms and 400ms (ca. 150ms duration) and the average proportionate stay/switch difference within this period was 0.18. TMS reduced the size and duration of priming (see Figure 6.8(b)), and this reduction appeared to be greatest in the LFEF condition. To assess priming curve differences statistically, the area under each curve was calculated and submitted to a one-way repeated measures ANOVA. The main effect was not significant ($F(4,16) = 1.77$, $p = 0.184$), but planned contrasts of each TMS condition against the baseline revealed that the area under the LFEF curve was significantly smaller than the area under the baseline priming curve ($F(1,4) = 14.452$, $p = 0.019$)(mean difference: 1.266 units^2, 95% C.I.s: 0.34, 2.19). None of the other TMS conditions approached significance.

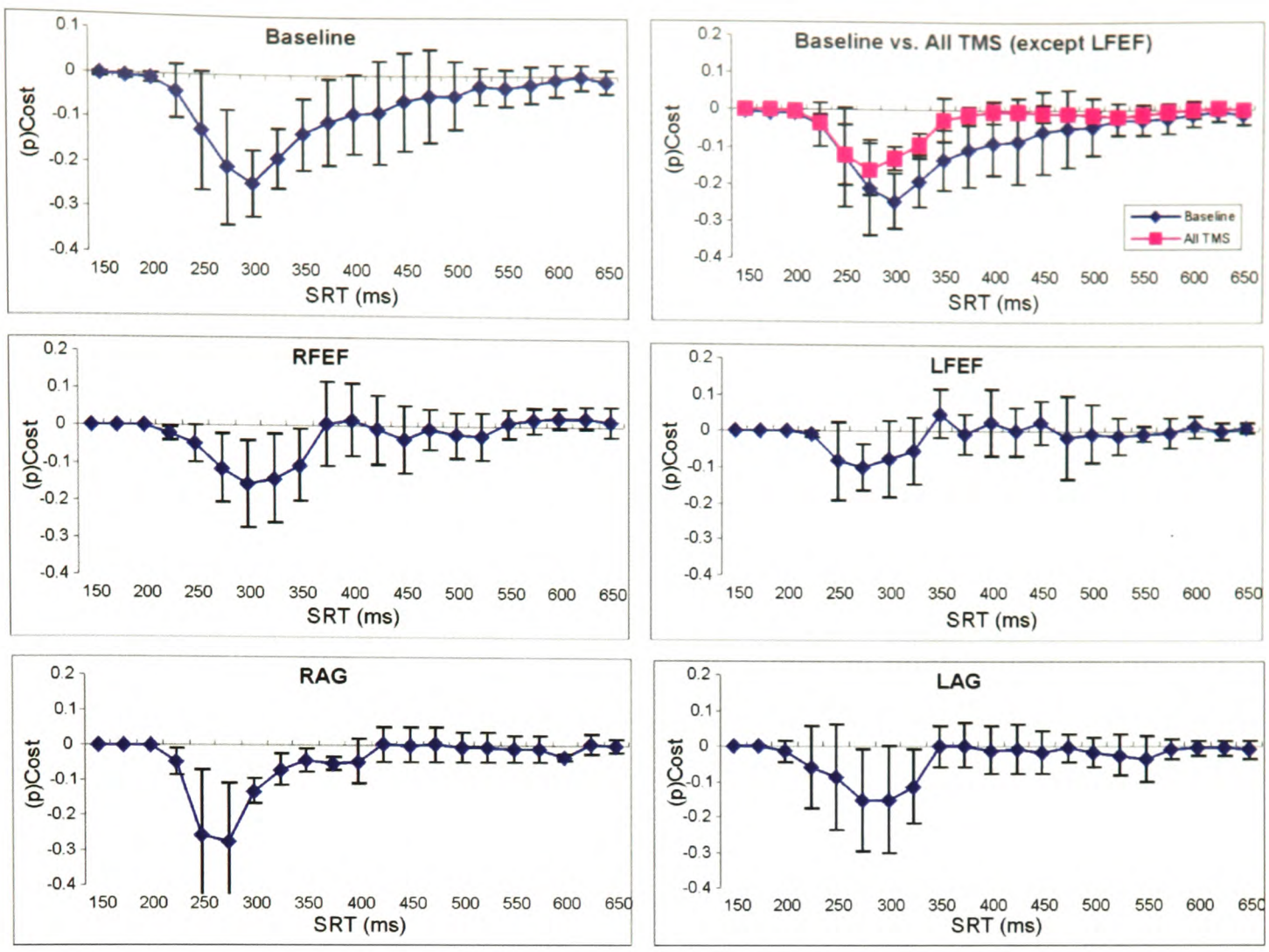


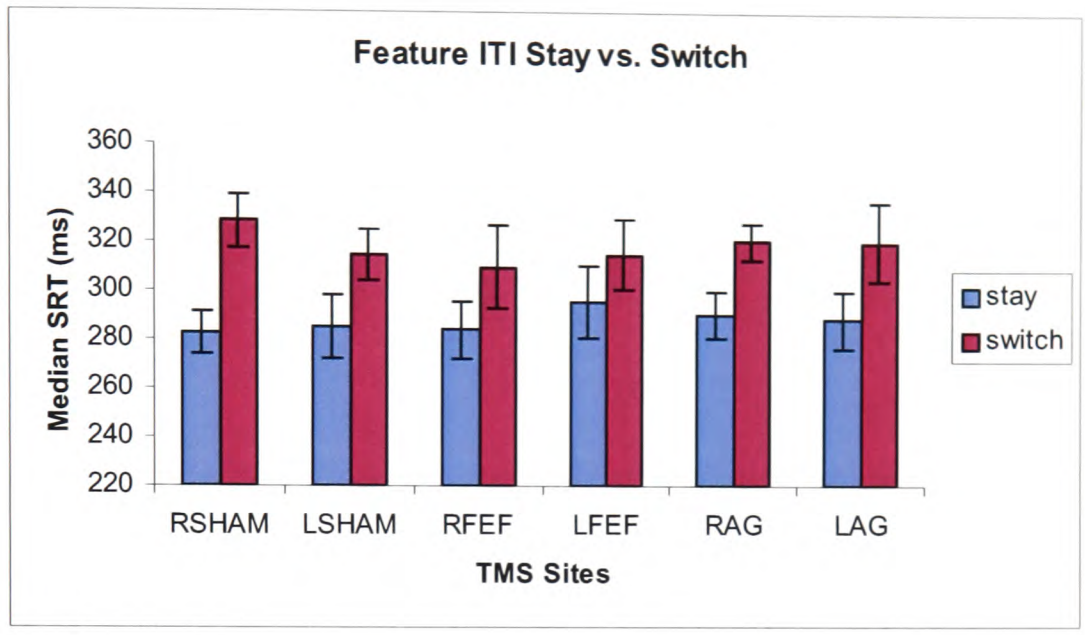
Figure 6.8. Priming distributions for Spatial Priming ("TMS at stimulus onset") Experiment. Each graph plots the proportionate difference ((p)cost) between switch and stay trial saccadic reaction times (SRT, y axis), indicating the size of the priming effect at each time interval. The baseline sample consisted of 160 trials. Each TMS condition sampled 80 trials. Error bars = 95% C.I.s. **From top left: (a)** baseline priming curve **(b)** priming curve for all TMS conditions combined against baseline **(c)** RFEF priming curve **(d)** LFEF priming curve **(e)** RAG priming curve **(f)** LAG priming curve.

Feature Priming:

Expt 3 (Feature Priming - TMS in ITI):

Median SRTs from the five subjects showing baseline priming were entered into a three-way repeated measures ANOVA (TMS Site (Sham/FEF/AG) * Side (Left/Right) * Prime (Stay/Switch)). There was a significant effect of Prime ($F(1,4) = 82.181$, $p = 0.001$) with median switch latencies being significantly longer than stay latencies (mean difference: 30.48 ms, 95% C.I.s: 21.14, 39.81). There were no other effects, trends or

interactions (see Figure 6.9). The pattern of errors matched that of SRTs. There was a significant effect of Prime ($F(1,4) = 112.061$, $p < 0.001$), with greater accuracy on stay versus switch trials, but no other effects, trends or interactions (Table 6.3).



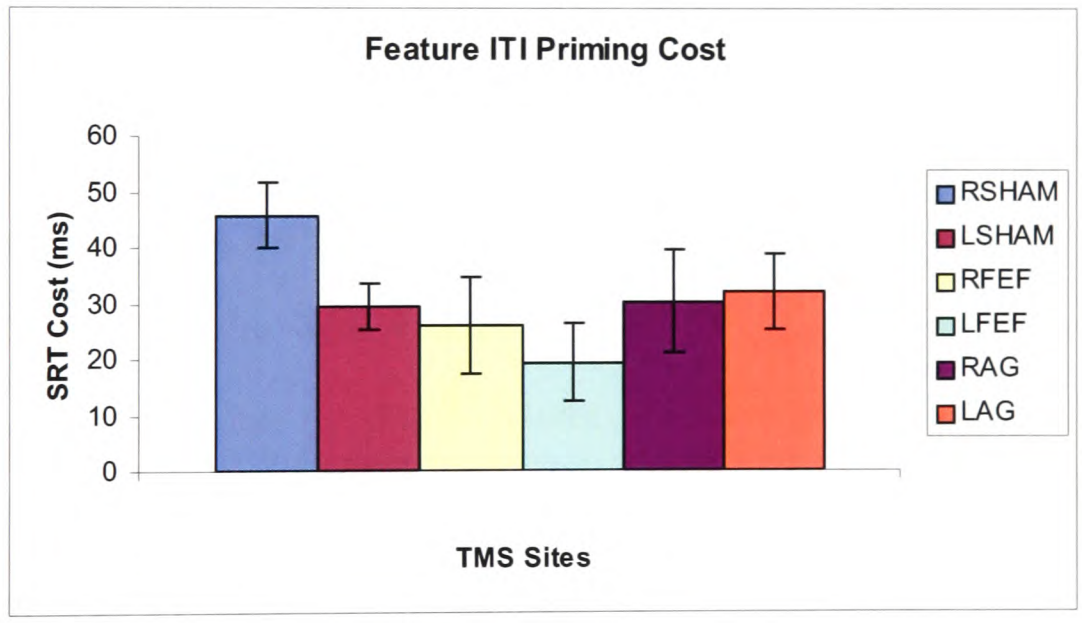


Figure 6.9. Feature Priming Median Data ("TMS in ITI"). The upper graph shows median saccadic reaction times (SRTs) (ms) in all conditions for the trials in which the target colour repeated ("Stay") or changed ("Switch"). The lower graph plots the mean stay/switch difference (cost), indicating the size of the priming effect (error bars in both graphs = 1SEM). TMS had no effect on baseline priming.

Mean % Correct	RSham	LSham	RFEF	LFEF	RAG	LAG
Stay	45	46.25	41.25	42.5	42.5	46.25
	(3.6)	*(3.38)*	*(5.55)*	*(3.6)*	*(6.22)*	*(8.32)*
Switch	38.75	38.75	38.75	40	40	42.5
	(3.58)	*(4.2)*	*(9.41)*	*(4.73)*	*(5.93)*	*(6.4)*
Total	83.75	85	80	82.5	82.5	88.75
	(6.22)	*(7.36)*	*(14.54)*	*(8.05)*	*(12.07)*	*(14.43)*

Table 6.3. Feature Priming Accuracy Data ("TMS in ITI"). Table shows mean performance accuracy in each of the experimental conditions. SD in brackets.

The baseline priming curve (see Figure 6.10) shows that priming extended between 225ms and 575ms (ca. 350ms duration) and the average proportionate stay/switch difference throughout this period was 0.12. There was significant priming in each of the individual TMS conditions, though it tended to be somewhat shorter in duration and smaller in size, which likely reflects the smaller number of trials (max. 80) in each TMS condition compared with the baseline (max. 160 trials). Since the TMS conditions did not differ significantly, the data were pooled over TMS site and a TMS priming curve was plotted against the baseline (see Figure 6.10(b)). Although the size and extent of the priming effect varied across TMS conditions, the shape of the combined TMS priming distribution closely matched the baseline.

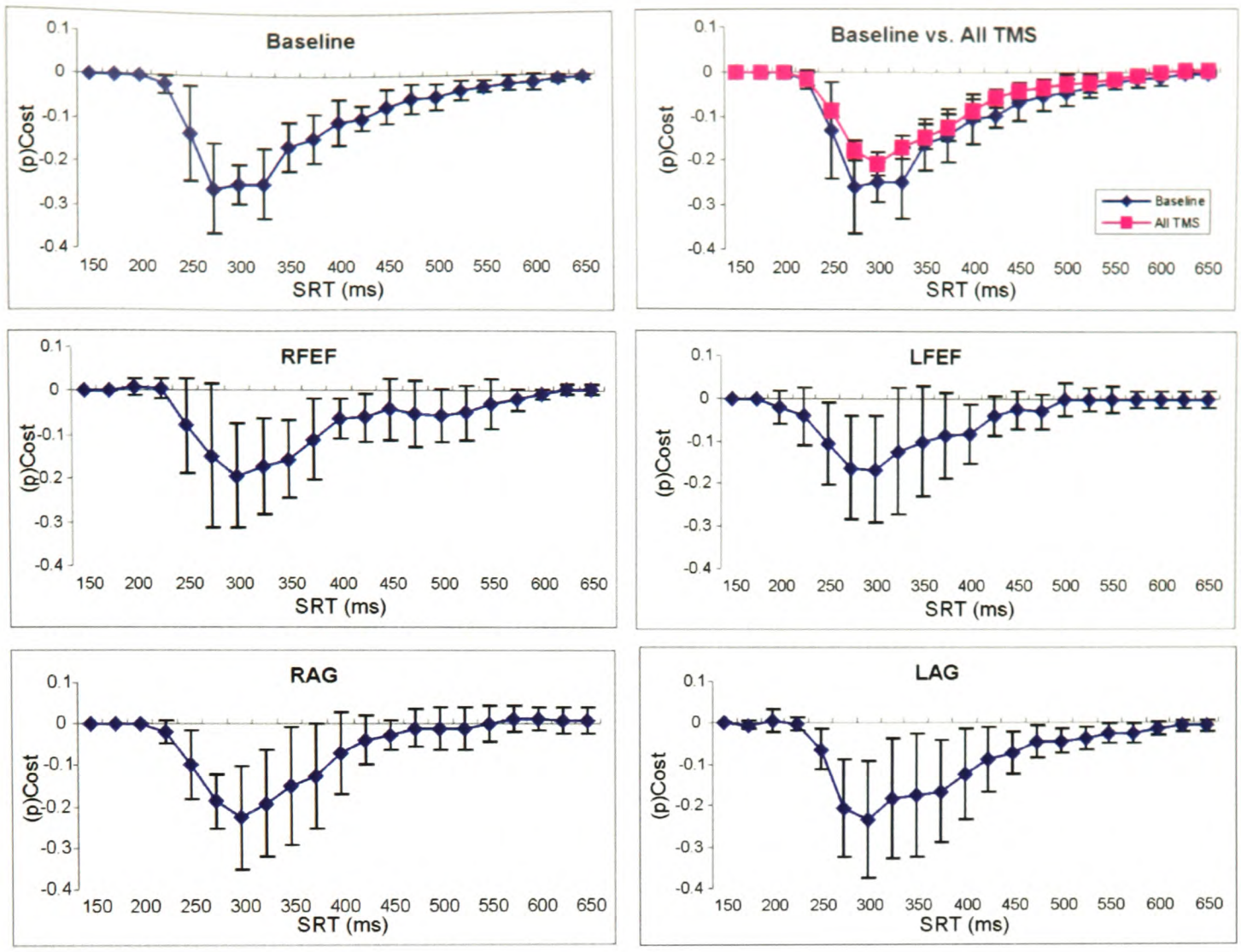


Figure 6.10. Priming distributions for Feature Priming ("TMS in ITI") Experiment. Each graph plots the proportionate difference between switch and stay trial saccadic reaction times (y axis), indicating the size of the priming effect at each time interval. The baseline sample consisted of 160 trials. Each TMS condition sampled 80 trials. Error bars = 95% C.I.s. **(a)** baseline priming curve **(b)** priming curve for all TMS conditions combined against baseline **(c)** RFEF priming curve **(d)** LFEF priming curve **(e)** RAG priming curve **(f)** LAG priming curve.

Expt 4 (Feature Priming - TMS at stimulus onset):

Median SRTs from the five subjects showing baseline priming were entered into a three-way repeated measures ANOVA (TMS Site (Sham/FEF/AG) * Side (Left/Right) * Prime (Stay/Switch)). There was a significant effect of Prime ($F(1,4) = 61.052$, $p = 0.001$) with median switch latencies being significantly longer than stay latencies (mean difference: 29.71 ms, 95% C.I.s: 19.15, 40.27). There were no other effects, trends or interactions (see Figure 6.11). The pattern of errors matched that of SRTs. There was a

significant effect of Prime ($F(1,4) = 7.694$, $p = 0.05$), with greater accuracy on stay versus switch trials, but no other effects, trends or interactions (Table 6.4).

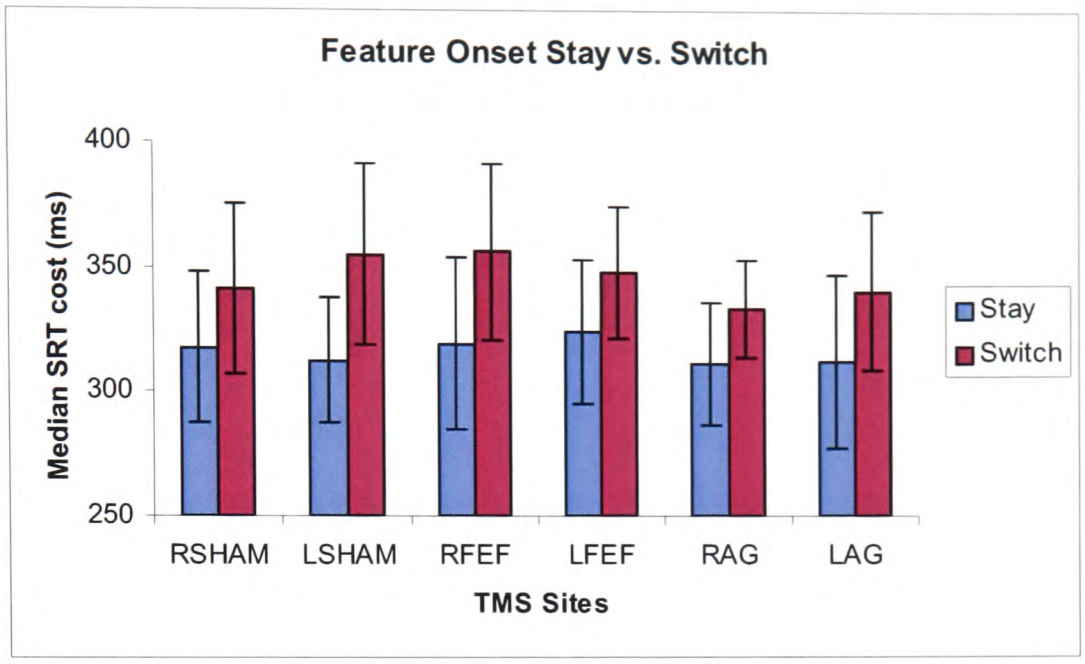


Figure 6.11. Feature Priming Median Data ("TMS at stimulus onset"). The upper graph shows median saccadic reaction times (SRTs) (ms) in all conditions for the trials in which the target colour repeated ("Stay") or changed ("Switch"). The lower graph plots the mean stay/switch difference (cost), indicating the size of the priming effect (error bars in both graphs = 1SEM). TMS had no effect on baseline priming.

Mean % Correct	RSham	LSham	RFEF	LFEF	RAG	LAG
Stay	47.5	45	47.5	46.25	47.5	50
	(1.97)	*(2.33)*	*(3.47)*	*(5.45)*	*(2.27)*	*(6.88)*
Switch	50	47.5	46.25	46.25	43.75	43.75
	(5.11)	*(7.97)*	*(5.56)*	*(7.78)*	*(4.97)*	*(5.82)*
Total	97.5	92.5	93.75	92.5	91.25	93.75
	(6.7)	*(9.54)*	*(8.81)*	*(12.7)*	*(6.61)*	*(11.87)*

Table 6.4. Feature Priming Accuracy Data ("TMS at stimulus onset"). Table shows mean performance accuracy in each of the experimental conditions. SD in brackets.

Baseline priming (see Figure 6.12) extended between 225ms and 500ms (ca. 275ms duration) and the average proportionate stay/switch difference throughout this period was 0.23. There was significant priming in each of the TMS conditions. Since the TMS conditions did not differ statistically, the data were pooled over TMS site and a TMS priming curve was plotted against the baseline. The TMS priming distribution tended to have a higher peak and a shorter tail (see Figure 6.12(b)). The LFEF distribution showed less priming than any of the other TMS conditions: the 95% C.I.s for the stay/switch curve difference overlapped with zero at all but two time-points: 300 and 425ms. To test whether this priming curve differed significantly from baseline, the area under each curve was calculated and submitted to a paired samples t-test. The difference was not significant: $t(4) = -1.87$, $p = 0.135$).

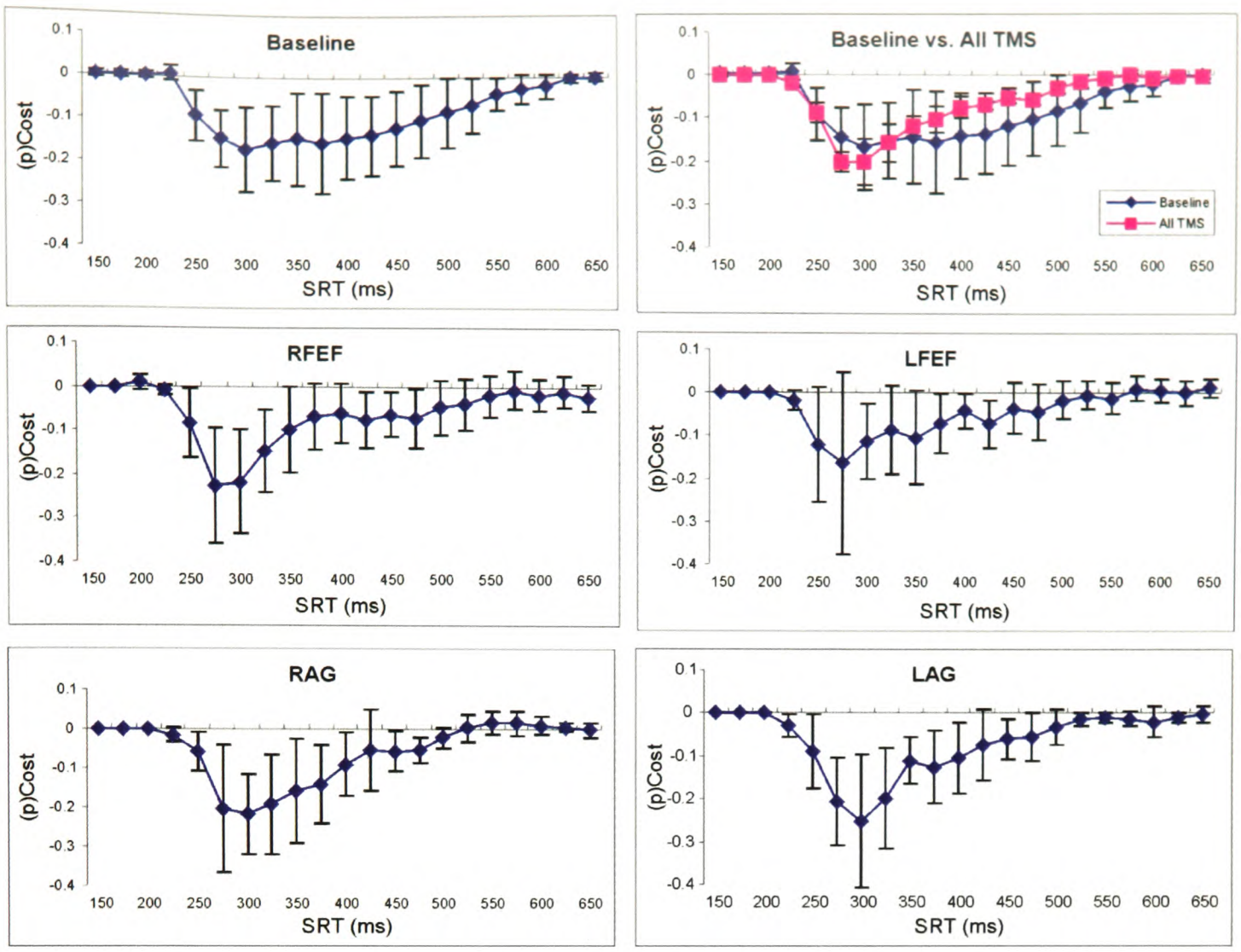


Figure 6.12. Priming distributions for Feature Priming ("TMS at stimulus onset") Experiment. Each graph plots the proportionate difference ((p)cost) between switch and stay trial saccadic reaction times (SRT, y axis), indicating the size of the priming effect at each time interval. The baseline sample consisted of 160 trials. Each TMS condition sampled 80 trials. Error bars = 95% C.I.s. **From top left: (a)** baseline priming curve **(b)** priming curve for all TMS conditions combined against baseline **(c)** RFEF priming curve **(d)** LFEF priming curve **(e)** RAG priming curve **(f)** LAG priming curve.

Summary of Results:

TMS applied over the left FEFs at stimulus onset, but not during the inter-trial interval, significantly reduced spatial priming. This effect was specific to trials on which target location was repeated – TMS increased saccadic reaction time on these trials, almost abolishing the reaction time benefit of location repetition. There was no effect of any other TMS condition, nor any effect on feature priming.

6.4. Discussion

The experiments reported in this chapter tested the effect of TMS over the right and left frontal eye fields (FEFs) and angular gyri (AGs) on the priming of colour pop-out with saccadic responses. TMS applied over the left FEFs disrupted spatial priming when applied at search array onset. Priming was disrupted not just at the mid-point, but throughout the distribution of saccade latencies. The effect was specific for trials in which the target location was the same as on the previous trial; there was no effect when the previous trial's target location differed. Since the target/distractor colours always switched on consecutive trials, there was no colour priming, meaning visual selection demands were constant across trials. Hence, the only difference between stay and switch trials was the influence of a spatial memory signal, which resulted in shorter saccade latencies on stay trials. TMS over the LFEF removed the benefit of spatial repetition by increasing stay trial latencies while leaving switch trials unaffected. This suggests that TMS abolished a spatial memory signal within the left FEFs that is necessary for location priming. The fact that TMS in the ITI had no such effect indicates that this signal is not stored within the FEFs. Rather, it suggests that the left FEF reads out this spatial memory signal when a saccade is being programmed to a repeat location.

TMS was applied in the inter-trial interval (ITI) in order to disrupt the maintenance of a between-trial memory trace that might potentially be stored in the FEFs or the AGs. There was no effect of TMS in the ITI on feature or spatial priming at any of the cortical sites tested, suggesting that none of these areas acts as a storage site for the kind of short-term memory that supports visual or spatial priming. The absence of an effect of TMS in the ITI during feature priming fits with the predictions of the sensory memory hypothesis (Tulving & Schacter, 1990), which holds that sensory adaptation in colour-

selective cortex is critical for colour priming (Walsh et al., 2000; Girard et al., 2001a; Rossi et al., 2001). The failure to disrupt colour priming with TMS over the FEFs or the AGs is consistent with the claim that fronto-parietal repetition suppression reflects downstream effects of sensory adaptation. Neither the FEFs nor the AGs are critical substrates for colour priming.

It was argued in the Introduction that spatial priming may depend critically on changes in the FEF target discrimination function in a way that feature priming does not. The findings of the present experiments support this claim. Since the task was the same for subjects on every trial in both experiments (saccade to the odd-coloured target), many of the computations performed by the FEFs and AGs would have remained constant. The selective delay induced by left FEF TMS on stay trial SRTs rules out generalized disruption of target discrimination, response selection or oculomotor programming as the basis for the TMS effect. If these processes had been disrupted, then TMS at stimulus onset would have also affected feature priming, which it did not. Rather, the selective effect implies disruption of a spatial memory signal that is read out by the left FEFs when a saccade is executed to a repeat location. It is also worth highlighting the absence of a TMS-induced delay on contralateral SRTs (Figure 4), replicating the findings of Chapter 3 with a different paradigm.

The selective effect of left FEF stimulation on spatial priming, which disrupted within-trial rather than between-trial processes, was unexpected. However, Kristjansson, et al.'s (2004) fMRI study reported fronto-parietal repetition suppression when either the target colour or location was repeated. In common with the current study, these neural correlates were obtained *during* the processing of a repeated stimulus, rather than between trials. Further, the authors reported significantly greater suppression in left hemisphere

sites (LFEF, LIPS, LAG) for both feature and spatial priming. Left FEF activations were significant for targets in either hemifield, but right FEF reached significance only for contralateral targets. A number of other imaging studies have reported a left hemisphere bias in various spatial working memory tasks (eg: Klingberg et al., 1997). Since many of these studies used linguistic stimuli, lateralization has often been ascribed to strategy effects or 'the left hemisphere specialization for linguistic processing', even when it is not clear how linguistic factors could account for the effects (eg: Giesbrecht et al., 2003). This may be motivated by conflict with an explanatory scheme that has proposed a right /spatial, left /non-spatial hemispheric specialization for working memory, although the evidential basis for this scheme is inconsistent (Cabeza & Nyberg, 2000; Glabus et al., 2003). The advantage of the implicit memory paradigm used in the present study is that strategic and linguistic factors do not figure, strengthening the claim that implicit spatial memory is lateralized to the left FEFs. Gaymard, et al. (1999) reported data from a patient with a discrete left FEF lesion. This patient executed normal contralateral saccades, but there was a marked reduction in memory-guided saccade gain, which worsened as the delay increased. Performance was normal, however, when the initial eye position was displaced by whole-body rotation. These authors concluded that the left FEF deficits reflected impairment of a spatial memory signal in oculomotor coordinates. They suggested that the (left) FEFs may be particularly important for memorization during short delays that do not depend on dorso-lateral prefrontal cortex. A robust interpretation of this study would suggest that, even after a recovery period, the right FEFs are incapable of taking over the spatial memory read-out functions of the left FEFs.

The selective left FEF effect undermines the suggestion that the data may have resulted from erroneous stimulation of a proximate spatial working memory site in the superior

frontal sulcus (SFS) (Courtney et al., 1998). The SFS activations were bilateral and were situated on average 8.5mm anterior to the FEFs. Parenthetically, it is worth noting that among the authors' *a priori* criteria for a neural correlate of spatial working memory was the stipulation that delay period activation "must be distinct from the FEF" (pg. 1348). The present selective effect of left FEF TMS, interpreted as a preparatory response set effect, also offers a potential explanation for the unexpected lFEF activation observed in the control task of a feature/spatial cueing experiment when the cues were not informative (Giesbrecht et al., 2003). Finally, the left lateralization marries well with other imaging work implicating left frontal and parietal cortex in studies of manual response set (Rushworth et al., 2001b; Shulman et al., 2002).

According to the view that the cortical areas specialized for spatial selection may also encode short-term spatial memory, the absence of an effect of TMS in the ITI may seem surprising. However, the FEFs are also involved in eye movement programming, and the demands of spatial memorization versus gaze-shifting can conceivably conflict. Gaze shifts between trials would be associated with a host of movement-related signals in the FEFs that could be deleterious to a spatial memory signal. To investigate such potential conflict, Balan & Ferrera (2003) used a delayed spatial match-to-sample task to test the effect of intervening saccades on delay period sustained activity in the FEFs. They reasoned that an ideal spatial memory storage mechanism would be unaffected by gaze shifts. Although a sustained signal was maintained by FEF neurons throughout the delay, fewer than 5% of neurons were significantly tuned for retinal stimulus location and were unaffected by gaze shifts. Following re-centring saccades, the sustained signal was abolished and FEF cells showed a general loss of tuning over the next 100ms. This tuning re-appeared before the execution of the final choice saccade. The authors found a similar pattern of effects when reflexive saccades intervened during the delay period

(Balan & Ferrera, 2003b). Balan & Ferrara's data indicate that the FEFs are capable of holding online multiple saccade plans that do not interfere with one another. However, when one of these saccade plans is executed, there seems to be a general re-setting of FEF activity, followed by the subsequent saccade plan being restored, presumably from a memory buffer located outside the FEFs. Given that we make, on average, 2-3 saccades each second (Carpenter, 2000; Findlay & Gilchrist, 2003), such persistent perturbation of sustained signals by gaze shifts likely make the FEFs an unreliable spatial memory storage substrate. Consistent with this, the subjects in the present experiments were not given eye position instructions for the inter-trial interval and tended to produce many and varied saccades. Despite this, behavioural priming remained intact, indicating that it is not the memory of the last saccade, but of the last intentional saccade that is retained across trials, and that this persists irrespective of intervening gaze shifts. By this argument, sustained spatial signal in the FEFs during the delay period reflects the read-out rather than storage of location information (Balan & Ferrera, 2003a). Further support for this interpretation comes from a patient with a left FEF lesion (Gaymard et al., 1999). Although the patient's contralateral saccades were normal, he was impaired on contralateral memory-guided saccades. Importantly, intervening gaze shifts during the delay period did not worsen performance. These observations may explain why TMS applied during array onset but not during the ITI disrupted spatial priming: read-out is critically important during saccade programming to a repeat location. Consistent with this, short-term spatial memory signals recorded from FEF visual neurons have been shown to be much weaker during the inter-trial period than during the within-trial period prior to the saccadic response (Umeno & Goldberg, 2001).

An alternative possibility is that TMS in the inter-trial interval was ineffectively targeted. Throughout the ITI of approximately 2000ms, TMS was applied for only 500ms. Hence,

it is possible that spatial or feature priming traces were laid down after the period of stimulation, or that they were stored in these structures and transiently disrupted, but there was sufficient time for the trace to be re-laid prior to the next trial. Against this argument, Campana, et al (2002) effectively disrupted motion (but not colour) priming by stimulating V5 with this same TMS protocol. To the extent that storage mechanics are likely conserved across visual feature dimensions, this provides good *a priori* grounds on which to expect the same stimulation protocol to disrupt colour priming if targeted at the appropriate storage site. In common with the findings reported here, the authors found no effect of right angular gyrus stimulation on colour (or motion) priming. The argument against a primed memory storage role for the FEFs or AGs predicts that even if TMS were applied throughout the entire ITI, priming would be unaffected. It further predicts that even with maintained fixation throughout the delay, TMS would still not disrupt priming. Both of these predictions remain to be tested.

Despite having a critical role in visual search (Walsh et al., 1999), the current findings suggest that the angular gyri are not necessary for either spatial or feature priming. The current study used small-diameter 55mm TMS coils, rather than the 70-mm coils used in previous studies of the angular gyrus. Hence, it could be argued that a reduced amount of stimulation is responsible for the null effects. However, Campana, et al. (2002) stimulated the angular gyrus with 70-mm coils during the inter-trial interval and also found no effect on colour (or motion) priming, by contrast with the effects of V5 TMS. More compellingly, right parietal patients with damage to the superior temporal gyrus and inferior parietal lobe (including the rAG) showed intact feature and spatial priming (Kristjansson et al., 2005). Other work has argued that the FEFs, but not the parietal cortex, are critical for oculomotor preparatory set (Connolly et al., 2002). Whilst recognising the difficulties with negative evidence, the present results concur with other

lesion data and suggest that the angular gyri are not important for either spatial or feature priming of pop-out.

The findings reported here suggest that the left frontal eye fields are specialized for the read-out, but not storage, of spatial memory signals during priming of pop-out. The dissociation between TMS effects on feature versus spatial priming indicates that the FEFs play a critical role in tracking spatial locations, but not visual features, across saccades. Thus, feature and spatial priming appear to have distinct causal mechanisms. While the FEFs are not critical for feature priming (sensory memory), the left FEFs are critical for reading out a 'motor memory' signal that facilitates the execution of saccades to repeat locations.

CHAPTER 7. Overall Conclusions and Future Research Directions

The experiments reported in this thesis used transcranial magnetic stimulation (TMS) while subjects performed visual search tasks to test the hypothesis that the human frontal eye fields (FEFs) engage in visuospatial information processing. This hypothesis was motivated by neurophysiological studies, which have shown that the monkey FEFs compute a visual target discrimination function that is dissociable from oculomotor commands. Experiments were designed with the aim of disrupting visuospatial performance, while ruling out accounts of the TMS effects that are based on saccade programs. Using this strategy, the experiments aimed to answer the following questions about human FEF function:

1. Are the FEFs necessary for visual search performance even when eye movements are not required? (Chapter 4)
2. Are the FEFs important early during search performance, as would be expected from neurophysiological data? (Chapter 4)
3. Do the FEFs continue to make critical contributions to search performance, even after a search task has been extensively practised? (Chapter 5)
4. Are the FEFs critical for spatial or feature priming? (Chapter 6)

This section discussions the results of each of these investigations and their interpretation and suggests potential future research directions.

7.1. Localizing the human Frontal Eye Fields

In order to guide coil placement for the TMS experiments, Chapter 3 compared the correspondence in eight subjects between FEF coordinates obtained using anatomical landmarks, with those derived from physiological mapping of the FEFs using functional

magnetic resonance imaging (fMRI). There was good correspondence between the coordinates obtained using each technique. Based on this, the FEFs were localized for all subsequent TMS experiments using anatomical landmarks (coil placement was rostral to the junction of the superior frontal sulcus and precentral sulcus). In each subsequent experiment, this placement was further validated by transforming subjects' FEF image space coordinates into MNI coordinates, and confirming that these were within the typical range identified by imaging studies as the FEFs (Paus, 1996).

In half of these subjects, TMS was subsequently applied at these FEF coordinates in order to assess a TMS protocol that has been proposed as a functional localization technique for identifying the FEFs in single subjects. The proposed criterion for identifying the FEFs is that contralateral but not ipsilateral saccade latencies should be increased when TMS is applied during an endogenous orienting paradigm (Ro et al., 2002). The results obtained in Chapter 3 failed to replicate this effect using imaging-derived FEF coordinates and the coil orientation and stimulation parameters used throughout this thesis. Instead, TMS appeared to modulate subjects' baseline biases to make faster saccades to either left or right space.

It is possible that use of a larger TMS coil, which would increase the amount of stimulation, exploratory testing at a number of adjacent scalp coordinates, and experimentation with various coil orientations, might have induced the saccadic delay effect. In fact, all three parameters appear to play a critical role in obtaining the effects reported in the literature (Ro et al., 1997; Ro et al., 1999; Ro et al., 2002). However, since the aim of the experiment was to assess the proposed functional criterion against the stimulation parameters used throughout this thesis, these strategies were not appropriate. Based on the results obtained, and on a review of the data on which this TMS

localization protocol has been proposed, it was concluded that the robustness of this technique for single-subject FEF localization remains to be adequately demonstrated. Further, the localization approach used in this thesis (anatomical landmarks verified against published MNI range coordinates for the FEFs) was independently validated by the demonstration of a range of behavioural interference effects in subsequent experimental chapters.

7.2. The Timing of TMS Interference during Visual Search Performance

Chapter 4 had two aims. The first was to demonstrate that the human FEFs are critical for normal visual search performance when eye movements are not required. The second was to investigate the time at which this FEF contribution is critical for performance accuracy.

Subjects made manual target present/absent responses while searching for a colour/orientation conjunction target in an array of distractors. The search array was small, was presented briefly and was then masked. Fixation was monitored throughout. Compared to two control sites (Vertex, V5), repetitive-pulse (r)TMS (10Hz, 500ms) applied over the right FEFs degraded subjects' search performance (d'), replicating the findings of Muggleton, et al. (2003). Eschewing an account based on latent saccade programs, it was argued that TMS had disrupted a visual target discrimination process. To further this argument, a set of follow-up experiments could be run in which search efficiency and spatial response mapping are manipulated independently. It has been demonstrated that while degrading search efficiency delays target discrimination time (Sato et al., 2001), manipulations that affect response processes (eg: stimulus-response incompatibility, Sato & Schall, 2003) delay reaction time, but do not affect the timing of

target discrimination. If this is the case, then it should be possible to manipulate response time without affecting the early timing of TMS interference. For instance, follow-up work could re-run the double-pulse TMS experiment, but with a cue presented during the mask period that indicates one of a number of spatially separated keyboard locations at which the subject's response should be signalled. This would increase the variability and duration of manual response times, but the 40/80ms interference time should be unaffected. Manipulating search efficiency, by parametrically varying relative target/distractor salience (eg: luminance), should also cause a corresponding increase in the magnitude of TMS interference. However, if it is correct that the 40/80ms window reflects disruption of the initial flow of visual signals into the FEFs, then this manipulation may not affect the timing of TMS disruption.

To assess the critical timing of TMS interference, two further conditions were tested in which repetitive-pulse TMS was applied over the right FEFs starting 100ms or 200ms after search array onset. Performance accuracy (d') in the control condition (vertex stimulation) was greater than in all three frontal eye field stimulation conditions, but this difference was largest and was statistically significant only when TMS over the FEFs began at search array onset. Based on this, a follow-up experiment used a double-pulse TMS protocol and isolated a discrete, early window of interference. Dual TMS pulses applied at 40 and 80ms significantly reduced d'. There was no effect of TMS applied at any other time during search array viewing.

It is unlikely that the FEFs make a critical contribution to search at just one time. Witness the dense reciprocal and nodal connectivity of the FEFs with multiple dorsal and ventral areas: task-relevant signals likely pass through the FEFs at a number of different time points. This is also intimated by the pattern of results in the repetitive-

pulse timing conditions. Although not significant, when rTMS (10Hz, 500ms) was applied over the FEFs at 100 and 200ms after search array onset, d' scores were lower than in the control condition, despite the fact that stimulation did not include the 40/80ms time window.

Based on the discrete and early effect of double-pulse TMS, and the correspondence between these timing parameters and the temporal response profile of FEF visual neurons during search (Thompson et al., 1996), it was argued that TMS had disrupted an evolving visuospatial signal in the FEFs, which enables accurate target discrimination and localization during visual search. This interpretation is intended to claim that, like the monkey FEFs, the human FEFs accumulate visual evidence towards a perceptual decision threshold, the outcome of which guides the observer's discrimination response. The timing of TMS interference coincides with the first wave of activation of FEF neurons in response to visual stimulation (min. response latency = 35ms, mean = 70ms)(Thompson et al., 1996; Schmolesky et al., 1998). Hence, I have argued that the early TMS effect disrupts the first feed-forward flow of information into the FEFs. In a detection and backward masking paradigm (Thompson & Schall, 2000), it was shown that small differences in spiking activity in the FEFs during the initial period of visual signal build-up correlated with monkeys' subsequent perceptual reports. The authors attributed the differences in the monkeys' detection responses on trials in which the visual information was the same (hit versus miss, false alarm versus correct rejection) to noisy fluctuations in the baseline firing rate of FEF neurons at the time of visual activation. Accordingly, TMS applied at 40/80ms could have disrupted discrimination by increasing the variability of baseline neural firing in the FEFs. Alternatively, TMS may have reduced the fidelity of signals that enter the FEFs from extrastriate cortex, carrying the visual feature information on which discrimination is based.

In an attempt to distinguish between these possibilities, a new paradigm needs to be devised that would enable temporal interactions between the FEFs and extrastriate cortex to be explored. One potentially fruitful approach, designed by analogy with monkey studies (Kim & Shadlen, 1999), would require observers to discriminate the direction of motion of a random dot stimulus containing various proportions of motion coherence. Repetitive-pulse TMS applied over V5 should disrupt performance on this task (Hotson et al., 1994). Using a single- or double-pulse TMS protocol, of the kind used above, it might then be possible to isolate a discrete time window of V5 interference. By applying this same two-stage stimulation protocol to the FEFs, comparable data could be obtained about the critical timing of V5 and FEF contributions to discrimination performance. Follow-up work could extend this further by probing temporal interactions between the two areas with TMS (Pascual-Leone & Walsh, 2001; Silvanto et al., 2005b). This kind of approach in future work should help to illuminate further the role of the FEFs in integrating visual evidence to form the basis for a perceptual decision.

Data from this kind of experiment might reveal an early time window of TMS interference that overlaps in the case of the FEFs and V5. Together with the results of the current double-pulse TMS and search experiment, such a finding could be construed as support for Bullier's model of visual processing (Bullier, 2001b). This model proposes that rapidly-activated dorsal stream areas (V5, FEF) generate an initial global 'gist' interpretation of a visual scene, alerting slower-responding extrastriate areas to potential areas of interest via fast feedback signals that coincide with the first feedforward activation of feature-selective cortex. One potential way of testing this hypothesis might be to combine TMS with EEG recordings. Specifically, an experiment could be designed

to determine the effect of FEF stimulation on event-related potential (ERP) correlates of target discrimination that appear be generated in extrastriate cortex (eg: Vogel & Luck, 2000). Evidence that early TMS over the FEFs disrupted the earliest portion of an ERP would support this proposed functional role for the FEFs in vision.

The present double-pulse TMS and search experiment could also be extended to include the right angular gyrus. Stimulating both the FEFs and the PPC in the same subjects with these same timing parameters would enable a test of a hypothesis suggested by TMS data on visual search. Such a hypothesis proposes that the FEF is critically involved in target/distractor discrimination (and hence is disrupted early during search), while the PPC is important for stimulus-response mappings (and hence is disrupted later).

7.3. Role of the FEFs in well-practised search

Chapter 4 provided evidence that the FEFs make a critical contribution to visual search performance when eye movements are not required. The aim of Chapter 5 was to determine whether this remains the case after a search task has been extensively practised. Familiarity and expertise are rarely manipulated in studies of search. In the angular gyrus, it has been shown that TMS no longer disrupts performance after a search task has been learned (Walsh et al., 1998a). To test whether this is also the case for the FEFs, repetitive-pulse TMS (10Hz, 500ms) was applied over the right or left FEFs during conjunction search performance, and the data were compared before and after training. Half the subjects were tested on an array of laterally-reflected 'C' stimuli (Group A); the other half were tested on an array of vertically-reflected 'V' stimuli (Group B).

Prior to training, TMS over the right FEFs disrupted search performance (d') in both groups. In the case of Group B, this effect disappeared after training, and re-emerged upon transfer to the untrained (laterally-reflected) array. This pattern of performance corresponds with the data on angular gyrus stimulation, suggesting that neither the FEFs nor the PPC are critical for search performance after extensive task practice.

Training on visual search (Bichot et al., 1996), and learning colour-response associations (Toth & Assad, 2002), has been shown to induce colour-selectivity in FEF visual neurons and in LIP neurons, respectively. After extensive training on visual search, 50% of FEF visual neurons discriminated the target from a distractor in their initial, normally non-selective, response (ca. 50ms after search array onset). This experience-induced colour selectivity was likely a downstream reflection of training effects in feature-selective cortex (Jagadeesh et al., 2001). As the monkeys' search performance improved with repeated exposure to the same target/distractor colour pairings, the difference between the output of neurons tuned to target versus distractor colours likely increased in magnitude and robustness. Such a sharpening of the neuronal response in colour-selective cortex could account for the immediate discriminative signal detected in the FEFs, where the initial response is normally non-selective.

Applying these observations to my experiment, training-induced changes in feature-selective cortex could induce feature-selectivity in the initial visual response of the FEFs, and/or reduce the criticality of discriminative signal build-up for accurate behavioural performance. Notional support for this latter idea derives from the fact that a thresholding procedure was used to equate subjects' performance across all stages of the task. Although subjects were performing with ca. 75% accuracy at the pre- and post-training stages of the experiment, TMS disrupted performance only when the search task

was novel. Alternatively, or in addition, sharpening of feature representations in temporal and extrastriate cortex should cause discriminative signal build-up in the FEFs to occur faster and to be more robust. Such effects could explain the reduced susceptibility to TMS interference after training.

For Group A, who tested on the array of laterally-reflected 'C' stimuli, TMS over the right FEFs disrupted search performance (d') at the pre-training stage. After training, performance was impaired when TMS was applied over right or left FEF. Group A did not show any TMS deficit after transfer to the array of vertically-reflected 'V' stimuli.

The different pattern of TMS effects between Group A and B could not be explained by search efficiency (RT slope), as this did not differ between the groups. Neither were the differences a simple effect of task difficulty, since accuracy was equated across subjects, arrays and stages of the experiment. Instead, it was argued that stimulus factors explained the divergent pattern of TMS effects. Specifically, it was argued that the laterally-reflected stimuli imposed additional computational demands over processing of the vertically-reflected stimuli. This claim was supported by the fact that viewing thresholds were longer for the laterally-reflected stimuli at all stages of the task. In addition, the same group of subjects (Group A) had almost identical viewing thresholds for the two arrays (165 ms on the lateral array post-training, 168 ms on the vertical array at transfer). However, TMS over right or left FEF disrupted search performance on the lateral array, but there was no effect of TMS on search of the vertical array. Hence, the pattern of TMS effects could not be accounted for by a simple difference in viewing time of the two arrays.

The claim that left-right discriminations are more difficult, and impose a distinct computational load compared to up-down discriminations, is supported by a body of behavioural, neuropsychological, lesion and unit recording data (for reviews see: Gross & Bornstein, 1978; Walsh & Butler, 1996). What is novel about the findings reported here is the suggestion that the FEFs play a critical role in resolving left-right discriminations, and that this contribution remains critical even after extensive practice. This hypothesis proposes a computational role for the FEFs in visuospatial discrimination that extends beyond the domain of visual search. It also claims another function for the FEFs that has long been attributed to the parietal cortex. To further investigate this hypothesis, follow-up experiments could apply TMS over the FEFs and posterior parietal cortex during mental rotation tasks. These may constitute a potentially fruitful approach to distinguishing the visuospatial processing capacities of the FEFs and the PPC.

7.4. Role of the FEFs in spatial and feature priming

Chapter 6 tested a potential role for the frontal eye fields and the posterior parietal cortex in the priming of pop-out. 'Priming of pop-out' refers to the behavioural advantage (fewer errors, faster reaction times) accrued when a target's features or location repeat across consecutive trials of an odd-man out search task. When the target features or location change, performance becomes slower and/or less accurate. Repetitive-pulse TMS was applied over the right or left FEFs or the PPC in two different time periods while subjects performed a feature or spatial priming task. The series of four experiments was designed in an attempt to reveal potential dissociations between the cortical areas, the hemispheres, the critical timing of involvement or the two forms of priming.

To test the hypothesis that the FEFs or the PPC play a critical role in short-term memory storage, TMS was applied during the inter-trial interval. To test whether these areas are critical when a saccade is being programmed to a repeated target colour or location, TMS was applied during stimulus processing. There was no effect of TMS over any of the sites when applied during the inter-trial interval of either the spatial or the feature priming task. TMS applied over the left FEFs during stimulus processing abolished spatial priming, but had no effect on feature priming. This effect resulted from a selective increase in saccadic reaction time on trials in which the target location repeated. There was no effect on trials in which the target location switched. An account of the data in terms of target discrimination was ruled out, since the visual selection demands ('saccade to the odd-coloured target') were the same across spatial (and feature) target repeat and switch trials, but the interference was selective. Based on this pattern of results, it was argued that TMS had disrupted a spatial memory signal in the left FEFs that is evident when a saccade is being programmed to a repeated location. As this effect did not occur with TMS in the inter-trial interval, it was further concluded that the left FEFs play a role in the read-out, but not the storage, of this spatial memory signal.

Whilst it has been shown that the FEFs are capable of storing more than one saccade plan at the same time by a process of vector superposition (Balan & Ferrera, 2003a; Balan & Ferrera, 2003b), intentional or reflexive gaze shifts that occur during the delay period of a memory-guided saccade task caused a general re-setting of FEF activity, during which the sustained signal was temporarily abolished. The saccade plan to the remembered location then gradually re-emerged in the FEFs, suggesting that information about the remembered target location is restored from a spatial memory buffer located elsewhere. Convergent evidence for this claim comes from a patient with a restricted lesion of the left FEF (Gaymard et al., 1999). This patient performed poorly on memory-

guided saccades, but his performance was no worse when a gaze shift was cued during the delay period. Hence, the present results are consistent with other recording and lesion data, supporting the claim that the (left) FEFs are critical for the 'read-out', but not the storage, of a short-term spatial memory signal that facilitates saccades to a repeated location.

The left lateralization of the FEF effect fits with an imaging study (Kristjansson et al., 2004), which reported greater priming-induced repetition suppression effects in the left fronto-parietal network (LFEF, LAG, LIPS). It also fits with other imaging data reporting left fronto-parietal activations during studies of manual preparatory set (Rushworth et al., 2001b; Shulman et al., 2002). Whether the present results could be replicated in a manual response paradigm is worth testing. The memory-guided saccade deficits of a patient with a left FEF lesion (Gaymard et al., 1999) were attributed to disruption of a spatial memory signal that is stored in oculomotor coordinates. If it is correct that the spatial memory signal on which priming depends is buffered outside the FEFs, then response modality may be critical for the TMS effect reported here. A follow-up experiment using a manual response paradigm would enable a test of the hypothesis that, in a manual response paradigm, the spatial memory signal would route to the limb motor system, by-passing the FEFs, and so the left FEF effect would disappear. Should the effect be replicated, this might suggest that the spatial memory read-out functions of the left FEFs extend to a priming paradigm that relies on spatial hand-eye coordination.

Sustained activity recorded in the FEFs (and other structures) during the delay periods of various kinds of task has been ascribed the functional roles of: attention to a spatial location; intention to generate an action to that location; or a form of motor memory for

a spatial location. Any of these interpretations are consistent with the hypothesis that sustained signal in the FEFs in the inter-trial intervals of a spatial priming task constitutes the basis for behavioural priming. The present results, however, indicate that any such between-trial signal in the FEFs is not critical. Against this interpretation, it could be argued that stimulation lasting 500ms in an inter-trial interval of 1500+ms allows sufficient time for a temporarily disrupted memory signal in the FEFs to be re-established prior to the next trial. A follow-up experiment with a shorter ITI should be run to address this issue. However, I would argue that such a manipulation would not change the current results, as there are good reasons (as argued in Chapter 6) for believing that the FEFs do not offer a suitable substrate for spatial memory storage.

The absence of an effect of TMS in the ITI during feature priming fits with the predictions of the sensory memory hypothesis (Tulving & Schacter, 1990), which holds that sensory adaptation in colour-selective cortex (eg: V4) is critical for colour priming (Walsh et al., 2000; Girard et al., 2001a; Rossi et al., 2001). The failure to disrupt colour priming with TMS over the FEFs or the PPC in either of the two time periods suggests that priming-induced fronto-parietal repetition suppression reflects downstream effects of sensory adaptation in extrastriate cortex. Neither the FEFs nor the PPC are critical substrates for colour priming. This claim is supported by converging data from patient (Kristjansson et al., 2005), TMS (Campana et al., 2002) and imaging studies (Connolly et al., 2002), which have shown that a parietal lesion or parietal TMS does not disrupt priming, and which suggest that the FEFs, and not the PPC, are activated by oculomotor preparatory set. A follow-up experiment to reinforce this argument could attempt to disrupt feature priming by stimulating V4. However, only dorsal V4 is accessible to TMS, and so a negative result would not be conclusive.

In summary, the results of these experiments supplement an emerging database which indicates that the PPC is not important for either spatial or feature priming of pop-out. Instead, they suggest that the left FEFs play a critical role in tracking spatial locations, but not visual features, across saccades. Whilst the (left) FEFs do not themselves act as a memory storage site, they read out a spatial memory signal which facilitates saccades to repeated locations. The results indicate that feature and spatial priming have distinct causal mechanisms.

7.5. Summary Conclusions

This aim of this thesis was to establish functional homology between the frontal eye fields (FEFs) in the human and macaque monkey brains, by presenting evidence that, as in the monkey, the human FEFs have visuospatial functions that are dissociable from oculomotor commands. To test this hypothesis, TMS was applied over the FEFs while subjects performed a variety of visual search tasks. The results of these experiments broadly support this hypothesis, and establish a number of new findings about the contribution of the FEFs to visual search performance.

The results from the timing experiments (Chapter 4) indicate that computations within the right FEFs are task-critical during the earliest stages of visual search performance. As this early timing (40-80ms after search array onset) cannot easily be explained in terms of eye movement programs, this suggests that the right FEFs make a critical perceptual contribution to visual search. By analogy with monkey neurophysiology, the timing of interference suggests that TMS disrupted the build-up of visual evidence in the FEFs towards a perceptual decision on which subjects' target present/absent judgements were based.

The learning experiment (Chapter 5) suggests two new findings that are worthy of further investigation. The results from the search array of vertically-reflected stimuli suggest that, as is the case for posterior parietal cortex, TMS over the right FEFs does not disrupt search performance once a task has been extensively practised. Since most everyday search tasks are highly routine, this finding has implications for our understanding of how daily searches are conducted. The overall pattern of learning data suggests a novel hypothesis: that both the right and left FEFs may be critical for resolving left-right discriminations, even after extensive practice. This hypothesis should be further investigated using mental rotation tasks.

The experiments in Chapter 6 indicate that spatial and feature priming of pop-out have distinct causal mechanisms. They further suggest that the left FEFs access a short-term spatial memory signal during oculomotor programming, and that this process constitutes the critical basis of the spatial priming effect. Follow-up work should test whether this finding is specific to oculomotor responses, or whether it could be replicated in a manual response paradigm.

In summary, the experiments in this thesis suggest that, as in the monkey brain, the human FEFs make a perceptual contribution to vision, that is distinct from its oculomotor role. The right FEFs are critical early during search performance, at least when a search task is novel. Both FEFs appear to be involved in resolving left-right symmetry. Finally, the left FEFs integrate a spatial memory signal during oculomotor programming, which can speed up eye movements to a repeated location.

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