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Top-Down Signals in Visual Selective Attention

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Note

I, Christian Carl Ruff, confirm that the work presented in this thesis is my own.

Some of the work in the thesis is now also described in the following published journal papers:

Ruff, C. C., Driver, J. (2006). Attentional preparation for a lateralized visual distractor: Behavioral and fMRI evidence. *Journal of Cognitive Neuroscience, 18,* 522-538 (relates to Chapter 3 of this thesis).

Ruff, C. C., Blankenburg, F., Bjoertomt, O., Bestmann, S., Freeman, E., Haynes, J. D., Rees, G., Josephs, O., Deichmann, R., Driver, J. (2006). Concurrent TMS-fMRI and Psychophysics Reveal Frontal Influences on Human Retinotopic Visual Cortex. *Current Biology, 16,* 1479-1488 (relates to Chapters 4 and 5 of this thesis).

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Abstract

This thesis describes experimental work on the brain mechanisms underlying human visual selective attention, with a focus on top-down activity changes in visual cortex. Using a combination of methods, the experiments addressed related questions concerning the functional significance and putative origins of such activity modulations due to selective attention.

More specifically, the experiment described in Chapter 2 shows with TMS-elicited phosphenes that anticipatory selective attention can change excitability of visual cortex in a spatially-specific manner, even when thalamic gating of afferent input is ruled out. The behavioural and fMRI experiments described in Chapter 3 indicate that top-down influences of selective attention are not limited to enhancements of visual target processing, but may also involve anticipatory processes that minimize the impact of visual distractor stimuli. Chapters 4-6 then address questions about potential origins of such top-down activity modulations in visual cortex, using concurrent TMS-fMRI and psychophysics. These experiments show that TMS applied to the right human frontal eye field can causally influence visual cortex activity in a spatially-specific manner (Chapter 4), which has direct functional consequences for visual perception (Chapter 5), and is reliably different from that caused by TMS to the right intra-parietal sulcus (Chapter 6).

The data presented in this thesis indicate that visual selective attention may involve top-down signals that bias visual processing towards behaviourally relevant stimuli, at the expense of distracting information present in the scene. Moreover, the experiments provide causal evidence in the human brain that distinct top-down signals can originate in anatomical feedback loops from frontal or parietal areas, and that such regions may have different functional influences on visual processing.

These findings provide neural confirmation for some theoretical proposals in the literature on visual selective attention, and they introduce and corroborate new methods that might be of considerable utility for addressing such mechanisms directly.

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Chapter I
Introduction

Only a fraction of the information entering our senses at any given time is relevant for ongoing behaviour. Perception and action thus depend on *selective attention*, a set of mechanisms that allows us to process the currently important aspects of our environment in the face of potential distraction by irrelevant stimuli (for reviews see Driver, 2001; Duncan & Humphreys, 1989; Lavie, 2005; Pashler, 1998; Posner, Snyder, & Davidson, 1980). Selective attention has been investigated since the early days of cognitive psychology, with several models attempting to specify how and at what stage sensory information is either selected for further processing or successfully ignored (Broadbent, 1958; Deutsch & Deutsch, 1963; Duncan & Humphreys, 1989; Heinke & Humphreys, 2003; Lavie, 1995; Neisser, 1967; Treisman, 1969). More recently, such 'information-processing' accounts have been refined and transformed by neurobiological studies of selective attention, using single-cell recording in non-human primates or neuroimaging methods such as fMRI or PET in humans (for reviews see Corbetta & Shulman, 2002; Driver & Frackowiak, 2001; Kanwisher & Wojciulik, 2000; Kastner & Ungerleider, 2000; Reynolds & Chelazzi, 2004; Yantis & Serences, 2003; Frith, 2001). These studies have characterised more directly the mechanisms by which selective attention can influence sensory processing, showing that attentional selection can apparently lead to activity increases in those parts of sensory cortex that code the currently attended stimulus attributes. In line with a prominent theoretical framework known as 'biased-competition' account of selective attention (Desimone & Duncan, 1995; Duncan, Humphreys, & Ward, 1997), these findings are often interpreted as indicating that *top-down signals* may bias processing in sensory cortex towards behaviourally relevant information.

Several specific issues arising from this general view of the brain processes underlying selective attention were addressed by the investigations described in the present thesis. Using a variety of complementary methods such as fMRI, TMS, concurrent TMS-fMRI, and psychophysics, the experiments deal with questions concerning the *functional significance* and the potential *origins* of top-down activity modulations in visual cortices, as observed during visual selective attention. In the following pages, I will motivate the experimental work by giving a brief outline of the abovementioned 'biased-competition' theoretical framework, followed by a summary of previous studies on the neural processes involved in selective attention. In line with the topic of the experimental work, I will focus on selective *spatial* attention in the *visual* modality. This means that I will have to largely leave aside studies on attention to non-spatial stimulus features (see e.g., Chawla, Rees, & Friston, 1999; Coull, Vidal, Nazarian, & Macar, 2004; O'Craven, Downing, & Kanwisher, 1999) and selective attention research in other senses (see e.g., Stein & Meredith, 1993; Driver & Spence, 1998; Macaluso, Frith, & Driver, 2000).

Visual selective attention: Resolution of neuronal competition?

Based on neurobiological considerations, John Duncan and colleagues (Desimone et al., 1995; Duncan et al., 1997) have outlined a general theoretical framework that has guided much of the current thinking about visual selective attention. This framework, often referred to as the biased-competition or integrated-competition hypothesis, rests on the assumption that multiple objects in the visual field usually compete for the limited processing resources of cortical and subcortical neuronal populations involved in coding different aspects of the incoming sensory input and their behavioural implications. Such specialised neuronal 'processing modules' exist in visual cortex for a whole range of stimulus features, and have been studied at different scales, ranging from the tuning properties of individual neurons (Hubel &

Wiesel, 1959; Hubel & Wiesel, 1968) to the apparent functional specialisations of cortical regions as a whole (DeValois & DeValois, 1990; Zeki, 1993). For example, neurons in primary visual cortex are laid out (and interconnected) in terms of functional preferences for a specific retinotopic location (Tootell, Silverman, Switkes, & DeValois, 1982), orientation (Hubel et al., 1959), or spatial frequency (Tootell, Silverman, & De Valois, 1981). A retinotopic layout seems present to a certain degree within many different areas in occipital cortices (Sereno et al., 1995; Wandell, Brewer, & Dougherty, 2005), and non-spatial stimulus features also seem to receive some preferential processing in distinct functionally specialised visual areas, for example colour in V4 and/or V8 (Hadjikhani, Liu, Dale, Cavanagh, & Tootell, 1998; Lueck et al., 1989; Shipp & Zeki, 1985; Wandell et al., 2005), motion in V5/MT+ (Rees, Friston, & Koch, 2000; Newsome, Wurtz, Dursteler, & Mikami, 1985; Watson et al., 1993), or specific shapes and/or object categories in LOC, IT, or FFA (Reddy & Kanwisher, 2006; Logothetis & Sheinberg, 1996; Malach et al., 1995; Sereno, Trinath, Augath, & Logothetis, 2002).

Any object present in a visual scene will thus activate neurons in numerous functionally specialised but interconnected cortical modules. The processing resources of such areas may be limited, for example, by physiological limits on their maximum firing rates, by competitive interactions via lateral inhibition or inter-regional neuronal connections, or by other computational constraints (Dayan & Abbott, 2001; Rolls & Deco, 2001). The activity patterns related to a specific object may thus compete with those elicited by other incoming sensory inputs. Consistent with this general assumption, *competitive interactions* between multiple visual stimuli have now been demonstrated in single-cell recording studies in non-human primates (Moran & Desimone, 1985; Reynolds, Chelazzi, & Desimone, 1999; Reynolds et al., 2004), and with fMRI in humans (Kastner, De Weerd, Desimone, & Ungerleider, 1998). Such studies have shown that the neuronal response to a given stimulus can

be greatly diminished when a second non-preferred stimulus is presented within the same receptive field. Recent neuroimaging data in humans suggest that some competitive processing limitations can also exist between neuronal populations with *separate* receptive fields, as BOLD responses to a stimulus in one part of the visual field can be diminished during the presence of a second stimulus in a different location (Geng et al., 2006; Fink, Driver, Rorden, Baldeweg, & Dolan, 2000; Pinsk, Doniger, & Kastner, 2004), especially when one of these multiple visual stimuli is attended (Schwartz et al., 2005; Lavie, 2005; Rees, Frith, & Lavie, 1997). It is now often assumed that neuronal competition may exist at all stages of cortical processing, ranging from sensory input to the associated motor output (Desimone et al., 1995; Duncan et al., 1997).

Based on such considerations about neuronal processing limitations, the biased- or integrated-competition hypothesis has proposed three very general principles about how competition could be resolved in order to yield stable perception and action. First, intense or salient stimuli - that elicit strong neuronal responses against background noise - may presumably tend to win this competition and dominate the system in a 'bottom-up' fashion, offering an explanation for why objects in bright colours or with sudden onsets are normally easily noticed and hard to ignore (Franconeri, Simons, & Junge, 2004; Folk & Remington, 1998; Yantis & Egeth, 1999). Second, 'top-down' influences such as behavioural goals or expectancy of the observer can lead to biases in this sensory competition that favour certain aspects of the visual scene over others. For instance, expectancy about the spatial position of an object normally leads to faster and more accurate detection there (Posner et al., 1980; Connor, Egeth, & Yantis, 2004), while distractors that share features with the desired targets of a visual search can be harder to ignore than more perceptually salient yet non-overlapping distractors (Duncan et al., 1989). Last but not least, although neural competition may arise in each of the specialised

processing modules, the 'winning' activity pattern in one module may come to dominate activity in all other modules of the network as well. This might offer a potential explanation for effects of 'object-based' attention (Egly, Driver, & Rafal, 1994; O'Craven et al., 1999), for other competition-related phenomena such as binocular rivalry (Blake & Logothetis, 2002; Stoner, Mitchell, Fallah, & Reynolds, 2005), or for influences of attended non-spatial features across the whole visual field (Maunsell & Treue, 2006; Melcher, Papathomas, & Vidnyanszky, 2005; Saenz, Buracas, & Boynton, 2002).

The present thesis focuses mainly on the mechanisms underlying the second of the potential mechanisms described above: Top-down influences on visual areas. Although more of a general theoretical framework than a detailed model that posits testable predictions (though see Heinke & Humphreys, 2003; Mavritsaki, Heinke, Humphreys, & Deco, 2006; for instantiations), the biased-competition framework has had a strong influence on the development of neurophysiological selective attention research, and is often used as a 'guide' to the interpretation of empirical findings. The following paragraphs will summarise how attention-related top-down influences on visual cortex have been assessed with neuroimaging methods to date. The emphasis here will be on spatial attention, with only few references to studies of attention to non-spatial visual stimulus attributes. Note also that top-down signals in visual cortices will be mostly considered from the perspective of selective attention, leaving aside other types of activity modulations in visual cortex, e.g., related to reward (Shuler & Bear, 2006), stimulus history (Crist, Li, & Gilbert, 2001; Kourtzi & DiCarlo, 2006; Schwartz, Maquet, & Frith, 2002), or task structure (Jack, Shulman, Snyder, McAvoy, & Corbetta, 2006).

Visual selective attention: Sensory modulations and baseline shifts

Attention to a specific spatial location can enhance perceptual sensitivity for targets presented there (Posner et al., 1980; Carrasco, Ling, & Read, 2004; Pestilli & Carrasco, 2005). Such behavioural improvements are now known to often be accompanied by enhancements of the neuronal response to the attended stimulus, relative to the identical stimulus when not attended. This has now been demonstrated with single-cell recording in non-human primates (Luck, Chelazzi, Hillyard, & Desimone, 1997; Reynolds et al., 2004), as well as with ERPs (Hillyard & Anllo-Vento, 1998), PET (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1990; Heinze et al., 1994), and fMRI (Corbetta et al., 2002; Driver et al., 2001; Kanwisher et al., 2000; Liu, Pestilli, & Carrasco, 2005; Serences & Yantis, 2006) in humans. Activity modulations by spatial attention are present in multiple visual areas, and are usually largest in relatively higher-order visual areas such as V4 or TEO (Tootell et al., 1998; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999). In some instances, however, attentional modulation of visual input can be present at much earlier stages of the visual hierarchy, such as V1 (Brefczynski & DeYoe, 1999; Gandhi, Heeger, & Boynton, 1999; Somers, Dale, Seiffert, & Tootell, 1999) or even the lateral geniculate nucleus of the thalamus (O'Connor, Fukui, Pinsk, & Kastner, 2002). The main cortical locus at which spatial attention modulates neuronal activity is not exclusively determined by the spatial position of an attended object, but may also depend on characteristics of the task or stimulus. For example, whether modulations due to spatial attention are mainly present in V4 or LOC can flexibly change on a trial-by-trial basis, depending on the match between receptive field size of neurons in these different visual areas and the size of the object feature relevant for the present task (Hopf et al., 2006). Such task factors may even interact with the principle of purely spatiotopic representation. For instance, contralateral activity

modulations may be stronger in the left or right hemisphere, depending on whether attention is directed to temporal properties or the orientation of visual stimuli, respectively (Macaluso & Frith, 2000).

Several features of the activity modulations due to selective attention appear quite consistent with the notion of top-down signals that may bias processing towards behaviourally relevant information. For instance, attention-related influences on visual areas are often spatially highly specific. They usually take the form of increased activations in those parts of visual cortex representing the hemifield, quadrant, or retinotopic location in which the attended stimulus is located. The spatial resolution of such 'top-down' influences in early retinotopic visual areas can parallel the spatial resolution of 'bottom-up' activity elicited by retinal visual input, as detected with fMRI (Brefczynski et al., 1999; Somers et al., 1999; Tootell et al., 1998); see Figure I-1 overleaf for an example. Within a single visual area, attentional modulations are not always restricted to one contingent patch of cortex, but can occur simultaneously in retinotopic representations of separate parts of the visual field if multiple objects are attended (McMains & Somers, 2004).

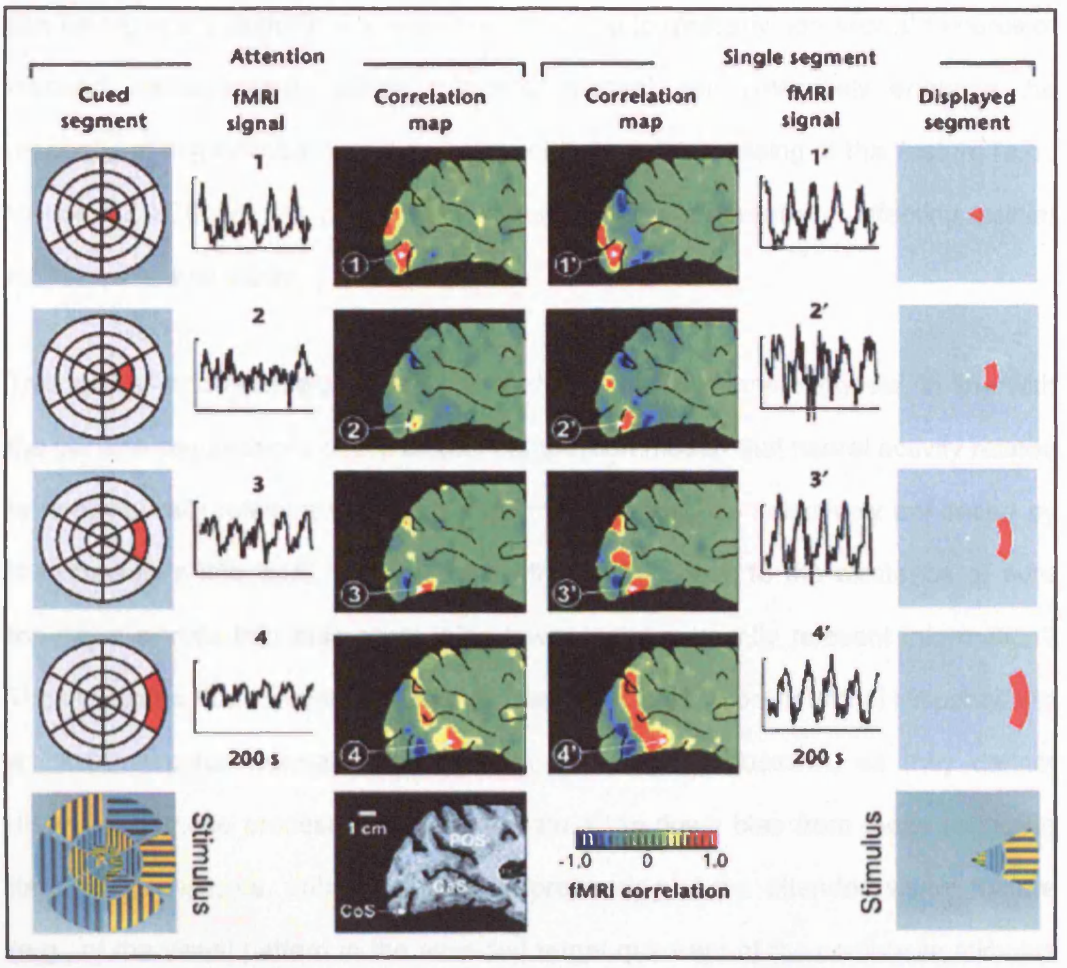

Figure I-1. Retinotopic specificity of activity modulations due to spatial attention.

This graph illustrates that fMRI activity modulations due to spatial attention (left panel) can show a similar retinotopic specificity as activity changes elicited by presentation of the cued visual target stimuli alone (right panel) (Brefczynski et al., 1999). The leftmost column shows a schematic sequence of target segments of a constant visual stimulus (displayed on the bottom left) cued for attentional scrutiny. The corresponding correlation maps (left middle panel) indicate the current locus of attention, evident in the correlation of fMRI signal modulations at individual voxels with the timing of attentional shifts towards the cued segment (red = positive, blue = negative correlations). The displayed segment in the rightmost column shows a schematic sequence of single segments of a composite stimulus (shown on bottom right) that were presented during an otherwise identical control experiment. The fMRI signal correlation map in the right middle panel shows the results of this visual stimulation control experiment. The structural MRI on the bottom is a para-sagittal section (13.6 mm left of midline) through the occipital lobe, in the same plane as correlation maps. Sulcal landmarks; CaS, calcarine sulcus; CoS, collateral sulcus; POS; parieto-occipital sulcus. Adapted from (Brefczynski et al., 1999).

The neural representations of currently *unattended* parts of the visual field (or other stimulus features) can show reductions in BOLD activity as a function of the locus of attention (Chun & Marois, 2002; Pinsk et al., 2004; Schwartz et al., 2005; Slotnick, Schwarzbach, & Yantis, 2003; Smith, Singh, & Greenlee, 2000; Tootell et al., 1998; Vanduffel, Tootell, & Orban, 2000; Rees et al., 1997). Finally, attentional influences

can be *regionally specific*. For example, attending to explicitly non-spatial features of identical displays (e.g., either colour or motion) can selectively enhance the response of higher-order visual areas specialised for processing of this feature (e.g., V4 or V5; Chawla et al., 1999), without always differentially affecting earlier retinotopic visual areas.

This space- and feature-specificity of attentional modulations suggests, in line with the general assumptions of the biased-competition model, that neural activity related to behaviourally relevant visual information can indeed be selectively enhanced by the observer's intention. However, does this really speak to the existence of pure top-down signals that bias processing towards behaviourally relevant information? Those studies that have demonstrated attentional effects on neuronal responses to a visual stimulus normally cannot really answer this question, as they cannot disentangle those processes that *instantiate* a top-down bias from those reflecting its *consequence*, i.e. enhanced sensory processing of the attended visual feature (e.g., of the visual pattern in the attended target quadrant of the composite stimulus shown in Figure I-1). Some further information on this issue may be provided by studies on the timecourses of attentional enhancements, as investigated with ERPs. Such studies have argued that the initial volley of activation elicited in striate cortex (assessed as the C1 ERP component, at around 50 ms after stimulus onset) may be of similar magnitude for attended vs unattended inputs (Martinez et al., 1999), whereas the first attentional activity enhancements localised to this region were found only at a later stage (e.g., at around 140-200 ms; Noesselt et al., 2002). This appears consistent with the notion that attentional modulations in striate cortex may be brought about by re-entrant feedback from higher cortical areas via anatomical feedback projections (Pascual-Leone & Walsh, 2001). However, note that such feedback influences might not necessarily indicate a uniquely attentional process, highlighting the often ambiguous use of the term 'top-down' to characterise neuro-

cognitive processes from either a physiological (i.e., neural feedback from upstream areas) or psychological (i.e., volitional / attentional processes) perspective (see Frith, 2001). From a physiological point of view, re-entrant feedback loops have been proposed as a fundamental property of processing in visual cortex (Bullier, 2001; Lamme, Super, & Spekreijse, 1998), and may underlie other, explicitly non-volitional top-down effects on visual cortex (Crist et al., 2001; Kourtzi et al., 2006; Schwartz et al., 2002). Some of the fMRI findings described until now may thus also indicate a *consequence* rather than a specific causal mechanism of selective attention that is under volitional control.

For this reason, several recent fMRI studies (Hopfinger, Buonocore, & Mangun, 2000; Jack et al., 2006; Kastner et al., 1999; Macaluso, Eimer, Frith, & Driver, 2003; Ress, Backus, & Heeger, 2000) have employed a different approach to study purely top-down contributions to visual selective attention. Such studies have attempted to temporally separate the processes underlying preparatory selective attention from their subsequent effects on perceptual processing, by examining neuronal activations during attentional *preparation* for particular stimuli and judgments, prior to the actual presentation of the stimuli, and thus in the absence of changes in sensory input. Some spatiotopic modulations of visual cortex were also found in these studies, but now in advance of stimulus presentation, when participants were only anticipating that a cued stimulus might appear at a specific spatial location (see Figure I-2A for an example).

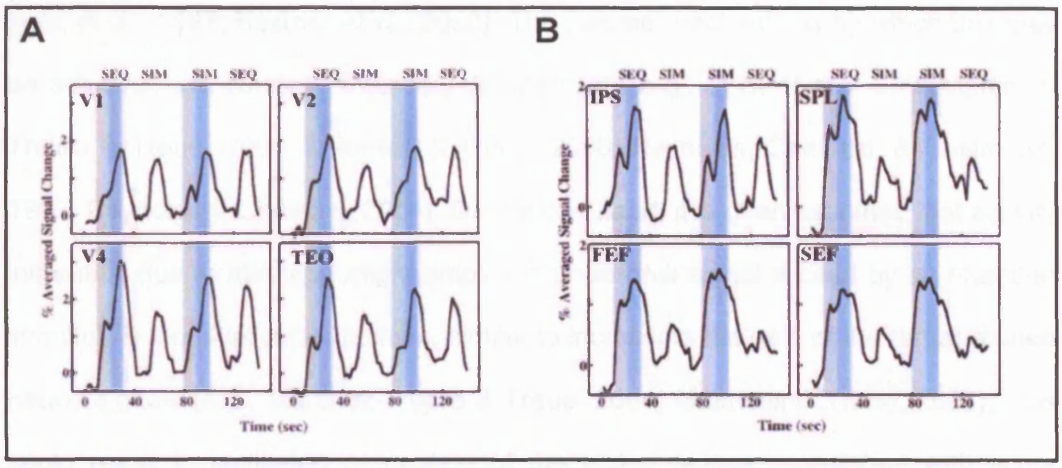

Figure I-2. Baseline shifts during directed visual attention in the absence of stimulation.

This figure shows averaged timeseries of group fMRI data (Kastner et al., 1999) for visual occipital (panel A) or fronto-parietal brain areas (panel B), during the anticipation (grey shades) or the actual presentation (blue shades) of visual stimuli in a spatially corresponding part of the visual field. Blocks with unattended presentations are shown without shading. The figure shows that directing attention to the target location during the expectation period can lead to activity increases in the absence of visual presentations (and to further activity increases after the onset of visual stimuli), in multiple visual (panel A) and fronto-parietal areas (panel B). IPS = intraparietal sulcus; SPL = superior parietal lobule; FEF = frontal eye fields; SEF = supplementary eye fields. Adapted from (Kastner et al., 1999).

Such preparatory activations, termed "baseline shifts" by some authors (Chawla et al., 1999; Kastner et al., 2000), are usually of lower amplitude than attentional modulations of stimulus-evoked activity (Luck et al., 1997; Kastner et al., 1999; Ress et al., 2000). However, they can nevertheless be similarly spatially specific to those parts of visual cortex representing the hemifield, quadrant, or retinotopic location in which the visual target is anticipated (Hopfinger et al., 2000; Kastner et al., 1999; Macaluso et al., 2003; Ress et al., 2000). These anticipatory effects in visual cortex apparently provide direct empirical support for the notion that visual selective attention operates in part by means of top-down signals that can modulate activity in occipital cortex in a preparatory fashion.

What may be the function of such anticipatory occipital activity modulations? Some authors speculate, in line with the general biased-competition proposals, that they might give some neuronal populations a competitive advantage by specifically increasing their excitability in response to incoming visual input (Chawla et al., 1999;

Luck et al., 1997; Kastner et al., 2000). The precise mechanisms by which this may be achieved are currently intensely debated (see e.g., Luck et al., 1997; Martinez-Trujillo & Treue, 2004; Maunsell & Treue, 2006; Reynolds, Chelazzi, & Desimone, 1999; Reynolds & Chelazzi, 2004). On the one hand, it is often assumed that activity increases due to attention might amplify the neuronal signal elicited by an attended stimulus in a multiplicative fashion, similar to increasing the gain of the target-related neural signals (e.g., Martinez-Trujillo & Treue, 2004; Maunsell & Treue, 2006). This could result in facilitated perception of the coded feature, consistent with some psychophysical findings that selective attention can increase the perception of many visual features such as contrast (Carrasco, Penpeci-Talgar, & Eckstein, 2000; Carrasco et al., 2004), luminance (Hawkins et al., 1990), or spatial frequency (Gobell & Carrasco, 2005). A related notion posits that baseline shifts due to anticipatory top-down influences might instead facilitate processing of target-related signals mostly by limiting the effects of noise in the system, e.g., by sharpening neuronal selectivity and counteracting specifically the competitive activity elicited by behaviourally irrelevant distractor stimuli (e.g., Luck et al., 1997; Reynolds, Chelazzi, & Desimone, 1999; Reynolds & Chelazzi, 2004). Such a proposal might be consistent with findings of psychophysical studies on distractor-exclusion/noise-reduction by attention (Awh, Matsukura, & Serences, 2003; Cheal & Gregory, 1997; Lu, Lesmes, & Dosher, 2002; Dosher & Lu, 2000; Mavritsaki et al., 2006; Pestilli & Carrasco, 2005; Watson & Humphreys, 1997; Watson, Humphreys, & Olivers, 2003). Finally, from a more cognitive point of view, it has been argued that the top-down signals observed during anticipatory spatial attention may relate to some form of attentional template (Duncan et al., 1989; Driver & Frith, 2000) that might 'predispose' activity in the perceptual system towards the stimulation pattern subsequently elicited by the target stimulus. From a psychological perspective, this mechanism might be similar to imagining the target one is looking for (Farah, 1989), potentially consistent with neuroimaging findings that visual imagery can equally

lead to spatially specific activity increases in visual cortex in the absence of visual stimulation (Kosslyn, Ganis, & Thompson, 2001; Slotnick, Thompson, & Kosslyn, 2005). However, no studies currently decisively speak for either of these hypotheses; moreover, there is as yet no clear experimental evidence for a *causal* influence of anticipatory activity increases on the subsequent modulations of stimulus-evoked activity (see also Chawla et al., 1999; Driver, Eimer, Macaluso, & van Velzen, 2004). Nevertheless, the consensus emerging from the studies on baseline shifts to date is that activity in visual areas, as early as V1 or even the LGN, can be increased by selective attention in a preparatory fashion. This appears broadly consistent with the hypothesis that visual areas are cortical 'sites' at which attention exerts its modulatory effects (Posner & Driver, 1992; Frith, 2001; Frith & Dolan, 1997), raising questions about possible neural 'sources' of such top-down signals.

Visual selective attention: Putative control structures

Neuroimaging studies

Directed spatial attention does not only elicit activity modulations of visual cortex, but often also results in increased activity in a widespread bilateral network of frontal, temporal, and parietal areas. This network may comprise, among other regions, the human homologue of the frontal-eye-fields (FEF), the superior parietal lobule (SPL), the temporo-parietal junction (TPJ), and the intra-parietal sulcus (IPS; Corbetta et al., 2002; Frith, 2001; Kastner et al., 2000; Yantis et al., 2003); see Figure I-2B, plus Figure I-3 for a meta-analysis.

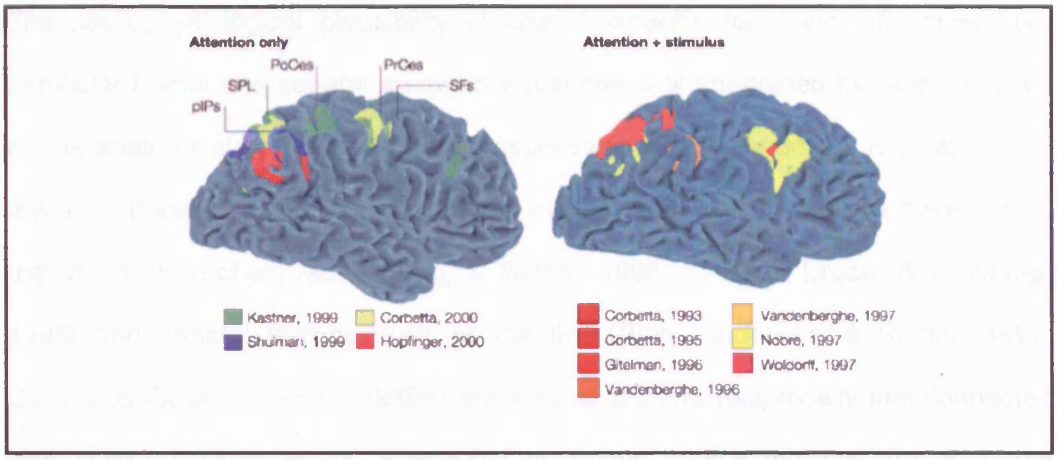

Figure I-3. Dorsal fronto-parietal network for top-down control of visual attention.

The figure shows multiple bilateral areas in frontal and parietal cortex that are activated during the direction of spatial attention. The panel on the left shows a meta-analysis of studies of visual attention in the absence of visual stimulation. Foci of activation from the expectation period (subjects expected a simple visual attribute in a specified location) are smoothed and projected onto a normalised 3D brain template. The panel on the right shows a similar meta-analysis of imaging studies of visual attention and detection in the presence of visual stimuli. FEF, frontal eye field; pIPs, posterior intraparietal sulcus; PoCes, postcentral sulcus; PrCes, precentral sulcus; SFs, superior frontal sulcus; SPL, superior parietal lobule. Adapted from (Corbetta et al., 2002).

Many of these regions jointly show activity increases in a variety of situations where attention needs to be (re)directed (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Hopfinger et al., 2000), held (Rees, Frackowiak, & Frith, 1997a), or shifted (Corbetta, Miezin, Shulman, & Petersen, 1993; Macaluso et al., 2001; Nobre et al., 1997; Yantis et al., 2002) in the visual field, even during preparatory spatial attention before any stimulus is presented (Hopfinger et al., 2000; Kastner et al., 1999; Macaluso et al., 2003). The activity found in many of these regions is sustained throughout periods of directed attention and can be unaffected by the onset or the presentation rate of visual stimuli (Culham, Cavanagh, & Kanwisher, 2001; Corbetta et al., 2002; Rees et al., 1997a). This has led to suggestions that superior regions in frontal and parietal cortex might be potential sources for top-down bias signals that may affect activity in occipital regions (Driver et al., 2004; Kastner et al., 2000; Miller, 2000; Duncan et al., 1997).

The neurophysiological plausibility of spatially-specific top-down influences from particular frontal and parietal areas on visual cortex is underlined by recent studies on the anatomical connectivity, visual responsiveness, signal timing, and retinotopic layout of these structures. For instance, tracing studies in macaques have shown that the FEF (Schall, Morel, King, & Bullier, 1995; Stanton, Bruce, & Goldberg, 1995) and parietal regions such as the IPS (Blatt, Andersen, & Stoner, 1990; Cavada & Goldman-Rakic, 1989b) are extensively and reciprocally interconnected with occipital visual areas. Single-cell recording studies indicate that both the macaque FEF and IPS contain neurons that respond preferentially to behaviourally relevant visual stimuli, as defined by task context (Andersen & Buneo, 2002; Bichot & Schall, 1999; Schall & Thompson, 1999; Sato, Watanabe, Thompson, & Schall, 2003). These visually responsive neuronal populations are distinct from those involved in purely oculomotor behaviour (Thompson, Biscoe, & Sato, 2005), making them good candidates for flexible neuronal representation of visual objects that should receive enhanced processing in occipital cortex (Miller, 2000). The latency at which neurons in the FEF and IPS show responses to visual stimuli is comparable to that of area V2, at around 70 ms after stimulus onset (Pouget, Emeric, Stuphorn, Reis, & Schall, 2005; Schmolesky et al., 1998). This underlines that feedback signals may be generated in these structures at similar temporal latencies as some of the attentional modulations observed in visual cortex with single-cell recording in macaques (Khayat, Spekreijse, & Roelfsema, 2006) or MEG in humans (Noesselt et al., 2002). Moreover, studies assessing 'effective connectivity' (the influence of activity in a given region upon other activity in other connected brain areas) between frontal, parietal, and extra-striate visual areas with mathematical models suggest that trial-by-trial variations in the timing and amplitude of BOLD changes during attention to motion are consistent with the idea that parietal and frontal brain regions might increase functional coupling with extra-striate visual areas relevant for the current task (Buchel & Friston, 1997; Buchel & Friston, 1998; Friston & Buchel,

2000). Finally, recent studies indicate that both the IPS and the FEF may show some degree of contralateral (Serences & Yantis, 2007; Macaluso et al., 2000) or even retinotopic (Hagler, Jr. & Sereno, 2006; Silver, Ress, & Heeger, 2005) organisation, which may be required for *spatially specific* influences upon retinotopic visual areas. For example, some retinotopic representation of the contralateral visual periphery has recently been observed in the human FEF (Hagler, Jr. et al., 2006) or IPS (Sereno, Pitzalis, & Martinez, 2001; Schluppeck, Curtis, Glimcher, & Heeger, 2006), during the delay in memory-guided saccade paradigms and during directed covert attention (Silver et al., 2005); see Figure I-4 for examples. Moreover, recent fMRI studies on visual properties of the IPS in macaques and humans (Orban et al., 2006) show that distinct parts of this region may contain spatiotopic representations of the central visual field, or may preferentially respond to specific non-spatial visual stimulus attributes such as motion or shapes (Bremmer et al., 2001; Williams, Elfar, Eskandar, Toth, & Assad, 2003). Taken together, such findings emphasise that activity changes in the FEF and IPS during selective attention might plausibly reflect enhanced visual coding of behaviourally relevant stimuli and their spatial position. This may be a neurophysiological prerequisite for spatially specific functional influences upon processing in occipital visual areas.

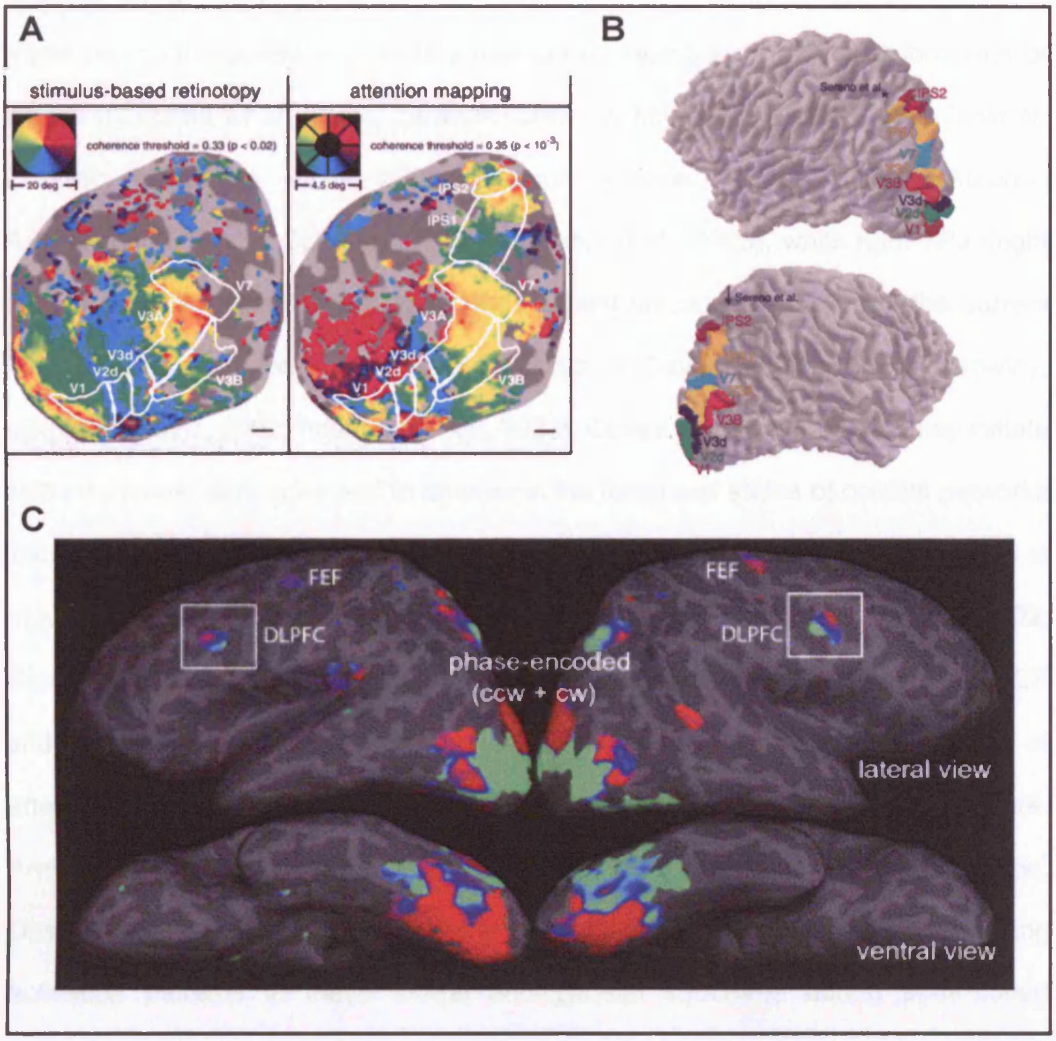

Figure I-4. Retinotopic maps in parietal and frontal cortex.

The top of the figure shows (A) the retinotopic response profile and (B) the localisation in stereotactic space of two areas in intraparietal sulcus (IPS1 and IPS2) that exhibit some retinotopic representation of the contralateral visual field during covert spatial attention. Panel (A) displays the angular component of retinotopic maps, measured using conventional visual stimulation (left) or during covert spatial attention (right), rendered unto a flattened representation of occipital and parietal cortex of a single subject. Colour indicates fMRI response phase, and the colour wheel inset defines the corresponding angular position in the visual field. Panel (B) shows the two retinotopic parietal areas as renderings onto a normalised 3D version of the individual's brain. The bottom of the figure (C) shows prefrontal regions in the FEF and DLPFC that exhibit retinotopic maps of the contralateral visual field during a 2-back face identity working memory task on phase-encoded polar angle mapping stimuli. The plots show visual field preferences during this task, rendered on lateral and ventral views of the inflated left and right hemispheres of an individual subject. Red, blue, and green areas represent preference for upper, middle, and lower contralateral visual field, respectively. (A-B) adapted from (Silver et al., 2005), and (C) adapted from (Hagler, Jr. et al., 2006).

Despite the agreement on the general plausibility of functional influences from frontal and parietal areas on visual cortex, this has rarely been shown directly, and it is currently debated which precise functional roles different regions might play in this

context. Some theorists propose that bilateral dorsal regions in FEF and SPL/IPS might be more involved in voluntary maintained selection of particular locations or stimuli (Corbetta et al., 2002; Downar, Crawley, Mikulis, & Davis, 2000; Downar, Crawley, Mikulis, & Davis, 2002; Humphreys et al., 2004; Kincade, Abrams, Astafiev, Shulman, & Corbetta, 2005; Pollmann et al., 2003), while right TPJ might contribute to the fast reorienting towards salient visual events outside the current focus of attention (Downar, Crawley, Mikulis, & Davis, 2000; Downar, Crawley, Mikulis, & Davis, 2002; Pollmann et al., 2003). Others posit that the SPL may initiate shifts from one 'attractor-state' to another in the functional states of cortical networks involved in representing a particular visual stimulus, for example when attention is moved to a new target in a different part of the visual field (Yantis et al., 2002; Serences et al., 2006). Yet others maintain that oculomotor signals from the FEF and IPS related to planned but not executed saccades may be the neural basis of attentional signals in visual cortex ('premotor theory of attention', e.g., Moore, Armstrong, & Fallah, 2003; Sheliga, Riggio, & Rizzolatti, 1994; Rizzolatti, Riggio, Dascola, & Umilta, 1987), apparently consistent with the largely overlapping activation patterns in these frontal and parietal structures during both covert attention and the planning of eye movements (Astafiev et al., 2003). However, it is presently difficult to perform such clear functional assignments to different areas, due to the vast diversity of paradigms and comparisons used in previous neuroimaging studies to identify putative attentional 'control processes' (Corbetta et al., 2002; Frith, 2001; Driver et al., 2004; Wojciulik & Kanwisher, 1999).

Lesion and intervention studies

The idea that regions in frontal and parietal cortices may be directly involved in attention-related influences on the processing of visual stimuli appears also broadly consistent with clinical observations. Patients with lesions of regions in parietal and frontal cortex, usually in the right hemisphere, can present with severe spatial-

perceptual deficits despite intact visual acuity across the visual field, and some of these deficits may be considered 'attentional' in nature (Duncan et al., 1999; Heinke & Humphreys, 2003; Humphreys, Romani, Olson, Riddoch, & Duncan, 1994). Such patients can miss visual stimuli presented contralateral to the lesion, sometimes detecting them when these are presented alone, but missing them when these are presented with a competing stimulus in the opposite hemifield ('extinction'; Driver & Mattingley, 1998; Milner & McIntosh, 2005; Mesulam, 1999; Karnath, Milner, & Vallar, 2002). Such deficits may indicate an involvement of the lesioned sites in the direction of spatial attention (Kinsbourne, 1970; Rossetti et al., 1998), in spatial exploration behaviour (Parton et al., 2006; Wojciulik, Husain, Clarke, & Driver, 2001), in selection of objects by perceptual as opposed to action-based features (Humphreys & Riddoch, 2001), or the representation of space in general (Pouget & Driver, 2000). However, it has also been suggested that extinction in particular may result from a lack of top-down enhancement of visual representations in occipital cortex of the lesioned hemisphere (Deco & Zihl, 2004; Marzi, Girelli, Natale, & Miniussi, 2001). Interestingly, neuroimaging studies conducted in a patient with a right parietal lesion have demonstrated that extinguished visual stimuli can still elicit residual category-specific processes in visual areas of the damaged hemisphere (Rees et al., 2000; Rees et al., 2002). This suggests that visual stimuli might go unnoticed despite apparently largely 'intact' occipital neural processing, due to a lack of functional interactions of such early stimulus presentations with the lesioned parietal or frontal areas (see also Beck, Rees, Frith, & Lavie, 2001; de Fockert, Rees, Frith, & Lavie, 2001).

Some recent data obtained with event-related potentials (ERPs) in patients with unilateral lesions of prefrontal cortex may speak to such a crucial role of higher-level areas (in prefrontal cortex) for occipital activity modulations related to stimulus selection (Barcelo, Suwazono, & Knight, 2000; Yago, Duarte, Wong, Barcelo, &

Knight, 2004; Padilla, Wood, Hale, & Knight, 2006). The lesion patients in these studies had to detect rare targets occurring unpredictably in bilateral streams of rapidly presented visual stimuli. The ERPs elicited by the targets were significantly reduced in electrodes over occipital cortex of the lesioned hemisphere, when compared to the intact hemisphere or to healthy controls, indicating the absence of a potential remote effect of the lesioned frontal region on visual cortex. Target detection rates were also significantly lower in the contra-lesional hemifield, suggesting that a lack of occipital cortex modulation by the lesioned prefrontal areas may indeed impair visual selection of target stimuli. Direct comparison of error trials with successful target detections confirmed that lapses were associated with lower activity over prefrontal cortex before stimulus presentation, and weaker extra-striate ERP modulations during visual processing (Padilla et al., 2006). However, interpretation of the results of lesion studies and comparison with neuroimaging findings in healthy participants can be complicated by several issues (Humphreys & Price, 2001). Such issues may comprise, among others, the extent and overlap of the lesion in different participants, potential damaging effects of the lesion on structures remote from the initial site ('diaschisis'), neural reorganisation following the brain injury, or effects of medication (Andrews, 1991; Butefisch, Netz, Wessling, Seitz, & Homberg, 2003; Bogousslavsky, 2002; Humphreys et al., 2001; Seitz et al., 1999).

For these reasons, the putative involvement of frontal and parietal areas in attentional control is now increasingly studied with experimental techniques that allow the direct and reversible experimental manipulation of neuronal activity (Chambers & Mattingley, 2005), such as TMS in humans (Walsh & Cowey, 2000; Walsh & Pascual-Leone, 2005; Hallett, 2000; Pascual-Leone, Walsh, & Rothwell, 2000), or microstimulation (Cohen & Newsome, 2004; Tehovnik, Tolias, Sultan, Slocum, & Logothetis, 2006) and neurochemical inactivation techniques (Malpeli,

1999; Martin & Ghez, 1999) in non-human primates. For example, Wardak and colleagues (Wardak, Olivier, & Duhamel, 2004; Wardak, Ibos, Duhamel, & Olivier, 2006) applied muscimol, a GABA-A agonist, to the LIP or FEF in macaques, and examined the effects of this intervention on performance in a variety of visual search tasks. Temporary inactivation of the FEF or the IPS significantly increased the latency and error rates for target detection in the hemifield contralateral to the injection (in the absence of differential eye movements), suggesting a causal role for both structures in the control of visual selective attention. Interestingly, there were also some qualitative differences in the effects of inactivating the two sites, as only the effects of IPS inactivation depended on visual properties of the to-be-detected target stimuli (e.g., single-feature vs conjunction search), while the effects of FEF inactivation yielded comparable performance deficits for all types of target stimuli.

Recent TMS studies in humans have similarly suggested an involvement of parietal and frontal regions in visual selection. For example, temporary excitability reductions (Chen et al., 1997; Muellbacher, Ziemann, Boroojerdi, & Hallett, 2000) of right parietal cortex, following long periods of low-frequency rTMS to this site, can impair detection of contralesional visual stimuli, mirroring the effect of visual extinction as observed in patients with lesions of this structure (Hilgetag, Theoret, & Pascual-Leone, 2001). Moreover, low-frequency TMS applied over either left or right posterior parietal cortex can lead to dissociable deficits on salience-based visual selection or disengagement (Mevorach, Humphreys, & Shalev, 2006). Other studies have employed short trains of rTMS during task performance at high frequencies, which is thought to disturb functionally relevant activity in the targeted sites on a trial-by-trial basis (Walsh et al., 2005). Such studies have revealed that applying TMS to human FEF or IPS can influence a whole range of visuo-spatial judgements such as visual search (Muggleton, Juan, Cowey, & Walsh, 2003; O'Shea, Muggleton, Cowey, & Walsh, 2004), single-target detection (Pascual-Leone et al.,

1994), target identification (Chambers, Stokes, & Mattingley, 2004; Kreiman et al., 2006; Muggleton et al., 2006; Pourtois, Vandermeeren, Olivier, & de Gelder, 2001), or phosphene judgements (Silvanto, Lavie, & Walsh, 2006). Some *facilitatory* effects on visual detection of peripheral targets have also been reported for TMS to FEF (Grosbras & Paus, 2002; Grosbras & Paus, 2003) or parietal cortex (Chambers, Stokes, Janko, & Mattingley, 2006). However, while consistent with the notion that the stimulated/inactivated regions are involved to some degree in successful perception, purely behavioural TMS/inactivation findings cannot show that this is due to top-down influences of the implicated frontal and parietal areas upon activity in occipital visual areas. This methodological limitation has led to an emerging interest in the application of TMS (and other invasive stimulation techniques) to frontal and parietal areas, during the measurement of neuronal activity changes in occipital cortex with neuroimaging methods such as EEG or single-unit recording.

Studies combining intervention and neuroimaging techniques

Based on the many suggestive findings mentioned above, Moore and colleagues examined directly whether activity changes in the macaque frontal eye fields may indeed result in activity modulations in occipital visual areas (Awh, Armstrong, & Moore, 2006; Moore et al., 2003). Using a combination of microstimulation and single-cell recording, they found that microstimulation of neurons in the frontal eye fields, at intensities too low to elicit a saccade, could indeed lead to activity modulations of neurons in area V4 with spatially congruent receptive visual fields (Moore & Armstrong, 2003). These single-unit activity modulations following FEF microstimulation strongly resemble those observed during directed selective visual attention, as revealed by similar effects on competitive interactions between preferred and non-preferred visual stimuli within the receptive field of V4 neurons (Armstrong, Fitzgerald, & Moore, 2006). Moreover, the FEF microstimulation protocol was also shown to lead to lower psychophysical detection thresholds by

macaques for stimuli presented at spatially congruent locations (Moore & Fallah, 2004).

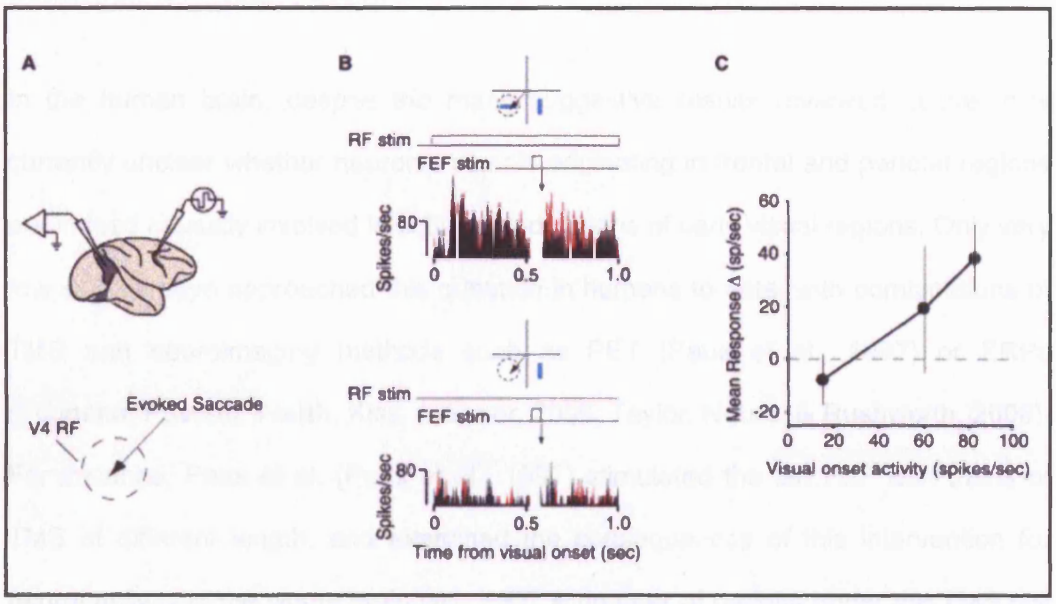

Figure I-5. Effect of FEF microstimulation on the visual response of macaque V4 neurons.

(A) Microstimulation of sites within the FEF was carried out at intensities too low to elicit a saccade, while simultaneously recording the responses of single V4 neurons to visual stimuli in monkeys performing a fixation task. The FEF microelectrode was positioned so as to align the vector of the saccade elicited by suprathreshold microstimulation with the RF position of the V4 cell under study (bottom cartoon).(B) (Top) Example of the effect of subthreshold FEF microstimulation on the response of a single V4 neuron to an oriented bar presented to the cell's RF (cartoon above) when the saccade vector represented at the FEF site (arrow) overlapped with the V4 RF. Mean response during control trials is shown in black, and the mean response of trials on which a 50 ms microstimulation train (FEF stim) was applied to the FEF site is shown in red. (Bottom) Same as in top, but histograms show responses during trials on which a visual stimulus is only presented outside of the RF. The response of the cell was elevated immediately following the stimulation train but only when the cell was being driven by a RF stimulus (i.e., top versus bottom histogram). (C) The stimulation-driven enhancement of the cell's response depended critically on the effectiveness of the visual stimulus. When there was no RF stimulus, there was a near zero change in the cell's response, compared to control trials. When there was a non-optimally oriented vertical bar in the RF, there was an intermediate enhancement. The greatest enhancement was observed when a horizontally oriented bar stimulus was presented inside the RF. Adapted from Moore & Armstrong (2003).

Taken together, these pioneering macaque studies provide strong evidence for the physiological plausibility of top-down signals originating in the FEF that may causally modulate activity in visual cortex to bias perception towards a particular visual target stimulus. Interestingly, recent studies in the barn owl have shown that microstimulating the acropallial gaze field (the owl 'functional homologue' of the primate FEF) has comparable effects on thalamic nuclei involved in auditory processing, suggesting that spatial influences of frontal gaze control areas upon

sensory processing may be restricted neither to the primate brain nor to vision, but may rather be a general feature of different sensory systems, in different species (Winkowski & Knudsen, 2006).

In the human brain, despite the many suggestive results reviewed above, it is currently unclear whether neuronal signals originating in frontal and parietal regions are indeed causally involved in activity modulations of early visual regions. Only very few studies have approached this question in humans to date, with combinations of TMS and neuroimaging methods such as PET (Paus et al., 1997) or ERPs (Fuggetta, Pavone, Walsh, Kiss, & Eimer, 2006; Taylor, Nobre, & Rushworth, 2006). For instance, Paus et al. (Paus et al., 1997) stimulated the left FEF with trains of TMS of different length, and examined the consequences of this intervention for neural activity in the whole brain with PET. A number of regions under the TMS coil and in more posterior areas displayed activity changes that correlated with the number of administered TMS pulse trains, demonstrating that TMS of FEF can indeed result in activity changes both under the coil as well as in remote neural structures. However, this pioneering study was unable to examine influences on visual areas in occipital cortex, due to the limited spatial resolution of PET and the fact that (unlike fMRI) individual retinotopic visual areas cannot be readily mapped by PET. Similar methodical limitations apply to the interpretation of recent studies that have combined TMS and ERPs to study top-down influences of frontal or parietal brain areas on visual cortical activity. These studies have demonstrated changes in voltage fluctuations at posterior electrode positions, presumably located over occipital cortex, as a function of TMS application to FEF (Taylor et al., 2006) or posterior parietal cortex (Fuggetta et al., 2006), during tasks requiring selective attention to cued visual stimuli. While the timecourse of these effects clearly illustrates how TMS to these frontal or parietal structures can affect temporally distinct stages of processing, it is unclear at present whether visual areas of occipital

cortex may be affected directly. This is mostly due to the spatial uncertainty associated with the putative neural origins of ERPs, particularly at scalp electrode positions such as those examined in the studies mentioned above (Hopf et al., 2000). As a further complication, scalp ERPs may selectively reflect activity changes in only some types of neurons located in the gyri of the outer cortical surface, and may thus strongly depend on the individual pattern of cortical folding (Rugg, 1998).

Summary of prior work and relation to questions of the thesis

Neuroimaging studies have shown that visual selective attention is associated with specific activity modulations of those visual areas that code the attended stimulus attribute. Such activity changes can occur during the mere anticipation of visual stimuli, and thus in the absence of any changes in bottom-up input to visual cortex, demonstrating that visual selective attention may operate in part by means of top-down signals that can modulate occipital cortex in a preparatory fashion. The precise functional significance of these mechanisms is currently unclear, but it has been proposed that they may reflect neural signals that bias processing in visual areas towards behaviourally relevant stimuli. Such top-down signals in visual areas may originate in neural feedback loops from frontal and parietal brain regions, consistent with neuroimaging studies that have shown sustained activity in such areas during covert selective attention. However, despite suggestive results from lesion and inactivation/stimulation studies, the assumed causal influences of frontal and parietal regions on visual cortex have not been demonstrated directly in the human brain so far. It is furthermore unclear to what degree different frontal and parietal regions may exert qualitatively different modulatory influences. The seven experiments described in this thesis will address questions concerning the *functional significance* (Chapters 2-3) or the potential *origins* (Chapters 4-6) of top-down activity modulations in visual cortices, as observed during selective attention.

Chapter 2 describes a TMS experiment that examines the question whether spatial selective attention may influence the excitability of neurons in spatially corresponding parts of early visual cortex, as often assumed. The experiment applies TMS unpredictably over occipital cortex during a covert visual attention task, showing that the TMS output intensity needed to elicit a phosphene is significantly lower when the cortical locus of stimulation matches the retinotopic representation of the attended visual location. This demonstrates a direct top-down influence on the sensitivity of occipital cortex for any kind of visual input that matches the spatial focus of selective visual attention, even if the stimulus is irrelevant for the present task.

The two experiments in Chapter 3 address the question whether activity changes in occipital cortex during preparatory spatial attention may relate to the anticipation of distractor stimuli, rather than just of targets that should receive further processing. Using psychophysics and fMRI, the studies show that anticipatory information about the presence of a distractor in a particular location of the visual field can reduce the behavioural impact of that distractor, and can elicit anticipatory activity increases in spatially corresponding occipital visual areas. This underlines that specific components of anticipatory top-down signals in visual cortex may be devoted to minimizing the impact of distractors, not just to enhancements of target processing, as often assumed.

Chapter 4 describes two studies conducted with concurrent TMS-fMRI that focus on the question whether the human frontal eye fields are a plausible source for top-down influences on activity in visual cortex. The experiments show that TMS of the right FEF elicits a characteristic pattern of activity changes in early retinotopic visual areas V1-V4. This pattern functionally differentiates the central vs peripheral visual field, is independent of concurrent visual input, and is not present during application

of the identical TMS protocol to a vertex control site. This demonstrates the physiological plausibility of spatially specific top-down influences of the human FEF on retinotopic visual cortex.

Chapter 5 describes a TMS experiment that tests a behavioural prediction derived from the studies in Chapter 4. The same TMS protocol is again applied to right FEF or the vertex control site, now during psychophysical judgements on the perceived contrast of visual stimuli presented in the central and peripheral visual field. FEF TMS results in influences on contrast perception that mirror the spatiotopic pattern of influences observed on visual cortex, demonstrating that the activity modulations observed in Chapter 4 have direct functional consequences for visual perception.

Finally, Chapter 6 describes a study testing the specificity of parietal and frontal modulatory influences on activity in visual cortex. This is examined by applying the same TMS protocol as before to the right intra-parietal sulcus, while again measuring the effects of this intervention on activity in retinotopic visual cortex with fMRI. This reveals a distinct pattern of activity modulations in visual cortex, which now depends on the presence or absence of concurrent visual input, and does not differentiate the central vs peripheral visual field. Direct comparisons with the data presented in Chapter 4 show that frontal and parietal regions in the human brain can indeed have distinct top-down influences on activity retinotopic visual cortex.

All chapters are self-contained, but cross-referenced throughout. The final discussion in Chapter 7 will focus on the implications of the experiments for current neurobiological models of selective attention, but will also briefly outline possible future extensions of the experimental approaches developed for this thesis.

Chapter 2

Selective attention changes visual cortex excitability as revealed by phosphene thresholds

As reviewed in detail in Chapter I, BOLD activity in visual cortex can increase when attention is covertly directed to a corresponding part of the visual field, even in the absence of visual stimulation (Chawla et al., 1999; Hopfinger et al., 2000; Kastner et al., 1999; Macaluso, Driver, & Frith, 2003; Rees et al., 2000). The function of such 'top-down' activity modulations is under debate, but it is generally assumed that they might represent bias signals that may give a competitive advantage to neural activity related to the visual location and/or features of the attended object (Desimone et al., 1995; Duncan et al., 1997; Kastner, 2000). However, there have been no clear demonstrations to date of a causal relationship between such anticipatory baseline shifts in visual cortex and modulations of the neuronal response to the subsequent visual input (Driver et al., 2004). It is furthermore unclear by which precise mechanisms attentional baseline shifts, as found with fMRI, might bias processing towards the expected object. One putative mechanism often mentioned in this context relates to preparatory *gain control* of visual neurons involved in coding the attended object features (Luck et al., 1997; Chawla et al., 1999). An increase in baseline activity might bring relevant neurons into their optimal dynamic range, and thus increase their sensitivity to incoming input. However, whether attention can indeed increase the *excitability* of neurons in human visual cortex to incoming input has not been directly shown to date.

A related issue concerns which neuronal pathways might bring about such attention-related activity increases observed in early visual areas. Recent demonstrations that

even the lateral geniculate nucleus of the thalamus can be affected during covert spatial attention (O'Connor et al., 2002; Casagrande, Sary, Royal, & Ruiz, 2005) have re-opened the long-standing question (Hillyard, Vogel, & Luck, 1998; Vanduffel et al., 2000; Sherman & Guillery, 2002) of whether thalamic gating of retinal inputs might make critical contributions to attentional effects in cortical areas of the visual processing hierarchy. That is, an initial modulation of feed-forward signals at the LGN might conceivably be a necessary prerequisite for spatial-attention effects at subsequent cortical stages. Such effects may possibly increase at each successive stage, but only if seeded with initial thalamic gating. Alternatively, it is conceivable that activity changes in early visual cortices might be largely initiated via cortico-cortical feedback connections from higher level-areas (e.g., in frontal and parietal cortex; Kastner et al., 2000; Moore et al., 2003), while empirically observed effects at subcortical stages (O'Connor et al., 2002; Casagrande et al., 2005) might largely reflect cortico-subcortical recursive interactions following on from such initial cortico-cortical top-down influences. Some ERP studies on the timecourse of attentional effects (Martinez et al., 2001; Noesselt et al., 2002) may appear more consistent with the second of the alternatives outlined before, and it should also be noted that attention can be directed on the basis of non-spatial properties (e.g., colour), which initial thalamic gating seems unlikely to explain. However, for the particular case of spatial attention, it is still largely unknown in the human brain to what degree feed-forward thalamic gating of initial retinal afferents may account for attentional activity modulations at later cortical stages of the visual processing hierarchy.

The present experiment tested directly via transcranial magnetic stimulation (TMS) to occipital cortex whether sustained covert spatial attention to one location may indeed increase the excitability of corresponding parts of visual cortex. When applied to human visual cortex, TMS above a distinct threshold-intensity induces illusory visual perceptions called 'phosphenes' (Brindley, Donaldson, Falconer, &

Rushton, 1972; Kammer, Beck, Erb, & Grodd, 2001; Walsh et al., 2000). Phosphenes are thought to originate from early visual cortex (V1/V2; Walsh et al., 2000; Brindley & Lewin, 1968; Brindley et al., 1972), as they depend on the integrity (Walsh et al., 2000) and excitability (Aurora & Welch, 1998; Muellbacher et al., 2000) of these occipital regions. The perceived location of a phosphene falls within the visual hemifield contralateral to the stimulated cortical hemisphere, and shows some degree of retinotopic organisation. For example, TMS of superior right occipital cortex elicits a phosphene in the lower left quadrant (Kammer, 2005), reflecting the retinotopic structure of visual cortex (Sereno et al., 1995; Wandell et al., 2005).

This spatial specificity enabled the present approach of using thresholds for TMS-induced phosphene perception as a probe to measure changes in visual cortical excitability during directed spatial attention. Participants were cued to hold their attention covertly at a specified location in either the left or right hemifield throughout a block of trials, for a task on external visual stimuli presented on a computer screen for a random half of the trials per block (the 'visual' conditions). On such trials, bilateral visual stimulus arrays consisting of a random number (1-4) of faint grey rectangles were presented in the peripheral locations. Participants were instructed to report by button press the number of rectangles in just the cued hemifield. This task required continuous covert attention to the putative stimulus location in the cued hemifield, since the stimuli were temporally unpredictable, present for a short time only, and followed by a strong bilateral mask (see Figure II-1 and Methods). A control condition was also included, in which participants were instructed not to pay attention to either of the two hemifields throughout the block, but simply to press a specific button as soon as any visual stimulus appeared, without further perceptual judgments. In total, the experiment thus comprised three 'visual' conditions that

differed in where spatial attention was directed throughout a block of trials for stimuli on an external computer screen ('left', 'right', or 'neutral').

Crucially, on the other half of the trials in each block, no external visual stimuli were presented, but instead a TMS pulse was administered to right occipital cortex ('TMS' conditions). This could elicit a phosphene in the left visual hemifield, in a location that was chosen to retinotopically correspond to the location where left visual stimuli could be present on 'visual' trials. Note that this location was thus either currently attended (for blocks with attention cued to the left hemifield) or unattended (for blocks with attention to the right, or the neutral control blocks). The TMS output intensity was varied from trial to trial according to an adaptive converging staircase algorithm (see Methods), and the task on the TMS trials was simply to indicate by button press whether a phosphene was experienced or not. These responses were used to determine the TMS-intensity required to induce a phosphene ('phosphene threshold', PT), separately for the conditions where its location was currently attended or unattended. Such PTs are widely held to reflect the excitability of early visual cortex (Aurora et al., 1998; Boroojerdi et al., 2000a; Boroojerdi, Prager, Muellbacher, & Cohen, 2000b), in a similar way as motor thresholds are often considered to indicate the excitability of the stimulated primary motor cortex (Pascual-Leone et al., 1998). Moreover, there have been some demonstrations that cortical excitability of occipital cortex, as measured with phosphene thresholds, can vary depending on context factors that may influence the activity state of visual cortex, such as presence of visual stimuli (Rauschecker, Bestmann, Walsh, & Thilo, 2004), short-term light deprivation (Aurora, Ahmad, Welch, Bhardhwaj, & Ramadan, 1998), or imagery (Sparing et al., 2002). By interleaving measurement of phosphene thresholds here with an experimental variation of where cued visual attention was directed for an external visual task, the present design allowed for a direct test of whether covert spatial selective attention can indeed change excitability of visual

cortex. If this were the case, then PTs should differ when the location corresponding to the possible phosphene was attended rather than unattended for the external 'visual' task. Such a finding would also provide evidence that excitability of visual cortex can be changed directly by spatial attention, even when thalamic feed-forward gating of retinal inputs in the LGN is bypassed via direct TMS stimulation of occipital cortex.

Experiment 1: Methods

Participants

Eleven participants (aged 19–31 years, mean 23.5 years, 6 females) performed a sustained spatial-attention task in a darkened room. They were selected for reliably perceiving phosphenes in a well-circumscribed location, with eyes open, at 90% of TMS stimulator output (see Pascual-Leone et al., 2001). Two were excluded from subsequent analysis due to excessive eye movement (see Methods). All participants had normal or corrected visual acuity and reported no history of neuropsychiatric illness or epilepsy. All gave informed consent in accord with local ethics approval.

Setup and procedure

Participants wore earplugs and headphones, and performed the task in a dark and soundproof room. All visual stimuli were presented on a 21 inch computer screen (60 Hz refresh rate, viewing distance 45 cm), while stable viewing and head position were ensured with a chinrest and nose-bridge. Throughout a block of trials, participants were either asked to direct their attention to a specific visual quadrant (bottom left or bottom right), or to attend centrally (neutral condition). This instruction was achieved by means of spatial cues (left: <, right: >, neutral: ^) presented in the screen centre for 2000 ms prior to each block of trials. Each participant performed one practice block of 96 trials. The order of experimental blocks (two blocks each of

attend left, attend right, or neutral) and trial types was randomized. After two blocks, a break of approximately 5 min was given. Trials were self-initiated by button press, and subjects were repeatedly instructed to avoid eye movements, as confirmed by eye-tracking (see below).

External visual stimuli

Each of the two lower quadrants contained a target area (each 8° square), centred 8° below the horizontal meridian, at an eccentricity of 19°. These areas were divided into a virtual 8 x 8 grid (with equally-spaced elements), and marked on the outer corners by small grey dots (2 pixels each) in order to facilitate spatial attention. In 'visual' trials, target stimuli were presented in these areas of both quadrants simultaneously. The targets consisted of 1-4 faint grey rectangles, the number and position of which was randomly determined per hemifield. Based on pilot measurements, exposure-durations for the visual stimuli were selected to titrate counting performance for attended stimuli to ~60% correct – clearly above chance (25%), but far from saturation – to provide a demanding spatial attention task. This resulted in target presentation times of 180 ms, followed 30 ms later by a masking black-and-white checkerboard (presented for 150 ms) covering the whole target area (see Fig II-1A and II-1C). Responses had to be given within 2430ms after presentation of the masking checkerboard, but otherwise there was no emphasis on speed for this difficult discrimination (response latency was equivalent for all trial types in the counting task: left correct, 1299 ms; left incorrect 1309 ms; right correct, 1285 ms; right incorrect, 1277 ms; Friedman Test, $\chi^2[3] = 1.93$; $p = 0.57$). In the neutral attention blocks (not depicted in Figure II-1), participants were instructed to direct their attention to the central visual field, and to press a button as quickly as possible after onset of any visual stimulus, whilst ignoring the number of targets. Not surprisingly, participants responded significantly faster when no targets had to be detected (neutral condition, 817ms; Friedman Test, $\chi^2[4] = 19.289$; $p < 0.001$).

Transcranial magnetic stimulation

On 'TMS' trials (50% in each block, randomly determined; see Fig II-1B and II-1D), no visual stimulus appeared, but a single TMS pulse instead was administered to a fixed scalp position over the right occipital cortex, determined to yield perception of a phosphene in one of the two target areas (see below). On these trials, subjects reported the presence or absence of a phosphene, via button press of the left index or middle finger, respectively. No emphasis on speeded responses was given.

No visual stimuli were presented during 'TMS' trials, as PTs are known to change with visual input (e.g., as a function of its luminance contrast; Rauschecker et al., 2004). Indeed, this is one of the reasons why PTs are widely considered to reflect excitability of visual cortex (Aurora et al., 1998; Boroojerdi et al., 2000a; Boroojerdi et al., 2000b), just as TMS thresholds for induced movements reflect excitability of motor cortex (Pascual-Leone et al., 2000). TMS application produces a 'click' sound, but this was equivalent across the different conditions of visual attention here, so could not confound the results.

On such TMS-trials, TMS was applied using a 70mm, figure-of-eight coil (Super Rapid, Magstim, Dyfed, Wales, UK). A two-joint holder was used to place the coil to one side of the occiput, approximately 4cm above the inion, at a laterality for which phosphenes were reliably reported (Walsh et al., 2000). The initial phase of the induced biphasic current (~250μs duration) had a temporo-medial orientation, optimal for inducing visual phosphenes (Kammer et al., 2001). The stimulation site over right occipital cortex was chosen to maximise spatial congruence of phosphenes with the fixed target area for external visual stimuli in the lower-left quadrant on the computer screen. Note that TMS-evoked phosphenes are more readily elicited for lower quadrants of the visual field (Walsh et al., 2000).

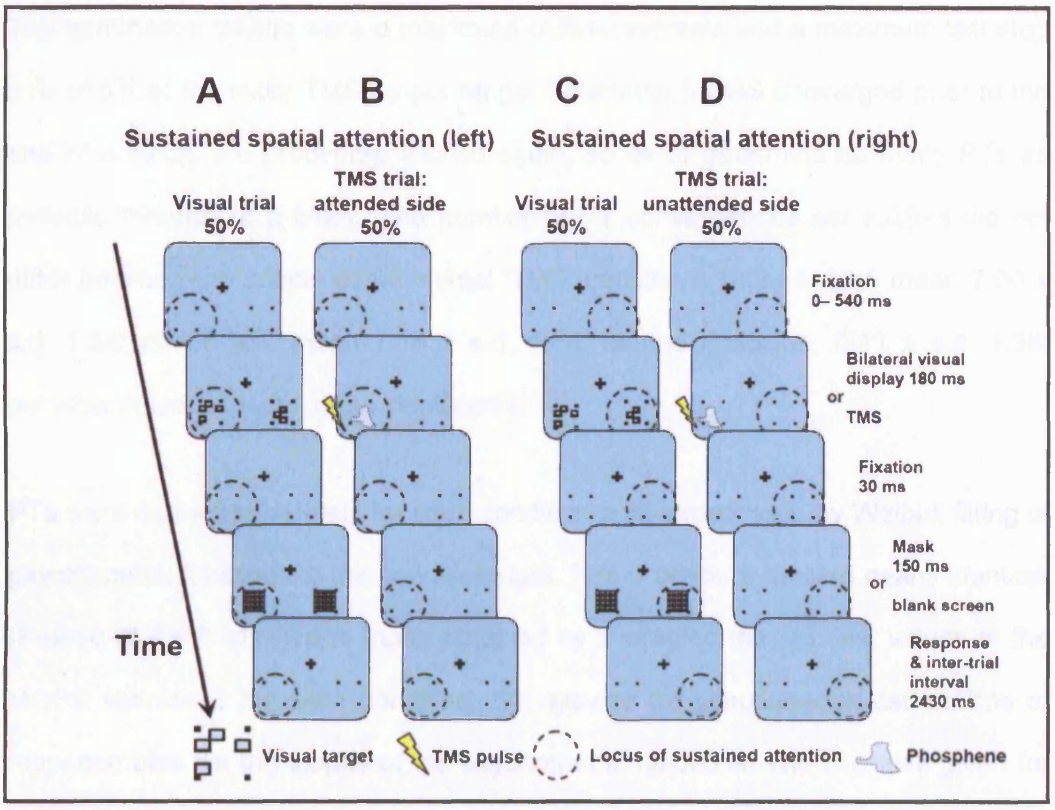

Figure II-1. Experiment 1: Schematic timecourse of trials.

A–D show event sequences for four different types of trial. During central fixation, covert spatial attention was directed continuously towards either the left (A, B) or the right (C, D) lower quadrant throughout each block (no example of the 'neutral' control condition is shown here). Within each block, 50% of trials were 'visual' (A, C) and 50% were 'TMS' (B, D), randomly interleaved. The visual stimuli were groups of 1–4 grey rectangles on either side of 1° each, bilaterally presented within a defined square target region in each hemifield, below the horizontal meridian, and followed by a masking checkerboard covering the target area (8° square). On 'visual' trials, participants had to report via key press the number of rectangles in the target area on the attended side only. On 'TMS' trials, with spatial attention sustained towards one side or the other for the external task, a TMS pulse was applied to the right side of the occiput (instead of any external visual stimuli), and the observer had to indicate whether or not a phosphene was experienced.

Phosphene threshold measurement

TMS intensities were varied on each trial depending on the participants' responses, using the Modified Binary Search (MOBS) algorithm (Tyrell & Owens, 1988; Thilo, Santoro, Walsh, & Blakemore, 2004). The use of this adaptive procedure (rather than, for example, method of constant stimuli) ensured that TMS intensities were held within a range optimally bracketing the phosphene thresholds in the respective conditions. The upper and lower boundaries for MOBS were 100% and 0% of TMS output, respectively. The initial presentation was midway between these boundaries.

The termination criteria were a maximum of five reversals and a maximum last step size of 5% of the initial TMS output range. Whenever MOBS converged prior to the end of a block, the procedure started again, so as to determine as many PTs as possible throughout a block. The number of PT convergences per subject did not differ between the critical experimental 'TMS' conditions (attend right: mean 7.00 ± s.d. 1.34; attend left: mean 7.18 ± s.d. 1.66; neutral condition: 6.11 ± s.d. 1.36; pairwise Wilcoxon tests, none significant).

PTs were derived separately for each condition post-experiment, by Weibull fitting of psychometric functions to the condition data. This procedure derived nearly identical (Pearson's r = 0.91) PTs to those obtained by averaging the terminal values of the MOBS staircases for each condition, but allowed for simultaneous estimations of response bias via the slopes of the psychometric functions. The Z-values given for comparisons of attended versus unattended conditions in the main text and figure legends were derived from Wilcoxon signed-ranks comparisons. These non-parametric analyses were employed due to the number of subjects and to avoid assumptions about the distribution of individual data. Nevertheless, parametric analysis (paired t-tests) always produced similar and significant p values.

Eye monitoring

Horizontal and vertical eye-position was monitored continuously using an infrared ASL 601 remote optics eyetracker (ASL, Applied Science Laboratories, Bedford, MA, USA; 50 Hz sampling frequency). Eye position data were analysed using the open-source toolbox ILAB (Gitelman, 2002). Eye blinks were identified and removed from the eye recordings prior to further analysis. 700 ms sweeps of horizontal and vertical eye movements were then analysed commencing 350 ms prior to target presentation or TMS, and temporally low-pass filtered by convolution with a Gaussian kernel with 100 ms FWHM. Saccades (eye velocity >30 deg/s) or

significant ocular drift (>1° per 100 ms epoch) were identified using previously published criteria (Fischer et al., 1993; Fischer, Biscaldi, & Otto, 1993). Any trial on which gaze deviated, by these criteria, outside the 1° square window around the fixation point was rejected. On average, 7.47% (inter-participant range 3.79 – 13.27%) of trials were discarded because of such loss of fixation.

Experiment 1: Results

At or above threshold TMS intensity, phosphenes were experienced as small brief illusory white flashes of light, clearly localized at a particular position in the hemifield opposite to the cortical stimulation site (Kammer et al., 2001; Thilo et al., 2004; Rauschecker et al., 2004). PTs were determined by adjusting TMS intensity as a function of participant response, according to an adaptive converging staircase algorithm (Tyrell et al., 1988; Thilo et al., 2004). TMS trials were randomly interleaved with trials in which real visual stimuli were presented for judgement, at the same eccentricity in space as the possible TMS phosphene. Varying the side to which covert attention was directed, for the interleaved task on external visual stimuli, thus allowed measurement of PTs with and without spatially congruent attention.

Critically, PTs were significantly reduced for phosphenes corresponding to the location attended for the interleaved external task (see Figure II-2), as compared with PTs when the other side was attended instead (Wilcoxon, $Z = 2.67$, $p = 0.008$). The comparison with PTs in the neutral condition - which did not require attention to one side versus the other - indicates that the spatial-attention effect on PTs indeed reflected enhanced excitability for the attended quadrant (Wilcoxon, $Z = 2.19$, $p = 0.028$), rather than reduced excitability and hence heightened PTs for the unattended. No significant difference was found for PTs in the unattended and neutral condition. Moreover, the slopes of the psychometric functions for the three

different conditions did not differ (pairwise Wilcoxon tests, all not significant), indicating that the effect of attention on PTs did not reflect an increase in noise or a change in response bias, but rather a genuine change in cortical excitability due to attention.

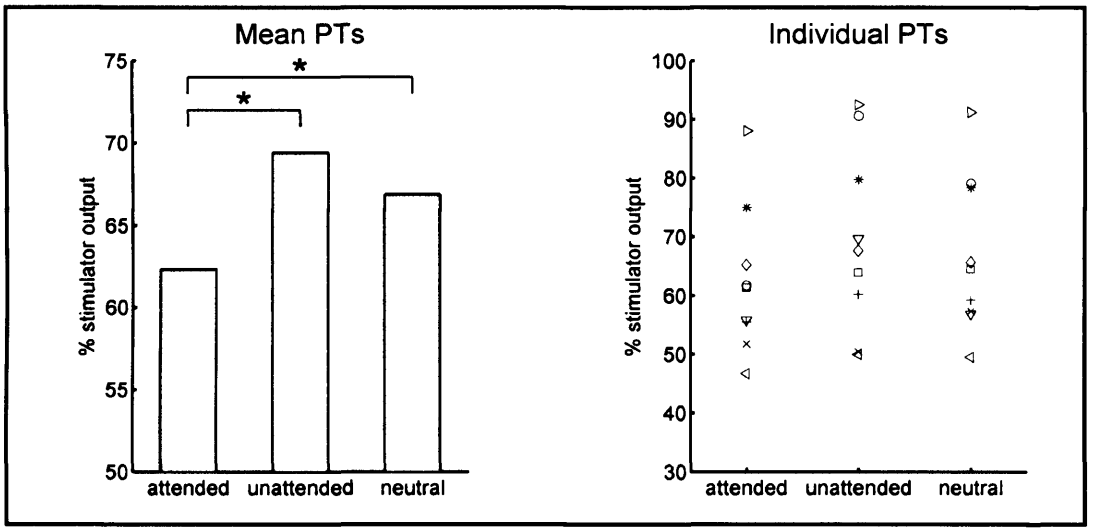

Figure II-2. Experiment 1: Phosphene thresholds are lower at the locus of spatial attention.

Left panel: The group mean PT was significantly lower for the attended quadrant than for the unattended quadrant, or for the neutral condition. Right panel: Individual PT values. In 8 out of 9 subjects, the PT was lower in blocks where sustained spatial attention was directed towards the area of the phosphene, relative to either the unattended or neutral condition.

Experiment 1: Discussion

It has often been suggested that selective attention may change the excitability of neuronal populations in visual cortex for incoming stimuli (Luck et al., 1997; Kastner et al., 1999). This notion was tested for humans in the present experiment with TMS of occipital cortex, which provides direct input to visual cortex that by-passes the feed-forward retino-geniculate pathway (Brindley et al., 1972; Kammer et al., 2001; Walsh et al., 2000). For a task on external visual stimuli, participants held their attention throughout a block of trials on one of two locations in opposite hemifields, to judge visual stimuli presented unpredictably there. On some trials, TMS was applied to visual cortex of one hemisphere instead of the bilateral visual stimuli. This could lead to perception of phosphenes in the contralateral visual field, in one of the

locations where visual stimuli could appear on 'visual' trials of the experiment. The critical finding was that the intensity needed to elicit a phosphene (phosphene threshold, PT) was reliably lower when spatial attention was congruent with the side of the possible phosphene, versus when the other side was attended for the external task. In line with the interpretation of phosphene thresholds as direct measures of local cortical excitability (Aurora et al., 1998; Boroojerdi et al., 2000a; Boroojerdi et al., 2000b), these results indicate that such excitability is increased for an attended locus in visual cortex.

Interestingly, the pattern of results suggested an increase of cortical excitability corresponding to the locus of attention, rather than a decrease when attention was directed away from a phosphene. PTs measured during a 'neutral' condition - that did not require selective attention to one specific hemifield versus the other - were not significantly different from those when participants had to judge visual stimuli in the hemifield opposite to a possible phosphene. However, PTs for both these conditions were significantly higher than thresholds for phosphenes that appeared at the attended target location. Cortical excitability thus seemed selectively increased for stimulation of visual regions coding the attended hemifield.

The present results may also shed light on the neuronal pathways involved in implementing the effects of selective attention on visual processing. Recent human fMRI work has shown that even thalamic LGN responses to visual inputs can be modulated by attention (O'Connor et al., 2002). This has re-opened the longstanding question (Crick & Koch, 1995; Hillyard et al., 1998; Martinez et al., 1999; Sherman et al., 2002) of whether attentional influences upon early visual cortex (and on visual awareness) may depend upon thalamic gating of initial feed-forward afferent inputs (Shipp, 2004; Casagrande et al., 2005), rather than direct modulatory influences upon visual areas themselves, possibly from higher cortical regions (Kastner et al.,

2000; Hopfinger et al., 2000; Martinez et al., 1999). The present study used TMS as a direct input to visual cortex, by-passing the retino-geniculate pathway, which rules out feed-forward gating of initial retinal input as a mechanism for the effects of attention on phosphenes observed here. Although the present results cannot exclude that recursive interactions with the thalamus may normally occur during spatial attention, they thus provide a clear example for direct effects of attention on excitability of visual cortex that do not appear mediated by initial thalamic gating.

Which cortical visual areas may be involved in the generation of phosphenes and their modulation by spatial attention? As discussed before, it is commonly assumed that phosphenes originate in visual areas with a precise and extensive retinotopic layout (such as V1/V2), in line with previous demonstrations that phosphenes depend on the integrity (Walsh et al., 2000) and excitability (Aurora et al., 1998; Muellbacher et al., 2000) of these occipital regions. The spatial specificity of the effect observed here may broadly accord with this assumption. However, it has been proposed that other retinotopic parts of the cortical visual system might also contribute to phenomenal aspects of phosphenes (cf. Kammer, 2005), such as extra-striate areas beyond V2 (Epstein, Verson, & Zangaladze, 1996; Kastner, Demmer, & Ziemann, 1998) or cortico-cortical tracts projecting back to V1 from V2/V3 (Kammer 2001) or V5 (Pascual-Leone & Walsh, 2001). The present results cannot resolve the issue whether phosphenes and their attentional modulation exclusively reflect activity in V1/V2, or may also involve extra-striate areas and their feedback projections to V1. However, recursive processing between visual areas is likely to be a ubiquitous feature of visual processing in general (Bullier, 2001; Lamme et al., 1998), and cortical feedback of higher visual regions to V1 has indeed been proposed as a putative mechanism for spatially specific effects of selective attention on activity in area V1 (Martinez et al., 1999; Noesselt et al., 2002). This suggests that the attention-related modulations of phosphene perception found here

may not exclusively reflect effects on striate cortex, but potentially also modulations of feed-forward and feedback processing in several of those visual areas that show quadrant-specific retinotopic organisation (cf. Kammer, 2005). However, such considerations about the precise networks of structures involved do not affect the central conclusion of the present study: Covert spatial attention can increase the excitability of cortical visual areas, in a manner that apparently does not depend on initial thalamic gating of retinal input.

Finally, it should be noted that the present results indicate that ongoing spatial attention may indeed act on the visual cortex so as to 'highlight' a particular region in the visual field, in a way that evidently generalises across the two very different inputs and featural properties of the two stimuli used here (checkerboards vs TMS-induced phosphenes). This again seems consistent with the notion that attention may selectively change the excitability of patches of cortex with a retinotopic preference for a particular location of the visual field, independent of other non-spatial stimulus features such as, say, shape and colour.

Chapter 3
Top-down signals related to distractor anticipation

The previous chapter showed, via phosphene thresholds for occipital TMS, that sustained spatial attention may increase visual cortical excitability at attended locations. In psychophysical studies of visual selective attention, it has been debated whether selective attention mainly operates by enhancing target-related signals (e.g., Carrasco et al. 2000; Carrasco et al. 2004; Hawkins et al. 1990), by suppressing signals from surrounding distractors (e.g., Awh et al., 2003; Lu et al., 2002; Mavritsaki et al., 2006; Watson et al., 1997; Watson et al., 2003), or by a combination of both mechanisms (e.g., Cheal and Gregory 1997; Dosher and Lu 2000; Pestilli & Carrasco, 2005). However, as outlined in Chapter 1, most previous neuroimaging studies on anticipatory top-down modulations of visual cortex have focused mainly on an upcoming expected *target* (by manipulating its location), rather than seeking to isolate any anticipatory modulations that might relate to expectation of a *distractor* at a particular location. Kastner et al. (1999) did vary whether a target at a known upcoming location would subsequently be presented with or without concurrent distractors, but the focus was nevertheless on how this might affect activation in visual cortex corresponding to the target quadrant. More recently, Serences et al. (2004) began to examine whether anticipatory modulations of visual cortex may relate to the anticipation of distractors surrounding the target stimuli. However, distractor arrays in that study, when present, were tightly packed into the same retinal quadrant as the target (see also Awh et al., 2003). Thus, any modulation of spatiotopic visual cortex corresponding exclusively to the location of an expected distractor, rather than the target, could not be isolated. Hence, it is unclear at present whether anticipatory selective attention can be employed to

prepare for a single distractor stimulus that is spatially remote from a target, and whether any such distractor anticipation may involve modulation of occipital representations for that part of the visual field that would subsequently contain the distractor rather than the target.

The present study therefore focused on any behavioural and fMRI effects specific to expecting a distractor at a known location that was distinct and remote from the expected target location. Specifically, the study employed a single distractor stimulus in the opposite hemifield to a target, and hence projecting to a different cortical hemisphere. An initial behavioural experiment manipulated on a trial-by-trial basis any advance information about whether or not such a distractor would appear on the opposite side to the cued target location. To anticipate the findings, such advance knowledge about distractor presence reduced the behavioural cost of that distractor, relative to no foreknowledge about distractor presence/absence, even when advance knowledge about target location was held constant. Advance knowledge about distractor absence had no behavioural effect, relative to no foreknowledge. This behavioural pattern of results thus indicates that participants can prepare beneficially for the presence of a single distractor, at a particular location remote from the anticipated target.

A subsequent fMRI experiment with a similar paradigm then examined the neural activations associated with such attentional preparation for a single distractor at a known location, on the opposite side to the target. Using opposite hemifields for the target and distractor in this way made it possible to test whether anticipation of a visual distractor would modulate activity in the occipital hemisphere representing the distractor location; or in the other occipital hemisphere representing the target location (as might be expected if participants simply attended more strongly, or with

a different strategy, to the target location when expecting a distractor); or whether both types of modulation exist when anticipating a distractor.

Experiment 2:

Behavioural consequences of distractor anticipation

Design

This experiment examined whether trial-by-trial advance knowledge about the presence or absence of a distractor at a specific location could reduce the cost of this distractor for processing of a target in the opposite hemifield. On every trial, participants were randomly cued by a small central arrow to either the left or the right hemifield (with 100% validity), and performed a speeded discrimination task on the target appearing there. These targets were either presented alone (D-absent), or with a distractor present in the other hemifield (D-present), in a randomly intermingled fashion. The cost of distractor presence vs absence on target processing speed (i.e. latencies for D-present minus D-absent trials) was measured in two types of blocks that differed in whether participants could or could not anticipate, on a trial-by-trial basis, the presence or absence of a distractor in the target-opposite hemifield.

In those blocks with foreknowledge about distractor presence or absence (D-cued, as in the subsequent fMRI study also), the colour of the central cue (red or green) was 100% informative as to whether the following display would contain a distractor or not, on the opposite side to the target. In control blocks providing a behavioural baseline (implemented only in the behavioural Experiment 2, not during the subsequent fMRI study of Experiment 3), participants were given no foreknowledge about distractor presence or absence (D-unknown); that is, the colour of the central cues (now blue) no longer gave any information about the possible presence or

absence of a distractor. Comparing the behavioural distractor cost in the D-cued and the D-unknown blocks made it possible to examine whether advance foreknowledge about the presence or absence of a distractor in a particular location allowed participants to minimise the behavioural impact of this distractor.

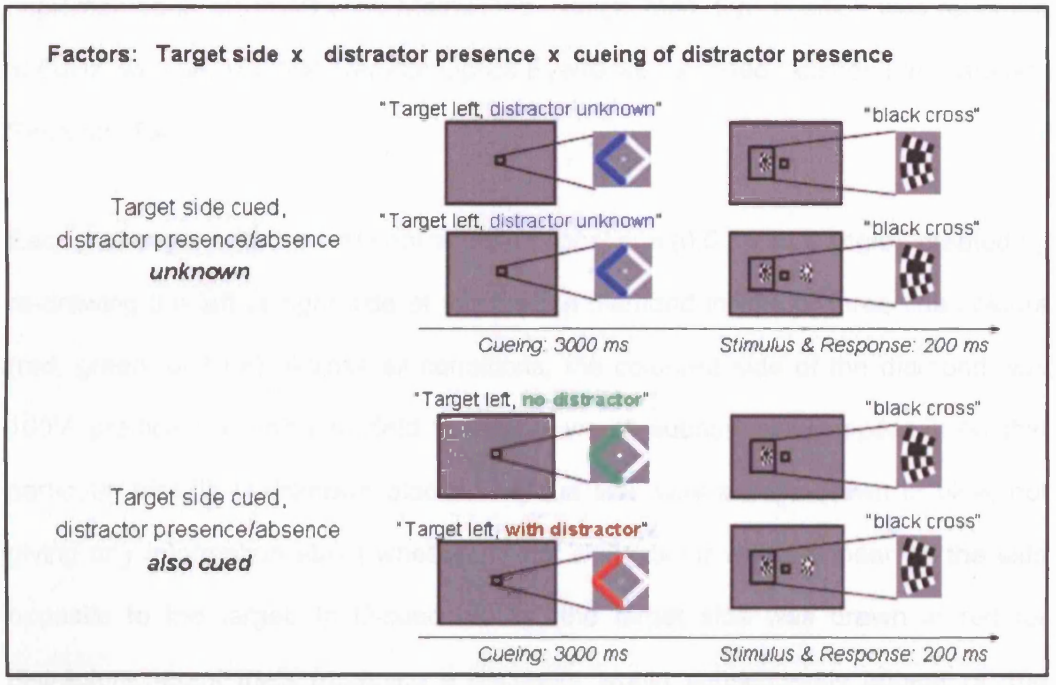

Figure III-1. Experiment 2: Schematic timecourse of trials.

The top and bottom panel show schematic timelines for trials on which distractor presence/absence was either unknown in advance (top), or indicated (with 100% validity, bottom) by means of the colour of a central arrow cue. This arrow was also used on every trial to indicate (also with 100% validity) the hemifield the target would appear in, but note that this target cuing was constant across all conditions. The task in all conditions was to indicate by button press the colour (black or white) of an 'oddball' in the checkerboard stimulus on the cued side (see illustrations to the right of each panel). Participants maintained central fixation throughout all trials, and were instructed to "use all the information given by the cues, i.e. target side and distractor presence/absence, to prepare optimally for this judgment". Trials with or without advance distractor foreknowledge were run in blocks of 96 trials, with identical and constant target presentation times and cue-target ISIs (see the two timelines on the bottom of each panel). In both types of blocks, the target hemifield was randomly varied from trial to trial. See Methods for further details of the task, stimuli, and experimental procedures.

Methods

Participants

Seventeen volunteers (9 female, 22 to 39 years) had normal or corrected vision and no history of neurological or psychiatric illness. All gave written consent in compliance with local ethics, and were paid £10.

Materials and procedure

All testing was conducted in a dark sound-proof booth. Stimuli were displayed on a PC-screen (30° by 23°, grey background, 0.5° by 0.5° white central fixation diamond always present), using the custom software Cogent (www.fil.ion.ac.uk/Cogent2000) implemented in MATLAB (The Mathworks, Natick, MA). Eye position was recorded at 60Hz, with an ASL 504 Remote Optics Eyetracker (Applied Science Laboratories, Bedford USA).

Each trial began with a small central instructional cue (0.5 ° visual angle), created by re-drawing the left or right side of the fixation diamond in one of three cue colours (red, green, or blue). Across all conditions, the coloured side of the diamond was 100% predictive of the hemifield the target would subsequently appear in on that particular trial. In D-unknown blocks, the cue side was always drawn in blue, not giving any information about whether or not a distractor would appear on the side opposite to the target. In D-cued blocks, the target side was drawn in red for distractor-present trials (meaning a distractor would subsequently appear on the opposite side), and in green for trials with no distractor. This allowed participants to prepare, on each single trial, for the subsequent appearance or absence of a distractor at a particular location opposite to the upcoming target, whose side was always cued. The target and any distractor, displayed 3000 ms after cue onset for 200 ms, were curved black and white checkerboards (four by four matrix, 3.5 by 6 ° visual angle, 4.5 ° gap to central fixation symbol), which contained one black or one white 'deviant' check (black or white deviance randomly determined, see Figure III-1 and Figure III-3 for example stimuli, as also employed in the neuroimaging experiment). Participants judged whether the deviant check in the target checkerboard was black or white, as rapidly as possible via a 2-choice button press with the right hand, and were instructed to "use all the information given by the cues,

i.e., target side and distractor presence/absence, to prepare optimally for this judgment", while still maintaining central fixation throughout the trial.

Participants completed two training blocks (not analysed), then four D-unknown and four D-cued blocks in alternating order. Each block comprised a randomly determined sequence of 96 trials, representing an equal number of the four types of stimuli (left target-only; right-target only; target left with right distractor; target right with left distractor). The only difference between the two types of blocks was whether stimuli were preceded by cues informative only with respect to target side on a trial-by-trial basis (D-unknown); or informative about both target side and distractor presence/absence on the other side (D-cued). The experimental session lasted 45 minutes and resulted in 96 trials for each of the eight conditions.

Data analysis

Error and response-time data were analysed with conventional non-parametric statistical tests, at a significance level of alpha = 0.05 (one-tailed for tests with a directional hypothesis). Note that employing corresponding parametric tests did reveal the same pattern of significant results. Data were pooled across the factor of target side, after initial analyses confirmed no behavioural differences between trials with targets in the left or right hemifield for both D-absent and D-present blocks, and no interactions of target side with any other experimental factor.

Eye-tracking data were available for each trial from onset of the cue until response to the target (~ 3500 ms). These traces were filtered for blinks, and a trial trace was classified as loss of fixation if any deviation exceeded 2 ° from initial fixation. There was no difference in the mean number of identified fixation-losses between trials with and without a distractor, both in the D-unknown condition (1.82% vs 1.68%, $\chi^2[1] = 0.77$, $p = 0.78$), and the D-cued condition (2.17 vs 1.87%, $\chi^2[1] = 1.67$, $p =$

0.20). Moreover, there was no difference in mean eye-position between trials with the target in the left or right hemifield, both for D-unknown trials (0.27° vs 0.50°, $\chi^2[1] = 0$, $p = 1$), and D-cued trials (0.30° vs 0.44°, $\chi^2[1] = 1$, $p = 0.32$).

Results

The results for Experiment 1 (see Figure III-2) pool over left and right targets, as these led to similar outcomes for all conditions (see Methods). In both types of block (D-cued and D-unknown), distractor presence led to a significant slowing of response times (Friedman analysis of variance, $\chi^2[1] = 17$, $p < 0.0001$). Critically, this behavioural cost due to the distractor was smaller when participants were given foreknowledge that a distractor would be presented opposite to the target side (i.e., smaller distractor cost in the D-cued blocks than in the D-unknown blocks). This was confirmed by a significant interaction between the presence/absence of a distractor and distractor foreknowledge ($\chi^2[1] = 13.24$, $p < 0.001$), and by the significant reduction in response times for D-present trials when the appearance of the distractor on that side was foreknown, as compared to D-present trials without distractor foreknowledge ($\chi^2[1] = 2.88$, $p < 0.05$).

In contrast, advance knowledge about distractor absence (as compared to D-absent trials from the other blocks without distractor foreknowledge) had no impact on trials where only a target was presented ($\chi^2[1] = 0.06$, $p = 0.81$). This lack of any difference in performance for D-absent trials in the D-cued versus D-unknown condition (i.e., with distractor-absence known or unknown) indicates that participants were not just more alert in general when given some foreknowledge about the distractor. Instead they could specifically counteract the impact of a subsequent distractor at a known location when given foreknowledge of distractor presence there. The next experiment used fMRI to examine the possible neural mechanisms for such distractor anticipation on a particular side.

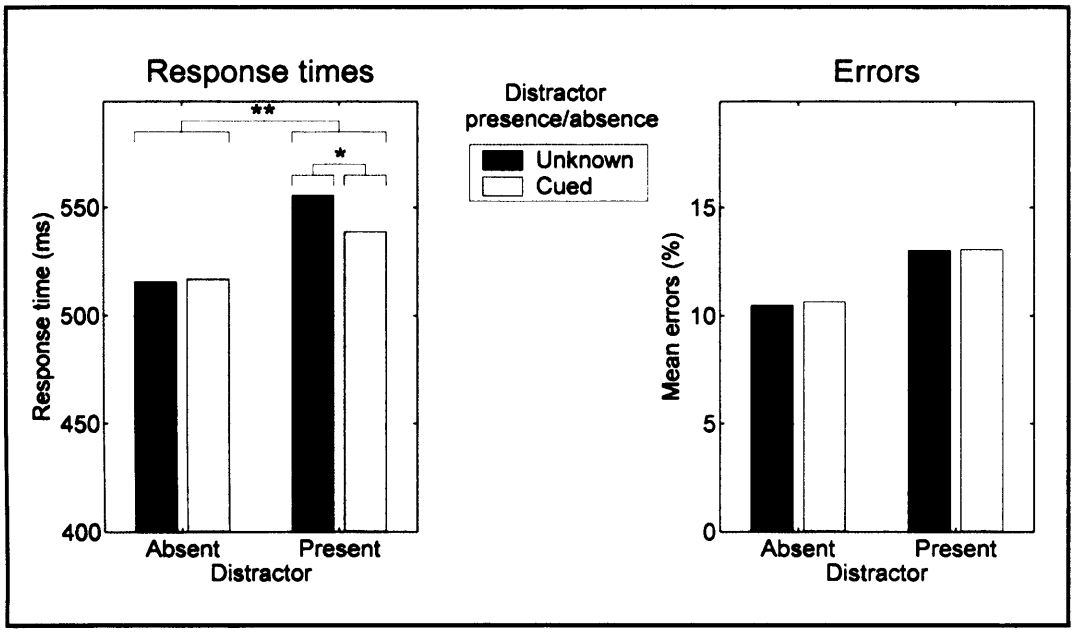

Figure III-2. Experiment 2: Advance knowledge about distractor presence on a known side reduces the behavioural cost of the distractor.

*Left panel shows mean response times and right panel shows mean error rates in behavioural Experiment 1, with N=17. Significant differences are marked by the top horizontal brackets (**p < 0.001, *p < 0.05).*

Experiment 3:

Baseline shifts in visual cortex due to distractor anticipation

Design

This study used the same task and stimuli, but now presented only D-cued blocks, which contain the critical comparisons of expecting a distractor to appear on a particular side, versus expecting no distractor there. Note that presenting targets and distractors to opposite hemifields (thereby projecting initially to different occipital hemispheres) made it possible to disambiguate whether any preparatory activity changes in occipital cortex concerned the location of the expected target, or of the expected distractor, or both. Importantly, the design also entailed that the cued target side was held constant when comparing preparation for the presence versus absence of a distractor on the other side. Moreover, this particular comparison nicely equates for the information and interpretative demands conveyed by the

central cue. This cue now always provided two bits of information (both with 100% validity), namely target side plus presence/absence of a distractor on the other side, exactly as in the D-cued blocks of behavioural Experiment 1. Thus, by comparing preparation for trials with anticipated distractor presence versus absence on a particular side, neural mechanisms specifically involved in preparing for distractor presence at a known location could be isolated, and separated from any effects of cued target side.

Figure III-3 shows a schematic timeline for the paradigm as implemented in the scanner. Target side was again cued by a central arrow on each trial, and the stimuli, instructions, and task were as for the previous behavioural experiment. However, as explained above, the fMRI experiment now only employed central cues that were 100% informative with respect to both target side and distractor presence/absence (i.e., just as in the D-cued blocks of the behavioural experiment). This strategy led to a simple 2x2 design, with factors of: Target side (*T-left* and *T-right*; distractor side opposite to the target, if present) and distractor presence (*D-present* and *D-absent*). In addition, the design contained a low-level control condition with similar sensory inputs and motor outputs, but no attentional preparation, to use as a baseline for testing for any general activity changes elicited by attentional preparation for all kinds of active trials. In this control condition, the task was simply to respond to any peripheral visual stimulation with a button press.

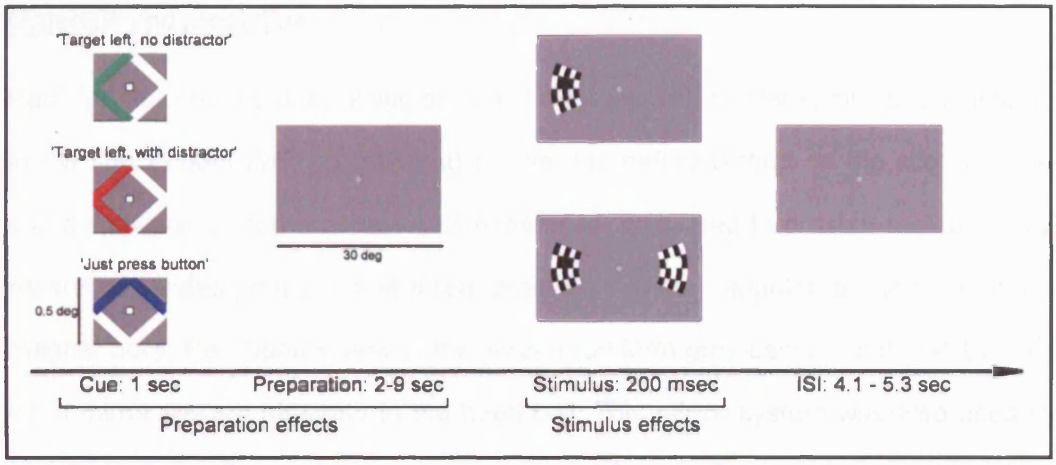

Figure III-3. Experiment 3: Schematic timecourse of trials.

Each active trial began with the presentation of one of the three possible types of central arrow symbols. On active trials, a central arrow validly cued participants for target side, and its colour also indicated with 100% validity the presence (red, here dark grey) or absence (green, here light grey) of a distractor in the hemifield opposite to the target. On sensorimotor control trials, a blue central arrow (here medium grey) pointing upwards was not informative with respect to any aspect of the subsequent stimuli, but instructed participants to simply press one button whenever any subsequent stimulus appeared. The cue was followed by a preparation interval, during which only a central fixation symbol was displayed. A single target, or a target with a distractor on the other side, were presented after the preparation interval and responded to by button press to discriminate the deviant check (making a small black or white 'cross' in the target checkerboard).

Crucially, for all types of trials, the interval between cue and subsequent stimulation was now varied over an extended interval (see Methods), to allow separation of the hemodynamic response elicited by attentional preparation from that related to the subsequent peripheral visual stimulation (for a similar methodology see Sakai & Passingham, 2003). Given the concern with preparatory attentional processes, the focus of this study was on activations associated with this cue period rather than the subsequent stimulus period, as explained further below.

Methods

Participants

Sixteen new right-handed volunteers (7 female, from 20 to 40 years) had good health, normal or corrected vision, and no history of neurological or psychiatric illness. All were screened for MRI compatibility and gave written informed consent in accord with local ethics. Participants were paid £15 and given a CD of brain images.

Materials and procedure

Participants completed a training session (four runs with similar stimuli and timing as in the subsequent fMRI experiment) on the day before testing. In the scanner, the same software as in the behavioural experiment was used to present the stimuli by means of a video projector and a rear projection screen mounted at the back of the magnet bore. Participants viewed the screen (uniform grey background, 29° by 15°) via a mirror system attached to the head coil. This mirror system was also used to monitor eye position at 60 Hz, again with an ASL 504 Remote Optics Eyetracker. Volunteers held a custom MRI-compatible response device with four buttons (three of which were used here) in their right hand for responses.

The fMRI experiment comprised five different cued attentional-preparation conditions. In the four 'active' task conditions, participants were cued with 100% validity for both target side (left/right) and for distractor presence/absence on the other side to the target, by re-drawing the left or right side of the fixation diamond in red or green, respectively (see Figure III-3 for examples and stimulus timing). Note that these intermingled conditions thus fully correspond to those in the D-cued blocks from behavioural Experiment 1. The instruction was again "to use the cue information about both target side and distractor presence/absence to prepare optimally for judging the subsequent target cross" (black or white in the checkerboard on the target side) for that trial as fast as possible, while maintaining central fixation. This was also emphasised on the preceding training day. Since the experiment mainly sought to determine whether any BOLD effects occurred during the preparation period, the SOA between the onset of the cue and the appearance of the stimuli was varied between 3-10 seconds, in steps of 1 second. This permitted the regressors used to estimate the hemodynamic responses elicited by preparation to be de-correlated from those for the subsequent stimuli (for a similar methodology see Sakai & Passingham, 2003; and Visscher et al., 2003). The multiple linear

regression procedure used by SPM only identified the unique effects of each regressor (e.g., the preparation period) after the effects of all other regressors (e.g., the stimuli) were partialled out (Friston et al., 1995). Note also that timecourse analyses of the occipital activations (right panels of Figure III-4 and Figure III-5) were conducted to confirm that the reported effects really did reflect anticipatory activations, and not just modulations of the subsequently presented stimuli (see Figure III-4 and III-5 legends). The target and distractor stimuli shown after the cue interval were identical in appearance, visual angle, and spatial arrangement to those used in the behavioural study (see Figure III-3 for examples and stimulus timing).

In contrast to these four active task conditions, there was an additional more 'passive' sensori-motor control condition, in which participants were instructed simply to press a third button unrelated to the target judgments as fast as possible whenever any peripheral stimulus appeared. The stimuli and display timing for this condition were identical to the active task conditions, but the small central cues now consisted of drawing the upper half of the fixation diamond (instead of the left or right half) in blue instead of in red or green, which was thus not predictive of the type of stimulus to appear subsequently.

Each experimental run contained 8 trials for each of the four active task conditions (prepare for target left or right, with distractor expected to be present or absent on the other side), each with a different cue-stimulus SOA between 3 and 10 seconds; plus 18 trials of the sensorimotor control condition. Half of these control cues were followed by bilateral stimulation distractor present, the other half by unilateral distractor absent stimulation. The cue-stimulus SOAs for these control events were two instances of 4-10 seconds and four instances of 3 seconds in order to shorten the experiment overall. Each participant completed four runs, resulting in 32 trials for

each of the four active task conditions and 64 trials for the sensorimotor control condition.

Imaging was performed with a SIEMENS 3T ALLEGRA MRI head scanner (Siemens, Erlangen, Germany). BOLD-contrast images were collected with a T2*-weighted echo-planar imaging sequence effectively covering the whole cortex (32 slices, 3x3 mm in-plane resolution, 3.75 mm slice thickness, TR 2080 ms, TE 30 ms, FoV 192 x 192 mm, 64x64 Matrix, 3551 Hz/Pixel Bandwidth). A total of 300 images were acquired in each run of 624 seconds, and each participant completed four of these runs see above. At the end of the session, a high-resolution T1-weighted MPRAGE anatomical image of each participant's brain was acquired.

Data processing and analysis

The behavioural data obtained inside the scanner were analysed with the same procedures as the data from Experiment 1 (see above). All image processing and analysis steps were performed with SPM2 (http://www.fil.ion.ucl.ac.uk/spm). Functional images were reconstructed offline, and the first six images of each run were discarded. Images were realigned to the first image of the series by rigid-body corrections, underwent slice-time correction to the middle slice of each volume, were normalised to the Montreal Neurological Institute (MNI) anatomical standard space, and were spatially smoothed with a 6mm FWHM Gaussian Kernel. All reported peak voxel coordinates correspond to the original anatomical Talairach space (Talairach & Tournoux, 1988).

Data were analysed with a two-step random-effects procedure. The voxel-wise effects of the experimental conditions were estimated separately for each participant by a multiple regression of the voxel timeseries onto a composite model containing twelve covariates per session. These covariates corresponded to the preparation

periods and stimuli during the four active conditions and during the sensorimotor control condition, with the latter randomly split into two separate regressors to allow for conjunction analyses (see below). Preparation periods were modelled as a sustained 'mini-block' of the respective duration (continuous series of delta functions from onset of cue to onset of stimuli; 3-10 seconds), while stimuli were modelled as discrete events. Both types of covariates were then convolved with the canonical hemodynamic response function employed in SPM2. In addition to the experimental conditions (effects of interest), the model also contained regressors representing a high-pass filter (128 s cut-off) and an AR(1) process to exclude low-frequency drifts and short-term temporal autocorrelation of scans, respectively (Friston et al., 2002). After model estimation, linear compounds (contrasts) were used to assess and compare the regression parameters for the different conditions. In the second step of the random-effects analysis, the contrast images representing the subject-specific parameter estimates for the condition comparisons were submitted to t-tests. Please note that any variance shared between two non-orthogonal regressors in a multiple linear regression as here is not considered by t-contrasts of SPMs, such as those employed here. This means that any results reported here only reflect variance unique to one or the other regressor (e.g., preparation or stimulation), but not any shared variance (Friston et al., 1995).

The common effects of attentional preparation for all types of displays on activity in putative frontal and parietal control regions were tested by means of a "conjunction analysis" (Price & Friston, 1997). For this purpose, the differential contrast of preparation for targets-with-distractors versus baseline trials (one half of these trials, randomly selected) was masked inclusively with the differential contrast of preparation for single targets versus baseline trials (the other half of trials). This analysis thus only displayed those regions that showed activations during both

preparation for single targets and targets-with-distractors, relative to the sensorimotor baseline.

Two "psychophysiological interaction" (PPI) analyses of functional coupling (Friston et al., 1997) were calculated to separately identify candidate control structures coupling with the left or right lingual gyrus. Mean-adjusted data were extracted from all voxels within a spherical ROI (radius 6mm), centred in the left or right lingual gyrus peak identified for preparation for targets in the right or left visual hemifield, respectively. The PPI procedure embedded in SPM2 was used to create regressors representing the neuronal timecourse of activation in these source regions and their interaction with preparation for single targets or targets and distractors (Gitelman, Penny, Ashburner, & Friston, 2003). These regressors were then added to the existing subject-specific models, and two new random effects models were calculated to identify any regions across the whole brain that reliably displayed differential coupling with the side-specific target regions during preparation for a single target versus for a target with a distractor, or for the opposite direction.

Given the a priori hypotheses of the experiment concerning occipital cortices contralateral to targets or distractors, as well as attentional control structures, the statistical threshold for all analyses was set to $p < 0.001$, with a cluster extent threshold of $u = 4$ voxels to minimise noise and false positives. For region-of-interest (ROI) analyses outside of SPM2, the mean parameter estimates extracted from the relevant ROIs (one per participant and condition) were directly contrasted with conventional non-parametric tests, at a significance level of $p < 0.05$ (one-tailed for comparisons with a directional hypothesis). Note that employing corresponding parametric tests did reveal the same pattern of significant results.

Eye-position data in the scanner

Eye-position data were available during scanning for each trial from the onset of the central cue until the response to the subsequent peripheral target, and were analysed as for the eye-data from the behavioural experiment (see above). There was no difference in mean eye position during preparation for trials with targets on the left or right, both for target-only trials (-0.10° vs 0.11°, Friedman analysis of variance, $\chi^2[1] = 2.57$, $p = 0.11$), and for target–with-distractor trials (0.01° vs 0.05°, $\chi^2[1] = 0.29$, $p = 0.59$). In accord with these results, the mean number of classified losses of fixation was not different for target-only trials or target-with-distractor trials either, both for trials with the target on the left side (3.8 vs 5.4; $\chi^2[1] = 3$, $p = 0.08$), and on the right side (5.0 vs 4.66; $\chi^2[1] = 0.69$, $p = 0.41$).

Results

Behavioural results inside the scanner

Table III-1 summarises the behavioural data acquired inside the scanner. As in behavioural Experiment 1, data were pooled across target side, as no response-time or error-rate differences were found between trials with targets on the left (586 ms and 7.4 %) or right (577 ms and 7.3 %; both $\chi^2[1] = 0$, n.s.). Participants were again slower for trials on which distractors were present (595 ms) than for trials with single targets (568 ms; $\chi^2[1] = 16$, $p < 0.0001$), with similar error rates in both conditions (7.7 % vs 7.3%; $\chi^2[1] = 0$, $p = 1$). There was also no interaction of target side and distractor presence behaviourally ($\chi^2[1] = 0.25$, $p = 0.62$). Finally, and unsurprisingly, participants responded faster to the sensorimotor baseline that did not require perceptual discrimination (354 ms) than to trials with single targets ($\chi 2[1] = 16$, $p < 0.0001$) or to trials with a target plus a distractor ($\chi 2[1] = 16$, $p < 0.0001$).

The behavioural pattern found inside the scanner thus corresponded to that found for the equivalent trial types within the D-cued blocks of Experiment 1; recall that

inside the scanner, participants were always provided with foreknowledge about both target side and distractor presence/absence, as in the D-cued blocks of Experiment 1, for reasons explained above. We confirmed this similarity of behaviour for equivalent trial-types inside and outside the scanner by a direct comparison of the distractor cost elicited in the corresponding conditions in the behavioural and the neuroimaging experiment. This revealed no significant differences in the distractor-elicited cost between both experiments, neither in terms of slowing (22 ms vs 27 ms, Ranksum test, $z = 0.88$, $p = 0.38$) nor in terms of accuracy changes (2.43% vs 0.72%, Ranksum test, $z = 0.59$, $p = 0.55$).

	Expected target location	
Distractor expectation	**Left**	**Right**
Absent	572 ms (75 ms) 5.9 % (5.5 %)	564 ms (86 ms) 8.0 % (6.0 %)
Present	600 ms (86 ms) 8.9 % (4.3 %)	590 ms (86 ms) 6.6 % (4.2 %)

Table III-1. Experiment 3: Behavioural data inside the scanner.

Mean reaction time in ms (top of each cell) and the mean percentage errors (bottom of each cell) for the four types of active trials. Standard deviations are given in brackets. Note that the four types of trials listed correspond to the four types of trials in the D-cued blocks of the purely behavioural Experiment 1.

Anticipatory fMRI activations related to expectation of a target on a particular side

These results are depicted in Figure III-4. When comparing preparation for targets in the right hemifield versus left hemifield, regardless of anticipated distractor presence or absence, all differences were as expected in the left hemisphere, contralateral to the anticipated right target. Most of these activations were located in occipital gyri, with a peak in left lingual gyrus (xyz = -12, -84, 4), but smaller target-contralateral

clusters were also found in several parietal and frontal regions (see Table III-2). The inverse comparison (prepare T-left minus prepare T-right) again revealed differences only in the hemisphere contralateral to the anticipated target, i.e., now in the right hemisphere, here restricted to occipital structures. Note that as when preparing for right minus left targets, the peak response was again located in lingual gyrus, but now in the right hemisphere (xyz = 18, -82, -3).

Region-of-interest extraction of mean BOLD signal during the different preparation conditions (see plots in left panel of Figure III-4) confirmed that the lingual gyrus regions in each hemisphere always showed higher signal during preparation for contralateral than ipsilateral targets, both when the targets were expected to be presented alone, and when distractors were expected to be presented as well on the target-opposite side (Friedman analyses of variance; Right lingual gyrus: D-absent trials, $\chi 2[1] = 4$, $p < 0.05$, D-present trials $\chi 2[1] = 4$, $p < 0.05$; left lingual gyrus: D-absent trials, $\chi 2[1] = 12$, $p < 0.001$, D-present trials $\chi 2[1] = 9$, $p < 0.05$). Thus, the anticipation of a contralateral target elicited increased activity in these regions in a similar manner, regardless of anticipated distractor presence/absence. Finally, timecourse plots of the activation differences between trials with contralateral versus ipsilateral targets (see right panels of Figure III-4) confirmed that these effects genuinely reflected anticipatory activations, rather than stimulus-related responses, as the effects of preparation for target side were clearly time-locked to cue onset, and thus began prior to presentation of the peripheral stimuli for trials with longer cue-target SOAs.

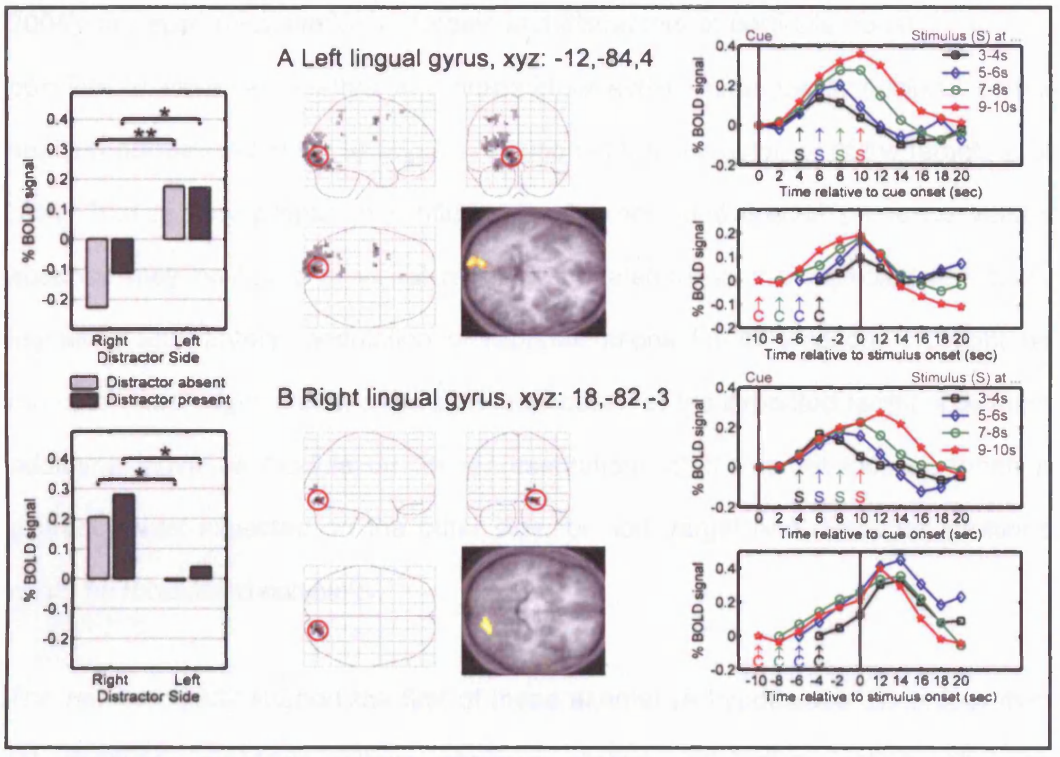

Figure III-4. Experiment 3: Target expectation on a particular side leads to anticipatory baseline shifts in contralateral occipital cortex.

*The middle panels show the activations elicited by (a) preparation for right targets > left targets, and (b) preparation for left targets > right targets, as renderings of the whole-brain SPM(T), thresholded at p<0.001 and k>4 voxels. The left panels display plots of the mean-adjusted signal for all four preparation conditions, extracted from both activation peaks indicated. Significant differences are marked by the top horizontal brackets **p<0.001, *p<0.05. Finally, the timecourse plots in the right panels show the activation increase in the best-fitted adjusted data for trials with contralateral targets, relative to the corresponding periods for trials with ipsilateral targets, plotted over time (X-axis) separately for trials with different preparation durations (in different colours). The first and third plots show this temporally aligned to the cue onset (with stimulus onset marked by the coloured arrows); while the second and fourth plots show shows the same data now re-aligned to the stimulus onset (with cue onset marked by the coloured arrows). These plots confirm that the circled regions indeed showed preparatory activity increases, as BOLD signal started to increase before stimulus onset.*

Anticipatory activations related to expectation of a distractor on a particular side

This was examined by comparing the neural activity during preparation for trials where distractors were expected to be present versus expected to be absent in a particular location of the visual field. Two separate analyses compared D-present versus D-absent preparation periods for a constant target side (i.e., separately for right or for left targets). Thus, a distractor was expected to be either present or absent in the corresponding fixed location in the target-opposite hemifield (i.e., on the left or right, respectively). In contrast to previous studies (e.g., Serences et al

2004), this spatial separation of targets and distractors at particular location made it possible to examine whether any preparatory activity changes in occipital cortex spatially correspond to the anticipated location of the distractor, or of the target, or of both. That is, any preparatory influences of expected distractor presence versus absence may be found in visual regions contralateral to the expected distractor, signalling anticipatory modulation of representations for its location; or might be found in visual regions contralateral to the location of the expected target, indicating additional advance modulation for representations of the target location when a distractor was expected on the other side; or both target and distractor locations might be modulated conjointly.

The results clearly support the first of these alternative hypotheses, as preparation for distractor presence versus absence elicited anticipatory activity changes exclusively in occipital cortices contralateral to the expected distractor location, with no distractor-expectancy modulations in occipital cortex corresponding to the anticipated target location (neither increases nor decreases; see Figure III-5). These distractor-expectation activations (Figure III-5) were less extensive and not quite as symmetric as those found for expecting a target on one side versus the other, regardless of distractor expectancy (Figure III-4), but they followed an analogous contralateral logic (albeit, importantly, now contralateral to the expected distractor).

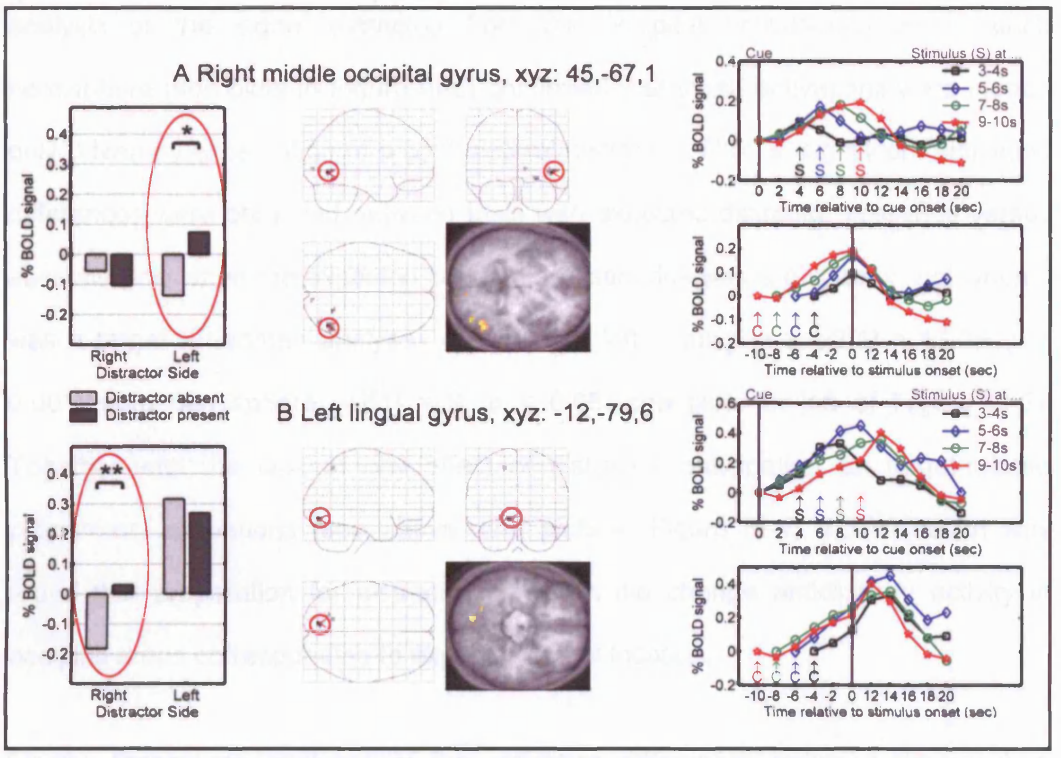

Figure III-5. Experiment 3: Distractor expectation leads to anticipatory baseline shifts in occipital cortex contralateral to the expected distractor.

The middle panels show the activations elicited by preparation for D-present>D-absent, i.e. for expectation of distractor presence, separately calculated for a trials with (a) distractor on the left (target on the right); or (b) a distractor on the right (target on the left), as renderings of the whole-brain SPM(T), thresholded at p<0.001 and k>4 voxels. The left panels give plots of the mean-adjusted signal for all four preparation conditions, extracted from the peaks indicated in the glass-brain rendering. The timecourse plots in the right panel show the activation increase in the best-fitted adjusted data for trials with contralateral distractors, relative to the corresponding periods for trials without contralateral distractors, plotted over time (X-axis) separately for trials with different preparation durations (in different colours). The first and third plots show this temporally aligned to the cue onset (with stimulus onset marked by the coloured arrows); while the second and fourth plots show shows the same data now re-aligned to the stimulus onset (with cue onset marked by the coloured arrows). These plots again confirm that the circled regions indeed showed preparatory activity increases, as BOLD signal started to increase before stimulus onset.

The activation peak when a distractor was expected versus known to be absent on the right was located in left fusiform gyrus (xyz = -12, -79, -6); while that for a distractor expected on the left was located in right middle occipital gyrus (xyz = 45, -67, 1). These clusters found for distractor preparation (Figure III-5) did show some spatial overlap with those for the other separate effect of expecting a target on one side versus the other regardless of distractor expectancy (Figure III-4), in left lingual gyrus for a distractor or target expected in the right hemifield, and in right lingual gyrus and cuneus for a distractor or target expected in the left hemifield. Further

analysis of the signal extracted from the occipital activation-peaks in each hemisphere (see plots in Figure III-5) confirmed that these activations were indeed only driven by expectation of a contralateral distractor. That is, significant activation differences were observed between trials with expected distractor presence versus absence only when the expected contralateral stimulus was a distractor, not when it was a target (Friedman analyses of variance; left hemisphere: $\chi 2[1] = 12.25$, $p < 0.001$; right hemisphere: $\chi 2[1] = 9$, $p < 0.05$; see plots at left of Figure III-5). Together with the lack of any effect of distractor anticipation on target-related preparatory activations (see above, and plots in Figure III-4), no indication was found that preparation for distractor presence did change anticipatory activity in occipital areas corresponding to expected target location.

Finally, timecourse analyses of the activation differences between trials with a contralateral distractor expected to be present versus absent (right panels of Figure III-5) confirmed that the effects contralateral to the expected distractor really did reflect anticipatory activations, and not just modulations of the subsequently presented stimuli, as they were time-locked to cue onset and could begin prior to stimulus onset (see Figure III-5 legend).

Parietal and frontal structures involved in attentional preparation

The next analysis attempted to identify structures that were active during preparation for all trials, independent of expected target side and anticipated distractor presence or absence. The results of a conjunction analysis (Price et al., 1997) testing for such activation with the contrast [D-absent minus baseline 1] & [D-present minus baseline 2] for the cue regressors (see Methods) are shown in the top panel a of Figure III-6. Strong and extensive activations were observed bilaterally in superior parietal lobule (SPL) and middle frontal gyri / precentral gyri, in close

proximity to the putative location of the human frontal eye fields (FEF, e.g., Grosbras, Laird, & Paus, 2005).

In contrast to these structures apparently involved in spatial attention and task preparation in general, the present analyses also identified some neural structures that may be specifically involved in preparation for distractor trials, by comparing the preparatory periods of D-present vs D-absent trials, pooled over expected stimulus side (B and C in Figure III-6). Apart from the expected activation of occipital structures (lingual and middle occipital gyri, as also in Figure III-5), now arising bilaterally due to pooling over expected distractor side, this analysis also revealed areas in right angular gyrus, and left anterior and dorsomedial superior prefrontal gyrus, that showed higher activation during preparation for distractor trials (see Table 3). Conversely, no neuronal structures were activated more strongly overall during preparation for D-absent trials than for D-present trials.

The final analysis addressed whether any regions might show stronger functional coupling with occipital cortex in that context. Two "psychophysiological interaction" analyses (Friston et al., 1997) were conducted, to identify any regions that showed higher coupling during D-absent preparation than during D-present preparation with the signal timeseries extracted from the right lingual gyrus, or from the left lingual gyrus. Remarkably, both these independent analyses led to similar results (see Figure III-6d), each providing a conceptual replication of the other. Specifically, clusters in right temporo-parietal junction TPJ, their peaks less than 1 cm apart, showed stronger coupling with the left or right lingual gyrus during preparation for single targets than during preparation for targets-with-distractors. Note that these two similar TPJ clusters were identified in independent analyses of timecourses from visual cortex in one or the other hemisphere, which displayed separate but complementary contralateral occipital preparation effects.

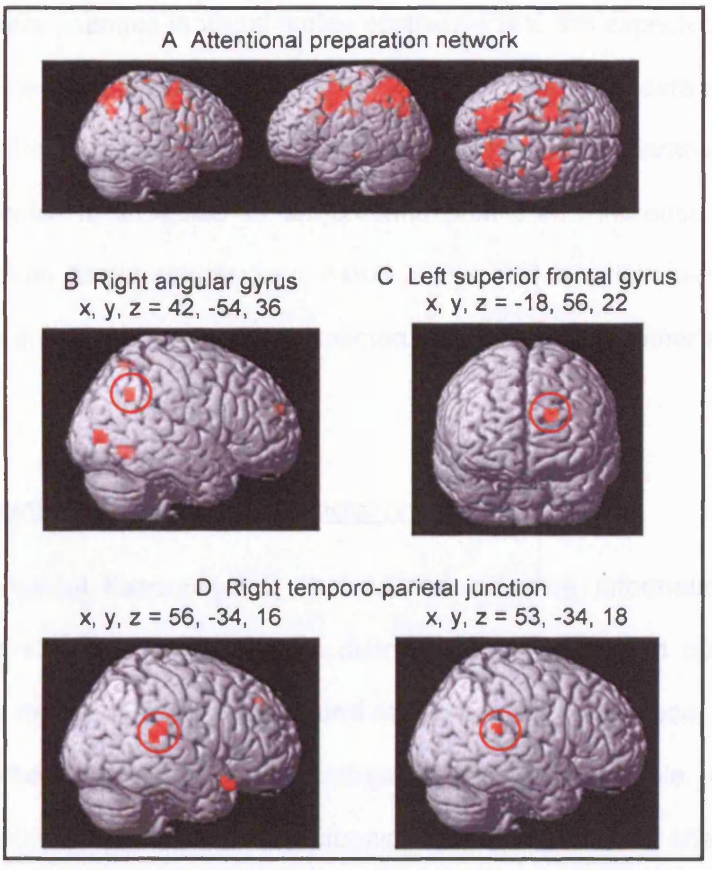

Figure III-6. Experiment 3: Control regions involved in different aspects of attentional preparation.

(A) Bilateral superior parietal lobule and precentral sulci (frontal eye fields) activated by attentional preparation for both a single target and a target with a distractor, relative to the sensorimotor control condition, and regardless of expected target side. (B+C) Right angular gyrus and left superior prefrontal gyrus are more active during preparation for a target-with-distractor than for a single target, again regardless of target side. (D) Two independent psychophysiological interaction (PPI) analyses reveal similar clusters in the right temporo-parietal junction TPJ, which show stronger functional coupling with the left (left side of figure) and right (right side of figure) lingual gyrus peak during preparation for a single target vs a target-with-distractor. (A-D) All SPM(T)s were thresholded at $p < 0.001$ for height and $k > 4$ voxels for extent, and rendered onto the mean of the participants' normalised structural images.

Experiments 2 and 3: Discussion

Experiment 2 showed psychophysically that trial-by-trial knowledge that a distractor will be presented in the hemifield opposite to an upcoming target can reduce the behavioural impact of that distractor. Experiment 3, which used fMRI and an analogous design to the cued-distractor blocks from the behavioural experiment, showed that expecting a distractor on a particular side can lead to preparatory activations of visual cortex contralateral to the expected distractor, without any

additional activity changes in visual cortex contralateral to the expected target (to be presented in the opposite hemifield to the distractor). The fMRI data also identified candidate control structures that may be associated with preparation specifically when a distractor is expected to be present; plus some increase in functional coupling between target-contralateral visual cortex and the right temporo-parietal junction when an isolated target was expected to be present on either side without a distractor.

Behavioural benefit of expecting a distractor on a particular side

The psychophysical Experiment 2 showed that advance information about the presence and side of a single remote distractor in the hemifield opposite to the target led to a reduction in the behavioural cost it went on to produce, as compared with blocks where distractor presence/absence was unpredictable. On the other hand, advance knowledge that a distractor would be absent did not affect behaviour. This indicates that the effect of distractor foreknowledge was not merely due to arousal or other non-specific effects, but specifically allowed participants to counteract the impact of an upcoming distractor when forewarned of its presence and side.

With just a few exceptions, most previous psychophysical cuing studies of spatial attentional preparation have studied preparation for a target at one or another location (e.g., Pashler, 1998), rather than preparation for a distractor at a different particular location. Nevertheless, some prior psychophysical work has been taken as indirect evidence for attentional mechanisms that may specifically exclude distractor information rather than just enhancing target information. Awh et al. (2003) reported that the disruptive effects of presenting many visual distractors close to a target can be reduced to some extent with advance knowledge about the likelihood (in terms of long-term probabilities, rather than just trial-by-trial information as here)

of multiple distractors being presented near a particular target location or not. Humphreys and co-workers (see e.g., Humphreys, Stalmann, & Olivers, 2004; Kunar & Humphreys, 2006; Mavritsaki et al., 2006; Watson et al., 1997; Watson et al., 2003) have repeatedly shown that the behavioural impact of distractors on visual search can be greatly reduced if the distractors (but not the targets) are pre-viewed before presentation of the to-be-inspected scene. The present behavioural results provide further evidence that preparation for distractors can aid performance. But importantly they go beyond prior work in showing that the disruptive influence of a single distractor presented at location remote from a target (i.e. in the opposite hemifield) can be reduced by covert spatial preparation regarding that distractor. Indeed, it was this spatial separation between target and distractor here that made it possible to examine in the fMRI experiment any spatial preparatory modulations specific to one or the other type of anticipated stimulus (i.e., for the expected target, or for an expected distractor instead, see below).

Occipital activations related to an expected target or distractor

Several previous fMRI studies (Hopfinger et al., 2000; Kastner et al., 1999; Macaluso et al., 2003) have shown modulation of visual cortex contralateral to an expected upcoming visual target, as also found here (see Figure III-4). The most novel and striking result of the present study is that expectation of a distractor on a particular side, in the opposite hemifield to the target, leads to anticipatory modulation of distractor-contralateral visual cortex (see Figure III-5). To my knowledge, this is the first demonstration of anticipatory modulation of spatiotopic visual cortex representing the location of an expected distractor rather than the location of an expected visual target.

One recent fMRI study (Serences et al., 2004) sought to examine how preparatory activations may be related to distractor anticipation. It reported that anticipatory

activations in visual cortex were stronger for target quadrants in which the target was expected to be surrounded by multiple distractors, than for target quadrants in which targets would be presented alone. However, because the anticipated distractor-arrays were located close to the upcoming target within a particular quadrant, that study could not examine whether spatiotopic occipital representations of the locations corresponding to the expected distractors were activated differentially as a function of distractor anticipation. Thus, the reported anticipatory effect in those regions of interest (Serences et al., 2004) could have several possible explanations, potentially including participants concentrating harder, or with a different strategy, on the target locations where nearby distractors were expected additionally. The present study, by contrast, could distinguish visual cortex corresponding spatially to a target from that corresponding to a distractor in opposite hemispheres. The anticipatory effects in distractor-contralateral occipital cortex (Figure III-5) clearly implicate preparatory processes related to the expected distractor location.

Indeed, analyses did not reveal any differential preparatory modulations of occipital cortex (neither increases nor decreases) contralateral to the upcoming target when a distractor was expected on the other side, versus when distractor-absence was expected (see Figure III-5). Thus, attentional modulation of occipital visual cortex when expecting a competing distractor only affected occipital distractor representations here; not those occipital regions that would subsequently process the target (at least in the context of targets/distractors in opposite hemifields as here; a different outcome may have applied in Serences et al., 2004). The present finding may thus have some implications for the longstanding debate about whether visual selective attention mainly involves enhancement of target-related signals (e.g., Carrasco et al., 2000; Carrasco, Ling, & Read, 2004; Hawkins et al., 1990), exclusion of signals from distractors (e.g., see Awh et al., 2003; Lu et al., 2002), or a

combination of both mechanisms (e.g., Cheal et al., 1997; Dosher et al., 2000; Pestilli et al., 2005). The present data indicate that expecting a distractor on the opposite side to the target can lead to modulations of representations for that distractor location, consistent with a role of these neurobiological processes in anticipatory distractor exclusion, in addition to the separate modulations reflecting the expected target side.

However, it is noteworthy that the preparatory modulations in the hemisphere contralateral to the expected distractor here took the form of an increase in BOLD signal (see Figure III-5). Several previous studies observing such preparatory BOLD increases when anticipating targets had assumed that these reflect top-down enhancement of target properties in particular (e.g., Hopfinger et al., 2000; Kastner et al., 1999; Macaluso et al., 2003). This interpretation might now need to be re-examined in the light of the present finding. One possible way to explain these observations is that anticipatory positive BOLD increases related to both targets and distractors may index occipital 'predictive coding' (cf., Friston, 2003; Rao & Ballard, 1999; Summerfield et al., 2006) of the pattern of expected stimulation. While targets and distractors differed in their response-relevance here, both could be 'predicted' under the appropriately cued conditions, which might therefore have led to analogous predictive effects on spatiotopic visual cortex. A related possible explanation is that preparatory selective attention for any type of visual display may take the form of imagining the precise pattern of expected visual input (i.e., by means of an attentional template or 'master map' that may comprise both the target and the distractor, see also Farah, 1985; Kunar, Humphreys, & Smith, 2003). It is now known that imagery can increase activity in spatiotopic occipital regions, via top-down feedback connections from higher-level areas (Kosslyn et al., 2001; Mechelli, Price, Friston, & Ishai, 2004). Moreover, a possible relation between the neural mechanisms of attention and of imagery has been proposed elsewhere

(Driver et al., 2000). Finally, the distractor-related baseline shifts found here could in principle indicate anticipatory neuronal inhibition, as no fMRI study can determine on its own whether an increase in BOLD signal is due to excitatory or inhibitory neural processes (see Caesar, Gold, & Lauritzen, 2003; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). The above possibilities are not mutually exclusive, and could be addressed by further variations on the paradigm introduced here, with a combination of methods (e.g., fMRI plus recording of local field potentials, etc.). But the novel and most critical point from the present study is independent of these further issues: Advance knowledge of the location of an expected distractor side can lead to modulation of visual cortex spatiotopically corresponding to the anticipated distractor rather than target.

Control structures and distractor preparation

During attentional preparation for all types of active trials (as compared with the sensorimotor baseline), regardless of target or distractor side and of anticipated distractor presence, activity was found in a bilateral network comprising the superior parietal lobule plus prefrontal regions in close proximity to the putative location of the human frontal eye fields (FEF, e.g., Grosbras, Laird, & Paus, 2005). This pattern resembles the activations of such higher-level control structures as found in many other studies of attentional preparation (e.g., Hopfinger, Woldorff, Fletcher, & Mangun, 2001; Kastner et al., 1999; Macaluso et al., 2003), and is consistent with the commonly suggested role for this "superior attentional network" (Corbetta et al., 2002) in endogenous aspects of attention, such as covertly directing attention to a part of the visual field (e.g., Shulman et al., 2003; Yantis et al., 2003). A more novel finding on control structures here was that preparation for target-with-distractor trials, as compared to preparation for target-only trials, additionally activated right angular gyrus and regions in left prefrontal cortex, independent of which side the distractor was expected to appear at. Thus, these regions may play specific control

functions when preparing to overcome distraction by visual stimuli that are irrelevant for the present task (for related results on the distractor preview benefit, see also Olivers, Smith, Matthews, & Humphreys, 2005; and Pollmann et al., 2003). The finding of anticipatory right angular gyrus activation in this context may be of clinical interest, given that right-sided lesions centred here are associated with spatial neglect and extinction, in patients who miss stimuli mainly when distracted by competing bilateral stimulation (Driver et al., 1998; Duncan et al., 1999; Humphreys et al., 2001; Karnath et al., 2002). The present data indicate that mere anticipation of such inter-hemifield stimulus competition can be sufficient to trigger top-down processes related to the resolution of such competition in right angular gyrus. The additional left superior prefrontal cortex activation during distractor preparation appears consistent with a putative role for prefrontal cortex in attentional control (Barcelo et al., 2000; Miller, 2000), although the reason for the apparent left laterality here remains unknown.

In contrast to these activations of higher-level structures in the context of distractor preparation, attentional preparation for trials with single targets minus that for target-with-distractor trials did not elicit higher overall activity in any region. But coupling analyses (PPI approach) indicated that left and right occipital cortex (lingual gyri) both showed, in separate independent analyses, stronger 'effective connectivity' (Friston et al., 1997) with the right temporo-parietal junction (TPJ) during preparation for single targets than for distractor trials. In previous work, right TPJ has been associated with the onset of an attention-attracting stimulus (Downar et al., 2002; Shulman et al., 2003), and has recently been proposed to play a role in stimulus-driven attentional selection by saliency (Corbetta et al., 2002). This may fit well with the present finding, since occipital cortex on either side was more strongly coupled in advance with right TPJ when isolated targets were expected. This context would allow stimulus-driven direction of attention to the single target on either side to be

successful, unlike anticipation of a target accompanied by a distractor on the other side, where stimulus-driven attention alone would be insufficient to determine which of the two stimuli should be selected. At a general level, this coupling result underlines that attentional control processes may not only involve activity changes in regions in frontal and parietal cortex, but may also operate by modulating the coupling between such putative control areas and sensory regions (see also Friston et al., 2000).

Experiments 2 and 3: Conclusion

The studies described in this chapter have shown with both behavioural and fMRI data that preparatory selective visual attention can be employed to prepare for an anticipated distractor that is spatially remote from an expected target. Trial-by-trial knowledge about the presence of an upcoming distractor in the opposite hemifield to the expected target led to a reduction in the behavioural cost produced by that distractor. Critically, such foreknowledge on distractor presence also elicited preparatory activity changes in occipital regions exclusively in the hemisphere contralateral to the expected distractor, without any additional influences on visual cortex contralateral to the expected target. These findings go beyond other work by showing unequivocally that contralateral spatiotopic representations of the distractor location (rather than just of the target location) can be modulated in advance when a distractor is anticipated. These data also provide initial evidence that distinct higher-level control structures, and distinct coupling with some of these, may be involved when anticipating either a single target or a target with a spatially remote distractor. In sum, these results underline that distinct neurobiological components of preparatory visual selective attention may be devoted exclusively to distractor processing, not just to target enhancements, as often assumed.

Chapter 4

Influences of frontal-eye-field TMS on activity in human retinotopic visual cortex

The previous chapters have described how selective visual attention can influence excitability of, or activity in, human visual cortex (as measured with TMS thresholds or fMRI). The literature review in Chapter 1 outlined proposals that activity modulations in visual cortex due to attention might reflect influences of frontal and parietal areas that may bias processing in visual cortex. In apparent congruence with such proposals, Chapter 2 showed direct influences of attention on excitability of visual cortex (as measured with TMS phosphene thresholds) that could not readily be explained by feed-forward thalamic gating of retinal input. Chapter 3 used fMRI to show distinct preparatory activity-modulations in visual cortex related to anticipation of target or distractor stimuli, accompanied by activation of distinct parietal and frontal brain structures. One of these latter areas showed selective functional coupling with visual cortex as a function of attentional condition, apparently congruent with the idea that higher-level regions may indeed be involved in imposing biases in visual cortex towards particular stimuli. However, since most functional neuroimaging studies are purely correlational, they cannot provide direct evidence for such proposed functional interactions between higher-level regions and visual cortex. New methodological approaches may be required for direct study of any such causal influences between remote but interconnected regions in the human brain.

The studies described in this chapter combined functional magnetic resonance imaging (fMRI) with concurrent transcranial magnetic stimulation (TMS) of the frontal eye fields (FEF), to test directly for causal influences of FEF upon retinotopic visual cortex. The combination of TMS and concurrent fMRI is technically demanding to

implement in the scanner, as the presence of the TMS coil in the MR scanner and the strong magnetic field generated by TMS application can induce severe artefacts in MR images (Baudewig et al., 2001; Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2004; Bohning et al., 1999). The experiments described in this thesis thus necessitated the use of considerable custom-built apparatus (such as non-ferrous custom-built TMS coils and appropriate filter devices) suitable for the on-line combination of TMS and fMRI. Moreover, extensive equipment testing, MR protocol development, and pilot work were required before the actual experiments, in order to ensure the artefact-free acquisition of MR images during the experiments where TMS could be applied inside the scanner itself. These steps will be described more extensively in the Methods section of this chapter, while the Results and Discussion will mostly focus on the main experiments of interest. These studied directly whether stimulation over a particular region of frontal cortex (human frontal eye-field, FEF; Experiment 5), can modulate fMRI activity in remote occipital visual areas V1-V4, in a manner that differs from the effects of stimulation over a vertex control site (Experiment 6). The vertex site was selected to control for non-specific effects of TMS, such as the 'clicking' sound and tactile sensation associated with TMS application, as vertex TMS would not be expected to affect visual cortex except by such non-specific means.

Frontal TMS was applied over the right posterior middle frontal gyrus, just ventral to the junction of superior frontal sulcus and ascending limb of precentral sulcus in each individual (see red star in Figure IV-1A for schematic, Figure IV-2 for TMS site in individual brains, and Methods for TMS-localisation procedures). This particular frontal site is widely held to correspond to human FEF, based on prior neuroimaging (Grosbras, Laird, & Paus, 2005), electrical stimulation (Blanke et al., 2000), and purely behavioural TMS studies (Grosbras et al., 2002; Grosbras et al., 2003; Muggleton et al., 2003; O'Shea et al., 2004; Ro, Cheifet, Ingle, Shoup, & Rafal,

1999). The FEF was chosen as the initial target for TMS for three reasons. First, as outlined in Chapter 1, it is often activated in PET or fMRI studies of directed attention (see e.g., Corbetta et al., 2002; and Chapter 3 of this thesis), and so might in principle relate to the occipital modulations observed in such paradigms. Second, recent elegant work in monkeys with invasive FEF microstimulation indicates that influences of this frontal site on visual cortex have some physiological plausibility in the primate brain, at the single-unit level (see Moore et al., 2003; and the description of this work in Chapter 1 and Figure I-V). Finally, TMS to right human FEF can affect some visual judgements behaviourally, in both hemifields (Grosbras et al., 2002; Grosbras et al., 2003; Muggleton et al., 2003; O'Shea et al., 2004; Silvanto, Lavie, & Walsh, 2006). This might reflect remote influences on activity in retinotopic visual cortex, as tested for directly by the present experiments with fMRI in humans. The BOLD signal provides an index of neural population activity (Attwell & Iadecola, 2002; Bandettini & Ungerleider, 2001; Lauritzen, 2005; Logothetis et al., 2001; Niessing et al., 2005) that should allow the measurement of any TMS-evoked remote effect on multiple visual areas of the human brain concurrently.

In both fMRI experiments (right FEF or vertex control), TMS was applied in short temporal "gaps" between the acquisition of subsequent MR image volumes (see Figure IV-1), ensuring that TMS pulses did not corrupt MR image quality (see Methods). Sensitivity for visual cortex (areas V1-V4 and V5/MT+) was maximised by using an occipital surface coil for fMRI, in combination with retinotopic mapping (Sereno et al., 1995; Kastner et al., 1998; Wandell et al., 2005) of cortical visual areas for each individual participant. Although TMS does not induce eye-movements (Grosbras et al., 2002; Grosbras et al., 2003; Muggleton et al., 2003; O'Shea et al., 2004; Ro et al., 1999), care was taken to assess and eliminate any possible influences on visual cortex from blinks, pupil dilations, or losses of fixation (all measured throughout scanning).

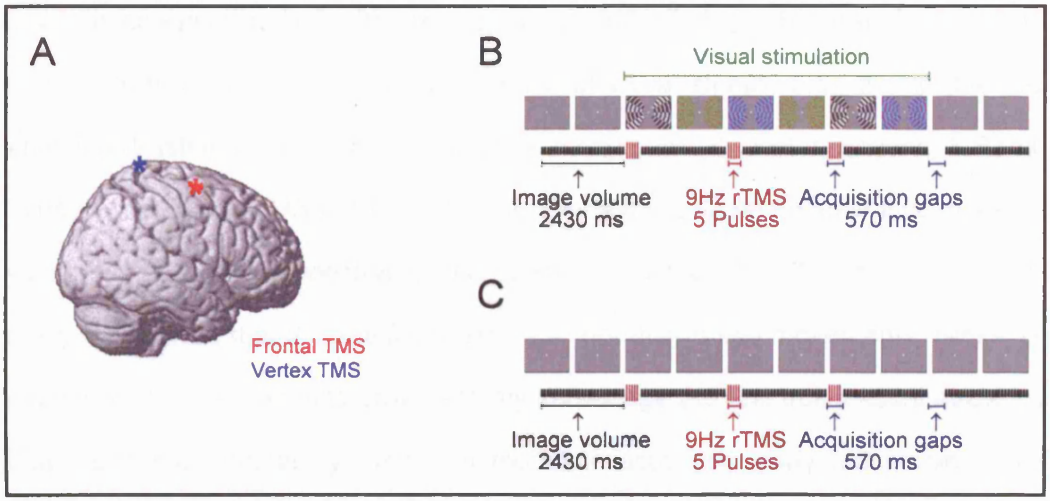

Figure IV-1. Experiments 4 and 5: Stimulation sites and interleaved TMS/fMRI protocol.

Panel (A) indicates the frontal (red star, over right human FEF) and vertex-control (blue star) TMS sites on a normalised brain template (see Figure IV-2 for TMS sites on each individual's brain). Panels (B) and (C) display the schematic timecourse of TMS relative to MR volume acquisition during combined TMS-fMRI: (B) trials with visual stimuli on the screen during TMS, (C) trials without visual stimuli. For each trial, three TMS trains were delivered in the 570 ms gaps between acquisition of subsequent image volumes, and seven rest scans were included between successive trials. Visual stimuli (when present, as in B) remained visible during all three TMS trains and during the acquisition of the three image volumes following the TMS trains.

TMS was administered to either site (FEF or vertex) at four different intensities, allowing the identification of any visual brain areas that showed activity changes due to the intensity of TMS, rather than merely its presence vs absence. Participants had to fixate centrally, with no other task during scanning, to ensure that any remote physiological influences of TMS on activity in visual cortex could not be contaminated by TMS-induced changes in behaviour. However, TMS was administered either while subjects passively viewed a blank display, or while they were presented with bilateral moving/changing visual stimuli designed to activate many visual regions (see Figure IV-1B-C). It could thus be tested whether any TMS influences on activity in visual cortex might depend on the level of bottom-up activation via visual inputs.

To anticipate the findings, increasing the intensity of FEF TMS produced a characteristic pattern of activity modulations in early retinotopic visual areas V1-V4. These activity changes arose in a top-down manner regardless of current visual

input, in apparent accord with some previous fMRI findings that visual cortex can show activity changes even in the absence of visual stimuli, e.g., during directed attention (Kastner et al., 1999) or saccades in darkness (Sylvester, Haynes, & Rees, 2005). By contrast, TMS to the control site (vertex) produced no such influences on visual cortex, thus demonstrating the specificity of the FEF-TMS effects. Further analyses showed that those effects were also not due to eye movements, blinks, or pupil dilation. These results provide to my knowledge the first truly causal evidence that the human frontal eye-field can modulate activity in early retinotopic visual cortex, in a manner that differentiates the central vs peripheral visual field.

Experiments 4 and 5: Methods

Participants

The same four male participants (29-35 years) took part in both neuroimaging experiments. All were right-handed, and reported normal vision and no history of neurological or psychiatric illness. They participated with informed consent in accord with local ethics. All procedures complied with safety guidelines on the use of TMS (Wassermann, 1998).

Localisation of TMS stimulation sites

Scalp coordinates for placing the TMS probe were determined in each participant with the Brainsight frameless stereotaxy system (Rogue Research, Montreal, Canada), using individual T1-weighted anatomical MR images. The human FEF was localised in the right hemisphere for each subject (see red dots in Figure IV-1) in the posterior middle frontal gyrus, just ventral to the junction of superior frontal sulcus and ascending limb of precentral sulcus, in accord with the anatomical consensus on this region in humans (Grosbras et al., 2005; Blanke et al., 2000; Tehovnik, Sommer, Chou, Slocum, & Schiller, 2000).

For completeness it was also confirmed that the chosen region was included in activations for a functional saccade localizer, derived from a 5-minute fMRI session of interleaved rest and auditorily-paced voluntary saccades in total darkness. The selected frontal TMS site resulted in mean MNI coordinates at the cortical surface site of x, y, z = 33, 1, 62 (standard errors: 2.3, 1.4, 3.6), corresponding well with coordinates used in other TMS studies for localisation of putative human FEF (Grosbras et al., 2002; Grosbras et al., 2003; Muggleton et al., 2003; O'Shea et al., 2004; Paus et al., 1997; Ro et al., 1999), and with the mean position of reported FEF activation peaks found in neuroimaging studies (e.g., Grosbras et al., 2005).

A position over the vertex was chosen as the control site (blue dots in Figure S1), individually defined as the meeting point of the postcentral gyri from both hemispheres. Vertex sites are routinely used in the behavioural TMS literature as a control for any non-specific, general effects of TMS application (such as arousal or click-sound etc.; see for example Terao et al., 1997; Cooper, Humphreys, Hulleman, Praamstra, & Georgeson, 2004; Walsh et al., 2005). Such a general control for non-specific TMS effects was ideal for the present purposes, since TMS to the control site should not be expected to affect visual cortex other than by the indirect means of arousal or click-sound, etc.

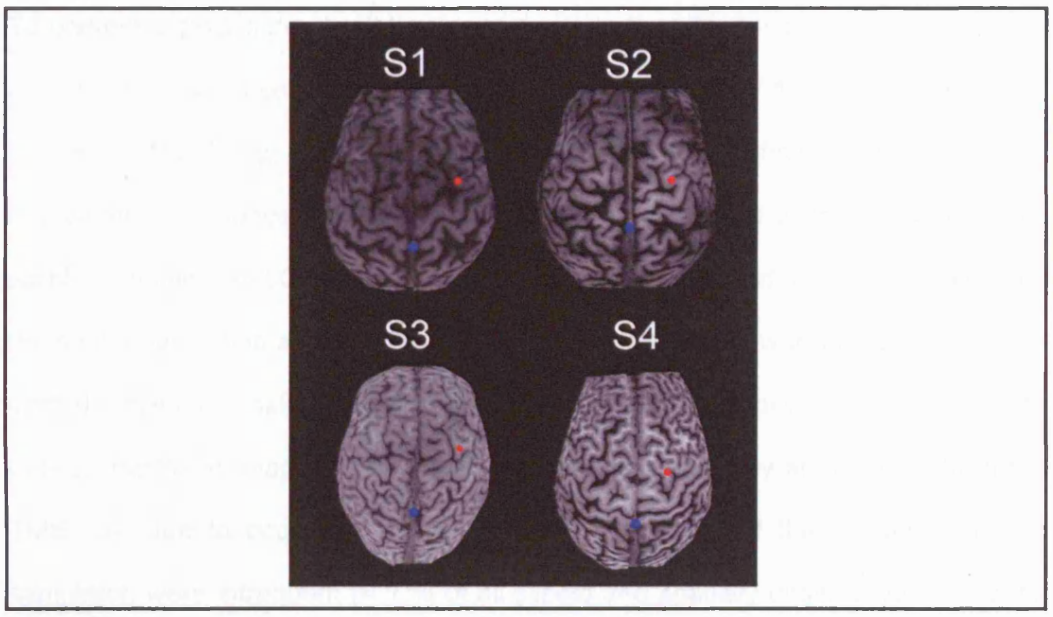

Figure IV-2. Experiments 4 and 5: FEF and vertex-control TMS locations.

TMS sites over right FEF (red dots) and the vertex-control site (blue dots), shown on a 3-D representation of each participant's structural scan (Left = Left, viewed from above, S1 = Subject 1, etc). The frontal site over FEF was selected according to anatomical landmarks and a localiser scan (see Methods). The vertex control site was used to assess any non-specific effects of TMS application, and was determined as the intersection of the postcentral gyri from both hemispheres. The scalp coordinates corresponding to these anatomically selected points (see Methods) were determined using the BRAINSIGHT frameless stereotaxy system (Rogue Research, Montreal, Canada).

Pilot work: Eliminating possible artefacts from TMS during fMRI

Many different steps had to be taken prior to the main experiments, to ensure that RF and magnetic interference due to TMS could not interfere with MR image acquisition. RF interference was prevented by housing the stimulator box in a shielded metal cabinet in the scanner room, and channelling the custom stimulator cable connecting the box to the TMS coil through a custom filter box (The MAGSTIM Company, Dyfed, UK), Moreover, pilot work established that a custom-built three-quarter trap made of further ferrite sleeves (Wuerth Elektronik, Waldenburg, Germany) further reduced the RF interference caused by the presence of the TMS coil inside the MR scanner. This optimised setup was subsequently used for all experiments described in this chapter and in subsequent Chapter 6.

To prevent artefacts due to TMS pulse administration, TMS was exclusively applied during temporal 'gaps' in image acquisition (see Figure IV-1 and main text, and Bestmann, Baudewig, & Frahm, 2003; Shastri, George, & Bohning, 1999; for related approaches). Moreover, a custom MRI sequence was used in the TMS sessions, which implemented 50 % over-sampling in the phase-encoding direction, keeping the spatial resolution at 3 mm, but increasing the field-of-view in this direction. This shifted potential residual Nyquist ghosts in the direct vicinity of the TMS probe outside the brain image. Any remaining artefacts caused by small currents in the TMS coil, due to occasional fluctuations of the charge of the capacitors in the stimulator, were infrequent (< 1 % of all slices) and spatially unselective across the image slice, and thus could not produce specific TMS effects in retinotopic visual cortex, like those observed (see Results). Nevertheless, for all experiments, all slices (< 1 %) containing any TMS-capacitor-induced artefacts were removed from the raw images before image processing. These slices were readily identified by the magnitude of their difference to the anatomically corresponding slice in the previous image volume (> 3 SD from mean slice difference in time series), and were replaced by the mean of the spatially equivalent slices from the previous and the subsequent image volume. As a further precaution, pilot runs of the exact TMS-fMRI protocol and analysis as used for both TMS-fMRI experiments were also extensively tested with a gel phantom (a device that gives some form of standard fMRI signal, which is thus commonly used for testing of fMRI sequences). With this phantom, no voxels were found that displayed any image changes as a function of TMS intensity or presence vs absence, confirming that the setup, protocol, and image-processing steps did ensure artefact-free acquisition of MR images here.

Main experiments: Setup

T1-weighted anatomical images and functional data for retinotopic mapping were acquired on a 3T head scanner (ALLEGRA, Siemens, Erlangen, Germany).

Functional data for the TMS experiments were acquired on a 1.5T whole-body scanner (SONATA, Siemens, Erlangen, Germany), using a custom surface coil (Nova Medical Inc., Boston, USA) centred over occipital cortices and extending over temporal cortex. This setup allowed maximum sensitivity for the detection of any FEF-TMS influences on retinotopic visual cortex, and for individual retinotopic analyses. By contrast, a previous study that combined FEF TMS with other neuroimaging methods (e.g., PET in Paus et al., 1997) may have been unable to detect influences on retinotopic cortex, as PET precludes retinotopic mapping, has lower spatial resolution, and must average activity over much longer time-periods.

A multi-slice gradient echo EPI sequence was used to acquire BOLD contrast volumes with 27 transverse slices (slice TR 90 ms, 64 x 64 matrix, in-plane resolution: 3 x 3 mm, 2.5 mm slice thickness, 50% spatial gap between adjacent slices, TE=50ms). For the TMS-fMRI sessions, a 570 ms gap was included between acquisitions of subsequent volumes (see Figure IV-1 B-C) to allow enough time to implement TMS without corrupting MR images. See the separate section above for further technical procedures implemented to avoid MR artefacts when combining TMS with fMRI.

TMS was employed inside the MR scanner using a Magstim Super Rapid stimulator and a custom-built, figure-of-eight, MRI-compatible coil (30mm inner diameter, 70mm outer diameter, 15 turns each winding, 22.9 μH inductance, 4.7 kVA predicted maximal current at 100 % stimulator output; from the MAGSTIM Company, Dyfed, UK). The coil was positioned over either stimulation site (right FEF or vertex, see Figure IV-1) in a tangential orientation, with the initial flow of the induced biphasic current in posterior-anterior direction. The coil was fixed by means of an MR-compatible custom coil holder, and the participant's head was firmly held in place by a standard vacuum-suction cushion (Siemens, Erlangen, Germany). The

stimulator box was remotely controlled by the PC also used to deliver concurrent visual stimulation. The order of conditions within each fMRI experiment was randomly determined by the program used to deliver all experimental stimulation, which was implemented in a MATLAB (The Mathworks, Natick, MA) custom stimulus presentation toolbox (http://www.fil.ion.ac.uk/Cogent2000).

Main experiments: Design

The same experimental protocol was used for both scanning experiments, except for TMS site. Each stimulation block comprised three equal-intensity trains of five TMS-pulses (9 Hz, intensity either at 85%, 70%, 55%, or 40% of total output), administered in the temporal gap between acquisitions of three subsequent image volumes (see Figure IV-1 B-C). Due to the custom nonferrous TMS coil used and the resistive properties of the MR-compatible connecting cable, the maximum stimulation intensity (85 %) used during scanning only corresponded to 118 % (+/- 14 %) of resting motor threshold for our subjects when placed over motor cortex. Note that during all experiments, TMS at the selected frontal or vertex sites did not induce any muscle twitches, as confirmed by piloting and by reports of the participants. In each run (606 volumes), 48 TMS blocks were delivered, each interleaved with seven image volumes without any TMS stimulation. An equal number of TMS blocks (six) were delivered at each of the four TMS intensity levels, with or without visual stimulation (see Supplemental Text). The run also contained twelve control blocks without any TMS, during which visual stimuli could be present or absent also.

The visual stimuli were patterns that spared the fovea and the vertical meridian, and which randomly moved for each frame (whole-pattern movement, maximum translation in both horizontal and vertical direction 0.3 degrees per 16 ms frame). The patterns randomly changed form and colour every 500 ms, and were projected

onto a screen (30 x 22 degrees visual angle, grey background, 0.5 x 0.5 degree central fixation cross always present) that was mounted at the rear end of the bore, which participants viewed via a mirror system attached to the surface coil.

Main experiments: Eye-tracking

To account for any effects of TMS administration on the participant's eyes, eye position, pupil diameter, and any blinks were monitored at 60Hz throughout scanning with an ASL 504 Remote Optics Eye tracker (Applied Science Laboratories, Bedford USA), via the same mirror used for visual stimulus viewing. Raw eye-position data were filtered to identify and then exclude blinks, and then transformed to degrees of visual angle. Blinks were identified as continuous losses of pupil signal for more than 5 frames (80 ms).

Main experiments: Image processing

Data from both experiments (frontal or vertex TMS) underwent identical analyses with SPM2 (http://www.fil.ion.ucl.ac.uk/spm). Two complementary analysis approaches were used for both datasets. Group analyses of activity across the image volume (EPI images covering occipital cortex and extending into temporal cortex, acquired with a visual surface coil) identified any regions in stereotactic space that reliably displayed activity changes as a function of TMS intensity (or mere TMS presence). Following this, standard retinotopic mapping procedures (Kastner et al., 1998) were conducted within each individual, in conjunction with cortical flattening (Teo, Sapiro, & Wandell, 1997; Wandell, Chial, & Backus, 2000), to visualise the topography of any TMS effects on early retinotopic areas.

For *pre-processing*, images were realigned to the first of the series (the first six images of each run were discarded prior to this); corrected for movement-induced image distortions (Andersson, Hutton, Ashburner, Turner, & Friston, 2001);

normalised to the MNI stereotactic standard space; and spatially smoothed with a three-dimensional 6 mm full-width-at-half-maximum Gaussian kernel.

For the *group analyses*, voxel-wise effects of experimental conditions were first estimated in a multi-subject fixed-effects model, by multiple linear regression of the voxel time-series onto a composite model containing ten covariates of interest per session (four TMS stimulation intensities plus no TMS, each with and without visual stimulation). These were represented by appropriately placed series of delta functions sustained over three image volumes, convolved with the canonical hemodynamic response function employed in SPM2. The model also contained one regressor representing eye blinks (mean 242 per 30-minute-scan, modelled as delta functions convolved with the canonical HRF) and another regressor for mean pupil diameter per scan, taking into account hemodynamic delay. A high-pass filter (128 seconds cut-off) and an AR(1) process excluded low-frequency drifts and short-term temporal autocorrelation of scans, respectively (Friston et al., 2002). Linear contrasts were used to assess and compare the regression parameters for the different conditions, at a statistical threshold of $T > 3$ and $p < 0.05$, corrected at the cluster-level for multiple comparisons across the whole image volume. Correlations of BOLD with TMS intensity were modelled as a weighted linear combination of the four covariates representing different TMS intensities (linear parametric modulation). Effects of TMS presence were estimated as the weighted contrast of trials with TMS present versus the trials with TMS absent. All reported peak coordinates correspond to anatomical MNI space, as used in SPM2.

For the *individual retinotopic analyses*, the borders of visual areas V1-V4 were determined for each subject by standard retinotopic meridian mapping procedures (Kastner et al., 1998). Visual areas V1-V4 were determined in each participant with data acquired in a separate fMRI session of subjects viewing alternating flickering

checkerboards, presented along either the horizontal or vertical meridian. To identify cortical regions driven by these two stimuli, the unsmoothed data were modelled voxel-wise using a general linear model that included two experimental conditions. The borders of visual areas V1-V4 were then plotted onto cortical flatmaps derived by segmentation and cortical flattening in MrGray (Teo et al., 1997; Wandell et al., 2000). These flatmaps were used to display flattened representations of the SPM(T)s quantifying the correlation of TMS intensity with BOLD signal. For analysis of BOLD changes in visual area V5/MT+, the putative location of this area was determined for each participant by means of a separate 5 minute fMRI session with alternating presentations of moving or static starfields, which spared the fovea by two degrees to each side. Cortical regions driven by these two starfield stimuli were determined with a voxel-wise general linear model (two conditions) of the unsmoothed data.

Experiments 4 and 5: Results

Two complementary analysis approaches were used for the fMRI data. Group analyses of activity across the image volume identified any regions in stereotactic space that reliably displayed activity changes as a function of TMS intensity (or mere TMS presence). In addition, standard retinotopic mapping procedures were conducted within each individual to define early retinotopic areas V1-V4, as well as visual area V5/MT+, while cortical flattening was applied to visualise the topography of any TMS effects on V1-V4.

Group analyses in stereotactic space

Group whole-volume analysis revealed two bilateral sets of occipital regions with activity levels related to FEF-TMS intensity. A significant negative relationship between BOLD signal and TMS intensity was found in bilateral regions close to the occipital poles (hence representing central visual locations), with stronger FEF-TMS

leading to lower activity there (Figure IV-3A and Table IV-1). The opposite pattern, of significantly higher activity with stronger FEF-TMS, was found for bilateral regions in anterior calcarine sulci (representing the more peripheral visual field; Figure IV-3B and Table IV-1). These opposite effects on anterior calcarine sulci vs occipital poles were present in each participant, as shown in plots of mean activity for these regions under high or low TMS intensities (see graphs on either side of Figure IV-3). These plots additionally demonstrate that the influence of FEF-TMS intensity on these occipital regions was equivalent during the presence or absence of visual stimuli (Figure IV-3A-B), even though overall activity was higher during visual stimulation, as expected. No region in the acquired volumes displayed any interaction of frontal TMS intensity with presence/absence of visual stimuli.

By contrast, increased intensity of vertex TMS did not elicit any significant activity changes in visual cortex (the corresponding results to Figure IV-3 show no significant effects). This difference between frontal vs vertex TMS was formally confirmed by extracting mean signal-per-condition estimates (SPM parameter estimates, scaled for each voxel as percent of the session mean) from spherical regions-of-interest (ROIs, 6mm radius) centred in the regions that displayed activity changes during FEF-TMS (see circles in Figure IV-3). For simplicity, these estimates were then collapsed across the two high (85% and 70% total output) and the two low TMS intensities (55% and 40% total output), separately for trials with and without visual stimuli present on the screen. Comparisons of these values from both experiments revealed that for both the occipital-pole (central visual field) and anterior-calcarine (peripheral visual field) regions, the modulatory effects of TMS intensity (two highest vs two lowest intensities) were significantly bigger for FEF than for vertex TMS (2 x 2 repeated-measures ANOVA on the signals from these ROIs; interaction of TMS intensity x TMS site, $p < 0.05$, for each ROI). Pairwise comparisons showed that TMS intensity had significant effects only for FEF TMS

(paired *t*-tests, all $p < 0.05$) but not for vertex TMS (all n.s.). Finally, the differences in TMS effects between the ROIs (occipital poles vs calcarine sulci, i.e., the differential effects for central vs peripheral visual field) were also significantly stronger for FEF than for vertex TMS (2x2 repeated-measures ANOVA, interaction of ROI x TMS site, $p < 0.05$).

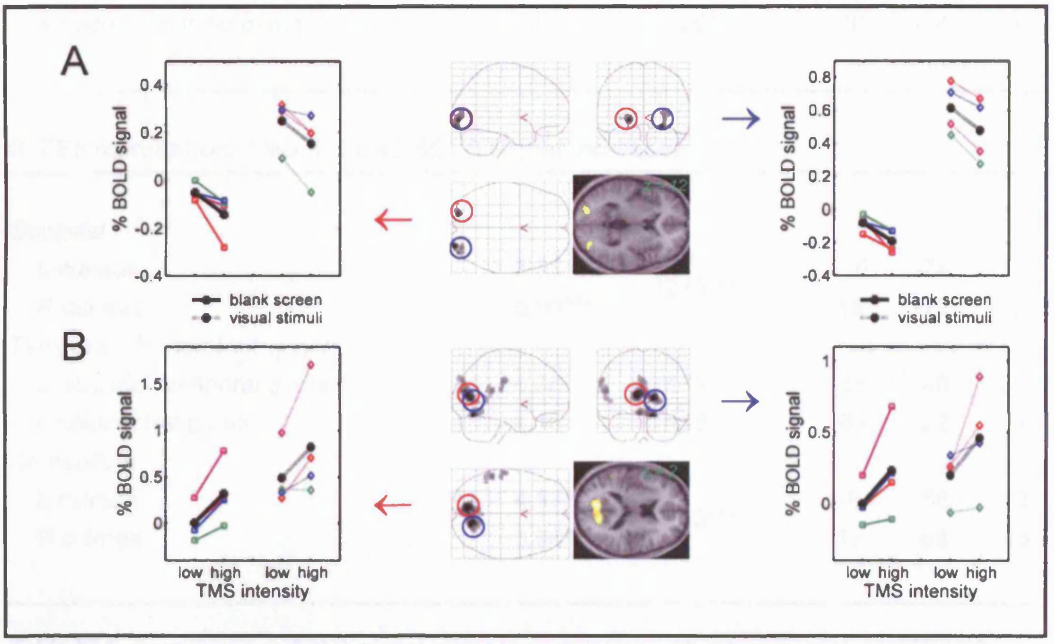

Figure IV-3. Experiment 4: Activity changes due to FEF TMS in the group analysis for stereotactic space.

The brain-displays and associated graphs show: (A) significant negative correlations or (B) significant positive correlations of BOLD with FEF-TMS intensity. In the central images these effects are shown as 2D projections of the whole-volume SPM(T) onto a transparent schematic of the MNI template brain, and as renderings onto a transverse slice of the mean structural scan. All thresholds are set to $T > 3$ and cluster-level $p < 0.05$ (corrected for multiple comparisons). The graphs on either side show single-subject plots of mean signal intensity (different colours for different subjects, group average in black) in the left-hemisphere regions circled by red (left graphs), or for the right-hemisphere regions circled by blue (right graphs). For simplicity, the mean signal is shown here averaged across the two highest (85% and 70% stimulator output) vs the two lowest (55% and 40% stimulator output) TMS intensities. The plots show that the described effects in the calcarine and occipital pole regions were consistently present across subjects, both when visual stimuli were present (dotted lines) or absent (solid lines) during TMS. Overall activity in these visual regions was higher with visual stimulation (dotted) than without (solid), but the impact of high versus low intensity of frontal TMS was additive to this.

	Z-score	Extent (voxels)	MNI-coordinates		
			X	Y	Z
A FEF stimulation: TMS-induced BOLD signal decreases					
Occipital					
L lingual/middle occipital gyrus	4.10	158**	-20	-90	-2
R lingual/inferior occipital gyrus	4.21	100*	28	-94	-12
R middle occipital gyrus	3.57	126*	30	-84	0
B FEF stimulation: TMS-induced BOLD signal increases					
Occipital					
L cuneus	5.96***	1219***	-10	-74	12
R cuneus	5.93***		16	-72	8
Temporal / Parietal					
L superior temporal gyrus	4.58	173*	-56	-40	20
L postcentral gyrus	4.15	118*	-62	-22	34
Cerebellum					
L culmen	4.97*	453***	-6	-68	-12
R culmen	5.94***		12	-68	-18

Table IV-1. Experiment 4: BOLD-signal changes correlating with intensity of right-FEF TMS.

*Peak MNI coordinates, Z-values, and spatial extent for all clusters that showed (A) negative or (B) positive correlations of BOLD with FEF-TMS intensity at T > 3 and a cluster-level p < 0.05, corrected for multiple comparisons across the registered brain volume. Statistical significance is marked according to the following scheme: *** p < 0.0001, ** p < 0.001, * p <0.05, all corrected for multiple comparisons. The table shows that apart from the occipital effects described in the main text (which are the most significant), TMS intensity also induced some weaker activations in cerebellum and in auditory/somatosensory cortex, presumably due to slight increases in auditory and somatosensory input associated with the increased intensity of the TMS pulse (but see also Figure IV-5 for the effects of mere TMS presence versus absence, which activated auditory cortex much more strongly, but not visual cortex).*

Taken together, these initial group analyses in stereotactic space indicate that TMS intensity over the FEF, but not the vertex, modulated activity in occipital cortex differentially for representations of the peripheral vs central visual field. This pattern was confirmed in further detail below by examining individually flat-mapped retinotopic visual areas.

Individual retinotopic analyses

The individual locations of early visual areas can vary considerably between individuals, e.g., by as much as 1cm for V1 (see Dougherty et al., 2003). For this reason, the topography of the pattern of FEF-TMS effects across early visual areas was examined for each participant in individual retinotopic analyses. For these analyses, flattened representations of the individual SPM(*T*)s quantifying the correlation of TMS intensity with BOLD signal were plotted onto cortical flatmaps, which contained the borders of visual areas V1-V4 as determined by standard retinotopic meridian mapping procedures (Kastner et al., 1998).

Figure IV-4 shows the flatmaps resulting from these analyses, for each participant and cortical hemisphere. A topographic pattern of FEF-TMS effects on fMRI activity in occipital visual cortex was reliably found in early retinotopic visual areas, for all participants and hemispheres. Specifically, activity increases with stronger FEF TMS were found in peripheral visual field representations for each retinotopic visual area (notably including even V1), while activity decreases were located in representations of the central visual field around the foveal confluence. Although individual flatmaps in Figure IV-4 show minor variations, as typical for such data, the overall pattern was clearly present in each.

In contrast to early retinotopic visual areas V1-V4, no effect of FEF-TMS was found on BOLD activity in visual area V5/MT+, as determined by a motion localiser scanning session (see Methods). These data are described and extensively discussed in Chapter 6, and will thus not be further illustrated here.

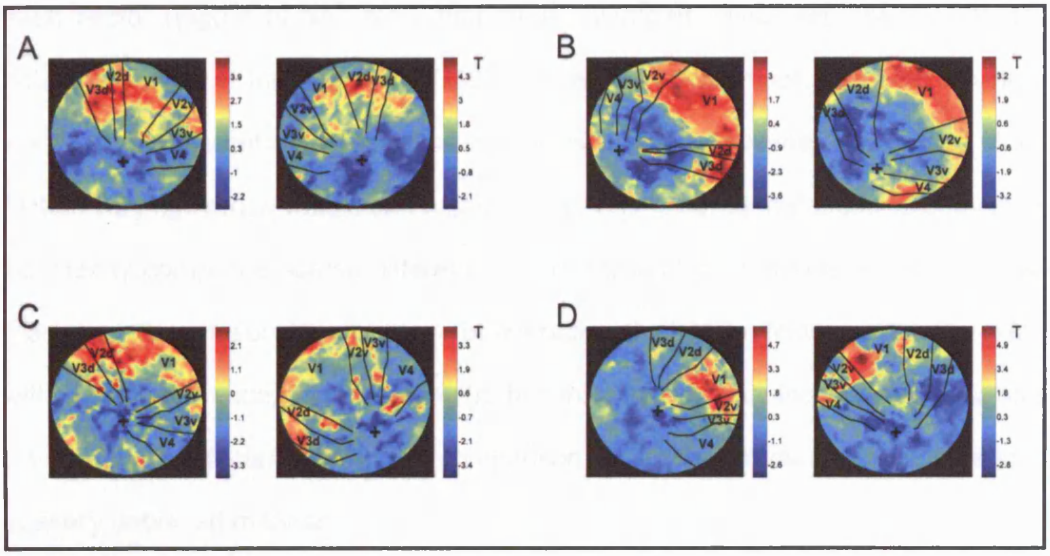

Figure IV-4. Experiment 4: Peripheral-central retinotopic pattern of FEF-TMS influences, in each individual and hemisphere

(A-D) Flatmaps of retinotopic visual areas in all participants and hemispheres. BOLD signal increases due to stronger FEF-TMS can be seen for peripheral visual field representations, while BOLD signal decreases are present for central visual field representations. Panels (A-D) show different participants, the left hemisphere is always shown on left. The voxel-wise correlation of BOLD with FEF-TMS intensity is plotted as a standardised T-value (in relation to voxel-wise residuals of the model), according to the colour bar given at the right of each map, with hot colours indicating positive and cold colours indicating negative correlations with FEF-TMS intensity. The representation of the fovea lies approximately where indicated by a cross, while the borders of all mapped visual areas are indicated by black lines. Note that for every participant and hemisphere, hot colours appear at representations of more peripheral locations in the flatmap of each visual area, whereas the cold colours appear closer to the foveal confluence.

The apparent consistency of FEF-TMS influences on V1-V4 was confirmed by quantifying the pattern across subjects. For this purpose, each visual area was divided into four different eccentricity sectors, treating the meeting point of the extended exterior borders of V4 and V3d in the foveal confluence as origin for all visual areas and borders. Each voxel within these boundaries was then assigned to one area and eccentricity sector, by dividing each area into four sectors of equivalent length along its centre-periphery axis (Schwartz et al., 2005). Note that different parts of the foveal confluence were thereby assigned to different visual areas, but for both of the TMS-fMRI experiments the TMS-induced effects in these different central sectors were equivalent, so this did not affect the results. The correlation of BOLD-signal with TMS-intensity was quantified as *T*-value in relation to voxelwise residuals of the model, and averaged across the voxels contained in

each sector (Figure IV-5A). Note that these averaged values represent signal-to-noise measures of the effects of TMS upon each of the retinotopic sectors, which are thus not differentially affected by scanner sensitivity, baseline activity, and other factors varying across voxels and experiments. This ensured that these values could be directly compared across different eccentricity sectors and across experiments. Moreover, the conservative strategy of averaging the TMS effects across all voxels within particular eccentricity sectors (rather than just picking the voxels displaying the maximum effects) allowed the comparison of effects between experiments in a spatially unbiased manner.

Figure IV-5B shows the mean effect of FEF-TMS intensity for the most peripheral (light bars) and for the most central (dark bars) retinotopic sector in visual cortex. Averaged across areas V1-V4 (leftmost pair of bars in Figure IV-5B), activity in the peripheral sector was significantly increased by higher-intensity FEF-TMS, but activity in the central sector was instead significantly decreased by higher intensity FEF-TMS (t-tests, both $p < 0.001$). This same pattern also applied significantly when each retinotopic area was considered individually (Figure IV-5B, t-tests, all $p < 0.05$, except for the trend in the peripheral V4 sector). In direct paired comparisons, the FEF-TMS influence was significantly different for the peripheral than for the central sector in all visual areas (Figure IV-5B, asterisks indicate $p < 0.05$ in paired *t*-tests). These retinotopic analyses show that TMS over right human FEF had distinct effects on fMRI activity in representations of the peripheral vs central visual field, in early retinotopic visual areas. This accords with the spatially normalised group analysis presented earlier (Figure IV-3), but the retinotopic analyses (Figures IV-4 and IV-5) additionally show that this topographic pattern of influences holds for multiple areas of early retinotopic human visual cortex, including even area V1.

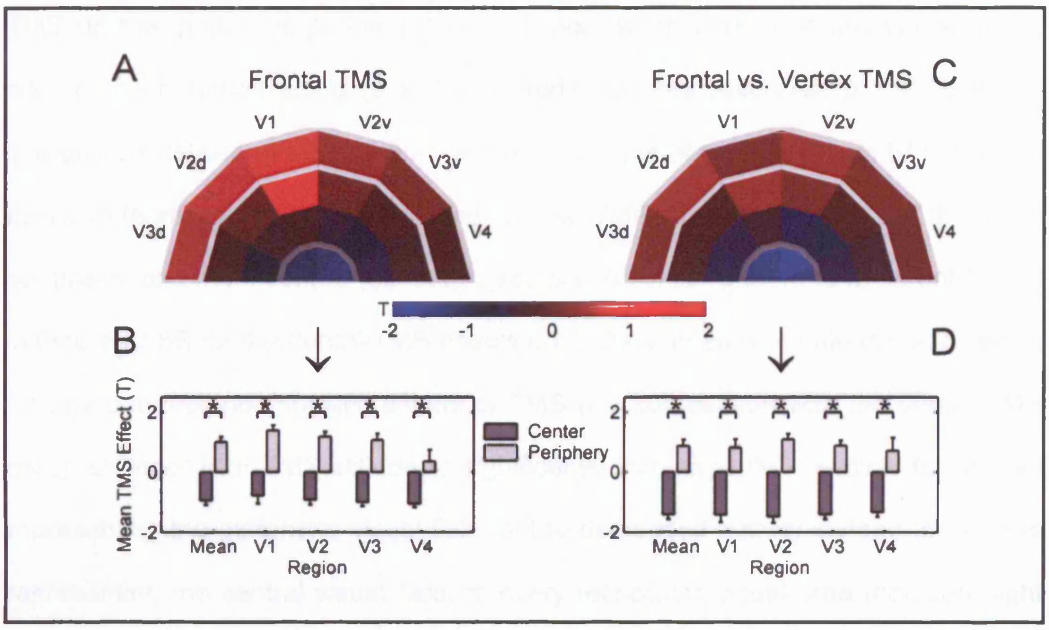

Figure IV-5. Experiment 4: Mean effects of FEF-TMS intensity for different eccentricity sectors in retinotopic visual areas.

(A-D) The correlation of TMS-intensity with BOLD (quantified as T-value) was extracted from each individual retinotopic flatmap, separately for four different eccentricity sectors in each region. Panel (A) depicts the mean effect of frontal TMS-intensity for each area and eccentricity sector, averaged across flatmaps and voxels within each sector (which is conservative, given the larger effects at peak voxels). The effects are colour-coded according to the scale below. Panel (C) shows an analogous representation, but now for differences between effects of frontal versus vertex TMS. Both (A) and (C) indicate that increased intensity of frontal TMS produced activity increases for peripheral visual field representations in V1-V4, but activity decreases in the most central eccentricity sector. Panels (B) and (D) plot the corresponding mean TMS-induced effect with its standard error (B for frontal TMS; D for frontal-minus-vertex difference) for the most central and the most peripheral eccentricity sectors, when averaged across visual areas (leftmost two bars) or separately for area V1 through to V4 (pooling across dorsal and ventral subdivisions). In all these retinotopic visual areas, increased frontal TMS-intensity produced activity increases for the peripheral sector but activity decreases for the central sector (stars indicate $p < .05$ in paired t-tests).

Thus far, the retinotopic analyses only considered activity in visual areas during FEF TMS. In the subsequent analysis, this was compared directly to the vertex-TMS scanning data, by calculating the differences between FEF- and vertex-TMS intensity effects for each eccentricity-sector, in each retinotopic visual area (Figure IV-5C). This analysis showed essentially the same pattern as for the FEF-TMS data alone, because only that TMS site produced the topographic pattern of changed activity in retinotopic visual cortex (again consistent with the group analysis in stereotactic space, where vertex TMS was found to have no effect on occipital cortex). Significant differences were found between the influences of FEF vs vertex

TMS on the central vs peripheral sectors, both when pooled across visual areas, and for each region alone (2 x 2 repeated-measures ANOVAs; $p < 0.05$ for all interactions between TMS site and central vs peripheral sector). Figure IV-5D shows these differences between FEF and vertex TMS-intensity effects for the most peripheral and most central retinotopic sectors. A similar pattern is apparent to that in Figure IV-5B for the frontal-TMS effects only. Thus, even when directly accounting for any potential non-specific effects of TMS (via comparison with the vertex TMS data), stronger FEF TMS still led to significantly increased fMRI activity for sectors representing the peripheral visual field, but to decreased activity instead for sectors representing the central visual field, in every retinotopic visual area (compare light and dark bars for each pair in Figure IV-5D).

Analysis of unspecific TMS effects

On-line eye-tracking throughout scanning (see Methods) measured eye-position, blinks, and pupil diameter. Changes in any of these eye-related variables with TMS at the FEF site are unlikely to explain the observed retinotopic pattern of fMRI effects upon occipital visual cortex (Figures IV-3 – IV-5), as those went in opposite directions for central vs peripheral visual field representations, did not interact with the presence or absence of visual stimuli, and reflected TMS intensity rather than mere TMS presence. Nevertheless, several further steps were undertaken to ensure that eye-position, blinks, and pupil diameter could not have influenced the critical results.

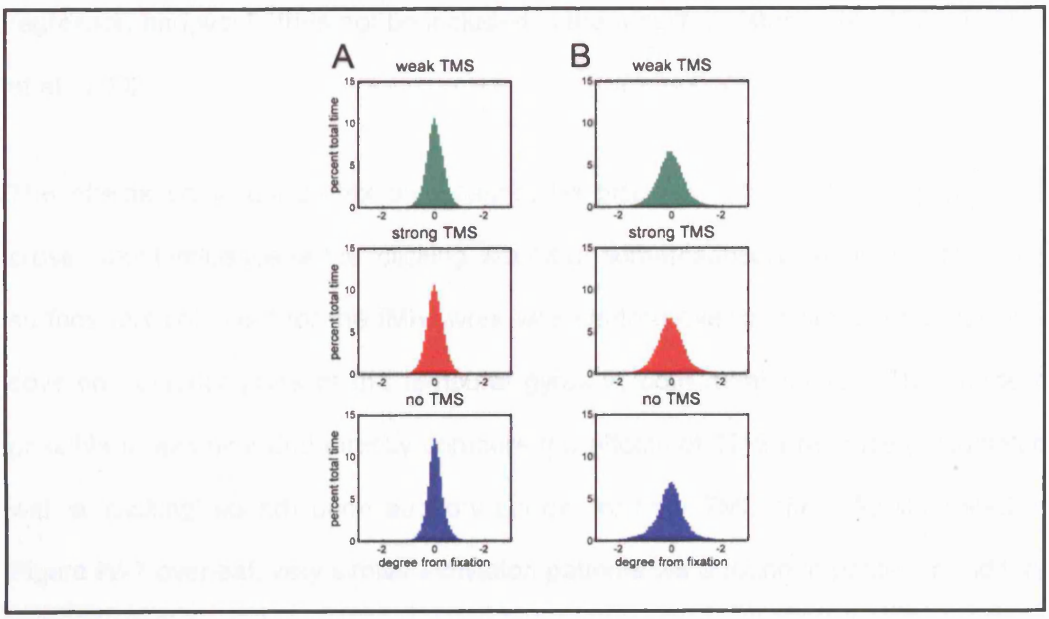

Figure IV-6. Experiment 4: FEF-TMS effects upon fMRI activity in visual cortex cannot be explained by changes in eye position.

Histograms of (A) horizontal and (B) vertical eye position during trials with weak TMS (lowest two TMS intensities pooled, blue); strong TMS (highest two intensities, red); or no TMS (green) to the FEF site. The histograms show for each condition a density function of the eye-position data in percent time spent (ordinate) at different degrees of visual angle of deviation from fixation point (abscissa). These plots confirm that differential eye position cannot account for the observed FEF-TMS effects, as the pattern of eye position was equivalent in both mean and variance during trials with strong, weak, or no FEF-TMS. This is consistent with the known fact that TMS does not induce eye-movements.

First, mean horizontal and vertical eye position, and their variability, did not differ between conditions with strong, weak, or no TMS (Figure IV-6), confirming that the frontal TMS protocol employed here did not induce eye-movements, in accord with previous purely behavioural studies using a similar TMS site (Grosbras et al., 2002; Muggleton et al., 2003). Second, trials with strong, weak, or no TMS did not differ with respect to mean pupil diameter either (F[2, 237] = 1.35, n.s.), and blinks occurred equally often during the three different trial types (χ^2[2] = 1.25, n.s.). Third, it was ensured that blinks and pupil diameter could not have contaminated the fMRI data from visual cortex, by including blink events and parametric pupil-size as independent regressors (see above) in all the fMRI analyses reported. This entails that any variance in brain activity that was shared by two regressors (e.g., correlated with both TMS intensity and pupil width) was not considered a unique effect of one

regressor, and would thus not be included in the results (Friston et al., 1995; Friston et al., 2002).

The effects on visual cortex also cannot be plausibly attributed to any possible cross-modal influence of the 'clicking' sound or somatosensory impact of TMS. The surface MR coil used for the fMRI work was centred over occipital cortex, but also covered posterior parts of the temporal gyrus in both hemispheres. This made it possible to examine and directly compare the effects of TMS presence (associated with a 'clicking' sound) upon auditory cortex, for both TMS sites. As illustrated in Figure IV-7 overleaf, very similar activation patterns were found in posterior auditory cortex during TMS to the FEF or the vertex site, when comparing trials with TMS present versus absent. These comparable auditory effects for FEF and vertex TMS make it very unlikely that any non-specific cross-modal effects potentially associated with the auditory 'click' could account for the differential effects of frontal but not vertex TMS upon visual cortex. Moreover, it is also noteworthy that fMRI signals in visual cortex were specifically affected by the *intensity* of FEF (but not vertex) TMS, while auditory cortex was instead similarly activated in the two experiments by the mere *presence* of the TMS 'clicking' sound.

It should also be noted that none of the participants in either study reported any artificial visual (phosphene-like) percepts during FEF or vertex TMS. This is in line with previous studies, as such 'phosphenes' are usually only obtained during TMS of occipital cortex (Walsh et al., 2005); see also Chapter 2.

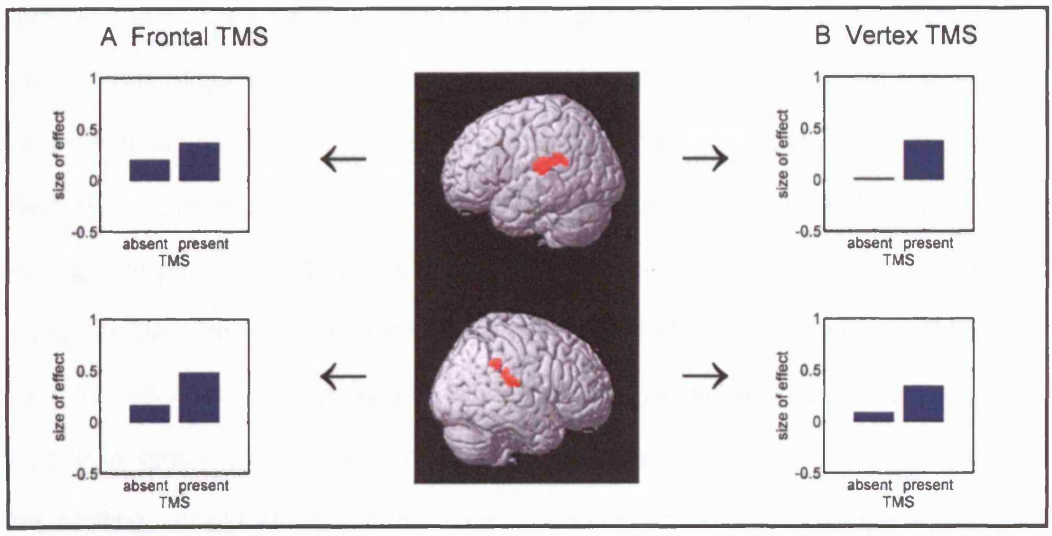

Figure IV-7. Experiments 4 and 5: Mere presence versus absence of TMS activates auditory cortex equivalently for the FEF and vertex site.

Regions that were more active for both TMS sites during trials with TMS present than absent (rather than the effect of TMS intensity reported in main text and Figures IV-3 - IV-5), rendered onto a 3-D version of the normalised template brain employed in SPM2. The rendering shows the contrast of TMS present (all intensities pooled) minus TMS absent, for both FEF TMS and vertex-control TMS (conjunction determined with inclusive masking). Thresholded at T = 3 and p < 0.05 corrected (cluster-level), with different shades of red indicating different distances from the cortical surface. Note that this comparison reveals similar activation in auditory cortex for both experiments, as expected due to the 'click' sound associated with TMS presence per se, but no activation of any visual area by this simple TMS present/absent contrast (as also confirmed by separate inspection of this comparison for either the FEF or vertex TMS datasets). Activity changes in visual regions during frontal TMS were specifically related to different TMS intensities (see Figure IV-3 in main paper), quite unlike the common effects of mere TMS presence upon auditory cortex shown here. The side panels plot the mean signal extracted from the peak voxel for TMS present or absent conditions, plotted separately for (A) FEF-TMS and (B) vertex-control TMS. Note that direct statistical comparisons (paired t-tests) also confirmed that these effects of mere TMS presence upon auditory cortex were equivalent for the two TMS sites, and did not show lateralisation.

In sum, these fMRI results show directly that TMS to frontal cortex, over right human FEF, can causally modulate activity in retinotopic visual cortex (V1-V4) in a top-down manner. Stronger FEF-TMS led to a specific retinotopic pattern of increased activity for the peripheral visual field but decreased activity for central visual field representations, that was not produced by control TMS to the vertex.

Experiments 4 and 5: Discussion

By combining fMRI with concurrent TMS in the scanner, the present experiments show directly that stimulating a region of frontal cortex (right human FEF) can produce systematic remote effects on fMRI signal in early human retinotopic cortex,

including even area V1. The present effects of frontal TMS on visual cortex took a specific retinotopic form, with stronger TMS of right FEF increasing fMRI activity for representations of the peripheral visual field, but reducing activity for the central field, in all retinotopic visual areas. These effects could not be attributed to blinks, changes in pupil size, or losses of fixation. The direct comparison with vertex TMS suggests that these effects also did not reflect any non-specific effects of TMS, such as the associated 'clicking' sound. These results thus provide causal evidence that signals originating in human frontal cortex (specifically in the FEF) are capable of modulating activity in early human visual cortex, as previously proposed only on much more indirect grounds (Barcelo et al., 2000; Miller & D'Esposito, 2005; Desimone et al., 1995; Miller, 2000; Kastner et al., 2000).

The present results echo but also extend recent findings from monkey studies. Elegant work by Moore and colleagues has shown that electrical microstimulation of macaque FEF neurons with implanted microelectrodes, at intensities too low to elicit a saccade, can modulate activity in V4 neurons with spatially corresponding receptive fields (Moore et al., 2003a; Moore et al., 2003b; see Chapter 1 and Figure I-5). At an abstract level, the present results accord well with those monkey studies in establishing a causal effect of FEF on occipital visual cortex, now for the human brain. However, the studies differ in more concrete details. For instance, the current data show that human FEF can influence even the earliest retinotopic visual areas (V1, V2, and V3). Moreover, the present effect of TMS FEF on visual cortex was independent of the concurrent changing and moving visual input, while the previous FEF-microstimulation effects on single-unit firing in V4 depended on the visual preferences of the individual neuron, and on the preferred static stimulus being present for some time prior to microstimulation (Moore et al., 2003a; Moore et al., 2003b). Such differences in the details of the present findings and the recent monkey work may be explained by methodological aspects, and one must be

cautious in extrapolating from fMRI findings to single-unit findings, or vice versa (see also Ress et al., 2000 for a discussion of this issue). Neural activity was indexed here from large populations using BOLD-contrast fMRI, which may correlate better with local field potentials (Logothetis et al., 2001; Bandettini et al., 2001) and synchronised population activity (Niessing et al., 2005) than with spiking output. It has been suggested that BOLD-contrast fMRI may more closely index the input into an area than its local firing rates (Attwell et al., 2002; Logothetis & Wandell, 2004; Lauritzen, 2005). For this very reason, fMRI may be particularly sensitive to top-down influences (Scannell & Young, 1999; Niessing et al., 2005), as here. It should also be noted that TMS is very different to microstimulation, and will target sizeable neural populations (Walsh et al., 2005). But the present findings are fully consistent with other demonstrations that fMRI signal changes in visual cortex can arise without a visual stimulus being present (e.g., during directed attention; see Kastner et al., 1999; Ress et al., 2000; and also Chapter 3). The present study shows directly that human FEF is a plausible source for such modulations. Moreover, it corroborates a new methodology for studying causal influences between brain areas that can now be readily used in humans, unlike the invasive approaches employed in monkeys.

The general point that TMS to frontal cortex can have some remote physiological effects in the human brain was first demonstrated in a pioneering PET study (Paus et al., 1997), which showed that frontal TMS (again over FEF) could lead to some changes in PET activity for posterior brain regions, such as the parieto-occipital sulcus. Moreover, one recent EEG study reported that TMS over a similar frontal site can change voltage fluctuations recorded from electrodes over posterior scalp positions (Taylor et al., 2006). While PET and EEG studies cannot examine retinotopic visual cortex in any detail (due to methodological limitations, see Methods), the present study was able to maximise power for visual cortex (albeit

inevitably with less power for more anterior structures such as frontal or parietal cortex), by using fMRI with an occipital surface-coil, in conjunction with individual retinotopic mapping. This allowed the demonstration that TMS of human FEF can affect early retinotopic visual areas, including even V1, with a specific topographic pattern. The new methodological combination of TMS during fMRI of retinotopic visual cortex now opens up many possibilities for future work, including TMS to different sites, as outlined in the following chapters of this thesis.

The specific pattern of FEF-TMS influences found in human visual cortex may have implications for further research on the structure, function, and connectivity of the human FEF. The effects on visual cortex here arose bilaterally (despite right FEF stimulation; see later chapters for discussion of possible TMS application to homologous left-hemisphere target regions instead), and affected even area V1, for which monosynaptic connections with the FEF have not been reported so far in the macaque brain (Schall et al., 1995; Stanton et al., 1995). Although humans might differ from monkeys, it seems likely that the FEF-occipital circuits underlying the present effects may be poly- rather than mono-synaptic, and might involve intervening frontal (Schlag, Dassonville, & Schlag-Rey, 1998), parietal (Cavada & Goldman-Rakic, 1989a; Schall et al., 1995; Stanton et al., 1995), or subcortical (Sommer & Wurtz, 2000) brain regions. The precise pathways underlying the effects found here might be investigated in future experiments with a combination of FEF TMS and whole-brain fMRI, as discussed in more detail in Chapter 7. But independent of the specifics of the anatomical pathways involved, the main aim here was to characterise any frontal influences on retinotopic visual cortex, which was achieved by maximizing the power to detect such effects with an MR surface-coil centred over occipital cortex.

It is also noteworthy that the present results revealed distinct effects of FEF-TMS on peripheral vs central visual field representations. This difference may accord with some known anatomical details of macaque FEF, where the central and the peripheral visual field appear functionally differentiated by two neuronal subpopulations. These code for either large saccades and peripheral visual locations, or small saccades and more central locations; and they are mainly connected to occipital regions via separate pathways involved in more peripheral or more central vision, respectively (Schall et al., 1995; Stanton et al., 1995; Stanton et al., 1995). Subdivisions and anatomical connections for human FEF are not as well established as in monkeys, but there are now some initial demonstrations that the peripheral visual field may be represented spatiotopically in human FEF, in a patch of cortex readily targeted by TMS (Hagler, Jr. et al., 2006). The present results encourage further research into the question of whether the peripheral and central visual field might be separately represented within human FEF, with distinct connections to occipital cortex, in analogy to the macaque brain.

In sum, the results presented in this chapter establish that TMS of human frontal cortex, over the right human FEF, can causally modulate functional activity in early retinotopic visual cortex, in a systematic fashion that distinguishes the central and peripheral visual field. As outlined in the previous chapters of this thesis, regions in frontal cortex had been proposed to be possible sources for the activity modulations observed in visual cortex during selective attention. The experiments described in the present chapter provide a clear 'proof-of-principle' for such influences on activity in retinotopic visual cortex from the FEF. Such activity modulations may provide a neurophysiological basis for top-down influences on visual *perception*, as tested for in the next chapter.

Chapter 5

TMS of the frontal eye-field: Functional relevance of activity changes in visual cortex for perception

The fMRI results described in the previous chapter showed that TMS applied to right human FEF resulted in increased activity in bilateral representations of the peripheral visual field in early retinotopic visual areas, including V1. This pattern of influences suggests a behavioural prediction that was tested in a further psychophysical experiment. If the activity changes observed in visual areas are indeed functionally relevant for visual perception, it could now be predicted that TMS to right FEF may enhance peripheral relative to central vision, for both hemifields. Given that early visual areas were modulated by FEF TMS, including even V1, this behavioural prediction was tested using visual stimuli and a judged property that should involve early visual cortex; namely, the perceived contrast of Gabor patches.

Although extrapolating from fMRI signals to visual perception often requires many caveats (see e.g., Chapter 3, for findings on lateral occipital areas), in the specific case of contrast there is already some evidence that BOLD increases in *early* visual cortex (such as V1) can be associated with increases in contrast perception (Boynton, Demb, Glover, & Heeger, 1999; Olman, Ugurbil, Schrater, & Kersten, 2004; Ress & Heeger, 2003). Moreover, perceived contrast can be enhanced by top-down influences (e.g., by attention; Carrasco et al., 2004), which might extend to the present top-down influences from FEF TMS also. Finally, it is often argued (e.g., Desimone et al., 1995; Duncan et al., 1997; Kastner et al., 2000) that top-down increases in baseline occipital activity may lend a competitive advantage to corresponding visual stimuli when presented. Based on these findings and

suggestions, it was predicted that the topography of top-down occipital activity changes found during FEF TMS in the fMRI experiment (described in Chapter 4) may lead to enhancements of perceived contrast for peripheral relative to central stimuli.

To test this prediction, TMS was applied to the same frontal (right FEF) or vertex sites as before, but now during a psychophysical task that required participants to judge which of two concurrent stimuli (one central and one peripheral Gabor patch, the latter presented randomly on the left or right) appeared higher in perceived contrast (see Carrasco et al., 2004 for a similar measure). Central fixation was again ensured with on-line eye-tracking. The central patch had a fixed (25%) contrast, while the peripheral patch on the left or right varied in contrast via an adaptive algorithm (see Methods). The point of subjective equality (PSE) between central and peripheral contrasts was derived by fitting psychometric functions to the behavioural data (e.g., see Figure V-1B). Separate PSEs were determined for each visual hemifield, for TMS at the frontal or vertex site. If the pattern of FEF-TMS influences upon early visual cortex indeed results in functional consequences for perception, then it could be predicted that FEF TMS (relative to vertex TMS) should result in enhancements of perceived contrast for peripheral relative to central visual stimuli.

Experiment 6: Methods

Participants

Seven males (29-36 years, 3 of whom also took part in the fMRI experiments described in Chapter 4) gave informed consent to participate in the psychophysical studies. All were right-handed, and reported normal vision and no history of neurological or psychiatric illness. The study was approved by the local ethics committee, and all procedures complied with established safety guidelines for the use of TMS (Wassermann, 1998).

Setup and procedure

Stimuli were displayed in a dark room, on a 19" CRT at 57 cm viewing distance. Video mode was 1600x1200 at 60 Hz, using BITS++ hardware (Cambridge Research Systems, Rochester, UK) to obtain true 14-bit grey-level resolution with gamma correction. Background luminance was 51 cdm^2. Stimulus control was provided by a PC using the MATLAB toolbox COGENT (http://www.fil.ion.ucl.ac.uk/cogent2000). Eye position, pupil diameter, and any blinks were monitored at 50Hz with an ASL 504 Remote Optics Eye tracker (Applied Science Laboratories, Bedford USA). Raw eye-position data were filtered to identify and then exclude blinks, and then transformed to degrees of visual angle. Blinks were identified as continuous losses of pupil signal for more than 4 frames (80 ms).

The same frontal and vertex TMS sites were used as for the fMRI experiments in Chapter 4; see Methods in that chapter for localisation routines, and Figure V-2A in that chapter for schematic. TMS was administered to these two sites in separate sets of four blocks (approx. 40 trials per block), while participants judged which of two concurrent Gabor stimuli had higher perceived contrast (see below for visual stimulus details). To rule out order effects for the critical FEF vs vertex comparison, the procedure was repeated on a second day with the opposite order of TMS sites (i.e. AB-BA or BA-AB, counterbalanced between subjects). A training set preceded each session, and each of the two sessions ended with four additional blocks without TMS (these could not readily be permuted in order, but were analysed for completeness). Each trial was self-initiated by button-press, triggering a brief display (500ms) comprising one central, vertically oriented Gabor patch (carrier wavelength and envelope standard-deviation both .75 degrees of visual angle, at 25% Michelson contrast) and one similar Gabor patch of varied contrast, positioned at 13 degrees visual angle unpredictably to either the right or left of centre in the peripheral visual field. This eccentricity was comparable to the outer edge of the

visual stimulation in the neuroimaging experiment of Chapter 4, and the outer retinotopic sector where strong FEF TMS had produced enhancement of fMRI activity in retinotopic visual cortex (see Chapter 4). Participants pressed one of three keys (using separate fingers on their right hand) to indicate which stimulus of the current Gabor pair appeared to have the higher contrast ('left', 'right' or 'centre').

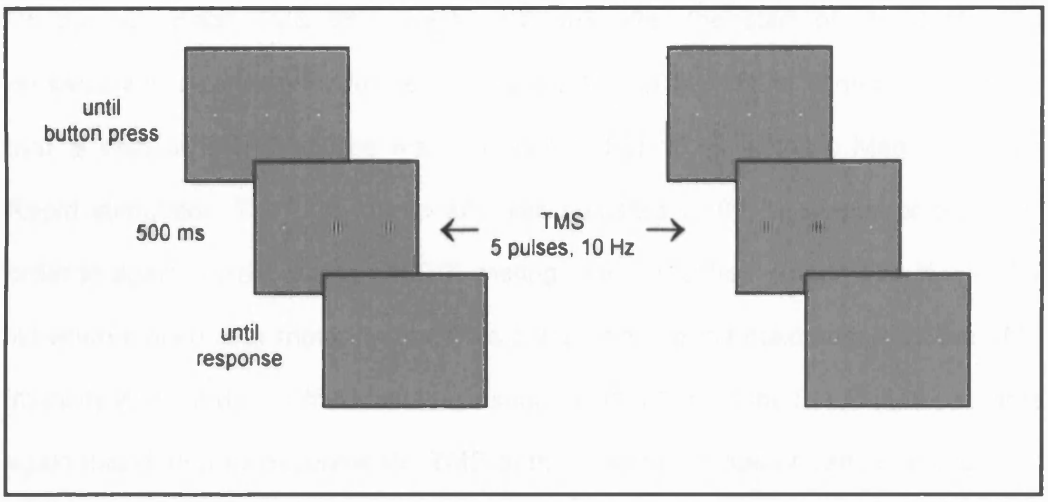

Figure V-1. Experiment 6: Schematics of trial structure in the psychophysical TMS experiment.

Each trial was self initiated, and consisted of the presentation (for 500 ms) of one central and one peripheral Gabor patch, the latter unpredictably on the left (right panel) or right (left panel) side. TMS was administered throughout the full presentation of these stimuli, at 10 Hz. Participants indicated by button press which of the two patches appeared higher in contrast. The central patch had fixed contrast, while the peripheral stimuli varied in contrast according to an adaptive algorithm, to derive PSEs for the different experimental conditions (see main text).

Any rare trials with strictly erroneous key presses (e.g., 'right' for a pair of central and left stimuli) were re-run. The contrasts of left and right stimuli were independently adjusted from trial to trial using two interleaved adaptive staircases (Modified Binary Search algorithm; Tyrell et al., 1988), in order to probe a contrast range optimally bracketing the point of subjective equality (PSE, derived using PSIGNIFIT toolbox, http://www.bootstrap-software.com). For each of the four critical types of trials (left and right hemifield, frontal or vertex TMS), the peripheral PSE contrast was estimated offline by least-squares fitting of a Weibull curve through the obtained psychometric function.

TMS parameters

TMS during psychophysics was administered using a 70 mm figure-of-eight coil connected to a Super Rapid stimulator (Magstim, Dyfed, Wales, UK). The coil was locked firmly in place over the participant's frontal or vertex site by means of a two-joint holder, in the same orientation as for the neuroimaging experiment (see Chapter 4). Each TMS train began 100 ms after the start of visual stimulus presentation, covering the full remaining duration of the visual stimulus. On every trial, a train of 5 TMS pulses was administered at 10 Hz using a Magstim Super Rapid stimulator. The output intensity was adjusted to 65 % stimulator output in order to again correspond to ~120 % resting motor threshold (mean 121 % +/- 10.7 %) when placed over motor cortex, thus comparable to the maximum effective TMS intensity applied during the scanning experiments, as described in Chapter 4. Note again that during all experiments, TMS at the selected frontal or vertex sites did not induce any muscle twitches, as confirmed by piloting and by reports of the participants.

Experiment 6: Results

The psychophysical results fully accorded with the predictions derived from the fMRI results (see Chapter 4), indicating that the effects of FEF-TMS on activity in visual cortex can have perceptual consequences for vision. Perceived contrast judgements were altered systematically by FEF as compared to vertex TMS, with peripheral stimuli having stronger perceived contrast relative to central during FEF TMS (see Figure V-2B-C). Moreover, this pattern applied equivalently for either peripheral hemifield, again just as expected from the fMRI results in bilateral retinotopic cortex during FEF TMS (see Chapter 4). This outcome was confirmed in a 2 (frontal or vertex TMS) x 2 (peripheral patch on left or right) repeated-measures ANOVA of the

PSE data, which showed a reliable effect of TMS site ($F[1,6] = 7.69$, $p < 0.05$), but no effect or interaction due to hemifield.

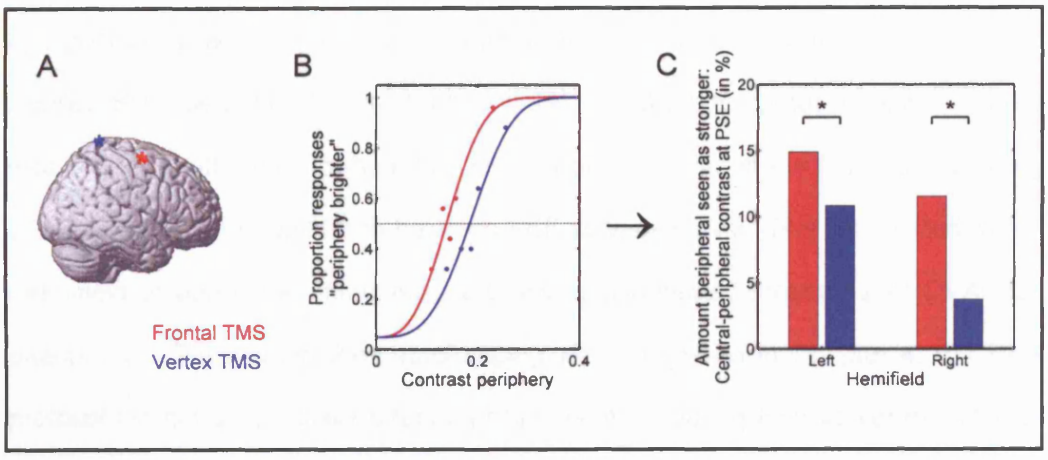

Figure V-2. Experiment 6: Frontal but not vertex TMS enhances perceived contrast for peripheral relative to central visual stimuli, for both hemifields

Panel (A) depicts the frontal (red star) and vertex-control (blue star) TMS sites, selected according to the same criteria as in the neuroimaging experiments (cf. Chapter 4). Panel (B) shows psychometric curves fitted to the psychophysical data of an illustrative participant (who had also taken part in neuroimaging) for one hemifield, when judging which of two concurrent Gabor patches appeared higher in contrast (either the central patch of fixed contrast, or a peripheral patch of varied contrast, unpredictably on left or right). Separate psychometric functions were obtained with frontal TMS (red curve) or vertex TMS (blue curve) co-occurring with the visual displays, in counterbalanced order. The intersection of the dashed horizontal line with either curve indicates the Point of Subjective Equality (PSE) value for the peripheral patch (contrast at which perceived as equivalent to the fixed central patch) in the corresponding TMS condition; note the lateral shift of the psychometric curve due to frontal versus vertex TMS. Panel (C) displays inter-participant mean contrast-value differences between central and peripheral stimuli at the derived PSE (in % of contrast of central patch), for both TMS conditions (red: FEF TMS; blue vertex TMS) and both hemifields. Due to the subtraction of contrast values at the PSE (central minus peripheral contrast value), higher values represent more enhancement of peripheral relative to central perceived contrast. The graph shows that frontal TMS significantly enhanced peripheral relative to central perceived contrast, as compared with vertex TMS, in both hemifields (stars indicate $p < 0.05$ for main effects of TMS site in ANOVA, in the absence of significant effect or interaction due to hemifield).

Note that this effect corresponded to a lateral shift in the psychometric functions (see example in Figure V-2B), since while the PSEs differed significantly due to TMS site, the slopes of the underlying psychometric functions did not (all terms n.s. in a corresponding ANOVA on slopes). Finally, for completeness the two TMS conditions (which were run in counterbalanced order) were also compared to a no-TMS condition run at the end of each session. PSEs during frontal TMS were also significantly shifted from those for a TMS-absent condition ($F[1,6] = 7.416$, $p < 0.05$), while those during vertex TMS were not (ANOVA, all terms n.s.), confirming that

peripheral versus central contrast perception was unaffected by vertex TMS. Hence, the effects shown in Figure V-2B-C reflect the influence of the frontal TMS.

Eye-position was recorded with a remote-optics infrared eye-tracker (ASL 504; Applied Science Laboratories, Bedford USA), at 60 Hz temporal resolution. There was neither a difference in the mean number of blinks, nor in the mean or variability of eye-position and pupil width between FEF vs vertex TMS. This was tested with 2 (hemifield of peripheral stimulus) x 2 (TMS site) repeated-measures ANOVAs (all effects n.s.). Thus, as in the neuroimaging work described in Chapter 4, the TMS protocol did not differentially affect participants' eyes during FEF vs vertex TMS for the psychophysical task.

In sum, TMS applied to right human FEF significantly enhanced perceived contrast for peripheral visual stimuli relative to central stimuli, in either hemifield. This accorded with the pattern of peripheral enhancement but central suppression that had been observed for early retinotopic visual cortex in the fMRI experiments of Chapter 4, during TMS of the same frontal site.

Experiment 6: Discussion

The psychophysical experiment described in the present chapter took the (to my knowledge) novel approach of testing a behavioural prediction derived from a pattern of fMRI activity modulations observed during combined TMS-fMRI. In line with the fMRI findings described in Chapter 4, the present experiment showed that TMS applied to the right FEF (versus vertex) enhanced perceived contrast for peripheral relative to central visual stimuli, in both visual hemifields. Although it can be difficult to extrapolate from fMRI effects to visual perception, for the specific case of stimulus contrast a systematic relation with fMRI signals in early visual cortex has been established (Boynton et al., 1999; Olman et al., 2004; Ress et al., 2003). This

permitted the new approach of using a pattern of remote activity changes found with concurrent TMS-fMRI (see Chapter 4) to derive (and confirm) a prediction for behavioural effects of TMS, as tested for in the present Chapter 5. These combined results show that the right human frontal eye-field is a physiologically plausible source for top-down activity modulation of visual cortex, with corresponding consequences for visual perception.

The enhancement observed here for peripheral relative to central visual stimuli during TMS of the FEF may conceivably play a functional role during saccade planning/execution and covert attention to the visual periphery, consistent with the known involvement of the FEF in those situations (Kastner et al., 2000; Corbetta et al., 2002; Grosbras et al., 2005; Serences et al., 2006a). Possible targets for covert shifts of attention or eye movements are inevitably located in the peripheral visual field, competing with currently fixated objects. Processing of the latter may benefit from the high perceptual sensitivity of foveal vision, as determined by the layout of the retina and subsequent cortical magnification (DeValois et al., 1990; Zeki, 1993). The present results indicate that signals generated in the FEF (e.g., by TMS as here) may enhance the neuronal signals elicited by objects in the peripheral visual field, which might conceivably help the visual system to overcome the foveal bias of vision during eye movement preparation (Super, van der Spekreijse, & Lamme, 2004) or covert attention to the periphery (Kastner et al., 2000). Such a putative link between the mechanisms observed here and those underlying attention may be further underlined by findings that transient spatial attention can enhance the perceived contrast of peripheral Gabor stimuli (Carrasco et al., 2004), in close similarity to the perceptual effects of FEF TMS found here. Note, however, that the present TMS design - in contrast to Carrasco et al's psychophysical work - precluded anticipatory attention to one side or the other before the stimuli appeared:

On each trial in Experiment 6, it was unknown which hemifield the peripheral stimulus would appear in.

The present results may also reconcile seemingly discrepant results from prior, purely behavioural TMS studies that had likewise reported some bilateral effects on visual judgments when stimulating right human FEF. For example, Grosbras et al. showed that TMS to this site can facilitate detection of visual stimuli presented in the left or right hemifield (Grosbras et al., 2002; Grosbras et al., 2003). Other studies, in contrast, found impairments of visual search instead, again in both hemifields (Muggleton et al., 2003; O'Shea et al., 2004). Although those prior behavioural studies differed from each other in several methodological details, the present results highlight a previously overlooked factor. The previous reports of facilitated visual judgments due to TMS of right FEF had presented visual targets more eccentrically (Grosbras et al., 2002; Grosbras et al., 2003) than those reporting behavioural impairments instead (Muggleton et al., 2003; O'Shea et al., 2004), which used more central targets (~2 degrees). The fMRI results of Chapter 4 now show that TMS to this cortical site has opposing effects on representations of the peripheral versus central visual field within retinotopic visual cortex, congruent with the psychophysical finding presented here in Chapter 5, showing that TMS of right FEF increases perceptual sensitivity of the visual periphery versus the central visual field.

In sum, the experiment described in the present chapter indicate that the activity changes observed in retinotopic visual cortex during FEF TMS (see Chapter 4) may have direct functional consequences for perception. This strongly suggest that signals generated in the right FEF may influence perception in a spatially specific fashion via changing the level of neuronal activity in interconnected areas of retinotopic visual cortex. This view is in line with general proposals in the attention

literature that regions in frontal (and possibly parietal) cortex may generate top-down signals that can influence processing in occipital cortex to bias perception. Whether such signals may differ for frontal and parietal sites is tested in the final experimental chapter of this thesis, Chapter 6.

Chapter 6

Influences of intra-parietal-sulcus stimulation on activity in human retinotopic visual cortex

As outlined on several occasions in the previous chapters, recent models of visual processing and attention propose modulatory roles for feedback projections from *several* higher-level regions in parietal (Macaluso & Driver, 2005) or frontal cortex (Moore et al., 2003b; Tehovnik et al., 2000). Consistent with these proposals, neuroimaging studies have often demonstrated that a wide network of areas in both frontal and parietal cortex show correlated activity increases in situations where visual activity is modulated in a top-down manner (Corbetta et al., 2002; Hagler, Jr. et al., 2006; Schluppeck et al., 2006; Silver et al., 2005). Moreover, behavioural TMS studies show that TMS to both frontal and parietal areas can affect some types of visual judgments (Grosbras and Paus, 2002; Grosbras and Paus, 2003; Muggleton, 2003; O'Shea, 2004; Pourtois, 2001; Silvanto Walsh 2006), which might in principle reflect remote influences from all of these sites on activity in visual cortex. However, it remains unclear whether (distinct regions within) frontal and parietal areas might contribute similarly to such modulations of visual activity, or may exert qualitatively *different* modulatory influences upon visual cortex.

The present study used concurrent TMS-fMRI to directly examine and compare the pattern of activity modulations in visual cortex elicited by stimulation of regions in human parietal (right IPS) or frontal (right FEF) cortex. Results presented in Chapter 4 described that increased intensity of TMS to FEF leads to a characteristic pattern of activity modulations in early retinotopic visual areas, independent of concurrent visual input, and with corresponding functional consequences for visual perception (see Chapter 5). The study described in the present chapter was conducted to examine the regional *specificity* of such influences on fMRI activity in retinotopic

visual cortex. The identical stimulation protocol as in Chapter 4 was applied, in the same participants, but now over a different region in right parietal cortex (intra-parietal sulcus, IPS). Like the FEF (Tehovnik et al., 2000), this parietal region has also been implicated in covert spatial attention (Behrmann, Geng, & Shomstein, 2004; Macaluso et al., 2005; Silver, Ress, & Heeger, 2006) and the control of eye movements (Schluppeck et al., 2006; Sereno et al., 2001; Grosbras et al., 2005). The work presented in this chapter now characterised the effects of stimulating the right IPS upon activity in retinotopic visual cortex, and directly compared them to the effects of right FEF stimulation with the same experimental protocol, as already described in detail in Chapter 4. Any qualitative difference in the effect of TMS to the two sites might constrain the potentially distinct roles that influences from right-hemisphere frontal or parietal regions may have upon early visual regions, for example during selective visual attention.

TMS was again administered at four different intensities, but now to the IPS, to identify any visual brain areas that showed activity changes due to IPS-TMS intensity. Participants again simply had to fixate centrally with no other task during scanning, as confirmed by eye tracking, so that any remote physiological influences of TMS on activity in visual cortex could not be contaminated by TMS-induced changes in behaviour. However, TMS was administered either during a blank visual display, or during the presentation of bilateral moving/changing visual stimuli designed to activate many visual regions (see Figure VI-1B-C). This allowed the test whether IPS-TMS influences on activity in visual cortex might depend on the level of bottom-up activation via visual inputs, in contrast to the effects of FEF TMS which did not (see Chapter 4).

Experiment 7: Methods

Participants

The same four participants took part in the experiments described here as in Chapter 4. Written informed consent in accord with local ethics was again obtained from each participant, and all procedures complied with published guidelines on TMS usage (Wassermann, 1998).

TMS stimulation locations

The scalp coordinates for placing the TMS probe over IPS (green dots in Figure VI-1A) were determined in individual T1-weighted anatomical MR images of each participant, with the Brainsight frameless stereotaxy system (Rogue Research, Montreal, Canada). As for the FEF, TMS was applied to the IPS in the *right* hemisphere, since in humans there may be right predominance in networks for top-down (e.g., attentional) modulation of visual processing (Driver and Mattingley, 1998; Karnath, 2002; Mesulam, 1999). More importantly, this kept the stimulated hemisphere constant, thus allowing close comparison of the two different TMS sites here.

For human intraparietal sulcus/posterior parietal cortex, there is currently little consensus on exact anatomical/structural criteria for specific regions involved in attention and eye movements. A normalized MNI coordinate (xyz=36,-48,45) was thus used here to specify the IPS, based on the mean coordinates of published activation peaks in right IPS during covert shifts of attention or eye-movement planning/execution (Brown et al., 2004; Connolly, Goodale, DeSouza, Menon, & Vilis, 2000; Connolly, Goodale, Menon, & Munoz, 2002; Corbetta et al., 1998; Curtis, Rao, & D'Esposito, 2004; Perry & Zeki, 2000). For completeness it was also confirmed that this location fell within the region activated in a functional saccade

localizer (a 5 minute fMRI session of rest interleaved with auditorily-paced voluntary saccades in total darkness). This saccade localiser had also been used in combination with established anatomical landmarks to select the locations chosen for the right FEF (red dots in Figure VI-1A, see Chapter 4).

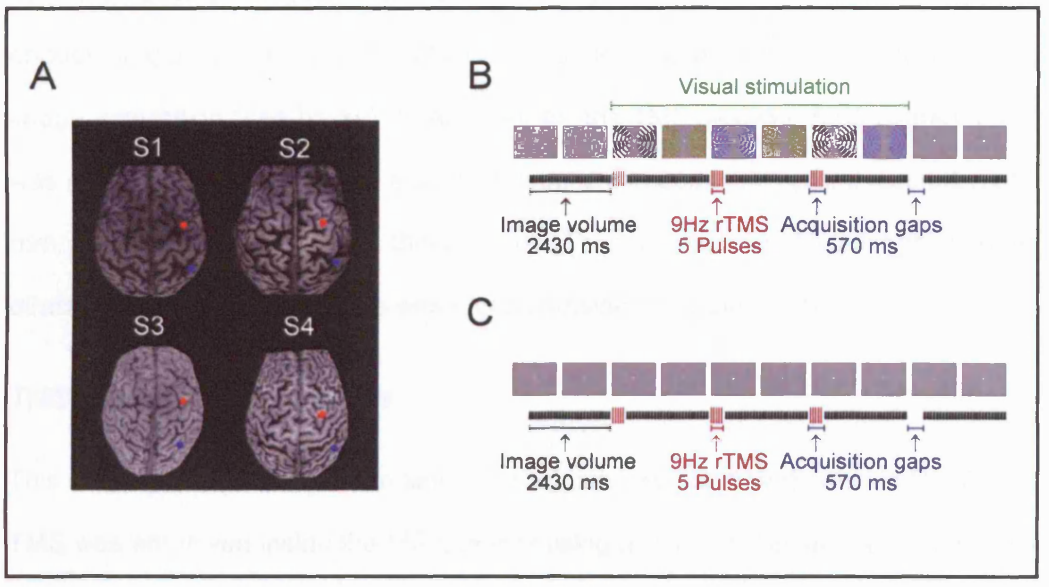

Figure VI-1. Experiment 7: TMS sites and experimental protocol.

Panel (A) shows the parietal (blue dot, over IPS) and frontal (red dot, over FEF) TMS sites projected on images of the individual structural scans of our participants (S=Subject). The corresponding scalp positions were determined in each individual with Brainsight frameless stereotaxy (see Methods). Panels (B) and (C) show a schematic timecourse of a single block of interleaved TMS-fMRI, either (B) with visual stimuli on the screen during TMS or (C) without visual stimuli. For each block, three TMS trains were delivered in the 570 ms gaps between acquisitions of subsequent image volumes, at one of the four intensities used (see Methods). Seven rest scans were included between successive blocks. Visual stimuli (when present, as in B) remained visible during all three TMS trains and during the acquisition of the three image volumes following the TMS trains.

fMRI setup and data acquisition

Functional data for the experimental TMS sessions were acquired on a 1.5T whole-body scanner (SIEMENS SONATA, Siemens, Erlangen, Germany). The same custom-built visual surface-coil (Nova Medical Inc., Boston, Massachusetts, USA) as before (see Chapter 4) was used for the TMS experiment. This occipital surface-coil maximized power for early visual cortex, and was thus ideal for testing for differences in the way frontal or parietal TMS might influence visual cortex functionally. An identical multi-slice gradient echo EPI sequence was used for all

datasets (27 slices, 64 x 64 matrix, in-plane resolution: 3 x 3 mm, 2.5 mm slice thickness, 50% spatial gap between adjacent slices, TE=50ms, 2298 Hz/pixel bandwidth, echo spacing 500μs). The acquisition time per slice was 90 ms. For the TMS session, a 570 ms gap (see Figure VI-1B-C) was included between the acquisitions of subsequent volumes (resulting in a TR of 3 seconds), to allow enough time to implement TMS within the scanner during this gap without corrupting image acquisition (see below). In addition, for the TMS session, 50% oversampling was implemented in the phase encoding direction, keeping the spatial resolution at 3 mm, but increasing the FOV in this direction. Thus, any residual Nyquist ghost in the direct vicinity of the TMS probe was shifted outside the brain image.

TMS setup and procedures

This experiment used the same setup as that used for the experiments in Chapter 4. TMS was employed inside the MR scanner using a Magstim Super Rapid stimulator and a custom-built, figure-of-eight, MRI-compatible non-ferrous coil (53mm inner diameter, 10 turns each winding, 20μH inductance, 5kVA predicted maximal current at 100%; from the MAGSTIM Company, Dyfed, UK). The coil was positioned over the scalp coordinate of each participant's IPS (see above and Figure VI-1A) in a tangential orientation, with the initial flow of the induced current in anterior-posterior direction, tilted anticlockwise by about 45 degrees (biphasic pulses were applied). The coil was fixed by means of a non-ferromagnetic custom coil holder; the participant's head was firmly held in place by a standard vacuum-suction cushion (Siemens, Erlangen, Germany). To eliminate RF interference of TMS with image acquisition, the stimulator box was housed in a shielded metal cabinet in the scanner room, and the custom stimulator cable connecting the box to the TMS coil was channelled through a custom filter box (The MAGSTIM Company, Dyfed, UK) and further ferrite sleeves (Wuerth Elektronik, Waldenburg, Germany). Again, for completeness all those slices (<1%) containing TMS-capacitor-induced artefacts

were identified by the magnitude of their difference to the anatomically corresponding slice in the previous image volume (> 3 SD from mean slice difference in time series), and were replaced by the mean of the spatially equivalent slices from the previous and the subsequent image volume. The stimulator box was remotely controlled by the PC that was also used to deliver concurrent visual stimulation (see below).

The same protocol was used here as for Chapter 4, except for the change in TMS site from frontal to parietal. In each stimulation block, three equal-intensity trains of five TMS-pulses (9 Hz, with intensity either at 85%, 70%, 55%, or 40% of total output) were applied in the 570 ms temporal gap between acquisitions of three subsequent image volumes, thus avoiding image corruption by TMS pulses. This TMS protocol did not induce any muscle twitches, as confirmed by piloting and by reports of our participants. In each run, 48 TMS-stimulation blocks were delivered, each interleaved with seven image volumes without any stimulation, thus complying with published safety limits for repetitive TMS (Wassermann, 1998). An equal number of stimulation blocks (six) were delivered at each of the four TMS intensity levels, crossed with presence or absence of peripheral visual stimulation. The run also contained twelve control blocks without any TMS, during which visual stimuli could be present or absent also. The order of conditions within each experiment was randomly determined by the program used to deliver all experimental stimulation, which was implemented in a MATLAB (The Mathworks, Natick, MA) custom stimulus-presentation toolbox (www.fil.ion.ac.uk/Cogent2000).

Visual stimuli

The visual stimuli (when present) were the same patterns also used for the experiments in Chapter 4. These patterns spared the fovea and the vertical meridian, and moved (whole pattern movement, direction randomly determined,

maximum translation in both horizontal and vertical direction 0.3 degrees per 16 ms frame) and randomly changed their form and colour every 500 ms (16 different combinations were possible). The stimuli were projected onto a screen (30 x 22 degrees visual angle, grey background, 0.5 x 0.5 degree central fixation cross always present) that was mounted at the rear end of the bore, which participants viewed via a mirror system attached to the MR surface coil.

Eye-tracking

Importantly, eye position, pupil diameter, and any blinks were again monitored at 60Hz during scanning with an ASL 504 Remote Optics Eye tracker (Applied Science Laboratories, Bedford USA) via the same mirror used for visual stimulus viewing. Raw eye position data were filtered for blinks, and transformed to degree visual angle. Pupil diameter was recorded by the eye tracker, and blinks were identified as continuous losses of pupil signal for more than 5 frames (80 ms).

Image processing and analyses

The data from this experiment underwent identical analyses as the FEF-TMS fMRI data described in Chapter 4. All image pre-processing and general linear model (GLM) analysis steps were performed using SPM2 (www.fil.ion.ucl.ac.uk). Functional images were reconstructed offline, and the first six images of each run were discarded. Images were realigned to the first of the series, corrected for movement-induced image distortions (Andersson et al., 2001), normalized to the MNI anatomical standard space, and spatially smoothed with a three-dimensional 6mm FWHM Gaussian kernel. All reported peak voxel coordinates correspond to the MNI space employed in SPM2.

For initial *group analyses*, the voxel-wise effects of experimental conditions were again estimated in a fixed-effects model by multiple regression of the voxel time-

series onto a composite model containing ten covariates of interest per session (four TMS stimulation intensities plus no TMS, each with and without visual stimulation). All conditions were again modelled as continuous series of delta functions sustained over three image volumes (9 seconds), which were convolved with the canonical hemodynamic response function employed in SPM2. In addition to the experimental conditions (effects of interest), the model also contained one regressor representing eye blinks (modelled as delta functions convolved with the canonical HRF) and another regressor for mean pupil diameter per scan, taking into account hemodynamic delay. A high-pass filter (128 seconds cut-off) and an AR(1) process excluded low-frequency drifts and short-term temporal autocorrelation of scans, respectively (Friston et al., 2002). Linear compounds (contrasts) were used after model estimation to assess and compare the regression parameters for the different conditions. Correlations of BOLD with TMS intensity were modelled as the corresponding weighted linear combination of the four covariates representing different TMS intensities (linear parametric modulation contrast in SPM2). Any effects of mere TMS presence on BOLD signal were estimated as the weighted contrast of trials with TMS present versus the trials with TMS absent. The statistical threshold for all analyses was again set to $T > 3$ and a cluster threshold of $p < 0.05$, corrected for multiple comparisons across the whole image volume.

For the *retinotopic analyses*, the identical flatmaps, boundaries of visual areas V1-V4, and V5/MT+ localiser as in Chapter 4 were used. See Methods in Chapter 4 for details on how all these were derived.

Experiment 7: Results

As for the experiments described in Chapter 4, two complementary analysis approaches were used. Group analyses of activity across the image volume (acquired by the visual surface coil centred over occipital cortex) identified any

regions that reliably displayed activity-changes as a function of IPS TMS intensity (or of its mere presence). To further characterize the pattern of IPS TMS effects on specific regions of visual cortex, standard retinotopic mapping procedures and functional localizers for V5/MT+ were used in each individual participant, in conjunction with cortical flattening to visualize the topographical nature of any TMS effects upon early retinotopic areas V1-V4.

Group analyses

The group analyses revealed that occipital activity modulations elicited by increased TMS intensity over the IPS differed qualitatively from those observed for TMS over the FEF (cf. chapter 4). During IPS TMS, two sets of areas displayed significant interactions of TMS intensity with the presence/absence of visual stimuli on the screen. A region in the bilateral cuneus (encompassing the calcarine sulci) showed significant activity increases only in the *absence* of visual stimuli (Figure VI-2A). In contrast, for bilateral regions in lateral occipital cortex beyond retinotopic visual areas (corresponding to V5/MT+, as confirmed below), stronger IPS TMS led to significant decreases in activity, but only during the *presence* of the moving visual stimuli (Figure VI-2B). Localisation of these visual-context-dependent BOLD signal decreases to V5/MT+ was confirmed by their spatial overlap with activations induced in the individual movement localiser scan (see Materials and Methods; and individual retinotopic analyses below), and by the close vicinity of their stereotactic peak coordinates (xyz = 50, -66, -3; and xyz = -51, -56, 3) to the location of visual area V5/MT+ as reported in other studies (e.g., Rees et al., 2000a; Watson et al., 1993).

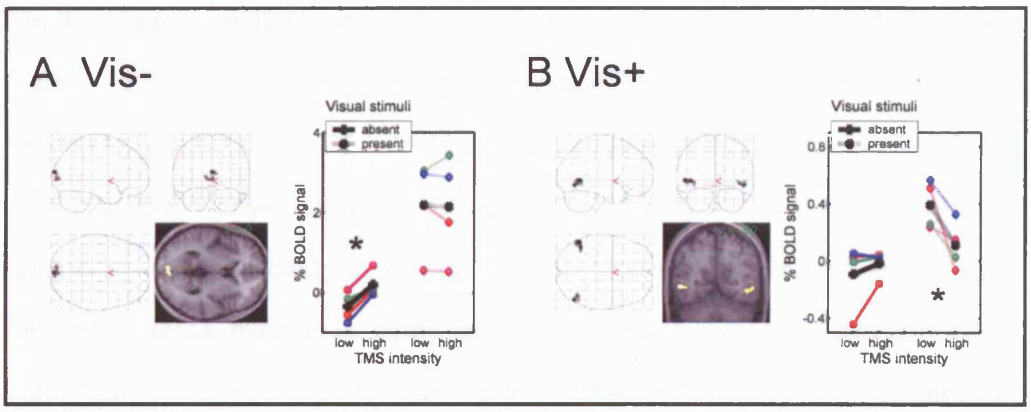

Figure VI-2. Experiment 7: Effects of IPS TMS depend on visual context.

The images in both panels show the SPM(T) quantifying (A) positive correlations of BOLD and TMS intensity during the absence of visual stimuli (Vis-), or (B) negative correlations of BOLD and TMS intensity during the presence of visual stimuli (Vis+), as 2-D projections onto a transparent schematic of the MNI template brain, and as renderings onto a transverse slice of the mean structural scan. All thresholds are set to T > 3 and p < 0.05 (corrected for multiple comparisons at cluster-level). The single-subject plot displayed in each panel shows the mean signal intensity during the different experimental conditions, extracted from a circular region-of-interest (6mm radius) centred in the peak voxel of the SPM(T) displayed next to each plot. For ease of visualization, the signal has again been collapsed across the two lowest and highest TMS intensities; individual subjects are plotted in different colours, while the mean is plotted in black. Panel A shows a region in the calcarine sulcus that displayed activity increases with greater intensity of TMS over IPS, but only during the absence of visual stimulation, not when visual stimuli were present (significant positive correlation of BOLD with TMS intensity during blank-screen trials only, and significant interaction with absence/presence of visual stimuli). Note that the TMS effect is only apparent with a blank screen (asterisked pairs of points in the corresponding single-subject plot). Panel B displays a bilateral region in occipito-temporal cortex (V5/MT+) that showed negative correlations of BOLD signal with intensity of TMS to IPS (i.e. reduced activity with higher intensity of TMS), but only when moving visual stimuli were concurrently presented (significant negative correlation of BOLD with TMS intensity only during visual stimulation; and significant interaction with absence/presence of visual stimuli; see asterisked pairs of points in the single-subject plot). Note also that applying the same TMS protocol over a different site (FEF) elicited occipital activity modulations that did not depend on visual context, and no effect in V5/MT+ (see main text, and Figures VI-3 and VI-4).

In contrast, the occipital BOLD-changes that had been observed during application of the identical TMS protocol to the FEF were identical for both visual contexts, and localized more anteriorly in the cuneus and around the occipital poles. Moreover, no effect of FEF-TMS intensity had been found in V5/MT+ (see Chapter 4). These apparent differences between both experiments were confirmed by region-of-interest analyses of the mean BOLD signal changes elicited in the prior FEF-TMS experiment 5, in those regions that now showed TMS-intensity-dependent effects during IPS TMS.

For these analyses, the search volume was set to the cuneus or the V5/MT+ regions shown in Figure VI-2A or VI-2B (using masking and small-volume correction), looking for interactions of FEF-TMS intensity and presence/absence of visual stimuli similar to those observed during IPS TMS (i.e., by means of the identical linear contrasts). No significant voxel was found for these hypothesis-driven region-of-interest analyses, even when employing a sensitive statistical threshold of $p < 0.05$, corrected for the small search volume in the respective ROI only (as opposed to the whole image volume, which is used for the more exploratory group analyses in Chapter 4 and here). This *absence* of the same pattern of context-dependent activity changes in the FEF-TMS data (see Chapter 4) confirms that these effects were indeed specific to TMS to the parietal IPS site (see also Figure VI-3). The differences between IPS- and FEF-TMS effects upon activity in early visual cortex were further confirmed and specified in analyses of BOLD changes in retinotopic visual areas and V5/MT+ in each individual, as described below.

Individual retinotopic analyses

Figure VI-3A shows the IPS-TMS intensity effects upon retinotopic visual areas as a function of visual stimulus presence and eccentricity in the visual field. The IPS-TMS effects on individual retinotopic visual areas were in full accordance with the results of the initial group analyses in stereotactic space. IPS-TMS intensity only elicited activity increases in retinotopic visual areas during the absence of visual input (Figure VI-3A, top graph). In contrast, the effects of FEF TMS upon the early visual regions were similar in both visual conditions (Figure VI-3B, top graph; and Chapter 4). As a second major difference, the effects observed for the two TMS sites also differed in their spatial topography. Activity increases elicited by IPS-TMS during the absence of visual stimuli were similarly present in the different eccentricity sectors of V1-V4 (Figure VI-3A, bottom graph), while increased intensity of FEF-TMS had

opposite effects on the sectors representing the central (BOLD decrease) vs peripheral (BOLD increase) visual field (Figure VI-3B, bottom graph).

These two apparent differences between the effects of the parietal and the frontal stimulation sites were confirmed by direct statistical comparisons of the effects of IPS and FEF TMS upon the retinotopic areas. For this purpose, the mean effect of IPS TMS on individual retinotopic sectors in V1-V4 was derived with the identical procedures as for the FEF-TMS data (see Chapter 4 for details of this procedure). Each visual area was again divided into four such eccentricity sectors, treating the meeting point of the extended exterior borders of V4 and V3d in the foveal confluence as origin for all visual areas and borders, and assigning each voxel within these boundaries to one area and eccentricity sector. The correlation of BOLD-signal with IPS-TMS-intensity (quantified as *T*-value in relation to voxelwise residuals of the model) was then extracted from each of these sectors. Averaged across areas V1-V4, only the IPS-TMS effects depended on visual context, in a similar manner for all eccentricity sectors (2x2x4 ANOVA; interaction of TMS site and presence/absence of visual stimuli: $F[1,21] = 8.98$, $p < 0.05$; all interactions involving the factors visual context and eccentricity n.s.). Pairwise comparisons showed that IPS TMS elicited activity increases in early visual areas that were significantly stronger during the absence than presence of visual stimuli (see Figure VI-3A, top graph), with this effect being most marked in visual area V1 and V2. In contrast, the effects of FEF stimulation did not depend on visual context, in any visual area (Figure VI-3B, top graph).

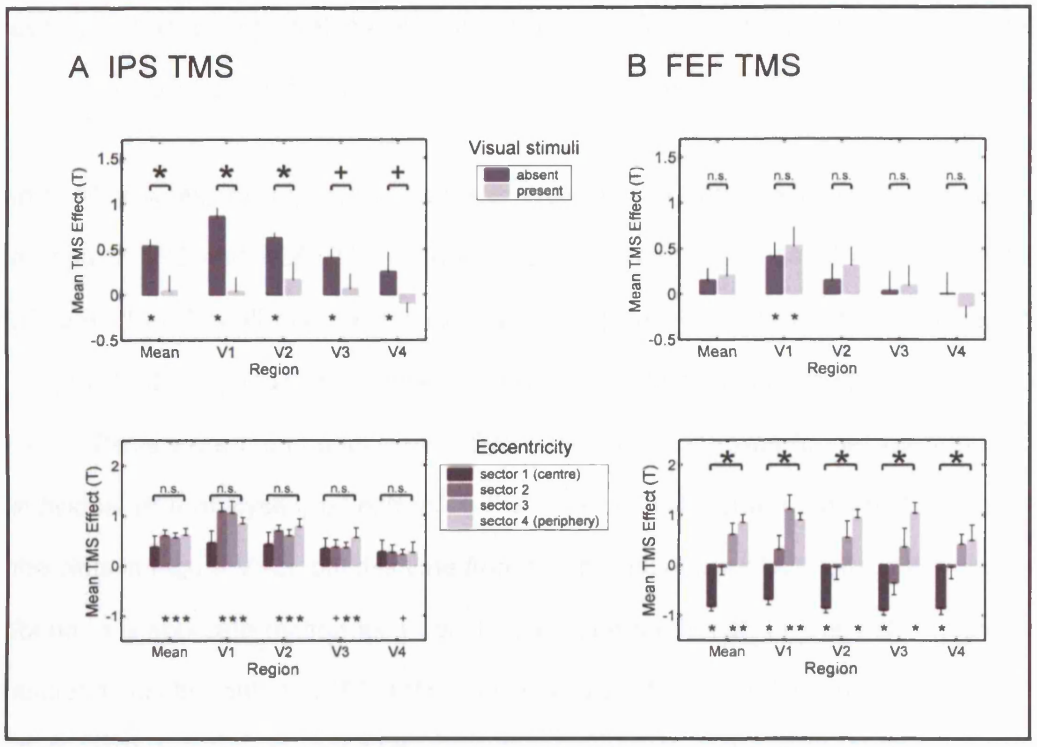

Figure VI-3. Experiments 7 and 4: Retinotopic analyses of areas V1-V4 confirm two main differences in the effects of IPS and FEF TMS.

*The plots show the mean T-values (+/- s.e.m) coding the correlation of (A) IPS-TMS or (B) FEF-TMS intensity with BOLD, averaged across dorsal and ventral visual regions V1-V4 (leftmost bars in each plot), and for each individual visual region (averaged across dorsal and ventral cuneus). The top plot in each panel shows the IPS- or FEF-TMS effects separately for trials with visual stimuli absent or present (averaged across all eccentricity sectors), while the bottom plot in each panel shows the IPS- or FEF-TMS effects for each eccentricity sector (during the absence of visual stimuli, where significant effects of IPS TMS were found). See main text and methods for how the eccentricity sectors were derived, but note that eccentricity sector number 1 corresponds to the representation of the central visual field, with increasing sector numbers coding increasingly eccentric visual field representations. Statistical significance of paired (top of each graph) or simple (bottom of each graph) t-tests is marked according to the following scheme: * p<0.05, + p<0.1, n.s. not significant; see main text for results of ANOVAs. Comparison of the top plots in both panels illustrates that only the effects of IPS TMS depended on visual context (i.e., were significantly different when visual stimuli were present or absent), while the two plots on the bottom of the figure shows that only FEF TMS had opposite effects on the central vs peripheral visual field (i.e., significantly negative effects on central sector, and significantly different effects on the central and peripheral sector).*

The analyses also confirmed that FEF versus IPS TMS differentially affected central vs peripheral sectors of the visual field in retinotopic visual cortex (interaction of TMS site and eccentricity sector, $F[1,21] = 6.47$, $p < 0.05$). Direct comparisons showed that the BOLD increases observed with increased IPS-TMS intensity (during the absence of visual stimuli) were similar for peripheral and central sectors (Figure VI-3A, bottom graph), in contrast to FEF stimulation which induced significant BOLD

decreases in the central sector, and different effects on central vs peripheral sectors, in all visual areas (Figure VI-3B, bottom graph).

In addition to examining retinotopic visual areas V1-V4, mean BOLD signal changes elicited by IPS and FEF TMS were also further examined in visual region V5/MT+ (Figure VI-4). Recall that the group analyses had already indicated that increased IPS-TMS intensity leads to reduced BOLD signal bilaterally in this region, while no such effects were found during FEF TMS. This difference was further confirmed in individual ROI analyses, by extracting the mean BOLD signal from V5/MT+ (as for the plots in Figure VI-2), but this time from the individual peak locations in this region found in a separate motion localiser dataset (see Methods). In line with the group analysis results, only the IPS-TMS effects in V5/MT+ depended on visual context (2x2 ANOVA; interaction of TMS intensity and presence/absence of visual stimuli: $F[1,28] = 6.16$, $p < 0.05$), while the effects of FEF-TMS did not ($F[1,28] = 2.24$, n.s.). In direct comparison, the BOLD decrease elicited by IPS-TMS (during the presence of visual stimuli, determined as for Figure VI-2) was significantly larger than during FEF-TMS ($t[1,7] = 1.99$, $p < 0.05$).

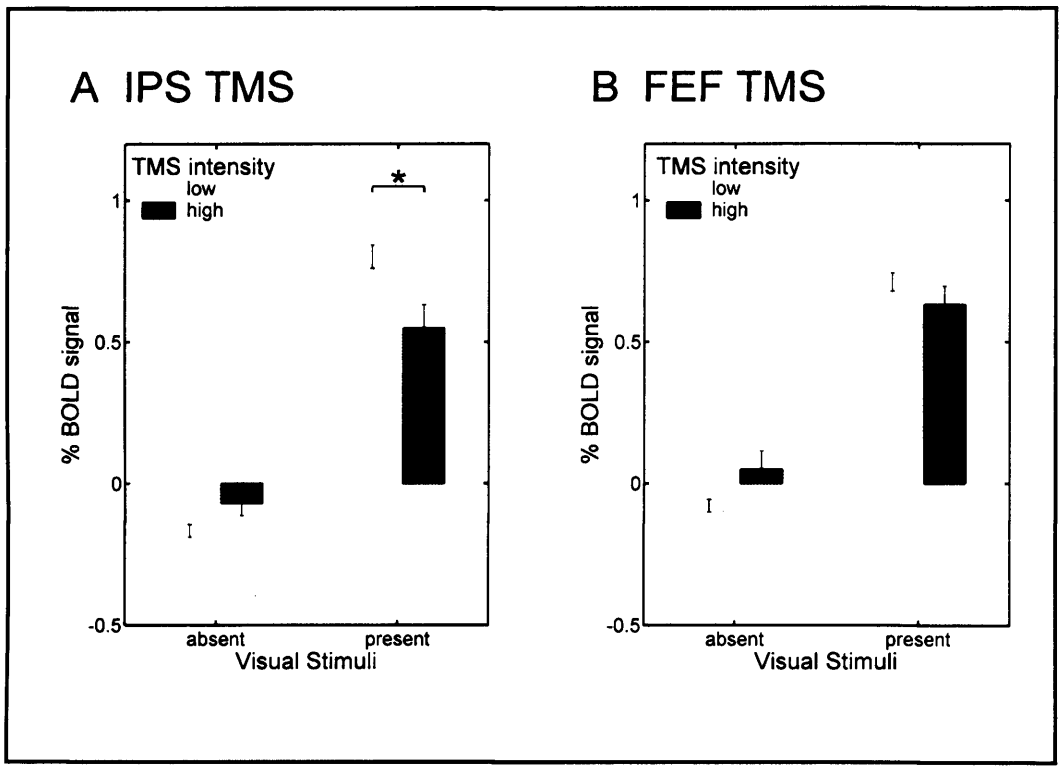

Figure VI-4. Experiments 7 and 4: IPS TMS (but not FEF TMS) elicits BOLD decreases in V5/MT+ in the presence of moving visual stimuli.

The bar graphs show the mean BOLD signal intensity in V5/MT+ during (A) IPS TMS or and (B) FEF TMS, derived and plotted like the estimates for Figure 2, but now collapsed across hemispheres. Error bars represent the s.e. of the mean difference between high- and low-TMS-intensity trials for each condition (i.e., each pair of adjacent bars). Stars indicate $p < 0.05$ in paired t-tests (see main text for results of an ANOVA). The bar graphs show that increasing the intensity of IPS TMS leads to activity decreases in V5/MT+ only when the moving visual stimuli were present (to activate this visual area), while no such effect was found for increased intensity of TMS over FEF.

Analysis of unspecific TMS effects

The effects on BOLD activity in visual regions found here during TMS to IPS were specifically related to the intensity of TMS (rather than its mere presence). Moreover, they were clearly distinct from the effects observed earlier during the identical stimulation protocol over a different site in frontal cortex (i.e., the effects depended on visual context only for IPS TMS, and differentiated the central and peripheral visual field only for FEF TMS). This intensity-dependence and site-specificity makes it seem unlikely that unspecific effects of TMS administration *per se* might have influenced visual cortex, but the data were nevertheless examined for such effects (in a similar manner as for the data in Chapter 4). For instance, data

from both experiments were compared for effects of the mere presence or absence of TMS (as opposed to effects of TMS intensity). This revealed activations in bilateral regions in auditory cortex that were similarly present for TMS to both sites (see Figure VI-5), presumably reflecting processing of the 'clicking' sound associated with TMS presence versus absence.

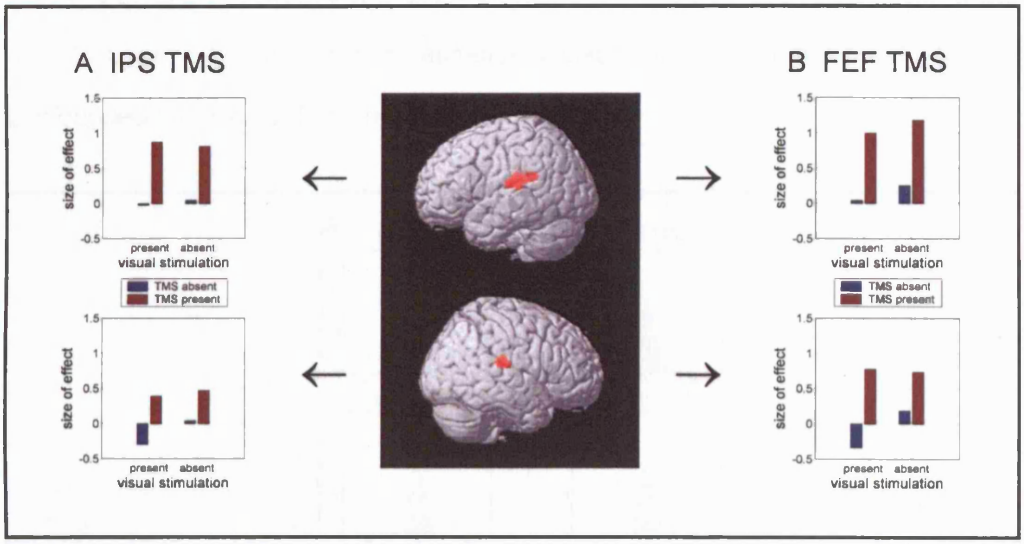

Figure VI-5. Experiments 7 and 4: Activity increases in auditory cortex are similar for IPS and FEF TMS.

Regions that were more active during trials with TMS present than absent, for both IPS and FEF TMS. The central images show the SPM(T) of the conjunction contrast (inclusive masking) of TMS present (all intensities pooled) minus TMS absent, for both IPS and FEF TMS, rendered onto a 3-D version of the normalized template brain employed in SPM2. The same statistical threshold as in Figure Vi-2 was used, with different shades of red indicating different distances from the cortical surface. Note that TMS to either region elicited similar activation in auditory/somatosensory cortex, due to the presence of the sound and scalp sensation associated with TMS. The side panels show the mean signal extracted from the peak voxel in the respective hemisphere (as indicated by the arrows), plotted separately for (A) IPS and (B) FEF TMS. Direct statistical comparisons (paired t-tests) revealed that the effects of mere TMS presence on auditory cortex (TMS present minus absent) were equivalent in for both stimulations sites, and did not show lateralization.

Moreover, on-line eye tracking throughout scanning (see Materials and Methods) measured eye-position, blinks, and pupil diameter, in detail. Similar to what had been observed for FEF TMS (see Chapter 4), mean horizontal and vertical eye position, and their variability, did not differ between conditions with strong, weak, or no IPS TMS (3-way ANOVAs, all n.s.; see Figure VI-6), confirming once again that the TMS protocol employed here did not induce eye-movements. Moreover, trials

with strong, weak, or no IPS TMS also did not differ with respect to mean pupil diameter (3-way ANOVAs, all n.s.), and blinks occurred equally often during the three different trial types (chi-square tests, n.s.). Note also that blink events and parametric pupil-size had been included as independent regressors in the fMRI analyses reported above (see Methods). This ensured that any variance in brain activity due to these factors was separated from the experimental effects of interest (i.e., TMS-intensity, and presence/absence of visual stimulation) and could not have confounded the results (Friston et al., 1995).

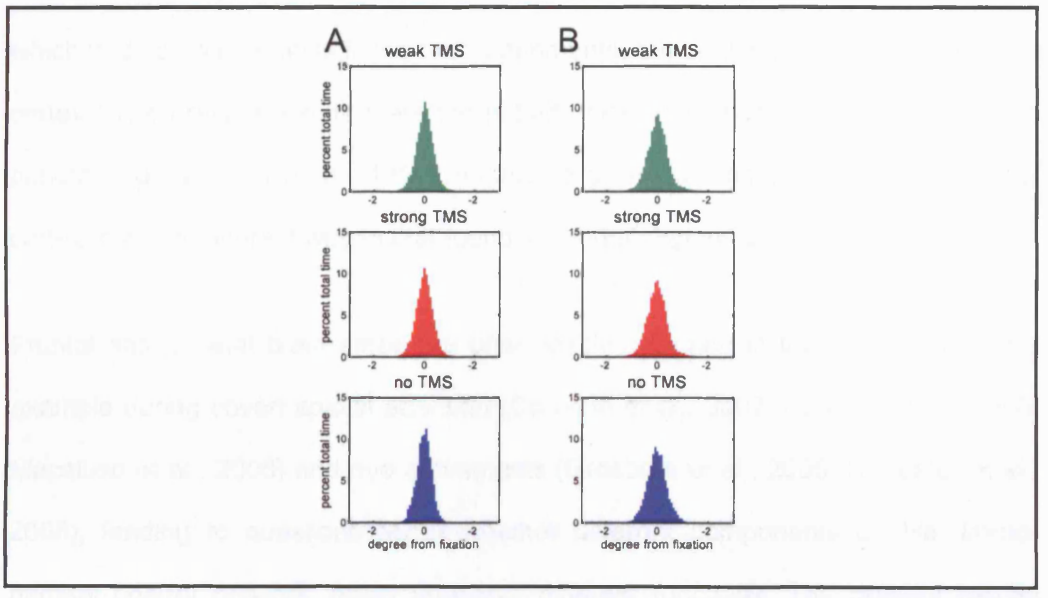

Figure VI-6. Experiment 7: IPS-TMS effects upon functional activity in visual cortex cannot be explained by changes in eye position.

Histograms of (A) horizontal and (B) vertical eye position during trials with weak TMS (lowest two TMS intensities pooled, blue), strong TMS (highest two intensities, red), and no TMS (green) to IPS. The histograms plot for each condition the eye position as percent time at different degrees of visual angle of deviation from fixation. No statistical differences were found in the mean or variance of these eye position distributions across the displayed conditions (see main text), confirming that differential eye movements cannot account for the observed TMS effects.

Experiment 7: Discussion

By combining fMRI with concurrent TMS in the scanner, Experiment 7 described in this Chapter found that stimulation of a region in human parietal cortex (right IPS) could produce reliable and distinct effects upon BOLD activity in remote human

retinotopic cortex, including area V1. The activity changes observed in visual cortex were specifically related to changes in IPS-TMS intensity, not merely to the presence versus absence of TMS, and they did not reflect eye-movements, blinks, or changes in pupil size. Moreover, the effects of IPS TMS on visual cortex were qualitatively distinct from the effects that had been observed during application of the same stimulation protocol to a region in frontal cortex (right FEF) in the same participants, as outlined below. This qualitative difference between the two stimulation sites rules out any account of the results in terms of general, non-specific effects potentially associated with TMS application (such as the clicking sound, which had common effects in the two experiments, but on auditory rather than visual cortex). The present results therefore provide clear evidence that circuits involving parietal regions such as the IPS are capable of modulating activity in early visual cortex, but in a different way to that found for frontal regions such as the FEF.

Frontal and parietal brain areas are often jointly activated in the human brain, for example during covert spatial attention (Corbetta et al., 2002; Kastner et al., 2000; Macaluso et al., 2005) and eye movements (Grosbras et al., 2005; Sylvester et al., 2005), leading to questions about whether different components of this 'fronto-parietal control network' might subserve different functions. The present results indicate that the human IPS and FEF can have clearly distinct influences on activity in retinotopic visual cortex. Specifically, the effects of FEF stimulation upon functional activity in early visual cortex (see Chapter 4) had applied in the same 'top-down' manner, irrespective of current bottom-up visual input, and hence regardless of the overall level of activity in visual cortex. By contrast, the effects of IPS stimulation here strongly depended on the current visual context. Unlike frontal stimulation, parietal TMS led to increased activity in retinotopic visual areas (V1-V4) only in the absence of retinal input to these visual regions, possibly indicating that the presence of 'bottom-up' input can dominate functional connections between

early visual cortex and IPS. This pattern may fit the idea that neural signals in frontal cortex may operate in a more purely 'top-down' fashion, while activity in parietal regions (and specifically in the IPS) might be more involved in the on-line coding of sensory information (Connolly et al., 2002; Miller, 2000; Shulman et al., 2003). Such proposals are currently emerging in the literature on visual attention (Culham, 2001; Miller, 2000; Kastner 1999; Shulman et al., 2003; Wardak 2006), eye movement control (Connolly et al, 2002), and spatial working memory (Curtis et al, 2006; Postle 2003). It has even been proposed that the human IPS might represent an intermediate stage of visual processing, between extra-striate visual areas and other parietal and frontal areas (such as the SPL or the FEF; Kastner et al., 1999). The present results suggest that functional distinctions between frontal and parietal regions may at least partially relate to functional properties of their anatomical connections with remote retinotopic visual cortex.

A further difference between the fMRI effects of IPS and FEF TMS found here concerned functional activity in V5/MT+. This was unaffected by FEF TMS. By contrast, effects of IPS TMS were found on V5/MT+, but only in the presence of moving visual stimuli. This dependence of the IPS-TMS effects upon current visual input provides a particularly clear example of context-dependent changes in interactions between brain areas, or "effective connectivity", as previously proposed in some fMRI work without TMS (see e.g., Friston, 2002; McIntosh, 2000). Note that the concurrent use of TMS and fMRI here made it possible to test for such context-dependent influences of a particular brain region upon others with standard fMRI analyses, without requiring more complex mathematical approaches to this issue. The finding that the influence of IPS upon visual cortex can vary with contextual state (here as a function of current visual input) generally implies that such remote TMS effects may reflect functional coupling between areas, rather than just fixed anatomical connections whose functional role may change with state (Friston, 2002;

see also Massimini et al., 2005). This functional-coupling aspect may explain why IPS TMS affected V5/MT+ activity here while FEF TMS did not, even though both FEF and IPS have some anatomical connections with V5/MT+ in the macaque brain (e.g., Blatt, Andersen, Stoner; Schall et al., 1995; Stanton et al., 1995). Presumably, IPS and V5/MT+ form a more integrated circuit when processing moving stimuli in particular (Friston et al., 2000; Huk & Shadlen, 2005), consistent with a role for parietal cortex as well as V5/MT+ in aspects of motion processing (Battelli 2001; Bremmer et al., 2001; Claeys 2003; Orban et al, 2006; Williams et al., 2003).

Frontal and parietal TMS also differed in the retinotopic pattern of TMS influences upon early visual cortex here. Effects of IPS TMS on early visual cortex, during the absence of visual input, did not differentiate the central and peripheral visual field, while increasing TMS intensity to FEF (see Chapter 4) led to increased activity for peripheral-visual-field representations in early visual cortex, but to activity decreases instead for central-visual-field representations. This dissociation might relate to distinct neural circuitry for more peripheral versus more central locations in FEF (and for its connections with visual cortex), as suggested by tracing studies in non-human primates (Schall et al., 1995; Stanton et al., 1995). In contrast, no distinction of central and peripheral visual field representations was found here for the effects of IPS TMS. Interestingly, recent studies have shown some retinotopic representations of the visual periphery in both human FEF (Hagler, Jr. et al., 2006) and IPS (Schluppeck et al., 2006; Sereno et al., 2001; Silver et al., 2005), but have so far identified *central* visual field representations only for sites in the IPS (Raiguel, Vogels, Mysore, & Orban, 2006; Wandell et al., 2005). The distinct patterns present in the current TMS-fMRI results suggest differences in the layout and/or anatomical connectivity of central and peripheral visual field representations in the human FEF or IPS.

In light of the differences between the effects of FEF versus IPS stimulation, one noteworthy common aspect here was that all effects observed in both experiments arose bilaterally in visual cortex. This may presumably reflect inter-hemispheric callosal or subcortical influences, underlining that the effects of both IPS and FEF TMS upon visual cortex may be poly-synaptic, and may involve intervening brain regions (Blatt et al., 1990; Cavada et al., 1989a; Cavada et al., 1989b; Schall et al., 1995; Stanton et al., 1995). Here an occipital surface MR coil was used by design in order to maximize sensitivity for retinotopic visual cortex, which enabled the characterisation and comparison of the distinct patterns of effects of IPS and FEF TMS upon retinotopic visual areas. This inevitably meant less sensitivity for more anterior structures (e.g., in parietal and frontal cortex). Future experiments may use a combination of TMS with whole-brain imaging instead, to reveal any influences on such more anterior structures. Moreover, comparing further TMS sites in the same or in different hemispheres might also prove fruitful, as discussed in the final chapter of this thesis.

In summary, the present experiment (together with Chapter 4) shows directly that neural circuits involving the IPS or the FEF can modulate functional activity in human retinotopic visual cortex, and can do so in a qualitatively distinct fashion. These data therefore provide a clear 'proof-of-principle' that human parietal and frontal regions can have distinct and specific functional influences on activity in early visual cortex, including area V1, as often proposed previously but on much more indirect grounds. Only the effects of IPS TMS depended on visual context, while only the effects of FEF TMS differentiated the central vs peripheral visual field. These qualitative distinctions in the effects of IPS vs FEF stimulation suggest possible differences in the retinotopic layout and connectivity of these two areas in the human brain, and underline the physiological plausibility of differences in the functional contributions of parietal vs frontal sites to modulations of visual

processing. On a more general closing note, the present experiment (and those described in Chapter 4) illustrate how the new methodological approach of combining TMS with fMRI can provide information about distinct functional influences of various brain regions upon the same given target area in the human brain.

Chapter 7
General Discussion

The experimental work presented in this thesis examined some of the neuronal mechanisms underlying human visual selective attention with a combination of different methods (fMRI, TMS, psychophysics, and concurrent TMS-fMRI). The investigations mostly focussed on possible causal top-down influences on activity or excitability in visual cortices. As outlined in Chapter 1, previous neuroimaging studies had demonstrated activity modulations due to selective attention at multiple stages of the visual system, including early cortical visual areas such as V1 and even the thalamus, but also in higher-level frontal and parietal brain regions. Such modulations can occur in the absence of any changes in retinal input, and even before any visual stimulus is presented. These findings are often interpreted in the context of theoretical proposals that attention might act via top-down signals, potentially generated in frontal and parietal regions, which may bias visual processing towards behaviourally relevant information. The series of experiments presented in this thesis directly addressed several open issues related to this general notion.

More specifically, the experiments in Chapters 2 and 3 addressed questions concerning the potential functional significance of modulations observed during visual selective attention. Using TMS over occipital cortex as a means to assess cortical excitability, Chapter 2 showed that phosphene thresholds were reliably lowered when covert attention was directed to the part of the visual field that contained the possible phosphene. These results show that selective attention may change the excitability of visual cortex in a spatially specific manner, even when the LGN is bypassed (via direct cortical TMS input) to preclude feed-forward thalamic gating. However, Chapter 3 showed with behavioural and fMRI data that top-down

influences of selective attention on visual processing may not exclusively reflect enhancements of information that should receive further processing (i.e., visual targets), but may also comprise anticipatory processes that minimize the impact of *distractor* stimuli (see also Mavritsaki et al., 2006; Watson et al., 1997; Watson et al., 2003). These findings constrain the potential functional roles of preparatory activity modulations during visual selective attention, as discussed further below.

The experiments presented in Chapters 4-6 then addressed related questions about the potential *origins* of top-down activity modulations in visual cortex during selective attention. It has often been speculatively proposed that regions in frontal and parietal cortex might be involved in the generation of such signals, but limitations of current neuroimaging methods had so far precluded direct causal demonstrations of such proposals. To address this issue, a lot of technical pilot work was conducted as part of this thesis in order to establish and corroborate the on-line combination of TMS and fMRI, which should allow for the direct study of causal influences of one brain region (stimulated with TMS) on activity in other areas (measured with fMRI). Chapter 4 described studies that used this specific new approach of concurrent TMS-fMRI to show that stimulation of the right human frontal eye-field (FEF) can elicit a characteristic pattern of activity changes in retinotopic visual areas that is independent of concurrent visual input. These activity changes were not present during stimulation of a vertex control site, underlining that circuits originating in the human FEF can indeed influence activity in visual cortex in a specific causal manner. Moreover, the experiment described in Chapter 5 confirmed with psychophysics that the topographic pattern of activity changes observed in visual cortex during FEF TMS had corresponding functional consequences for visual perception. Thus, the FEF-TMS influences on visual cortex may indeed result in spatially specific biases of visual processing, as hypothesized for the analogous top-down activity modulations on visual cortex that are often found during selective

attention. Finally, the experiment described in Chapter 6 showed that TMS over an area in parietal cortex (the right intra-parietal sulcus, IPS) also elicited modulatory influences upon activity in visual cortices, but that these were reliably different from those observed during FEF TMS, in several respects. Regions in frontal or parietal cortex may thus exert *different* influences on activity in visual cortex, which might indicate distinct functional roles of these areas during selective visual attention.

The following paragraphs will expand on the implications of these experiments for emerging neurobiological views of human visual attention, while also raising issues for further research and discussing possible limitations. In line with the two main general questions of the experiments, the first part of the discussion will focus on the potential *functional roles* of top-down signals observed in visual cortex during selective visual attention. This will be followed by a discussion of the putative contributions of different *control structures*, outside of traditional visual cortex, for top-down modulations of visual areas. It will become apparent in both these parts that fMRI, the main method used here to index neural activity, has many strengths but also some limitations, which have to be considered carefully when interpreting the present results. Moreover, I will also describe how the new methods developed and corroborated for the present thesis may allow for new approaches to some longstanding questions in research on selective attention, or in cognitive neuroscience more generally. Finally, the following paragraphs will also contain suggestions for putative future experiments that could be directly derived from the research described in the present thesis.

Functional roles of top-down signals in visual cortex during preparatory selective attention

There is now wide agreement that selective attention can change cortical activity at multiple stages of the visual system (see Chapter 1), but it remains less clear how such neurobiological modulations due to attention may bring about influences on *perception*. It is often generally assumed that anticipatory activity modulations in visual cortex may represent some form of bias signal that may enhance the neural coding of related visual targets presented subsequently, relative to any other stimuli present in the visual scene (Desimone et al., 1995; Duncan et al., 1997; Kastner et al., 2000). However, such perceptual modulations might be implemented in various ways. Some psychophysical studies have been taken to show evidence for actual enhancements of the signals related to targets (Carrasco et al., 2000; Carrasco et al., 2004; Hawkins et al., 1990); for a reduction or exclusion of 'noise' signal related to other distracting visual stimuli (Awh et al., 2003; Lu et al., 2002; Mavritsaki et al., 2006; Watson et al., 1997; Watson et al., 2003); or for interactions of both these mechanisms (Cheal et al., 1997; Dosher et al., 2000; Pestilli et al., 2005). fMRI studies on purely top-down effects of attention (i.e., recorded in the absence of visual stimulation) have shown increases in BOLD activity related to expected target location, in retinotopically appropriate sectors of visual cortex (Kastner et al., 1999; Hopfinger et al., 2000; Macaluso et al., 2003; Ress et al., 2000). However, BOLD signal increases are often thought to relate more to the input to a given region rather than its spiking output (Attwell et al., 2002; Lauritzen, 2005; Logothetis et al., 2004; Niessing et al., 2005; Scannell et al., 1999). Although still a controversial issue, this view implies that BOLD changes alone may be ambiguous with respect to the nature of the underlying neuronal processes. For example, anticipatory BOLD increases in a retinotopic sector corresponding to the expected target location might reflect excitatory influences on the baseline activity of neurons processing target features

(Chawla et al., 1999), inhibitory processes related to local distractor/noise suppression (Serences et al., 2004), or some mixtures of these processes. Consistent with this interpretative 'gap', there have not as yet been any clear empirical demonstrations of a direct relationship (e.g., trial-by-trial) between anticipatory BOLD baseline shifts in visual cortex and subsequent modulations of stimulus-evoked activity (see Driver et al., 2004). Moreover, it is also noteworthy that anticipatory baseline shifts have been found only rarely for neuronal firing rates at the single-cell level, as determined with single-unit recording methods in non-human primates (for a discussion of this issue see Luck et al., 1997; and Ress et al., 2000).

The experiments presented in Chapters 2-4 provide some new information on the potential functional significance of top-down signals in visual cortex. Experiment 1 in Chapter 2 used phosphene thresholds as direct measures of the excitability of neurons in early visual cortex (V1/V2), in an analogous way to the use of TMS applied over motor cortex to measure local motor cortex excitability (Munchau, Bloem, Irlbacher, Trimble, & Rothwell, 2002). Phosphenes depend on the integrity (Walsh et al., 2000) and excitability (Aurora et al., 1998; Muellbacher et al., 2000) of early visual cortex, and their perceived position in space reflects the retinotopic layout of these regions (Brindley et al., 1972; Kammer, Puls, Erb, & Grodd, 2005). In Experiment 1, participants directed their covert attention to a part of the visual field where they expected visual targets to appear. Although neural activity was not simultaneously recorded during Experiment 1 (as it might be in a future concurrent TMS-fMRI follow-up study, using the new methods developed here), such sustained covert direction of attention should be associated with top-down modulation of activity in the spatially corresponding parts of visual cortex, as shown by numerous previous studies and Experiment 3 in Chapter 3. With attention directed to one visual quadrant or to the opposite hemifield in Experiment 1, TMS was then unpredictably administered over occipital cortex in place of visual stimuli, eliciting a

potential phosphene that could (or might not) overlap spatially with the current focus of attention. The crucial finding was that phosphene thresholds were reliably lowered at the attended location. This pattern of results provides particularly direct evidence that anticipatory spatial attention may indeed heighten the excitability of neuronal populations in early visual cortex for input (in this case for the direct cortical TMS), specifically for those sub-populations that spatially correspond to the current locus of attention. In contrast, visual cortex corresponding to currently *unattended* parts of the visual field seemed unaffected in its excitability as a function of where covert attention was directed: Phosphene thresholds were not different for the two experimental control conditions where subjects either sustained covert attention to the hemifield opposite to the hemifield of the potential phosphene, or were not required to perform perceptual judgments on a particular location.

The results of Chapter 2 furthermore imply that initial thalamic gating of retinal inputs is not a necessary condition for the effects of selective attention on visual processing. Experiment 1 used TMS as a direct input to visual cortex. This form of by-passing the retino-geniculate pathway rules out feed-forward gating of initial retinal input as a mechanism for the effects of attention on phosphenes observed here. While the present results cannot exclude that other forms of recursive interactions with the thalamus may normally occur during spatial attention, they provide a clear example for direct effects of attention on excitability of visual cortex that do not appear mediated by initial thalamic gating.

Moreover, the results of Experiment 1 provide evidence for the idea that top-down signals during visual selective attention may act so as to highlight a particular region in the visual field, independent of the specific visual features relevant for the present visual task (such as shape, colour, etc.; see also Tsal & Lavie, 1993). Potential phosphenes were enhanced by covert spatial attention if their location was currently

attended, even though they are perceptually different in many respects from the target stimuli used for the external task. This appears consistent with the view that BOLD signal increases in visual areas due to preparatory spatial attention may indeed reflect shifts of baseline activity into the more excitable dynamic range of neurons. This could make early retinotopic visual regions generally more sensitive for any form of *spatially corresponding* retinal input, irrespective of other visual properties analyzed in detail in higher-level visual regions.

It may be noteworthy in this context that anticipatory attention to explicitly *non-spatial* visual stimulus features (e.g., colour or motion) can increase perceptual sensitivity for the attended feature across the whole visual field (Melcher et al., 2005), and can elicit BOLD signal increases in the relevant specialized visual areas even when these do not show a detailed retinotopic layout (e.g., V5/MT+ or V4, see Chawla et al., 1999). Future TMS-phosphene studies might assess the specific relation of these two sets of phenomena, by testing whether baseline shifts due to non-spatial attention may increase neuronal sensitivity in a manner that reflects the non-spatial properties of the affected visual areas. For example, such studies could test whether anticipatory attention to motion can decrease the thresholds for moving phosphenes elicited by TMS over V5/MT+, irrespective of the expected spatial position of the moving visual stimuli.

The idea that increased BOLD activity in early visual areas due to selective attention may reflect enhanced excitability of those retinotopic regions also appears broadly consistent with the results of Chapter 4-5 of the present thesis. Although the work in those chapters did not experimentally manipulate attention, it directly tested with concurrent TMS-fMRI and psychophysics whether circuits originating from a region in frontal cortex have the physiological capability of modulating activity in visual cortex and influencing visual perception. This approach can thus be considered a

direct experimental test of assumptions about neurophysiological top-down influences often thought to underlie visual attention (see Duncan et al., 1997; Frith, 2001; Kastner et al., 2000). Experiment 4 in Chapter 4 showed that TMS to the right FEF led to systematic BOLD increases for peripheral visual field representations in visual areas V1-V4. Experiment 6 in Chapter 5 showed that the same FEF-TMS protocol indeed led to an enhancement of perceived contrast for Gabor patches located in the peripheral visual field (relative to central patches), at an eccentricity that retinotopically corresponded to the sector of visual cortex where top-down BOLD increases had been observed as a consequence of FEF TMS. A systematic relationship between BOLD signal in V1 and perceived (rather than actual) Gabor contrast had already been established in some previous studies (Boynton et al., 1999; Olman et al., 2004; Ress et al., 2003). The studies described in Chapter 4-5 now provide – to my knowledge – the first case where a pattern of top-down activity changes in early retinotopic visual cortex (induced here by FEF TMS) could be used to predict and confirm perceptual changes. This appears to confirm that top-down BOLD increases in visual cortex can indeed result in changed perception at affected retinotopic locations.

It should be noted in this context, however, that FEF TMS in Chapter 4 also had the effect of *decreasing* BOLD signal for representations of the central visual field in V1-V4. The point-of-subjective-equivalence (PSE) measurements used in Chapter 5 required direct comparisons of perceived contrast for Gabor patches located in the central and the peripheral visual field. The observed perceptual effects may thus also (or even primarily) reflect some decrease in effective contrast for the central visual field (although note that the direction of the inferred relationship between BOLD signal and perceived contrast would remain unaffected by such considerations). Based on the present results, future studies may examine whether the pattern of BOLD changes in early retinotopic visual cortex during FEF TMS may

indeed index *separable* opposite effects on perceived contrast in the central and peripheral visual field. This might be examined with psychophysical methods that allow separate measurements for two simultaneously presented visual stimuli (such as detection paradigms). Independent of such further issues, Chapters 4-5 generally establish that FEF TMS can lead to modulations of BOLD signal in visual areas V1-V4 that differentiate the central and peripheral visual field, and to changes in contrast perception that apparently correspond to this spatial pattern. These findings establish that top-down modulations of BOLD signal in early visual areas (i.e., occurring in the absence of visual input, as in Chapter 4) can indeed directly affect perception for corresponding retinotopic sectors (as in Chapter 5).

Chapter 3, however, described distractor-related results that only partially accord with the notion that preparatory BOLD signal increases in visual cortex may index increases in perceptual sensitivity at spatially corresponding locations. Like many other previous studies (Hopfinger et al., 2000; Kastner et al., 1999; Ress et al., 2000; Macaluso et al., 2003), Experiment 3 showed that expectation of a target in a pre-specified location was associated with preparatory BOLD signal increases in visual cortex of the contralateral hemisphere. However, while all such previous studies on anticipatory activity modulations in visual cortex had exclusively studied anticipation of visual *targets* (e.g., by manipulating the location of this), it had been largely unclear whether and how the brain may prepare for a *distractor* at a pre-specified location (though see Olivers et al., 2005; Pollmann et al., 2003; Serences et al., 2004; for other recent results on distractor preparation for cluttered visual displays). Experiments 2 and 3 now showed that anticipation of a distractor at a specific location, remote from the target, crucially also reduced the behavioural impact of that distractor, and elicited preparatory BOLD signal modulations in visual cortex corresponding to the location of the anticipated distractor. These results show that distinct preparatory top-down signals in visual cortex may be devoted to

minimising the influence of distractors, not just to enhancements of target processing, as previously often assumed.

However, an unexpected finding in this context was that the distractor-related activity modulations also took the form of BOLD *increases* in those parts of visual cortex that spatiotopically corresponded to the anticipated *distractor* location, without further changing the BOLD signal increases contralateral to the expected target. As outlined in the discussion of Chapter 3, these observations might indicate specific neuro-cognitive mechanisms underlying attentional preparation for a distractor, potentially related to predictive coding (Friston, 2003; Rao et al., 1999; Summerfield et al., 2006), to a distractor 'template' map (Kunar et al., 2003), and/or imagery of the anticipated stimuli (Driver & Frith, 2000). It is also noteworthy that the modulations of visual areas related to distractor anticipation might in principle also index anticipatory *inhibitory* influences, as no fMRI study on its own can determine whether BOLD increases reflect neuronal excitatory or inhibitory processes (Caesar et al., 2003). Such an inhibitory account of the distractor-related anticipatory BOLD changes in Experiment 3 might be reconciled with the rather different findings of Chapters 2 and 4-6 if such inhibitory modulations of visual processing might take place in higher-level visual areas (such as lateral occipital cortex, where the distractor-related activations were found in Experiment 3) that more selectively process specific features of the anticipated distractor (such as its shape). Excitatory enhancements, in contrast, may act predominantly on earlier visual areas that process initial visual input in a strictly retinotopic fashion. Apparently consistent with this possibility, Chapter 3 showed that the anticipatory BOLD increases related to distractor expectation were largely located in lateral portions of distractor-contralateral occipital cortex, and apparently did not encompass regions in the calcarine sulcus that correspond to earlier visual areas such as V1. In contrast, the anticipatory BOLD signal increases related to target anticipations in that study were

largely located in medial occipital regions (including the calcarine sulcus), but overlapped with those related to distractors in the lingual gyri. Definitive knowledge about the precise neuronal underpinnings of the present BOLD increases due to distractor-expectation may only be obtained once fMRI can be safely combined with more direct electrophysiological measures (such as local field potentials) in human studies (Logothetis et al., 2004). Nevertheless, the results of Experiment 3 show that distinct neurobiological components of preparatory selective attention may be devoted to anticipatory modulatory influences on distractor processing in visual cortex, not just to target enhancements, as previously assumed. This general point was further confirmed by the results for activation in frontal and parietal control structures, as discussed in the next section.

Putative sources for top-down modulations of visual cortex during selective attention

All the neuroimaging experiments presented in this thesis highlighted candidate neural sources for top-down activity modulations observed in visual cortex, although some did this much more directly than others. As outlined in detail in Chapter 1, neuroimaging, lesion, and brain (in)activation studies have suggested indirectly that several regions in parietal and frontal cortex may exert influences on visual processing. However, whether such effects on visual processing might indeed involve causal modulations of neuronal activity in remote areas of early visual cortex has rarely been directly addressed so far (but see Moore et al., 2004; Armstrong et al., 2006). Moreover, activations in human neuroimaging studies of selective attention characteristically contain an extensive and often bilateral network of many frontal, parietal, and temporal regions, often leaving it unclear whether such areas may play functionally distinct roles (but see Humphreys et al., 2004; Kastner et al.,

1999; Pollmann et al., 2003; Shulman et al., 2003; Silvanto et al., 2006, for suggestions).

Experiment 3 showed common activations of bilateral fronto-parietal areas – including the FEF, IPS, and SPL – during attentional preparation for all the different kinds of trials, independent of target side, and of whether a distractor was expected to be present opposite the target or not. This concurs with many previous studies that have shown a general involvement of such structures in anticipatory attention and preparatory activity modulations in visual cortex (Hopfinger et al., 2000; Kastner et al., 2000; Macaluso et al., 2003). As a more novel and unexpected finding, Experiment 3 also found evidence for a specific involvement of distinct lateralized parietal and frontal structures during preparation for visual *distractors*. More specifically, the right angular gyrus and the left superior prefrontal gyrus showed higher activity during preparation for trials with distractors expected present versus expected absent (independent of anticipated distractor side), suggesting that these areas might implement preparatory neuronal processes that can specifically counter the impact of a subsequently presented visual distractor (for potentially related results in the context of visual search paradigms see also Humphreys et al., 2004; Pollmann et al., 2003). Apparently in accord with such a role for these regions in the resolution of visual competition, many clinical studies have shown that lesions of the right angular gyrus are involved in syndromes such as visual extinction, where patients miss contralesional stimuli particularly when competing stimuli are presented in the opposite visual hemifield (Driver et al., 1998; Duncan et al., 1999; Karnath et al., 2002; Milner & McIntosh, 2005). Lesions of prefrontal cortex have been found to impair performance in visual detection tasks (Barcelo et al., 2000), and prefrontal cortex has been proposed to play a general role in the top-down control of vision (Miller, 2000; Miller et al., 2005). The results presented in Chapter 3 now suggest a specific role for two of these particular regions (i.e., right angular

gyrus and left superior prefrontal gyrus) in *anticipatory* processes related to distractor exclusion. This proposal could be further tested in future TMS experiments of the behavioural paradigm introduced in Chapter 3, stimulating the right angular gyrus or left prefrontal regions (or their symmetric counterparts in the opposite hemisphere) during the preparatory interval where cues are administered that inform about subsequent distractor presence or absence. Such TMS might interfere with distractor-specific preparatory processes (as compared to TMS to a control site), and might thus eliminate the behavioural benefit associated with distractor foreknowledge, as found in Experiment 2. Moreover, examining such a design with the concurrent TMS-fMRI approach developed in the context of this thesis (see Chapters 4 and 6) might allow further conclusions about whether the anticipatory activity modulations in occipital cortex, contralateral to an expected distractor, may directly relate to the activation of right angular gyrus and/or left prefrontal regions. This could be inferred if the anticipatory effects on occipital distractor representations are systematically altered as a consequence of, say, right angular gyrus TMS during the preparatory interval, when compared to TMS to a control site.

The results of Chapter 3 also showed that a region in the right temporo-parietal junction may be specifically involved in preparatory attention for trials where *no* distracting stimulus is expected to appear. For such trials, the right TPJ region showed enhanced functional coupling (as determined with a PPI analysis) with the lingual gyrus regions activated by expectation of a contralateral target. This condition-specific enhancement of functional coupling may be broadly consistent with the emerging notion that the right TPJ may be involved in salience-driven orienting towards novel stimuli (Kincade et al., 2005; Downar et al., 2000; Pollmann et al., 2003). Setting up such orienting might be a good strategy to prepare the visual system for situations that can be anticipated to involve a single salient target stimulus, as opposed to anticipated scenes with several items that demand for

further attentional selection. It may also be noteworthy that the processes implemented by the TPJ were not expressed as an overall activity increase in this region (unlike the distractor-related results discussed before for the angular gyrus), but rather as enhanced *functional coupling* with those occipital regions that would subsequently process the expected isolated target. This distinction of increases in activation vs functional coupling may speak to a different causal involvement of the angular gyrus vs TPJ regions in the anticipatory activity modulations observed in occipital cortex, which could be tested directly in future experiments with the concurrent TMS-fMRI methodology described in Chapter 4 and 6. But independent of such further considerations, the present results clearly underline that attentional control processes implemented in areas outside occipital cortex can sometimes be highly *specific* in both a regional and functional sense. Moreover, such processes may already be triggered during the mere *anticipation* of situations (with distractors expected present or absent) where they may be required for efficient visual performance.

The question of whether specific frontal and parietal regions may be *causally* involved in activity modulation of visual areas was examined more directly in Chapters 4-6. Previous neuroimaging studies (e.g., see Chapter 3, and Hopfinger et al., 2000; Kastner et al., 2000; Macaluso et al., 2003) and some theoretical frameworks (Desimone et al., 1995; Duncan et al., 1997; Corbetta et al., 2002) had suggested such causal influences, but could not show them directly in the human brain due to the strictly correlative rather than interventionist nature of typical fMRI studies. Chapter 4 and Chapter 6 now demonstrated that direct TMS stimulation of the human FEF or IPS could indeed elicit BOLD systematic activity changes in retinotopic visual areas. These activity changes were specific to the stimulated site, as they were not present during stimulation of a control site (at the vertex), and were significantly different for the FEF and IPS stimulation sites in direct comparisons.

This shows that anatomical circuits originating in different frontal and parietal areas are indeed plausible sources of the activity modulations observed during visual selective attention, and may make different contributions. The psychophysical investigation described in Chapter 5 further underlined the point of potential causal influences, showing that the activity modulations observed in visual cortex during FEF TMS had corresponding functional consequences for visual perception. Moreover, the systematic effects of FEF TMS on perceived contrast closely resembled corresponding effects of visual attention on such judgments, as found in psychophysical studies (Carrasco et al., 2004).

Apart from providing general 'proofs-of-principle' that frontal and parietal brain regions may influence activity in visual cortex, the results of Chapter 4-6 also may give more specific information about the possible structure and anatomical connectivity of the stimulated sites. For instance, it was found that only the results of FEF TMS differentiated the central vs peripheral visual field. This implies that the human FEF (but perhaps not the IPS) may contain separate retinotopic representations of central and peripheral visual field locations, which may be connected with the corresponding parts of occipital visual areas via distinct projections. Such a distinction of the central and peripheral visual field in the FEF and its connections has in fact been found in tracing studies of the macaque brain (Schall et al., 1995; Stanton et al., 1995), while some initial results suggest that the *human* FEF may show some retinotopic organization (Hagler, Jr. et al., 2006). The present results clearly encourage further research into the structure and anatomical connectivity of the human FEF, using conventional neuroimaging methods as well as the concurrent TMS-fMRI approach introduced here. For instance, future studies may use whole-brain imaging extensions of the present method, to examine the precise neural pathways and intervening areas that may mediate the opposite effects on the central vs peripheral visual field representations in occipital cortex,

found here for FEF stimulation. Moreover, it may also be fruitful to vary the precise location of the TMS coil over regions such as the FEF (while taking into account the spatial resolution of TMS; see e.g., Walsh et al., 2000; Walsh et al., 2005), to examine whether this may target different neuronal populations having distinct patterns of connections with different sectors of retinotopic visual cortex. Such an approach might also be very interesting for the human IPS, where neuroimaging studies are starting to elucidate several potentially distinct sub-areas that may subserve distinct visual or visuo-motor functions (Schluppeck et al., 2006; Orban et al., 2006), apparently in close similarity to the functional parcellation of the IPS in the macaque brain (Colby & Goldberg, 1999; Andersen et al., 2002; Grefkes & Fink, 2005; Gottlieb, 2002). Finally, it may be interesting to study the potential influences of TMS to the FEF and IPS in the *left* hemisphere, as lesion studies in humans suggest some right-hemisphere predominance in networks for top-down (e.g., attentional) modulation of visual processing (Driver and Mattingley, 1998; Karnath, 2002; Mesulam, 1999). This notion could be addressed directly, by comparing the patterns of influences upon visual cortices elicited by TMS to the FEF or IPS in the right versus left hemisphere.

The results of chapter 4 and 6 also highlight that influences of regions in frontal and parietal cortex on visual processing may not be invariant, but can sometimes strongly depend on context. For instance, the effects of IPS TMS (but not those of FEF TMS) strongly depended on the presence or absence of concurrent visual stimulation. IPS TMS elicited activity increases in early visual areas V1-V4 only for trials with a blank screen, but led to activity decreases in V5/MT+ when moving and flickering visual stimuli were concurrently presented. This pattern of results suggests that parietal regions (such as the IPS) and their connections with visual cortex may be closely involved in the on-line coding of visual information, which may thus overshadow or modulate any influences of IPS TMS on neural activity in visual

cortex. Such a dependence of activity in parietal - but not frontal - regions on details of current visual processing has been suggested by several previous neuroimaging studies on preparatory visual attention (Kastner et al., 1999), visual search (Shulman et al., 2003), spatial working memory (Curtis, 2006), and eye movement control (Connolly et al., 2002). The results of chapters 4 and 6 now provide direct evidence that frontal regions may influence visual cortex in a more 'top-down' manner than parietal regions, as the FEF TMS results were equally present during the presence or absence of visual stimulation. This divergence of FEF and IPS results seems broadly consistent with the general assumption that activity in parietal cortex may reflect on-line computations about the current sensory environment (Andersen & Buneo, 2002; Colby et al., 1999; Macaluso et al., 2005), which necessarily take into account properties of the current visual input. Frontal regions, in contrast, may be involved in more *endogenous* aspects of action-planning or task-performance that may be more independent of the current environment, or may even have to 'override' present sensory input (Connolly et al., 2002; Miller, 2000). On the other hand, invasive single-unit recording studies have often emphasised the visual responsiveness of macaque FEF neurons (see e.g., Schall, 2004; Thompson, Bichot, & Sato, 2005). It may be interesting for future studies to examine whether the fMRI and psychophysical effects of FEF-stimulation may vary with more endogenous context factors that may specifically engage this frontal region, such as covert direction of spatial attention or eye movement preparation (Kayser & Logothetis, 2006).

At a more general level, the results of chapter 4-6 demonstrate how the on-line combination of TMS and fMRI may now be used to study causal interactions between different areas of the human brain, constraining the putative roles of different regions for visual selective attention. Such approaches might link otherwise apparently conflicting results obtained with different methods, for example in

neuroimaging vs lesion studies (see also Humphreys et al., 2001). Chapter 1 outlined that neuroimaging studies (such as fMRI) typically find increased activity during selective attention in fronto-parietal structures of both hemispheres (but see Serences et al., 2006), while clinical studies have emphasised that attentional deficits are most often found after lesions of such structures in the right hemisphere. Based on the latter observation, the experiments presented in this thesis applied TMS over right-hemisphere structures; but it may now be interesting to go on and examine the effects of stimulating homologous regions in the left hemisphere. Any remote effects on activity in visual cortex found to be specific for one of the stimulated hemispheres (e.g., only for the right) may indicate particular circuits that could underlie attentional deficits after lateralised brain damage, such as neglect or extinction (see also Hilgetag et al., 2001).

Moreover, the present thesis also introduced the approach of deriving psychophysical predictions from patterns of brain-activity changes during concurrent TMS-fMRI. This particular approach may also be extended further; for example, it may now be hypothesized that TMS of the IPS could impair motion perception, given the decreases in activity of bilateral V5/MT+ found during stimulation of this site, in the presence of moving visual stimuli (see Chapter 6). There are initial demonstrations that lesions of right IPS may lead to some impairments for aspects of motion perception (Battelli et al., 2001), but corresponding effects of TMS to this structure are unclear at present (though see Cowey, Campana, Walsh, & Vaina, 2006, for results from left-IPS TMS). Finally, the new methodical combinations introduced here to study functional interactions of fronto-parietal and occipital brain regions need not be limited to the study of selective attention, but could be usefully employed to address other questions in Cognitive Neuroscience, concerning how interplay between several brain areas may give rise to particular cognitive functions (such as executive control, working memory, social cognition, or numerosity). All

such fields of study could potentially benefit from the new perspective afforded by concurrent TMS-fMRI: the direct characterisation of functional interactions between remote but interconnected regions in the human brain.

Summary and Conclusions

The present thesis used a combination of fMRI, TMS, psychophysics, and concurrent TMS-fMRI, to examine mechanisms underlying visual selective attention in the human brain. Previous neuroimaging studies had found that selective attention can elicit spatially specific activity changes in visual cortex. The experiments described in the present thesis now dealt with questions related to the possible functional significance and the putative origins of such top-down activity modulations of visual areas.

With respect to the first of these questions, Chapter 2 used phosphene thresholds for occipital TMS to show that cortical excitability increased at a currently attended location. Chapter 4-5 showed that the topographic pattern of BOLD signal increases in retinotopic visual areas V1-V4 caused by FEF TMS allowed for the successful prediction of spatially specific enhancements for perceptual judgements. These results provide direct empirical support for the notion that BOLD increases in early retinotopic visual areas observed during selective attention may index spatially specific increases in cortical excitability. However, Chapter 3 showed that not all anticipatory BOLD increases in visual cortex may reflect enhancements of information that should receive further processing, but may also indicate anticipatory processes that minimize the impact of *distractor* stimuli. This underlines that top-down modulations of visual cortex during selective attention can be functionally diverse, and may relate to both enhancements of target processing and to influences on distractor processing.

With respect to the second set of questions concerning possible origins of top-down modulations for visual cortex, Chapters 3-6 showed that different regions in frontal and parietal cortex are physiologically plausible sources for such functionally distinct activity modulations in visual areas during selective attention. Chapter 3 showed a specific involvement of distinct fronto-parietal regions during preparatory spatial attention, as a function of whether distractors were expected to be present or absent in the subsequent visual scene. This may indicate specific attentional control processes devoted to countering the anticipated presence of a distractor. Chapters 4 and 6 showed that direct TMS stimulation of the FEF or the IPS elicited systematic and spatially specific patterns of influences upon activity in retinotopic visual areas V1-V4, plus V5/MT+. These TMS influences were not present for TMS to a vertex control site; were systematically different for the FEF and IPS TMS sites; differentiated the central and peripheral visual field only for FEF TMS; and depended on visual context only for IPS stimulation. Moreover, Chapter 5 showed that the FEF-TMS influences had direct functional consequences for visual perception. Taken together, these results indicate that projections from frontal and parietal areas in the human brain are indeed able of causally influencing activity in early retinotopic visual areas, in a fashion that is distinct for each site, and with some consequences for visual perception. These results provide a new line of direct empirical support for long-standing (but previously rather speculative) proposals in the literature on selective attention. They furthermore indicate possible differences in the nature of influences that frontal and parietal sites may have on retinotopic visual cortex in the human brain. Last but not least, the present thesis illustrates how the new approach of combining TMS with concurrent fMRI, and relating this to psychophysics, may now be used to study causal functional interactions between remote but interconnected areas of the human brain.

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