

**Balancing stimulus and goal-driven attentional demands:
Investigating the role of gamma oscillations in human early
visual cortex using magnetoencephalography**

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Table of contents

Table of contents.....	i
Thesis abstract.....	v
Statement	vii
Acknowledgements.....	viii
Author note	xi
Chapter 1 – General introduction	1
1.1 Balancing attentional demands	3
1.2 The effects of stimulus and goal-driven attentional demands on behaviour	5
1.3 Attentional processing in the brain	8
1.4 Oscillatory activity and attentional processing	23
1.5 Summary and conclusion	27
1.6 Approach in this thesis and overview of experimental chapters	27
1.7 References.....	30
Chapter 2 – Manipulating behavioural relevance of a salient item: an MEG experiment	49
2.1 Abstract	51
2.2 Introduction.....	52
2.3 Methods.....	55
2.4 Results	62
2.5 Discussion	75
2.6 Acknowledgements	81
2.7 References.....	82

Chapter 3 – Induced and evoked neural correlates of orientation selectivity in human visual cortex.....89

3.1 Abstract.....	91
3.2 Introduction	92
3.3 Materials and methods.....	94
3.4 Results	98
3.5 Discussion.....	111
3.6 Acknowledgements	116
3.7 References	117

Chapter 4 – Sustained visuo-spatial attention increases high-frequency gamma synchronisation in human medial visual cortex123

4.1 Abstract.....	125
4.2 Introduction	126
4.3 Results	129
4.4 Discussion.....	135
4.5 Materials and Methods	140
4.6 Acknowledgements	144
4.7 References	146

Chapter 5 – Investigating effects of stimulus salience and behavioural relevance on gamma synchronisation in early visual cortex155

5.1 Abstract.....	157
5.2 Introduction	158
5.3 Methods	161
5.4 Results	168

5.5 Discussion	183
5.6 Acknowledgements	189
5.7 References.....	190
Chapter 6 – General discussion	197
6.1 Overview of thesis	199
6.2 Overview and implications of findings	199
6.3 Discussion and outstanding questions.....	205
6.4 Summary and conclusions.....	220
6.5 References.....	221
Appendix 1.....	232

Thesis abstract

Salient events tend to capture our attention. When such events are irrelevant to something we are looking for they need to be inhibited not to distract us. Efficient allocation of attention involves balancing of attentional demands driven by both salient events and current goals. To deal with the constantly changing visual input in light of attentional goals, it is crucial that visual brain areas participate in this balancing. The aim of this thesis is to investigate the role of early visual areas in the balancing of stimulus and goal-driven attentional demands. I primarily focus on the synchronisation of oscillatory activity in the gamma band, because its role in both neural communication and visual processing makes it a prime candidate for mediating the dynamic balancing of attentional demands.

In Chapter 1 I review the literature on behavioural effects and neural processing of attentional demands. In Chapter 2, I focus on how evoked responses in early visual cortex are modulated when stimulus salience and behavioural relevance compete for attentional allocation. I then address how these factors interact to modulate gamma activity in three steps. In Chapter 3, I use a strong gamma-inducing stimulus to investigate how orientation, a stimulus property strongly represented in early visual cortex, affects the gamma response. In Chapter 4, I investigate how directing voluntary attention towards or away from that optimal stimulus affects the gamma response it induces. Finally, I address how stimulus and goal-driven factors combine to influence the gamma response when they compete for attentional allocation in Chapter 5.

The main findings in this thesis are that stimulus and goal-driven factors influence gamma synchronisation in early visual cortex at different frequencies, and interact to modulate the gamma response when attentional demands are actively balanced. These findings contribute to our understanding of the role of early visual cortex in both low-level and attentional visual processing. I address the implications of these findings in Chapter 6.

Statement

I certify that the research presented in this thesis has not previously been submitted for a higher degree nor has it been submitted as part of the requirements for a degree to any university or institution other than Macquarie University.

I also certify that this thesis presents my original work. I have appropriately acknowledged any help or assistance I received during the research presented in and the preparation of this thesis, as well as any sources of information I used.

The research presented in this thesis was approved by the Macquarie University Ethics Review Committee (Human Research), reference number: HE01MAY2009-D06471. The work performed at the Cardiff University Brain Research Imaging Centre (CUBRIC) was approved by the Cardiff University local Ethics Committee.

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Author note

All the work presented in this thesis has been performed under PhD candidature at Macquarie University. The experimental work reported in Chapter 2 was conducted completely at Macquarie University. The experimental work reported in Chapter 3-5 was performed in collaboration with the Cardiff University Brain Research Imaging Centre (CUBRIC) (School of Psychology, Cardiff University, Cardiff, Park Place, CF10 3AT Cardiff, United Kingdom). All work involved for Chapter 3 was completed at the CUBRIC. For Chapter 4 and 5, the data were collected at the CUBRIC, and were further worked on partially at the CUBRIC and partially at Macquarie University.

This thesis has been prepared in the form of a 'Thesis by Publication'. The reference style reflects the APA Publication Manual (6th edition), except Chapter 3 which has been referenced following the style of the journal it was published in (*NeuroImage*). Chapter 4 follows the formatting of the journal it was submitted to (*PNAS*). Due to the 'Thesis by Publication' format, there is a degree of repetition in some of the chapters, particularly in the Introductions. I have tried to avoid repetition as much as possible whilst still allowing each chapter to stand on its own. I am first author on the work of each experimental chapter.

Chapter 1 – General introduction

General introduction

1.1 Balancing attentional demands

In everyday life, we are continuously subjected to a multitude of visual information. To make sense of all this information, we need to selectively focus on things that are relevant to a current goal, while ignoring irrelevant information. For example, if we are searching for our keys on a cluttered table, we need to voluntarily shift our attention from object to object to find them. We may be able to improve our efficiency by selecting objects with certain features (e.g., key-shaped, metallic) and ignoring others that do not match our feature-set (e.g., a coffee cup). At the same time as these voluntary shifts of attention, we need to avoid being distracted by sudden, unexpected, or otherwise salient irrelevant events or objects. During our key search, an insect might fly close to us. If this is a bee or a wasp, this event is important to pay attention to, and we should halt our key search to avoid getting stung by the insect. The fact certain events can capture our attention involuntarily is a useful and necessary means of signalling danger. However, often, such events are not relevant to our current goal. If the insect is a fly, we need to continue our key search, it is an irrelevant distraction. If we were constantly distracted by irrelevant events, we would never achieve our goals. Thus, the success of carrying out visual tasks and reaching our goals depends on the balance between voluntarily directed attention to goal-relevant items and attention that is involuntarily captured by sudden or prominent ('salient') items in the environment (Jonides, 1980; Posner, 1980; Remington, Johnston, & Yantis, 1992; Yantis, 1993). The outcome of this balance allows us to 'guide' our attention to the event with greatest priority at a particular time (Wolfe, 1994).

To successfully balance stimulus and goal-driven attentional demands, correct functioning of brain areas involved in visual processing is crucial. For example, damage in certain brain areas can cause trouble detecting visual events and directing attention to regions of the visual field (Corbetta & Shulman, 2002), or inability to inhibit irrelevant salient items (Friedman-Hill, Robertson, Desimone, & Ungerleider, 2003). In the brain, visual information processing is orchestrated by a large network of areas. Within this network, two 'flows' of information processing can broadly be distinguished that match the processing of stimulus-driven and goal-

driven demands. Visual information that arrives at the retina of the eye first reaches the cortex in the occipital lobe. The occipital lobe contains several areas which are specialised in processing visual input. Early visual areas analyse very detailed information (e.g., lines, corners, contrasts), and project this information to higher visual areas, which then gradually process more global information (e.g., parts of objects or whole objects). From higher visual areas, visual information is passed on to other brain areas, where further processing takes place. Because this path of visual information processing flows from the outside world to simple visual areas, to brain areas that process more complex information, this is often referred to as ‘bottom-up’ processing. In contrast, brain processing of goal-driven attentional signals is thought to start in frontal and parietal areas. These regions send signals that influence activity in the visual areas (Bisley, 2011), and this opposite flow of information is therefore called ‘top-down’ processing.

These opposite flows of information processing need to communicate with each other, to mediate the dynamic balance of the constantly changing visual input with current goals and efficiently guide attention. To enable efficient processing of incoming visual information, it would be optimally efficient if all brain areas involved in visual processing participate in the balancing of these attentional demands and communicate this information to each other. There is clear evidence for a critical role of parietal and frontal regions in the processing of both stimulus-driven factors, such as signalling the presence of physically salient items, and the control of goal-directed attention (Baluch & Itti, 2011; Corbetta & Shulman, 2002). This suggests that these areas are crucial for orchestrating the balance of these competing attentional demands. There is also evidence of a similar role for higher visual areas (e.g., Reynolds & Desimone, 2003). However, whether earlier visual areas play a role in this system of balancing stimulus and goal-driven attentional demands is less clear.

In this thesis, I investigate how stimulus properties and goal-driven demands influence activity in early visual areas by comparing situations in which these types of information are presented separately, and when they are competing for attentional allocation. I focus on the role of oscillatory neural activity in the gamma range (30-70 Hz) because this type of neural activity is thought to play a crucial role in neural communication (Fries, 2005; Schnitzler & Gross, 2005), as well as a functional role in visual processing (Friedman-Hill, Maldonado, & Gray, 2000).

In this introduction, I will first review the literature on how attentional processes influence behaviour. Then, I will provide an overview of how attentional processes influence neural activity. I will highlight converging animal and human evidence showing that early visual areas play a prominent role in attentional selection. I will conclude with open questions regarding attentional processing in early visual areas and how I have approached these questions in this thesis.

1.2 The effects of stimulus and goal-driven attentional demands on behaviour

A widely-used paradigm measuring the effects of stimulus and goal-driven information on attention is the visual search paradigm (Treisman & Gelade, 1980; Wolfe, 1994). In visual search, multiple, usually simple, items are presented in a visual display and subjects are asked to find one target item with a specific feature, or combination of features (such as colour, orientation, or shape). When the target differs in only one feature from a homogeneous array of distractors (e.g., a red line amongst green lines), it appears to ‘pop-out’ of the display and captures attention, irrespective of the number of distractors. In contrast, it takes time and effort to find a target that is defined as a conjunction of two or more features in a heterogeneous display of distractors randomly containing either of those features (e.g., a red vertical line amongst red horizontal and green vertical lines). This effortful search is reflected in the increase of reaction times with an increase in the number of items (set size, Treisman & Gelade, 1980; Wolfe, 1994).

In the pop-out case, the unique target (or ‘singleton’, Müller, Heller, & Ziegler, 1995; Pashler, 1988) is both the goal of the search and the item that attracts attention involuntarily, whereas a conjunction search requires making attentional shifts from item to item to actively search for the target in the absence of such salient cues. The efficiency of a pop-out stimulus in guiding search highlights how stimulus-driven factors can capture attention. Stimulus-driven attentional capture can also be seen in more effortful search (Theeuwes, 1991, 1992; Theeuwes & Burger, 1998), for items that appear suddenly (Yantis, 1993; Yantis & Jonides, 1984), in paradigms using a cue to direct attention towards a distractor location before the search display appears (Remington et al., 1992), and when a physically salient item is embedded in a stream of items that are presented in

series in one location (rapid serial visual presentation, RSVP, Folk, Leber, & Egeth, 2002; Maki & Mebane, 2006). A salient target can be found within 50 ms, showing that stimulus-driven capture can guide attention very rapidly (Müller & Rabitt, 1989). These converging findings suggest that bottom-up physical stimulus factors play an important role in efficiently guiding attention.

Directing attention voluntarily, based on goal-driven factors, can also strongly influence which stimuli in a visual display are attended. For example, a target that appears at a pre-cued location is identified faster than a target that is preceded by a cue directing attention elsewhere, with performance in between if the cue is spatially uninformative (Jonides, 1980) or there is no cue (Posner, 1980). These advantages and disadvantages of directing attention to locations ('spatial attention') are much reduced when it is known that the cue has low validity (Jonides, 1980). Attention can similarly be voluntarily directed to a certain feature, facilitating search for items that share this feature across the visual field, irrespective of their location ('feature-based attention')¹. Voluntarily directing attention can facilitate target processing within 30 ms if the target is a singleton (which may of course be partially due to stimulus-driven guidance), and within 60 ms if the target requires the conjunction of features (not driven by stimulus factors, Kim & Cave, 1995). Thus, in addition to involuntary stimulus-driven attentional capture, voluntarily directing attention to goal-relevant items or locations is also an important determiner for the allocation of attention, with similar early effects.

The important role of goal-driven factors in attentional selection is highlighted by the fact that stimulus-driven attentional capture can in many instances be avoided if the salient item is not behaviourally relevant for target search (Yantis, 1993; Yantis & Egeth, 1999). Capture by a salient item will often only take place if it appears in a relevant location (Yantis & Jonides, 1990) or shares a feature with the target (Folk & Remington, 2006; Folk, Remington, & Johnston, 1992;

¹ Next to spatial-based and feature-based attention, a third type of voluntary attention is often distinguished. This type refers to attention to whole objects or parts of objects (object-based attention), although the distinction between feature-based and object-based attention is not always clear. This thesis focuses on simple stimulus properties in low-level vision. I will therefore not further discuss object-based attention.

Folk, Remington, & Wright, 1994). Top-down control can also overcome bottom-up capture when a salient item shares more global aspects with the target such as being an onset item (Yantis, 1993) or a singleton (Bacon & Egeth, 1994) regardless of feature or modality. Top-down control of attentional capture is evident even in very simple visual search tasks (Leonard & Egeth, 2008; Wolfe, Butcher, Lee, & Hyle, 2003), suggesting that it does not require a demanding task for top-down guidance to be deployed. Moreover, top-down factors can overcome bottom-up capture very rapidly. For example, Kim and Cave (1999) asked subjects to search a display containing several items including one singleton distractor to determine the presence or absence of a unique target. Subjects also had to respond to a probe which was present at one of the locations at a variable time after the stimulus display had disappeared. If the probe appeared at the same location as the target, subjects were fastest at detecting the probe at longer interval times (150 ms), whereas they were fastest at detecting the probe when it appeared at the location of the salient distractor at the shorter interval times (60 ms). This suggests that salient items capture attention initially, and top-down factors ‘take over’ at slightly later times. However, practising this task for a long time avoided attentional capture by the salient distractor, showing an early influence of goal-driven factors. Moreover, in a follow-up experiment, Lamy, Tsai, and Egeth (2003) showed that attention was not captured by the irrelevant salient distractor if the target was a feature conjunction item instead of a singleton, even at the 60 ms stimulus-probe interval. These findings suggest that top-down factors can rapidly prevent attentional capture under certain circumstances and thus exert an influence early in visual processing.

Despite strong goal-driven attentional guidance, attentional capture by physical stimulus factors is not always successfully overcome (Chen & Cave, 2006; Theeuwes, 1992, 2004; Theeuwes & Burger, 1998; Theeuwes, Reimann, & Mortier, 2006). For example, the success of top-down control is influenced by search strategies (Leber & Egeth, 2006; Leonard & Egeth, 2008), and even when a non-target item falls within the behaviourally relevant search, salience still plays a role in determining the ability of an irrelevant item to capture attention (Folk et al., 1994). There has been, and still is, extensive debate on whether attentional capture is automatic and always occurs first whenever a salient item is present (see Theeuwes (2010) for a current review), or whether this is completely dependent on being behaviourally relevant, and thus part of the

attentional goal or ‘set’ (see Egeth, Leonard, and Leber (2010) for a reply). Regardless of this debate, these findings together strongly suggest that both stimulus-driven and goal-driven factors can guide attention at an early stage in visual processing, and imply that these factors are combined (or balanced for priority) to guide attentional allocation in visual tasks, allowing us to efficiently interact with our visual environment.

1.3 Attentional processing in the brain

1.3.1 The visual system

Visual information falling onto the retina is projected via the Lateral Geniculate Nucleus (LGN) of the thalamus to the primary visual cortex (also called V1, or striate cortex) located medially in the calcarine sulcus of the occipital cortex. Visual processing is relatively straightforward in V1, reflecting simple stimulus properties such as orientation and location, at least immediately after stimulus onset (<100 ms, Lamme & Roelfsema, 2000). The primary visual cortex maintains the spatial organisation of the visual field as it falls onto the retina (retinotopy). The simplicity and retinotopic organisation of responses in the primary visual cortex makes it ideal for investigating how bottom-up stimulus-driven factors modulate responses, particularly if stimuli contain properties V1 cells are highly responsive to, such as orientation (Hubel & Wiesel, 1963; Hubel, Wiesel, & Stryker, 1978). Processing gets progressively more complex in more anterior and lateral ‘higher’ brain areas (Van Essen & Maunsell, 1983), which is reflected physiologically, in terms of larger receptive fields (the area of the visual field a cell responds to); anatomically, in terms of more complex connectivity; and functionally, as areas are more responsive to complex feature and object processing.

This progressive divergence in functional anatomy suggests that integration of information may occur higher up in the processing chain, in higher visual areas or outside the visual cortex. However, the behavioural evidence for an early interplay of bottom-up and top-down information presented above suggests integration can have effects very early in visual processing and might therefore involve early visual areas. Below, I will first review evidence for attentional modulation of activity throughout brain areas involved in visual processing in monkeys and humans. Then, I

will present findings of interactions of bottom-up and top-down factors that have been reported in higher parietofrontal and visual areas, and how these areas feed back this integrated information to early visual cortex.

1.3.2 Attentional modulations throughout the visual cortex

1.3.2.1 Measuring firing rate changes using monkey single-cell recording

Throughout the visual cortex, attention is associated with enhanced neural responses: the amplitude of cell responses increases and the tuning towards preferred features becomes sharper (Maunsell & Cook, 2002). In single-cell recording studies, monkeys receive a reward for correct eye movements or button presses to a target in a stimulus display following a directional cue or instruction (e.g., Motter, 1993). A stimulus that falls within the receptive field of a cell will excite this cell, increasing its firing rate (the rate at which electrical signals are transmitted onto connecting cells), whereas a stimulus outside the receptive field will not excite the cell. Directing attention towards the stimulus within the receptive field increases firing rates further, compared to when attention is directed to a stimulus in a different location. These location-related attentional enhancements have been observed for neurons in visual areas V1 (McAdams & Maunsell, 1999; McAdams & Reid, 2005; Motter, 1993), V2 (Luck, Chelazzi, Hillyard, & Desimone, 1997; Motter, 1993), V4 (Luck, Chelazzi, Hillyard, & Desimone, 1997; McAdams & Maunsell, 1999; Motter, 1993; Reynolds, Pasternak, & Desimone, 2000), and the middle temporal area (MT; Treue & Maunsell, 1996). In V2 and V4, some increase in firing rate can even be seen in the pre-stimulus baseline period, when attention is already directed towards a location where a stimulus is expected (Luck et al., 1997; Reynolds et al., 2000; but not in V1, Luck et al., 1997). Thus, attending to a location increases firing rates of cells with receptive fields corresponding to the attended location, regardless of whether a stimulus is present in that receptive field.

Attention towards features can also increase firing rates. If a stimulus that shares the attended feature is present in the receptive field of a cell, its firing rate is increased compared to when a stimulus does not share this feature. These feature-related enhancements are independent of

spatial location² and have been found in V1 (Haenny & Schiller, 1988; McAdams & Maunsell, 1999), V4 (Haenny & Schiller, 1988; Maunsell, Sclar, Nealey, & DePriest, 1991; McAdams & Maunsell, 1999; Motter, 1994), and MT (Katzner, Busse, & Treue, 2009; Treue & Martinez Trujillo, 1999). Although these effects of feature-based attention seem very similar to effects of spatial-based attention, spatial-based attention is expressed in a serial manner (a ‘spotlight’, which shifts from item to item, Posner, Snyder, & Davidson, 1980), and feature-based attention in parallel across the visual field (more like several simultaneous spotlights, Desimone & Duncan, 1995). This difference in attentional deployment to locations and features suggests that different neural mechanisms underlie these attentional mechanisms, possibly involving different neural networks. Moreover, spatial and feature-based attentional effects can combine additively (at least in MT; Treue & Martinez Trujillo, 1999), and may interact to modulate neural firing in areas such as V4 (Bichot, Rossi, & Desimone, 2005; McAdams & Maunsell, 2000). Thus, spatial and feature-based attention are both effective ways of enhancing neural responses to stimuli and are likely to interact or compete with each other to determine priority of stimuli for attentional allocation.

The correspondence of increased neural firing rate and the advantage in behavioural performance of directing attention to a stimulus suggests that increased neural firing reflects enhanced stimulus processing. However, this increase does not explain the disadvantage for items that are actively unattended (or ignored) compared to a ‘neutral’ item that is neither attended nor ignored (Jonides, 1980; Posner, 1980). If neural firing reflects stimulus processing, changes in firing should correspond to this behavioural trend. There is indeed a reduced response when attention is directed away from the location of a stimulus, but this seems to require competition between two or more stimuli (Moran & Desimone, 1985). In their classic study, Moran and Desimone (1985) showed that even in the presence of the preferred stimulus for a particular

² McAdams and Maunsell (1999) used a matching-to-sample paradigm where monkeys had to discriminate items containing different features in each side of space separately. The authors note that it is not clear whether the attentional modulations were due to spatial or feature-based attention, or a combination of both. In contrast to the other studies cited above, it cannot be claimed for this study that feature-based attention is independent of spatial location.

neuron, directing attention towards a different item within the receptive field reduces the response as if the preferred stimulus is not present. Importantly, this is only observed if the two items are both within the receptive field; there is no such modulation when the non-preferred item is outside the receptive field even when the items have the same physical separation. This was found for cells in V4 and the inferotemporal cortex (IT), and was later replicated for V2 and V4 cells by Luck et al. (1997). Such a decrease for unattended items compared to an increase for attended items is similarly present for feature-based attention effects in MT: MT cells reduce their firing rates in response to their preferred stimulus if a stimulus with a different feature is attended elsewhere in the visual field, and this decrease scales gradually with the degree of difference from the preferred feature (Martinez-Trujillo & Treue, 2004). In contrast to the spatial attention decrease, however, this feature-based decrease does not require stimulus competition within the receptive field.

In contrast to these attentional enhancements and suppressions in higher visual areas, such effects are not always found in monkey V1 (Luck et al., 1997; Moran & Desimone, 1985). This absence has been explained by the need for stimulus competition, which cannot be achieved in V1 because receptive fields are too small to encompass two items (Luck et al., 1997; Moran & Desimone, 1985). Supporting this notion, attentional modulations have consistently been found to be much stronger when stimuli are competing for attention within one receptive field in areas V2 and V4 (Reynolds, Chelazzi, & Desimone, 1999), and MT (Treue & Maunsell, 1996). In at least one of these studies, however, stimulus competition cannot explain the lack of V1 effects. Luck et al. (1997) failed to find even baseline modulations in V1 in the absence of stimuli, whereas these modulations did occur in V2 and V4. Moreover, although attentional modulations are of a much smaller magnitude in V1 than in higher visual areas (Haenny & Schiller, 1988; McAdams & Maunsell, 1999; Treue, 2001), increases in V1 neuron firing rates due to attention have been found, even without closely-positioned competing stimuli (Haenny & Schiller, 1988; McAdams & Maunsell, 1999; McAdams & Reid, 2005; Motter, 1993). To summarise, then, stimuli competing for attention within one receptive field can modulate and strongly enhance attentional effects (Bisley, 2011), and this may be particularly pronounced for suppressive effects of unattended items. However, attentional modulations can occur in the absence of close stimulus competition along the visual processing pathway. These occur in the same manner throughout the cortex,

including V1, and effects get stronger as more information becomes available along the path of processing.

1.3.2.2 Converging and additional findings using non-invasive human neuroimaging

Attentional modulations have also been measured in human cortex. In humans, electrophysiological brain responses can be measured non-invasively with electroencephalography (EEG) or its magnetic equivalent, magnetoencephalography (MEG). EEG measures fluctuations in the voltage potential through a number of electrodes placed on the scalp arranged in a cap or grid, and aided by a conductive gel. MEG measures tiny fluctuations in the magnetic field at the scalp and requires superconducting sensors that are supercooled by immersing them in liquid helium. These sensors are arranged in a helmet-shaped device, which is placed in a magnetically shielded room to reduce interfering magnetic signals from the environment as much as possible. Both MEG and EEG can measure fluctuations with great temporal precision in the order of milliseconds. EEG has the advantage that sensors can be placed close to the scalp and adjusted to the individual's head shape, and is fairly low-cost to run and maintain. MEG has a better spatial resolution, because it suffers less from signal smear than EEG. Magnetic fields go straight through intervening tissues rather than travelling the path of least resistance, which makes the inverse calculation of the sources that generated the measured fluctuations at the scalp more straightforward, although by no means unique (Baillet, Mosher, & Leahy, 2001; Singh, 2006). This additionally makes MEG less prone to artefacts caused by tiny fluctuations in eye movements (microsaccades) that have been argued to cause certain changes in visual cortex activity (Schwartzman & Kranczioch, 2011; Yuval-Greenberg, Tomer, Keren, Nelken, & Deouell, 2008).

Human neural activity can alternatively be measured with neuroimaging techniques that have a much greater spatial resolution, such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI). These methods measure changes in the regional cerebral blood flow, by means of an injected radioactive tracer in PET, and the ratio of saturated versus unbound oxygen-carrying haemoglobin molecules (the blood-oxygen-level-dependent (BOLD) response) in fMRI. Both techniques are based on the assumption that enhanced neural activity in a region requires an increased flow of oxygen and nutrients carried by the blood

(Logothetis, 2002). These techniques are therefore referred to as ‘indirect’ measures of neural activity, as opposed to EEG and MEG, which are said to measure neural activity ‘directly’³. Because changes in blood flow in response to enhanced activity in a neural region has a delay in the order of seconds, PET and fMRI have a much lower temporal resolution than EEG and MEG.

Early EEG studies have characterised the average time-locked electrophysiological response (Event Related Potential, ERP) to a visual stimulus as the Visual Evoked Potential (VEP) (Halliday, 1982; Odom et al., 2004). The VEP consists of three consecutive amplitude fluctuations at occipital electrodes. The first is a negative deflection 50-75 ms after stimulus onset (N75). The second is a positive deflection around 100 ms (P100). The final peak is a negative deflection at 145 ms (N145). The three main fluctuations are often alternatively described by their chronological occurrence and scalp localisation or polarity: C1 (the first fluctuation, located at central electrodes), P1 (first positive deflection), and N1 (first negative deflection, e.g., Mangun, Hillyard, & Luck, 1993). These three components are very similar in the MEG signal, and have been termed N75m (sometimes occurring at 50 ms⁴), P100m, and N145m, respectively (Nakamura et al., 1997), although sometimes the P100m is not visible (Tabuchi et al., 2002). Using MEG, the sources of the first two components have been localised to striate cortex contralateral to the visual field location of the stimulus (Nakamura et al., 1997; Tabuchi et al., 2002), whereas the later component has been found to originate in striate (Tabuchi et al., 2002) or extrastriate cortex (Nakamura et al., 1997).

³ These direct and indirect denominations are based on conventions in the neuroimaging literature.

However, any non-invasive neuroimaging method is essentially indirect. MEG and EEG are direct measures of neural activity in terms of measuring the electromagnetic activity elicited by active neurons as opposed to an indirect deflection of this such as changes in blood flow or composition. However, they are indirect in terms of measuring bulk activity at the scalp. The only really direct measures of neural activity are single-cell or intracranial recordings.

⁴ The variety in component times of the VEP is likely due to the convention that the VEP, and other ERP components, are sometimes referred to and named according to the times their *peak* occurs, and sometimes according to the time of the *onset* of the fluctuation from baseline.

The sources of all components follow the retinotopic organisation of the visual field (Tabuchi et al., 2002).

Similar to monkey studies, human ERP studies show increased amplitudes of activity contralateral to a stimulus that is attended versus unattended, and decreased amplitudes ipsilateral to this stimulus (Luck, Fan, & Hillyard, 1993; Mangun et al., 1993). These increases have been shown both with spatial cueing paradigms (Mangun, Buonocore, Girelli, & Jha, 1998; Mangun et al., 1993), sustained cueing paradigms (i.e., attending one hemifield per block, Clark & Hillyard, 1996; Heinze, Luck, Mangun, & Hillyard, 1990; Mangun & Hillyard, 1988), with visual search tasks (Hillyard & Münte, 1984; Luck et al., 1993), and also for feature-based attention (Anllo-Vento, Luck, & Hillyard, 1998; Zhang & Luck, 2009). Increased amplitudes associated with attentional processes have been found for components 90-100 ms post-stimulus onset (Anllo-Vento et al., 1998; Hillyard & Münte, 1984; Mangun & Hillyard, 1988), particularly the P1 and N1 (Clark & Hillyard, 1996; Heinze et al., 1990; Luck et al., 1993; Mangun et al., 1998; Mangun et al., 1993; Zhang & Luck, 2009), whereas latency is not affected. These amplitude modulations due to attention happen regardless of stimulus properties (Hillyard & Münte, 1984), and correlate with performance (Mangun & Hillyard, 1988).

In contrast with the P1 and later components, the earliest C1 VEP (or M1 MEG component) is not affected by either spatial (Clark & Hillyard, 1996; Di Russo, Martínez, & Hillyard, 2003; Martinez et al., 1999; Noesselt et al., 2002) or feature-based attention (Anllo-Vento et al., 1998). The C1/M1 starts 50-55 ms post-stimulus onset and has a source in contralateral striate cortex (Clark & Hillyard, 1996; Di Russo et al., 2003; Martinez et al., 1999; Noesselt et al., 2002). The C1/M1 is therefore thought to reflect the earliest feedforward sweep of bottom-up information flow. In line with this suggestion, this early component is affected by an irrelevant change in colour of a stimulus (Anllo-Vento et al., 1998). These findings suggest that attentional processes can influence activity early on in visual processing, but do not modulate the earliest part of the feedforward sweep. Combined with the localisation of both the C1 and P1 components to striate cortex (Nakamura et al., 1997; Tabuchi et al., 2002), this therefore suggests that activity in primary visual cortex is modulated by attentional processes via top-down feedback connections from other brain areas.

The limited spatial resolution of MEG and EEG leaves considerable uncertainty concerning source localisation. Studies combining M/EEG with PET or fMRI have greatly contributed to localising the sources of these M/EEG attentional effects. For example, one PET study showed convergence between spatial-based attentional modulations of both the early P1 and PET activity of the fusiform gyrus, which proved a good fit for modelling the source of the P1 ERP (Heinze et al., 1994). Several fMRI studies confirmed this extrastriate source, adding the middle occipital gyrus to the fusiform gyrus as the source underlying the spatial P1 modulation (Mangun et al., 1998; Martinez et al., 1999; Noesselt et al., 2002). Thus, combining M/EEG with techniques with greater spatial resolution suggests that the attentional P1 modulations may in fact reflect modulations in extrastriate areas.

Despite the P1 being localised to extrastriate areas, several of these combined EEG-fMRI studies, and other fMRI studies have found that spatial attention modulates the response of V1 to stimuli (Gandhi, Heeger, & Boynton, 1999; Martinez et al., 1999; Noesselt et al., 2002; O'Connor, Fukui, Pinsk, & Kastner, 2002; Tootell et al., 1998). Combined ERP and fMRI studies have replicated the absence of attentional effects on the earliest C1 ERP (Martinez et al., 1999; Noesselt et al., 2002), which supports the notion that effects of spatial attention in V1 do not reflect modulation of the feedforward sweep, but are most likely due to feedback projections from higher brain areas. In fact, Noesselt et al. (2002) found a temporal marker for this later V1 activation at 140-250 ms post-stimulus onset, using MEG in addition to EEG and fMRI. Di Russo et al. (2003) confirmed the V1 localisation of this later activity, by showing polarity inversion of this later attentional effect for upper and lower visual field presentations, excluding the possibility that this component was due to a poorly modelled V2 source.

Like ERP studies, these fMRI studies also mirror the attentional increases found in monkey studies. Increases in the BOLD response due to directing attention to locations or features have been observed throughout the visual cortex (e.g., V1, V2, V3, V4, MT, IT), but are smaller in V1 than in subsequent visual areas (Kastner, De Weerd, Desimone, & Ungerleider, 1998; O'Connor et al., 2002; Saenz, Buracas, & Boynton, 2002; Tootell et al., 1998), and follow the retinotopy of the cortex (Tootell et al., 1998). The strongest effects seem to occur when multiple stimuli compete for attention (Kastner et al., 1998), and effects have also been observed in the pre-stimulus baseline

period (Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; O'Connor et al., 2002; Saenz et al., 2002)⁵. Furthermore, areas contralateral to unattended locations display a decreased BOLD response (O'Connor et al., 2002; Serences & Boynton, 2007; Tootell et al., 1998), reflecting the facilitating and inhibiting effects of directing attention towards or away from stimuli, respectively. However, decreases in activity with fMRI are hard to interpret, because one cannot exclude the possibility that these are a secondary effect of increased blood flow at active sites (Tootell et al., 1998). In summary, findings in both ERP and fMRI studies converge with the major findings of monkey research showing that attentional effects can modulate activity throughout the visual cortex, and that effects in early visual cortex are due to feedback from higher visual areas.

1.3.3 The parietofrontal network

1.3.3.1 Attentional modulation in parietofrontal areas

Modulatory attentional signals in visual areas are likely to come from subregions in parietal and prefrontal areas, which have traditionally been proposed to mediate the top-down control of attention (Corbetta & Shulman, 2002; Desimone & Duncan, 1995). Two parietofrontal areas in particular that play a clear role in planning and directing saccadic eye movements seem to play a similar role in directing covert attention. The monkey Lateral Intraparietal Area (LIP), a subpart of the Posterior Parietal Cortex (PPC), is active before and during saccades (Andersen, Brotchie, & Mazzoni, 1992), even in the absence of a visual stimulus and also when attending to an item that does not require a saccade (Colby, Duhamel, & Goldberg, 1996). The Frontal Eye Fields (FEF), an area within the prefrontal cortex (PFC), serves a similar purpose as the LIP. The FEF is retinotopically organised and contains cells that are responsive to visual stimuli, cells that fire during the planning of saccades, and cells that fire in response to both visual stimuli and saccade planning (Bruce & Goldberg, 1985). FEF cells are particularly responsive to visual stimuli that are targets for a saccade or covert attention.

⁵ Unlike the monkey study by Luck et al. (1997), baseline modulations in the human fMRI study by Kastner et al. (1999) included V1.

Microstimulation of LIP and FEF cells generates saccades (Bruce, Goldberg, Bushnell, & Stanton, 1985; Cutrell & Marrocco, 2002), highlighting their crucial role in eye movement control. However, inactivating either the LIP or FEF by injecting the GABA_A antagonist muscimol has effects beyond impairing saccades. Inactivation in these areas also leads to deficits in covert attention, showing that both the LIP and FEF play a causal role in mediating covert attention (Wardak, Ibos, Duhamel, & Olivier, 2006; Wardak, Olivier, & Duhamel, 2004). In humans, increased fMRI activity in the parietal and frontal cortex is associated with voluntary shifts in spatial attention (Corbetta & Shulman, 2002), particularly in the intraparietal sulcus (IPS) (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000), located very close to the LIP, and considered its human homologue (van Essen et al., 2001). Most of the network is specifically tuned to aspects of spatial-based attention, particularly its dorsal areas (including the IPS). However, some ventral areas are more responsive when feature-based attention is deployed (Giesbrecht, Woldorff, Song, & Mangun, 2003).

Both the LIP and FEF also reflect the behavioural relevance of visual stimuli, further supporting a role in the top-down direction of attention. Parietofrontal areas are activated very rapidly (~ 30 ms) in response to visual input (Foxy & Simpson, 2002). The LIP responds specifically to a physically salient or behaviourally relevant item that is brought into its receptive field by a saccade, or when the item is already in the receptive field and is assigned a behaviourally relevant role by means of a feature-based cue making it the next saccade target (Gottlieb, Kusunoki, & Goldberg, 1998). LIP activity correlates with a monkey's attentional performance (Bisley & Goldberg, 2003) and is increased in response to a stimulus that is attended based on location, or both feature and location compared to a neutral or unattended location (Saalmann, Pigarev, & Vidyasagar, 2007). The FEF is similarly responsive to the planning of directing spatial attention based on the salience and behavioural relevance of items (Thompson & Bichot, 2005). Thus, the LIP and FEF are important for the top-down control of attention including, but not limited to, saccade planning and reflect the behavioural relevance of items as they are spatially distributed in the visual field. Together with the subcortical Superior Colliculus (SC), which shows similar characteristics (Cavanaugh & Wurtz, 2004; Ignashchenkova, Dicke, Haarmeier, & Thier, 2004; McPeck & Keller, 2004), these areas have been proposed to represent a 'salience map'

(Gottlieb et al., 1998; Thompson & Bichot, 2005), or ‘priority map’ (Fecteau & Munoz, 2006; Ipata, Gee, Bisley, & Goldberg, 2009) reflecting the use of salient information for guiding overt or covert attention in space.

1.3.3.2 How are bottom-up and top-down information combined in the brain?

The concept of a salience or priority map reflects a combination of physical stimulus salience and top-down factors such as behavioural relevance (Fecteau & Munoz, 2006). This suggests that the parietofrontal network plays an important role in combining these types of information to determine the priority of visual items for attentional allocation. This can be viewed as weighing or balancing bottom-up factors such as salience with top-down goals, and thus serves a function of integrating these types of information. The extensive interconnection pattern of these areas with each other and with visual cortical and subcortical areas makes it ideal for such an integrating role (see Baluch and Itti (2011) for a review). Visual information from the retina can reach the cortex indirectly via the SC and the pulvinar nucleus of the thalamus, which in turn reaches the LIP via several routes. From the LIP, signals are projected to the PFC via the FEF or via higher visual areas. The PFC in turn sends feedback projections to the FEF, visual areas, SC, and other subcortical areas. The FEF also feeds back to the SC and V4 (Baluch & Itti, 2011; Bisley, 2011; Blatt, Andersen, & Stoner, 1990; Corbetta & Shulman, 2002). Thus, the functional evidence and anatomical connectivity of parietofrontal areas FEF, SC, and in particular LIP/IPS suggest that these areas are ideally situated to orchestrate the flow and integration of bottom-up and top-down signals.

Evidence for an integrating role for parietofrontal cortex comes from studies using tasks that include a behaviourally irrelevant but physically salient item. In monkeys, cells in the LIP/IPS increase their firing rate in response to an irrelevant singleton embedded in a field of other irrelevant items compared to a homogeneous field, almost to the degree of the response to a single item within their receptive field (Constantinidis & Steinmetz, 2005). This suggests that besides its presumed top-down role, the parietal cortex also codes for salient items based on bottom-up information. However, when a salient distractor item is actively ignored, it evokes lower spiking activity in monkey LIP than a non-salient distractor (Ipata, Gee, Gottlieb, Bisley, & Goldberg,

2006). A non-salient distractor in turn evokes lower spiking activity than a target item, but only when this non-salient distractor is successfully suppressed. This difference is evident after approximately 90 ms, supporting an early involvement for the LIP in top-down and bottom-up integration.

In humans, similar findings have been reported supporting a dual involvement of the parietal and frontal cortex in bottom-up and top-down information processing. Human bilateral superior parietal activity, as well as activity in the lateral precentral gyrus of the frontal lobe, has been associated with the presence of an irrelevant singleton (de Fockert, Rees, Frith, & Lavie, 2004). Furthermore, the BOLD response in IPS and the ventral frontal cortex is enhanced to a spatially unattended item sharing a feature with the attended stimulus compared to a similarly salient but irrelevant unattended feature (Serences et al., 2005; Serences & Yantis, 2007). However, the findings of these fMRI studies can alternatively be explained by the need for a spatial shift of attention. More convincing evidence in humans comes from lesion and Transcranial Magnetic Stimulation (TMS) studies. A lesion in the posterior parietal cortex impairs the ability to inhibit irrelevant items when resolving stimulus competition (Friedman-Hill et al., 2003), and altering PPC functionality by TMS affects the ability to inhibit attentional capture by a salient stimulus (Hodsoll, Mevorach, & Humphreys, 2009; Mevorach, Humphreys, & Shalev, 2006, 2009). Human findings thus converge with monkey findings in suggesting that certain parietal and frontal areas play a role in both bottom-up and top-down information processing. Together, these findings suggest that the parietofrontal areas may play a role in integrating these types of information to orchestrate prioritising visual stimuli for attentional allocation.

There is evidence that activity in visual areas also reflects a combination of bottom-up and top-down information, similar to parietofrontal areas, although there are some important differences in the activity patterns. First, in visual search, IT and V4 responses are increased and stimulus competition is influenced in favour of a behaviourally relevant object (Chelazzi, Duncan, Miller, & Desimone, 1998; Chelazzi, Miller, Duncan, & Desimone, 2001; Reynolds & Desimone, 2003). However, in visual areas, the effects of behavioural relevance are typically observed 150-200 ms post-stimulus onset (Chelazzi et al., 1998; Chelazzi et al., 2001), in contrast to the 90 ms of parietal areas (Ipata et al., 2006). For example, several studies reported that the initial response of a

V4 cell (<100 ms) reflects stimulus features such as contrast (Chelazzi et al., 1998; Chelazzi et al., 2001; Reynolds & Desimone, 2003) or physical salience (Ogawa & Komatsu, 2004, 2006), regardless of behavioural relevance. In contrast, FEF cells respond to the global presence of any target-relevant item (Ogawa & Komatsu, 2006), and the PPC contains cells that show both of these response patterns (Ogawa & Komatsu, 2009). These findings in turn suggest that the visual areas are only influenced by top-down information at a later stage of processing.

Second, when attention is captured by a salient item that shares the target colour, this salient item increases the BOLD response compared to an equally distinct item with an irrelevant colour in both visual and parietofrontal areas (Serences et al., 2005). However, in extrastriate visual areas this increase is present contralateral to the salient item, whereas activity is increased bilaterally in parietofrontal areas. Finally, attentional modulations in visual areas are generally transient, whereas they are sustained in parietofrontal areas, as has been shown for both spatial (Corbetta et al., 2000) and feature-based attention (Shulman et al., 1999). Together, these findings suggest that visual areas initially process bottom-up information, and subsequently receive feedback from parietofrontal areas, which is then used to update their bottom-up representation. Importantly, the feedback signal may not just reflect goal-driven factors, such as spatial and feature-based attentional processes, but may already contain a combination of the outcome of balanced bottom-up and top-down factors, which is then used to bias the processing of subsequent incoming visual information.

A series of EEG and MEG studies investigating attentional modulations over time support parietofrontal feedback of a priority signal to visual cortex. Actively ignoring a certain feature can lead to decreased detection performance of a subsequent presentation of the same feature, which is indexed by frontocentral activity as early as 60 ms post-stimulus onset. In contrast to this early enhancement in frontal areas, posterior evoked components are not affected until 300 ms post-stimulus (Nobre, Rao, & Chelazzi, 2006). Like parietofrontal areas, some visual areas may thus also have a salience/priority map representation (e.g., as proposed for V4 by Mazer and Gallant (2003)).

A substantial number of studies have focussed on the N2pc component, a negative component that is larger contralateral than ipsilateral to a target, occurring ~200 ms post-stimulus

onset over posterior electrodes, and therefore thought to be due to feedback (Luck & Hillyard, 1994b). The N2pc was initially thought to reflect spatial filtering or distractor-target competition (Luck & Hillyard, 1994a; Luck & Hillyard, 1994b). However, Eimer and colleagues recently demonstrated that the N2pc is not only present for an attended side of space containing a target, but also for target-set contingent distractors or expectation of a target, whereas it does not reflect attentional shifts (Eimer & Kiss, 2008; Kiss, Van Velzen, & Eimer, 2008). This suggests that the N2pc reflects attentional processing at an attended location in space. Using MEG, the N2pc has been localised to two sources, one in parietal cortex for the earliest part, and a later higher extrastriate source, which likely reflects IT or V4 (Hopf, Boelmans, Schoenfeld, Luck, & Heinze, 2004; Hopf et al., 2000). Wykowska and Schubö (2010, 2011) subsequently used the N2pc to show that it reflects the outcome of attentional allocation to the target after top-down influences on bottom-up salient capture had been weighted for priority. These findings suggest that visual processing in higher extrastriate areas reflects the outcome of attentional priority based on both bottom-up and top-down factors, which is likely the result of feedback from parietofrontal areas. However, Wykowska and Shubö (2010, 2011) did not distinguish between the two sub-components of the N2pc, nor did they conduct any source localisation, leaving uncertainty whether these findings reflected activity from parietal or visual cortex.

1.3.3.3 The role of early visual cortex in the signalling of attentional priority

It is clear that visual cortex plays a role in processing both bottom-up and top-down information, and that top-down feedback can convey the outcome of the balance of these types of information indicating priority of stimuli in the visual field for attentional allocation. Most of the attentional modulations in visual cortex reviewed here reflect effects in higher extrastriate areas such as V4 and IT. It is less clear how bottom-up and top-down factors modulate activity in the earliest visual areas, such as V1 and V2. To efficiently process the dynamic stream of incoming visual information in light of the current attentional goal, the parietofrontal network should interact with all areas involved in visual processing, including early visual cortex. I turn now to the question of whether bottom-up and top-down factors each influence activity in these areas independently, such

as at different times during stimulus processing, or whether these factors combine to modulate neural activity in these early areas.

A number of fMRI studies suggest that the earliest visual areas are particularly involved in processing bottom-up stimulus properties and salience. For example, Serences and Yantis (2007) found that in contrast to the gradual increase of neural activity in response to spatially attended items from V1 to V4, the response to the physical salience of an item gradually decreases from V1 to V4. Beck and Kastner (2005) found similar gradual results within visual cortex in an fMRI study using a unique target in a homogenous display (pop-out) versus heterogeneous stimuli, where competition determined by top-down factors invoked larger responses in V4 than V2. In contrast to these extrastriate areas, activity in V1 reflected competitive interactions based on bottom-up stimulus factors and seemed particularly sensitive to pop-out stimuli (Beck & Kastner, 2005, 2009; Nothdurft, Gallant, & Van Essen, 1999).

In contrast to this emphasis of early visual areas for bottom-up stimulus processing, a number of studies have shown that activity in V1 can play a role in higher-level stimulus processing. For example, activity in V1 can already reflect the perception of stimuli based on more than just physical properties, as shown by a correlation with behavioural responses (Lee, Mumford, Romero, & Lamme, 1998; Ress & Heeger, 2003), pop-out effects in V1 can be enhanced when monkeys are extensively trained on a task (Lee, Yang, Romero, & Mumford, 2002), and V1 may even play a role in visual awareness (Lamme & Roelfsema, 2000). Those studies showing high-level effects in V1 that contained high temporal resolution showed effects at later stimulus-evoked times (>100 ms, Lee et al., 1998; 2002), consistent with the notion that these are due to feedback. These high-level perceptual effects suggest that feedback of priority signals from parietofrontal areas may similarly influence activity in early visual cortex. In line with this proposal, a recent fMRI study showed that the degree of top-down modulation in visual areas appears to reflect the amount of stimulus competition left unresolved by bottom-up processes (McMains & Kastner, 2011). Although in this fMRI study these gradual effects were mainly reflected in extrastriate areas, V1 activity was modulated in the most demanding case, when competition could not be resolved by bottom-up processes at all. However, fMRI studies do not possess the temporal resolution to denote whether these processes occur early or later in stimulus processing. Thus, comparing the temporal

22

pattern of how bottom-up salience that captures attention and top-down factors that guide attention influence activity in early visual cortex is crucial to distinguish whether they independently modulate activity or whether a combined signal influences responses to stimuli.

1.4 Oscillatory activity and attentional processing

1.4.1 Oscillatory synchronisation

In addition to changes in firing rate, visual processing in early visual cortex is strongly associated with rhythmic oscillatory firing. Oscillatory activity occurs throughout the brain at a wide range of frequencies and occurs spontaneously as well as in response to sensory stimuli (Hari & Salmelin, 1997). Oscillatory activity can be measured in a single cell or synchronised over a group of neurons with multi-unit recordings (e.g., Friedman-Hill et al., 2000; Gray & Singer, 1989) as well as non-invasively using EEG or MEG (e.g., Hoogenboom, Schoffelen, Oostenveld, Parkes, & Fries, 2006; Tallon, Bertrand, Bouchet, & Pernier, 1995). Non-invasive techniques measure the Local Field Potential (LFP), which is thought to reflect the synchronised synaptic *input* into a local neuronal population. This reflects the cumulative activity of intra and extracellular excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) at all dendrites in an area of thousands to millions of neurons aligned in parallel (Hämäläinen & Hari, 2002; Henrie & Shapley, 2005; Kruse & Eckhorn, 1996; Schnitzler & Gross, 2005). This is in contrast to single or multi-unit recordings, which measure action potential *outputs* of specifically targeted neurons. Synchronised oscillatory activity can be evoked, that is, time and phase-locked to a stimulus event; or induced, that is, time-locked but not phase-locked. The latter cancels out when simply averaging over time-locked stimulus trials, and thus requires analysis techniques that extract spectral components whilst allowing for a level of temporal jitter (Hillebrand, Singh, Holliday, Furlong, & Barnes, 2005; Singh, 2006).

The phases of oscillatory patterns can be synchronised and desynchronised. These changes in synchronisation have been linked to neural processing associated with many cognitive processes. For example, there is a reduction in the level of synchronisation in lower-frequency alpha activity (around 8-12 Hz) when a person opens their eyes compared to having them closed (Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Berger, 1933; Cohen, 1968), which has been linked to

processes of arousal and attention. Moreover, a large body of research has linked modulations in amplitude and phase of the alpha range of oscillatory activity to spatial attention specifically. Alpha-band activity in visual cortex strongly decreases relative to baseline levels when attention is directed to the contralateral visual hemifield (Fries et al., 2008; Siegel et al., 2008; Yamagishi et al., 2008; Yamagishi et al., 2003; Yamagishi et al., 2005), and increases can be seen in visual areas ipsilateral to the focus of attention (Rihs et al., 2007; Siegel et al., 2008; Worden et al., 2000).

Although alpha oscillations are of interest in visual processing, higher frequency gamma activity (30-100 Hz⁶, e.g., Jensen, Kaiser, & Lachaux, 2007) is more directly linked to the processing of visual input and has therefore been a major focus of research in vision. Higher-frequency oscillations are generated by a smaller neural population than lower-frequency oscillations, and thus represent local rather than global processing (Schnitzler & Gross, 2005). In line with this notion, gamma synchronisation has been found to be largest in response to a cell's optimal visual stimulus in V1 and V2 of cat and monkey (Eckhorn, Fries, Bauer, Woelbern, & Kehr, 1993; Friedman-Hill et al., 2000; Fries, Eckhorn, Bauer, Woelbern, & Kehr, 1994; Gray & Singer, 1989), and is similarly stimulus-selective and localised in humans (Hoogenboom et al., 2006; Müller et al., 1996; Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1997; Tallon et al., 1995). In contrast to lower-frequency activity, visual gamma oscillations have a cortical origin (Fries, Eckhorn, Bauer, Woelbern, & Gabriel, 2000; Gray & Singer, 1989), and do not usually appear spontaneously to the degree that lower-frequency oscillations do (Friedman-Hill et al., 2000). Gamma oscillations are therefore thought to play a functional role in local visual processing (e.g., Friedman-Hill et al., 2000).

Oscillatory activity, particularly in the gamma range, has potential to subserve neural communication. Neurons can synchronise their firing rates locally as well as between distant areas (Schnitzler & Gross, 2005), and synchronised input has an amplified effect on the activity of a post-synaptic neuron compared to regularly summed input (Fries, 2005; Schnitzler & Gross, 2005). Oscillatory synchronisation thus provides a functional means of communication that cannot be achieved by spiking rates alone (Fries, 2005). The combination of this communication potential

⁶ Please see Chapter 6 for a discussion on the definition of the gamma frequency range.

and effective gain suggests an ideal role in network processing, particularly higher-frequency activity which possesses the temporal parameters for fast modulation of activity (Fries, Nikolić, & Singer, 2007). For example, gamma synchronisation has been proposed to play a role in the ‘binding problem’ of object recognition, which addresses how features are bound together to form a coherent percept (Gray, König, Engel, & Singer, 1989; Tallon-Baudry & Bertrand, 1999). Gamma oscillations have further been observed in several brain areas and are viewed as a generic neural processing phenomenon, with specific functional links to motor (Schoffelen, Oostenveld, & Fries, 2005) and memory (Gruber, Tsivilis, Montaldi, & Müller, 2004) processing, as well as several neurologic and psychiatric disorders (Kwon et al., 1999; Willoughby et al., 2003).

1.4.2 Attentional effects on gamma synchronisation

The demonstrated role of gamma synchronisation in neural communication and local visual processing makes it a prime candidate for the mechanisms by which the brain integrates bottom-up and top-down information for the deployment of attention. Gamma synchronisation can have both a driving role, evoking neural activity in a region where it was previously absent, and a modulating role, influencing a certain existing level of activity. These two effects could correspond to how bottom-up and top-down processing are mediated in the brain, respectively (Schnitzler & Gross, 2005). In monkeys and cats, gamma synchronisation in the LFP correlates with firing rate changes as well as the BOLD response in V1 (Logothetis, 2002; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Niessing et al., 2005), the latter in fact providing a better correlate than single- or multi-unit activity (Logothetis, 2002; Niessing et al., 2005). Close correspondence between gamma oscillations and the BOLD response have also been shown in humans, using intracranial EEG in epileptic patients undergoing surgery (Lachaux et al., 2007). Moreover, sustained induced gamma oscillations have a very similar localisation and amplitude as the early transient evoked N75 VEP in both monkeys and humans (Rols, Tallon-Baudry, Girard, Bertrand, & Bullier, 2001; Tzelepi, Bezerianos, & Bodis-Wollner, 2000). Finally, spatial optimisation techniques such as beamforming can target sources of gamma synchronisation in local regions of cortex in non-invasive MEG data, such as visually-induced synchronisation in early visual cortex (Hadjipapas, Adjamian, Swettenham, Holliday, & Barnes, 2007; Hillebrand et al., 2005). These techniques have

allowed comparison between human gamma oscillations and monkey LFP patterns, showing great similarity in both localisation and spectral properties (Hall et al., 2005). These similarities to various other measures of brain activity, and the localisation power, suggest that investigating gamma synchronisation can greatly contribute to our understanding of cognitive processes such as visual attention in localised regions such as early visual cortex.

Several studies have investigated modulations of gamma activity with attentional processing. Both monkey and human studies have shown that a stimulus that is attended versus unattended enhances gamma synchronisation as well as the coherence between the LFP and neuronal firing (spike-field coherence) in visual cortex, both when spatial (Fries, Reynolds, Rorie, & Desimone, 2001; Fries, Womelsdorf, Oostenveld, & Desimone, 2008; Gruber, Müller, Keil, & Elbert, 1999; Siegel, Donner, Oostenveld, Fries, & Engel, 2008) and feature-based (Bichot et al., 2005; Müller et al., 2006) attention is deployed. Moreover, attentional modulations of gamma synchrony can also be seen in LIP as well as in the coherence between LIP and visual areas such as MT (Saalmann et al., 2007). Investigating the phase relationships between these areas showed that synchrony in LIP precedes synchrony in MT by about 5-10 ms, similar to the temporal patterns of firing rate. A similar gamma feedback pattern has also been reported for the FEF to V4 (Gregoriou, Gotts, Zhou, & Desimone, 2009). Finally, local modulations of gamma coherence in V1 reflect the priority of items under conditions of stimulus competition: coherence increases in response to the preferred stimulus and reduces in response to the suppressed stimulus (Fries, Schröder, Roelfsema, Singer, & Engel, 2002). These findings strongly suggest that attentional modulations in gamma synchronisation mimic other neural modulations as reviewed earlier, and could reveal how bottom-up and top-down attention interact (Müller & Gruber, 2001). However, most studies mentioned here have focussed on extrastriate areas such as V4 or MT, or did not possess the spatial resolution to designate which visual area was the source of the activity modulations. How bottom-up and top-down factors interact to modulate gamma oscillations in early visual cortex is therefore a crucial question to be answered.

1.5 Summary and conclusion

Humans are remarkably good at ignoring salient items if they are irrelevant for a current task. Neural activity in a network of parietofrontal and visual areas can explain how stimulus and goal-driven attentional demands are processed and balanced to generate a neural signal ‘guiding’ attention towards the item with highest priority. This balancing act is accomplished by dynamic interactions and neural communication based on feedforward and feedback processing. Several visual areas appear to play an important role in this dynamic interplay, but the role of early visual areas such as V1 and V2 is unclear. Attentional effects on oscillatory activity in the gamma band in visual cortex mimic firing rate and other activity modulations, supporting top-down feedback to visual areas by the parietofrontal network. Studying the time course of modulations of gamma activity in early visual cortex comparing situations in which stimulus and goal-driven information are presented separately, and when they are competing for attentional allocation can therefore reveal the role of early visual cortex in the dynamic balancing of attentional demands.

1.6 Approach in this thesis and overview of experimental chapters

In this thesis, I addressed the question of how bottom-up and top-down factors influence neural activity in human early visual cortex. Because gamma oscillations play a clear role in neural communication and visual processing, I primarily focused on stimulus-induced gamma activity. I tested neural responses to visual stimuli of healthy observers using MEG, which provides both the necessary temporal and spatial resolution to investigate the dynamic development of the gamma response induced by visual stimuli.

1.6.1 Chapter 2: Manipulating behavioural relevance of a salient item: an MEG experiment

In Chapter 2, I directly addressed the main research question: how and when do demands on attention due to stimulus and goal-driven factors influence activity in early visual cortex, and do these influences combine to modulate activity? I used a behavioural paradigm that strongly manipulated the behavioural relevance of salient items and measured evoked neural responses in early visual cortex. The stimuli in this study were designed to maximise the behavioural effects

while exploring evoked responses and were found to be unsuitable to induce gamma oscillations. I therefore then set out to develop a paradigm containing a robust gamma-inducing stimulus to step-wise address the main research question. These experiments are presented in the subsequent three chapters.

1.6.2 Chapter 3: Induced and evoked neural correlates of orientation selectivity in human visual cortex

In Chapter 3, I first established a clear and robust gamma response, using a stimulus optimal for inducing gamma synchronisation in early visual cortex, and investigated how a bottom-up stimulus property influenced the gamma response. I used orientation as the key stimulus feature, because this feature is very strongly represented in primary visual cortex, and much is known about its neural representation. I compared the gamma response with VEPs for comparison to the well-established EEG literature.

1.6.3 Chapter 4: Sustained visuo-spatial attention increases high-frequency gamma synchronisation in human medial visual cortex

In Chapter 4, I used the methodological developments outlined in Chapter 3 to investigate how directing spatial attention modulates the gamma response in early visual cortex. I developed a paradigm to strongly manipulate sustained covert spatial attention towards or away from the same optimal stimulus as used in Chapter 3. In this chapter, I thus investigated how a purely top-down effect influenced processing driven by the same physical input. The sustained manipulation of attention was supported by a behavioural measure as well as the well-established desynchronisation in low-frequency alpha power.

1.6.4 Chapter 5: Investigating effects of stimulus salience and behavioural relevance on gamma synchronisation in early visual cortex

In Chapter 5, the developments of Chapter 3 and 4 were combined to directly investigate the main research question of how stimulus and goal-driven factors combine to influence gamma synchronisation in early visual cortex. The same gamma-inducing stimulus of Chapters 3 and 4 was

again used, but was combined with a second stimulus on the opposite side of space that was non-optimal to induce gamma activity. I developed an adaptation of the behavioural task used in Chapter 2, where the behavioural relevance of salient items for target search was manipulated. This paradigm allowed me to investigate dynamic modulations of gamma power in the temporal and spectral domain in response to the grating when it was salient or non-salient (bottom-up property), and behaviourally relevant or irrelevant (top-down manipulation), and when these bottom-up and top-down factors competed for attentional allocation.

1.7 References

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Chapter 2 – Manipulating behavioural relevance of a salient item: an MEG experiment

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Manipulating behavioural relevance of a salient item: an MEG experiment

2.1 Abstract

Our busy visual environment requires us to balance stimuli that grab our attention with stimuli that we wish to attend to. It is well known that parietofrontal areas play an important role in balancing stimulus and goal-driven demands to efficiently guide attention. However, the role of early visual cortex is less clear. V1 and V2 are responsive to stimulus properties and contrasts, and their activity is also influenced by attentional factors. We investigated the contribution of stimulus and goal-driven attentional demands in early visual cortex in a visual search task where these two demands needed to be actively balanced. We extracted the time course of stimulus-locked activity in early visual cortex using source localisation techniques. When subjects ignored the presence of a rare salient item, the average evoked response 100-200 ms post-stimulus onset was enhanced compared to when subjects were attending the salient item and it captured attention. This enhanced response in early visual cortex was observed regardless of singleton presence and thus represented a goal-driven cognitive effect. In contrast to the evoked response, low-frequency induced activity did not differ with either stimulus salience or top-down goal. These findings support that neural activity in early visual cortex is influenced by attentional factors early on visual processing. Our results suggest that future studies including stronger stimuli that allow measuring responses to individual stimulus locations have great potential to reveal the interplay between stimulus and goal-driven demands in early visual cortex.

2.2 Introduction

In our visual world, we need to balance events that capture our attention and events that match our current goal. In the brain, processing of the current visual input and the current behavioural goal must be combined to generate a neural signal ‘guiding’ attention towards the item with highest priority (Itti & Koch, 2001; Wolfe, 1994). Parietofrontal areas are thought to play an important role in the balancing of stimulus and goal-driven attentional demands and guiding overt and covert attention (Baluch & Itti, 2011; Corbetta & Shulman, 2002; de Fockert, Rees, Frith, & Lavie, 2004; Serences & Yantis, 2007). The balance between stimulus-driven and goal-driven attentional demands is a continuous process, involving constant updating of the signal guiding attention with the current status of information in the visual field. Because any changes in the visual field will first be processed in the visual cortex, it is necessary that parietofrontal areas actively communicate with visual areas to achieve the balancing of bottom-up stimulus processing and goal-driven demands.

In line with a contributing role of early visual areas in the dynamic interplay of stimulus and goal-driven processing, activity in higher visual areas such as IT and V4 is known to be modulated by the behavioural relevance of a salient stimulus (Chelazzi, Duncan, Miller, & Desimone, 1998; Chelazzi, Miller, Duncan, & Desimone, 2001; Reynolds & Desimone, 2003). For example, Reynolds and Desimone (2003) demonstrated that the response of a V4 cell to a preferred low-contrast stimulus is suppressed if an irrelevant non-preferred item, which excites the cell only very little on its own, is simultaneously present in the receptive field. Moreover, the amount of suppression by the non-preferred distractor increases with the contrast of the distractor (its physical salience), and directing attention to the location of these stimuli enhances the suppressive effect compared to directing attention elsewhere. These findings suggest that, like parietofrontal areas, activity in some higher visual areas also reflects a combination of stimulus and goal-driven information. Visual areas might therefore aid in the dynamic interplay of these types of information to guide attention.

A number of functional Magnetic Resonance Imaging (fMRI) studies suggest that in contrast to higher visual areas, early visual areas are particularly involved in processing bottom-up

stimulus properties and salience (Beck & Kastner, 2005; McMains & Kastner, 2011; Serences & Yantis, 2007). For example, McMains and Kastner (2011) recently showed that bottom-up and top-down factors can interact to modulate activity in higher visual areas, but not in V1. In their study, gradually stronger levels of perceptual grouping amongst four stimuli forming an illusory shape were associated with a gradual increase in the BOLD response throughout visual areas V1-V4. This increase reflects a gradual reduction in the amount of activity suppression due to stimulus competition (i.e., non-coherent shapes have more competition). Directing attention towards versus away from these stimuli increased the BOLD response in all areas. In areas V2-V4 the activity increase due to attention was influenced by the amount of stimulus suppression due to perceptual grouping. In contrast, attention did not have this gradual effect in V1 and only increased activity when competition could not be reduced due to perceptual grouping. These findings suggest that bottom-up and top-down factors interact to modulate activity throughout the visual cortex, but that this may not be the case for V1.

In contrast to these fMRI findings, a number of electroencephalography (EEG) and magnetoencephalography (MEG) studies suggest that stimulus-driven and goal-driven factors influence activity in early visual areas at different times during stimulus processing, and might thus not interact directly to modulate activity in these areas. There are two problems with the above fMRI studies. First, the bottom-up manipulation of perceptual grouping in the McMains and Kastner (2011) study might still involve a degree of top-down guidance. Second, the low temporal resolution of fMRI studies cannot show dynamic temporal fluctuations in activity, and leaves the question of *how* early visual areas are modulated when stimulus and goal-driven demands compete for attentional allocation unanswered. Several M/EEG studies have shown that the C1 event-related potential (ERP), which is the earliest, initial part of the stimulus-evoked response (50-100 ms post-stimulus), is not affected by attentional demands and purely reflects processing of physical stimulus properties (Anllo-Vento, Luck, & Hillyard, 1998; Clark & Hillyard, 1996; Di Russo, Martínez, & Hillyard, 2003; Martinez et al., 1999; Noesselt et al., 2002). In contrast, components occurring 100 ms or later are clearly modulated by attentional demands (Anllo-Vento et al., 1998; Luck, Fan, & Hillyard, 1993; Mangun, Buonocore, Girelli, & Jha, 1998; Mangun & Hillyard, 1988). This

temporal pattern of neural modulation suggests that effects of bottom-up and top-down processing in early visual areas occur independently from each other.

At present, it is clear that early visual areas process physical aspects of stimuli, and that activity in these areas is also influenced by attentional, goal-driven factors. However, it is not clear whether and how stimulus-driven and goal-driven factors combine to influence activity in early visual areas. Studying the time course of activity modulations in early visual cortex whilst stimulus-driven and goal-driven factors compete for attentional allocation can reveal how the dynamic interplay of these factors affects activity in early visual areas. A vast body of behavioural research has shown that humans are very good at ignoring salient items when they are irrelevant for a visual search task (e.g., Bacon & Egeth, 1994; Folk, Remington, & Johnston, 1992; Yantis, 1993; Yantis & Egeth, 1999). These studies typically show that subjects are impaired at finding a target when a unique salient distractor (singleton) is present, particularly if this distractor is relevant for target search, for example by sharing a feature with the target (Folk et al., 1992; Folk, Remington, & Wright, 1994). Studying the time course of activity modulations using a visual search task where the relevance of a singleton for target search is manipulated is thus an effective way to study the contribution of early visual cortex to the balancing of attentional demands.

The study presented in this chapter was designed to investigate how evoked activity in early visual cortex is influenced by stimulus and goal-driven demands by requiring active inhibition of salient items that captured attention. Using MEG, we localised the evoked response in early visual cortex to displays that occasionally contained a singleton, whilst subjects performed a visual search task. We manipulated the relevance of the singleton for target search so that, in separate blocks, it was either a potential target, and thus attended ('Attend' block), or was always a salient distractor that could be actively ignored ('Ignore' condition). We first verified that the singleton captured attention by examining performance from the Attend block. If the singleton captured attention, performance should be best when it was the target, as it was the goal of both stimulus and goal-driven attention. Conversely, performance when the singleton was the distractor should be worse than when there was no singleton. Second, we verified that our manipulation of behavioural relevance was successful by comparing performance when the singleton was a distractor in the Attend and Ignore block, in each case relative to singleton-absent trials. If the

singleton was successfully ignored when it was never able to be the target, performance should not be impaired by its presence as a distractor (at least, less impaired than in the Attend block). We used these same comparisons on the amplitude of the evoked response to determine how a physically salient item that captured attention influenced neural activity in early visual cortex, and how this was altered when behavioural relevance inhibited the physically salient item from capturing attention.

In addition to evoked activity, we explored how salience and behavioural relevance modulate oscillatory activity in early visual cortex. As noted in Chapter 1 (section 1.4), oscillatory activity has been proposed to play an important role in the neural communication underlying feedback from parietofrontal to visual areas, particularly in the gamma range (30-70 Hz, Fries, 2005; Saalmann, Pigarev, & Vidyasagar, 2007; Schnitzler & Gross, 2005), and can thus reveal additional insights in visual processing. Note that as this was not the primary goal of the present study, the stimuli were not designed to induce oscillatory activity. The role of gamma oscillations in stimulus and goal-driven processing is further investigated in Chapters 3-5.

2.3 Methods

2.3.1 Subjects

Ten subjects with normal or corrected-to-normal vision and normal colour vision (4M, 6F, mean age: 30, range 24-38 years) participated in the experiment after giving informed consent, and received payment for their participation. All procedures were approved by the Macquarie University Ethics Review Committee (Human Research).

2.3.2 Stimuli and procedure

Stimulus displays contained four small lines spaced equidistant from a small white fixation ‘plus’ on a grey background (Fig. 1). Each line subtended 1.57° of visual angle in length and 0.25° in width, and the midpoints of all lines were placed 4.4° horizontally and vertically from each other. The target was a line tilted 40° either to the left or right of vertical. Target orientation was counterbalanced over subjects, but remained the same throughout the experiment per individual.

On every trial, one of these four lines matched the target orientation. Subjects were asked to identify the location of the target using one of four buttons whilst maintaining central fixation throughout the experiment. In each stimulus display, the three remaining lines were distractors, each with a different orientation randomly chosen from tilts 10 or 70° to the left or right of vertical. The target and all distractor orientations appeared equally often in each of the four stimulus locations. Displays were generated in MATLAB® (The MathWorks, Inc.), using the Psychophysics Toolbox extensions (Brainard, 1997) projected via a mirror onto a ground-glass rear-projection screen¹.

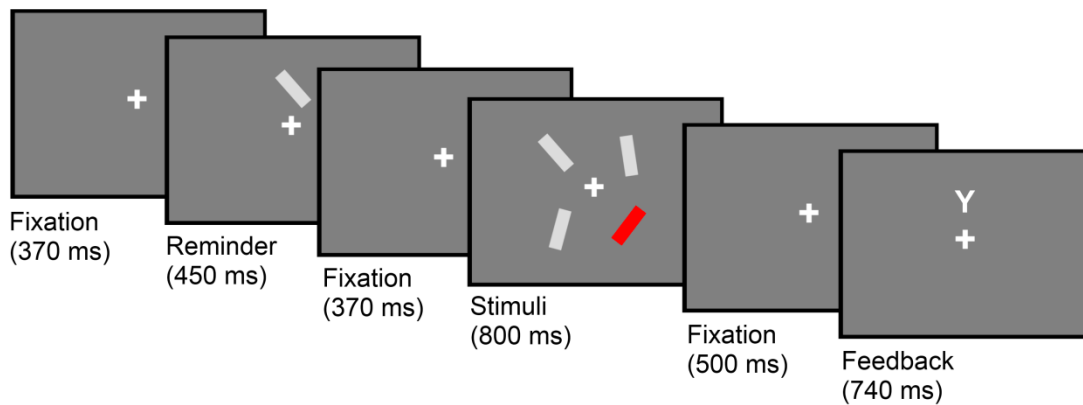


Fig. 1. Stimulus displays in a typical trial (not to scale). Subjects searched for the line with the target orientation and responded in which quadrant it appeared by pressing a button. The stimulus display in this example represents a ‘Singleton Distractor’ trial in which one salient (red) line was present amongst three non-salient (grey) lines. In this example, the correct response was to press the button corresponding to the upper left quadrant. The letter in the right-most display indicates feedback about target search performance, a ‘Y’ indicating a correct response (vs. ‘N’ for incorrect or ‘?’ for no response).

¹ Due to a slight distortion in the projection of the computer to the screen, midpoints of the lines in the upper visual field were placed 6.99° from fixation, and lines in the lower visual field 7.34°. Due to this distortion, lines in the lower visual field were also slightly larger than lines in the upper visual field.

Each trial started with a 370 ms fixation-only period, followed by a 450 ms reminder display in which an example of the target line was centred 2.2° above fixation. After a further 370 ms fixation-only period the stimulus display was presented for 800 ms. Following stimulus offset, another fixation-only period (500 ms) preceded a feedback display (740 ms), with either a 'Y', 'N', or '?' centred 2.2° above fixation, representing a correct, erroneous, or lack of response, respectively. Subjects could respond throughout presentation of the stimulus display and in the following fixation-only period by pressing one of four buttons. The buttons were spatially mapped to the four quadrants of the stimulus display. Subjects were instructed to respond as fast and accurately as they could.

The experiment started with a Baseline block in which all four lines were light grey. This Baseline block served to familiarise participants with the task and assess initial performance. In the subsequent blocks, on two-thirds of the trials, one of the four lines would appear in high-luminance red instead of light grey. This line was unique in hue, saturation, and luminance relative to the more common grey lines, making it a 'singleton'. We then manipulated the behavioural relevance of this singleton. In one block, when it was present, the red line was equally likely to be the target or a distractor (33.3% of trials each contained one red target, one red distractor, or no singleton), making it beneficial for participants to attend to the red line ('Attend' block). In the other block, the red line was only ever a distractor (50% of trials contained one red distractor, 50% contained no singleton). In this block, the red line could effectively be ignored, and, if participants were able to do this completely, they would only have to search three lines for the target ('Ignore' block). Subjects were informed of the behavioural relevance of the red line at the start of each block by a message on the screen. This message stated: 'The target orientation will SOMETIMES be the coloured line' for the Attend block, and: 'The target orientation will NEVER be the coloured line' for the Ignore block. In both blocks, the red line appeared equally often in each of the four possible stimulus locations.

In addition, we had a Localiser run to identify the spatial correlates of sources in visual cortex corresponding to the four stimulus locations. The Localiser task contained alternating black/white checkerboard stimuli consisting of four checks per stimulus with a central cross as a fixation point. Checkerboards were positioned at the locations of the four line stimuli in the main

stimulus displays, with checkerboard size identical to the length of one stimulus line (1.40°). The Localiser displays were arranged in three configurations: (1) one checkerboard in the upper left and one in the lower right quadrant; (2) one checkerboard in the upper right and one in the lower left quadrant; and (3) four checkerboards on the horizontal and vertical meridians in a 'plus' configuration. Following a 200 ms fixation-only period, checkerboard displays were presented for 800 ms, containing four 200 ms alternations of black/white checks. Subjects were instructed to maintain fixation and press a button when the fixation cross changed colour from white to green (10% of trials).

Preceding any recording, subjects received instructions and practiced the Baseline task until they were comfortable with the task and had acceptable performance. The main experimental blocks were subdivided into consecutive recording runs of 96 trials. For the Baseline block, there was only one recording run (Singleton Absent). The Attend block had three recording runs, so that we acquired 96 trials of each condition (Singleton Absent, Singleton Distractor, Singleton Target) during the experimental session. The Ignore block had two recording runs, similarly yielding 96 trials for both conditions within this block (Singleton Absent, Singleton Distractor). The order of Attend and Ignore blocks following the Baseline block was counterbalanced across subjects. Each recording run took approximately 5 minutes. Subjects practiced each task offline before the first run of each attentional block. Subjects performed the Localiser in between the two attentional blocks to reduce the effects of switching attentional set. The Localiser contained 88 trials per condition, yielding a total of 528 trials, taking approximately 10 minutes. The total recording session including instructions and short breaks took approximately one hour.

2.3.3 MEG data acquisition

Whole-head MEG recording was conducted with a 160-channel first-order axial gradiometer system (50 mm baseline) at the KIT-Macquarie Brain Research Laboratory. Data acquisition was performed using Yokogawa MEG160 software (Yokogawa Electric Corp., Eagle Technology Corp., Kanazawa Institute of Technology) at a sample rate of 1000 Hz with a 0.03 Hz high-pass filter and a 200 Hz low-pass filter. Subjects lay supine on a padded plinth within a magnetically shielded room throughout the experiment. Prior to MEG recording, the subject's head shape was

obtained with a Polhemus Fastrak digitiser (Polhemus, Colchester, VT, USA). To achieve co-registration between the MEG and a structural MR template image, three landmark fiducials (nasion and left/right pre-auricular points) were digitised along with the headshape. Additionally, five head position indicator (HPI) coils were attached to a tightly fitting elastic cap. Head location in the MEG was measured through the position of these coils at the start of each recording run, and subjects were asked to remain still with their head in the same position throughout the experiment. Digital triggers were sent to the acquisition computer at stimulus onset, offset, and button presses, and were also sent by a photo sensor attached to the presentation screen responding to stimulus display onset. Responses were recorded using a right-handed LUMItouchTM response keypad (Photon Control Inc., Canada), resting in inverted position on the subject's body. Subjects responded with the index and middle finger of each hand, so that the four buttons approximated the spatial mapping of the four stimulus items.

2.3.4 Behavioural data analysis

We discarded trials with a reaction time (RT) below 150 ms as anticipations, and calculated accuracy on the remaining trials. We arcsine transformed the accuracy scores to account for distribution inhomogeneity of performance near ceiling (Anscombe, 1948). Trials with an erroneous or lack of response were then discarded, and median RT was calculated on the remaining correct trials.

2.3.5 MEG data analysis

Data analysis was performed using SPM8 (www.fil.ion.ucl.ac.uk/spm/, Litvak et al., 2011) and FieldTrip functions (www.ru.nl/fcdonders/fieldtrip, Oostenveld, Fries, Maris, & Schoffelen, 2011).

The initial aim of the Localiser block was to identify the four stimulus locations in the visual cortex. Unfortunately, however, there was insufficient power to investigate individual stimulus locations separately (80 trials on average would yield only 20 trials per location on average). In addition, the Localiser data were not clear cut regarding cortical activation corresponding to the four stimulus locations. Instead, we maximised power by focusing on the response to the full stimulus display (source localisation based on the four items together). The

Baseline block was therefore used as an independent localiser of source activity, as it provided a more accurate representation of activation due to the four stimuli together, independent of attentional manipulation or saliency.

2.3.5.1 Source localisation of event-related fields

The raw data were first downsampled to 250 Hz and filtered with a 35 Hz low-pass filter, 1 Hz high-pass filter, and 48-52 Hz stop-band. We then epoched the data with a -200 to 1000 ms window around stimulus onset ($t=0$) and applied baseline correction (-200 to 0 ms). Trials with an erroneous or missing response from the behavioural analysis were discarded. We used the FieldTrip visual artefact rejection toolbox to identify trials with an extreme MEG signal and marked these as bad if they appeared clearly deviant after visual inspection. Following these pre-processing steps, we merged the recording runs belonging to one experimental block together, resulting in one file for each of the four experimental blocks (Baseline, Attend, Ignore, Localiser). After merging the data into the four experimental blocks, we averaged the data of each condition within each block (Baseline, Attend, Ignore, Localiser). The averaged data were then merged into one data file per condition, containing all nine conditions (Baseline: Singleton Absent; Attend: Singleton Absent, Singleton Distractor, Singleton Target; Ignore: Singleton Absent, Singleton Distractor; and the three localiser conditions), although note as mentioned above we did not use the Localiser data.

Source reconstruction of the averaged evoked response was established by first co-registering the data of each subject with the SPM8 template structural brain (4086 vertices canonical mesh). Co-registration was based on the three fiducials and the digitised headshape using an Iterative Closest Point algorithm. The global data (all six conditions together) were then localised using a multiple local-spheres forward model and an inverse solution based on a multiple-sparse priors (MSP) reconstruction using a greedy search (Friston et al., 2008).

Group-level analysis was achieved by calculating the average activity over the group ($N=10$) for the Baseline block in the following time windows: 50-150 ms (early peak evoked response), 150-250 ms (re-activation of primary visual cortex due to feedback, Noesselt et al., 2002), and from 250 to 650 ms in windows of 100 ms (times >650 ms are likely to include

response-related activity that is not of interest here)². The Baseline block was thus used as a localiser for source activity evoked by the stimulus display (the four stimuli grouped together) that was independent from attentional manipulation or salience. We obtained the MNI coordinates of peak activity from these average images by using a local maximum search in areas of key activity. These coordinates were then entered as a symmetrical bilateral pair of dipoles to extract time courses of average evoked source activity for each subject and condition. Because we did not have *a priori* knowledge of dipole orientation, this analysis yielded three time courses per source, one for each spatial dimension. We reduced each set of time courses to one by obtaining the first Principal Component (PCA, Jolliffe, 2002). Due to the rescaling steps involved in the inversion calculation, the amplitude of the time courses represents normalised arbitrary units (a.u.) of power.

2.3.5.2 Time-frequency analysis

Pre-processing of the raw data was identical to the event-related field analysis, except that the data were not filtered before epoching and not averaged. Behavioural and MEG bad trial selection was identical to the event-related field analysis.

To obtain source localisation of the single-trial data, the data were co-registered, localised, and inverted using identical parameters to the event-related field analysis. To capture the initial induced burst and sustained activity of the visual gamma-band response (e.g., Hoogenboom, Schoffelen, Oostenveld, Parkes, & Fries, 2006; Swettenham, Muthukumaraswamy, & Singh, 2009), oscillatory source power within a 30-70 Hz band was imaged within 0-200 and 200-800 ms time windows, respectively (using a Hanning window). This was done in the Baseline block for each subject to have a measure of source power that was independent of salience and behavioural relevance. The resulting normalised images of source power (MNI space) were smoothed with an 8

² We also generated statistical images (one-sample *t* test) of activity per condition. None of the statistical images showed activity that survived correction for multiple comparisons. The goal of the source localisation was to obtain coordinates to place a virtual sensor for spatially optimised analysis, with *a priori* expectations of activity in the cuneus. We therefore instead obtained maximum activity (unbiased via a global maximum search) in a simple group averaged image. Note that we do not draw any conclusions from the source distribution due to this lack of a statistical criterion.

mm kernel and an average image was calculated over the group (N=10) for each time window. The activity of each average image is represented in normalised arbitrary units (a.u.) of power, rescaled to the sum of power across conditions per time window.

We constructed virtual sensors based on the coordinates of peak activity within the resulting average images of the Baseline block³. We obtained these coordinates by calculating the global maximum activity source in the average image for each time window. For each subject, the lead fields were calculated for each virtual sensor location using the same inverse solution that was calculated for the source localisation. We subsequently extracted the spectral content of the single-trial data for all six conditions using each individual's virtual sensor, applying the 'multitaper' method as implemented in the FieldTrip toolbox. This time-frequency calculation is based on a Hanning taper, and was calculated over the full -200 to 1000 ms epoch in steps of 5 ms with a 40 ms time resolution, and over 5-100 Hz with a frequency resolution of 1 Hz. The data were subsequently averaged and rescaled so that spectrogram activity represents stimulus-evoked and induced spectral power relative to the -200 to 0 ms pre-stimulus baseline of each respective condition. Power was then averaged within a 0-200 and 200-800 ms time window to plot the average power over frequency, and separately within 30-70 Hz to plot the average power over time.

2.4 Results

2.4.1 Behavioural results

Eliminating trials with a reaction time below 150 ms yielded a data loss of 5.8% in the Baseline block, 7.9% in the Attend block and 5.7% in the Ignore block (averaged over conditions, recording runs, and subjects). The difference between the Attend and Ignore block was not significant (paired t test, $t(9)=1.61$, $p=0.142$). The Baseline block was not included in any statistical analyses, as this block only served to assess participants' initial performance on the visual search task and did not

³ The same rationale to obtaining the global maximum activity of these average images applies to the time-frequency analysis as to the event-related field source localisation (see previous footnote).

contribute to any crucial comparisons. In the Baseline block, subjects were on average 86.8% correct with a median RT of 719 ms.

Group average performance is displayed in Fig 2. Due to the unequal number of conditions (three conditions in the Attend block; two conditions in the Ignore block) we could not perform a regular two-way ANOVA on the behavioural data. Instead, we performed two separate statistical tests to assess the effect of our manipulation.

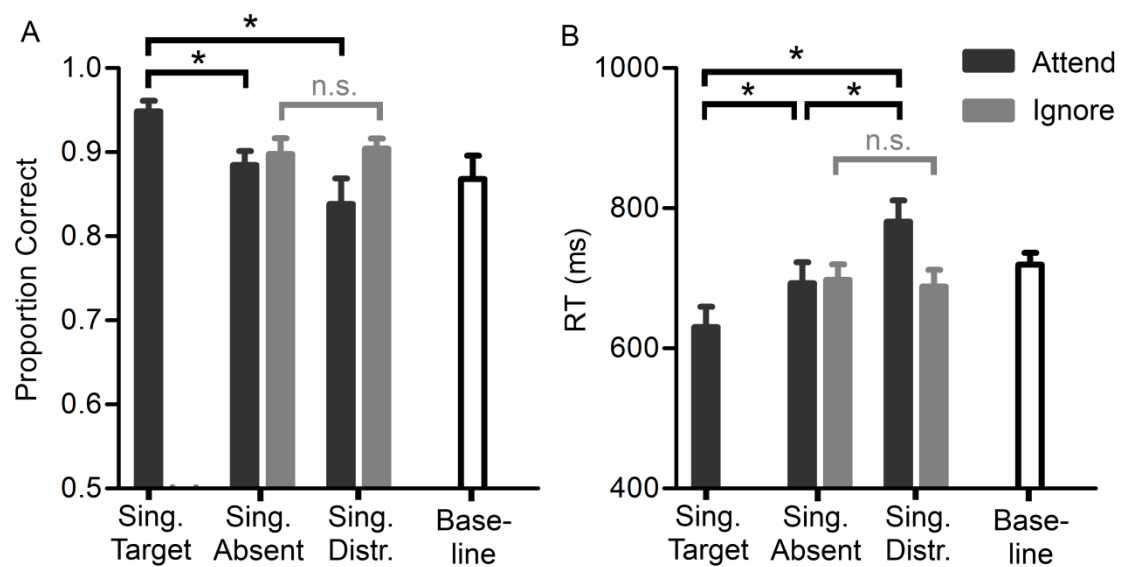


Fig. 2. Group average behavioural results ($N=10$). (A) Accuracy (reverted arcsine transformed percentage correct) and (B) group average median reaction times (RT). Error bars represent standard error of the mean. $*p<0.05$; n.s. not significant (posthoc comparisons per pair). Sing. Singleton; Distr. Distractor.

First, we verified that the singleton captured attention using the data from the Attend block, by performing a one-way repeated-measures ANOVA on the three conditions within this block. If the singleton captured attention, performance on trials in which the singleton was the target should be better than on trials in which there was no singleton. Conversely, performance on trials in which the singleton was the distractor should be worse than on trials in where there was no singleton. A one-way repeated measures ANOVA on the Attend block accuracy data with the factor of Condition (Singleton Absent, Singleton Target, Singleton Distractor) revealed a significant main

effect ($F(2,18)=7.49, p=0.004$). Posthoc comparisons showed that subjects were significantly more accurate in the Singleton Target condition than the other conditions (both $p<0.05$), whereas there was no difference between the Singleton Absent and Singleton Distractor conditions ($p>0.05$). The same analysis performed on median RT of correct trials also revealed a main effect of Condition ($F(2,18)=41.69, p<0.001$). Posthoc comparisons confirmed that subjects were fastest in the Singleton Target condition, slowest in the Singleton Distractor condition, and had intermediate RTs in the Singleton Absent condition (all $p<0.05$). This pattern of results supports that the singleton captured attention when it was relevant for target search.

Second, we verified that our manipulation of attention modulated the behavioural relevance of the salient line with a two-way repeated-measures ANOVA on the conditions that occurred in both blocks (i.e., Singleton Distractor, Singleton Absent). A two-way repeated measures ANOVA on the accuracy data with the factors of Attentional Block (Attend, Ignore) and Condition (Singleton Absent, Singleton Distractor) showed a main effect of Attentional Block ($F(1,9)=7.29, p=0.024$), but no effect of Condition ($F(1,9)=2.30, p=0.164$) and no interaction ($F(1,9)=1.04, p=0.334$). Subjects responded more accurately in the Ignore block than in the Attend block. The same analysis performed on RT yielded a significant main effect of Condition ($F(1,9)=25.90, p=0.001$) and a strong trend for a main effect of Attentional Block ($F(4.82, p=0.056)$). Importantly, there was a significant interaction ($F(1,9)=85.53, p<0.001$), with posthoc comparisons confirming that subjects were significantly slower in the Singleton Distractor than Singleton Absent condition within the Attend block ($p<0.05$). In contrast, RT did not significantly differ between these conditions within the Ignore block ($p>0.05$), suggesting that the singleton was successfully ignored when the task instructions excluded it as a possible target.

2.4.2 MEG results

After discarding the behaviourally erroneous trials and bad trials based on MEG artefacts, the average number of trials remaining in each condition was 77 in the Baseline block; 76 for both Singleton Absent and Singleton Distractor in the Ignore block; and 74, 69, and 76 in the Singleton Absent, Singleton Distractor, and Singleton Target conditions within the Attend block,

respectively. These numbers were not significantly different (one-way repeated measures ANOVA on all six blocks, $F(5,45)=1.67$, $p=0.162$).

2.4.2.1 Source localisation of event-related fields

Fig. 3 shows the average group activity in the six time windows within the Baseline block each overlaid in a different colour on the normalised brain. Over all time windows, the largest activity cluster was localised to early visual cortex (along the calcarine sulcus in medial visual cortex, MNI coordinates were within the Talairach database right ‘cuneus’: [4 -92 6]). For individual time windows, maximum activity was localised to the middle occipital gyrus (MOG) at 50-150 ms; the cuneus at 150-250 ms and 250-350 ms; the middle temporal gyrus (MTG) at 350-450 ms; again to the MOG at 450-550 ms; and to the inferior frontal gyrus (IFG) at 550-650 ms. Further major clusters of local maximum activity across time windows were identified in the inferior parietal lobe (IPL), middle frontal gyrus (MFG), and superior temporal gyrus (STG). Time courses extracted for all conditions (in the Baseline, Attend and Ignore block) using the obtained coordinates of the medial visual cortex from the Baseline block (left and right-lateralised pairs) are shown in Fig. 4. Time courses extracted for all conditions using the coordinates of remaining six peak sources (left and right-lateralised pairs) are shown in Fig. 5. Within the cuneus time courses, two activity peaks could clearly be distinguished. A first peak occurred between 80-170 ms post-stimulus with a maximum at around 120 ms, and a second peak between 170-250 ms with a maximum at around 185 ms. We set these two time periods as windows to test differences in average evoked activity between conditions. No further peaks could be clearly distinguished within the medial visual cortex time courses compared to the variation within the pre-stimulus baseline. The fluctuations in time courses of all other sources were not reliable enough to be assessed for effects of conditions. We therefore did not further analyse time courses from any other sources than the medial visual cortex (cuneus).

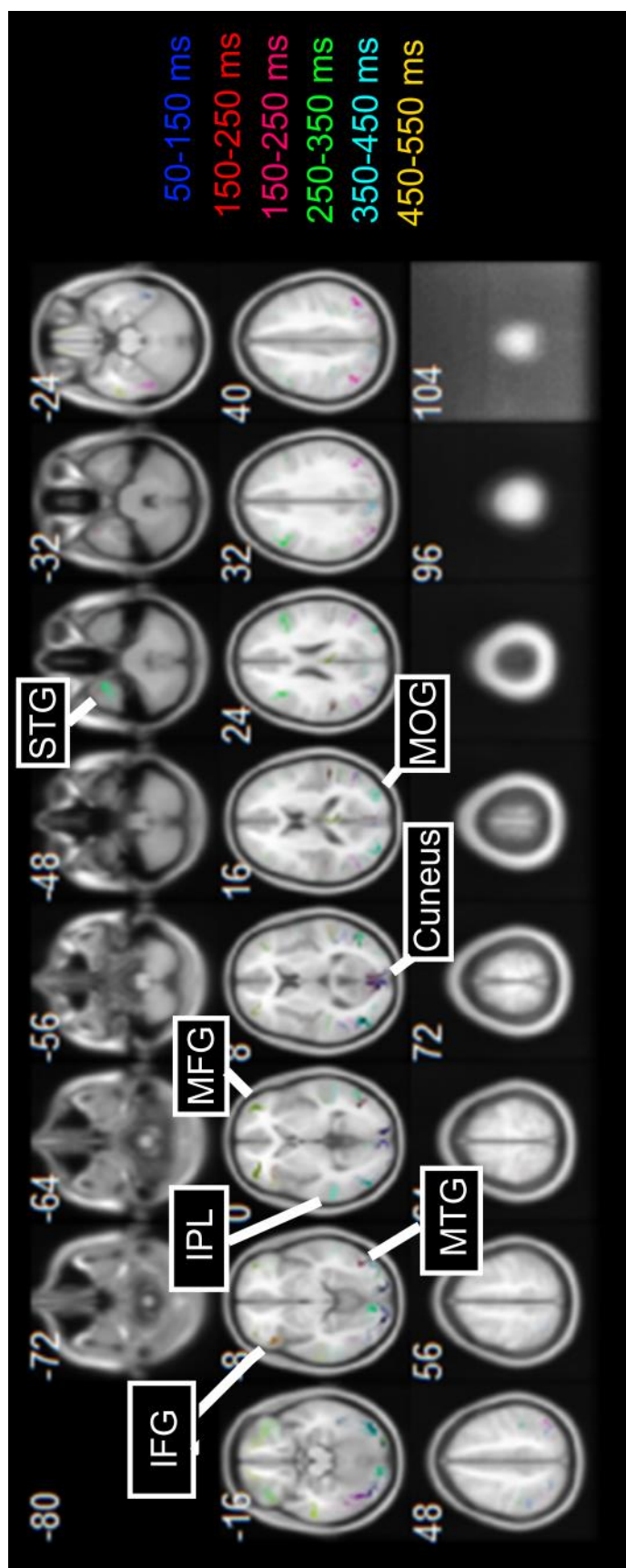


Fig. 3. Source localisation results of group average stimulus-evoked activity in the Baseline block. Displayed are a set of 8 mm transverse slices from ventral to dorsal of the group average of six time windows, as indicated in the legend. Numbers indicate transverse MNI coordinates. The largest consistent activity source was localised to the cuneus within the calcarine sulcus, as indicated (brown/black colours indicate a great degree of overlap amongst the time windows). Other prominent sources of activity are also indicated (see main text for abbreviations). Colours represent activity in normalised arbitrary units (a.u.) to a maximum of 1 (unthresholded).

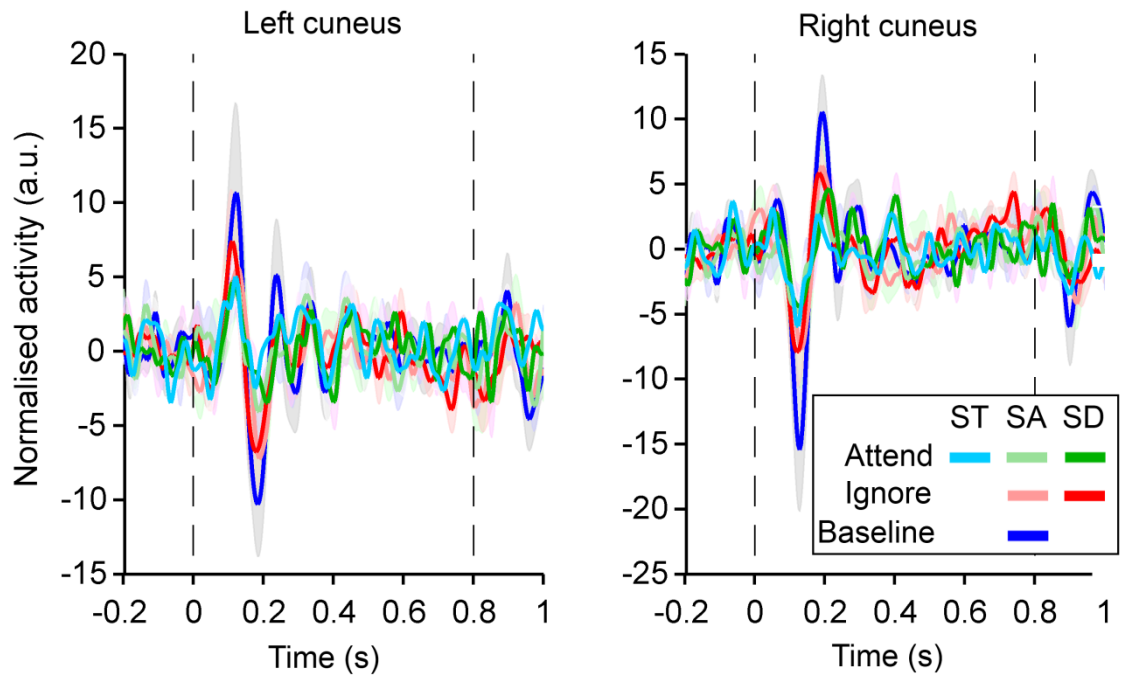


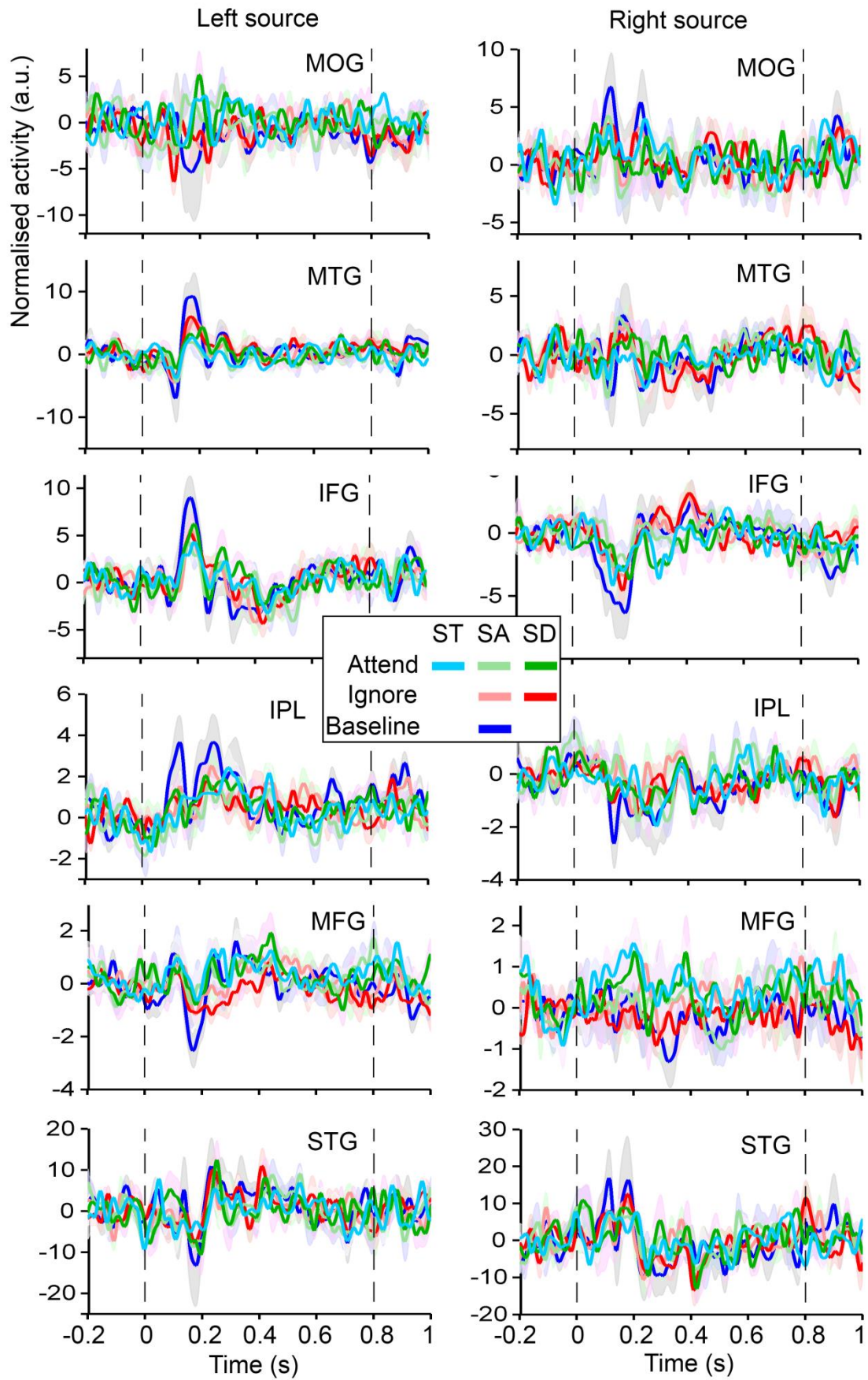
Fig. 4. Group average ($N=10$) source waveforms of stimulus-evoked activity in the cuneus derived from individual virtual sensors placed at peak activity of the normalised group average within the Baseline block. The left and right panels indicate source activity obtained from the left and right cuneus, respectively. Activity represents normalised arbitrary units (a.u.). Shaded regions represent standard error of the mean. The dashed lines indicate stimulus onset ($t=0$) and offset ($t=0.8$ s). Two similar activity peaks can be observed in both plots, one occurring approximately 120 ms and one 185 ms post-stimulus onset. ST, Singleton Target; SA, Singleton Absent; SD, Singleton Distractor.

To test the effect of a red singleton distracting attention on evoked activity in the cuneus, we performed a one-way repeated measures ANOVA on the area under the curve of individual absolute⁴ activity over the three conditions within the Attend block (Singleton Absent, Singleton

⁴ The sign of magnetic field fluctuations in MEG is not informative for this analysis. Magnetic field sign reflects magnetic field flow in and out of the scalp, which is perpendicular to the underlying electrical dipole orientation. Dipole orientation depends on individual local cortical curvature and can vary, even be opposite, over individuals. Averaging over signed evoked activity can therefore obscure variations in magnitude.

Distractor, Singleton Target). For the 80-170 ms time window, this comparison was not significant for either left or right cuneus ($F(2,18)=1.09$, $p=0.358$; $F<1$, *n.s.*, respectively). We therefore were not able to find any effect of the attentional capture evident in the behavioural data in the cuneus response. To test whether the behavioural relevance of the singleton affected evoked activity, we performed a two-way repeated measures ANOVA on the factors Condition (Singleton Absent and Singleton Distractor) and Attentional Block (Attend and Ignore). For both the left and right cuneus, there was a main effect of Attentional Block ($F(1,9)=14.01$, $p=0.005$; $F(1,9)=10.50$, $p=0.010$, respectively), but no main effect of Condition ($F(1,9)=1.94$, $p=0.197$; $F<1$, *n.s.*), nor an interaction ($F(1,9)=1.03$, $p=0.338$; $F<1$, *n.s.*). For both of these sources, the main effect of Attentional Block revealed that trials in the Ignore block evoked significantly larger responses in the cuneus than trials within the Attend block. These findings suggest that the attentional set of considering the salient line as a potential target (Attend) or excluding the salient line as a potential target (Ignore) modulated event-related responses in early visual cortex. However, neither the presence of a singleton nor its behavioural relevance modulated this evoked activity. Performing the same two ANOVAs on the latency of the maximum activity within each time window did not show any significant effects for either left or right cuneus.

Fig. 5. Group average ($N=10$) source waveforms of stimulus-evoked activity in six major sources derived from individual virtual sensors placed at peak activity of the normalised group average within the Baseline block. For each source (as indicated, see main text for abbreviations), activity is plotted for the symmetrically placed left (left panels) and right dipole (right panels). Activity represents normalised arbitrary units (a.u.). Shaded regions represent standard error of the mean. The dashed lines indicate stimulus onset ($t=0$) and offset ($t=0.8$ s). ST, Singleton Target; SA, Singleton Absent; SD, Singleton Distractor.



2.4.2.2 Time-frequency analysis

Source localisation results of group average oscillatory power between 30-70 Hz in the Baseline block for the two time windows are displayed in Fig. 6. In both time windows, maximum activity was localised to the cuneus along the calcarine sulcus, with the exact same MNI coordinates [-2 96 6]. Group average time-frequency spectrograms for each condition extracted from a virtual sensor placed in these coordinates are displayed in Fig. 7A. The spectrograms reveal event-related desynchronisation in the alpha/beta band (5-25 Hz) from approximately 100 ms post-stimulus for the duration of the stimulus. There was no clear change in activity relative to baseline in any higher frequencies, including the gamma band. Power-frequency and power-time plots derived by averaging over time windows and frequency bands, respectively (Fig. 7B), highlight the absence of any gamma-band activity in either burst (0-200 ms) or sustained (200-800 ms) time windows for all conditions.

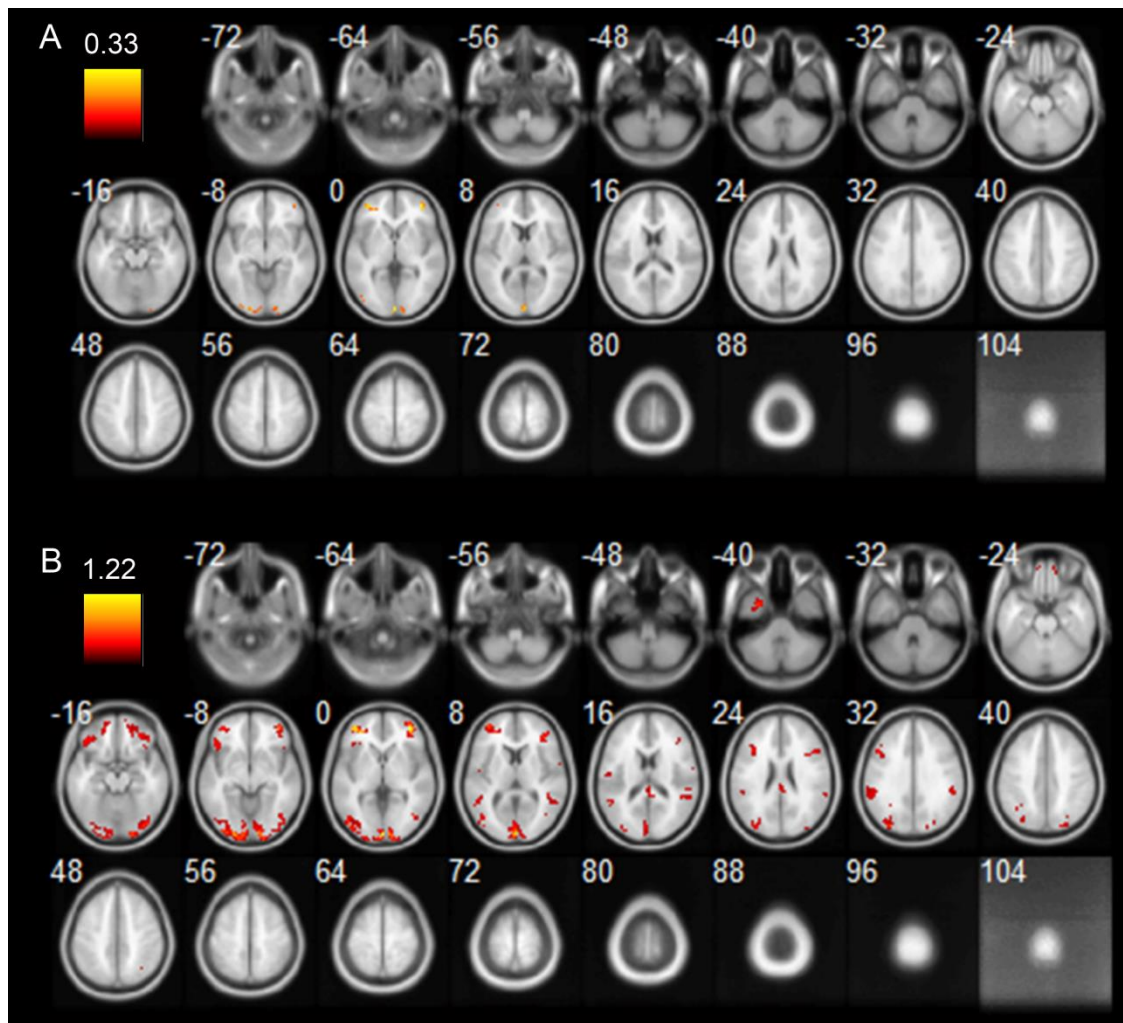


Fig. 6. Source localisation images of group average gamma activity (30-70 Hz) in the Baseline block. Displayed are a set of 8 mm transverse slices from ventral to dorsal of the group average over (A) 0-200 ms post-stimulus onset, capturing initial stimulus-evoked and induced gamma; and (B) 200-800 ms post-stimulus onset, capturing sustained induced gamma activity. Numbers indicate transverse MNI coordinates. In both images, the largest activity source was localised to the cuneus within the calcarine sulcus, as indicated. Colours represent activity in normalised arbitrary units (a.u.). Both sets of images were thresholded at 0.1 a.u.

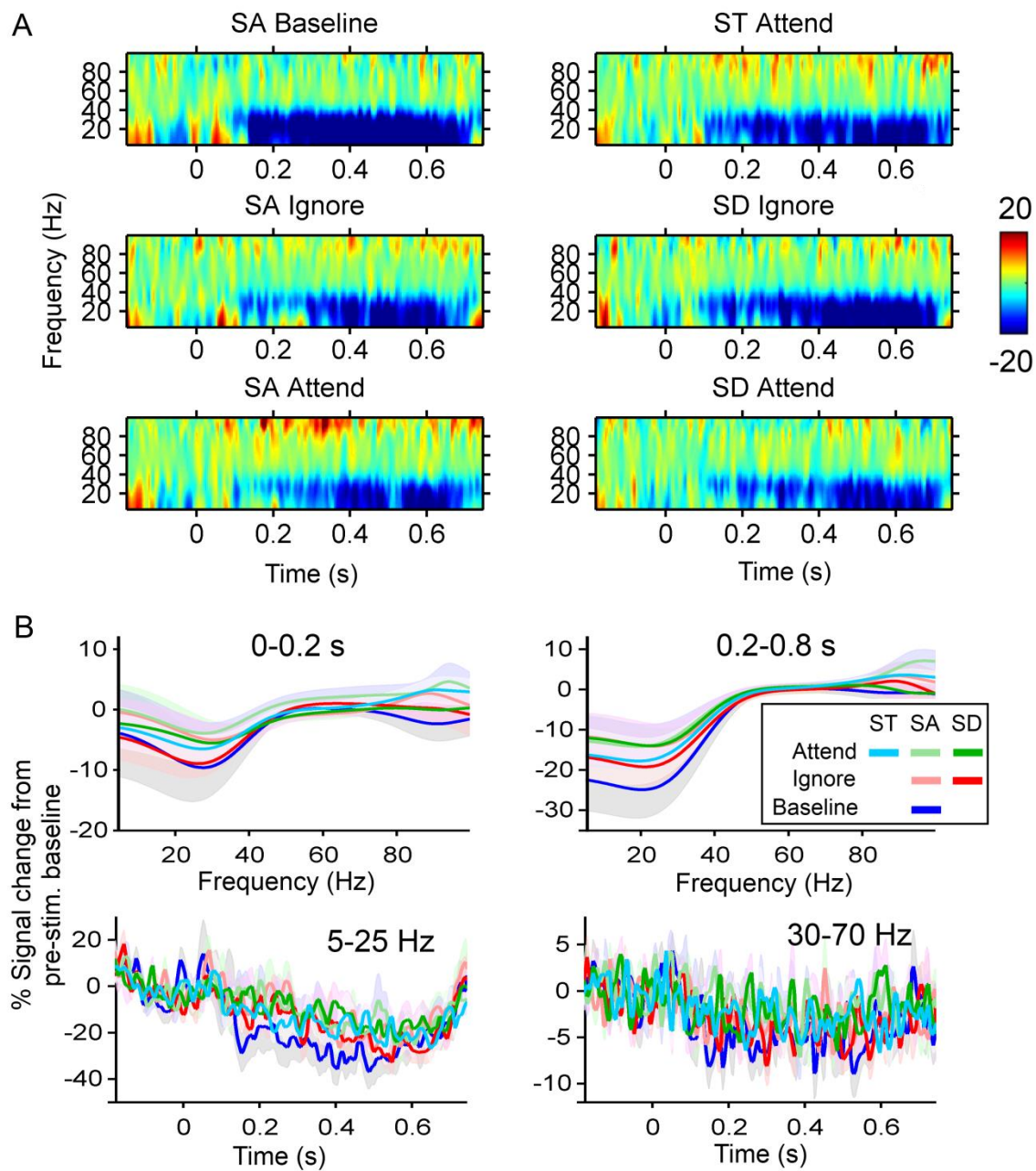


Fig. 7. Group average ($N=10$) time-frequency data of activity in the cuneus derived from individual virtual sensors placed at peak activity of the normalised group average within the Baseline block. (A) Spectrograms of activity between 5-100 Hz are displayed from -0.2 to 0.8 s around stimulus onset ($t=0$) for each condition. Colours represent percentage signal change from the -0.2 to 0 pre-stimulus baseline. The dark blue colours show the strong event-related desynchronisation in the lower-frequency alpha/beta range. The spectrograms reveal that there was no clear activity in the gamma range for any condition. (B) Power-frequency (top panels) and power-time plots (bottom panels) averaged over time windows and frequency ranges as indicated. Power is again represented as percentage signal change from the pre-stimulus baseline. Shaded regions represent standard error of the mean. ST, Singleton Target; SA, Singleton Absent; SD, Singleton Distractor.

To test whether the red singleton, that our behavioural data verified captured attention, influenced the power of induced alpha/beta activity in the cuneus, we performed a one-way repeated measures ANOVA on the average activity within 5-25 Hz over the three conditions within the Attend block (Singleton Absent, Singleton Distractor, Singleton Target). There was no significant effect of condition for either time window (0-200 ms: $F<1$, *n.s.*; 200-800 ms: $F(2,18)=1.05$, $p=0.370$). To test whether the behavioural relevance of the singleton affected alpha activity, we performed a two-way repeated measures ANOVA on the factors Condition (Singleton Absent and Singleton Distractor) and Attentional Block (Attend and Ignore). For this comparison, there were no significant effects in either time window (0-200 ms: Attentional Block: $F<1$, *n.s.*, Condition: $F(1,9)=3.27$, $p=0.103$, interaction: $F<1$, *n.s.*; 200-800 ms: $F<1$, *n.s.*, $F(1,9)=1.81$, $p=0.212$, and $F(1,9)=1.08$, $p=0.326$, respectively). These results do not show any effect of our key manipulations on low-frequency stimulus-induced alpha/beta activity.

2.4.2.3 Posthoc Baseline block power analysis

Cuneus activity of both evoked (Fig. 4) and time-frequency (Fig. 7) data showed a much stronger response for the Baseline block than any condition within the Attend and Ignore blocks. This may either be due to the fact that virtual sensors were based on and thus optimised for the Baseline block, or it suggests there were differences between the attentional set of each block (Attend singleton, Ignore singleton, or no singleton to attend/ignore in the Baseline block). To test whether the difference between these three blocks was statistically significant, and whether this depended on the attentional set (irrespective of salience), we performed a one-way repeated measures ANOVA on the Singleton Absent condition of each block.

For the area under the curve of absolute activity of the first evoked peak (80-170 ms), the ANOVA showed a significant main effect of attentional block for both the left and right cuneus ($F(2,18)=17.49, p<0.0005$; $F(2,18)=17.26, p<0.0005$). Posthoc comparisons between each pair of the three attentional blocks revealed that for both cuneus sources, the Singleton Absent condition of the Baseline evoked the largest activity, the Attend block the smallest and the Ignore block in between (all $p<0.01$). The same test on the second evoked peak (170-250 ms) was also significant for both left and right cuneus ($F(2,18)=7.92, p=0.003$; $F(2,18)=5.12, p=0.017$). Posthoc comparisons revealed that for the left cuneus, the same pattern of Baseline > Ignore > Attend was significant as for the first peak (all $p<0.05$), whereas for the right cuneus the only significant comparison showed that the Baseline was larger than Attend ($p<0.05$, both other comparisons $p>0.05$).

The same ANOVA on cuneus activity of low-frequency (5-25 Hz) power from the time-frequency analysis was not significant for average power within either of the 0-200 ms ($F<1, n.s.$), and 200-800 ms time windows ($F(2,18)=2.13, p=0.148$). Together, these results show that evoked activity within the cuneus, but not alpha power, was influenced by both the Baseline block and attentional set. The main effect of attentional block in the accuracy data showed that subjects made fewer errors in the Ignore block than in the Attend block, suggesting they found this block easier. This suggests that this modulation of evoked activity amplitude reflects the gradually increasing task demands of simple target search (Baseline), ignoring any potential red item (Ignore), and attending to any potential red item (Attend).

2.5 Discussion

In the present study, we found a modulation of the stimulus-evoked response in early visual cortex that reflects the ‘attentional set’ of the observer during visual search. First, we verified that our singleton captured attention in the ‘Attend’ block, when it was sometimes the target, and was effectively ignored in our ‘Ignore’ block, when it could never be the target. The behavioural data confirmed that participants discriminated a singleton target better than a non-salient target, and were most distracted by a singleton distractor when it was within a block where it was sometimes the target than in a block where it could safely be ignored. In this latter condition, when the singleton was never a target, the event-related peak amplitude of source activity in the cuneus was *enhanced* compared to when the salient line was equally likely to be a target or a distractor. The difference in peak amplitude was present for two event-related peaks occurring between 100-200 ms post-stimulus onset. Surprisingly, the overall presence versus absence of a salient line did not influence the amplitude of either of these peaks, regardless of attentional set. These findings suggest a goal-driven, top-down effect localised to early visual cortex.

The enhancement of the evoked response we found is likely due to the attentional set of ignoring a potentially appearing red item, which may reflect active inhibition of the salient item through enhanced tuning to red features. Within the Ignore block, behavioural performance was very similar whether or not there was a singleton. This pattern of results is consistent with the subjects being able to use the red item to their advantage in the Ignore block. Subjects were able to use the information of behavioural relevance of the colour red to either avoid attentional capture, or at the very least, to disengage rapidly from the salient distractor. In contrast, the behavioural performance in the Attend block suggests that the singleton captured attention if it appeared. The evoked activity showed an overall greater signal in the Ignore than Attend block. Based on our behavioural data, we know that the processing of the singleton differed between attentional blocks, consistent with attentional capture in the Attend and effective ignoring in the Ignore block. The association of successfully ignoring a salient item with a greater evoked response might therefore suggest that this process reflects active inhibition of the singleton location when it was present. However, the evoked response was similarly increased when the salient item was not present. This

increase may therefore reflect an active search strategy, filtering the display for a potential red item in the Ignore block, compared to the attentional capture in the Attend block. Feature-based attention can enhance sensitivity to features across the visual field, even in the absence of visual information (Serences & Boynton, 2007). The present amplitude enhancement of the evoked response may therefore be due to an effect of feature-based attention.

Alternatively, the increased evoked signal in the Ignore block compared to the Attend block may be due to different levels of task difficulty. Subjects made less errors in the Ignore block than in the Attend block, suggesting they found target search in the Ignore block easier. This suggests that an easier task may be associated with an increased early evoked response. Previous studies have shown that higher task load or difficulty is associated with an increase in evoked response amplitudes for a stimulus in a task-relevant location and a decrease for a stimulus in a task-irrelevant location (Handy, Soltani, & Mangun, 2001; O'Connell, Schneider, Hester, Mattingley, & Bellgrove, 2011; Senkowski & Herrmann, 2002), reflecting the limited capacity of attentional resources. This would suggest the opposite of what we observed here. However, these studies typically measured responses to single stimuli in each location. Our bulk response to four task-relevant stimuli may have yielded a different response than single stimuli due to local competitive effects. The speculation that an increased evoked response is associated with an easier task is additionally supported by our unexpected observation of an even larger evoked response in the Baseline block, which does not have any additional colour filtering or task set demands, and therefore may in some ways be easiest. Although behavioural results did not show better performance in the Baseline block than in the attentional blocks (see Fig. 2), this may be due to the fact that it was always performed first, in contrast to the counterbalanced Attend and Ignore blocks. A posthoc analysis comparing the singleton absent conditions in the Baseline, Ignore, and Attend blocks confirmed that there was a gradual increase in the evoked amplitude of these peaks in these respective conditions. This may suggest that our effect on evoked activity amplitude reflects the gradually increasing task demands of simple target search (Baseline), ignoring any potential red item (Ignore), and attending to any potential red item (Attend).

We did not find any modulations due to the presence of the salient item in either attentional block. This is surprising, as early visual cortex is known to be highly sensitive to stimulus

properties such as colour contrast (Conway, Hubel, & Livingstone, 2002; Henrie & Shapley, 2005) and stimulus-based salience (Beck & Kastner, 2005; McMains & Kastner, 2011; Serences & Yantis, 2007). Moreover, V1 has been proposed to contain a salience map similar to LIP and FEF (Li, 2002). This proposal has recently been supported empirically. Zhang, Zhaoping, Zhou, and Fang (2012) found that a briefly presented and masked (thus invisible) texture stimulus containing a high orientation contrast yielded an increased C1 ERP component and increased blood-oxygen-level-dependent (BOLD) response compared to lower contrasts. It is therefore surprising that we did not find any physical salience-based modulation.

There are a number of potential explanations for the lack of effect of bottom-up salience in our experiment. First, despite initially hoping to compare all four locations individually, our final analyses required looking at the display as a whole. The presence of the other three grey items may have blurred any increase caused by the salient line in the measured neural activity. Directing attention to features can not only increase responses to attended features, but can also reduce responses to unattended features (Martinez-Trujillo & Treue, 2004; Polk, Drake, Jonides, Smith, & Smith, 2008). Although such effects have only been reported in higher visual areas (Martinez-Trujillo & Treue, 2004) or areas outside the visual cortex (Polk et al., 2008), a similar system might apply to early visual cortex. If the salient line did indeed increase activity in V1/V2 cells corresponding to the relevant quadrant of the visual field, activity in V1/V2 cells corresponding to the three remaining quadrants containing non-salient lines may have been reduced at the same time. As we measured the bulk activity to four items, this may explain why we did not find any effects associated with physical stimulus salience. In addition to measuring the combined signal of one salient with three non-salient items, the response was averaged over displays in which the singleton appeared equally often in any of the four quadrants, further blurring any potentially spatially localised effects. To disentangle the responses to each individual stimulus, we need to do further experiments that maximise the power at fewer locations with stimuli that optimally activate early visual cortex. The experiments in the rest of this thesis work towards this goal.

One further possibility to explain the absence of a modulation due to physical salience is that, in our attempt not to bias our source localisation to any attentional set or salience effect, we actually biased our localisation towards the response to non-salient items. We based our sources on

the Baseline displays, which only contain the ‘non-salient’ grey lines. If displays with a singleton were associated with a different source pattern or even slightly shifted sources, obtaining evoked and induced responses from the sources based on non-salient baseline displays may have obscured or reduced any salience-specific responses. Note that this is unlikely to explain our evoked response enhancement in early visual cortex, because such source shifts would be very small-scale. Responses in these early areas are highly retinotopically organised, and small-scale retinotopic modulations within V1/V2 are unlikely to be observed using MEG. However, a bias towards sources responding to non-salient displays may explain why our responses from other sources in the brain, such as parietal and frontal areas, did not display any clear peaks or modulations due to salience or attentional set. Finally, the fact that we did not observe an M1 component, the MEG equivalent to the C1 ERP (Nakamura et al., 1997), suggests that our stimuli did not elicit strong stimulus-driven responses, which is a clear contributor to the absence of stimulus salience effects on neural activity.

The early latency of the neural modulations found by Zhang et al. (2012) suggests that the V1 salience map is purely based on stimulus-driven contrasts. However, the fact that V1 activity is also influenced by voluntarily attending to a location or feature (Luck, Chelazzi, Hillyard, & Desimone, 1997; McAdams & Maunsell, 1999; McAdams & Reid, 2005; Motter, 1993) suggests that V1 may well contain a similar salience map for goal-driven factors, or a combination of the two, similar to LIP and FEF. The notion of a combined stimulus and goal-driven salience map in V1 is supported by the fact that voluntary attention effects in V1, such as an enhanced BOLD response, also occur in response to a pre-cue in the absence of visual stimulation (Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999). Activity of V1 cells can thus be biased towards or away from a location or feature by top-down influences before stimulus onset, to then be influenced rapidly by stimulus-driven salience as the stimulus appears. Activity in V1 and/or higher visual areas is then further modulated by top-down signals at a later post-stimulus time. In short, this model implies a constant loop of updating both bottom-up and top-down information to bias neural activity within the visual system aiding the allocation of attention.

In the current study, the attentional modulation occurred at 100-200 ms post-stimulus. This timing suggests that this top-down effect is due to feedback from other cortical areas. The timing is

consistent with a comprehensive study that combined EEG and MEG with fMRI (Noesselt et al., 2002). Noesselt et al. (2002) cued attention towards either the left or right hemifield, and presented a pair of stimuli bilaterally. Subjects had to report the orientation of a letter superimposed on the stimulus in either the cued or uncued hemifield. When spatial attention was directed towards versus away from a stimulus, there was an increased amplitude contralateral compared to ipsilateral to the stimulus for several ERP and ERF components around 140-250 ms post-stimulus. Retinotopic mapping using fMRI strongly supported localisation of some of these components to V1. In contrast with these later effects, the earliest C1 ERP and M1 ERF (60-100 ms), which were also localised to V1, were not affected by attention. These findings suggest that after the initial feedforward sweep in V1, V1 is 'reactivated' by feedback from other cortical areas. The fact that in this study the P1 ERP, occurring 110-120 ms and localised to extrastriate visual cortex, was similarly increased led the authors to propose that the 140-250 ms attention-driven modulation in V1 was due to feedback from an extrastriate area. The localisation and temporal similarity of the attentional modulation we found in the present study may therefore represent an increase of neural activity in V1 due to feedback from an extrastriate area.

The attentional modulation in early visual cortex may alternatively be due to feedback from parietofrontal areas. Parietofrontal areas have traditionally been proposed to play an important role in top-down attentional processing (Corbetta & Shulman, 2002; Desimone & Duncan, 1995), and contain afferent projections to visual cortex (Baluch & Itti, 2011; Blatt, Andersen, & Stoner, 1990; Corbetta & Shulman, 2002). The latency of the top-down effect in early visual cortex in the present study is longer than what has been reported for effects in parietofrontal areas (60-100 ms) when ignoring or attending salient items (Ipata, Gee, Gottlieb, Bisley, & Goldberg, 2006; Nobre, Rao, & Chelazzi, 2006). This longer latency for our effect in visual cortex than effects in parietofrontal areas supports that our early visual modulation is due to feedback of processing in parietofrontal areas. Furthermore, studies that have directly compared attentional modulations across brain areas support this latency difference between visual and parietofrontal areas (Chelazzi et al., 1998; Chelazzi et al., 2001; Reynolds & Desimone, 2003; Saalmann et al., 2007). The present study was not designed to investigate activity in parietofrontal areas. Although we observed evoked activity sources in a number of parietofrontal regions, the waveforms extracted from these

sources did not display reliable amplitude fluctuations compared to fluctuations during the pre-stimulus baseline. We were therefore unable to reliably compare how stimulus salience or behavioural relevance modulated activity in these areas.

A feedback pattern of attentional modulations from parietofrontal to visual areas is additionally supported by studies investigating gamma oscillations. The phase relation of synchronised oscillatory activity in the gamma band between certain parietofrontal and visual areas suggests that directing attention modulates activity in visual areas such as MT and V4 in the same manner as in parietofrontal areas such as LIP and FEF (Gregoriou, Gotts, Zhou, & Desimone, 2009; Saalmann et al., 2007). As addressed in Chapter 1 (section 1.4), gamma oscillations are linked to neural communication as well as visual processing. The latter findings therefore provide particularly convincing evidence that parietofrontal areas feed back to visual areas and bias activity in these areas to suppress or facilitate processing of visual stimuli. Although such parietofrontal feedback projections are not as clearly established for V1 and V2, retrograde tracing in monkeys has shown that early visual areas receive widespread projections from several temporal and visual areas, and even some intraparietal projections (Rockland & Van Hoesen, 1994). Thus, top-down modulations of activity in early visual areas may be mediated by the parietofrontal network, possibly directly, or alternatively indirectly through higher visual areas, and gamma oscillations may play an important role in this feedback.

In the current study, we did not find any modulations in synchronisation within the gamma range for any of the stimulus displays. Gamma synchronisation is known to be strongly influenced by stimulus properties such as luminance (Rols, Tallon-Baudry, Girard, Bertrand, & Bullier, 2001) and contrast (Henrie & Shapley, 2005). Our stimuli were small, relatively far spaced apart, and quite faint due to the projector-screen combination. Our design was based primarily on behavioural literature (Bacon & Egeth, 1994; Folk et al., 1992; Yantis, 1993; Yantis & Egeth, 1999) to maximise the likelihood of attentional capture and effortful search. They were, however, non-optimal to induce gamma oscillations in early visual cortex. In contrast to the absence of gamma, we did find low-frequency synchronisation in all conditions. However, alpha power did not show any consistent variation over conditions. Alpha oscillations are thought to reflect inhibitory processes and attentional suppression (Worden, Foxe, Wang, & Simpson, 2000), and could have

80

contributed to identifying our top-down effect. However, alpha synchronisation is not tightly localised to contralateral visual cortex, and any effects of salient or non-salient items may therefore have been blurred for similar reasons as the evoked response.

In summary, the present results support the important role of top-down influences in early visual cortex occurring rapidly (~100 ms) after stimulus onset. The attentional effects in the averaged evoked response were not related to stimulus-induced low-frequency desynchronisation, and we did not observe any synchronisation in the gamma band. Future studies using stronger stimuli, with optimal parameters to induce gamma oscillations, and with activity sources that can be individually localised have great potential to identify the time course of stimulus and goal-driven attentional modulations in early visual cortex. This could help clarify its role in the constant balancing of these attentional demands required in everyday life.

The following chapters develop these optimal aspects towards addressing how bottom-up and top-down factors influence gamma synchronisation in early visual cortex. The study presented in Chapter 3 explored the gamma response to stimuli optimised for inducing robust gamma synchronisation in early visual cortex. This study addressed how bottom-up factors influence the gamma response, by investigating how the orientation of these optimal stimuli influences the induced gamma response. The study presented in Chapter 4 aimed to investigate how top-down processes associated with spatial attention modulate the gamma response. Finally, the study in Chapter 5 combined these studies, presenting a paradigm derived from the behavioural task in the current chapter, using the optimal gamma-inducing stimuli from Chapters 3 and 4. The study in Chapter 5 thus investigated how the gamma response in early visual cortex is modulated when stimulus and goal-driven factors compete for attentional allocation.

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Chapter 3 – Induced and evoked neural correlates of orientation selectivity in human visual cortex

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Induced and evoked neural correlates of orientation selectivity in human visual cortex

3.1 Abstract

Orientation discrimination is much better for patterns oriented along the horizontal or vertical (cardinal) axes than for patterns oriented obliquely, but the neural basis for this is not known. Previous animal neurophysiology and human neuroimaging studies have demonstrated only a moderate bias for cardinal versus oblique orientations, with fMRI showing a larger response to cardinals in primary visual cortex (V1) and EEG demonstrating both increased magnitudes and reduced latencies of transient evoked responses. Here, using MEG, we localised and characterised induced gamma and transient evoked responses to stationary circular grating patches of three orientations (0, 45, and 90° from vertical). Surprisingly, we found that the sustained gamma response was larger for oblique, compared to cardinal, stimuli. This “inverse oblique effect” was also observed in the earliest (80 ms) evoked response, whereas later responses (120 ms) showed a trend towards the reverse, “classic”, oblique response. Source localisation demonstrated that the sustained gamma and early evoked responses were localised to medial visual cortex, whilst the later evoked responses came from both this early visual area and a source in a more inferolateral extrastriate region. These results suggest that (1) the early evoked and sustained gamma responses manifest the initial tuning of V1 neurons, with the stronger response to oblique stimuli possibly reflecting increased tuning widths for these orientations, and (2) the classic behavioural oblique effect is mediated by an extrastriate cortical area and may also implicate feedback from extrastriate to primary visual cortex.

3.2 Introduction

The orientation preference of cells in visual cortex is systematically organised. Cells responding to a particular orientation are arranged in columns perpendicular to the cortical surface, with adjacent columns responding to similar orientations (Hubel and Wiesel, 1963; Hubel et al., 1978). This systematic organisation has subsequently been confirmed in physiological studies (Bauer et al., 1980; Kennedy and Orban, 1979; Li et al., 2003; Rose and Blakemore, 1974) as well as studies using optical imaging of intrinsic signals (Chapman and Bonhoeffer, 1998; Coppola et al., 1998; Shen et al., 2008; Wang et al., 2003; Xu et al., 2006) in several animals. These studies also point towards an unequal distribution of orientation selectivity in striate and extrastriate cortex, with a moderately larger number of cells optimally responding to horizontal and vertical than to oblique orientations, although some studies find no such bias (Sengpiel et al., 1999).

Recent advances in non-invasive neuroimaging have enabled the mapping of orientation preference in humans with high precision using high-resolution functional magnetic resonance imaging (fMRI). A study using this method has revealed striking similarities between monkeys and humans in cortical organisation (Yacoub et al., 2008). In addition, a small number of electrophysiological and neuroimaging studies seem to show a similar overrepresentation of cardinal orientations in human visual cortex. Visual evoked potentials (VEPs) in occipital cortex showed a smaller amplitude (Arakawa et al., 2000; Maffei and Campbell, 1970; Moskowitz and Sokol, 1985; Proverbio et al., 2002; Yacoub et al., 2008), as well as a longer latency (Arakawa et al., 2000; Moskowitz and Sokol, 1985) for obliquely oriented than horizontal or vertical gratings. One fMRI study has also reported an increased blood oxygen level-dependent (BOLD) response in primary visual cortex (V1) for orientations of 0 and 90° versus 45 and 135° (Furmanski and Engel, 2000).

Unsurprisingly, these findings have generally been interpreted as the neural correlate of the behavioural “oblique effect” in orientation discrimination, referring to the far superior capability to discriminate lines oriented around 0 or 90° (cardinal) versus lines around a 45 or 135° tilt (oblique) (Appelle, 1972; Campbell et al., 1966). The behavioural oblique effect is a well-replicated, robust, and rather striking phenomenon, with discrimination thresholds differing by up to a factor of four

(see Li et al. (2003) for a review). However, the amount of cardinal overrepresentation in cortical areas (e.g., Li et al., 2003), as well as the difference in signal in functional neuroimaging (e.g., Furmanski and Engel, 2000), is modest or non-existent (Sengpiel et al., 1999). These neural biases therefore seem insufficient to fully account for the large behavioural oblique effect and suggest that the orientation response in visual cortex is likely to be more complex than a simple bias in orientation representation.

Although coarse-angle orientation discrimination can be accounted for by firing of single cells, fine-angle orientation discrimination performance requires cooperation between multiple cells in V1 (Samonds et al., 2004). A specific role for synchronised cortical oscillations in the gamma range (30–70 Hz) in binding this cooperative assembly has been proposed (Samonds and Bonds, 2005) and monkey neurophysiology has shown that gamma oscillations are sensitive to stimulus orientation (Frien et al., 2000). Fast oscillations in the gamma range are a general neuronal feature in several brain areas, are robustly stimulus induced in primary visual cortex (e.g., Muthukumaraswamy et al., 2010), and are thought to play a functional role in visual perception (Friedman-Hill et al., 2000).

Establishing sustained synchronisation within the gamma-band is determined by, and critically dependent on, cortico-cortical networks of fast-spiking GABAergic interneurons that are in balance with glutamergic excitation of principal pyramidal cells (see Bartos et al. (2007) for a review). For example, both gamma power and frequency can be reversely influenced by GABA agonists and antagonists (Bartos et al., 2007), and resting GABA concentration in the human visual cortex correlates with the particular stimulus-induced gamma frequency of an individual (Muthukumaraswamy et al., 2009). Intracortical inhibition via GABAergic interneurons also appears to play an important role in orientation selectivity of cells in primary visual cortex. Electrophoretically applying the inhibitory neurotransmitter GABA in cat area 17 selectively increased tuning curves of cells that originally displayed weak orientation selectivity but did not alter orientation properties of already strongly selective cells (Li et al., 2008). Importantly, administering a GABA antagonist (e.g., bicuculline) showed the reverse effect (Li et al., 2008; Sillito, 1975; Sillito et al., 1980).

The role of GABAergic interneurons in both the establishment of gamma oscillations and sharpening orientation selectivity further supports a role for gamma synchronisation in responses to orientations. Interestingly, both gamma frequency and GABA concentration in the visual cortex of an individual have been found to negatively correlate with orientation discrimination thresholds (Edden et al., 2009). Moreover, both orientation selectivity (Frien et al., 2000; Li et al., 2003; Maffei and Campbell, 1970) and gamma oscillations (Frien et al., 2000) appear to originate at the cortical level. The gamma response in primary visual cortex could therefore contribute to our understanding of low-level orientation selectivity.

The present study aimed to investigate the role of gamma oscillations in orientation selectivity by measuring the induced gamma response in visual cortex to stimuli of different orientations using magnetoencephalography (MEG). Circular grating patches oriented 0, 45, and 90° from vertical were presented in one quadrant of the visual field, known to effectively and robustly induce gamma oscillations in contralateral V1 (Muthukumaraswamy et al., 2010). The high spatial and temporal resolution of MEG allowed us to study both the time course and localisation of oscillatory responses. If, as the modelling and animal literature suggest, gamma oscillations play a pivotal role in orientation selectivity, the gamma response for the three orientations is expected to differ in either the frequency or power at which it is evident, or both. We additionally measured the evoked response to enable comparison with previous electroencephalography (EEG) studies demonstrating the classic neural oblique effect.

3.3 Materials and methods

3.3.1 Subjects

Twelve healthy subjects participated in the experiment after giving informed consent and received payment for their participation. One subject was excluded due to excessive head movement and blinking, and one further subject due to inequality of artefacts between the conditions. All analyses are based on the remaining ten subjects (six males, four females; mean age 23.9 years, range 19–30) with normal or corrected-to-normal vision. All subjects had a previously acquired structural

MR scan (1 mm isotropic FSPGR) that was used for source localisation. All procedures were approved by the local Ethics Committee.

3.3.2 Stimuli and procedure

Each stimulus consisted of a stationary black/white sine-wave circular grating patch (maximum contrast, 3 cycle/degree, diameter 4.3°) presented in the lower left quadrant of a mean luminance grey background display, centred 2.2° both horizontally and vertically from a continuously present red fixation dot. All displays were generated using Presentation software (Neurobehavioral Systems Inc.), displayed on a Mitsubishi Diamond Pro 2070 monitor (1024×768 pixel resolution, 100 Hz refresh rate). The position of the stimulus on the screen combined with a full screen draw of 0.01 s yields a total stimulus draw lag of 5 ms (rounded upwards). All latencies reported are uncorrected.

The gratings had one of three orientations: 0 (“vertical”), 45 tangential to fixation (“oblique”), or 90° (“horizontal”) from vertical. Each trial consisted of a 2300-ms fixation-only period, followed by an 800-ms stimulus presentation, plus an additional 1–500 ms stimulus offset jitter (evenly distributed over trials), resulting in a total trial time of 3100–3600 ms. Subjects were instructed to maintain fixation for the entire experiment and to press a response key with their right index finger as fast as possible at the termination of each stimulation period, to maintain attention. These stimulus parameters and this experimental design were chosen because our previous studies have demonstrated that they robustly elicit both evoked responses and sustained narrowband gamma oscillations in human medial visual cortex (Edden et al., 2009; Muthukumaraswamy et al., 2009, 2010; Swettenham et al., 2009). Response times and errors were recorded using an MEG compatible response box. Reaction times over 700 ms resulted in a “response too slow” warning message, requiring the subject to press a button to continue. 150 Trials were presented per condition in a single randomised block, taking approximately 25 min in total.

3.3.3 MEG data acquisition and analysis

Whole-head MEG recordings were made using a 275-channel CTF radial gradiometer system sampled at 1200 Hz. An additional 29 reference channels were recorded for noise cancellation

purposes, and the primary sensors were analysed as synthetic third-order gradiometers (Vrba and Robinson, 2001). Two of the 275 channels were turned off due to excessive sensor noise.

Subjects were seated upright in the darkened magnetically shielded room. We monitored eye movements and blinks by recording vertical and horizontal electrooculograms (EOG). To achieve MRI/MEG co-registration, fiduciary markers were placed at fixed distances from three anatomical landmarks identifiable in the subject's anatomical MRIs. Fiduciary locations were verified afterwards using high-resolution digital photographs.

A TTL pulse was sent to the acquisition computer at stimulus onset, offset, and for button presses. Data were acquired continuously, then epoched offline using a window that extended 1300 ms both before and after the TTL pulse. Trials were excluded from analysis based on erroneous responses (i.e., too early, absent, or > 700 ms), eye movements/blinks (EOG measures), or visibly identifiable artefacts.

Eye movements were analysed by calculating the vector sum of the vertical and horizontal EOG traces (after baseline correction, -0.7 to 0 s), yielding one measure reflecting the overall variance per trial. The variance was then averaged over trials for each subject and condition, and the variance mean and standard deviation (SD) were calculated (0 to 0.7 s) to evaluate any general bias in eye movements and stability of fixation, respectively.

3.3.4 SAM beamformer analysis

Offline, each data set was band-pass filtered using a fourth-order bi-directional IIR Butterworth filter into 9 frequency bands: 5–15, 15–25, 25–35, 35–40, 40–50, 50–60, 60–80, and 80–100 Hz. The synthetic aperture magnetometry (SAM) beamformer algorithm as implemented in the CTF software (Robinson and Vrba, 1999) was used to create differential images of source power (pseudo-T statistics) for 0.8 s of baseline (-0.8 to 0 s) compared to 0.8 s of visual stimulation (0 to 0.8 s). Details of the calculation of SAM pseudo-T source image statistics are described elsewhere (Hillebrand et al., 2005; Robinson and Vrba, 1999; Singh et al., 2003a,b; Vrba and Robinson, 2001). For source localisation, a multiple local-spheres forward model (Huang et al., 1999) was derived by fitting spheres to the brain surface extracted by FSL's Brain Extraction Tool (Smith,

2002). Estimates of the three-dimensional distribution of source power were derived for the whole head at 5 mm isotropic voxel resolution for each subject, frequency band, and condition.

The individual SAM images of each subject were examined, and the coordinates of consistent peak activity locations were obtained. The coordinates of peak activations were separately extracted for each condition in each subject. This procedure avoided any spatial bias that could arise due to slight differences in the peak source locations for each of the three stimulus orientations. Virtual sensors were then generated separately in the extracted peak locations for each condition using SAM beamformer coefficients obtained using individual condition covariance matrices (-1.3 to 1.3 s) band-pass filtered between 30–70 Hz, 5–15 Hz, and 15–25 Hz (gamma, alpha, and beta, respectively), returning time-series from peak locations for each trial (Robinson and Vrba, 1999). Time–frequency analysis of virtual sensors was conducted using the Hilbert transform from 1 to 90 Hz in 0.5 Hz steps. Power–time and power–frequency spectrograms are represented as a percentage change from the average baseline amplitude for each frequency band. The peak amplitude, frequency, and latency were obtained for each condition from the power–frequency and power–time spectrograms between the same boundaries as the respective band-pass (e.g., 30–70 Hz for gamma), and the integrated power for each peak frequency ± 5 Hz was calculated (Muthukumaraswamy et al., 2010).

For group analysis, SAM images were normalised using FLIRT into MNI template space using an affine transform. Non-parametric permutation tests were conducted using the full permutation set (1024) for each condition with 5 mm variance smoothing and thresholded using the omnibus test statistic value at $p < 0.05$ (Nichols and Holmes, 2002; Singh et al., 2003a,b).

3.3.5 Event-related field analysis

Analysis of event-related fields (ERFs) in sensor space was conducted using the FieldTrip toolbox (www.ru.nl/fcdonders/fieldtrip). Time-locked analysis was performed on the epoched raw data after baseline correction (-0.7 to 0 s), averaging from -0.7 to 0.7 s around stimulus onset and low-pass filtering at 100 Hz. Evoked analysis was limited to 0–200 ms post-stimulus to avoid responses due to stimulus offset and motor-related activity.

Source reconstruction of the observed ERFs was done using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK; www.fil.ion.ucl.ac.uk/spm/), with identical baseline correction and averaging parameters as the sensor space analysis. After co-registration of a canonical cortical mesh with the individual's structural MRI, the averaged data were localised using a multiple local-spheres forward model and an inverse solution based on a multiple-sparse priors (MSP) reconstruction using a greedy search (Friston et al., 2008). Contrasts of current density in source space were squared and, in order to reduce inter-subject variance, normalised to an average of one (over vertices and conditions). The amplitude measures are therefore estimates of evoked signal-to-noise (SNR) power for each subject and each condition. After embedding in canonical (MNI) space, the resulting images were smoothed (with an 8 mm kernel) and peak activity was extracted.

3.4 Results

3.4.1 Task responses and performance

On average, subjects responded correctly on 97% of trials for each condition (range 90–100%), with a mean reaction time of 259 ms. A one-way repeated measures ANOVA did not show any differences between the three conditions [$F(2,18)=0.99$, $p=0.392$], suggesting that the task was easy and did not introduce any effects specific to each orientation. Excluding erroneous trials, eye blinks and macroscopic artefacts still resulted in a minimum of 97 trials for any condition in any subject (group mean: 123, 122, 122 trials for horizontal, oblique, vertical, respectively). Over conditions, the mean variance of the EOG trace in the remaining trials contained no difference in eye position bias, nor stability of fixation [one-way repeated measures ANOVA on the mean: $F(2,18)=0.04$, $p=0.959$, and SD: $F(2,18)=0.91$, $p=0.422$].

3.4.2 SAM analysis of gamma oscillations (30–70 Hz)

The individual SAM images consistently showed clear event-related synchronisation (ERS) in right medial visual cortex (contralateral to the stimulus) in the gamma range (30–80 Hz) for each of the ten subjects (Fig. 1A shows the group average one-sample t test map for the oblique condition as an

example). No other consistent loci were found for this frequency band. The mean Talairach coordinates were located within the cuneus (Brodmann area 17) for seven subjects, and the lingual gyrus (Brodmann area 18), for the remaining three subjects. For three subjects, slight differences in peak localisation resulted in a divergent annotation for one of the conditions (e.g., area 17 for two conditions and 18 for one, or vice versa), although all three locations were still adjacent, and divergence was not linked to any particular condition. In one subject, peak gamma activity for one condition (oblique) was localised to the right middle occipital gyrus, possibly corresponding to Brodmann area 18 or 19. The mean spatial difference in location between each subset of two conditions was small (5.41 mm H vs. O, 4.04 mm H vs. V, 3.94 mm V vs. O) considering that a voxel in this MEG analysis has a long side of 8.66 mm (5 mm isotropic). A one-way repeated measures ANOVA on the three individual dimensions of the Talairach coordinates showed that any spatial difference was non-systematic [$F(2,18)=0.70$, $p=0.509$; $F(2,18)=0.90$, $p=0.423$; $F(2,18)=0.19$, $p=0.826$], confirming the strong similarity in peak location for the three orientations.

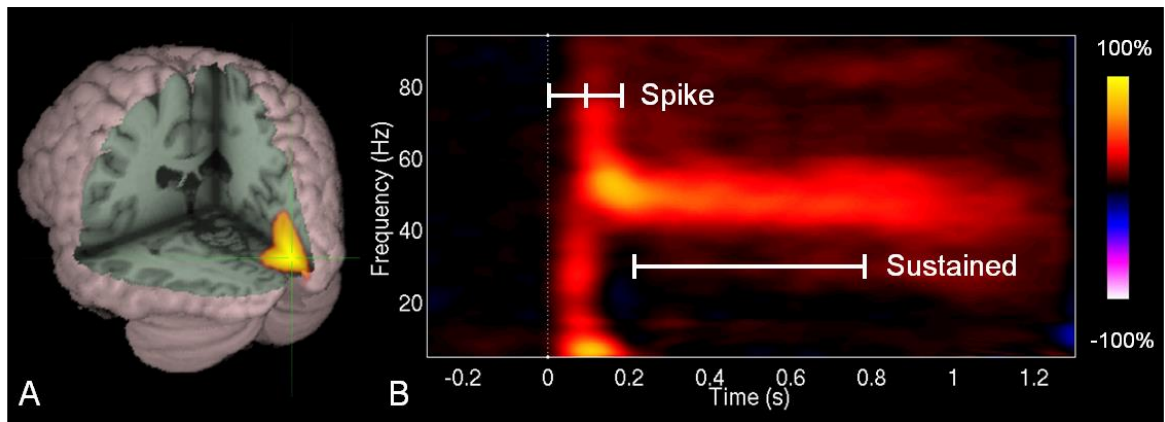


Fig. 1. (A) Group average ($N=10$) thresholded one-sample t test map ($p<0.05$, corrected for multiple comparisons) of the gamma SAM images (30–80 Hz), indicating an activity source in right medial visual cortex. Cross-hairs indicate peak activity. (B) Group average spectrogram derived from individual virtual sensors placed at peak activity in medial visual cortex. Colours represent the percentage signal change from baseline. Gamma activity (30–70 Hz) bursts in the first 200 ms post-stimulus onset (0 s), with the strongest response from 100 to 200 ms, and is sustained until stimulus offset (between 800 and 1300 ms). Both (A) and (B) are examples representing the oblique condition.

Time–frequency spectrograms created by constructing virtual sensors at peak locations in each individual's early visual cortex revealed a characteristic pattern that was consistent across subjects and conditions (Fig. 1B). Despite some variability in peak power change and time points between subjects, the spectrograms clearly show an ERS in the gamma range that is induced early (~100 ms) after stimulus onset and sustained for the duration of the stimulus (until 800 ms, then trailing off due to the 500-ms jitter). The gamma response bursts initially between 100 and 200 ms post-stimulus onset (gamma “spike”) at a higher frequency and power than the sustained activity (200–800 ms), consistent with previous animal and human MEG literature (Hoogenboom et al., 2006; Kayser et al., 2003; Swettenham et al., 2009). We therefore analysed these two time periods separately. In order to investigate the full post-stimulus time period, we also included the first 0–100 ms as a separate time window in the analysis. Note that this primarily reflects the higher frequency range (>30 Hz) of the transient pattern-onset evoked response (<50 Hz; see Figs. 1B and 2C).

The induced gamma power change appeared higher for oblique gratings than for both horizontal and vertical ones during the full stimulus time period (0–800 ms), between 30 and 70 Hz (Fig. 2A–B). A one-way repeated measures ANOVA indicated that this “inverse” oblique effect (Fig. 2D–F) was significant for both the initial 0–100 ms gamma [peak: $F(2,18)=4.98$, $p=0.019$; integrated power: $F(2,18)=7.52$, $p=0.004$], and the 200–800 ms sustained activity [peak: $F(2,18)=7.67$, $p=0.004$; power: $F(2,18)=7.65$, $p=0.004$; inter-subject variability is displayed in Fig. 3]. Post hoc comparisons revealed oblique gamma power was significantly higher than horizontal ($p<0.01$, $p<0.05$, for initial and sustained gamma, respectively) as well as vertical ($p<0.05$, $p<0.01$, respectively), whereas horizontal and vertical did not significantly differ (all post hoc p values were Bonferroni corrected for multiple comparisons). Although showing the same average pattern, gamma power differences in the 100–200 ms time window did not reach significance [peak: $F(2,18)=2.95$, $p=0.078$; power: $F(2,18)=2.60$, $p=0.102$]. Calculations of the full width at half maximum (FWHM) of the individual gamma peak between 30 and 70 Hz for the full stimulus time period (0–800 ms, Fig. 2A) showed no significant difference between conditions [$F(2,18)=1.51$, $p=0.249$], indicating that the gamma power inverse oblique effect was not due to differences in overall peak bandwidth.

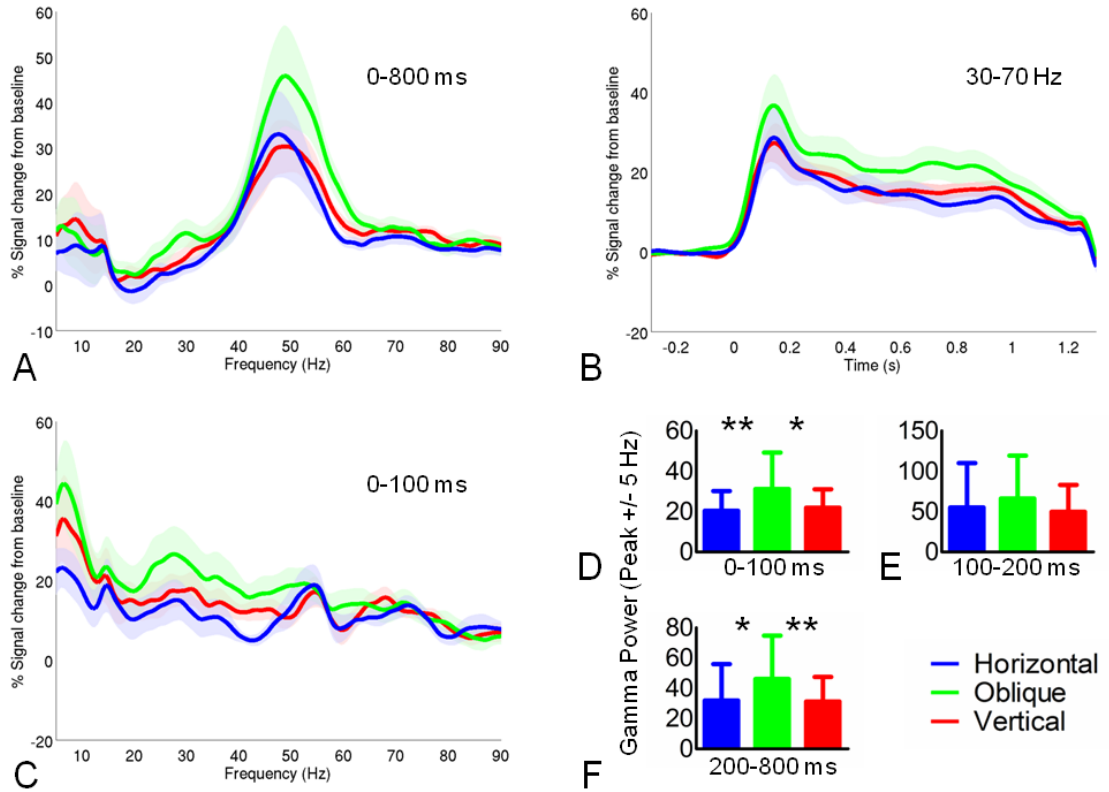


Fig. 2. (A–C) Peak SAM group average percentage signal change from baseline for the three conditions (blue: horizontal; green: oblique; red: vertical; shaded regions represent the standard error of the mean) over frequencies (A, C) and time (B) yielded from individual virtual sensors in medial visual cortex. Panel (A) and (B) demonstrate that the peak activity in the gamma range (between 0 and 800 ms, 30 and 70 Hz) for each condition is greatest for oblique. Panel (C) highlights that in addition to the transient evoked response (5–15 Hz), activity in the first 100 ms post-stimulus generally peaks at lower frequencies (20–40 Hz) than the later gamma response, particularly for the oblique orientation. (D–F) Group averages of integrated gamma power for a 10-Hz bandwidth around individual peak gamma (taken between 30 and 70 Hz) for spike (D–E) and sustained (F) gamma. Error bars indicate standard deviations. * $p < 0.05$, ** $p < 0.01$.

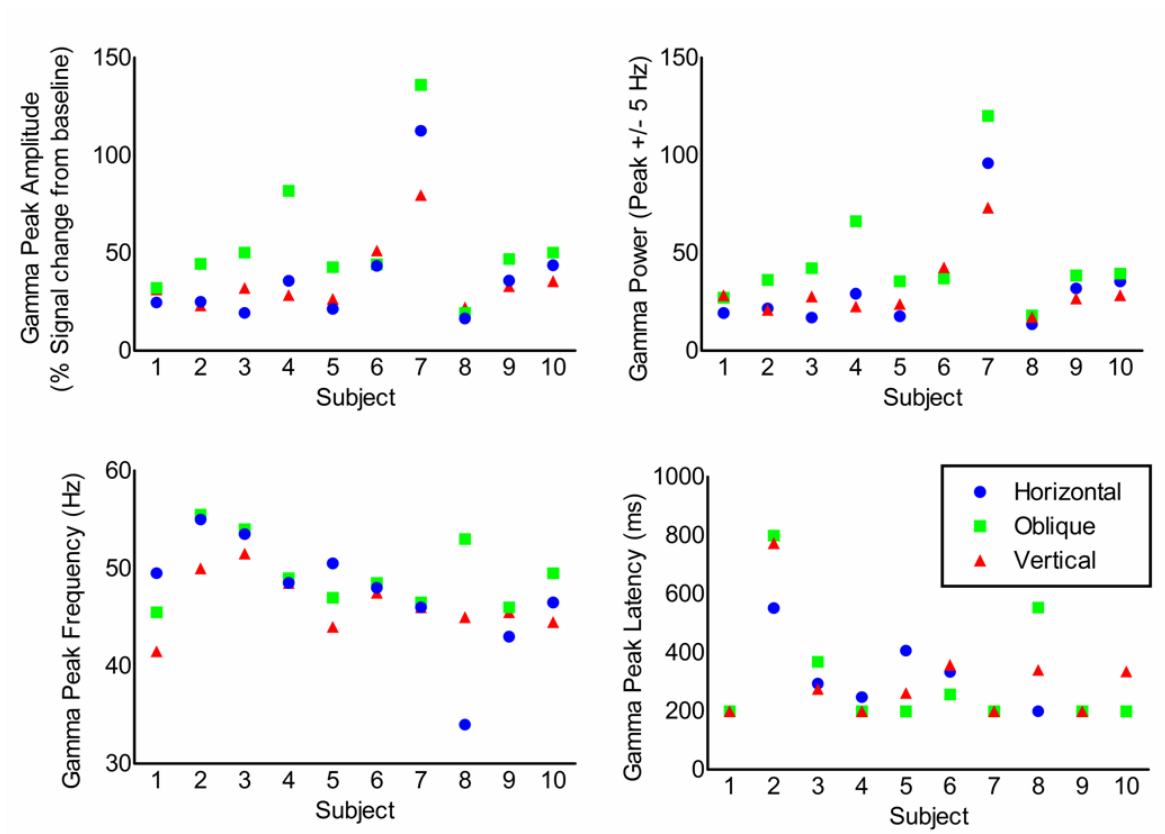


Fig. 3. Inter-subject variability in the sustained gamma response (200–800 ms post-stimulus) to the three different orientations (blue circle: horizontal; green square: oblique; red triangle: vertical). All measures were obtained between 30 and 70 Hz. The gamma power (B) was calculated as the integrated activity in a 10-Hz bandwidth around the individual's peak frequency (C). Panels (A) and (B) demonstrate that the peak amplitude and integrated gamma power measures were very similar and greatest to oblique stimuli for most subjects, whereas neither peak frequency (C) nor latency (D) differed systematically between conditions.

In contrast to gamma power, neither peak frequency nor latency of the gamma response differed consistently between the oblique and cardinal orientations. Peak frequency did not differ in either the 0–100 ms [grand mean \pm SD: 48.67 ± 15.86 Hz, $F(2,18)=1.45$, $p=0.26$] or 200–800 ms [47.77 ± 4.37 Hz, $F(2,18)=1.90$, $p=0.179$] time windows. However, there was a significant main effect of peak frequency for the 100–200 ms gamma spike [$F(2,18)=4.99$, $p=0.019$]. Post hoc tests showed that vertical (56.55 ± 6.77 Hz) peaked at a higher frequency than horizontal (52.25 ± 5.60 Hz; $p<0.05$), whereas oblique (53.30 ± 3.51 Hz) did not differ from either of the cardinal orientations. Peak latency did not differ for any of the three time windows [chronologically: $F(2,18)=0.56$, $p=0.581$; $F(2,18)=0.36$, $p=0.705$; $F(2,18)=0.46$, $p=0.636$].

Linear correlation analyses of the individual beamformer weights showed that, for all subjects, the correlations between the weights obtained separately for each condition were generally high but were not uniformly so (correlation coefficient range: 0.39–0.90, mean \pm SD: 0.76 ± 0.13 , all $p<0.0001$). This raises the possibility that the amplitude differences we see between conditions may be due to differences in the weights themselves. However, repeating the gamma response analysis using a global covariance matrix (i.e., calculated over all three conditions per subject) yielded a very similar inverse oblique effect that was significant for all three time windows [chronologically: peak: $F(2,18)=4.79$, $p=0.021$; $F(2,18)=7.86$, $p=0.004$; $F(2,18)=8.37$, $p=0.003$; power: $F(2,18)=3.87$, $p=0.040$; $F(2,18)=4.39$, $p=0.028$; $F(2,18)=11.07$, $p<0.001$]. It can be seen that the inverse oblique effect for the sustained induced gamma response in the 200–800 ms period was just as significant using this global analysis, compared to one using separate weights. Post hoc comparisons confirmed the inverse oblique effect for both measures in all time windows (all $p<0.05$), except for the earliest 0–100 ms time window (both peak and power) and the 100–200 ms window (power only), where oblique was higher than horizontal (all $p<0.05$), but not vertical. Peak frequency and latency again did not significantly differ for any time window (all $p>0.05$). The similarity of the global covariance matrix calculations to the previous analysis indicates that the inverse oblique effect in induced and sustained gamma amplitude was not due to projection through different linear channel weightings for the three conditions.

3.4.3 SAM analysis of low-frequency oscillations (5–15 Hz and 15–25 Hz)

In addition to the clear increase in synchronised activity in the gamma frequency band, the SAM images constructed for both the alpha (5–15 Hz) and beta (15–25 Hz) band showed a stimulus-induced event-related desynchronisation (ERD) that was located more laterally in contralateral visual cortex relative to the gamma ERS in medial visual cortex. Constructing virtual sensors at peak locations of this lateral occipital area and analysing the resulting time–frequency spectrograms (in time windows: 0–150, 150–250, 250–350, and 350–800 ms) did not yield any significant differences between the three conditions in either low-frequency band.

3.4.4 Event-related fields and source localisation

Sensor space distributions of individual activity averaged over trials per condition show a clear evoked peak elicited around 80 ms post-stimulus over right-lateralised posterior sensors (Fig. 4A, left). A second and third peak were typically observed between 100 and 200 ms, also localised over posterior sensors, although less focal and positioned slightly more laterally and parietally than the first peak (Fig. 4A, middle and right). These surface configurations were present for all subjects, with slight variation in peak time points and subset of occipitoparietal sensors involved. To investigate the behaviour of these surface distributions over subjects more closely, we focused on right-lateralised occipital and parietal sensors only (40 of 273 sensors; 18 occipital and 22 parietal; positions are highlighted in Fig. 4A in white).

The average ERFs over right occipital sensors (Fig. 4B, top) show a clear pattern for all three orientations, peaking initially around 80 ms and later around 150 ms, in line with the observed topographic plots, although right parietal sensors (Fig. 4B, bottom) show larger inter-subject variability. The parietal average contains a hint of the same 80-ms peak as observed occipitally, but only for the oblique condition, whereas a later peak is evident around 110–120 ms for all three conditions, slightly earlier than the occipital 150-ms peak. To better investigate the differences in evoked fields over time between the orientations, we calculated the absolute of the average ERF per subject and condition in each sensor, then averaged the resulting time courses over all right occipital and parietal sensors. We then conducted paired *t* tests on these values at each time sample between every subset of two conditions. The resulting *t* values are plotted in Fig. 5,

with green markers indicating a significantly larger response for oblique over the respective cardinal, red indicating the opposite, and black indicating a difference between the two cardinal orientations (uncorrected $p < 0.05$).

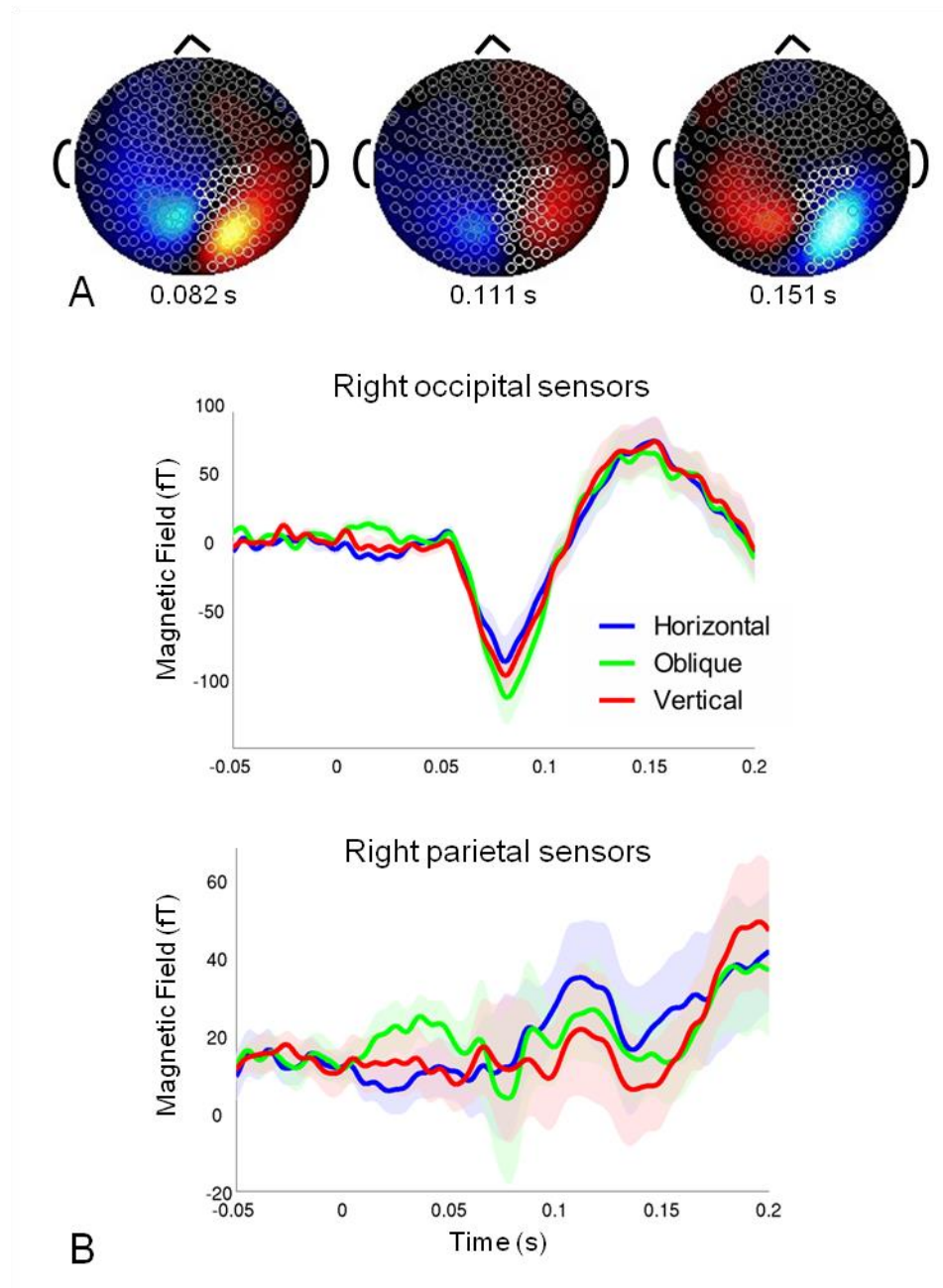


Fig. 4. Event-related fields. (A) Example for a single subject of a typical sensor-level response to oblique stimuli at the three main peak latencies. The MEG sensors selected for further analysis are highlighted in white. (B) Group average ERFs plotted by time for all right occipital (upper graph) and parietal (lower graph) sensors (blue: horizontal; green: oblique; red: vertical; solid lines \pm transparent area, group average \pm standard error of the mean).

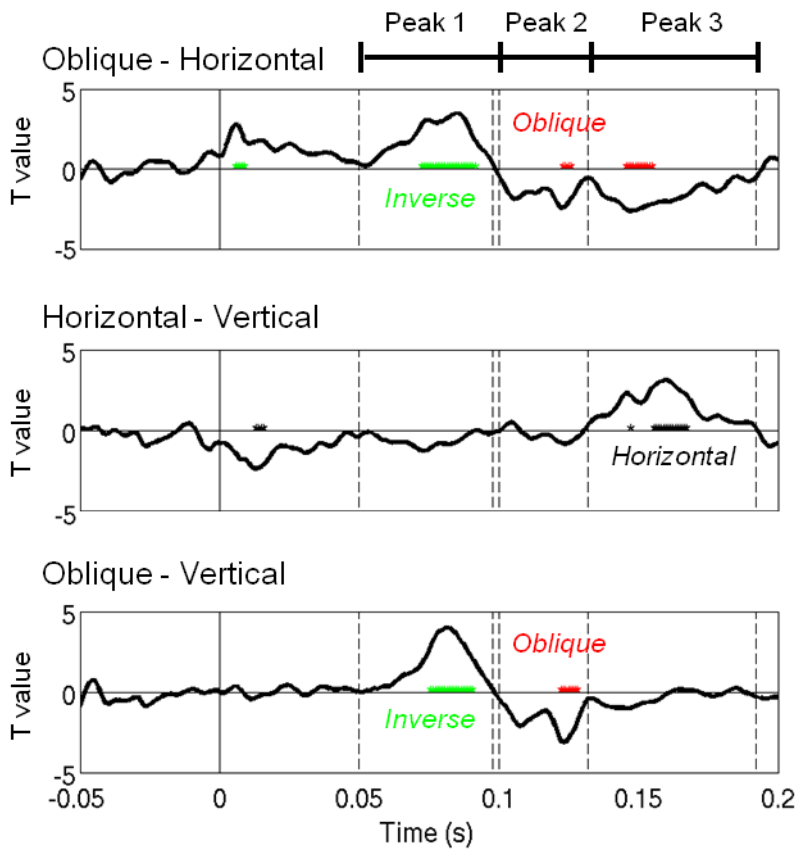


Fig. 5. Group average comparisons of the absolute ERF, averaged over all right occipitoparietal sensors, for each subset of conditions (paired t tests, asterisks indicate $p < 0.05$, uncorrected). Green asterisks represent an inverse oblique effect (“Inverse”); red a classic oblique effect (“Oblique”); black shows time periods when the response to horizontal was greatest. Dotted vertical lines indicate time window definitions: 50–98 ms (“Peak 1”), 100–132 ms (“Peak 2”), and 132–192 ms (“Peak 3”) after stimulus onset (0 s).

Interestingly, the t values suggest an inverse oblique effect for the 80-ms peak, that is, a greater response to oblique than cardinal orientations, whereas the classic oblique effect can be observed around 120 ms. A third pattern around 150 ms suggests a higher response for horizontal over both other orientations. Based on the observed peaks in ERFs over both the occipital and parietal sensors, and the t value patterns, we defined three windows for further analysis: 50–98 ms (“Peak 1”), 100–132 ms (“Peak 2”), and 132–192 ms (“Peak 3”).

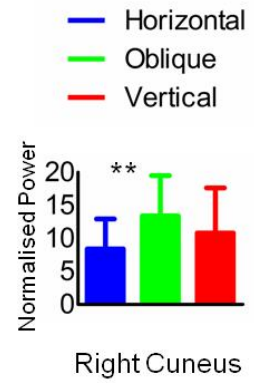
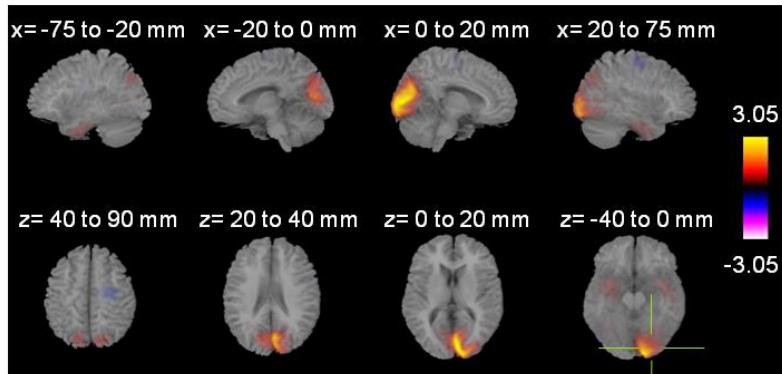
A one-way repeated measures ANOVA confirmed a significant inverse oblique effect for the maximum amplitude of the occipitoparietal absolute-average during Peak 1 [$F(2,18)=13.49$, $p<0.001$; post hoc comparisons $p<0.001$ H vs. O, $p<0.01$ V vs. O, no difference H vs. V]. Latency of the earliest ERF peak was very similar for all three conditions [81 ± 9 ms, 78 ± 7 ms, and 81 ± 8 ms on average (mean time point \pm SD), for H, O, V, respectively, $F(2,18)=0.48$, $p=0.630$]. In contrast, this average occipitoparietal activity did not significantly differ for Peak 2 or Peak 3, in either maximum amplitude [Peak 2: $F(2,18)=1.71$, $p=0.209$; Peak 3: $F(2,18)=1.37$, $p=0.280$] or latency [Peak 2: 123 ± 12 ms, 121 ± 13 ms, and 120 ± 10 ms, $F(2,18)=0.77$, $p=0.477$; Peak 3: 158 ± 23 ms, 150 ± 22 ms, and 153 ± 22 ms, $F(2,18)=1.04$, $p=0.374$].

SPM source configurations for the three peaks were reconstructed per subject using identical peak time points as the sensor space analysis. Because of the larger variability for the later two peaks, activity was imaged for a 10-ms window around Peak 1 and a 20-ms window around Peak 2 and 3. The resulting source configurations had very similar peak localisation coordinates for the three conditions, displayed in Fig. 6 as difference images in normalised power between the oblique and cardinal conditions (calculated by subtracting the mean of the group average activity in the vertical and horizontal conditions together from the group average activity in the oblique condition). Although for each time window, a source of evoked activity was localised to the calcarine in the right hemisphere (right cuneus), the consistency of this localisation varied for the three peaks. For Peak 1, the right cuneus (Brodmann area 17) was always clearly identified as a source for every subject, with no other identifiable consistent foci. For one subject, one condition (oblique) was localised to the lingual gyrus, whereas the other two conditions were also localised to the right cuneus.

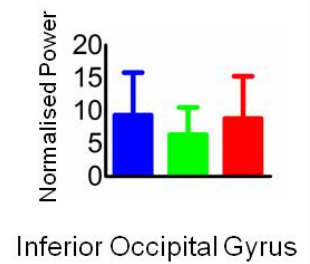
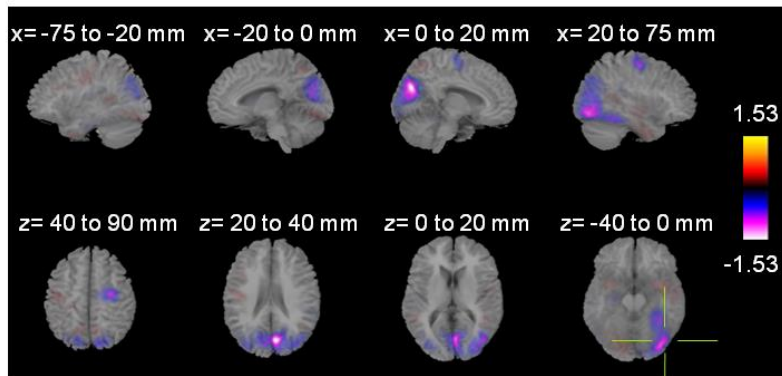
Fig. 6. SPM8 source localisation of evoked responses. All data shown are based on the normalised power estimates, relative to the mean across all vertices in all conditions for each subject. The activation maps on the left show four sagittal (top) and axial (bottom) slices representing relative difference images in normalised power for each peak (averaged over the *x* and *z* Talairach coordinates as indicated). The images were calculated by subtracting the mean of the group average activity in the vertical and horizontal conditions together from the group average activity in the oblique condition. A positive activity focus (orange–yellow) thus represents a larger response to oblique (“inverse oblique effect”), and a negative activity focus (blue–white), a smaller response to oblique compared to the cardinals (“classic oblique effect”). The colour bars in each panel indicate the maximum and minimum relative difference values displayed in that respective panel. Cross-hairs indicate the location of the most consistent peak activity, which was within the right cuneus for Peak 1 and within a more lateral occipital source for Peaks 2 and 3. The bar graphs on the right represent, for each stimulus condition, the mean across subjects of the normalised power estimates (relative to the mean across all vertices in all conditions for each subject) that was extracted at the indicated peak location for each individual. Error bars indicate standard deviations. ** $p < 0.01$.

Peak 1 (50-98 ms)

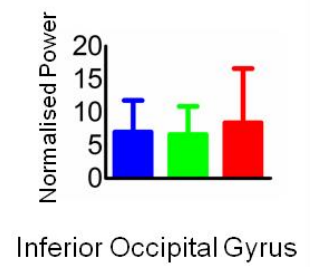
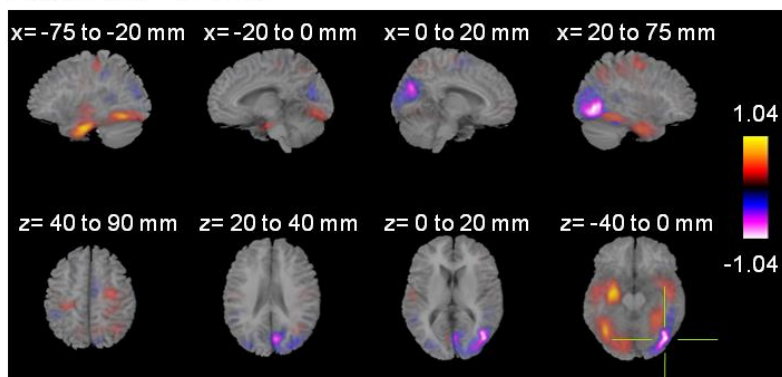
Oblique – Cardinals:



Peak 2 (100-132 ms)



Peak 3 (132-192 ms)



For both Peaks 2 and 3, the cuneus was less prominent, and not always clear for every subject individually. A more consistent focus for these later peaks around 120 and 150 ms was observed more laterally, although the exact spatial location of this source varied slightly more amongst subjects than the location of the right cuneus source. Coordinates of peak activity for both these peaks were located in a number of adjacent areas, including the inferior occipital and temporal gyri, middle occipital and temporal gyri, and in one case the lingual gyrus, and in one other the supramarginal gyrus. Separate one-way repeated measures ANOVAs on each of the three individual coordinate dimensions revealed no systematic spatial differences for any of the three peaks. There was a trend towards significance for one coordinate of Peak 3 ($p=0.059$), but none of the post hoc comparisons were significant, even uncorrected for multiple comparisons (all other $p>0.148$).

In line with the results from sensor space analysis, the group averages (Fig. 6) showed an inverse oblique effect for peak activity in the right cuneus during Peak 1, in contrast to a trend towards a classic oblique effect for both the right cuneus and inferior/middle occipital gyrus during Peak 2 and Peak 3. Individual source localisations confirmed a significant inverse oblique effect [$F(2,18)=12.26$, $p=0.0004$] for Peak 1, although the only post hoc comparison reaching significance was oblique > horizontal ($p<0.001$). For Peaks 2 and 3, we only extracted individual peak activity in the inferior/middle occipital gyrus, and not in the cuneus, because of the lack of inter-subject consistency for the latter source. However, there were no significant differences between the three orientations in this lateral occipital area for either Peak 2 [$F(2,18)=2.08$, $p=0.154$] or Peak 3 [$F(2,18)=1.29$, $p=0.299$].

Taken together, these results suggest that the early evoked activity peak around 80 ms post-stimulus shows a robust inverse oblique effect, where there is a greater response to oblique than cardinal orientations. This inverse oblique effect is mediated by early, possibly primary, visual cortex. Activity evident at later latencies, peaking between 100 and 132 ms post-stimulus, seems to show a trend towards the reverse pattern, reflecting the “classic” oblique effect as frequently reported in the literature. This classic oblique effect seems mainly mediated by a more lateral occipital area, although medial (“earlier”) visual areas may also contribute to the scalp distribution.

3.5 Discussion

In the present study, we unexpectedly found an inverse oblique effect in the amplitude of the induced gamma response in primary visual cortex to passively viewed stationary gratings. This greater response to oblique over cardinal orientations was also evident in the earliest evoked response (~80 ms post-stimulus), in sharp contrast to later latencies (100–150 ms), where we observed a trend towards the classic oblique effect. The source of the initial evoked response was localised to medial visual cortex, whereas the latter seems to have a more inferolateral origin. Peak gamma frequency did not show any consistent differences for oblique versus cardinal orientations.

Both the early evoked response and the induced gamma response displayed the exact opposite of the classic oblique effect that has frequently been reported in both the EEG and fMRI literature, where cardinal orientations generate greater responses than obliques. However, the EEG studies mostly focused on responses 100 ms post-stimulus or later, such as the P100 (Arakawa et al., 2000; Moskowitz and Sokol, 1985; Proverbio et al., 2002) or P300 (Proverbio et al., 2002), or the investigated latency was not clearly indicated (Maffei and Campbell, 1970). The three identified peaks in our evoked magnetic fields are in good agreement with the magnetic equivalents (i.e., N75m, P100m, N145m) of the visual evoked potentials N75, P100, and N135 in the EEG literature (e.g., Odom et al., 2004) that have been described for several visual stimuli in both pattern-reversal (Nakamura et al., 1997; Tabuchi et al., 2002), and pattern-onset studies (Tzelepi et al., 2001), although evoked response patterns may differ between the two paradigms (Shagass et al., 1976). Moreover, the source in medial visual cortex for the first peak is consistent with previous equivalent current dipole (ECD) localisation of the VEP N75 to striate cortex (Nakamura et al., 1997; Tabuchi et al., 2002), with fMRI strongly supporting the accuracy of this localisation (Di Russo et al., 2005). This combination of an early response latency and localisation to striate cortex suggests that the inverse oblique effect reflects an initial bottom–up response to orientation within primary visual cortex.

In line with this suggestion, the inverse oblique effect we found for induced gamma power was similarly localised to medial visual cortex, a region generally encompassing V1. For gamma power, the effect was most evident in the sustained period (>200 ms post-stimulus) but also in the

earliest transient response (0–100 ms) within the lower range of gamma frequencies. Although not significant, the power of the initial high-frequency gamma “spike” at 100–200 ms showed a similar trend towards an inverse oblique effect.

A behavioural inverse oblique effect has been reported previously using high-level stimuli resembling natural scenes (Essock et al., 2003; Hansen and Essock, 2004) and translational Glass patterns (Wilson et al., 2001). To our knowledge, the only EEG study that found a larger response for oblique than cardinal orientations also used a complicated high-level stimulus, and only found the effect for the P300 VEP (Heinrich et al., 2008). In contrast, we found this response pattern rapidly after onset of a passively viewed low-level grating patch. This suggests that the neural inverse oblique effect identified here is different from these late-processing effects and instead reflects an early bottom–up response.

In contrast to the inverse oblique effect in the earliest part of the evoked response, the trend towards a classic oblique effect at around 120 ms was less robust with greater inter-subject variability. Source localisation of the evoked response at around 100–150 ms indicated a prominent lateral occipital source in addition to a less consistent source in medial visual cortex. Although a striate origin is generally also found for the P100m (Nakamura et al., 1997; Tabuchi et al., 2002), comparing the localisation of ECDs with fMRI only supported this for a P125/N135 component. Dipoles modelled for P95 and later components were more complex involving additional areas over V1, at least for a pattern-reversal stimulus (Di Russo et al., 2005). Moreover, the P100m is not always evident (Tabuchi et al., 2002) or displays large inter-subject variability (Nakamura et al., 1997; Tzelepi et al., 2001) in response to a visual stimulus. When this component is present, it seems to recruit more neurons within V1 (i.e., is less focal) than the N75m (Nakamura et al., 1997). Thus, our finding of a more complex source geometry for the 100–150 ms response is in good agreement with the previous literature and suggests that the classic neural oblique effect may be mediated by a region separate from, or at least additional to, V1.

However, a discrepancy still remains between our findings and previous ERP (Maffei and Campbell, 1970) and fMRI (Furmanski and Engel, 2000) studies that show only a single neural response that is greater for cardinal stimuli, compared to obliques. We believe that this can be explained in terms of the greater spatial resolution of MEG, compared to EEG, and its greater

temporal resolution, compared to fMRI. In the current MEG study, we have demonstrated two spatially resolved sources (striate and extrastriate) that have opposite orientation tuning characteristics, whereas with EEG these two responses may be spatially smeared so that the “classic” oblique effect dominates. Alternatively, previous ERP studies may primarily reflect activity from a neural population that is indeed more tuned to cardinal orientations but is radially oriented such that MEG is much less sensitive to its effects. This could be assessed by repeating our study using simultaneous MEG and EEG recordings.

In a similar fashion, the BOLD oblique effect in V1 previously found by a single fMRI study (Furmanski and Engel, 2000) can be explained by the poor temporal resolution of fMRI, which leads to the temporal smearing of early inverse oblique effect responses with later responses that are bigger for the cardinal orientations. These later responses could reflect feedback mechanisms from extrastriate cortex to earlier visual areas mediating the classic oblique effect, after the initial bottom–up response in early visual cortex. Note that evoked components from 100 ms onwards still had an additional source in medial visual cortex for most subjects, albeit weak, that displayed the same general trend towards the classic oblique effect as the lateral area.

The hypothesis that orientation biases in medial cortex might be driven by feedback from extrastriate visual areas has some recent support from animal neurophysiology. Deactivating a middle temporal visual area (area 21a) in cat by local GABA administration abolished the neural oblique effect in primary visual cortex (Liang et al., 2007; Shen et al., 2008), whereas activating this area by injecting glutamate enhanced it (Liang et al., 2007). Moreover, the cardinal overrepresentation compared to obliques was 4.6 times larger in area 21a than in V1 (Huang et al., 2006). Although we cannot assess whether the lateral visual area we found corresponds to cat area 21a (equivalent to monkey V3/V4 (Liang et al., 2007)), these findings do support a feedback mechanism for orientation selectivity from a higher visual area to V1.

The orientation tuning of the V1 BOLD response seen in a previous study (Furmanski and Engel, 2000) could therefore reflect a mixture of early bottom–up effects and feedback from higher-level areas, which may well result in a bigger response, on average, to cardinal orientations. In fact, an inverse oblique effect for the BOLD response in V1 has recently been reported in another fMRI study (Swisher et al., 2010). Their inverse oblique effect was very small compared to

the present gamma response (~2% vs. ~10–15% signal change difference, respectively), which could be explained by a brief but strong inverse oblique effect in V1 being partially overruled by a later classic effect.

It is also possible that paradigmatic differences could contribute to the opposing findings. Orientation selectivity has been shown to be influenced by a number of parameters, such as spatial frequency (Arakawa et al., 2000; Moskowitz and Sokol, 1985), stationary versus drifting or reverse-alternating gratings (Frien et al., 2000; Xu et al., 2006), and eccentricity (Bauer et al., 1980; Huang et al., 2006; Xu et al., 2006). Also, some research points towards a “radial bias”, where neural responses are larger to orientations aligned with the radius from the centre of gaze than to tangentially oriented ones (Sasaki et al., 2006). We only presented stimuli in the lower left quadrant, with the oblique stimuli oriented perpendicular to the fixation point and compared them to cardinal ones, which were neither radial nor tangential. Therefore, this radial bias theory cannot explain our results. Radial bias would merely predict that the opposite oblique would generate an even larger inverse oblique response, although such bias may be most pronounced at the horizontal meridian (Huang et al., 2006). Whether opposed obliques yield a different response than the currently used perpendicular ones, or how altering spatial frequencies, moving gratings, eccentricities, and location in the visual field affect the present findings is a question for future research.

The fMRI studies mentioned above tested only 3–4 individuals. Although the inverse oblique effect in the present study was quite robust on average, it differed in magnitude over subjects (Fig. 3). This suggests that individual differences in orientation bias can be quite profound, which could well explain contradictory results in studies with very low numbers of subjects. In fact, even the generally reported overrepresentation of cells preferring cardinal versus oblique orientations is not always unequivocally replicated. A comprehensive study comparing single-cell data taken from more than 4000 cells in the striate cortex of cats found a general overrepresentation of horizontal-preferring cells over vertical, and vertical over oblique (Li et al., 2003). Another study found a vertical predominance in number of voxels using high-resolution fMRI, where the differences between horizontal and oblique varied over individuals (Yacoub et al., 2008). Others found both of these patterns in V1 cells within the same study (Sengpiel et al., 1999), variation in the strength of cardinal overrepresentation (Chapman and Bonhoeffer, 1998), or sometimes even a

predominance of oblique cells (Liang et al., 2007). These individual differences could also explain why the trend towards a classic oblique effect that we found for evoked activity around 100 ms was not significant in the source analysis.

The fact that, on average, anatomical studies demonstrate a moderate preference for cells representing the cardinals does, however, need to be reconciled with our finding of an early inverse oblique effect in medial visual cortex. One possible explanation is that cells preferring cardinal orientations exhibit a sharper orientation tuning function than those preferring obliques. If the width of the tuning function increases gradually from cardinal to oblique cells, cells preferring orientations slightly differing from oblique (e.g., 40 versus 45°) would also have a fairly broad tuning function, whereas tuning curves of cells preferring the same orientation difference from cardinal (e.g., 85 vs. 90°) would still be fairly sharp. An obliquely oriented stimulus would then induce firing in both cells preferring oblique and those slightly differing from oblique, whereas a cardinal stimulus would only activate the perfectly cardinally tuned cells. All of the non-invasive human neuroimaging tools (MEG, EEG, fMRI) are dependent on bulk integration of activity across several square millimetres of cortex, pooled across all cells whatever their orientation preference. This means that although there may well be a moderate preponderance of cells preferring cardinal orientations, if more cells are activated by an oblique stimulus, this could well lead to a bigger bulk signal, compared to the cardinals. Whether we see an inverse oblique effect or a classic oblique effect will then depend both on the relative number of cells tuned to each orientation and the width of the tuning curve for each orientation.

This speculation of different tuning curve widths for cells tuned to different orientations is partially supported by some animal neurophysiology studies showing sharper orientation tuning for cardinal over oblique-preferring cells in V1 (Kennedy and Orban, 1979; Rose and Blakemore, 1974), and V2 (Wang et al., 2003), although others only found this for horizontal compared to any other orientation in V1 (Li et al., 2003). This difference in tuning sharpness is most, if not exclusively, evident in simple cells (Li et al., 2003; Rose and Blakemore, 1974), underlining the critical role of V1 in orientation selectivity. Note that if the orientation tuning functions for oblique stimuli are indeed wider than for the cardinals, this could help explain why behavioural discrimination performance is so much poorer for oblique stimuli. In a previous study (Edden et al.,

2009), we reported a highly significant oblique effect in orientation discrimination thresholds to very similar stimuli as used in the present study. The present results, combined with these earlier behavioural results, support the idea that a larger neural response and possibly wider tuning functions may underlie poorer discrimination performance. However, future research should compare neural responses directly with behavioural performance measures to properly assess this correlation.

In summary, the present MEG study demonstrates a new finding of a neural inverse oblique effect in contralateral medial visual cortex in humans. The robust presence of this effect in both the initial evoked response and the induced gamma power in response to simple gratings suggests that these findings reflect an early low-level orientation response. Despite a possible overrepresentation of cardinal over oblique-preferring cells in visual areas, a sharper orientation tuning for those cardinally responding cells in V1 provides a potential explanation for the present results. We speculate that the subsequent trend of reversal towards a classic oblique effect in the evoked response, mainly contributed by higher visual areas, indicates a feedback mechanism underlying this well-reported neural effect that may also contribute towards the underlying neural mechanism for the behavioural oblique effect.

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Chapter 4 – Sustained visuo-spatial attention increases high-frequency gamma synchronisation in human medial visual cortex

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Sustained visuo-spatial attention increases high-frequency gamma synchronisation in human medial visual cortex.

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Sustained visuo-spatial attention increases high-frequency gamma synchronisation in human medial visual cortex

4.1 Abstract

Visual information processing involves the integration of stimulus and goal-driven information, requiring neuronal communication. Gamma synchronisation is linked to neuronal communication, and is known to be modulated in visual cortex both by stimulus properties and voluntarily-directed attention. Stimulus-driven modulations of gamma are particularly associated with early visual areas such as V1, whereas attentional effects are generally localised to higher visual areas such as V4. The absence of a gamma increase in V1 is at odds with robust attentional enhancements found with other measures of neuronal activity in this area. Here we used magnetoencephalography (MEG) to explore the effect of spatial attention on gamma activity in early visual cortex using an optimal gamma-inducing stimulus and strong attentional manipulation. In separate blocks, subjects attended to either a parafoveal grating patch that was optimal for inducing gamma activity in contralateral V1, or a small line at fixation, effectively attending away from the gamma-inducing grating. Both items were always present, but rotated independently and unpredictably around one of four angles. The rotating grating induced gamma synchronisation in medial visual cortex at 30-70 Hz, and in lateral visual cortex at 60-90 Hz, regardless of whether it was attended. In contrast, directing spatial attention at the grating increased gamma synchronisation in medial visual cortex at 60-90 Hz only. These results demonstrate that gamma activity in early visual cortex can be increased by spatial attention in humans, and suggest that stimulus and goal-driven modulations may be mediated at different frequencies within the gamma range.

4.2 Introduction

Voluntarily directing attention to an area in space markedly improves the processing of visual information in that region, making it faster and more efficient (Carrasco, Ling, & Read, 2004; Posner, 1980). This beneficial effect of spatial attention is reflected in the modulation of neuronal activity, enhancing firing rates in cells in monkey visual cortex (Luck, Chelazzi, Hillyard, & Desimone, 1997; Maunsell, 1995; McAdams & Reid, 2005; Moran & Desimone, 1985; Motter, 1993), as well as population activity measured in human neuroimaging studies (Mangun, Hillyard, & Luck, 1993; Martinez et al., 1999; Noesselt et al., 2002; Proverbio, Esposito, & Zani, 2002). These voluntary attention effects are thought to be mediated through a parietofrontal network, which modulates activity in visual areas via top-down feedback connections (Bisley, 2011; Corbetta & Shulman, 2002; Martinez et al., 1999; Noesselt et al., 2002; Serences, Saproo, Scolari, Ho, & Muftuler, 2009). The output of visual brain areas in response to a visual stimulus ultimately reflects a combination of the physical properties of the stimulus (bottom-up processing) with goal-related top-down influences. To establish such an interaction, neuronal communication is necessary not only between areas but also locally (Donner & Siegel, 2011; Fries, 2005).

A likely mechanism for mediating both between and within-region neuronal communication is synchronised oscillatory firing (Schnitzler & Gross, 2005). When neurons synchronise the phases of their oscillations, the impact of their post-synaptic potentials on the activity of the post-synaptic neuron is amplified, modulating the effective gain (Jensen, Kaiser, & Lachaux, 2007). This amplification, combined with the ability to rapidly synchronise and desynchronise, makes oscillatory synchronisation a prime candidate to mediate neuronal communication at the global and local level, enabling efficient visual processing (Fries, 2005). Visual processing is particularly associated with activity in the gamma range (30-70 Hz), which is thought to reflect local processing (Schnitzler & Gross, 2005). Gamma oscillations are robustly stimulus-induced (Hoogenboom, Schoffelen, Oostenveld, Parkes, & Fries, 2006; Muthukumaraswamy, Singh, Swettenham, & Jones, 2010), reflect the retinotopic organisation of the primary visual cortex (Rols, Tallon-Baudry, Girard, Bertrand, & Bullier, 2001), and are thought to be linked to neuronal firing (Rols et al., 2001).

The visual gamma response is modulated by stimulus properties (Friedman-Hill, Maldonado, & Gray, 2000; Koelewijn, Dumont, Muthukumaraswamy, Rich, & Singh, 2011) and is enhanced when spatial attention is voluntarily directed towards versus away from a stimulus (Fries, Reynolds, Rorie, & Desimone, 2001; Fries, Womelsdorf, Oostenveld, & Desimone, 2008; Gruber, Müller, Keil, & Elbert, 1999; Siegel, Donner, Oostenveld, Fries, & Engel, 2008), suggesting a functional role in the processing of both bottom-up and top-down information. To date, attentional gamma modulations have generally been localised to higher extrastriate visual areas, such as V4 (Fries et al., 2001; Fries et al., 2008). In contrast to bottom-up effects, in V1, attention has been found to either decrease (Chalk et al., 2010) or not affect (Siegel et al., 2008) gamma synchronisation. As gamma oscillations are linked to both firing rate (Rols et al., 2001) and the blood-oxygen-level-dependent (BOLD) response (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001), these findings seem at odds with the consistent finding of attention-related increases in V1 in studies using single-cell recording or functional Magnetic Resonance Imaging (fMRI) (Gandhi, Heeger, & Boynton, 1999; Martinez et al., 1999; McAdams & Reid, 2005; Motter, 1993; Noesselt et al., 2002). In the present study, we used MEG to measure the contralateral gamma response to a grating known to strongly induce gamma synchronisation in early visual cortex (Koelewijn et al., 2011; Muthukumaraswamy et al., 2010, Fig. 1A). Eighteen healthy participants traced the orientation of either this parafoveal grating ('attend grating') or a small line at fixation ('attend centre') with a joystick. Both items were always present, but rotated independently and unpredictably around one of four angles. The task therefore required covert sustained attention directed either towards or away from the grating. This provides a robust test of the hypothesis that gamma synchronisation in early visual cortex is subject to attentional modulation, reflecting the critical role of gamma oscillations in visual perception.

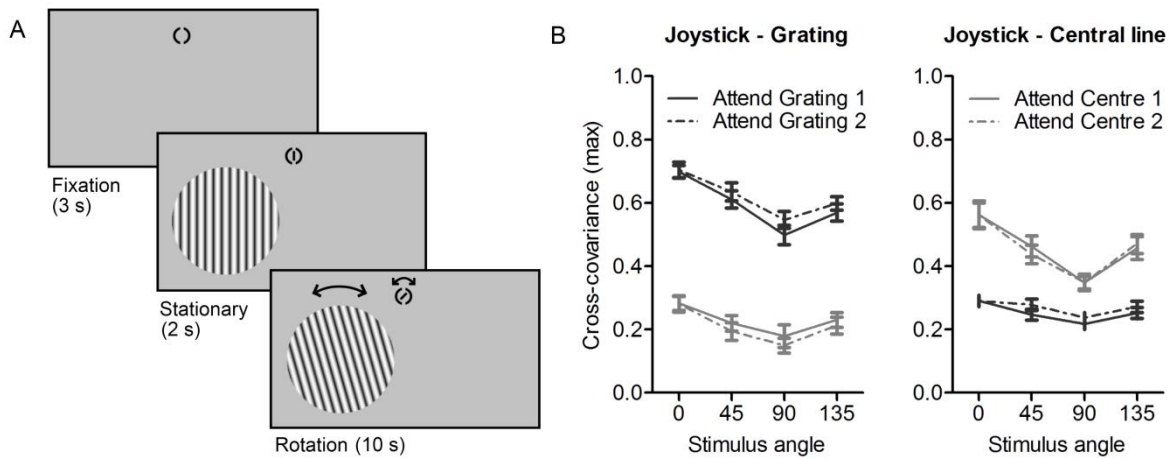


Fig. 1 Paradigm and behavioural results. (A) Example stimulus displays (not to scale). Using a joystick, subjects either matched the orientation of the parafoveal grating ('attend grating') or the small line at fixation ('attend centre'). The open circle at fixation provided feedback regarding the orientation of the joystick during both stationary and rotation periods (joystick feedback circle). At stimulus onset, the grating and central line appeared with the same orientation (one of four orientations, middle display; example shows a vertical start position (0°)). The last display is a static depiction of a possible stimulus configuration during the rotation period of the trial, where both central line and grating rotated $5\text{--}40^\circ$ around the trial angle, unpredictably and independently of each other. Arrows illustrate movement and were not present in the stimulus displays. (B) Behavioural results. Data points display the group average ($N=18$) of the maximum cross-covariance per orientation between the angle of the joystick and the parafoveal grating (left panel) and between the angle of the joystick and the central line (right panel) over the 12 s stimulation period. The two graphs clearly demonstrate the double dissociation between the 'Attend Grating' (dark gray lines) and 'Attend Centre' conditions (light gray lines), confirming that the correct item was attended in each condition. The solid lines (1; first run) and dotted lines (2; second run) demonstrate that the manipulation was successful in both recording runs, and the similarity between these two lines suggest that task practice did not affect performance. Error bars indicate SEM.

4.3 Results

4.3.1 Behavioural results

The joystick data showed our attentional manipulation was successful: subjects traced the item they were instructed to attend in each block, and this was consistent for both recording runs (Fig. 1B). A three-way repeated measures ANOVA on the maximum cross-covariance between the joystick and the *grating* angle showed significant main effects of both condition ($F(1,17)=192.67, p<0.0005$) and orientation ($F(3,51)=36.99, p<0.0005$), but not for run ($p=0.62$). These main effects were qualified by significant interactions for condition*orientation ($F(3,51)=8.15, p<0.0005$) and condition*run ($F(1,17)=5.04, p=0.04$), but not for orientation*run ($p=0.92$), nor the three-way ($p=0.41$). Posthoc tests revealed a greater covariance value for the attend-grating than the attend-centre condition (grand mean: 0.61 and 0.22, respectively; $p<0.0005$), confirming that subjects traced the grating when they were instructed to attend the grating. As hypothesised, analysis of the maximum cross-covariance between the joystick and the *central line* angle showed a very similar, but opposite pattern. There were significant main effects for condition ($F(1,17)=46.46, p<0.0005$) and orientation ($F(3,51)=18.80, p<0.0005$), but not for run ($p=0.37$), and only one significant interaction, that of condition*orientation ($F(3,51)=15.44, p<0.0005$; all other interactions $p>0.05$). Posthoc analysis indicated larger covariance values for the attend-centre than the attend-grating condition (grand mean: 0.46 and 0.26, respectively; $p<0.0005$), confirming that subjects traced the central line when they were instructed to attend the central line.

As the condition effect clearly holds over runs and orientations, we pooled these together in the MEG analysis to focus solely on the effect of attention. Despite the robust behavioural effects evident in the group average, one subject had nearly identical cross-covariance values for both conditions (0.65 and 0.58 for joystick-grating, 0.31 and 0.30 for joystick-centre line, in the attend-grating and attend-centre conditions, respectively). As we could not be sure that this subject followed our attentional instructions, the subject was excluded from the MEG analysis, leaving $N=17$.

4.3.2 MEG trial and eye movement artefacts

After excluding bad trials, 69 trials remained on average for the attend-centre condition (range 57-77), and 64 for attending the grating (range 47-78). This small difference was not significant over the seventeen subjects ($t(16)=1.91$, $p=0.07$). Inspecting the electrooculogram (EOG) traces revealed no bias in eye position in either the vertical or horizontal EOG (mean, $t(16)=1.79$, $p=0.09$; $t(16)=0.53$, $p=0.60$, respectively), nor in stability of fixation (standard deviation, $t(16)=0.83$, $p=0.42$; $t(16)=1.08$, $p=0.30$, respectively). Thus, we can be confident that subjects covertly attended towards or away from the grating rather than moving their eyes to the parafoveal location.

4.3.3 SAM analysis of gamma oscillations (30-70 Hz)

Individual paired t synthetic aperture magnetometry (SAM) images of thirteen of the seventeen subjects showed event-related synchronisations (ERS) in the gamma range (30-70 Hz) that were clearly localised to right medial visual cortex (contralateral to the stimulus) in both conditions. One subject only showed an identifiable gamma ERS in this area in the attend-grating but not in the attend-centre condition, two other subjects showed the opposite pattern, and one further subject did not show an ERS in either condition. As a result, coordinates for virtual sensor analysis could not be obtained in one or both conditions for these four subjects, excluding them from time-frequency analysis. The group average of the remaining thirteen subjects is displayed in Fig. 2A (top panel). Talairach coordinates of peak gamma ERS of these subjects were located within the right cuneus (Brodmann area 17) or the right middle occipital gyrus (Brodmann area 18). Paired t tests on the three Talairach coordinates showed that any spatial difference was non-systematic ($t(12)=0.10$, $p=0.92$, $t(12)=0.44$, $p=0.67$, $t(12)=0.69$, $p=0.50$, for sagittal, coronal, and axial, respectively). These results suggest that the grating induced 30-70 Hz gamma activity in highly comparable locations in early visual cortex regardless of the focus of attention. As an additional test, we generated paired t SAM difference images between the two conditions. Consistent with our interpretation, there was no identifiable source in this difference image (Fig. 2A, right-most image in top panel).

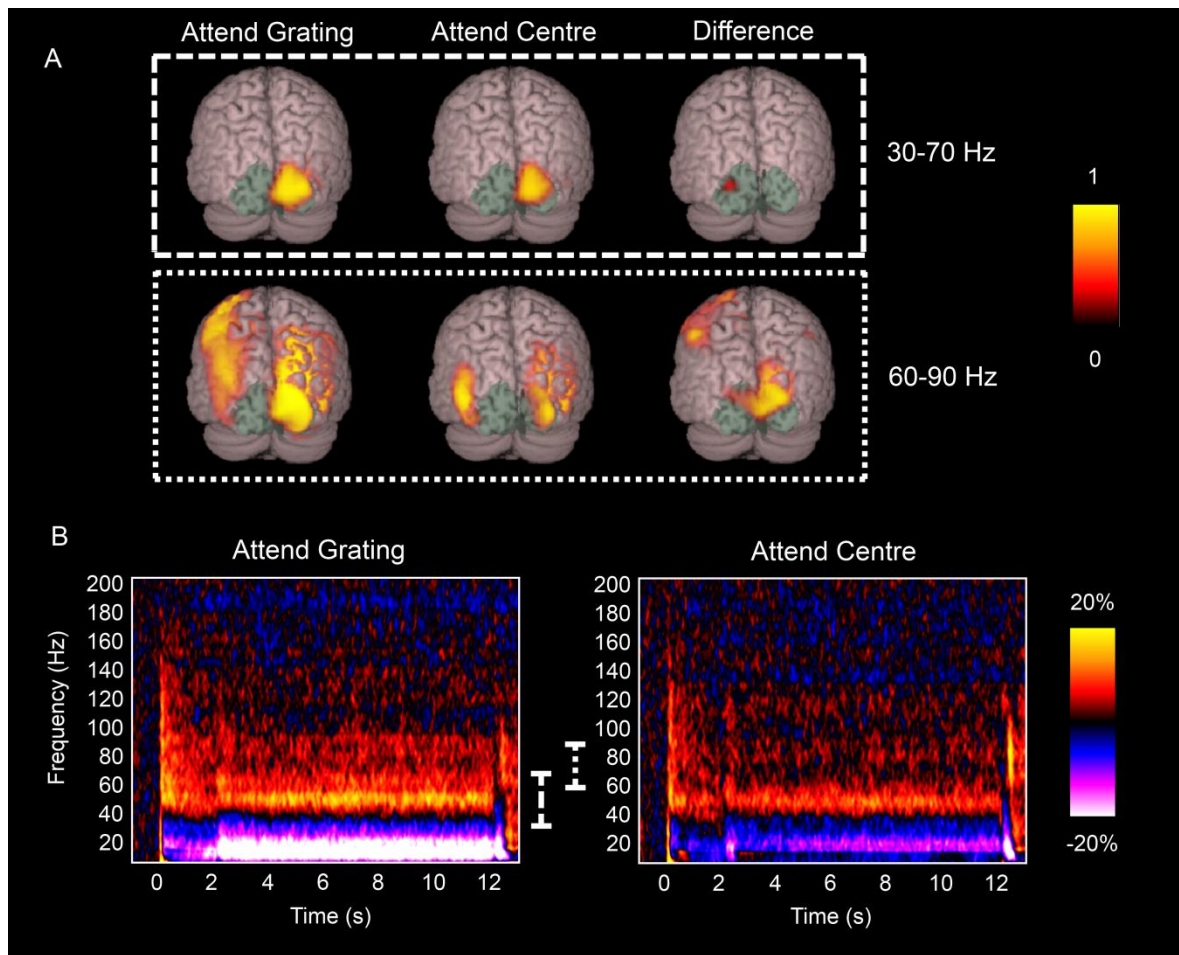


Fig. 2. Group average ($N=13$) SAM spectrograms and main effects. (A) Group SAM statistical images of gamma ERS comparing 0 to 12 s of stimulus presentation to -1 to 0 s of baseline activity projected onto a normalised brain. The left and middle images present the average group activity and the right images present the average difference of the two conditions within each respective frequency band (as indicated). Brains are viewed occipitally with a posterior coronal cut to show activity in medial visual cortex. Colours represent the omnibus-corrected 1- p value scaled to a maximum of 1. (B) Time-frequency spectrograms for the two conditions derived from individual virtual sensors placed at 30-70 Hz peak activity in medial visual cortex. Colours represent percentage signal change from baseline (the spectrograms are scaled identically). Stimulus presentation is from $t=0$ to 12 s (0-2 s stationary, 2-12 s rotation).

4.3.4 Time-frequency analysis

To inspect the time-frequency pattern of the induced gamma activity, we constructed virtual sensors at peak locations of gamma activity in each individual's medial visual cortex. Time-frequency spectrograms revealed a characteristic pattern that was consistent across subjects and conditions (Fig. 2B, group average). The spectrograms clearly show that the ERS in the gamma range was induced early (~0.1 s) after stimulus onset, and sustained for the duration of the stimulus (12 s). Four time windows could be distinguished within the temporal pattern of gamma synchronisation, matching the four subsequent stimulus events. In the first period after stimulus onset, there was a strong brief gamma burst and low-frequency transient evoked response (0-0.2 s), and gamma was then sustained for the remaining stationary presentation (0.2-2 s). A second burst could be observed at the stationary-to-rotation transient period (2-2.2 s), and finally, gamma remained sustained during the remaining rotation until stimulus offset (2.2-12 s). This temporal pattern of the stimulus-induced gamma response is consistent with previous human MEG and animal literature (Hoogenboom et al., 2006; Kayser, Salazar, & Konig, 2003; Swettenham, Muthukumaraswamy, & Singh, 2009). An event-related desynchronisation (ERD) in the lower frequency bands (alpha and beta, <30 Hz) could also be observed throughout stimulus presentation. Alpha/beta desynchronisation followed the same temporal pattern in both conditions, but was much stronger in the attend-grating condition.

Power-frequency graphs constructed over the four time windows displayed a similar pattern of synchronisation and desynchronisation in oscillatory activity in all windows for both conditions (Fig. 3). Power changes were strongest and most clearly defined in the sustained rotation period, which was constructed over the largest range of data samples, and also required the strongest focus of attention. Permutation analyses confirmed the stronger decrease in low-frequency (alpha) power with attention to the grating compared to attention to the central line. The decrease was present around 10-30 Hz for all time windows except the initial onset burst, where the lowest frequencies mainly reflected the high burst in transient evoked activity (as indicated by the grey lines, $p < 0.05$, uncorrected), and was significant for the sustained rotation period (black lines, $p < 0.05$, corrected for multiple comparisons). The stronger increase in power in the gamma range

when attending the grating versus centre could be observed roughly between 60-100 Hz over the three later time periods. This gamma increase was significant around 60-80 Hz in all three windows. Note that this attention-related increase occurred at a higher frequency range than the main stimulus-induced gamma peak (~50 Hz on average in both conditions; not modulated by attention).

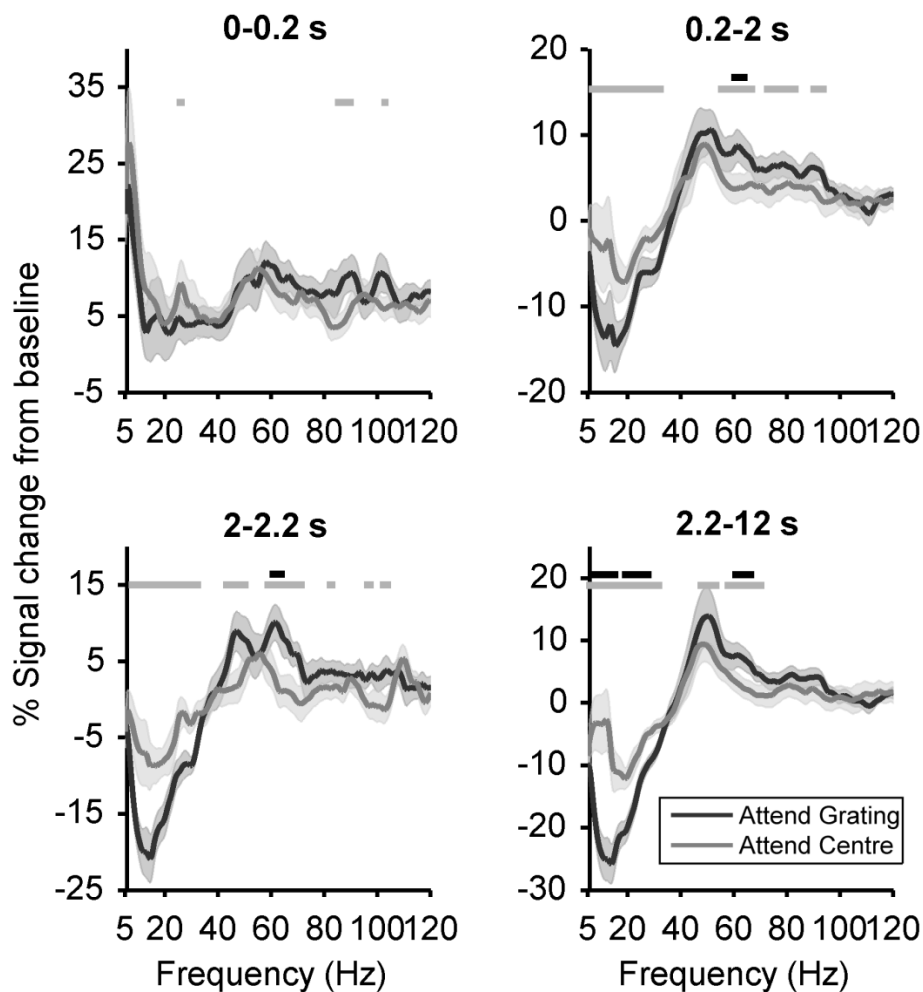


Fig. 3. Power-frequency spectra derived from individual virtual sensors in medial visual cortex ($N=13$). Solid lines represent the group average per condition (dark grey: attend grating; light grey: attend centre). Shaded regions represent the SEM. The four panels display the percentage signal change from baseline in the four defined time periods: initial onset response (0-0.2 s), sustained stationary response (0.2-2 s), stationary-to-rotation transients (2-2.2 s), and sustained rotation response (2.2-12 s). Grey bars: permutation test results on the difference $p < 0.05$ uncorrected, black bars: permutation results $p < 0.05$ corrected for multiple comparisons.

A two-way ANOVA on peak frequency within the two conditions and the four time windows showed that the attention-related gamma increase at higher frequencies was not due to a shift in the peak frequency at which each individual displayed their maximum gamma response (grand average between 30-100 Hz: attend grating 62.54 Hz, attend centre 60.09 Hz; ANOVA: condition $F(1,36)=0.35$, $p=0.57$, time window $F(3,36)=0.70$, $p=0.56$, interaction $F(3,36)=2.56$, $p=0.07$). In contrast to these low (alpha) and mid (gamma) frequencies, oscillatory power in frequencies above 100 Hz was very weak and did not differ between conditions.

4.3.5 SAM source localisation of higher visual gamma oscillations (60-90 Hz)

We observed effects of attention on the induced oscillatory power in high but not low gamma power in medial visual cortex. However, the time-frequency analysis was based on virtual sensors in early visual cortex obtained with a 30-70 Hz band. To assess where these higher-frequency effects were represented in the brain, we also generated SAM paired t images in the high gamma (60-90 Hz) bands (Fig. 2A, lower panel). The 60-90 Hz group averages revealed that activity in this band was localised more laterally in visual cortex than with a 30-70 Hz band-pass, and was expressed bilaterally in both conditions¹. These lateral areas may reflect higher-gamma frequency activity in V4 (Chalk et al., 2010), or motion activity in V5/MT (Anderson, Holliday, Singh, & Harding, 1996). Critically, however, the difference image showed that directing attention to the grating only increased 60-90 Hz gamma activity in *medial* visual cortex, in a similar region as 30-70 Hz gamma was induced. The main peak of occipital activity in the difference image was localised to the middle occipital cortex, including the right cuneus. This area is much more medial than the bilateral areas activated similarly by both conditions, and is therefore unlikely to represent V4 or V5/MT+, or direct spread of activity generated by these areas. Instead, these signals appear

¹ The 30-70 Hz and 60-90 Hz bands contain frequencies spanning 40 Hz and 30 Hz, respectively. Caution should be taken comparing effects *between* different bandwidths, as effects may be due to the difference in bandwidth, rather than the frequencies included (Hadjipapas et al., 2007). However, in this study, effects of attention on activity in different frequencies were based on un-biased permutation analysis over a broad frequency range. These different frequency ranges were then only used for posthoc comparisons *within* each bandwidth.

to be generated in primary visual cortex, a more medial extrastriate area such as V2, or a combination of the two.

4.4 Discussion

In the present study, we found that voluntarily directed covert spatial attention increased the amplitude of high frequency stimulus-induced gamma power in early visual cortex at a frequency different from that affected by physical stimulus properties. A rotating stimulus increased gamma synchronisation at 30-70 Hz in contralateral medial visual cortex and at 60-90 Hz in bilateral higher visual cortex regardless of the locus of attention. In contrast to these stimulus-driven effects, directing visuo-spatial attention towards the grating increased gamma activity at 60-90 Hz in medial visual cortex. This increase in higher-frequency gamma power was not due to a shift in peak frequency of the stimulus-driven response. Although an attention-related enhancement in gamma power is frequently reported (Fries et al., 2001; Fries et al., 2008; Gruber et al., 1999; Siegel et al., 2008), such modulations are not found in early visual cortex (Chalk et al., 2010; Siegel et al., 2008). The present findings demonstrate that top-down spatial attention can enhance oscillatory synchronisation in the gamma range in human early visual cortex, and that this is expressed at a higher frequency than stimulus-driven responses.

The lack of an enhancement of the gamma response in early visual areas in previous studies (Chalk et al., 2010; Siegel et al., 2008) may be due to differences in stimuli and paradigms. Here, we used a task requiring continuous sustained attention: participants had to match a joystick to a constantly changing unpredictable rotation, requiring a highly selective attentional focus. This is very different from the pre-cuing paradigm that is used in many attention studies investigating gamma modulations (e.g., Chalk et al., 2010; Fries et al., 2001; Fries et al., 2008; Siegel et al., 2008). Although pre-cuing paradigms have the advantage of allowing investigation of pre-stimulus attentional modulations, these pre-stimulus effects may obscure subsequent stimulus-induced effects. For example, in one MEG study, Siegel et al. (2008) directed attention to one of two bilaterally presented random-dot stimuli on a trial-by-trial basis using a small central pre-cue. They found an increased gamma-band response in higher visual areas, but no difference in the calcarine region contralateral to the attended versus unattended hemifield. However, in this calcarine region,

attention strongly decreased gamma power in the post-cue but pre-stimulus period, whereas in higher visual areas it was only slightly modulated during the pre-stimulus period. The lack of effect in V1 following stimulus onset may be due to the small stimulus-induced increase in synchronisation being further reduced by neurons remaining in a somewhat desynchronised state following the strong pre-stimulus cueing modulation (see Luck et al., 1997; Tallon-Baudry, Bertrand, Hénaff, Isnard, & Fischer, 2005). In fact, in the study by Siegel et al. (2008), even the usually robust reduction in alpha power was absent or very small post-stimulus in all visual areas, whereas it was very prominent following the pre-cue. The present study, using a blocked attentional manipulation and a task requiring sustained attention for a considerable time (10 s) on each trial, does not have a pre-stimulus modulation on a trial-by-trial basis, and therefore has the power to detect relatively small increases in stimulus-induced gamma synchronisation.

Consistent with the notion that a sustained attention task may be a powerful approach for exploring gamma responses, one previous study using sustained attention to a morphing shape found a very strong modulation in gamma amplitude ($>100\%$) in V4 cells, which correlated with varying attentional demands (Taylor, Mandon, Freiwald, & Kreiter, 2005). Moreover, the success of our attentional manipulation is supported by the pronounced alpha-band decrease at the occipital pole, in line with numerous previous studies (Fries et al., 2001; Fries et al., 2008; Hoogenboom et al., 2006; Rihs, Michel, & Thut, 2007; Siegel et al., 2008; Yamagishi, Callan, Anderson, & Kawato, 2008; Yamagishi et al., 2003; Yamagishi, Goda, Callan, Anderson, & Kawato, 2005). Alpha-band activity has been linked to inhibitory processes and attentional suppression (Worden, Foxe, Wang, & Simpson, 2000). A decrease in alpha-band power is therefore thought to reflect enhanced neuronal activity due to the excitatory effect of attention (Yamagishi et al., 2008), which may be regulated by a cholinergic top-down signal (Bauer et al., 2012). In fact, the difference in alpha power between the conditions was not evident for the first stationary onset, but became progressively stronger for the sustained stationary, stationary-to-rotation transition, and sustained rotation periods, respectively. This pattern nicely matches the attentional requirements in these stages: matching the joystick to the stationary stimulus is much less demanding than to the constantly rotating one, and the adjustment to the change from stationary to rotation may briefly lessen the attentional effect.

It is possible that attending to the peripheral grating might engage different mechanisms, strategies, or mental processes than attending to the central item. We took care to avoid a greater task difficulty for attending the peripheral grating due to it being non-foveal by making the central item very small. However, participants were still attending to a different sized stimulus in the two attention conditions, making it impossible to exclude this potential source of variance. Generic task differences such as memory load and task difficulty have indeed been found to modulate gamma activity, but are usually associated with higher areas such as frontal, parietal, and temporal cortices (Howard et al., 2003; Posada, Hugues, Franck, Vianin, & Kilner, 2003). The early visual, contralateral localisation of the gamma ERS in both attention conditions strongly suggests this ERS reflects perceptual processing of the peripheral grating, and is unlikely to be fully explained by task load or difficulty. Moreover, the stimulus we used is optimal for inducing gamma in V1, as it is large and parafoveal (Busch, Debener, Kranczioch, Engel, & Herrmann, 2004), the attended feature is present throughout the entire stimulus (Busch, Schadow, Fründ, & Herrmann, 2006), and orientation is a feature which is strongly represented in V1 cells (e.g., Hubel & Wiesel, 1962). In fact, the effectiveness of this stimulus in driving V1 neurons may be the reason we were able to observe changes in early visual areas, as attentional effects are indeed influenced by stimulus properties and effectiveness (Busch et al., 2004; Chalk et al., 2010; Proverbio et al., 2002; Reynolds, Pasternak, & Desimone, 2000).

Our results are consistent with a study reporting enhanced high-frequency gamma activity with modality-specific attention over auditory and somatosensory cortex using subdural electrocorticography (Ray, Niebur, Hsiao, Sinai, & Crone, 2008). This convergence suggests that a high-frequency gamma increase due to attentional processes may not be unique to vision, but rather reflects a more general mechanism of attention. Within the visual domain, one recent study also reported an attention-related increase in gamma in early visual cortex in the 54-69 Hz range (Kahlbrock, Butz, May, & Schnitzler, 2012), by manipulating the amount of attention devoted to a visual stimulus in a multimodal audio-visual paradigm. This study revealed a gradual increase in visually-induced gamma power for conditions with attention directed away from the visual modality, attention distributed evenly between an auditory and visual stimulus, and attention directed towards the visual modality. However, it is hard to assess whether a single source or

multiple sources actually underlie these findings as this study used a centralised stimulus, which induces activity in both hemispheres (for example, see Hoogenboom et al., 2006). Using a beamformer, a source distribution consisting of two bilateral sources in the calcarine could potentially look identical to a source distribution consisting of two more lateral sources in higher visual cortex. Here, we avoided this potential difficulty by using a unilateral stimulus. If attention mainly modulated gamma synchronisation in a higher visual area, the focus of activation when attending the grating would either have shifted to a more lateral occipital location, or we would have seen a second activity focus. Given that we did not observe either of these distributions, it is unlikely that the present modulation in gamma activity directly reflects a higher visual source.

Another possibility is that our V1 modulation above 60 Hz is due to spread of activity from a higher visual area. Chalk et al. (2010) found that in monkeys, spatial attention decreased 30-50 Hz gamma activity in V1, whereas an increase was seen in 55-70 Hz activity in V4. In our case, however, source localisation showed that the attentional modulation in the higher frequency band was associated with the same early visual region as the main stimulus-induced gamma synchronisation, including the calcarine. Although MEG lacks the spatial resolution to unequivocally claim our early visual source represents the primary visual cortex, the calcarine localisation of the visually-induced gamma-band response in the present study is highly similar to that shown in previous MEG studies (Hoogenboom et al., 2006; Koelewijn et al., 2011; Muthukumaraswamy & Singh, 2008; Muthukumaraswamy et al., 2010), and to the BOLD response in V1 (Muthukumaraswamy & Singh, 2008; Sharon, Hämäläinen, Tootell, Halgren, & Belliveau, 2007). Furthermore, an attention-driven modulation in V1 is consistent with both monkey and human studies demonstrating modulation of neuronal activity in V1 with spatial attention (Gandhi et al., 1999; Martinez et al., 1999; McAdams & Maunsell, 1999; McAdams & Reid, 2005; Motter, 1993; Noesselt et al., 2002). As V1 activity in particular correlates with attentional performance (Liu, Larsson, & Carrasco, 2007), suggesting a functional role for V1 in attentional processes, our findings are in line with both previous research using other neuroimaging modalities and models of attentional processes (Itti & Koch, 2001). MEG measures the bulk activity of a relatively large neuronal population, and synchronised oscillations actually reflect a combination of input and output modulations (Fries, 2005). This may explain why a decrease in synchronisation can be

138

found at the cellular level in V1 (Chalk et al., 2010), yet an increase was found with MEG here. Furthermore, the magnitude of attentional effects is known to increase from V1 up to higher visual cortex (McAdams & Maunsell, 1999; Treue, 2001), which may be why many studies that find a clear effect in V4 have failed to find significant effects in V1.

Different frequency bands have been proposed to underlie different functions in cognitive processing (Tallon-Baudry et al., 2005; Vidal, Chaumon, O'Regan, & Tallon-Baudry, 2006). Lower frequencies are thought to reflect long-range interactions and have been associated with top-down processing, whereas higher frequencies have been linked to local processing and bottom-up stimulus encoding (Donner & Siegel, 2011; Schnitzler & Gross, 2005; von Stein & Sarnthein, 2000). The fact that we did not see a clear modulation due to attention in gamma oscillations around 50 Hz is in line with a role for this frequency range in bottom-up stimulus encoding (Friedman-Hill et al., 2000; Koelewijn et al., 2011). The high-frequency synchronisation we see here was in addition to the 50 Hz peak in the frequency spectrum, making it likely that the higher gamma modulation reflects a different process than stimulus encoding. Based on the fact that the 60-100 Hz modulation was present locally in medial visual cortex, this finding may reflect the local processing of a top-down signal. Alternatively, the higher frequency modulation may be associated with the integration of bottom-up and top-down information. Our finding of 60-90 Hz gamma activity in bilateral higher visual areas, which was not altered by attention, is likely to represent bottom-up processing induced by a moving stimulus in V5/MT (Anderson et al., 1996). The attention-related increase in 60-90 Hz activity in medial visual cortex might therefore represent a synchronous network between higher visual (e.g., V5/MT) and early visual cortex.

Gamma activity is thought to reflect the deployment of attention, but not its maintenance (Doesburg, Roggeveen, Kitajo, & Ward, 2008). Our task may have required constant attentional shifts between the grating and the feedback item at fixation when the grating was attended, instead of maintaining a constant level of covert attention to the peripheral item. These attentional shifts would require continuous integration of the current stimulus orientation and the orientation of the feedback item, which is not required when the grating is not attended. Attentional shifts have been associated with increased gamma activity (Landau, Esterman, Robertson, Bentin, & Prinzmetal, 2007), and this scenario could therefore result in the present sustained enhanced gamma activity.

Whatever the underlying mechanism, the current data add to the growing body of evidence that high gamma oscillations play a specific functional role in brain processing. High gamma oscillations (>60 Hz) have recently been associated with a wide range of attentional and cognitive processes, and have been found to be impaired in neurological disorders such as epilepsy and schizophrenia (see Uhlhaas, Pipa, Neuenschwander, Wibral, and Singer (2011) for a review). This suggests that high gamma oscillations play a crucial role in healthy brain functioning. In the present study, we found that gamma oscillations in early visual cortex are modulated by attention in this higher frequency range, adding a role in visual processing to this body of evidence. Whether this high-frequency modulation reflects the processing of top-down input, or is associated with the integration of bottom-up and top-down factors specifically, is a question for future research. For now, it is clear that gamma oscillations are involved in both stimulus and goal-driven processes, and that both of these processes can modulate synchronisation in early visual cortex. Importantly, the present findings suggest that stimulus and goal-driven modulations may be mediated at different frequencies within the gamma range.

4.5 Materials and Methods

4.5.1 Subjects

Nineteen healthy subjects with normal or corrected-to-normal vision participated in the experiment after giving informed consent, and received payment for their participation. One subject was excluded due to excessive eye movement. Behavioural analysis was based on the data of the remaining eighteen subjects (9 M, 9 F; mean age 25.0 years, range 20-44), after which one subject was excluded for MEG analysis due to poor performance. All subjects had a previously acquired structural MR scan (1 mm isotropic FSPGR) that was used for source localisation. All procedures were approved by the local Ethics Committee.

4.5.2 Stimuli and procedure

The stimulus display consisted of two items on a mean luminance grey background. A small black line (diameter 0.22° , width 0.04°) was presented centred at the vertical meridian and 1.35° from the

top of the screen, surrounded by a black circle with two gaps at opposite ends (diameter 0.35° , width 0.04° , gaps 0.07° ; Fig. 1A). Subjects were instructed to keep their eyes fixated on this central item at all times. In the lower left quadrant of the display, a peripheral black/white sine-wave circular grating patch (maximum-contrast, 3 cycle/degree, diameter 4.33°) was presented, centred 2.44° both horizontally and vertically from fixation. Displays were generated in MATLAB® (The MathWorks, Inc.), using the Psychophysics Toolbox extensions (Brainard, 1997; Kleiner, Brainard, & Pelli, 2007; Pelli, 1997), and were presented on a Mitsubishi Diamond Pro 2070 monitor (1024x768 pixel resolution, 100 Hz refresh rate).

Each trial started with a 3 s fixation-only period, in which only the central circle was present, always stationary in vertical configuration. At stimulus onset ($t=0$), the grating appeared in one of four orientations ($0, 45, 90$, or 135° tilted clockwise from vertical), and the central line appeared with the same orientation as the grating. After remaining stationary for 2 s, both the grating and the central line randomly and independently rotated $5\text{--}40^\circ$ around the onset angle for 10 s. The items were programmed to start rotating either clockwise or anticlockwise, with equal probability and independent of each other, towards a random angle between $5\text{--}40^\circ$ from the start orientation. The stimuli subsequently rotated towards a new random angle between $5\text{--}40^\circ$ from the start orientation in the opposite direction, and so on. The items changed 1° in orientation every 30 ms, yielding a movement that appeared visually smooth.

In two separate blocks, subjects were asked to match the orientation of either the peripheral grating ('attend grating'), or the central line ('attend centre') with a MEG-compatible joystick (fORP, Cambridge Research Systems) in their right hand using a power grip hand position. The joystick was taped to the armrest of the MEG chair at a comfortable distance, and subjects were asked to try and move their wrist whilst keeping their lower arm rested to minimise body movement. The gaps in the circle at fixation provided feedback on the current joystick orientation, sampled at the same rate as the stimulus orientation changes (every 30 ms). A minimum of 30% outward displacement was required for the feedback item to respond. If this displacement was not reached, the feedback circle defaulted back to the vertical rest position. The subjects responded throughout the entire 12 s stimulus presentation (both stationary and movement), but rested their hand with the joystick in centre position during the fixation-only period.

The block instructions ('attend grating' vs. 'attend centre') were designed to direct covert spatial attention either towards or away from the peripheral grating to which we measured the contralateral induced gamma response. The central item is unlikely to contribute to this contralateral response, making the measured gamma a relatively pure measure of response to the peripheral grating. Condition block order was randomised and counterbalanced across subjects. Both experimental blocks were divided into two consecutive recording runs, yielding four runs per subject. Each run contained 10 trials of each orientation, randomly interleaved, yielding a total of 40 15-second trials, thus taking 10 minutes. Runs were separated by a short break. The total testing session including breaks took less than an hour.

4.5.3 Behavioural data analysis

To assess how well subjects traced the item of interest in the respective conditions, the cross-covariance (i.e., cross-covariance corrected for the means) was calculated between the trace of the joystick angle and the central line orientation, and between the joystick angle and the grating orientation over the 12 s response time per trial (0-12 s from stimulus onset, samples 1-67 stationary, samples 68-400 rotating). The covariance was normalised so that covariance at zero lag is identical to 1.0, and we limited the calculation to a difference of 25 samples (750 ms) between the traces. This limitation was chosen because a lag of more than 750 ms between the joystick orientation and the orientation of the stimulus of interest is unlikely to reflect accurate performance of the task. The maximum cross-covariance was calculated for each subject as a measure of the similarity between the joystick trace and each of the stimulus traces (Dartnall, Jaberzadeh, Miles, & Nordstrom, 2009).

We expected a higher maximum covariance between the joystick trace and the trace of the stimulus of interest than between the joystick trace and the other stimulus. This pattern of results would indicate that subjects successfully followed the item as instructed in each respective block. Note that correlations would not be perfect, because changes in the stimulus sequence were sharp, whereas the biological motion of the hand reflected in the joystick trace was smooth. Also, there was some correlation between the two stimulus traces on each trial, because their sequences always

changed in one of two directions, and thus changed in the same direction for part of the stimulus time, although the duration and times this happened was random.

4.5.4 MEG data acquisition and analysis

Whole-head MEG recordings were made using a 275-channel CTF radial gradiometer system sampled at 1200 Hz (0-300 Hz band-pass). An additional 29 reference channels were recorded for noise cancellation purposes and the primary sensors were analysed as synthetic third order gradiometers (Vrba & Robinson, 2001). Two of the 275 channels were turned off due to excessive sensor noise. Subjects were seated upright in the magnetically shielded room. To achieve MRI/MEG co-registration, fiduciary markers were placed at fixed distances from three anatomical landmarks identifiable in the subject's anatomical MRIs, and their locations were verified afterwards using high-resolution digital photographs. Head localisation was performed before and after each run, and a TTL pulse was sent to the acquisition computer at stimulus onset and offset. Data were acquired continuously, then epoched offline using a window extending -2 to 13 s around stimulus onset. We monitored eye movements and blinks by recording vertical and horizontal electrooculograms (EOG).

The MEG recordings of the two runs per attentional condition were grouped together, yielding a total of 80 trials per condition (20 trials of each orientation). Trials were excluded from analysis based on eye movements, excessive or time-locked blinks (EOG measures), or visibly identifiable artefacts. Eye movements of the remaining trials were analysed by averaging the horizontal and vertical EOG traces separately for each subject and attentional condition after baseline-correction (-1 to 0 s). The mean and SD were then calculated (0 to 12 s) to evaluate any general bias in eye movements and stability of fixation, respectively.

Offline, each data set was band-pass filtered using a fourth-order bi-directional IIR Butterworth filter into visual gamma (30-70 Hz, Koelewijn et al., 2011), and motor gamma (60-90 Hz, Kennedy, Singh, & Muthukumaraswamy, 2011) frequency bands. For source localisation, a multiple local-spheres forward model (Huang, Mosher, & Leahy, 1999) was derived by fitting spheres to the brain surface extracted by the FSL Brain Extraction Tool (Smith, 2002). The synthetic aperture magnetometry (SAM) beamformer algorithm (Robinson & Vrba, 1999) was then

used to create a set of beamformer weights for the whole brain at 4 mm isotropic voxel resolution for each subject, frequency-band, and attentional condition. Virtual sensor waveforms were then generated at each voxel location, these were band-pass filtered between 0-200 Hz, and paired t statistical images of source power (Student's t statistic) for 1 s of baseline (−1 to 0 s) compared to 12 s of visual stimulation (0 to 12 s) were generated for each condition.

For visual gamma activity (30-70 Hz), the individual paired t SAM images of each subject were examined and the coordinates of peak activity in right medial visual cortex were obtained for both attentional conditions. Virtual sensors were then further interrogated at these peak locations. Time–frequency analysis of each single virtual sensor was conducted using the Hilbert transform from 1 to 200 Hz in 0.5 Hz steps with an 8 Hz wide band-pass, 3rd order Butterworth filter (Le Van Quyen et al., 2001). Power–time and power-frequency spectrograms are represented as a percentage change from the average baseline (−1 to 0 s) amplitude for each frequency band. Peak gamma frequency was additionally obtained for each subject and condition.

Power-frequency data were statistically tested at the group-level by performing permutation tests on the difference between the conditions over the whole 0-200 Hz frequency range (1000 permutations, 2-tailed, $\alpha=0.05$, ‘tmax’ corrected for multiple comparisons (Blair & Karniski, 1993)). For imaging of group-level effects, SAM images were spatially normalised using FSL FLIRT into MNI space with an affine transform. Non-parametric permutation tests were conducted with FSL Randomise using 5000 permutations for each condition with 10 mm variance smoothing and the resulting p values were corrected for multiple comparisons using the omnibus test statistic (Nichols & Holmes, 2002; Singh, Barnes, & Hillebrand, 2003a; Singh, Kim, & Kim, 2003b). The same statistical group-level procedure was performed on difference images created by subtracting the attend-centre SAM image from the attend-grating SAM image per individual.

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Chapter 5 – Investigating effects of stimulus salience and behavioural relevance on gamma synchronisation in early visual cortex

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Investigating effects of stimulus salience and behavioural relevance on gamma synchronisation in early visual cortex

5.1 Abstract

Making sense of the visual world around us requires dynamic balancing of constantly changing visual input and attentional goals. An efficient neural system to allocate attention to the item with greatest priority requires constant communication between parietofrontal areas that are thought to guide attention and visual areas where incoming information is first processed. Higher visual areas reflect such combined processing, but it is not known what role early visual areas play in this dynamic interplay. Oscillatory activity in the gamma range (30-70 Hz) is linked to both neural communication and local processing of visual information, and is therefore a prime candidate to reflect this dynamic combination of bottom-up and top-down processing. In the present study, we investigated how stimulus-induced gamma synchronisation in early visual cortex is modulated when stimulus and goal-driven factors are actively balanced for attentional priority. We used an adaptation of the strong behavioural paradigm developed in Chapter 2, requiring subjects to find a target based on orientation, with a stimulus optimised for inducing gamma activity (Chapters 3, 4). Two stimuli were simultaneously presented: one grating optimal for inducing gamma in contralateral visual cortex, and one stimulus that should not induce gamma (disk). The grating or disk could appear in black (most often) or in red (less frequent, salient), and we manipulated the behavioural relevance of this salience for target search. We found a trend towards an increased gamma response around 100-300 ms within a 55-65 Hz band when the grating was a salient item that could not be the target, compared to when it was a potential target. We propose this reflects active inhibition of the salient item. These findings suggest that early visual cortex may be modulated by a signal conveying the priority of items after stimulus and goal-driven factors have been balanced.

5.2 Introduction

Efficient visual processing requires attention to be directed towards our current goal. The visual system integrates information from the environment (bottom-up factors) and our internal state (top-down information) to efficiently direct attention to the item with highest priority (Bisley, 2011). Neural mechanisms reflecting visual processing and perception should be dynamically modulated by interactions of bottom-up and top-down factors, above and beyond their individual modulations. Such interactions have been found in a number of parietofrontal areas, where items are rated for distinctiveness based on a combination of physical salience and behavioural relevance, with the most distinct item in the visual field generating the largest neural response (Fecteau & Munoz, 2006; Ipata, Gee, Bisley, & Goldberg, 2009; Serences et al., 2005). A dynamic system that integrates stimulus with goal-driven information requires communication between such a parietofrontal ‘priority map’ and visual areas where visual information is initially processed (Bisley, 2011; Serences & Yantis, 2007). As outlined in Chapter 1.4, oscillatory synchronisation is thought to underlie neural communication (Fries, 2005; Schnitzler & Gross, 2005), and synchronisation in the gamma frequency range (30-70 Hz) plays an important functional role in local visual processing (Friedman-Hill, Maldonado, & Gray, 2000). These properties make gamma synchronisation a prime candidate to play a role in the integration of these attentional demands. However, it is not known whether and how bottom-up and top-down factors interact in modulating the gamma response in early visual cortex.

Oscillatory synchronisation in the gamma frequency range (30-70 Hz) is induced in primary visual cortex in response to the onset of a stimulus (Hoogenboom, Schoffelen, Oostenveld, Parkes, & Fries, 2006; Muthukumaraswamy, Singh, Swettenham, & Jones, 2010). Synchronisation in this frequency band is strongly modulated by stimulus properties such as luminance and contrast (Adjamian et al., 2004; Henrie & Shapley, 2005; Rols, Tallon-Baudry, Girard, Bertrand, & Bullier, 2001), as well as certain basic features such as orientation (Koelewijn, Dumont, Muthukumaraswamy, Rich, & Singh, 2011 / Chapter 3). Gamma synchronisation is also influenced by top-down factors such as voluntary attention (Fries, Reynolds, Rorie, & Desimone, 2001; Gruber, Müller, Keil, & Elbert, 1999; Siegel, Donner, Oostenveld, Fries, & Engel, 2008; Chapter

4). When individually manipulated, stimulus-driven factors modulate gamma activity in a lower frequency range (30-70 Hz, Chapter 3) than goal-driven factors such as attention (60-90 Hz, Chapter 4). Studying the temporal and spectral dynamics of gamma oscillations when stimulus-driven and goal-driven attentional demands compete for attentional allocation may thus reveal the role of early visual cortex in the dynamic interplay between these two attentional demands.

Direct interactions of stimulus-driven with goal-driven attentional demands in oscillatory activity within the gamma band have been observed in higher visual areas. One EEG study found an interaction in the power of the early stimulus-evoked (phase-locked) visual gamma response between stimulus category (target or distractor) and the distribution area of a target-defining feature (orientation) within the stimulus, using a small circular grating superimposed on a much larger grating (Busch, Schadow, Fründ, & Herrmann, 2006). The difference in evoked gamma power between targets and distractors was larger when the target-defining feature, and thus the focus of attention, was represented over the larger area of the stimulus, whereas the physical input remained identical. The authors suggested that this effect was mediated by the larger stimulus exciting a larger neural network, resulting in a larger manifestation of the top-down modulation¹. Such an interaction effect was not evident in the averaged transient evoked response, suggesting that gamma synchronisation plays a specific role in mediating interactions of stimulus and goal-driven attentional demands. In addition to this effect in evoked gamma activity, a similar interaction has been demonstrated for induced (non-phase locked) gamma activity (Fries, Womelsdorf,

¹ The study by Busch et al. (2006) contains a potential confound. The target-defining feature in this study was orientation. Targets and distractors in the larger stimulus were one of two opposite oblique orientations (45° clockwise or counter-clockwise from vertical), whereas targets and distractors in the superimposed smaller stimulus were horizontal or vertical. Because the stimulus-induced gamma response and stimulus-evoked phase-locked response are influenced by orientation (Koelewijn et al., 2011 / Chapter 3), the larger response difference for the larger stimulus could have been due to the use of oblique orientations instead of stimulus size. However, this confound does not necessarily take away from an interaction between bottom-up and top-down factors, albeit potentially due to a different bottom-up factor.

Oostenveld, & Desimone, 2008). Fries et al. (2008) found that when monkeys performed a spatial cueing task, synchronisation of stimulus-induced oscillatory gamma activity increased in response to a colour change when an item was attended (target), whereas a colour change led to reduced synchronisation of the gamma response if an item was ignored (distractor). This dynamic interaction of physical stimulus property and attention on gamma synchronisation suggests a competitive mechanism that is similar to modulations in firing rates (Reynolds & Desimone, 2003); see Chapter 2, section 2.1).

To our knowledge, it is not currently known whether influences of stimulus-driven and goal-driven demands combine to modulate the gamma response to stimuli as early as V1 or V2. In previous studies, interactive effects on gamma synchronisation have been localised either with a broadly occipital scalp distribution in humans (Busch et al., 2006), or in area V4 in monkeys (Fries et al., 2008). Gamma synchronisation in visual cortex as early as V1 is modulated by both bottom-up stimulus properties (Adjamian et al., 2004; Koelewijn et al., 2011; Rols et al., 2001), as well as by whether or not stimuli or locations are within the focus of voluntary attention (Chalk et al., 2010; Siegel et al., 2008; Chapter 4). In addition, studies using other techniques (such as Transcranial Magnetic Stimulation) have shown that influencing neural transmission in the posterior parietal cortex can alter responses to stimuli in V1 and V2 (Mevorach, Humphreys, & Shalev, 2009; Silvanto, Muggleton, Lavie, & Walsh, 2009). Priority signals based on both stimulus and goal-driven information that are generated in parietal and frontal cortex could therefore feed back as far as early visual areas. Biasing neural responses with this combined information very early on in visual processing would ensure maximum efficiency of processing of subsequent incoming stimuli. Together, these findings suggest that gamma activity in early visual cortex may well be modulated by a combination of stimulus and goal-driven factors.

In the present magnetoencephalography (MEG) study, we aimed to investigate how stimulus and goal-driven attentional demands interact to modulate the stimulus-induced gamma response in early visual cortex. We designed a task in which subjects discriminated the orientation of one of two potential target stimuli. Whereas both stimuli were equally likely to be the target, one stimulus was a grating optimal for inducing gamma oscillations in early visual cortex (Koelewijn et al., 2011; Muthukumaraswamy et al., 2010 / Chapter 3), whereas the other stimulus should induce

160

minimal gamma. We compared the visual gamma response in conditions where there was stimulus salience in the presence and absence of behavioural relevance. This paradigm allowed us to dynamically investigate how bottom-up salience and behavioural relevance interact to direct the allocation of attention and modulate the spectral and temporal pattern of stimulus-induced gamma synchronisation in early visual cortex.

5.3 Methods

5.3.1 Subjects

Fourteen healthy subjects with normal or corrected-to-normal vision (4 M, 10 F, mean age: 22.4, range: 19-29 years) participated in the experiment after giving informed consent, and received payment for their participation. All subjects had a previously acquired structural MR scan (1 mm isotropic FSPGR) that was used for source localisation. All procedures were approved by the local Ethics Committee.

5.3.2 Stimuli and procedure

Stimulus displays consisted of two stimuli positioned in the lower visual field, equidistant to the left and right of a small black fixation dot on a mean luminance grey background (Fig. 1A). The lower left stimulus was a peripheral sine-wave circular grating patch ('grating', maximum-contrast, 3 cycle per degree spatial frequency), which is an optimal stimulus to induce gamma in early visual cortex (Koelewijn et al., 2011 / Chapter 3; Muthukumaraswamy et al., 2010). The lower right stimulus was a circle with a single bar spanning the diameter through the centre of the circle ('disk'). Both stimuli had a diameter subtending 4.33° of visual angle, and were centred 2.59° both horizontally and vertically from fixation. The circle and bar of the right item had a thickness of 0.10° of visual angle. Displays were generated in MATLAB® (The MathWorks, Inc.), using the Psychophysics Toolbox extensions (Brainard, 1997; Kleiner, Brainard, & Pelli, 2007), displayed on a Mitsubishi Diamond Pro 2070 monitor (1024x768 pixel resolution, 100 Hz refresh rate).

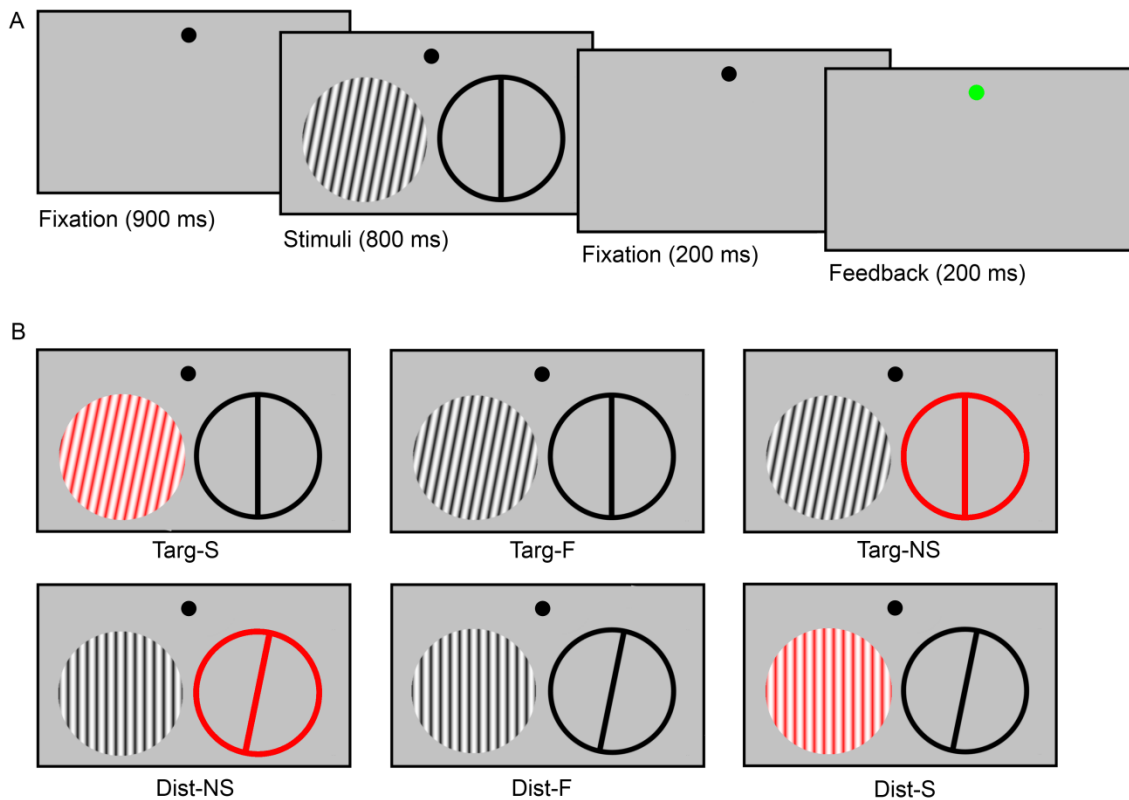


Fig. 1. Stimulus displays (not to scale). Note that only the lower half of the screen is displayed, the fixation dot was positioned in the middle of the screen. (A) Example of displays in a typical trial. In this example filler trial, the grating on the left is the target, and the disk on the right the distractor. The correct response is to press the right button (indicating that the target is tilted to the right). The feedback dot turned green for a correct response and blue for an erroneous or no response. (B) Possible stimulus displays for all conditions. Targ: the grating is the target (top row); Dist: the grating is the distractor (bottom row). The left two panels are both examples of trials where the red item is the target (Include block only), the middle panels are both fillers (both attentional blocks), and the right panels are both examples where the red item is the distractor (both attentional blocks). S, the grating is salient and the disk is black; F, filler condition (no salience); NS, non-salient, indicating that the grating is black and the disk is salient.

In each display, one of the stimuli was presented with a vertical orientation (the distractor), and the other was tilted 3 degrees from vertical, either to the left or to the right (the target). The task was to determine the orientation of the target stimulus: left or right of vertical. The grating and the disk were equiprobable as targets. The target was tilted to the left or right equally often, irrespective of the side of the display it appeared on. Participants maintained central fixation throughout the experiment, making it a covert attention task with ‘search’ (which is the target?) and ‘discriminate’ (which way is the target tilted?) steps. Note that both steps require orientation discrimination, but that discrimination is more fine-grained and difficult for the ‘discriminate’ stage. The latter thus demanded a high level of selective attention directed at the target, whereas the ‘search’ step was more transient. Responses were made with the right hand resting on a button-box, with a button press by the index finger indicating a tilt to the left and the middle finger indicating a tilt to the right. A trial started with a 900 ms fixation-only period, after which the stimuli appeared for 800 ms. Following the stimulus, there was a 200 ms fixation period to allow subjects further response time. A trial ended with a 200 ms feedback screen in which the fixation dot turned green if the subject had made a correct response and blue if they had made an erroneous response or no response had been recorded. The parameters of the task that determine task difficulty, such as target angle, stimulus duration, and response time, had been piloted to yield 85% correct performance on average (outside of the MEG), to avoid ceiling and floor effects.

On a given trial, the two stimuli were either both presented in black, or one of the two stimuli was black and the other was in high-luminance red (black/white and red/white sinusoid for the grating). The proportion of trials containing a red stimulus was 60%, so that the grating appeared in red on 30% of trials, the disk appeared in red on another 30% of trials, and the remaining 40% of trials contained no red stimulus (filler trials). As there were always two stimuli, this means that throughout the task, the ‘amount’ of red was 30%, whereas the ‘amount’ of black was 70%. The colour red was thus relatively salient. The higher luminance of red than black was chosen because (1) it further contributes to make red stimuli salient, and (2) higher luminance contrast is known to yield a stronger gamma response than lower contrast (Adjamian, Hadjipapas, Barnes, Hillebrand, & Holliday, 2008), optimising any effects of a bottom-up salience-based gamma modulation. In one block, we made the red item behaviourally relevant by having both the

target and distractor stimuli equally likely appear in red. Thus, the task required both red and black items to be attended as potential targets (the ‘Include’ block). In the other block, we set top-down and bottom-up signals against each other by making the red item *never* the target. Thus, although the colour red was still behaviourally relevant in that it signalled the location of the distractor (i.e., the non-target location), performance would be optimised by avoiding shifting attention to (excluding) this location during the search phase of the task (the ‘Exclude’ block). Before each block started, subjects were informed of the block manipulation both by the experimenter and by a message appearing on the screen. This message stated ‘The red item CAN be the target’ or ‘The red item is NEVER the target’, for the two blocks, respectively. The subject pressed a button to start the experimental block.

The combination of colours and orientations of the stimuli can be divided into three main conditions: (1) the red item is the tilted target; (2) there is no red item present; (3) the red item is the vertical distractor. For each of these main conditions, the grating can either be the target or the distractor, yielding six final conditions (Fig. 1B). Note that as we are interested in the response to the gamma-inducing grating in the left hemifield in all these conditions, our nomenclature refers to the status of the grating: *Target salient (Targ-S)*: the grating is a red target, the disk is black and vertical; *Distractor non-salient (Dist-NS)*: the grating is black and vertical, the disk is a red target; *Target filler (Targ-F)*: the grating is a black target, the disk is black and vertical; *Distractor filler (Dist-F)*: the grating is black and vertical, the disk is a black target; *Target non-salient (Targ-NS)*: the grating is a black target, the disk is red and vertical; *Distractor salient (Dist-S)*: the grating is red and vertical, the disk is a black target.

In order to gain a sufficient signal-to-noise ratio (SNR) for the MEG analysis, we had 80 trials for each individual condition containing a red item. To achieve the 60% ratio of trials containing a salient item in the Include block (30% for each stimulus), there were four conditions of 80 trials each (320 in total), which required 224 filler trials (112 trials for the Targ-F and Dist-F conditions each), and a grand total of 544 trials. In the Exclude block, there were two conditions of 80, thus 160 salient-containing trials, and 108 filler trials (54 for the Targ-F and Dist-F conditions

each), yielding a grand total of 268². Trials were pseudo-randomised, restricting the repetition of target or distractor items on the same side to a maximum of two in a row. This restriction was irrespective of target orientation, which was fully randomised.

There were two consecutive recording runs for the Include block, and a single one for the Exclude block. Block order was counterbalanced across subjects. All subjects first performed a practice block in which both stimuli were always black (40 trials, ~1.5 min duration) at the start of the experiment. The practice block was repeated if the participant was less than 60% correct. The Exclude block and the first run of the Include block were preceded by a verbal explanation and short practice (~0.5 min) of the experimental manipulation. All recording runs were separated by a short break. Each recording run took just under 10 minutes, with a total experiment session time of approximately 45 minutes, including instructions and breaks.

5.3.3 MEG data acquisition

Whole-head MEG recordings were made using a 275-channel CTF radial gradiometer system sampled at 1200 Hz (0-300 Hz band-pass). An additional 29 reference channels were recorded for noise cancellation purposes and the primary sensors were analysed as synthetic third order gradiometers (Vrba & Robinson, 2001). Two of the 275 channels were turned off due to excessive sensor noise. Subjects were seated upright in the magnetically shielded room resting their head on an adjustable chin support. To achieve MRI/MEG co-registration, fiduciary markers were placed at fixed distances from three anatomical landmarks identifiable in the subject's anatomical MR images, and their locations were verified afterwards using high-resolution digital photographs. Head localisation was performed before and after each run, and a TTL pulse was sent to the acquisition computer at stimulus onset and offset, feedback onset and offset, and when the subject

² The discrepancy in the number of filler trials per condition between the two experimental blocks is due to an upwards rounding error in an attempt to equalise the number of trials with targets tilted to the left and to the right within each condition. This discrepancy amounts to 2 trials per filler condition, yielding a proportion of trials containing a salient item of 0.588 versus 0.597 in the Include and Exclude block, respectively. As this difference is extremely minimal, we do not expect this error to have significantly influenced subject's target search or attentional deployment towards salient or non-salient items.

made a button press. Data were acquired continuously, then epoched offline using a window extending -0.9 to 1.2 s around stimulus onset ($t=0$). We monitored eye movements and blinks by recording vertical and horizontal electrooculograms (EOG).

5.3.4 Behavioural data analysis

We discarded trials with a reaction time below 200 ms, and calculated accuracy on the remaining trials. We arcsine transformed the accuracy scores to account for distribution inhomogeneity of performance near ceiling (Anscombe, 1948). Trials with an erroneous response or no response were then discarded, and median reaction time was calculated on the remaining correct trials.

5.3.5 MEG data analysis

Due to the trial design, the Include block contained twice the number of filler trials than the Exclude block. To make the number of trials in each respective condition comparable between the two attentional blocks, we randomly selected 58 trials (112 minus 54) from each filler condition in the Include block (Targ-F and Dist-F) for each subject, and discarded these from analysis. This approach avoids artefactual differences between conditions that are simply due to differences in SNR. Furthermore, trials were excluded from analysis if they contained eye movements, excessive or time-locked blinks (EOG measures), visibly identifiable artefacts, or an erroneous behavioural response. Eye movements of the remaining trials were analysed by averaging the horizontal and vertical EOG traces separately for each subject and attentional condition after baseline-correction (-0.6 to 0 s)³. The mean and standard deviation (SD) were then calculated (0 to 0.8 s) to evaluate any general bias in eye movements and stability of fixation, respectively.

Offline, each data set was band-pass filtered using a fourth-order bi-directional IIR Butterworth filter into alpha (5-15 Hz), beta (15-25 Hz), and gamma (30-70 Hz) frequency bands. For source localisation, a multiple local-spheres forward model (Huang, Mosher, & Leahy, 1999) was derived by fitting spheres to the brain surface extracted by FSL's Brain Extraction Tool

³ A baseline of -0.6 to 0 s was chosen because we observed that many subjects had a tendency to make eye blinks between -0.8 and -0.6 s before stimulus-onset. This pattern is likely due to a blink response to feedback offset of the previous trial.

(Smith, 2002). The synthetic aperture magnetometry (SAM) beamformer algorithm (Robinson & Vrba, 1999) was then used to create a set of beamformer weights for the whole brain at 4 mm isotropic voxel resolution for each subject, frequency-band, and attentional block (grouping together trials of all conditions within a block). Virtual sensor waveforms were then generated at each voxel location, band-pass filtered between 30-70 Hz, and paired t statistical images of source power (Student's t statistic) were generated for 0.6 s of baseline (−0.6 to 0 s) compared to 0.8 s of visual stimulation (0 to 0.8 s) for each condition.

For visual gamma activity (30-70 Hz), the individual paired t SAM images of each subject were examined and the coordinates of peak activity in right medial visual cortex were obtained for both attentional conditions. Virtual sensors were then further interrogated at these peak locations. Time–frequency analysis of each single virtual sensor was conducted using the Hilbert transform from 1 to 90 Hz in 0.5-Hz steps with an 8 Hz-wide band-pass, 3rd order Butterworth filter (Le Van Quyen et al., 2001). Power–time and power-frequency spectrograms are represented as a percentage change from the average baseline (−0.6 to 0 s) amplitude for each frequency band.

For imaging of group-level effects, SAM images were spatially normalised using FSL's FLIRT into MNI space using an affine transform. Non-parametric permutation tests were conducted with FSL's *randomise* using 5000 permutations for each condition with 10 mm variance smoothing and thresholded using the omnibus test statistic value at $p < 0.05$ (Nichols & Holmes, 2002; Singh, Barnes, & Hillebrand, 2003a; Singh, Kim, & Kim, 2003b). For group-level power-frequency analysis, we obtained the peak gamma frequency and amplitude for each subject and condition between 30-70 Hz. We also calculated the full width at half maximum (FWHM) for the gamma peak in the frequency spectrum to investigate if there were any differences in the range of frequencies involved within conditions.

For group-level power-time analysis, permutation tests were performed on data averaged within the frequency range of interest for −0.2 to 1.0 s around stimulus onset (1000 permutations, 2-tailed, $\alpha = 0.05$, 'tmax' (t test) or 'fdr' (f test) corrected for comparisons (Blair & Karniski, 1993)) to assess dynamic fluctuations in amplitude over time. For main effects of attentional block, salience, and grating role, activity was first averaged over conditions for each subject before permutation tests (paired t) were conducted over the group average.

5.4 Results

5.4.1 Behavioural results

One subject needed a repetition of the initial practice block for scoring below 60%, after which median performance of the fourteen subjects was 72.3% correct. For the recording blocks, trials of the two recording runs of the Include block were grouped together, and performance is expressed in percentage of the total number of trials for each block (544 and 268 for the Include and Exclude block, respectively). Discarding of trials with a reaction time (RT) below 200 ms yielded a loss of 1.93 and 1.81% of trials for the Include and Exclude block, respectively, and the difference between the blocks was not significant (paired t test, $t(13)=0.20$, $p=0.848$).

Group average performance is displayed in Fig. 2. Trials on which the grating was the target (Fig. 2A) and the grating was the distractor (Fig. 2B) yielded a very similar pattern of accuracy and RT. Due to the unequal number of conditions (three conditions in the Include block; two conditions in the Exclude block) we could not perform a regular two-way ANOVA on the behavioural data. Instead, we performed two separate statistical tests to assess the effect of our manipulation.

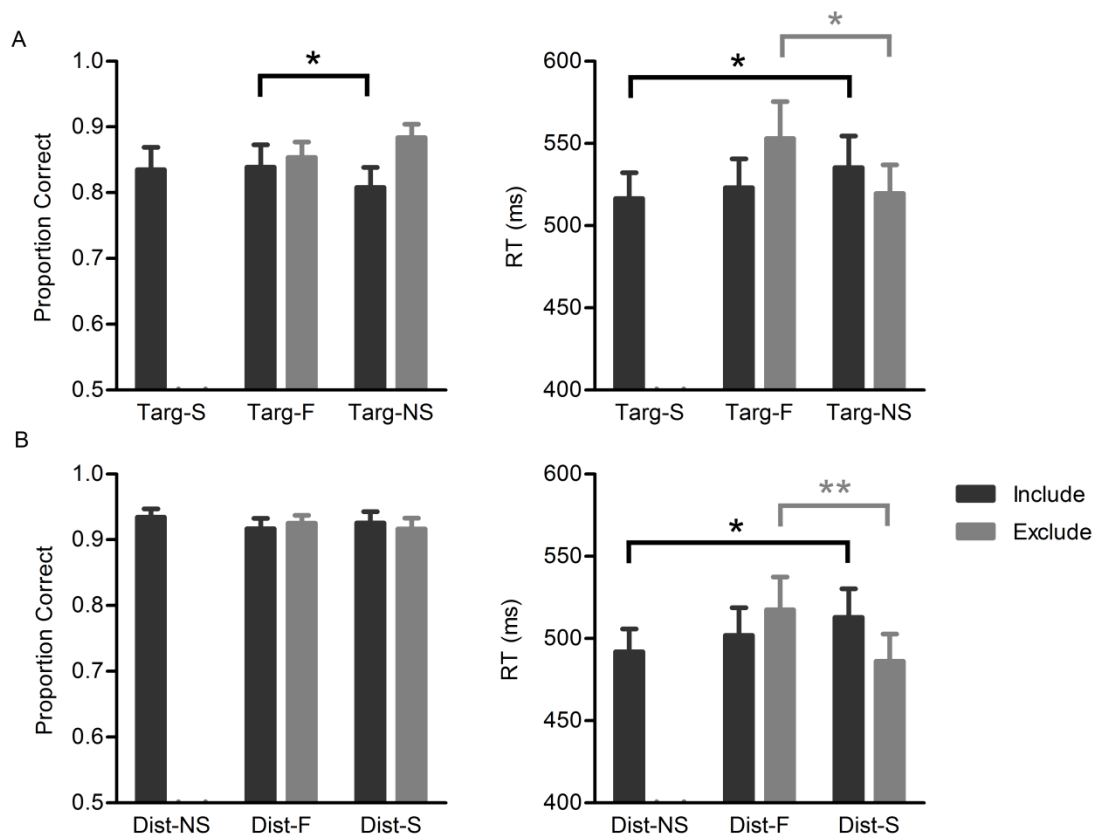


Fig. 2. Group average behavioural results ($N=14$). Displayed are responses to the target, presented separately for trials on which (A) the grating was the target (Targ), and (B) the grating was the distractor (Dist). Results for the attentional block in which the salient red item could be the target are presented in dark grey (Include), and for the attentional block in which the salient red item was never the target in light grey (Exclude). Proportion correct displays the reverted arcsine transformed accuracy. RT: reaction time (average of median RT per subject). S: the grating was salient; F: filler (no salient item present); NS: the grating was non-salient, indicating that the disk was salient. Error bars indicate standard error of the mean. $*p<0.05$, $**p<0.01$.

First, we verified that the red stimulus captured attention, and that this happened regardless of which stimulus was the target (and thus on which side was the target: grating on the left (grating is target) vs. disk on the right (grating is distractor)). If the red stimulus was salient and captured attention, trials in which it was the target (Targ-S & Dist-NS) should have faster and more accurate responses than trials in which no red stimulus was present (Targ-F, Dist-F). Conversely, trials in which the red stimulus was the distractor (Targ-NS & Dist-S) should be slower and less accurate

than when there was no red stimulus (Targ-F, Dist-F). To test this, we performed a two-way repeated-measures ANOVA on the three conditions within the Include block and the two potential roles the grating could play in target search ('grating role': target or distractor). For the accuracy data, this revealed a main effect of grating role, ($F(1,13)=15.34, p=0.002$, distractors > targets), but no main effect of condition ($F<1, n.s.$), nor an interaction ($F(2,26)=2.10, p=0.143$). The same analysis on correct median RT within the Include block revealed a main effect of grating role ($F(1,13)=5.80, p=0.032$); in addition to being more accurate, trials in which the grating was the distractor were also faster. Additionally, there was a main effect of condition on median RT ($F(2,26)=5.48, p=0.010$), but no interaction between condition and grating role ($F<1, n.s.$), suggesting that the effects of condition on RT were very similar when the grating was the target as when it was the distractor. Simple main effects (paired t tests) between the three conditions revealed that RTs were significantly faster when the red item was the target than when it was the distractor, for either grating role (both $p<0.05$). In contrast, none of the comparisons between trials containing a salient item and a filler condition reached significance (all $p>0.05$). The main trend in reaction times thus reflected that the red item captured attention when it was attended.

Second, we assessed the influence of behavioural relevance on the distracting effect of the salient line. To this end, we performed a three-way repeated-measures ANOVA on the two conditions that occurred in both attentional blocks (conditions: the red item is a distractor and no red item is present, attentional blocks: Include and Exclude), and the two potential grating roles (target/distractor). For accuracy data, there was a main effect of grating role (distractors > targets, $F(1,13)=16.12, p=0.001$), and no other main effects (attentional block: $F(1,13)=1.47, p=0.246$; condition: $F<1, n.s.$). There was also a three-way interaction ($F(1,13)=4.87, p=0.046$), but no other interactions reached significance (attentional block*condition: $F(1,13)=1.05, p=0.324$; attentional block*grating role: $F(1,13)=44.23, p=0.060$; condition*grating role: $F<1, n.s.$). Subsequent simple main effects by grating role revealed that when the grating was the target, there was a significant main effect of attentional block ($F(1,13)=7.17, p=0.019$) as well as an attentional block*condition interaction ($F(1,13)=8.94, p=0.010$), whereas condition yielded no significant main effect ($F<1, n.s.$). Further simple main effects (paired t tests) comparing the two conditions within each attentional block showed that accuracy was significantly lower when the grating was non-salient

than when it was a filler in the Include block ($t(13)=-2.33, p=0.037$), whereas accuracy did not differ significantly between these conditions in the Exclude block ($t(13)=1.70, p=0.114$). In contrast, there were no significant effects on accuracy when the grating was the distractor (all main effects and interaction: $F<1, n.s.$). This demonstrates that accuracy was not significantly affected by the behavioural relevance of the red item.

The three-way ANOVA on correct RT within the two conditions (red stimulus distractor and no red stimulus) in both attentional blocks (Include and Exclude) and grating role (target/distractor) revealed that there was a main effect of grating role, $F(1,13)=12.28, p=0.004$, and a main effect of condition ($F(1,13)=6.08, p=0.028$), but no main effect of attentional block ($F<1, n.s.$). There was also an interaction between attentional block and condition ($F(1,13)=12.94, p=0.003$), but no further significant interactions (attentional block*grating role: $F(1,13)=2.31, p=0.153$; condition*grating role: $F<1, n.s.$; three-way: $F<1, n.s.$). Subsequent simple main effects on condition and attentional block per grating role revealed a significant interaction both when the grating was the target ($F(1,13)=8.81, p=0.011$), and when the grating was the distractor ($F(1,13)=14.08, p=0.002$). Further simple main effects (paired t tests) revealed that in the Exclude block, subjects were significantly faster on trials where the red item was a distractor than when there was no red item (grating target: $t(13)=-2.92, p=0.012$; grating distractor: $t(13)=-3.72, p=0.003$). In contrast, in the Include block a trend towards significance was present for the opposite pattern of effects (grating target: $t(13)=1.94, p=0.074$; grating distractor: $t(13)=1.88, p=0.082$). Thus, we have evidence that participants did indeed attend and ignore the red item in the Include and Exclude block, respectively.

In summary, the behavioural results suggest that the presence of a red distractor was processed differently depending on its behavioural relevance. Red distractors were detrimental for performance when the red item was a potential target (Include block), whereas red distractors improved performance when they could not be the target (Exclude block). Furthermore, in the Include block, trials with a red target were faster than trials with a red distractor. This pattern of results suggests that subjects used the salient information to efficiently complete the task. Effects were stronger and subjects were faster and more accurate when the grating was the distractor than when the grating was the target, suggesting that subjects found the trials in which the right-

lateralised disk was the target easier. This could either be due to a preference for inspecting the disk on the right first, or to an easier distinction between left/right tilt for the disk than for the grating. Although the effect of the salient item was present in RTs both when the grating was the target or when it was the distractor, the lack of an effect in accuracy for trials when the grating was the target may be due to performance being near ceiling. The important finding for our purposes is that our attentional manipulation was successful in making subjects attend to or ignore the red item.

5.4.2 MEG results

5.4.2.1 SAM analysis of gamma oscillations (30-70 Hz)

For one subject, acquisition of one of the Include runs had failed due to technical difficulties. This subject was therefore excluded from further analysis. Paired *t* SAM images in the gamma range (30-70 Hz) showed that ten of the remaining thirteen subjects had a main source of event-related synchronisation (ERS) in right medial visual cortex, contralateral to the grating in both attentional blocks. One subject had an ERS in visual cortex that was localised to the left hemisphere, and two subjects did not have any identifiable ERS in visual cortex. These three subjects were excluded from further analysis. Group average images for the two blocks of the remaining ten subjects are displayed in Fig. 3.

Talairach coordinates of all gamma ERS sources were located within the right cuneus (Brodmann area 17) or the right middle occipital gyrus (Brodmann area 18). Over the group, there was a very small mean spatial difference in peak location (0.86 mm) between the two conditions. Paired *t* tests on the three Talairach coordinates showed that this spatial difference was non-systematic ($t(9)=0.21, p=0.84$; $t(9)=1.07, p=0.31$; $t(9)=1.08, p=0.31$; for sagittal, coronal, and axial, respectively).

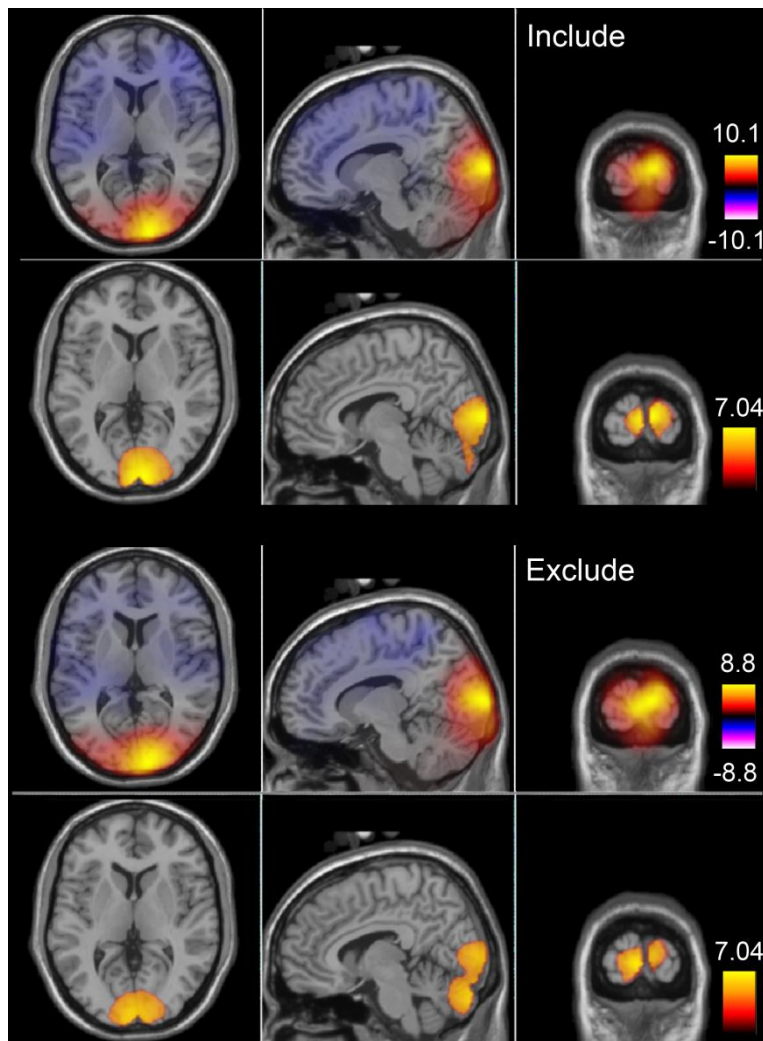


Fig. 3. Group average ($N=10$) 30-70 Hz SAM activity (top row of each panel) and thresholded one-sample t test map of the SAM images (bottom row of each panel). A transverse, sagittal, and coronal slice are displayed for the block in which the red item was a potential target (Include block, top row) and in which the red item could never be the target (Exclude block, bottom row). Colours indicate average percentage signal change from baseline (top) and t values (bottom, $p<0.05$, corrected for multiple comparisons).

5.4.2.2 MEG trial and eye movement artefacts

Excluding qualitatively bad MEG trials in addition to the behaviourally erroneous trials led to a total average data loss of 37.9% in the Include block and 38.9% in the Exclude block. Paired t tests on the remaining number of trials per individual condition between the two attentional blocks showed that these numbers were not significantly different (Dist-S: $p=0.760$; Targ-NS: $p=0.053$; Dist-F: $p=0.706$; Targ-F $p=0.971$; Dist-NS and Targ-S Include only).

Inspecting the EOG traces revealed that neither the vertical nor horizontal EOG contained any eye position bias between the two attentional blocks (paired t test on the mean: $t(9)=0.67$, $p=0.52$; $t(9)=2.04$, $p=0.07$, respectively). Stability of fixation did not differ either in either trace (paired t test on the SD: $t(9)=0.92$, $p=0.38$; $t(9)=0.46$, $p=0.66$, respectively).

5.4.2.3 Time-frequency analysis

5.4.2.3.1 Spectrograms

Average time-frequency spectrograms resulting from virtual sensors placed in peak gamma activity in individual right visual cortex are shown in Fig. 4. These spectrograms show a very similar temporal pattern of synchronisation in the gamma range post-stimulus onset for all conditions within both the Include (Fig. 4A) and the Exclude blocks (Fig. 4B). The induced gamma activity showed a strong burst at the initial 0.1-0.2 s post-stimulus, and was then sustained until stimulus offset ($t=0.8$ s) at a slightly lower power and frequency. A sustained post-stimulus decrease in alpha/beta power (<30 Hz) and an early burst of low-frequency power can also be seen, the latter of which likely reflects stimulus-evoked activity. Based on the temporal pattern, we analysed gamma power-frequency activity within time windows of 0-0.1 s (evoked activity), 0.1-0.2 s (burst), and 0.2-0.8 s (sustained, Koelewijn et al., 2011). We did not further analyse alpha/beta power because event-related desynchronisation within this range is known to be less focal than gamma activity (Schnitzler & Gross, 2005). The alpha desynchronisation may thus have originated from sources other than the gamma ERS on which the virtual sensor analysis was based, and may not reflect contralateral activity induced by the grating.

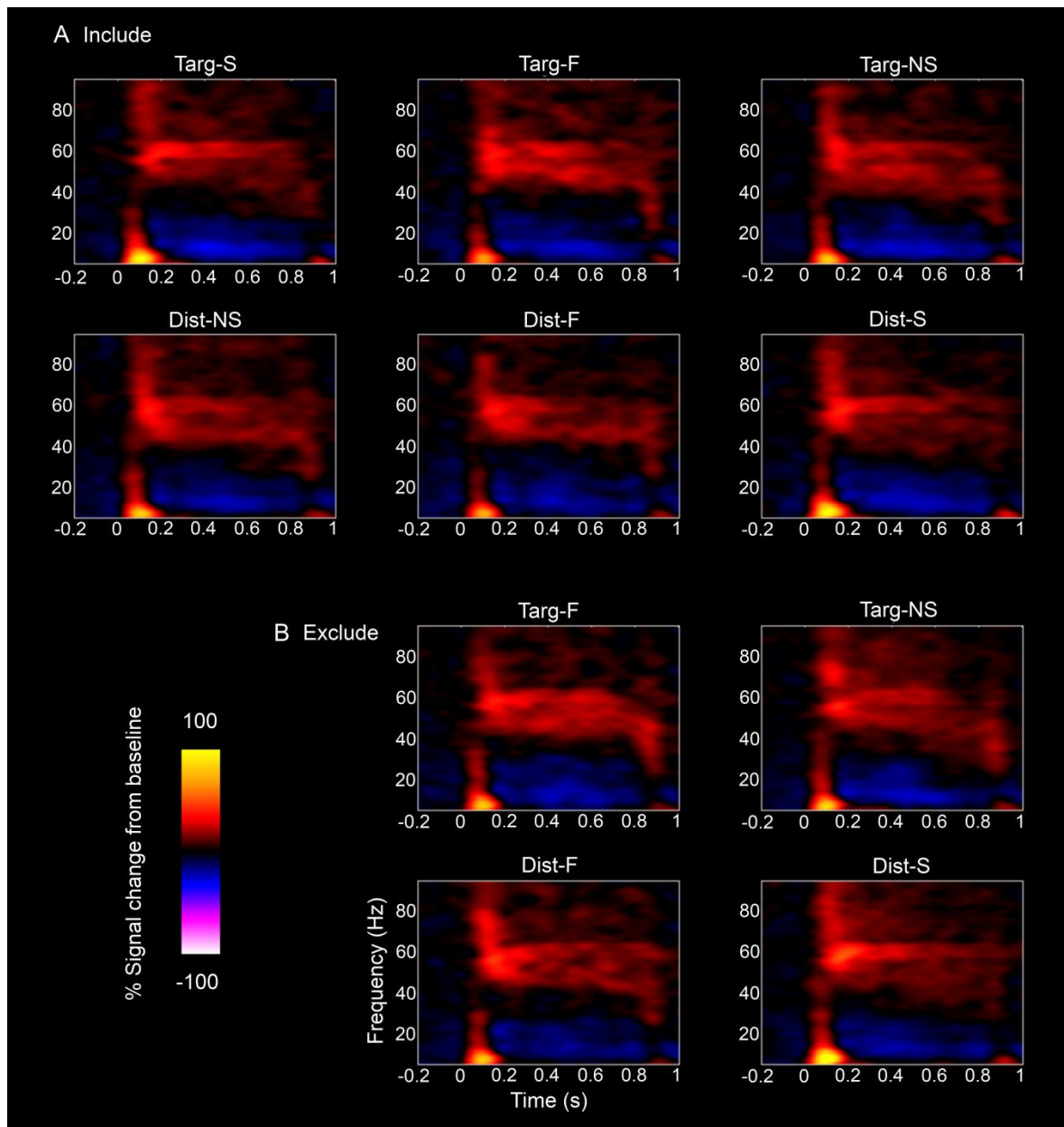


Fig. 4. Group average ($N=10$) spectrograms derived from individual virtual sensors placed at peak activity in right medial visual cortex, reflecting the contralateral response to the grating. Spectrograms are displayed for the six conditions within the Include block (A) and the four conditions within the Exclude block (B). All spectrograms within an attentional block were derived from the same virtual sensor reconstruction. Gamma event-related synchronisation occurred shortly after stimulus onset ($t=0$) until stimulus offset ($t=0.8$). Colours represent the percentage signal change from baseline.

5.4.2.3.2 Peak gamma frequency

To assess whether salience or behavioural relevance altered the frequency at which gamma was induced, we obtained the peak frequency for each condition. Peak frequency values were analysed with the same statistical tests as the behavioural data. A two-way repeated-measures ANOVA on condition and grating role within the Include block showed that peak frequency did not significantly differ for the initial 0-0.1 s of gamma activity (condition: $F(2,18)=2.32$, $p=0.127$; grating role: $F<1$, *n.s.*; interaction: $F(2,18)=2.03$, $p=0.160$). In the 0.1-0.2 s window, there was a main effect for condition ($F(2,18)=5.00$, $p=0.019$), but not for grating role ($F<1$, *n.s.*), nor an interaction ($F(2,18)=2.34$, $p=0.125$). Pairwise comparisons revealed that trials with a red distractor yielded a larger peak frequency than trials containing a red target or no red item (both $p<0.05$), whereas trials containing a red target did not differ from trials containing no red item ($p>0.05$).

For the sustained time window (0.2-0.8 s), peak frequency was highest in conditions in which the grating was salient, both when the grating was a target (Targ-S) and when the grating was a distractor (Dist-S). This pattern suggests that red items induced gamma at a higher frequency (~60 Hz) than black items (~55 Hz). Statistically, peak frequency did not have significant main effects (condition: $F(2,18)=1.181$, $p=0.192$; grating role: $F<1$, *n.s.*), but there was an interaction between condition and grating role ($F(2,18)=4.15$, $p=0.033$) that revealed the three conditions influenced peak frequency differently when the grating was the target versus distractor. Subsequent simple main effects on each grating role (grating target vs. distractor) revealed that peak frequency did not significantly differ amongst conditions for the grating being a target ($p=0.410$), but did when the grating was a distractor ($p=0.031$). Pairwise comparisons demonstrated that peak frequency was higher when the grating was a salient distractor (Dist-S) than when it was a filler (Dist-F) ($p<0.05$), whereas the other two comparisons were not significant (both $p>0.05$).

A three-way repeated-measures ANOVA on peak frequency of the two conditions (red stimulus distractor and absent), two attentional blocks, and grating role showed no three-way interactions for any of the three time windows (chronologically: $F<1$, *n.s.*; $F(1,9)=1.29$, $p=0.285$; $F<1$, *n.s.*). Peak frequency did yield an interaction between condition and grating role for the initial and sustained time windows ($F(1,9)=9.14$, $p=0.014$; $F(1,9)=8.02$, $p=0.020$), and a trend for 0.1-0.2 s ($F(1,9)=4.58$, $p=0.061$). The pattern of this interaction was reversed for the initial 0-0.1 s

compared to the subsequent two time windows. No other interactions or main effects were significant. Subsequent simple main effects on condition within each grating role revealed that for 0-0.1 s, peak frequency was higher for fillers than for salient distractors (main effect condition, $p=0.029$), whereas the opposite was true for 0.2-0.8 s ($p=0.031$). There were no differences when the grating was a target for either time window ($p=0.212$, $p=0.573$).

The amplitude associated with peak frequency and the FWHM of the gamma peak were not significantly different for either analysis in any of the time windows. Overall, the pattern of peak frequency results suggests that for the majority of the stimulus-induced gamma period, a red item induced gamma oscillatory activity at a slightly higher frequency than a black item did, particularly red distractors, irrespective of attentional block. This pattern is illustrated in the power-frequency plots over blocks, salience, and grating role for the sustained gamma period (Fig. 5A, B, C).

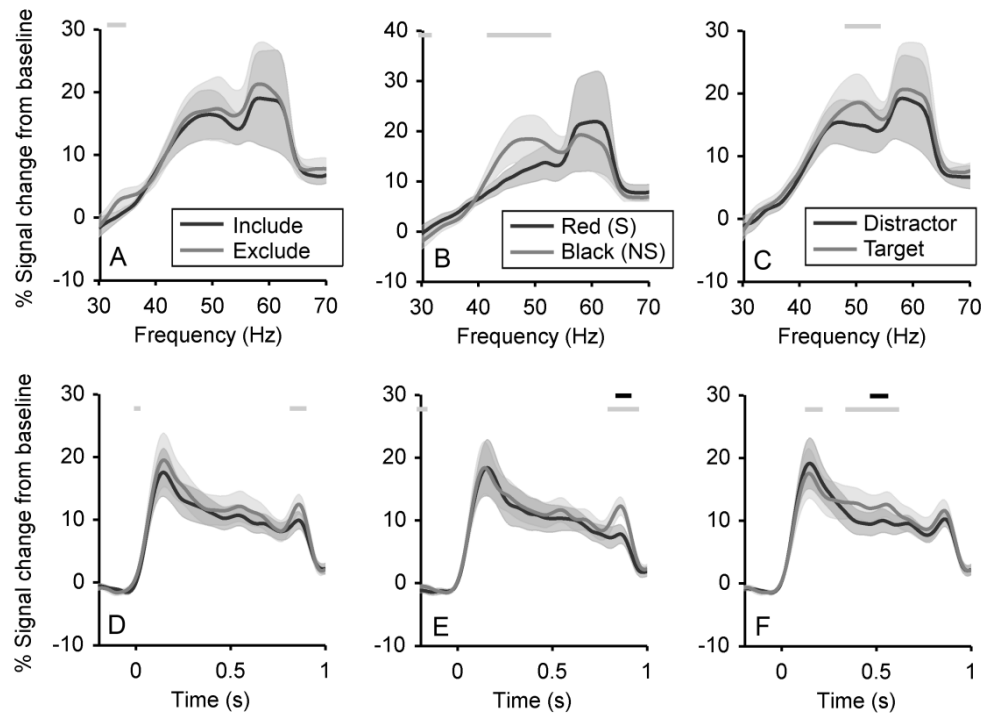


Fig. 5. Power-frequency (0.2-0.8 s) and power-time graphs (30-70 Hz) for main effects in medial visual cortex (N=10). Top and bottom panels per column present the data for the main effects of attentional block (A, D), salience (B, E), and grating role (C, F). Permutation statistics are indicated at the top of each panel (grey bars: $p < 0.05$ uncorrected, black bars: $p < 0.05$ corrected for multiple comparisons). Shaded regions represent the SEM.

5.4.2.3.3 Power-time permutations

To investigate how salience and behavioural relevance dynamically modulated induced gamma activity over time, we performed permutation tests on the power-time series. Here, we report which time periods of a set of compared time courses were significant. Permutation tests provide a strict method to correct for false positives due to multiple comparisons in a time series. However, if a large number of *consecutive* time samples (e.g., 50 ms or more) are significantly different when uncorrected for multiple comparisons, provided that the difference is in the same direction in the entire section, this can reveal trends that lack enough power to survive correction for multiple comparisons, but are not necessarily uninteresting (e.g., similar to reporting a *p* value *near* 0.05 in a regular statistical test, Hamandi, Singh, & Muthukumaraswamy, 2011). We therefore also report the uncorrected statistics, although we are cautious about drawing conclusions based on these uncorrected findings.

5.4.2.3.3.1 Main effects of attentional block, salience, and targets/distractors within gamma (30-70 Hz)

First, we assessed whether there were any main effects of attentional block (Include/Exclude), salience (red or black), and grating role (target or distractor) by performing a paired *t* permutation test over the two levels of each factor, each averaged over the remaining two factors. Permutation analyses revealed that there were no overall differences in the temporal pattern of gamma activity between the two attentional blocks for the duration of the stimulus (Fig. 5D). Similarly, there were no overall differences in the temporal signal between salient (red) and non-salient (black) items (Fig. 5E). Both comparisons did show a modulation in the stimulus-offset effect, which was slightly enhanced for the Exclude block relative to the Include block, and significantly for black relative to red items (0.8-0.9 s). Grouped over both blocks, grating role had a marked influence on induced gamma activity (Fig. 5F). The initial induced peak was slightly enhanced when the grating was a distractor, whereas target gratings induced a significantly elevated level of gamma synchronisation compared to distractors during part of the sustained response (from ~0.35 s, significant ~0.5-0.6 s post-stimulus). This elevation in gamma power is likely to reflect a shift of

attention away from the distractor towards the target item required to determine the direction of tilt once the tilted item had been located.

5.4.2.3.3.2 Condition effects on two spectral peaks within gamma (40-55 Hz and 55-65 Hz)

The power-frequency plots in Fig. 5 indicate variances of power within the gamma frequency spectrum. Two main peaks of activity could grossly be identified across all plots, one extending 40-55 Hz, and a second peak between 55-65 Hz. Variances in power within these peaks were clearly present for red versus black items (Fig. 5B), and could also be seen for targets versus distractors (Fig. 5C). It is therefore possible that temporal modulations of gamma within conditions were expressed to different degrees within these two frequency spectra and may be obscured when averaging within 30-70 Hz. We therefore performed power-time permutation analysis averaging power between 40-55 Hz, and 55-65 Hz separately. Note that power within these bands was not different between the two attentional blocks (Fig. 5A), verifying that this distinction in frequency bands does not bias the analysis of our attentional effect.

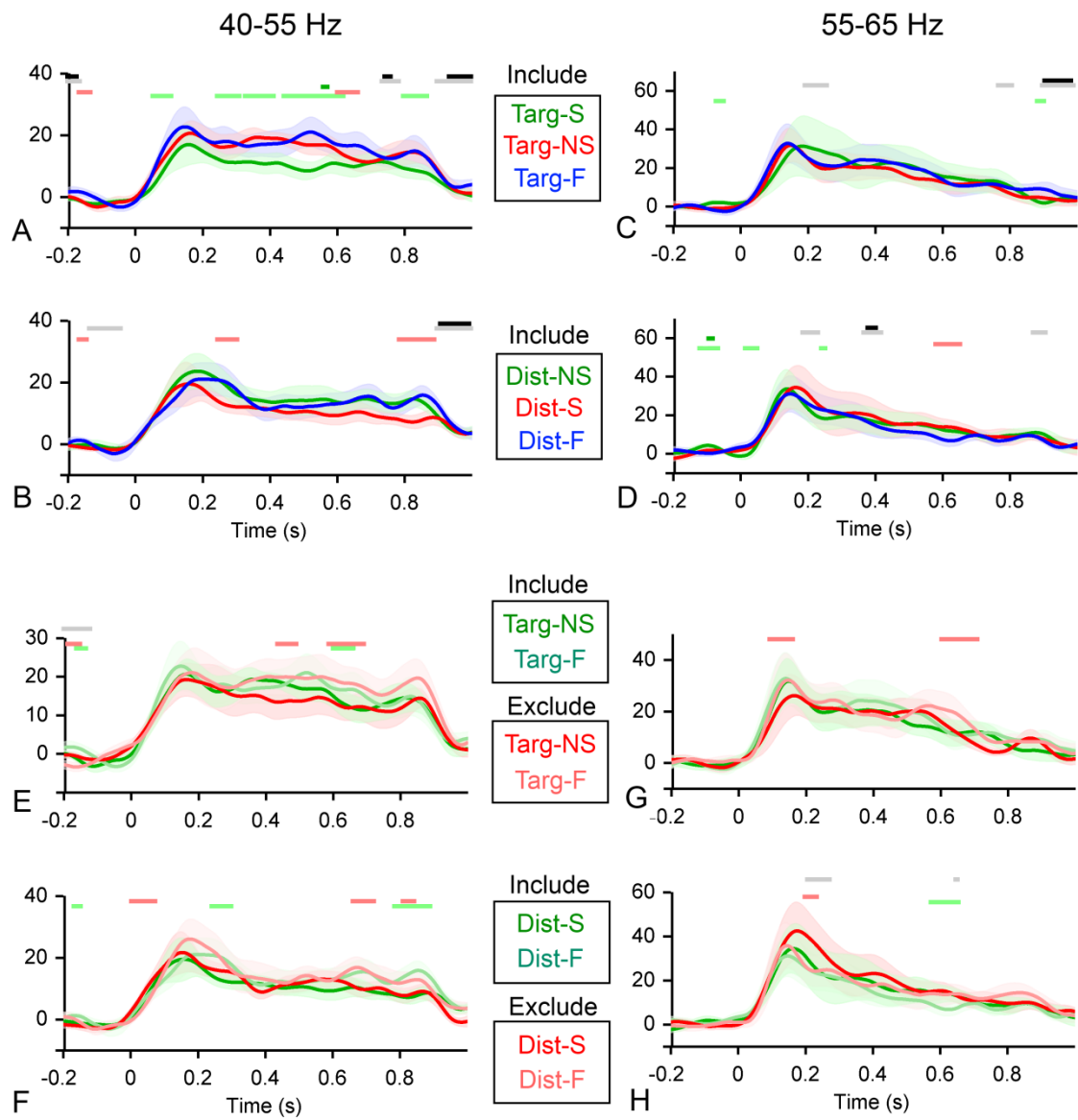
The gamma response to the grating was associated with different attentional processes when it was the target than when it was the distractor. In fact, attentional allocation during target search and orientation discrimination should be the exact opposite on corresponding trials within a main condition (i.e., Targ-S & Dist-NS; Targ-F & Dist-F; Targ-NS & Dist-S). We therefore assessed differences between the main conditions (salient item is target, absent, or distractor) separately for trials on which the grating was the target and for trials on which the grating was the distractor. This separation additionally avoids any confounds due to the fact that targets had a different orientation than distractors.

To statistically assess the effect of attentional capture by a salient item, we first performed a one-way repeated measures ANOVA permutation test on the three conditions within the Include block. We additionally performed two planned paired *t* permutation tests, one comparing the salient target versus filler condition, and one comparing the salient distractor versus filler condition. This way, time periods where both the ANOVA and a *t* test was significant could tell us whether differences in gamma power within the Include block were due to salient targets, distractors, or both. Power-time activity for the three conditions within the Include block is displayed in Fig. 6A-

D. For conditions within the Include block, salient gratings generally yielded lower amplitude activity than fillers within 40-55 Hz (green vs. blue in Fig. 6A, red vs. blue in Fig. 6B), whereas this was not the case for 55-65-Hz activity (Fig. 6C, D). This is in line with a trend in the main effect power-frequency plot in Fig. 5B. This power reduction due to salience appeared stronger for targets than for distractors. Note that this difference could also be due to the red colour of the grating. However, the ANOVA permutation test was only significant just before and after stimulus offset (~ 0.7 s and > 0.9 s, black bars), both when the grating was a target (Fig. 6A) and when it was a distractor (Fig. 6B). Although the difference between salient targets and filler targets showed a trend for significance over most of the stimulus time (Fig. 6A, light green bars), the time periods this difference was present did not match with the times the ANOVA was significant. For the 55-65 Hz band, the ANOVA was also significant after stimulus offset, showed a trend around 0.2 s when the grating was the target (Fig. 6C), and was also briefly significant around 0.4 s when the grating was a distractor (Fig. 6D). However, during these times no t test permutations were significant, making it difficult to interpret which conditions contributed to this main effect. In conclusion, the results showed a slight tendency for salient/red items to induce 40-55 Hz gamma at a lower power than non-salient/black items during stimulus presentation, but we did not see a clear correlate of the behavioural effect of capture by a salient attended item in the gamma response within either 40-55 or 55-65 Hz bands.

Fig. 6. Power-time plots for individual conditions within 40-55 Hz (left panels) and 55-65 Hz (right panels) frequency bands. Solid lines represent the group average and shaded regions represent the SEM. The Y axis reflects gamma power as percentage signal change from baseline. (A-D) The three conditions within the Include block presented separately when the grating was a target (A,C) and a distractor (B,D). Horizontal bars represent permutation test outcomes of an ANOVA ($p < 0.05$ grey: uncorrected; black: corrected for multiple comparisons) and t tests comparing the conditions with a salient item to the filler condition, each presented in the colour of the respective salient condition ($p < 0.05$, light red and green: uncorrected; dark red and green: corrected). (E-H) Similar plots comparing the salient distractor and salient absent conditions between both attentional blocks. In these plots, statistics represent the difference of salient minus filler

conditions. Note that these figures thus again show part of the data presented in A-C. Legends are indicated per row.



Because we derived virtual sensors separately for the two attentional blocks, time-frequency comparisons between the two attentional blocks could potentially be influenced by differences in the beamformer weights. We therefore did not compare conditions between the two blocks with a two-by-two ANOVA. Instead, we performed a paired t permutation test to compare the *difference wave* of the salient distractor and filler condition within each attentional block ('difference comparison', for example Targ-NS minus Targ-F within the Include block vs. Targ-NS minus Targ-F within the Exclude block). This way, we compared conditions with identical physical properties in the two attentional blocks (the filler condition effectively served as a baseline within each block). To assess what manipulation underlies any effect in the difference comparison, we additionally performed planned paired t permutation tests comparing the time courses of the salient distractor and filler condition within each attentional block.

There were no differences that survived correction for multiple comparisons in either frequency band when comparing conditions across the two attentional blocks (Fig. 6E-H). However, one interesting trend could be observed. When the grating was a distractor, there was a trend during the stimulus burst (around 0.2 s) for a larger response induced by a salient distractor than a filler when it was excluded from search than when it was included (Fig. 6H). This interaction overlapped with a trend for significance in the permutation t test comparing the salient distractor and filler within the Exclude block (Dist-S vs. Dist-F), suggesting that this trend was due to an enhanced response to the salient item when it was ignored for target search, whereas it was not clearly different if the salient item was attended as a potential target. No such modulation was present in the 40-55 Hz band. As this test compared the same physical stimuli (red or black, and all vertical distractors), this interaction trend represents an attentional modulation based on a physical stimulus property. Note that because we did not find clear effects on the gamma response when comparing the effect of a salient item that captured attention in the Include block, we cannot be sure whether this interaction is due to the salience of the item, or the red colour. Nevertheless, this trend was dependent on the behavioural relevance of a bottom-up property.

One noteworthy observation is that within both 40-55 and 55-65 Hz there were short-lived differences within the baseline. This suggests that the reason we did not observe significant effects may be due to baseline noise. This is surprising as the task required constant focus. Noise in the

baseline period may be due to offset effects from the previous trial, although this is not likely considering there was a 900 ms fixation-only period. Nevertheless, this was not present in the comparison where we found the main trend towards an interaction of salience and behavioural relevance (Fig. 6H). In summary, we found a trend towards a difference in modulation of the stimulus-induced burst of narrow-band gamma power within 55-65 Hz by the physical property of a stimulus (red/salient) when it was attended or ignored. Gamma power was largest when a salient distractor item was actively ignored.

5.5 Discussion

In the present study, we found a trend towards an interaction of bottom-up and top-down influences on the power of narrow-band 55-65 Hz gamma activity in early visual cortex. The initial burst (0.1-0.2 s) induced by a salient item was modulated depending on the behavioural relevance of the salient item. When red items were ignored in target search because they could never be the target, red distractors yielded an enhanced gamma burst compared to black distractors, whereas the burst was not clearly modulated when red items were attended as a potential target. We suggest this may reflect a neural marker of an interaction of bottom-up and top-down attentional demands in early visual cortex, although we need to be cautious as this was statistically only a trend.

First, it must be stressed that the behavioural relevance modulation we found at 55-65 Hz was not significant if the permutation test was corrected for multiple comparisons, although it did occur for multiple consecutive time points. This is likely to be due to a lack of statistical power, which could be caused by a number of factors. For example, only ten of the fourteen subjects had a measurable and properly localised gamma response. Although on average the behavioural results confirmed our manipulation, only six of these ten subjects reflected the average behavioural pattern in their individual behavioural results (i.e., best performance when the red item was a red target in the Include block, and best performance when the red item was a distractor in the Exclude block). The four subjects that did not display this average pattern may have reduced effects in the average power-time courses. Furthermore, all reaction times were in a fairly narrow range (~500-550 ms), and differences in reaction times between conditions were therefore small (but reliable). However, excluding these four subjects leaves us with very little statistical power, especially in the

permutation analyses. It is also possible that the measured gamma signal reflects to some degree gamma induced by the ipsilateral stimulus. Although the main source of gamma activity was mostly localised to visual cortex contralateral to the grating, the group average was somewhat centralised and not as clear as in previous studies using the same grating stimulus presented unilaterally (e.g., Koelewijn et al., 2011 / Chapter 3; Chapter 4). Also, attentional effects are known to increase over the visual pathway (Treue, 2001), and effects may have been quite small in V1. Furthermore, the contrast gain model states that the effect of directing attention towards versus away from a stimulus differs over contrast (Martinez-Trujillo & Treue, 2002; Reynolds, Pasternak, & Desimone, 2000). Our stimuli may have been too high-contrast to clearly reflect the attentional modulation. However, the contrast gain model was mostly based on findings in higher visual areas and this may not apply to V1, which is much more stimulus-dependent. Despite the insufficient statistical power to correct for multiple comparisons, the trend evident with consecutive time points suggests an intriguing pattern, which we discuss here. This effect does need replication with more statistical power to draw firm conclusions.

Behaviourally, strongest effects were seen comparing performance when the red item appeared as a distractor versus there being no red item. When it could be a target, the presence of a red item as a distractor impaired performance, whereas it enhanced target search performance when it could never be the target. This pattern of results suggests that in both cases, the red item was important for target search. The trend of performance in the block where the red item could be the target (i.e., fastest when the red item was the target, slowest performance when the red item was the distractor, and intermediate performance when there was no red item) supports that it was not just the presence of the red item modulating performance, but its specific role for target search. This pattern of behavioural results suggests that in both blocks, subjects located the red item first when it appeared. In the case of it being a potential target, subjects would then inspect its orientation, determine that it was a distractor, and switch attention to the target item, delaying the response. In contrast, when the red item could not be a target, subjects could quickly discard the red item based on its colour, without the need to inspect its orientation, and much more rapidly shift attention towards the target item to determine its orientation and make a response. As the physical input in this condition was identical in both attentional blocks, that is, in both cases a red item with the

same orientation induced the measured gamma synchronisation, any difference in the neural signal could only be due to the top-down modulation. The enhancement of the early gamma burst induced by a red item that is not a potential target may therefore reflect the initial rapid selection of the salient item (e.g., Theeuwes, 2010; Theeuwes & Burger, 1998).

Alternatively, subjects could have invoked a different search strategy in the two blocks. In the Include block, the behavioural results suggest that subjects are most likely to have adopted the aforementioned red-first search. In the Exclude block, however, the information of a red item not being a target could have been translated to a simple feature search for a black item (Saenz, Buraças, & Boynton, 2003). In this case, on filler trials there were two items to consider as a potential target, whereas on a salient distractor trial there was only one, yielding the same advantage in target search for distractor trials. However, attention to a feature is known to enhance neural responses to those features throughout the visual display, as has been shown for both neural firing (Hopf, Boelmans, Schoenfeld, Luck, & Heinze, 2004; Maunsell & Treue, 2006) and spike-field coherence in the gamma range (Bichot, Rossi, & Desimone, 2005). Although the *power* of gamma synchronisation does not necessarily increase with feature-based attention (Bichot et al., 2005), these findings would generally predict a larger response to black over red items at all times, which we did not find. In addition to enhanced responses to attended features, feature-based attention has been shown to yield reduced responses to unattended irrelevant features, although this has only been shown for higher level posterior and parietofrontal areas (Polk, Drake, Jonides, Smith, & Smith, 2008). To our knowledge, it is not currently known whether feature-based attention yields similar reductions for irrelevant items in early visual cortex. However, this scenario is unlikely to yield a selective *increase* in synchronisation to the red item. It is also not likely that this increase was purely caused by the bottom-up salience of the red item, because the post-stimulus time of the enhancement (0.1-0.3 s) was quite late and too prolonged for a purely sensory bottom-up saliency response, which is generally found 50-90 ms post-stimulus (Zhang, Zhaoping, Zhou, & Fang, 2012). Thus, it is not likely that subjects adopted a these different search strategies in the two attentional blocks.

One further possibility is that the burst enhancement reflects an inhibitory mechanism. The red item may have to be actively inhibited to achieve successful target search, disengaging the item

from attentional selection. Using EEG, shifts of voluntary attention have been shown to yield enhanced gamma-band synchronisation in occipital areas (Landau, Esterman, Robertson, Bentin, & Prinzmetal, 2007), much like enhanced cortical activity seen with other measures such as fMRI (Serences et al., 2005). Moreover, the post-stimulus timing of the attentional shift increase in this EEG study was short-lived and very similar to the gamma burst (0.15-0.25). However, if this were the case, we would expect to see a similar enhancement at a later stage for salient distractors when they were a potential target, and presumably a much reduced or no burst at all for salient targets, which would not require a shift of attention. On the other hand, the certainty of the red item always being a distractor, plus the fact that it can be discarded based purely on its colour without the need for inspection of its orientation (i.e., pre-attentively), could have yielded an amount of time-locked inhibition that would not be obtained in either salient condition of the other attentional block. Thus, the increased power during the gamma burst may reflect an inhibitory process associated with the pre-attentive filtering of features.

The mid-stimulus enhancement we observed for targets over distractors (0.4-0.6 s, Fig. 5F) is likely to reflect the active orientation discrimination after the attentional shift towards the target. Although humans are able to discriminate vertical orientations tilted as little as 0.05° at 3 cycle per degree (Edden, Muthukumaraswamy, Freeman, & Singh, 2009), the relatively slow average response times (>500 ms) confirm that the 3° from vertical discrimination was attentionally demanding. It is likely that the demanding task kept attention directed towards the target and away from the distractor until shortly before the response. The temporal evolution of the gamma response suggests that synchronisation contralateral to targets was strongly sustained. In contrast, distractors showed a reduction in the usually observed sustained plateau of activity that occurs even with lesser-demanding attentional tasks (such as a passive response to grating offset, Koelewijn et al., 2011 / Chapter 3). This is in line with findings in monkey V4, where, like firing rates, gamma synchronisation decreases when attention is directed away from a location (Womelsdorf, Fries, Mitra, & Desimone, 2006). Furthermore, gamma activity is known to correlate with an individual's orientation discrimination ability, although this concerns individual peak frequency rather than power (Edden et al., 2009).

It should be highlighted here that targets were always tilted whereas distractors were always vertical, because oblique gratings of 45° induce an enhanced level of gamma synchronisation compared to vertical items in early visual cortex (Koelewijn et al., 2011 / Chapter 3). However, the oblique-related enhancement was expressed throughout the stimulus-induced gamma response whereas the difference between targets and distractors here was short-lived mid-stimulus presentation. Although we cannot exclude a contribution of the orientation of the items to a difference in gamma power, for these reasons we do not think it likely that the dynamic development of mid-stimulus enhanced gamma power was fully due to the small orientation difference. Importantly, this potential orientation difference does not influence the trend of an interaction between bottom-up salience and behavioural relevance, because this interaction was present within conditions where the grating was a distractor in both attentional blocks.

In the present study, our manipulation of the salience of a stimulus was by having it appear in a high-luminance red less frequently than in black. Although the behavioural results suggested that red items captured attention, it is important to note that this may not be the same as the pop-out phenomenon in visual search because we only had two stimuli. Pop-out is typically demonstrated by no change in reaction time with increasing numbers of distractors (Desimone & Duncan, 1995; Treisman & Gelade, 1980). Here, we defined salience as a relative novelty of a feature in the global task (there was ‘more’ black than red overall), rather than in an individual display. In each display, however, we had the additional manipulation that the luminance of the red item differed from the black, a ‘bottom-up’ salience signal in itself (Itti & Koch, 2001). Using this manipulation of salience, we found an interaction between the distracting effect of the presence of a red item and its behavioural relevance in narrow-band 55-65 Hz gamma activity. However, one possible concern is that the interaction of frequency band was simply due to the physical colour of the item, not its ‘salience’ *per se*. Rols et al. (2001) found that red relative to green or yellow items enhanced evoked responses in monkey V1 and V4, as well as gamma-band responses within the 46-90 Hz range. We did not find an overall enhancement for red items, but a reduction at lower gamma frequencies and a similar or slightly enhanced power at higher gamma frequencies. However, Rols et al. (2001) used an array of coloured rectangles, and it is not known how red-white versus black-white gratings, as we used in the present study, modulate the power or spectrum of the induced

gamma response in the absence of an attentional modulation. Future research should address these questions by comparing the results of the present study to the opposite manipulation using a less frequently occurring black than red item, a different feature determining behavioural relevance, and/or including a condition in which no behavioural relevance is assigned to the red item.

The main finding in the present study is a trend towards a top-down effect of behavioural relevance on 55-65 Hz gamma activity induced by salient items in early visual cortex. The source of gamma-band activity was localised to the calcarine sulcus, very similar to previous MEG studies and most likely reflecting V1 (Hoogenboom et al., 2006; Koelewijn et al., 2011 / Chapter 3; Muthukumaraswamy & Singh, 2008; Muthukumaraswamy et al., 2010). The earliest modulation of the induced signal occurred around 100 ms post-stimulus. It is therefore unlikely that the observed enhancement due to behavioural relevance represents the bottom-up feedforward sweep from the retina. Instead, the top-down modulation in early visual cortex is likely to be due to feedback from a parietal or frontal area such as the IPS or FEF. Supporting this, areas within the parietofrontal network all contain projections to visual areas as well as to each other (Bisley, 2011; Corbetta & Shulman, 2002). Moreover, there is evidence that V1 is reactivated 150-250 ms after the onset of an attended stimulus (Noesselt et al., 2002), which coincides well with the present modulation of behavioural relevance. This reactivation in V1 due to parietofrontal feedback is likely to play a role in resolving stimulus competition (Baluch & Itti, 2011; Fries, Schröder, Roelfsema, Singer, & Engel, 2002). Interestingly, Buschman and Miller (2007) reported a distinction in the order in which areas in the parietofrontal network are active as well as the frequency range at which parietofrontal coherence is evident during bottom-up pop-out search and during top-down conjunction search in monkeys. During pop-out search, the LIP fires first, then frontal areas, and coherence is greatest between 35-55 Hz, whereas frontal areas fire before the LIP in conjunction search, and coherence is most evident between 22-34 Hz. This dichotomy suggests two separate feedback pathways to visual cortex. Considering the fact that gamma activity in monkeys is often expressed at a slightly lower frequency than in humans (stationary stimuli: 35 Hz vs. 44 Hz; moving stimuli: 47 Hz vs. 55 Hz, respectively; Friedman-Hill et al., 2000; Swettenham, Muthukumaraswamy, & Singh, 2009), we speculate that these narrow bands of differential synchronisation may correspond to the 40-55 Hz and 55-65 Hz bands identified in humans in the

188

present study. In that case, the early behavioural relevance effect at 55-65 Hz in the present study may reflect feedback from parietal areas, possibly in the form of a priority signal, whereas the late target-distractor orientation discrimination difference in the 40-55 Hz band may be more related to feedback from frontal areas. Future studies investigating cross-frequency coupling, and inter-area synchronisation for example using dynamic causal modelling, could shed light on this matter.

In summary, the present findings in light of the current literature suggest that interactions between bottom-up and top-down processing may not be limited to higher visual or parietofrontal areas, but are likely to also take place in early visual cortex. Such interactions may be expressed at a narrow-band 55-65 Hz frequency range, a range overlapping stimulus-driven effects around 50 Hz (Chapter 3) and attentional modulations above 60 Hz (Chapter 4). These findings support extensive feedforward and feedback communication between parietofrontal and early visual areas, and suggest these may involve a priority signal indicating a balance of stimulus and goal-driven factors. Although in visual neuroscience research we usually investigate visual processes using very simple visual displays, in the real world, visual input is constantly changing and the visual system will need to be dynamically updated to reach a current goal or perform a task. Dynamic communication between parietofrontal areas and early visual cortex can ensure constant updating of priority signals based on both bottom-up and top-down information to regulate attentional allocation for behavioural goals such as motor or oculomotor actions, as well as covert attention.

5.6 Acknowledgements

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5.7 References

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Chapter 6 – General discussion

General discussion

6.1 Overview of thesis

The aim of this thesis was to investigate the contribution of early visual cortex in the balancing of stimulus and goal-driven attentional demands in vision. I primarily focused on oscillatory activity in the gamma range which plays an important role in neural communication and cognitive processing. In four experiments using magnetoencephalography (MEG), I investigated how physical stimulus-driven factors that can capture attention, and goal-driven factors that reflect our voluntarily directed attention, modulate activity in early visual cortex. Specifically, I investigated how stimulus properties and goal-driven demands influence activity in early visual areas by comparing situations in which these types of information are presented separately, and when they are competing for attentional allocation. In this chapter, I will review the specific findings presented in each chapter. I will discuss their contribution towards the main research question and their implications in a broader context. I will then discuss a number of outstanding issues that pose questions for future research.

6.2 Overview and implications of findings

6.2.1 Chapter 2 – Manipulating behavioural relevance of a salient item: an MEG experiment

In Chapter 2, I directly addressed the main research question: how and when do demands on attention due to stimulus and goal-driven factors influence activity in early visual cortex, and do these influences combine to modulate activity? The behavioural results showed that subjects were very good at ignoring a salient item when it was not relevant for target search, whereas it captured attention when it was relevant for target search. This result is in line with many previous findings (Bacon & Egeth, 1994; Folk, Remington, & Johnston, 1992; Folk, Remington, & Wright, 1994; Theeuwes, 1991; Yantis, 1993; Yantis & Egeth, 1999; Yantis & Jonides, 1990). When the salient item was not relevant for target search, early components (100-200 ms post-stimulus onset) of the

stimulus-evoked response in the calcarine sulcus were increased compared to when the salient item could be the target. These increases occurred regardless of whether the salient item was present or absent, and were thus likely to reflect an effect of the top-down attentional set, possibly a combination of feature-based attention to the salient colour and spatial attention to the stimulus locations. These findings are consistent with earlier findings of modulations in early visual cortex due to voluntarily directing attention to locations or features (Gandhi, Heeger, & Boynton, 1999; Luck, Chelazzi, Hillyard, & Desimone, 1997; Martinez et al., 1999; McAdams & Maunsell, 1999; McAdams & Reid, 2005; Motter, 1993; Noesselt et al., 2002; Saenz, Buracas, & Boynton, 2002).

In contrast to the task set effect, I did not observe any modulation due to the presence of a physically salient stimulus. This is likely due to the limitation of this experiment to localise cortical responses to the four stimulus locations. A localiser designed to obtain individual sources for the four stimulus locations did not show clear localisations. I therefore used an independent baseline block instead to localise the evoked response to the full stimulus display. The activity that was measured was thus the bulk response to the four items. In the conditions containing a salient item, this bulk response would have reflected all salient and non-salient items, and targets and distractors in the display together. This may have blurred any effects driven by the bottom-up salience of items. This null effect does not take away from the attentional manipulation we found. However, the null effect of salience may have obscured any potential interactive effect of physical stimulus salience and behavioural relevance. In the next chapters, I therefore focused on developing a paradigm where I could reliably measure the response to a single item whilst similarly manipulating these attentional demands.

A secondary goal of Chapter 2 was to explore how gamma oscillations were influenced by these competing demands on attention. Although source localisation of induced gamma activity suggested a similar source in the calcarine as was identified for averaged evoked activity, time-frequency spectra extracted from this source did not show observable activity in the gamma range. There are at least two possible reasons for this discrepancy. First, statistical tests on the source images did not show any activity that survived correction for multiple comparisons. To still obtain our goal of exploring cuneus activity, I used a simple group average image instead. The sources I obtained were thus likely to have been weak and inconsistent across the group. Second, I did not

200

use a source localisation method that contrasted post-stimulus activity to pre-stimulus activity. Such a non-differential approach may have shown sources of gamma activity that was not time-locked to the stimulus whereas this non time-locked activity would have cancelled out in the virtual sensor time-frequency data. As outlined in Chapter 1 (section 1.4), gamma activity plays an important role in visual processing, and its link to a role in neural communication makes it an important focus for investigating effects of bottom-up and top-down processing. I therefore focused on developing a paradigm that strongly induced gamma synchronisation, with appropriate localisation techniques to target gamma activity in early visual cortex in the subsequent chapters.

In contrast to the absence of gamma activity, a pattern of sustained desynchronisation in the alpha range was present for each condition, which was induced from approximately 100 ms post-stimulus onset. Alpha-band activity has been linked to attentional and inhibitory processes and performance (Worden, Foxe, Wang, & Simpson, 2000; Yamagishi, Callan, Anderson, & Kawato, 2008), and could thus potentially contribute to unravelling influences of stimulus and goal-driven demands on neural activity. However, the alpha desynchronisation did not consistently differ amongst conditions in this study. In summary, Chapter 2 presented a study with a strong behavioural paradigm to capture interactions of physical stimulus salience and behavioural relevance on attentional allocation to stimuli, but had limitations for disentangling responses to individual stimuli and for inducing gamma activity. The following chapters were designed to overcome these limitations to step-wise address the main research question.

6.2.2 Chapter 3 – Induced and evoked neural correlates of orientation selectivity in human visual cortex

The stimuli used in Chapter 2 were not optimal for inducing gamma. In Chapter 3, I instead used a grating patch which had been shown previously to robustly induce gamma synchronisation specifically localised to contralateral early visual cortex in the calcarine sulcus (Muthukumaraswamy, Singh, Swettenham, & Jones, 2010; Swettenham, Muthukumaraswamy, & Singh, 2009). The aim of this experiment was to study how physical stimulus properties influence stimulus-locked gamma synchronisation in early visual cortex. The results of the experiment presented in Chapter 3 showed that the orientation of the grating patch modulated the gamma

response it induced. A grating with an oblique orientation induced gamma activity with a stronger level of synchronisation than a horizontal or vertical stimulus. In contrast, these different orientations did not alter the temporal pattern of the gamma response, nor its maximum frequency, which was around 50 Hz. Because the stimuli were passively viewed, this finding represents a modulation that was purely driven by the orientation of the stimulus, that is, a physical stimulus property.

The earliest evoked response (~ 80 ms) was similarly increased in response to oblique versus cardinal gratings. The orientation effect in both the sustained gamma and earliest evoked response (largest response to oblique) was in the opposite direction of what has frequently been reported in the literature as the ‘oblique effect’ (smallest response to oblique). The classic oblique effect is thought to reflect (1) that a slightly greater number of cells in visual cortex prefer cardinal than oblique orientations, and (2) that humans are much better at discriminating orientations around cardinal than oblique axes. In contrast to the gamma response and earliest evoked response, we found a trend towards this classic oblique effect at later peaks of the evoked response (100-150 ms), which was localised to extrastriate visual areas. These findings suggest that the initial stimulus-driven response in primary visual cortex was largest to oblique orientations, whereas a delayed feedback mechanism originating in extrastriate cortex underlies the subsequent classic oblique effect. The findings also suggest a sharper orientation tuning of cardinal-preferring than oblique-preferring cells.

The findings of Chapter 3 contribute to the understanding of low-level orientation selectivity in early visual cortex, which is still not completely understood, despite decades of research (Henrie & Shapley, 2005). Furthermore, comparing the results found in this chapter using MEG with other studies using EEG and fMRI highlight that the use of different imaging techniques can reveal different aspects of brain functioning, which can each contribute to reveal the underlying neural mechanisms of visual processing. Finally, the study presented in Chapter 3 verified that the grating stimulus induced a strong stimulus-driven gamma response. This stimulus could therefore be used for exploring attentional modulations on gamma activity in the next chapters.

6.2.3 Chapter 4 – Sustained visuo-spatial attention increases high-frequency gamma synchronisation in human medial visual cortex

In Chapter 4, I investigated how voluntarily directing spatial attention influenced the stimulus-induced gamma response, using the same gamma-inducing grating as in Chapter 3. The results showed that directing highly focused sustained selective attention to this parafoveal stimulus increased the gamma response in early visual cortex compared to when a same level of sustained attention was directed to a small line at fixation, leaving the parafoveal grating ‘unattended’. This increased level of gamma synchronisation due to spatial attention was observed around 60-90 Hz, in contrast to the increase around 50 Hz due to stimulus properties observed in Chapter 3. The selective frequency range of gamma enhancement can explain why some previous studies did not find an increased gamma response in primary visual cortex with attention (Chalk et al., 2010; Siegel, Donner, Oostenveld, Fries, & Engel, 2008), suggesting that it is important to include a wide range of frequencies when investigating attentional modulations. Moreover, the modulation at this higher gamma frequency range may reflect local processing of a top-down signal, or integration of stimulus and goal-driven information in early visual cortex. Importantly, the findings in Chapter 4 present a dissociation with the findings of Chapter 3, suggesting that bottom-up stimulus factors influence gamma activity at a different frequency range than top-down factors. Additionally, these findings support and extend the role of oscillatory activity in the higher gamma range, which is increasingly linked to healthy brain functioning (Uhlhaas, Pipa, Neuenschwander, Wibral, & Singer, 2011).

6.2.4 Chapter 5 – Investigating effects of stimulus salience and behavioural relevance on gamma synchronisation in early visual cortex

In Chapter 5, I combined the findings of Chapter 3 and Chapter 4 to address the same main research question as in Chapter 2, but specifically addressing the role of gamma activity. This allowed me to investigate the question of how modulations due to stimulus and goal-driven attentional demands interact to modulate gamma activity in early visual cortex. I developed a paradigm that approached the behavioural paradigm used in Chapter 2 but used the strong gamma-

inducing grating stimulus as in Chapters 3 and 4. The design of this experiment allowed (1) measurement of strong stimulus-driven gamma under conditions of competing stimulus salience and behavioural relevance; and (2) measurement of the neural response to a single stimulus, the inducing grating, which avoids measuring a bulk response that reflects contributions of several stimuli as in Chapter 2. Amongst two items, subjects searched for the non-vertical stimulus and discriminated its orientation tilt (to the left or right of vertical). One stimulus was optimal for inducing gamma in contralateral visual cortex (the grating), the other stimulus had equal behavioural relevance, but did not induce gamma. Similar to Chapter 2, the behavioural data demonstrated that when one of the two stimuli appeared in salient red, this item captured attention when it was a potential target (attended), and did not capture attention if it was never a target in a block (ignored).

The MEG results of Chapter 5 showed a trend towards an increased amplitude of the initial gamma burst and early part of the sustained response (100-300 ms) when a salient distractor was ignored compared to when it was attended (relative to a non-salient distractor within each same respective attentional set). This effect thus represents an interaction of stimulus-driven salience and top-down attentional goal localised to early visual cortex. This increase only occurred at a narrow-band higher-frequency part of the gamma response (55-65 Hz), not at a narrow-band lower frequency range (40-55 Hz). This trend suggests that top-down signals suppressing a physically salient item from capturing attention may be mediated by oscillatory activity at higher frequencies within the gamma band.

Such modulations of higher frequency gamma activity due to behavioural relevance are partially consistent with the role of higher gamma frequencies in increasing responses to spatially attended items reported in Chapter 4. In contrast to the attentional effect in Chapter 4, the effect in Chapter 5 was very narrow-band. However, the narrow-band range occurred at overlapping frequencies of the stimulus-driven effects found in Chapter 3 (30-70 Hz) and the goal-driven effects found in Chapter 4 (60-90 Hz). One could therefore speculate that when stimulus and goal-driven demands compete for attentional selection, the frequency ranges at which their effects are mediated are combined. Although the findings of Chapter 5 need replication with greater statistical power, these findings suggest a possible extension for the role of gamma oscillations in attention

and visual perception, and a potential mechanism of how oscillatory activity in different frequencies interact.

6.3 Discussion and outstanding questions

6.3.1 The role of primary visual cortex in visual perception

The notion that the role of the primary visual cortex is limited to the initial stages of bottom-up stimulus processing was discarded decades ago (Treue, 2001). Converging research from monkey single-cell recordings (McAdams & Reid, 2005; Motter, 1993) and human neuroimaging (Gandhi et al., 1999; Martinez et al., 1999; Noesselt et al., 2002; Saenz et al., 2002) has demonstrated that neural activity in V1 is biased by the behavioural relevance of stimuli, and that this bias is mediated by top-down feedback from higher brain areas. The findings in this thesis support the clear modulation of activity in early visual cortex by behavioural relevance of stimuli. In addition, they suggest that these attentional modulations can be quite strong and under certain circumstances even most prominent in V1 within the visual cortex (Chapter 4). This is in contrast to the common finding that attentional effects in V1 are much weaker than in other visual areas (Kastner, De Weerd, Desimone, & Ungerleider, 1998; Luck et al., 1997; Moran & Desimone, 1985; Saenz et al., 2002; Tootell et al., 1998). Thus, early visual cortex may play a more prominent role in attentional processing than is currently thought.

The modulations in early visual cortex reported in this thesis combined with the previous literature (e.g., Foxe & Simpson, 2002) are consistent with attentional deployment depending on a dynamic system. In this system, activity throughout areas involved in visual processing is enhanced or reduced reflecting the bias of stimuli for priority of attentional processing. Similar to higher visual areas, attentional bias effects already occur in V1 before stimuli appear (Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; O'Connor, Fukui, Pinsk, & Kastner, 2002), may reflect combinations of attention to locations and features (Chapter 2), and are actively updated as stimuli are identified and processed (Chapters 4 & 5). The findings of several studies investigating the timing of activity throughout cortical areas suggest that it is likely that top-down signals reflecting attentional goals and behavioural relevance are generated by parietofrontal areas (Corbetta &

Shulman, 2002; Desimone & Duncan, 1995). Stimulus processing starts in visual areas, which may already generate a spatial representation of the bottom-up salience of items (Mazer & Gallant, 2003; Zhang, Zhaoping, Zhou, & Fang, 2012). Bottom-up signals are then conveyed to parietofrontal areas, where areas in the posterior parietal cortex are most likely to combine both stimulus and goal-driven information to form a spatial representation of the priority of visual stimuli for attentional allocation (Fecteau & Munoz, 2006; Ipata, Gee, Bisley, & Goldberg, 2009). In addition to using this information to mediate a motor or oculomotor response, the results in this thesis suggest that parietofrontal areas may also send these priority signals to visual cortex, including early visual cortex. These signals then bias activity in early visual cortex in response to new incoming stimuli, and the process reiterates to accommodate dynamically developing attentional goals and incoming stimuli. Such a dynamic system of updating and integration is necessary for the brain to efficiently deal with the constantly changing stimulus input and attentional demands.

The results of the present thesis are consistent with previous research that visual cortex is influenced by combinations of behavioural relevance and physical stimulus salience (McMains & Kastner, 2011; Reynolds & Desimone, 2003; Serences et al., 2005), and suggest that this combined influence may also apply to early visual cortex (Chapter 5). However, none of the studies in this thesis showed clear modulation that was *only* based on the presence or absence of a salient item, not in the averaged evoked response (Chapter 2), nor in gamma oscillations (Chapter 5). In Chapter 5, red-and-white gratings induced gamma activity at a slightly more limited frequency range than black-and-white gratings, but it was not clear whether this frequency effect was due to stimulus colour or physical salience.

A number of fMRI studies show that V1 is highly responsive to bottom-up stimulus properties including salience, and is especially responsive to pop-out effects (Beck & Kastner, 2005, 2009; Nothdurft, Gallant, & Van Essen, 1999; Serences & Yantis, 2007), as addressed in Chapter 1 (section 1.3.3.3). Moreover, one recent study showed that V1 may even contain a bottom-up salience map (Zhang et al., 2012). Zhang and colleagues measured ERPs and the BOLD response to a briefly presented and then masked homogenous field of stimuli. The homogeneous field of stimuli, which was not consciously perceived by the observer, contained a small region

with an orientation that was different to the homogeneous background, which cued attention to this location. Subjects subsequently performed a discrimination task that was irrelevant to this orientation at either the cued or a symmetrical non-cued location. The degree of orientation contrast between the small deviating region and the background determined the cueing effect: the larger the deviation, the better performance. This enhanced effect of stimulus-driven capture correlated with the degree of modulation of the C1 ERP amplitude (the earliest stimulus-evoked response, which is thought to originate in V1) as well as the BOLD response in V1. The BOLD response showed the same gradual increase in modulation with increasing orientation contrast in V2-V4 and the intraparietal sulcus (IPS) as it did in V1, but did not correlate with the degree of attentional capture in these higher areas. These findings strongly suggest that V1 can code the salience of stimuli purely based on bottom-up content and suggest that this salience information is then propagated to extrastriate areas and the IPS.

The clear responsiveness of V1 to stimulus salience shown with these fMRI and ERP studies raises the question whether such effects were too weak to be observed with the paradigms used here. One possible reason the studies in this thesis did not report a bottom-up salience effect in V1 may be that it is restricted (or much stronger in response) to the pop-out orientation contrasts used in the study by Zhang et al. (2012). Many studies, including the studies in this thesis, have used colour to capture attention. Previous literature and the (inverse) oblique effect in Chapter 3 demonstrate that stimulus orientation can strongly influence responses in V1 (Hubel & Wiesel, 1963; Hubel, Wiesel, & Stryker, 1978). Perhaps a bottom-up salience effect in V1 is simply much stronger for orientation than for colour, or requires simple feature contrasts that can be processed pre-attentively (Treisman & Gelade, 1980; Wolfe, 1994), although the latter should include colour. Also, the stimuli used in the studies presented in this thesis were rather artificial, and did not resemble scenarios that are likely to be encountered in the real-world. Perhaps the pop-out orientation contrasts in the study by Zhang et al. more closely resembled realistic visual scenarios, yielding stronger effects of salience as these are more relevant to capture attention in the real world.

Alternatively, though not mutually exclusive, the effects of top-down attention may rapidly exert their influence on neural responses to stimuli, masking brief initial stimulus-based responses.

In addition, attentional set has a preceding influence on overall response, potentially minimising even an initial stimulus-based response in situations where the participant prepares a task-set like the experiments presented here. This would explain the absence of any purely bottom-up salience-based findings in this thesis, and can also explain the strong capability of top-down goals to overcome attentional capture by irrelevant salient stimuli (Folk & Remington, 2006; Folk et al., 1992; Folk et al., 1994). Such an interplay between bottom-up and top-down factors is supported by rapid feedforward processing and strong feedback projections in the visual cortex (Foxy & Simpson, 2002; Lamme & Roelfsema, 2000; Laycock, Crewther, Fitzgerald, & Crewther, 2007), and may require the stimuli to be non-consciously perceived (Foxy & Simpson, 2002). Thus, great potential exists for future studies to explore the interactions between stimulus-driven and goal-driven attentional demands in primary visual cortex by using displays that exhibit these strong properties such as orientation contrast.

Finally, the studies in this thesis may not have been optimal to capture salience-driven effects in visual cortex. The study in Chapter 2 used a very strong behavioural paradigm where a salient item captured attention if it was a potential target. However, MEG responses were measured to the full stimulus display, which may have blurred strong responses by individual salient items. Furthermore, the absence of a clear M1 component suggests the stimuli in Chapter 2 may have been too weak to generate a strong bottom-up response in V1. In contrast to Chapter 2, the stimuli in Chapter 5 strongly induced activity in early visual cortex, but in this chapter the behavioural manipulation, though significant, was weaker. This is likely the result of using displays with only two stimuli. Behavioural studies have shown that for a stimulus to pop-out and pre-attentively capture attention, a homogeneous background is required (Treisman & Gelade, 1980). In contrast to the four stimuli in Chapter 2, the salience of one of only two items in Chapter 5 cannot have generated a pop-out effect. However, the use of only two stimuli was carefully chosen to optimise power in a design with many factors, yet restrict the length of MEG acquisition. It will be a challenge for future research to develop a paradigm using strong stimuli, with cortical responses that can be individually distinguished, like Chapter 5, yet have strong enough stimulus-driven salience, like Chapter 2, to influence cortical activity in V1. A study investigating how salience affects both evoked responses and gamma activity can then reveal how salience and attentional

208

effects affect the feedforward sweep (e.g., the earliest component), later components due to feedback, the gamma response, and when and how these interact in early visual cortex.

6.3.2 The role of oscillatory activity in cognitive processing

6.3.2.1 High-frequency oscillations

A role for gamma activity in V1 processing of stimulus salience is likely, based on the great selectivity of V1 cells to stimulus features, including contrast, and the sensitivity of gamma synchronisation to these factors (Rols, Tallon-Baudry, Girard, Bertrand, & Bullier, 2001). A recent study by Ossandón et al. (2012) investigated effects of stimulus-driven pop-out in visual search on oscillatory synchronisation. Using intracranial EEG in humans, Ossandón and colleagues found activity in areas within the parietofrontal network that showed increased synchronisation post-stimulus compared to pre-stimulus in a broad range of frequencies within the high gamma band (50-150 Hz). This network displayed similar synchronisation when search was efficient (a homogeneous display of black items containing a light grey pop-out target) as when search was inefficient (a homogeneous field of light grey items). However, the temporal pattern of this synchronisation differed. Post-stimulus synchronisation lasted longer with inefficient compared to efficient search, which reflected the longer reaction times associated with inefficient search. Because the same network was active in both conditions, the authors suggested that this broad-band gamma synchronisation reflects the involvement of parietofrontal areas to guide responses to any visual task, even those requiring very little effort. They further suggested that the only scenario in which these parietofrontal areas would not be required is in the case of bottom-up capture without any top-down influence, which can only be achieved by purely passive viewing. Thus, to study modulations of gamma synchronisation due to purely stimulus-driven salience, it may be necessary to invoke a passive task.

Ossandón et al. (2012) did not focus on activity in visual areas. In contrast, I did not focus on activity in the parietofrontal network. *A priori* foci of interest are necessary to deal with the multidimensionality of EEG and MEG data, making it necessary to make a choice regarding the primary goal of the analyses. The rapid and sensitive recruitment of top-down guidance by the

parietofrontal network demonstrated by Ossandón et al. may, however, explain why I did not find any modulations in oscillatory activity reflecting purely stimulus-driven salience in early visual cortex. Whether oscillatory activity in early visual responses is similarly affected by bottom-up salience is therefore an open question and an exciting avenue for future research. Based on the research reviewed here, such studies should use a passive task and optimal stimuli to drive gamma synchronisation in V1 (such as the gratings used in Chapters 3-5). Pop-out salience is probably best defined based on pre-attentive properties such as orientation contrasts, or perhaps luminance contrasts, to which gamma synchronisation is more responsive than to colour contrasts (Adjamian, Hadjipapas, Barnes, Hillebrand, & Holliday, 2008). Furthermore, the findings in Chapter 3 suggest that stimulus-driven effects may be most clearly expressed at lower gamma frequencies (~50 Hz), which may therefore be a helpful *a priori* focus, although this was only investigated for the bottom-up property of orientation, and this may be different for other stimulus properties.

In contrast to the absence of bottom-up salience effects, the findings in this thesis clearly support a role for gamma synchronisation in top-down processing in early visual cortex. An attentional effect was observed in gamma frequencies above 60 Hz. In Chapter 4, I argued that one reason for results discrepant with previous literature (Chalk et al., 2010; Siegel et al., 2008) is that oscillatory activity has been investigated using many different frequency bands. The gamma range was originally defined as oscillatory firing every 10-30 ms, which roughly corresponds to 33-100 Hz (Jensen, Kaiser, & Lachaux, 2007). However, in the literature, gamma bands have been variously defined, ranging from anything >20 Hz (Gruber, Müller, Keil, & Elbert, 1999) to as narrow as 25-45 Hz (Saalmann, Pigarev, & Vidyasagar, 2007). As noted before, to obtain sufficient analytic power with multidimensional imaging techniques such as MEG, some (*a priori*) limitation needs to be made, be that in frequency, time, or space. However, the findings in this thesis highlight that when studying gamma or other oscillations, it is best to make that limitation in the space or time domain, at least at initial stages of analysis.

The general approach in the studies presented in this thesis was to first obtain localisation of early visual cortex (*a priori* limitation in the spatial domain), to then optimise time-frequency analysis at this location of interest. Although the time-frequency analysis was based on localisation obtained at 30-70 Hz (30-80 Hz in Chapter 3), it was otherwise independent of the previous

frequency filtering, and was run over a much wider range of frequencies (Chapter 3 excluded). The goal of this approach was to avoid any bias by averaging over a pre-defined frequency band, and potentially missing effects at frequency ranges not included, or effects expressed only at narrow bands being obscured by the lack of effects at other frequencies within a wider range. To this end, we employed permutation analysis over the full range of frequencies within a time window, the latter being defined based on events in the trial design (e.g., stationary or rotating stimulus in Chapter 4) or known parts of the gamma response (e.g., burst or sustained). Perhaps this approach has the limitation that attention-related effects on oscillatory activity were missed here that would have been obtained if analysis was optimised for a different frequency band (e.g., 80-100 Hz in Chapter 2). However, when we drew conclusions from modulations observed within a different range of frequencies than the initial 30-70 Hz (e.g., 60-90 Hz in Chapter 4), or when the data very clearly indicated an effect in a specific frequency range (Chapter 5), we investigated the source of these frequency-specific effects more closely using a post-hoc analysis. The approach employed in this thesis thus avoids unnecessary initial data-driven selection of parameters. In fact, averaging activity over a too wide or too narrow frequency band, without initially investigating the full power-frequency spectrum, may lead to overlooking frequency-specific effects. This may be especially important when studying attentional effects in regions where neural modulations are known to be fairly weak, such as early visual cortex (Haenny & Schiller, 1988; McAdams & Maunsell, 1999; Treue, 2001).

One outstanding question is how the higher-frequency gamma increase in early visual cortex found here relates to the frequently reported attention-related increases in other visual areas such as V4, which are usually observed between 35-60 Hz (Fries, Reynolds, Rorie, & Desimone, 2001; Fries, Womelsdorf, Oostenveld, & Desimone, 2008; Gruber et al., 1999). Interestingly, some of these studies included frequencies up to 70 Hz (Fries et al., 2008), and other studies actually showed an increase in gamma power of frequency ranges > 60 Hz in visual areas V4 and MT (Chalk et al., 2010; Siegel et al., 2008), and even in the IPS (Siegel et al., 2008). These findings suggest that attention-related increases can occur in both lower and higher gamma frequencies and the distinction between these frequency bands may not always be clear. Such differences may depend on species (monkey, human), attentional task, and stimulus features. Moreover, decreases

in gamma power in visual cortex have also been reported, both before and during stimulus presentation (Chalk et al., 2010; Siegel et al., 2008; Tallon-Baudry, Bertrand, Hénaff, Isnard, & Fischer, 2005), and have recently been linked to the resting default network of brain activity (Ossandón et al., 2011). However, the relationship between increases and decreases in gamma synchronisation is currently unclear. Further research, taking into account a broad non-biased frequency range, is needed to clarify the occurrence of these different frequency ranges, and whether they represent variations of the same phenomenon or whether the two ranges can be associated with different functions.

Because an increase (this thesis) and decrease (Chalk et al., 2010) in gamma synchronisation have both been found in V1 with attentional manipulations, further research is particularly necessary to clarify the role of gamma oscillations for attentional effects in V1. Single-cell monkey research is perhaps the most promising technique to confidently capture neural activity in V1, and moreover, can reveal spike-field coherence effects which are sometimes present when synchronisation power effects are absent (Bichot, Rossi, & Desimone, 2005; Fries et al., 2008). Spike-field coherence (SFC) is a measure of how well the pattern of spiking of a single cell correlates to the local field potential of a large group of neurons. The spike-field phase relationship, in particular, can contribute to our understanding of the role of gamma oscillations in visual cortex, because the phase relationship may more directly represent the proposed amplifying effect of gamma synchronisation on post-synaptic firing, provided that it is appropriately timed (Fries, 2005; Schnitzler & Gross, 2005). Monkey research has often focussed on V4 or MT cells, because these cells have fairly large receptive fields but still contain simple stimulus mapping, and thus represent an intermediate stage of visual processing (Maunsell & Cook, 2002). Studying attentional modulations on monkey V1 cells activity is therefore an essential focus for future research.

We should attempt non-invasive work whenever possible, but these SFC and SF phase relationships can only be studied invasively. However, single-cell recording is not free of limitations either, as it may for example suffer from sparse or arbitrary sampling effects. Moreover, although monkeys can be trained to perform covert tasks (e.g., Wardak, Ibos, Duhamel, & Olivier, 2006; Wardak, Olivier, & Duhamel, 2004), this always leaves the question whether the monkey brain is representative of human cognitive functioning. It is therefore equally important to study

effects on V1 processing using human neuroimaging techniques. Regarding oscillatory power, improvement in spatially optimised source localisation techniques such as beamforming are making MEG increasingly promising to accurately localise even small cortical areas, and for example, maybe enable mapping of the retinotopy of V1 (Perry et al., 2011). In addition, intracranial EEG in epileptic patients provides a valuable intermediate technique, although of course much less accessible than non-invasive techniques with some further limitations in terms of cognitive tasks and area of electrode localisation (Jerbi et al., 2009).

6.3.2.2 The relationship between activity in different frequency ranges

Although not the main focus of this thesis, changes in stimulus-locked low-frequency alpha oscillations were observed in all experiments, except in the bottom-up response in Chapter 3. Alpha desynchronisation in posterior areas has frequently been observed to co-exist with increased gamma synchronisation in attentional tasks (Fries et al., 2001; Fries et al., 2008; Siegel et al., 2008). Alpha desynchronisation is also observed when attention is cued to a stimulus location before stimulus onset (Yamagishi et al., 2008; Yamagishi et al., 2003; Yamagishi, Goda, Callan, Anderson, & Kawato, 2005), and correlates with subsequent attentional performance (Yamagishi et al., 2008). Alpha desynchronisation is therefore thought to reflect facilitation of processing in regional areas of cortex (and conversely, synchronisation to reflect regional inhibition, Worden et al., 2000).

It is not yet clear how alpha and gamma activity relate to each other. Preliminary analysis of the data presented in this thesis did not reveal any correlations between power changes within the two frequency ranges. However, the phase of alpha oscillatory activity has been linked to the power of 30-70 Hz gamma synchronisation in human posterior cortex during a resting state (Osipova, Hermes, & Jensen, 2008). This cross-frequency coupling resulted in the proposal that alpha and gamma activity mediate inhibition and excitation of cortical areas that are task-irrelevant and task-relevant, respectively (Jensen & Mazaheri, 2010). If this excitation and inhibition also applies at the retinotopic scale, this could be a very promising path of research to elucidate the neural mechanisms underlying the balancing of stimulus and goal-driven attentional demands. Studying the time course and correlations of alpha and gamma activity could then potentially reveal

how and at what stage irrelevant salient and non-salient items are inhibited, and at what stage target items are enhanced to guide attention.

In addition to the main analyses in this thesis, I investigated low-frequency oscillations in a broad 5-25 Hz band. Besides alpha (8-15 Hz), this frequency band also includes bands which are often defined as theta (4-8 Hz) and beta (15-25 Hz). Gamma power (above 20 Hz), particularly high gamma power (80-150 Hz), has been shown to be modulated in line with the phase of frontal theta oscillations, and this coupling has been linked to some aspects of cognitive processing (Canolty et al., 2006). Furthermore, using intracranial EEG, it has recently been shown that coupling of high-gamma activity to theta phase is present during a non-visual task (e.g., linguistic or auditory tasks), whereas high-gamma activity is coupled with alpha phase instead during a visual task (e.g., attentional tasks, Voytek et al., 2010). This task-related selective coupling, combined with the fact that coupling to theta was observed over frontal cortex, whereas coupling to alpha was present over posterior areas, supports an interplay of alpha and (high) gamma synchronisation in visual cortex that is likely to play a role in attentional processes. Voytek et al. (2010) did not use source localisation or analyse lower frequency gamma activity, leaving the question unanswered of where in the brain exactly this coupling happens and how it applies to lower gamma frequency activity. However, in a different study, oscillatory activity in the delta range (1.5 Hz) has been coupled to visually-induced gamma activity in the peak induced range (37-57 Hz) in primary visual cortex, which was stronger when the visual input (versus auditory input) was attended (Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008). Investigating how phase coupling between different ranges of low-frequency and gamma oscillations applies to early visual cortex (using source localisation), and how this compares to higher visual cortex such as V4 will be an important focus for future research and can contribute to revealing the functional role of lower (30-70 Hz) and higher gamma activity (>60 Hz) in these areas.

In contrast to the clear role of gamma activity in local processing, beta activity (15-25 Hz) is thought to play a role in communication of neural signals between distant cortical areas (Donner & Siegel, 2011; Schnitzler & Gross, 2005). Beta activity has been particularly associated with motor processes and communication between the motor cortex and parietal cortex (Schnitzler & Gross, 2005). However, synchronisation of beta activity is often decreased similar to alpha activity

in visual areas during attentional tasks (e.g., Fan et al., 2007; Siegel et al., 2008), in line with the findings in Chapters 2-5, and might thus play a similar role in mediating attentional allocation. Similar models of long-range versus local neural communication have been proposed focussing on theta, alpha, and beta oscillations as the long-range mediators (Canolty & Knight, 2010; Donner & Siegel, 2011; Schnitzler & Gross, 2005). Thus, the specific role each of these low-frequency oscillations serves in cognitive functioning and neural communication is not clear. However, their cortical localisation and functional association suggests that activity in these low-frequency ranges may well each contribute to different aspects of attentional allocation: deriving top-down signals from parietofrontal areas, mediating biasing of activity in visual cortices, and orchestrating behavioural responses. The role of these low-frequency ranges in stages of the attentional selection process can thus potentially contribute to reveal how attentional demands are balanced.

One further question is how transient evoked activity relates to sustained induced gamma activity, and to oscillatory activity in each of these low frequency ranges. Does the modulation of evoked activity with attentional set found in Chapter 2 relate to the enhancement in higher-range gamma synchronisation due to spatial attention, and to the interaction trend between stimulus and goal-driven demands in Chapters 4 and 5? Evoked responses have been found to correlate with, and be a product of, phase resetting of low-frequency rhythmic activity changes in cortical areas corresponding to stimuli within the focus of attention (Makeig et al., 2002; Mazaheri & Jensen, 2008). However, this correlation only applies to slow components of the evoked response (such as the P300), and does not explain fast components which generally occur early after stimulus onset (e.g., the N75, Mazaheri & Jensen, 2008).

It is unclear whether (slow) evoked components correlate similarly with the phase resetting of gamma activity. Evoked components show higher stimulus specificity in lower than higher frequency ranges, whereas induced activity is more stimulus-specific in the gamma range (Hadjipapas, Adjamian, Swettenham, Holliday, & Barnes, 2007). This difference suggests that the relationship with evoked responses may well be different for gamma than alpha activity. On the other hand, the findings of Chapter 3 showed a very similar effect of grating orientation in the earliest evoked response and induced gamma activity, and in Chapter 2 the earliest evoked response was absent as was any observable gamma oscillations. These findings suggest that these

two measures may be related. However, the absence of both the earliest evoked response and gamma activity in Chapter 2 may reflect the non-optimal stimuli in this study. Furthermore, I only investigated early, fast evoked components in this thesis, leaving the question unanswered whether there is any relationship between gamma activity and slow evoked components.

In summary, the studies highlighted here show that lower-frequency oscillatory activity in the theta, alpha, and beta range each display phase coupling to the power of gamma oscillations, predominate in different brain areas, and play a functional role in cognitive processing. It is likely that studying the specific role, occurrence, and timing of oscillatory activity in each of these low-frequency ranges in visual areas and in the parietofrontal network can reveal details of how stimulus-driven and goal-driven factors are processed throughout the cortex in time. This can further reveal how they mediate enhancing and suppressing of cortical representations of stimuli, and how these demands interact to guide attention. A particularly interesting avenue is to study how the phase of each of these oscillation ranges couples to gamma oscillations, and, based on the findings in this thesis, whether this coupling differs for power at lower and higher frequencies within the gamma range when attentional demands are competing for priority.

6.3.3 Updating and extending the parietofrontal network

The findings in this thesis extend the clear role of gamma synchronisation in attention identified in parietofrontal and higher visual areas in many previous studies to early visual cortex. The combination of a gamma-inducing stimulus and spatially optimised source localisation technique used in Chapters 3-5 make the findings in these chapters likely to reflect local processing in primary visual cortex. However, the spatial resolution of MEG restricts the certainty of this claim (as addressed in Chapter 4, section 4.4). One interesting possibility is that these findings actually reflect synchronisation between V1 and V2. Zero-phase coherence between gamma activity in V1 and V2 in response to visual stimuli has been demonstrated in monkeys (Frien, Eckhorn, Bauer, Woelbern, & Kehr, 1994), with the lack of temporal variation suggesting that this coherence is not a result of feedforward processing from V1. The gamma coherence between V1 and V2 may play a role in feature/object binding (Eckhorn et al., 2004), as it could combine the detailed stimulus responsiveness of V1 with the slightly larger receptive fields in V2. In fact, a similarly increased

gamma synchronisation above 55 Hz at the border of V1/V2 has been demonstrated in a MEG study involving binding of features during figure-ground segregation (Kinsey, Anderson, Hadjipapas, & Holliday, 2011). This suggests that higher frequency gamma activity in V1/V2 may well play a more generic role in visual processing than ‘merely’ mediating attentional processing.

The experiments in this thesis were not designed to investigate the role of parietofrontal areas. Although evoked activity during a visual search task was localised to parietofrontal areas in addition to early visual cortex in Chapter 2, source waves extracted from these regions did not reveal clear patterns of modulation over conditions. Nevertheless, the current findings may have consequences for our understanding of the parietofrontal network. The timing of the higher frequency gamma modulations in early visual cortex clearly suggest that these attentional effects are due to feedback from parietofrontal areas. In contrast, the role of early visual cortex in stimulus processing, and possibly in physical stimulus salience coding (Zhang et al., 2012), is inherently due to bottom-up processing. The difference in timing of bottom-up (early) and top-down (> 100 ms) effects suggests that the actual integration of these two types of information does not take place in early visual cortex. Parietal areas (LIP, IPS) are still the most likely areas to actually perform this integration. The fact that the LIP/IPS contains a salience map based on bottom-up properties as well as based on behavioural relevance (Ipata et al., 2009; Ipata, Gee, Gottlieb, Bisley, & Goldberg, 2006), makes it likely that this area is the main integrating station for these two types of attentional demands.

To link the parietofrontal network to the new findings in early visual cortex, future studies need to be conducted addressing the timing and power of coherence in different frequency ranges. Such studies are likely to reveal that early visual cortex first creates a bottom-up salience map (probably in the gamma range) and that this information is then relayed to LIP/IPS (possibly by means of lower-frequency coherence). At the same time, LIP receives top-down information regarding behavioural goals (probably from frontal areas, possibly also via lower frequency oscillations), and LIP then performs active integration of these types of information (which may again have a different spectral signature, perhaps in the gamma range (Buschman & Miller, 2007; Doesburg, Roggeveen, Kitajo, & Ward, 2008), and/or elevated firing (Bisley & Goldberg, 2010)). Finally, the LIP relays this information back to visual areas, whereby signals may reach the earliest

visual areas directly, or indirectly via higher visual areas (possibly again mediated by lower-frequency oscillations). Finally, this top-down information is locally processed in early visual areas (expressed at higher gamma frequencies, Chapter 4), and this information biases responses to newly incoming signals as early as V1 (possibly at combined low/high gamma frequencies, Chapter 5). This process would then be reiterated as long as visual input is received.

Although many of these aspects have been demonstrated individually, or seem reasonable speculations, studies combining all these aspects of modulations in parietofrontal and visual areas are crucial to couple them all together and reveal an integrated network. These studies should use techniques with sufficient spatial and temporal resolution such as MEG or intracranial EEG. Finally, questions remain to be answered on how these oscillatory patterns relate to networks identified in fMRI studies (e.g., Hahn, Ross, & Stein, 2006), non-oscillatory firing rate changes (Bisley & Goldberg, 2010), and what role sub-cortical areas play in guiding attention when there is competition between stimulus and goal-driven demands (e.g., the superior colliculus, Baluch & Itti, 2011).

6.3.4 A note on some promising recent developments

In light of future studies, it is worth noting some recent findings in the field of oscillatory brain activity and attention. As addressed in Chapter 3, GABAergic interneurons are known to be crucial for the generation of gamma oscillations (Bartos, Vida, & Jonas, 2007), and have been linked to orientation selectivity (Frien, Eckhorn, Bauer, Woelbern, & Gabriel, 2000). Gamma oscillation frequency has also been correlated to levels of GABA in visual cortex (Muthukumaraswamy, Edden, Jones, Swettenham, & Singh, 2009) and the size of an individual's V1 (Schwarzkopf, Robertson, Song, Barnes, & Rees, 2012), and has been shown to have a genetic component in a recent twin study (van Pelt, Boomsma, & Fries, 2012). These findings support the important role for GABAergic neurotransmission and gamma oscillations in the brain. Furthermore, higher-frequency gamma activity (Uhlhaas et al., 2011), levels of GABA (Yoon et al., 2010), and orientation selectivity (Rokem et al., 2011) have also been found to be altered in patients with Schizophrenia. These findings highlight that gamma activity does not just play a role in sensory processing or attention, but rather plays a broad and important role in cognitive functioning.

Studying the role of gamma oscillations in attentional processes can therefore contribute to our understanding of healthy and abnormal brain functioning.

A recent study showed that Acetylcholine, which is a neurotransmitter that can affect attentional processing in V1 (Herrero et al., 2008), is linked to alpha and beta, but not gamma activity (Bauer et al., 2012). In addition, Buffalo, Fries, Landman, Buschman, and Desimone (2011) showed that attention differentially affects alpha and gamma oscillations in different layers of V2 and V4, although these authors did not investigate high gamma activity. Finally, Moradi, Buračas, and Buxton (2012) showed that in V1 increases in blood flow due to neural activity reflect stimulus-driven responses, whereas top-down modulations associated with attentional processes lead to increases in the oxygen metabolism of the blood. These findings suggest that studying the relationship between GABAergic and cholinergic signalling in the brain, as well as blood flow and oxygenation can contribute to how bottom-up and top-down processing involved in the balance of stimulus and goal-driven attentional demands are mediated between and within brain areas. Linking these recent findings to oscillatory activity in low and high frequency ranges will be an exciting focus for future research.

6.4 Summary and conclusions

In summary, the findings presented in this thesis show that stimulus-driven neural activity in human early visual cortex can be strongly modulated by attentional demands. Purely bottom-up stimulus-driven processing modulates gamma activity around 50 Hz, whereas strong, sustained visuo-spatial attention increases gamma activity above 60 Hz. These findings suggest that stimulus and goal-driven modulations may be mediated at different frequencies within the gamma range. When stimulus and goal-driven demands compete for attentional allocation, modulations in gamma activity in early visual cortex may reflect this competition, with largest gamma power devoted to salient items that need to be actively ignored. This competition may be expressed at overlapping parts of these frequency ranges.

These findings confirm previous findings of strong attentional modulations in the gamma range in visual cortex due to feedback from parietofrontal areas, and extend them to early visual cortex. In addition, the findings in this thesis extend the important role of higher-frequency gamma oscillations in cognitive functioning. This contributes to our understanding of low-level as well as goal-driven attentional influences on visual processing. The findings of this thesis in combination with the present literature suggest that gamma oscillations in both the lower and higher gamma range, and their correlation to power and phase of oscillatory activity in lower frequency ranges, are an important focus for future research on the neural correlates of attentional processing.

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Appendix 1

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6 May 2009

Ms Loes Koelewijn
Building C5C, Room 480
Macquarie Centre for Cognitive Science
Macquarie University

Reference: HE01MAY2009-D06471

Dear Ms Koelewijn,

FINAL APPROVAL

Title of project: Neural Mechanisms of visual attention and saliency

Thank you for your recent correspondence. Your response has addressed the issues raised by the Ethics Review Committee (Human Research) and you may now commence your research.

Please note the following standard requirements of approval:

1. Approval will be for a period of twelve (12) months. At the end of this period, if the project has been completed, abandoned, discontinued or not commenced for any reason, you are required to submit a Final Report on the project. If you complete the work earlier than you had planned you must submit a Final Report as soon as the work is completed. The Final Report is available at: http://www.research.mq.edu.au/researchers/ethics/human_ethics/forms
2. However, at the end of the 12 month period if the project is still current you should instead submit an application for renewal of the approval if the project has run for less than five (5) years. This form is available at http://www.research.mq.edu.au/researchers/ethics/human_ethics/forms. If the project has run for more than five (5) years you cannot renew approval for the project. You will need to complete and submit a Final Report (see Point 1 above) and submit a new application for the project. (The five year limit on renewal of approvals allows the Committee to fully re-review research in an environment where legislation, guidelines and requirements are continually changing, for example, new child protection and privacy laws).
3. Please remember the Committee must be notified of any alteration to the project.
4. You must notify the Committee immediately in the event of any adverse effects on participants or of any unforeseen events that might affect continued ethical acceptability of the project.
5. At all times you are responsible for the ethical conduct of your research in accordance with the guidelines established by the University http://www.research.mq.edu.au/researchers/ethics/human_ethics/policy

ETHICS REVIEW COMMITTEE (HUMAN RESEARCH)
MACQUARIE UNIVERSITY

http://www.research.mq.edu.au/researchers/ethics/human_ethics

www.mq.edu.au

- 2 -

If you will be applying for or have applied for internal or external funding for the above project it is your responsibility to provide Macquarie University's Research Grants Officer with a copy of this letter as soon as possible. The Research Grants Officer will not inform external funding agencies that you have final approval for your project and funds will not be released until the Research Grants Officer has received a copy of this final approval letter.

Yours sincerely



P.P. Ms Karolyn White
Director of Research Ethics
Chair, Ethics Review Committee (Human Research)

Cc: Dr Anina Rich, Macquarie Centre for Cognitive Science

ETHICS REVIEW COMMITTEE (HUMAN RESEARCH)
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