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Spatial Attention Improves Retinotopic Mapping

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Abstract

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The visual world is represented in the brain in numerous retinotopic maps that extend along the cortical surface. Directing spatial attention to a given location in the visual scene enhances perception of that location, and strengthens the neural response to visual stimulation at the attended location. However, the effects of attention on neural responses differ across visual cortical regions.

This thesis is concerned with the study of the variety of effects of visual spatial attention on cortical responses. In the following chapters, we describe results from three major research projects. In the first project, we discovered that spatial attention improves response reliability (a signal-to-noise measure) in every cortical region we measured. The magnitude of these effects were greatest in regions with weak retinotopic signals, suggesting the importance of attention for discovering new areas of cortex with topographic organization. In the second project, we demonstrate that the attention-induced enhancement of response reliability results not only from a strengthening of the cortical response, but also a suppression of slow fluctuations in brain activity that are unrelated to the visual input. Moreover, the suppression of these slow fluctuations predicted performance on a visual detection task, whereas the enhancement of response magnitude did not. Finally, in the third project, we demonstrate attention's effect on response magnitude differs as a function of eccentricity; in early visual areas attention enhanced response strength the most for representations of central vision, whereas in dorsal regions attention enhanced response strength most for representations of peripheral vision. Moreover, we discovered that attention expanded the extent of visual space that generated a significant cortical response, and that this effect also differed across eccentricities and visual regions.

Chapter 1

The visual world is a rapidly changing scene in which many objects compete for perceptual resources and limited neural representations. Successful navigation of the visual world often requires selecting certain behaviorally-relevant objects while ignoring irrelevant objects (for example, focusing on the road and ignoring flashy billboards while driving). Spatial attention is a useful mechanism for filtering the constant stream of complex visual input to the brain so that salient visual representations are enhanced and irrelevant inputs are suppressed.

There is much evidence that spatial attention enhances perception of an attended object. Directing covert attention to a peripheral location decreases reaction time (Posner, Snyder, & Davidson, 1980) and enhances accuracy (Bashinski & Bacharach, 1980) for detecting targets at the attended location. Moreover, visual attention worsens performance at unattended locations (Hawkins, et al., 1990) and reduces the effects of distracting nearby stimuli (Lu, Lesmes, & Dosher, 2002; Zenger, Braun, & Koch, 2000). Therefore, visual attention enhances perception through both improving the representation of the attended object and suppressing other irrelevant information.

These behavioral findings are mirrored by neurophysiological effects. When a visual stimulus is presented at an attended location, the amplitude of the neural response in many cortical areas is greater than the response to the same stimulus when it is not attended (Bushnell, Goldberg, & Robinson, 1981; Motter, 1993; Treue & Maunsell, 1996). Similar results have been obtained in fMRI experiments; directing attention to a visual location increases fMRI responses in portions of the visual field maps representing the attended location (Gandhi, Heeger, & Boynton, 1999; Somers, Dale, Seiffert, & Tootell, 1999), even in the absence of visual stimulation (Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Silver, Ress, & Heeger, 2007). In addition, visual attention suppresses fMRI activity in cortex that represents unattended locations (Silver, et al., 2007).

However, the effects of attention vary significantly across cortical regions. In neurophysiology, attention increases the neural response in extrastriate areas but not in V1 (Luck, Chelazzi, Hillyard, & Desimone, 1997), although BOLD studies do show an attentional enhancement in V1 (Buracas & Boynton, 2007; Murray, 2008). In general, the influence of spatial attention (compared to passive visual stimulation) progressively increases from early visual areas to higher dorsal areas (Serences & Yantis, 2006; Silver, et al., 2007). There is also ample evidence that there are stronger attentional modulations for ventral compared to earlier visual areas (Brefczynski & DeYoe, 1999; Hansen, Kay, & Gallant, 2007; Kastner, et al., 1999; Serences & Yantis, 2007).

In the following chapters, we set out to investigate how spatial attention changes fMRI responses to visual stimuli and how these effects differ across visual cortical areas. In each of these experiments we presented a flickering stimulus at locations across the visual field that induced strong fMRI BOLD responses in many visually sensitive regions of cortex. The BOLD responses in each of these visual regions are retinotopically organized; that is, there is a one-to-one mapping between locations in visual space and locations on the cortical surface. However, it is not clear what are the precise functional differences between these retinotopically organized maps, nor is it clear why the visual system needs so many maps to represent the same visual field locations. In our experiments, we discovered that although some attention effects are common to all visual cortical regions, some reveal functional differences between regions.

In the second chapter, we present the first quantitative analysis of the benefits of a spatial attention task for retinotopic mapping studies. When attention was directed to a retinotopic mapping stimulus instead of a central fixation point, the signal-to-noise ratio (SNR) of fMRI retinotopic mapping signals increased. This increase in SNR was observed in early visual (V1, V2, V3, V3A/B, hV4), lateral occipital (LO1 and LO2), and ventral occipital (VO1) cortical areas, as well as in posterior parietal areas that contain topographic maps of spatial attention (IPS0, IPS1, and IPS2).

In the third chapter, we find that the improved reliability of the BOLD response to a periodic visual stimulus that results from attending the stimulus is due to both enhancement of the stimulus-evoked response and a reduction in the strength of endogenous slow fluctuations that are unrelated to the stimulus. The relative contributions of signal enhancement and suppression of endogenous fluctuations to improved response reliability varied across cortical areas. Ventral regions improved due to strong response amplitude enhancement and weak suppression of endogenous fluctuations, early regions improved due to both effects, and finally lateral-occipital and intra-parietal regions improved due to strong suppression of endogenous fluctuations but little to no enhancement of the visual response. In addition, the magnitude of suppression of slow endogenous fluctuations predicted subjects' performance on a visual target detection task in all eleven of the topographic occipital and parietal cortical areas that we studied. Surprisingly, we did not find a relationship between the strength of the stimulus-evoked response and behavioral performance in any cortical area.

In the fourth chapter, we sought to discover how attentional effects differ across locations in the visual field. In this study, we analyzed the effects of visual spatial attention both on the strength of the response evoked by visual stimuli and on the set of visual field locations that activated each cortical location. We found that attention's effects on these measures depended upon the eccentricity of the visual field location to which a cortical location was most sensitive. In early visual areas, attention enhanced responses most at near compared to far eccentricities, consistent with early areas' role in detection of fine spatial details at the fovea. In contrast, attention enhanced responses greatest at far eccentricities in dorsal regions, consistent with these regions' role in planning shifts in spatial attention or gaze. Finally, attention's pattern of effects in ventral regions is consistent with their role in integrating bottom-up inputs and top-down feedback for extraction of salient visual objects. In general, these three studies show that although spatial attention improves perception across the visual field, the mechanisms through which this takes place varies significantly across visual areas.

Chapter 2

Introduction

In many human cerebral cortical areas, there is a one-to-one mapping between points in visual space and corresponding cortical locations, and locations in the visual field are represented as a topographic map on the cortical surface of these areas. The advent of functional magnetic resonance imaging (fMRI) has greatly facilitated the study of topographic organization in the human brain (Silver & Kastner, 2009; Wandell, Dumoulin, & Brewer, 2007). Presentation of a stimulus that traverses the visual field generates traveling waves of activity in many topographically-organized areas. Retinotopic mapping refers to the process of characterizing topographic organization by identifying the visual field locations represented by each of a set of cortical locations and then determining the spatial patterns of these visual field representations on the cortical surface. The ability to objectively define topographic cortical areas in individual subjects yields significant advantages for the study of functional specialization of these areas. This provides motivation for developing methods to allow more efficient identification of the boundaries of topographic cortical areas and characterization of visual field representations in these areas.

There is substantial evidence to suggest that visual attention should improve the reliability of fMRI retinotopic mapping signals. Psychophysical research has established that allocation of attention to a location in visual space improves processing of stimuli at that location. Specifically, directing covert attention to a peripheral location decreases reaction time (Posner, et al., 1980) and enhances accuracy (Bashinski & Bacharach, 1980) for detecting targets at the attended location. Additionally, electrophysiological studies in monkeys have demonstrated neural correlates of the enhancement of visual perception by spatial attention. When a visual stimulus is presented at an attended location, the amplitude of the neural response in many occipital and parietal cortical areas is greater than the response to the same stimulus when it is not attended (Bushnell, et al., 1981; McAdams & Maunsell, 1999; Motter, 1993; Treue & Maunsell, 1996). Similar results have been obtained for human early visual cortical areas in fMRI experiments; directing attention to a visual location increases fMRI responses in portions of the visual field maps representing the attended location (Gandhi, et al., 1999; Somers, et al., 1999), even in the absence of visual stimulation (Kastner, et al., 1999; Silver, et al., 2007). Finally, recent studies report that in addition to increasing firing rate, attention also enhances the reliability of visual responses in monkey hV4 neurons (Cohen & Maunsell, 2009; Mitchell, Sundberg, & Reynolds, 2007, 2009).

Further evidence that spatial attention could enhance retinotopic mapping responses comes from the discovery of topographic maps of visual spatial attention signals in regions outside of visual cortex. IPS1 and IPS2 are two regions in posterior parietal cortex that, like early visual cortical areas, contain a topographic map of the contralateral visual field (Silver, Ress, & Heeger, 2005). Unlike visual cortex, IPS1 and IPS2 respond poorly to visual stimulation in the absence of attentional demands (Silver, et al., 2005). In addition, allocation of attention to a rotating wedge stimulus containing point-light biological motion figures reveal topographic organization of fMRI responses in numerous areas, including lateral and ventral temporal cortex, superior temporal sulcus, parietal cortex, frontal eye fields, precentral sulcus, V6, and precuneus (Saygin & Sereno, 2008). Responses to the rotating wedge in these areas are reduced when subjects perform a difficult task at central fixation (Saygin & Sereno, 2008).

Although the evidence summarized above suggest that spatial attention would improve the quality of fMRI topographic mapping signals, many studies have employed passive viewing or a central fixation task during retinotopic mapping experiments. In this chapter, we present the first quantitative analysis of the benefits of a spatial attention task for retinotopic mapping studies. Subjects viewed a rotating wedge stimulus that periodically traversed the visual field. On half of the fMRI runs, they continuously directed attention to the wedge stimulus and performed a target detection task within the wedge. On the other half, subjects performed an equally challenging target detection task within the fixation point. When attention was directed to the retinotopic mapping stimulus instead of the central fixation point, the signal-to-noise ratio (SNR), or reliability, of the fMRI retinotopic mapping signals increased. This increase in SNR was observed in early visual (V1, V2, V3, V3A/B, hV4), lateral occipital (LO1 and LO2; (Larsson & Heeger, 2006)), and ventral occipital (VO1; (Brewer, Liu, Wade, & Wandell, 2005)) cortical areas, as well as in posterior parietal areas that contain topographic maps of spatial attention (IPS0, IPS1, and IPS2). The benefits of attending to the retinotopic mapping stimulus may be particularly important for investigators who seek to establish topographic maps with as little scanning time as possible, leaving more time for other research questions. Finally, the increase in response reliability due to attending the retinotopic mapping stimulus was observed in all identified cortical areas, spanning multiple levels of the visual processing hierarchy. This finding suggests that there may be a general mechanism by which allocation of attention to a stimulus enhances the reliability of its representation in the cerebral cortex.

Materials and methods

Subjects

Eight healthy subjects participated in the study, all of whom had extensive experience as participants in psychophysical and fMRI experiments. One subject was also an author of the study. All participants provided written informed consent, and the experimental protocol was approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley. Each subject participated in one session to acquire high-resolution whole-brain anatomical MRI images and in one retinotopic mapping fMRI session. Prior to the retinotopic mapping session, each subject practiced the two target detection tasks for a total of four hours in a behavioral testing room, allowing the behavioral performance of the subjects to reach asymptotic levels. In addition, behavioral data from the practice sessions were used to determine the target sizes for each subject that resulted in equivalent performance of the two tasks in the fMRI experiment.

fMRI data acquisition

Functional MRI experiments were conducted for five subjects with a 4 Tesla Varian INOVA MR scanner and for three subjects with a 3 Tesla Siemens Trio MR scanner. A transmit/receive surface radiofrequency coil was used to maximize contrast-to-noise ratio in occipital cortex. Functional echo-planar images were acquired using a gradient-echo EPI sequence. The field of view was 180 x 180 mm (4T) or 200 x 200 mm (3T), and the matrix size was 64 x 64 (4T) or 96 x 96 (3T), resulting in an inplane voxel resolution of 2.81 x 2.81 mm (4T) or 2.08 x 2.08 mm (3T). The repetition time (TR) was 1.067 s (4T) or 2.133 s (3T), and the echo time (TE) was 28 ms (4T) or 26 ms (3T). Twenty (4T) or twenty-two (3T) slices were prescribed with an interslice gap of 0.3 mm and a slice thickness of 3 mm (4T) or 2 mm (3T). The slices

were angled between the coronal and axial planes to provide coverage of occipital and posterior parietal cortex. A set of T1-weighted anatomical images that were coplanar with the EPI images was acquired at the beginning of every imaging session.

fMRI data preprocessing

Each run lasted 281.6 s, and the first 8.53 s of the fMRI time series were discarded. Head movements were corrected offline using a 3D image registration algorithm (MCFLIRT; (Jenkinson, Bannister, Brady, & Smith, 2002)). Finally, each voxel's time series was divided by its mean intensity to convert the data from arbitrary units to percent signal modulation and to compensate for the decrease in mean image intensity as a function of distance from the surface coil. Neither high-pass filtering nor temporal detrending was applied to the time series.

Visual stimuli

A checkerboard wedge stimulus rotating about a central fixation point (Engel, Glover, & Wandell, 1997; Engel, et al., 1994; Sereno, et al., 1995) was continuously presented during acquisition of each fMRI time series. The check size within the stimulus was scaled according to the cortical magnification factor in human V1 (Slotnick, Klein, Carney, & Sutter, 2001), and the stimulus contrast was 100%. Stimuli were presented using MR-compatible goggles (Resonance Technology, Northridge, CA) in the 4T scanner and an LCD projector (Avotec, Stuart, FL) in the 3T scanner. The wedge subtended 45 degrees and extended from 0.5 degrees (inner radius) to 10.9 degrees (outer radius) of visual angle. Each wedge reversed contrast at a rate of 7.5 Hz. The wedge was presented for 2.13 s in each location, and the subsequent wedge location was displaced 22.5 degrees in a clockwise direction. Therefore, there were a total of 16 wedge positions, and each position overlapped 50% with the neighboring positions. The wedge completed a full rotation once every 34.13 seconds. Subjects were instructed to continuously maintain fixation on a central fixation point (0.25 degrees of visual angle) throughout each scan.

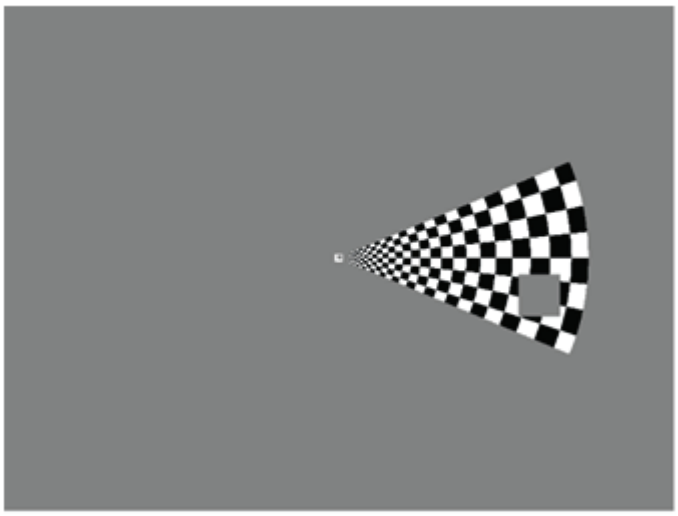

Figure 1. **Stimuli and tasks**. Subjects maintained fixation while viewing a wedge-shaped stimulus that rotated around the central fixation point. In the attention-to-wedge condition, subjects pressed a button when they detected a target within the wedge. The target was a square region of zero contrast with luminance equal to the average luminance of the wedge. In the attention-to-fixation condition, subjects detected contrast decrement targets within the fixation point. For both attention conditions, contrast decrements were presented in both the wedge and fixation point, but the timing of contrast decrement presentation was independent in the wedge and fixation point.

Task

In the attention-to-wedge task, subjects were instructed to maintain fixation on the central point and to press a button whenever they detected a target within the wedge. The target was a square region of zero contrast (luminance equal to mean luminance of the wedge), and the target duration was one full cycle of contrast reversal of the checkerboard wedge stimulus (0.27 s). There was a 50% probability of target presentation at each wedge position, and the target could appear anywhere within the wedge stimulus at unpredictable times. This spatial and temporal uncertainty regarding target presentation encouraged subjects to continuously maintain spatial attention over the entire rotating wedge. The target sizes in three eccentricity bands (0.5-4.0, 4.0-7.4, and 7.4-10.9 degrees of visual angle) were scaled to equate the percentage of targets correctly detected for these bands, but the boundaries between the eccentricity bands were not visible to the subjects.

In the attention-to-fixation task, subjects were instructed to maintain fixation on the central point and to press a button when they detected a square region of zero contrast within the fixation point. The targets in the attention-to-fixation and attention-to-wedge tasks had identical durations, contrasts, and probabilities of presentation. During behavioral practice sessions, the size of the fixation target was adjusted to insure that the task difficulty (percentage of fixation targets correctly detected) was equal to that of each of the three eccentricity bands in the attention-to-wedge task.

If necessary, the sizes of the wedge and fixation targets were adjusted during the fMRI experiments to maintain equal performance for each of the three eccentricity bands and for both task conditions for each subject. To equate sensory stimulation in the two tasks, the square zero contrast regions were presented in both the fixation point and the wedge for both attention conditions (although the temporal sequence of presentation within the fixation point and the wedge were independent and were based on a 50% probability of presentation for each wedge position). The attention-to-wedge and attention-to-fixation runs always occurred in pairs, and any changes to the target sizes were applied to both runs in the pair. Thus, the only difference between the two conditions was that the subjects responded to wedge targets in the attention-to-wedge task and responded to fixation targets in the attention-to-fixation task. Eye movements were not recorded during the experiment; however, all participants were highly trained in maintaining fixation through participation in numerous prior psychophysical experiments.

Definition of visual areas

The boundaries of visual cortical areas V1, V2, V3, V3A/B, hV4, LO1, LO2, VO1 and posterior parietal areas IPS0, IPS1, and IPS2 were defined using well-established phase-encoded retinotopic mapping methods (DeYoe, et al., 1996; Engel, et al., 1997; Engel, et al., 1994; Sereno, et al., 1995; Silver, et al., 2005). First, the time series obtained for each voxel was averaged across all runs. In all cases, there were equal numbers of attention-to-wedge and attention-to-fixation runs. Cortical area boundaries were defined based on this average time series, thereby eliminating potential bias in the location of areal boundaries in favor of one of the task conditions.

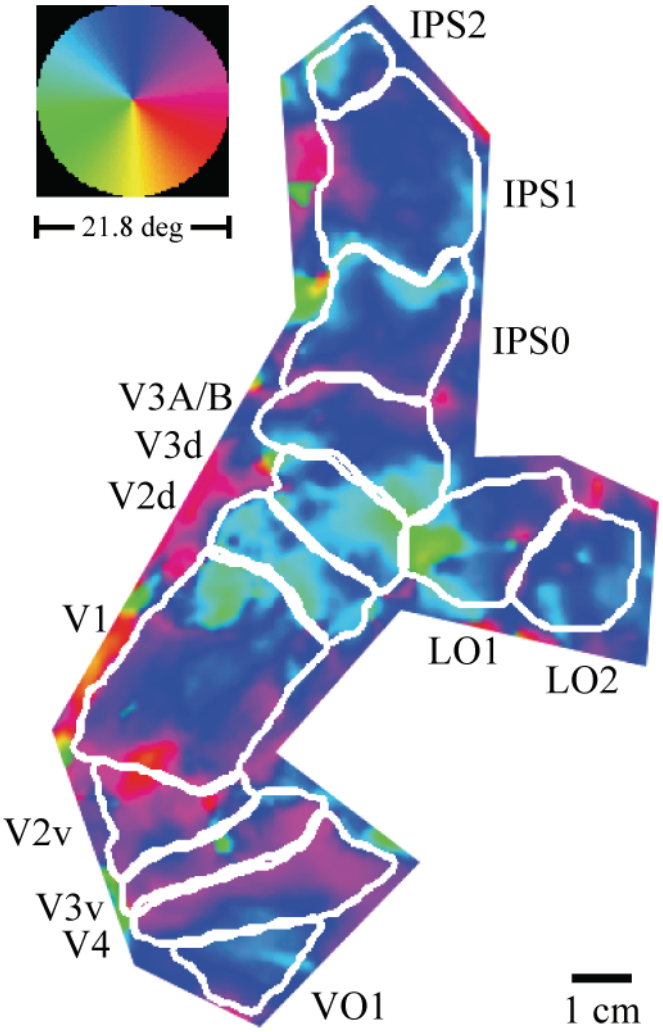

Figure 2. **Visual field representations in occipital and parietal topographic areas.** For each voxel, an equal number of attention-to-wedge and attention-to-fixation time series were averaged together, and the response phase (temporal delay of the fMRI response relative to the stimulus cycle) was computed for this average time series. The color wheel indicates the one-to-one mapping between response phase values and the angular component of the visual field location. In this computationally-flattened patch of right occipital and parietal cortex (Subject #4), each topographic area represents the contralateral right visual field.

The duration of the stimulus cycle was 34.13 s, resulting in a modulation of fMRI signals in visually-responsive voxels of 1/34.13 s = 0.0293 Hz. The coherency between a sinusoid of this frequency and the average fMRI time series for each voxel was calculated (Engel, et al., 1994; Rosenberg, Amjad, Breeze, Brillinger, & Halliday, 1989). Computation of coherency generates two quantities: the response phase (the temporal phase of the sinusoid that provides the best fit to the recorded fMRI time series) and the coherency magnitude (the strength of coupling between the best-fit sinusoid and the fMRI time series). The phase corresponds to the delay in the fMRI

response relative to the stimulus cycle and is used to estimate the angular component (in polar coordinates) of the visual field location that is represented by a given voxel.

These response phases were spatially transformed into computationally flattened cortical patches (Figure 2). The visual field maps were of sufficient quality to allow identification the boundaries of V1, V2, V3, V3A/B, hV4, IPS0, IPS1, and IPS2 in both hemispheres of all subjects (total of 16 hemispheres). LO1 was defined in all hemispheres except one (left hemisphere of Subject #2), LO2 was defined in all hemispheres except two (left hemisphere of Subjects #2 and #4), and VO1 was defined in all hemispheres except two (right hemisphere of Subjects #6 and #8). Our slice prescription was chosen to provide coverage of posterior parietal cortex and therefore did not consistently include area VO2.

Time series analysis

Each subject completed between five and seven attention-to-wedge runs and an equal number of attention-to-fixation runs. The order of runs was interleaved for the two attention conditions. For each fMRI run, values of coherency magnitude and phase were generated for each voxel. The coherency magnitude, also known as coherence, is a measure of signal-to-noise ratio of the stimulus response and is equal to the amplitude of the fMRI response at the stimulus frequency divided by the square root of the power across all frequencies in the time series (Engel, et al., 1997). Coherence values are bounded by zero and one and are therefore not normally distributed, so they were converted into normally distributed z-scores by Fisher transformation. To quantify the effects of spatial attention on fMRI retinotopic mapping signals, baseline measures of coherence were generated by averaging across attention-to-fixation runs. The percent change in coherence for each attention-to-wedge run relative to this baseline value was then computed to quantify the effects of spatial attention on response reliability.

Results

Behavioral results

Subjects viewed a rotating wedge stimulus while maintaining fixation on a central square (Figure 1). Gray square targets (luminance equal to the mean luminance of the wedge) were presented at random times in both the fixation point and in the wedge, and the timing of target presentation in the fixation point was independent of target presentation in the wedge. On alternating fMRI runs, subjects were instructed to continuously direct their attention to either the fixation point (attention-to-fixation condition) or the wedge (attention-to-wedge condition). They pressed a button every time they detected a target at the attended location. The size of the contrast decrement targets were selected to produce equivalent (approximately 70% correct) behavioral performance for fixation and wedge targets (Table 1) and for targets in each of three eccentricity bands within the wedge (Table 2).

Table 1
Percentage of targets correctly detected in attention-to-wedge and attention-to-fixation tasks.

Subject	Attention-to-fixation	Attention-to-wedge
1	78	80
2	72	72
3	64	62
4	73	72
5	67	69
6	60	63
7	78	67
8	80	65
Mean	71	69

Six of eight subjects showed less than 5% difference in performance on the two attention tasks. However, despite efforts to equate difficulty for both conditions, two subjects performed 10-15% better in the attention-to-wedge condition than the attention-to-fixation condition (Table 1). However, these differences in performance were not statistically significant for either subject (subject #7: p=0.07, two-tailed t-test, n=6 pairs of runs; subject #8: p=0.19, two-tailed t-test, n=6 pairs of runs). We conducted all fMRI analyses after excluding these two subjects and found the same pattern of results that was obtained from the entire group of eight subjects. We therefore report results from all eight subjects. There was no significant group difference in performance for the two attention tasks (p=0.30, two-tailed t-test, n=8 subjects). The fact that performance on the two tasks was equivalent controls for a number of possible confounds, including differences in fMRI signals due to task difficulty, attentional effort, and/or arousal. In addition, performance was similar for detecting wedge targets at near, middle, and far eccentricities (Table 2), indicating that the selected relationship between wedge target size and eccentricity encouraged subjects to distribute their attention over the entire stimulus in the attention-to-wedge condition.

Table 2
Percentage of targets correctly detected in each of three eccentricity bands in attention-to-wedge task.

Subject	Near (0.5–4.0 deg)	Middle (4.0–7.4 deg)	Far (7.4–10.9 deg)
1	74	87	78
2	70	68	81
3	65	68	56
4	74	70	78
5	64	68	72
6	59	55	69
7	67	84	80
8	69	85	87
Mean	68	73	75

Attention increases reliability of retinotopic mapping signals

Functional MRI was used to measure the reliability of cortical responses to the rotating wedge stimulus while subjects attended either the wedge stimulus or a central fixation point. The retinotopic mapping stimulus was a high-contrast counterphase-flickering checkerboard wedge that rotated about a central fixation point at a rate of 0.0293 Hz. The coherence between a voxel's fMRI time series and a sinusoid with frequency of 0.0293 Hz is a measure of signal-to-noise ratio (SNR), or reliability, of the response (Engel, et al., 1997). Coherency was computed for every voxel for each run. Because coherence values are bounded by zero and one, they were normalized by transformation into Fisher z-scores. The effect of attending to the rotating wedge was then expressed as the percent change in coherence z-score, relative to the attention-to-fixation baseline condition (Figure 3 and Supplementary Figures 1-8). Then, for each run, we averaged these percent change values across all voxels within a topographic cortical area.

Attending to the wedge stimulus substantially increased the reliability of fMRI responses in each defined cortical area ($p<0.0001$ in each area, two-tailed t-test, n=50 runs). For the group of eight subjects, all areas (V1, V2, V3, V3A/B, hV4, IPS0, IPS1, IPS2, LO1, LO2, and VO1) showed increases in reliability that ranged between 20 and 35% (Figure 4). This same pattern of results was obtained when assessing reliability for individual subjects (Figure 5). Area hV4 showed significant ($p<0.05$, two-tailed t-test, n=5, 6, or 7 runs per subject) enhancement of response reliability when attending to the wedge stimulus in all eight subjects; V1, V2, V3, and VO1 in seven of eight subjects; V3A/B and IPS1 in five subjects; LO1 and IPS0 in four subjects; and IPS2 and LO2 in three subjects.

Attention improves reliability of retinotopic mapping signals for averaged time series

The data presented in Figures 4 and 5 demonstrate the improvement in SNR for single fMRI runs that results from attending to the wedge stimulus. However, retinotopic mapping analyses are typically performed on time series averaged over several runs. Averaging across runs reduces noise (since the phases of fluctuations at non-stimulus frequencies are generally independent across runs), but preserves signal (since the phase of the evoked fMRI response relative to the visual stimulus cycle is similar across runs). We quantified the increase in response reliability caused by attending to the retinotopic mapping stimulus for time series that were averaged across runs. For a given subject, 5-7 attention-to-wedge runs were averaged, and coherence z-scores were computed for the average time series. Analogous values were computed for the average of an equal number of attention-to-fixation runs for that subject, and the effect of attending to the wedge was quantified as percent change in coherence z-score relative to the mean attention-to-fixation baseline. Compared to analysis of individual runs, attending to the wedge stimulus produced an even greater improvement in SNR when time series were averaged prior to computing reliability (Figure 6). In early visual areas (V1-hV4) and ventral occipital cortex (VO1), attending to the visual stimulus increased reliability by approximately 50%. This effect was more pronounced in higher cortical areas, with reliability increases of approximately 65-90% in LO1, LO2, IPS0, IPS1, and IPS2.

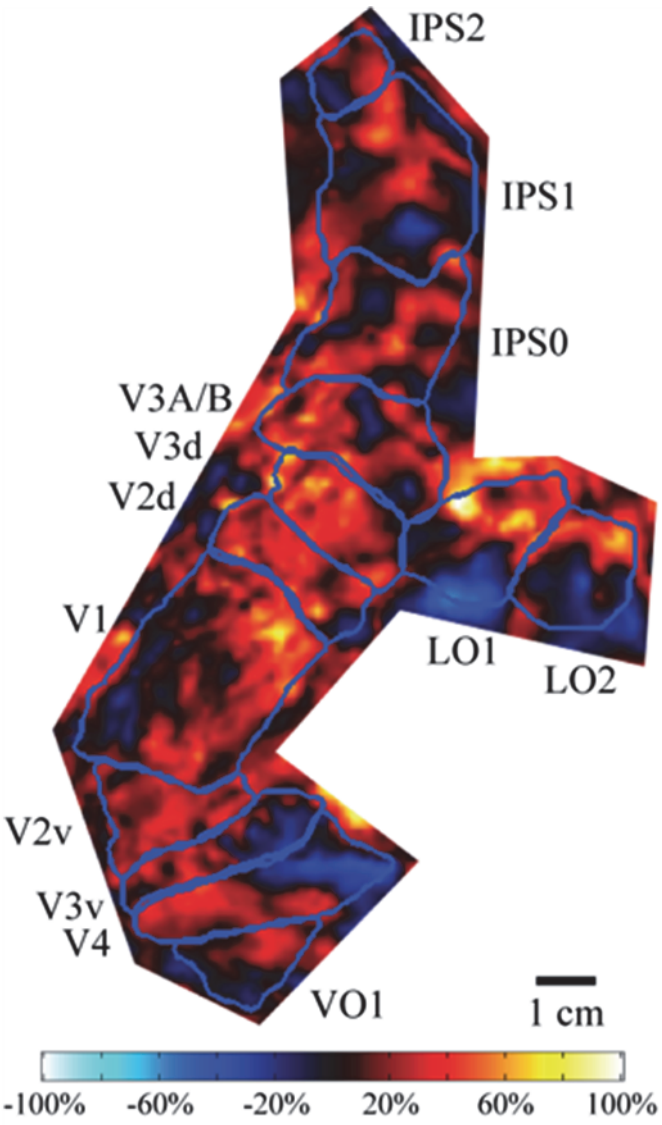

Figure 3. **Attending to the retinotopic mapping stimulus increases reliability of fMRI responses.** The z-transformed coherence value for the average attention-to-fixation time series served as a baseline for each voxel, and the percent change in z-scores in the average attention-to-wedge time series relative to this baseline quantifies the change in response reliability resulting from attending to the retinotopic mapping stimulus. In this example right hemisphere (Subject #4), attending to the wedge increased coherence in all identified topographic areas.

Several attention-to-fixation runs are necessary to achieve reliability that is equivalent to a single attention-to-wedge run

One practical benefit of increased response reliability resulting from attending the wedge stimulus is that a given SNR value can be reached in fewer fMRI runs. We quantified how many

attention-to-fixation runs would be needed to equal the SNR from a single attention-to-wedge run. Coherence z-scores from the first run of the attention-to-wedge condition were compared to z-scores from an average of multiple attention-to-fixation runs. In cortical areas V1-hV4 and V3A/B, the reliability of retinotopic mapping responses of a single attention-to-wedge run was equivalent to the reliability of the average of three to five attention-to-fixation runs. That is, for the attention-to-wedge condition, a given SNR was reached in approximately 20-35% of the scan time required to attain the same SNR for the attention-to-fixation condition (Figure 7). For higher cortical areas (IPS0, IPS1, IPS2, LO1, LO2, and VO1), a single attention-to-wedge run produced greater SNR than the average of five attention-to-fixation runs (Figure 7).

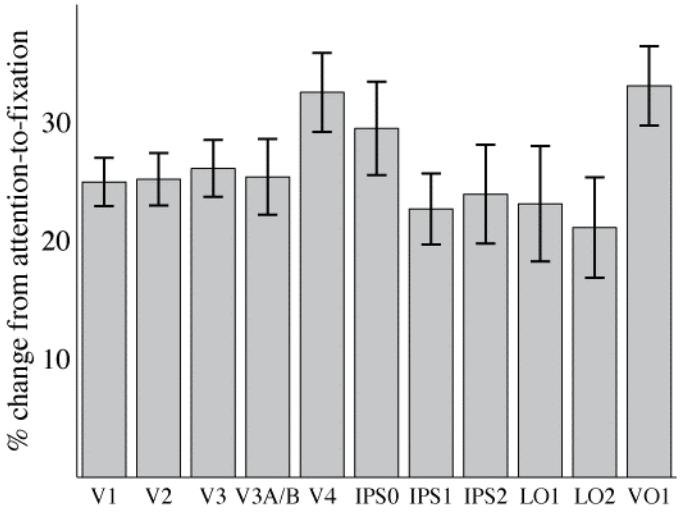

Figure 4. **Attending to the retinotopic mapping stimulus increases response reliability.** Coherence z-scores were computed for the attention-to-fixation baseline for each topographic area. For each attention-to-wedge run, a coherence z-score was computed for each area, and the effects of attention were expressed as percent change from the attention-to-fixation baseline. Attending to the wedge significantly increased response reliability (coherence) for all eleven areas.

Discussion

Effects of spatial attention on reliability of retinotopic mapping signals

Retinotopic mapping has proven to be extremely useful for the objective identification of topographically-organized areas in cerebral cortex (Silver & Kastner, 2009; Wandell, et al., 2007). In the present study, subjects either attended to or ignored the rotating wedge stimulus used for retinotopic mapping. We demonstrate that attending to the stimulus increased the SNR of single retinotopic mapping runs approximately 25% across several occipital and parietal topographic cortical areas. This beneficial effect of attention on response reliability was magnified when comparing averaged time series from the two conditions. In this case, attention increased response reliability by approximately 50% in early visual and ventral occipital areas and 65-90% in higher areas. Our results suggest that retinotopic mapping studies would benefit greatly from requiring subjects to allocate spatial attention to the mapping stimulus. Our results are highly relevant for researchers seeking to define early visual cortical areas with minimal

scanning time: for these areas, the SNR of one run of attention-to-wedge mapping is equivalent to that obtained from an average of 3-5 attention-to-fixation runs.

Relative to early visual cortex, posterior parietal and lateral occipital cortical regions showed an even greater improvement in response reliability with attention. In particular, the largest improvement in reliability occurred in posterior parietal (IPS1, IPS2) and lateral occipital (LO1, LO2) cortical areas that are often difficult or impossible to define using conventional retinotopic mapping data collection and analysis methods. This result in posterior parietal cortex is consistent with previous findings that the relative influence of sensory responses compared to attentional modulation decreases at higher levels of the dorsal visual cortical processing hierarchy (Serences & Yantis, 2006; Silver, et al., 2005). A direct comparison of the effects of averaging and the effects of attending (Figure 7) provides further evidence that attention signals are particularly important for revealing the topographic organization of higher-order topopgraphic areas: in IPS0, IPS1, IPS2, LO1, LO2, and VO1, even an average of five attention-to-fixation runs did not yield the reliability produced by a single attention-to-wedge run. These results suggest that studies aiming to discover new cortical areas that potentially contain only weak topographic organization would substantially benefit from the inclusion of a task that directs attention to the mapping stimulus. This is supported by the finding that an "attention-to-stimulus" task revealed topographic organization in many higher-order cortical areas but that this organization was not apparent in these areas when subjects directed attention to the fixation point (Saygin & Sereno, 2008).

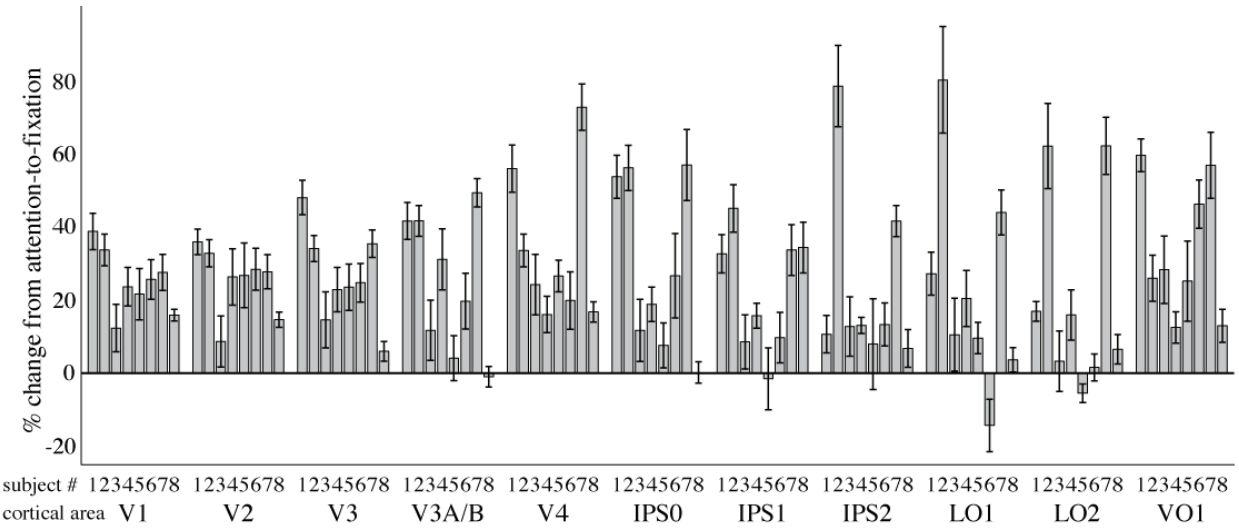

Figure 5. **Attending to the retinotopic mapping stimulus increases response reliability – individual subject data.** Conventions are the same as in Figure 4, but individual data for all eight participants are displayed.

Methodological advances in topographic mapping with fMRI have greatly improved the fidelity of retinotopic maps. Some recent advances include scanning at high magnetic field strength (Hoffmann, Stadler, Kanowski, & Speck, 2009), employing two simultaneous periodic mapping stimuli (Slotnick & Yantis, 2003), and including an estimate of population receptive field size in the model of the fMRI time course for each voxel (Dumoulin & Wandell, 2008). The spatial and temporal characteristics of the standard checkerboard wedge stimulus are often chosen based on estimates of receptive field size and temporal frequency tuning of cortical area V1. A number of studies have modified the checkerboard wedge in order to study higher-order

areas, including adding color (Swisher, Halko, Merabet, McMains, & Somers, 2007), complex spatial patterns (Hansen, et al., 2007), biological motion (Saygin & Sereno, 2008), or video of natural images (Sereno & Huang, 2006). Other groups have employed memory-guided saccade, spatial working memory, and/or spatial attention tasks to identify a number of novel topographic areas in parietal and frontal cortex (Hagler & Sereno, 2006; Kastner, et al., 2007; Konen & Kastner, 2008; Schluppeck, Glimcher, & Heeger, 2005; Sereno, Pitzalis, & Martinez, 2001; Silver, et al., 2005). However, the enhancement of retinotopic mapping responses due to these modifications of the conventional stimuli has not been quantitatively measured. Our results quantify the benefits of attending to the retinotopic mapping stimulus for SNR of single fMRI runs, SNR of averaged time series, and the amount of fMRI scan time required to perform retinotopic mapping.

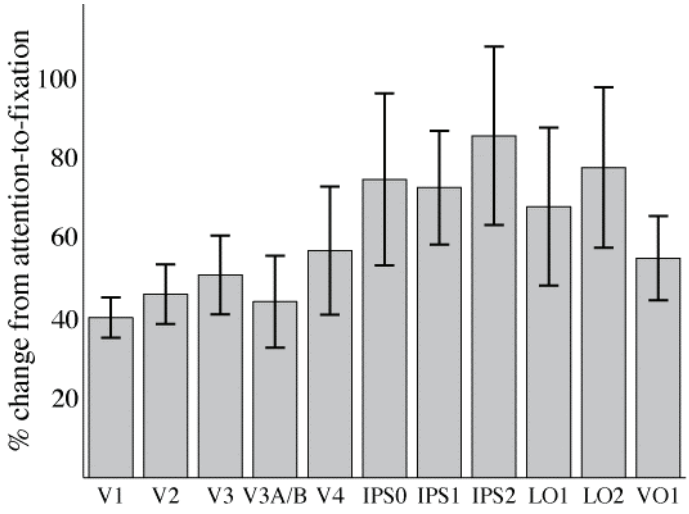

Figure 6. **Attending to the retinotopic mapping stimulus increases response reliability in averaged fMRI time series.** Conventions are the same as in Figure 4, except that the time series within a given attention condition were averaged before computing coherence. Attending to the wedge significantly increased response reliability (coherence) for all eleven areas.

Possible neural mechanisms for the enhancement of response reliability by attention

The improvement in reliability described in this study indicates that the allocation of attention causes the time course of fMRI responses to more closely match the visual stimulus. This could occur by an increase in the gain of the neuronal response to the visual stimulus. There is substantial evidence that spatial attention enhances the neural response to an attended visual stimulus (Bushnell, et al., 1981; McAdams & Maunsell, 1999; Motter, 1993; Treue & Maunsell, 1996). In fMRI studies in human early visual cortex, this enhancement by attention is largely independent of stimulus contrast, suggesting that much of it is due to an additive gain increase (Buracas & Boynton, 2007; Li, Lu, Tjan, Dosher, & Chu, 2008; Murray, 2008). Indeed, allocation of spatial attention selectively increases fMRI responses in portions of early visual cortex that represent attended locations, even in the absence of visual stimulation (Kastner, et al., 1999; Silver, et al., 2007).

Recent evidence suggests that the spatially-specific effects of attention on fMRI responses in early visual areas may be modulated by top-down attention signals from IPS1 and IPS2. These posterior parietal cortical areas contain a topographic map of the contralateral visual field but respond poorly to visual stimuli that are not attended (Silver, et al., 2005). A direct link between attention signals in IPS1/2 and those in visual cortex comes from fMRI functional connectivity measurements during sustained spatial attention in the absence of visual stimulation. Relative to fixation, sustained spatial attention increases the strength of coupling between IPS1/2 and several visual cortical areas (Lauritzen, D'Esposito, Heeger, & Silver, 2009). Additionally, analysis of the temporal relationships among these areas during sustained attention indicates that IPS1/2 leads several early visual cortical areas by a few hundred milliseconds (Lauritzen, et al., 2009). Therefore, it is likely that IPS1 and IPS2 transmit spatially specific top-down attention signals to early visual cortex.

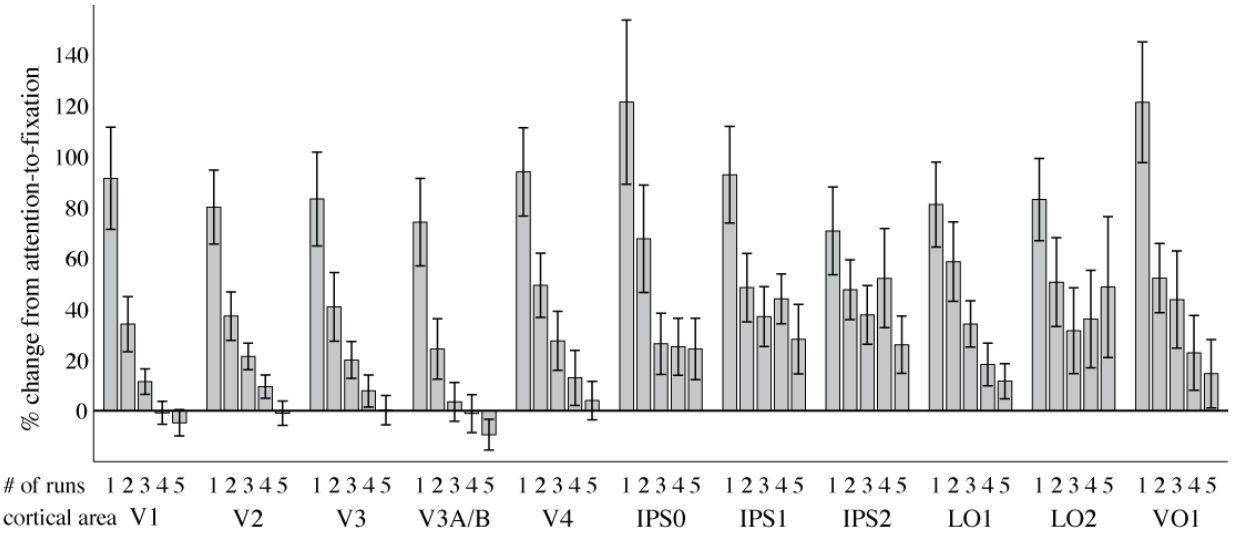

Figure 7. **Comparison of the effects of attending to the retinotopic mapping stimulus versus averaging multiple attention-to-fixation runs.** The coherence for the first attention-to-wedge run was computed and compared to the coherence of an average of one to five attention-to-fixation runs. For early visual cortical areas, three to five attention-to-fixation runs must be averaged in order to obtain a coherence value that is comparable to a single attention-to-wedge run. For posterior parietal, lateral occipital, and ventral occipital cortical areas, an average time series of five attention-to-fixation runs exhibits lower response reliability than a single attention-to-wedge run.

In addition to an additive gain increase, an alternative (but not mutually exclusive) mechanism for attention to improve SNR is a reduction in brain activity that is unrelated to the visual stimulus. Independent of the effects of attention on the amplitude of visual responses, a reduction in spontaneous noise fluctuations would improve SNR. There is recent evidence that attention improves reliability of representations of visual stimuli in monkey hV4 neurons by decreasing interneuronal correlations in firing rate that are unrelated to the stimulus (Cohen & Maunsell, 2009; Mitchell, et al., 2009). Additional studies are needed to clarify the mechanisms by which attention improves the reliability of fMRI signals in topographic cortical areas.

The influence of eye movements on our results is likely minimal. Although we did not record eye movements, all participants were highly trained at maintaining fixation in visual psychophysical experiments. Even if there were significant eye movements away from fixation in the attention-to-wedge condition, this would change the mapping between visual field location

and retinal location and would be expected to reduce fMRI response reliability. However, we found a robust increase in response reliability in the attention-to-wedge condition in all subjects and all identified cortical areas, suggesting that the benefits of spatial attention outweigh any potential artifacts due to eye movements.

Contributions of spatial attention in previous studies of topographic organization of parietal and frontal cortex

Other fMRI topographic mapping studies have used tasks that, although not explicitly manipulating attention, may have involved spatial attention. Hagler and Sereno (Hagler & Sereno, 2006) employed a spatial working memory task to reveal topographic maps in frontal and prefrontal cortex, and a memory-guided saccade task has been used to map topographic areas in parietal cortex (Schluppeck, et al., 2005; Sereno, et al., 2001), parietal and superior frontal cortex (Hagler Jr, Riecke, & Sereno, 2007), and frontal cortex (Kastner, et al., 2007). Both of these tasks require visual spatial attention, and the results of these studies are consistent with the attentional enhancement of fMRI retinotopic mapping signals we have found. However, the experimental design we have used has substantial advantages for characterizing the effects of attention on the representation of visual stimuli in a large number of cortical areas. Unlike the memory-guided saccade task, eye position is stable throughout the recording in our covert attention task. In addition, comparison of attention-to-wedge and attention-to-fixation conditions allows quantitative assessment of the effects of attending to the stimulus without stimulus or task difficulty confounds.

Swisher et al. (Swisher, et al., 2007) reported robust topographic mapping signals in IPS1 and IPS2 despite the fact that subjects continuously maintained their attention at the fixation point. The same task was used to discover two novel topographic areas in parietal cortex, IPS3 and IPS4. These results appear to be at odds with the current study, in which we emphasize the importance of attending to the periodic mapping stimulus, especially for posterior parietal cortical areas. It is notable that Swisher et al. (2007) employed a novel mapping stimulus that contained bright flashing colors embedded in the rotating checkerboard wedge. Since behavioral performance on the central fixation task in the Swisher et al. (2007) study was greater than 95%, it is possible that the dynamic color changes in the rotating wedge drew attention to the retinotopic mapping stimulus. This could explain the difference between the findings of Swisher et al. (2007) and those of previous studies using monochromatic periodic mapping stimuli that failed to detect topographic organization in posterior parietal cortex. While Swisher et al. (2007) and other groups have argued for using a central attention task to improve fixation stability during fMRI retinotopic mapping, our direct comparisons of attention-to-fixation and attention-to-wedge suggest that the benefits of covertly attending to the retinotopic mapping stimulus outweigh possible improvements in fixation stability resulting from attending to the fixation point. An important topic for future research is the characterization of the relative contributions of exogenous and endogenous attention to response reliability in the brain.

Conclusions

Recent methodological advances have greatly improved the fidelity of fMRI retinotopic mapping, enabling precise descriptions of the representation of the visual field in early visual cortical areas as well as the discovery of new topographically-organized regions. In this study, we quantified the benefits of attending to a retinotopic mapping stimulus and found that attention

improves the reliability of averaged fMRI responses in early visual and ventral occipital cortex by approximately 50%. This enhancement in response reliability was even greater in lateral occipital and posterior parietal cortical areas. Our results are of particular importance for the study and discovery of regions with topographic organization of signals that are not purely sensory. In addition, employing an attention task greatly increases the efficiency of retinotopic mapping: it requires no extra scanning time, and a single attention-to-wedge run generates retinotopic mapping signals with a reliability equivalent to that of an average of several attention-to-fixation runs for the same visual stimulus. Finally, attention increased the SNR of retinotopic mapping responses in every cortical area that was studied and at multiple levels of the visual processing hierarchy, thereby demonstrating the generality of the beneficial effects of spatial attention on the reliability of neural representations of sensory stimuli.

Chapter 3

Introduction

Neurons in sensory cortex display what seems to be spontaneous activity, even in the absence of sensory stimulation. This endogenous activity exhibits coherent structure over a range of spatial and temporal scales, that it plays a functional role (Ringach, 2009). For example, in visual cortex, spontaneous activity in the absence of visual stimulation reflects the functional architecture of cortex and exhibits spatiotemporal patterns that resemble those evoked by visual stimulation (Kenet, Bibitchkov, Tsodyks, Grinvald, & Arieli, 2003). However, little is known regarding the factors that regulate the spatial and temporal properties of structured endogenous activity or the relationships between this activity and behavior. Previous studies have shown that spontaneous activity immediately prior to a visual stimulus can affect perceptual performance (Busch, Dubois, & VanRullen, 2009; Mathewson, Gratton, Fabiani, Beck, & Ro, 2009; Super, van der Togt, Spekreijse, & Lamme, 2003; van der Togt, Kalitzin, Spekreijse, Lamme, & Super, 2006). In addition, higher levels of endogenous BOLD signal unrelated to task predict behavior in a variety of visual perceptual tasks (Boly, et al., 2007; Hesselmann, Kell, Eger, & Kleinschmidt, 2008; Hesselmann, Kell, & Kleinschmidt, 2008; Scholvinck, Friston, & Rees, 2012; Weissman, Roberts, Visscher, & Woldorff, 2006).

Other studies have shown that endogenous activity at much slower time scales also affects performance. Slowly developing (~5s) negative shifts in mean EEG cortical signals predict successful detection of threshold stimuli (Devrim, Demiralp, Kurt, & Yucesir, 1999). In addition, the phase of slow (<0.1 Hz) oscillations in EEG activity predicts detection of somatosensory stimuli (Monto, Palva, Voipio, & Palva, 2008). Recent studies show that slow fluctuations in neural activity, particularly in power within the gamma frequency band, correlate with the blood oxygenation level-dependent (BOLD) signal across large areas of cortex (Leopold, Murayama, & Logothetis, 2003; Scholvinck, Maier, Ye, Duyn, & Leopold, 2010; Shmuel & Leopold, 2008). Functional magnetic resonance imaging (fMRI) is well suited for studying the relationship between these slow fluctuations in activity and behavior, as the low-pass temporal filtering of neurovascular coupling preserves frequencies below 0.15 Hz (Cordes, et al., 2001; Sun, Miller, & D'Esposito, 2004).

We employed a periodic visual stimulus, a spatial attention task, and fMRI to study the effects of attention on stimulus-evoked responses and endogenous fluctuations and to assess the relationships between attentional modulation of neural activity and perception. Allocation of spatial attention to a visual field location enhances visual processing and perception at the attended location (Carrasco, 2011; Lu & Dosher, 1998, 2000). In many visual cortical areas, stimulus-evoked responses of individual neurons are greater if spatial attention is directed within compared to outside the neuron's receptive field (Reynolds, Chelazzi, & Desimone, 1999). In human fMRI studies, the visual cortical BOLD response to stimuli at a specific visual field location is greater if attention is directed to that location (Buracas & Boynton, 2007; Gandhi, et al., 1999).

In addition to increasing the gain of the stimulus-evoked response, spatial attention improves visual processing by suppressing activity that is unrelated to the attended item. Single-unit studies show that visual cortical responses to unattended stimuli can decrease when attention is directed to another stimulus within the receptive field (Reynolds, et al., 1999; Womelsdorf, Anton-Erxleben, Pieper, & Treue, 2006). Additionally, attending to a location causes a sustained

decrease in BOLD signal in portions of early visual cortex that represent unattended visual field locations (Muller & Kleinschmidt, 2004; Silver, et al., 2007). Recent studies have found that spatial attention decreases variability of the response to a visual stimulus in single neurons (Mitchell, et al., 2007) as well as the shared variability of the response of a population of neurons (Cohen & Maunsell, 2009; Mitchell, et al., 2009).

We used a visual stimulus that periodically traversed the visual field and employed Fourier decomposition to simultaneously and independently estimate both stimulus-evoked and endogenous fMRI signals in the same time series. Because the stimulus evoked a periodic response in cortical areas containing a topographic map of the visual field, this evoked response could be distinguished from ongoing endogenous fluctuations in the frequency domain (Engel, et al., 1997; Engel, et al., 1994). Subjects performed a target detection task that required them to maintain spatial attention either within the periodic visual stimulus or at a central fixation point. I chapter 2 we showed that, relative to attending to the fixation point, directing attention to a rotating wedge stimulus improves the reliability of the fMRI BOLD response to this stimulus in many topographically-organized cortical areas. This improvement in reliability could be due to an increase in the strength of the stimulus-evoked response and/or a reduction in the amplitude of endogenous fluctuations at non-stimulus frequencies. Slow (<0.1 Hz) endogenous fluctuations in BOLD signals are a major source of variability in fMRI data (Biswal, Yetkin, Haughton, & Hyde, 1995; Cordes, et al., 2001; Zarahn, Aguirre, & D'Esposito, 1997), and much of the variability in evoked BOLD responses may be due to these fluctuations (Fox, Snyder, Vincent, & Raichle, 2007; Fox, Snyder, Zacks, & Raichle, 2006).

In the present study, we find that the improved reliability of the BOLD response to a periodic visual stimulus that results from attending the stimulus is due to both enhancement of the stimulus-evoked response and a reduction in the strength of endogenous slow fluctuations that are unrelated to the stimulus. The relative contributions of signal enhancement and suppression of endogenous fluctuations to improved response reliability varied across cortical areas. In ventral cortical areas, attending to the stimulus enhanced response reliability primarily through an increase in the amplitude of the stimulus-evoked response. In posterior parietal and lateral occipital cortical areas, improved response reliability occurred mainly through reduction in the strength of slow endogenous fluctuations. Finally, early visual cortical areas exhibited a combination of these effects.

In addition, the magnitude of suppression of slow endogenous fluctuations predicted subjects' performance on a visual target detection task in all eleven of the topographic occipital and parietal cortical areas that we studied. Specifically, target detection performance was greatest when the amount of suppression of slow endogenous fluctuations was largest. Surprisingly, we did not find a relationship between the strength of the stimulus-evoked response and behavioral performance in any cortical area. These results suggest that endogenous fluctuations in neural activity are modulated by spatial attention and that suppression of this endogenous activity is associated with improved visual perception.

Materials and methods

Visual stimuli, task design, fMRI data collection and preprocessing, and definition of topographically-organized cortical areas have been previously described in chapter 2 and will only be summarized here.

Subjects

In addition to the eight subjects described in chapter 2, two additional subjects participated in the present study. All ten subjects participated in one session to acquire high-resolution whole-brain anatomical MRI images and in one fMRI session.

fMRI data acquisition and preprocessing

Functional MRI experiments were conducted for five subjects with a 4 Tesla Varian INOVA MR scanner and for the other five subjects with a 3 Tesla Siemens Trio MR scanner. In the 4T scanner, a transmit/receive surface radiofrequency coil was used to maximize contrast-to-noise ratio in occipital cortex and in the 3T scanner, a 12-channel head coil was used. Functional echo-planar images were acquired using a gradient-echo EPI sequence. The field of view was 180×180 mm (4 T) or 200×200 mm (3 T), and the matrix size was 64×64 (4 T) or 96×96 (3 T), resulting in an inplane voxel resolution of 2.81×2.81 mm (4 T) or 2.08×2.08 mm (3 T). The repetition time (TR) was 1.067 s (4 T) or 2.133s (3T), and the echo time (TE) was 28ms (4T) or 26ms (3T). Twenty (4 T) or twenty-two (3 T) slices were prescribed with an interslice gap of 0.3 mm and a slice thickness of 3 mm (4 T) or 2 mm (3 T). Each run lasted 281.6 s, and the first 8.53 s of the fMRI time series were discarded. Head movements were corrected offline using a 3D image registration algorithm (MCFLIRT; (Jenkinson, et al., 2002). Neither high-pass filtering nor temporal detrending was applied to the time series.

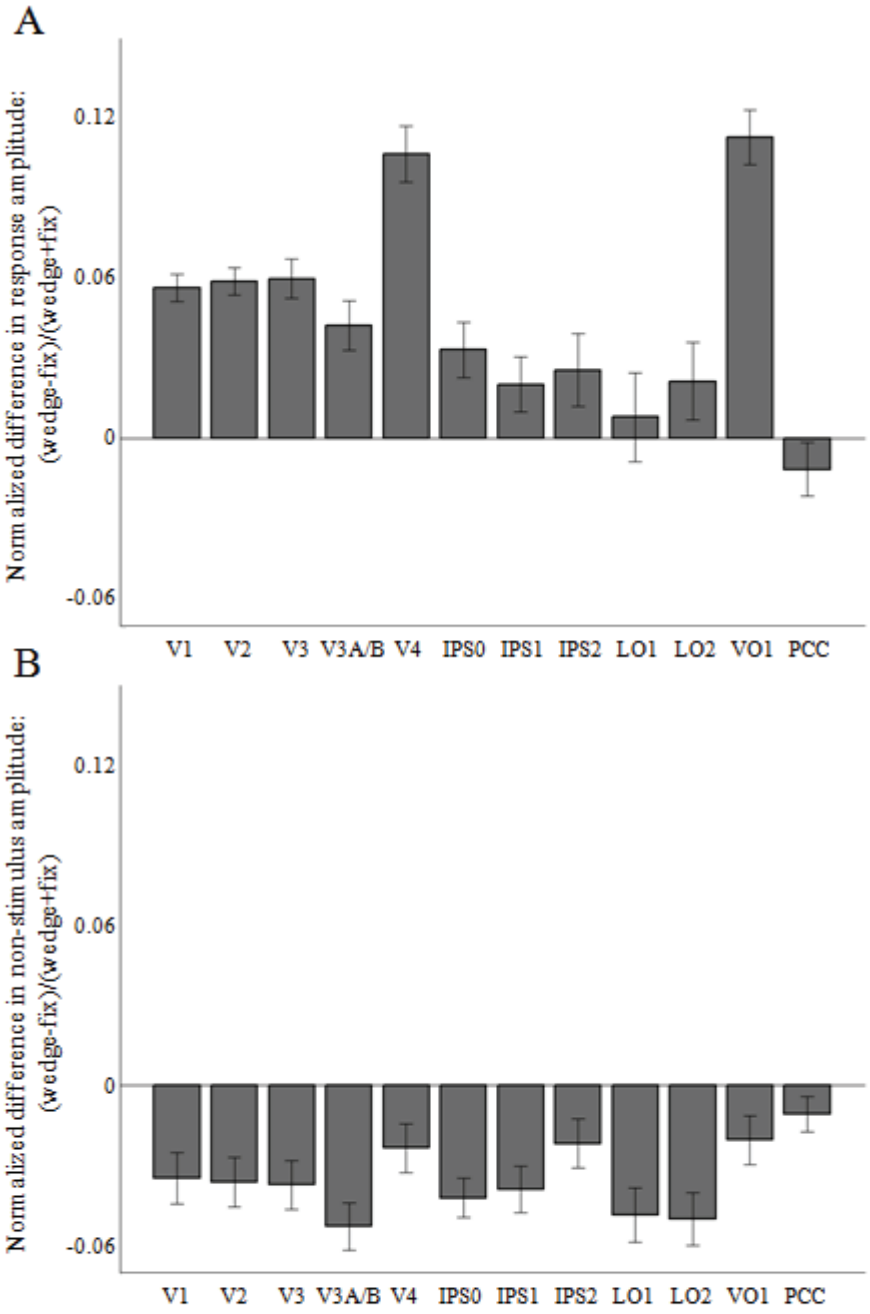

Figure 8. **Attention-induced changes in amplitude of the evoked response (stimulus frequency) and in amplitude at non-stimulus frequencies.** Attending to the rotating wedge increases the amplitude of the visual response in early and ventral cortical areas, but not in IPS1, IPS2, LO1, or LO2 (A), and decreases the strength of non-stimulus fluctuations in every measured topographically-organized area (B). These changes are not observed in a PCC control region.

Visual stimuli and task

A checkerboard wedge stimulus rotating about a central fixation point (Engel, et al., 1997; Engel, et al., 1994; Sereno, et al., 1995) was continuously presented during acquisition of each fMRI time series (Figure 1). The wedge subtended 45 degrees and extended from 0.5 degrees (inner radius) to 10.9 degrees (outer radius) of visual angle. Each check within the wedge reversed contrast at a rate of 7.5 Hz and the stimulus contrast was 100%. The wedge was presented for 2.13 s in each location, and the subsequent wedge location was displaced 22.5 degrees in a clockwise direction. Therefore, there were a total of 16 wedge positions, and each position overlapped 50% with the neighboring positions. The wedge completed a full rotation once every 34.13 seconds. Subjects were instructed to continuously maintain fixation on a central fixation point (0.25 degrees of visual angle) throughout each scan.

In the attention-to-wedge task, subjects were instructed to maintain fixation on the central point and to press a button whenever they detected a brief (0.27 s) presentation of a square region of zero contrast within the wedge (Figure 1). There was a 50% probability of target presentation at each wedge position, and the target could appear anywhere within the wedge stimulus at unpredictable times. The target sizes in three eccentricity bands (0.5–4.0, 4.0–7.4, and 7.4–10.9 degrees of visual angle) were adjusted to equate the percentage of targets correctly detected in these bands, but the boundaries between these eccentricity bands were not visible to the subjects.

In the attention-to-fixation task, subjects were instructed to maintain fixation on the central point and to press a button when they detected a square region of zero contrast within the fixation point. The targets in the attention-to-fixation and attention-to-wedge tasks had identical durations, contrasts, and probabilities of presentation. To equate sensory stimulation in the two tasks, the square zero contrast regions were presented in both the fixation point and the wedge for both attention conditions (although the temporal sequence of presentation within the fixation point and the wedge were independent and were based on a 50% probability of presentation for each wedge position). The attention-to-wedge and attention-to-fixation runs always occurred in pairs, and any changes to the target sizes were applied to both runs in the pair. Thus, the only difference between the two conditions was that the subjects responded to wedge targets in the attention-to-wedge task and to fixation targets in the attention-to-fixation task. Eye movements were not recorded during the fMRI experiments. However, all participants were highly trained in maintaining fixation through participation in numerous prior psychophysical experiments.

Prior to fMRI data collection, each subject practiced the two target detection tasks for a total of four hours in a behavioral testing room, allowing behavioral performance to reach asymptotic levels. In addition, behavioral data from the practice sessions were used to determine the target sizes for each subject that resulted in equivalent performance of the two tasks in the fMRI experiment. During behavioral practice sessions, the size of the fixation target was adjusted to insure that the task difficulty (percentage of fixation targets correctly detected) was equal to that of each of the three eccentricity bands in the attention-to-wedge task. Similar to the eight subjects reported in chapter 2, there was no significant difference in performance between the attention-to-wedge and attention-to-fixation tasks for the additional two subjects reported in this study.

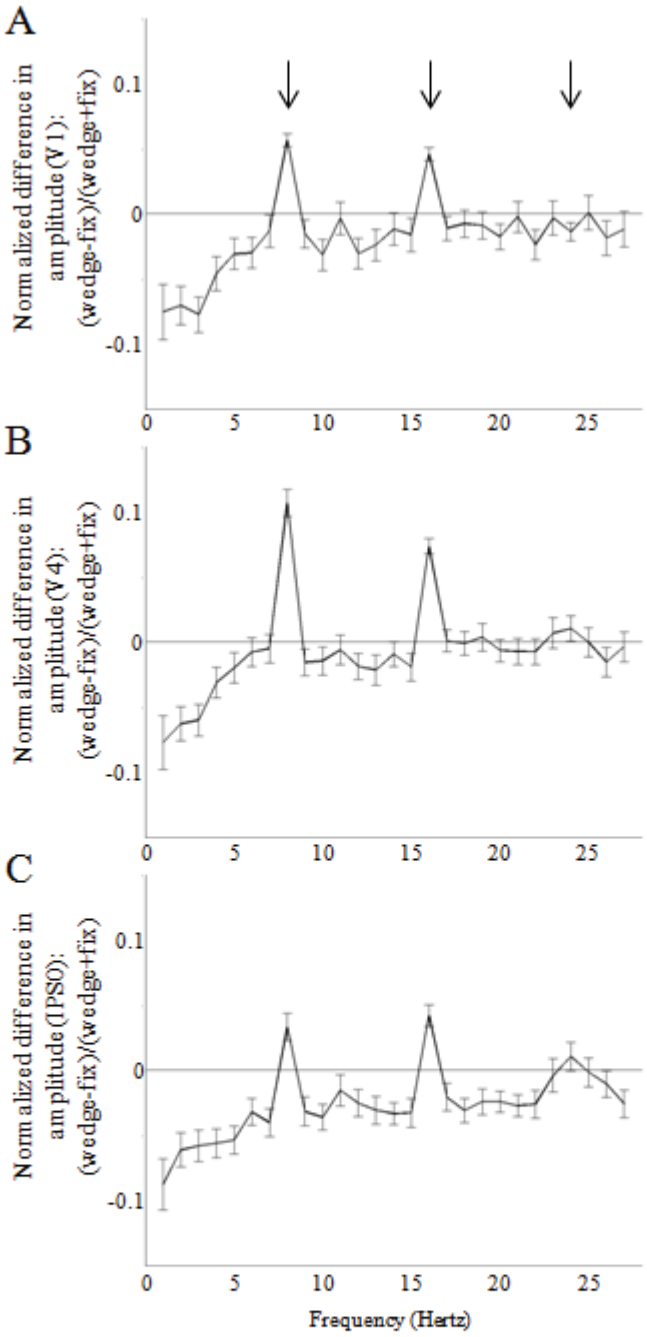

Figure 9: **Attention-induced changes in magnitude of fluctuation at different frequencies (V1, V4, IPS0).** In all cortical areas, attentional suppression of non-stimulus fluctuations is greatest for the lowest frequencies (approximately less than 0.03 Hz), whereas only a subset of areas show a significant reduction in higher non-stimulus frequencies. Stimulus frequency (0.0293 Hz) and associated harmonics (0.0586 and 0.0879 Hz) are indicated with arrow. A: Early visual areas (here, V1) show both attention-induced enhancement of the strength of the visual response and suppression of the strength of fluctuation at non-stimulus frequencies. B: Ventral visual areas (here, V4) show the strongest attention-induced enhancement of the visual response and the weakest attention-induced suppression of non-stimulus fluctuations. C: Lateral occipital and intraparietal areas (here, LO2) show the weakest enhancement of the visual response and the strongest suppression at non-stimulus frequencies.

Definition of topographic cortical areas and regions of interest (ROIs)

The boundaries of visual cortical areas V1, V2, V3, V3A/B, hV4, LO1, LO2, and VO1 and posterior parietal areas IPS0, IPS1, and IPS2 were defined using well-established phase-encoded retinotopic mapping methods (DeYoe, et al., 1996; Engel, et al., 1997; Engel, et al., 1994; Sereno, et al., 1995; Silver, et al., 2005). Each subject completed between five and seven attention-to-wedge runs and an equal number of attention-to-fixation runs; the order of runs was interleaved for the two attention conditions. The time series from each voxel were converted to units of percent signal change and averaged across all runs (including both attention-to-wedge and attention-to-fixation).

The duration of the stimulus cycle was 34.13 s, resulting in a modulation of fMRI signals in visually-responsive voxels of 1/34.13 s= 0.0293 Hz. Voxels that respond to the visual stimulus in a spatially specific manner will therefore exhibit activity modulations at this stimulus frequency. The fast Fourier transform (FFT) was computed for each time series from each voxel, and response phases at the stimulus frequency (relative to the cycle of the rotating wedge) were spatially transformed into computationally flattened cortical patches. The phase of the FFT of the time series at the stimulus frequency corresponds to the angular component (in polar coordinates) of the visual field location that is represented by a given voxel. The spatial distribution of these response phases on the cortical surface was then used to define the locations and boundaries of topographically organized cortical areas.

Using these procedures, the boundaries of V1, V2, V3, hV4, IPS1, and IPS2 were successfully defined in both hemispheres of all subjects (total of 20 hemispheres). Of the twenty hemispheres in our sample, V3A/B, IPS0, and LO1 (Larsson & Heeger, 2006) were defined in 19 of these, LO2 (Larsson & Heeger, 2006) and VO1 (Brewer, et al., 2005) were defined in 18 hemispheres, and each topographic area was defined in at least one hemisphere for each subject. In addition to these topographic areas, we also defined a bilateral ROI centered in the posterior cingulate cortex (PCC) / precuneus (Talairach (Talairach & Tournoux, 1988) coordinates [-2,-51,27], [2,-51,27] (Greicius, Krasnow, Reiss, & Menon, 2003)). For each subject, the PCC/precuneus ROI was expanded isotropically from the Talairach-defined center within the cortical gray matter (Wandell, Chial, & Backus, 2000) until its volume was equal to the average volume of all defined topographic cortical areas for that subject.

Time series analysis

For each voxel and fMRI run, the mean fMRI signal across all time points in the run (DC component) was subtracted from each motion-corrected time series, but no additional transformations were applied to normalize the signal (such as transformation to Fisher Z-scores or conversion to percent signal change). Then, the FFT was used to compute the amplitude at the stimulus frequency and non-stimulus frequencies. The strength of fluctuation at the stimulus frequency is the amplitude of the FFT component centered on 0.0293 Hz (+/- 0.007 Hz), corresponding to the rate of wedge rotation. We defined the strength of fluctuation at non-stimulus frequencies as the average of amplitudes of frequency components ranging from 0.0073 - 0.0220 Hz, 0.0366 - 0.0513 Hz, 0.0659 - 0.0806 Hz, and 0.0952 - 0.0989 Hz (i.e., frequency components below 0.1 Hz, not including 0 Hz (DC), the stimulus frequency, harmonics of the stimulus frequency, and frequency bands immediately adjacent to these components in the FFT).

For each voxel, attentional modulation of amplitude at stimulus and non-stimulus frequencies was expressed as a contrast index: (w-f)/(w+f), where w is attention-to-wedge and f is attention-to-fixation. This contrast index is similar to a percent change relative to the attention-to-fixation baseline ((w-f)/(f) * 100), but unlike percent change values, contrast indices are symmetric for increases and decreases. Contrast indices were computed for every pairwise combination of attention-to-wedge and attention-to-fixation runs, generating unbiased estimates of attentional modulation for every voxel. These contrast index values were averaged across all voxels within an ROI to obtain attentional modulation values for each brain area in each subject. We corrected for multiple comparisons for the 12 ROIs using the false discovery rate (FDR) method (Genovese, Lazar, & Nichols, 2002). In addition, at each voxel the contrast index for change in stimulus strength was correlated across runs with the change in non-stimulus strength. These values were then converted to normally distributed z-scores by Fisher transformation and averaged across all voxels within a given cortical area for each subject.

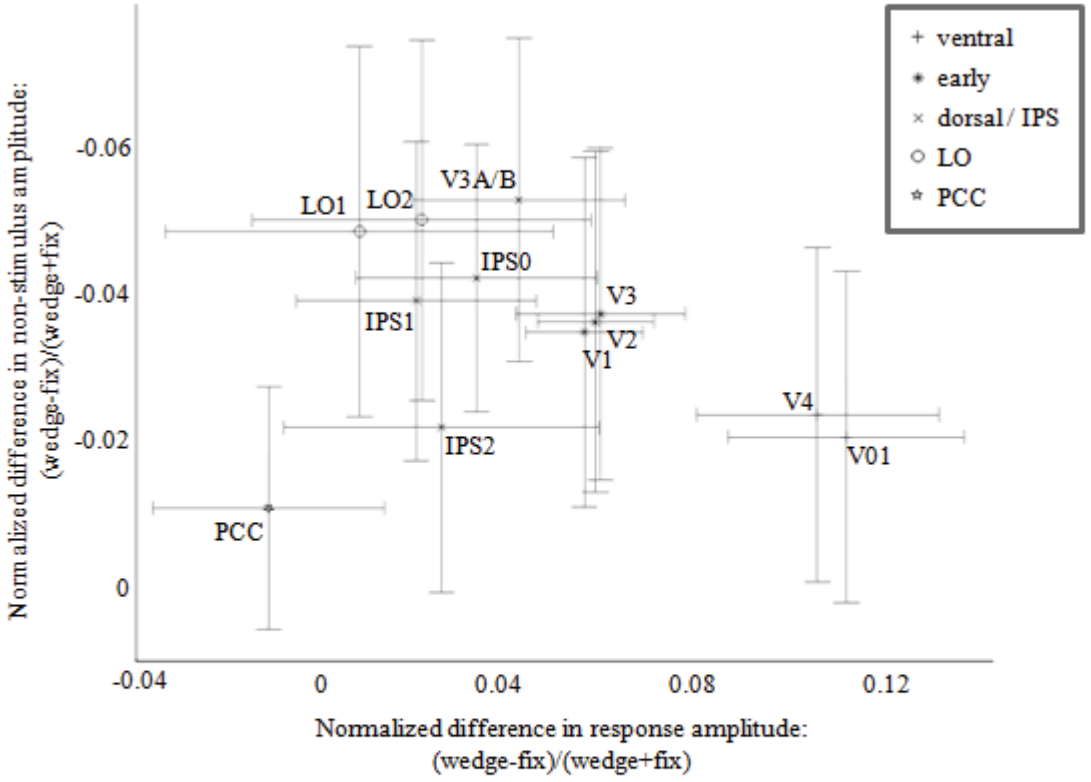

Figure 10. **Relationship between attention effects on stimulus and non-stimulus frequencies.** Plotting attention-induced enhancement of visual response versus magnitude of suppression of non-stimulus fluctuations reveals clustering of topographically-organized cortical areas. Ventral visual areas (+) show the strongest attention-induced enhancement of visual response strength but the weakest attention-induced suppression at non-stimulus frequencies, lateral-occipital (o) areas show the opposite pattern of results, and early visual cortical areas (*) exhibit both enhancement of the visual response and suppression at non-stimulus frequencies.

Correlation with performance analysis

For each attention-to-wedge run, behavioral performance was correlated with amplitude at stimulus and non-stimulus frequencies. Although target size was occasionally adjusted in order to maintain equal difficulty in the attention-to-fixation and attention-to-wedge tasks, each subject had at least five attention-to-wedge runs with the same target size. Correlation coefficients were converted to normally-distributed z-scores by Fisher transformation and were averaged across all voxels within a given cortical area for each subject.

Results

Subjects maintained central fixation while viewing a wedge-shaped visual stimulus that rotated around the screen once every 34.13 seconds (Figure 1). On separate runs, attention was either maintained at the central fixation point or directed towards the rotating wedge stimulus. During attention-to-fixation runs, subjects detected targets that were presented within the fixation point, and in the attention-to-wedge runs, subjects detected targets that were presented at random locations within the rotating wedge. Subjects pressed a button whenever they detected a low-contrast target in the attended region. The difficulty of the task was controlled by adjusting target size for each subject so that subjects detected approximately 70% of the targets in each attention condition. Functional MRI responses were recorded from topographically-organized cortical areas V1, V2, V3, V3A/B, hV4, IPS0, IPS1, IPS2, LO1, LO2, and VO1.

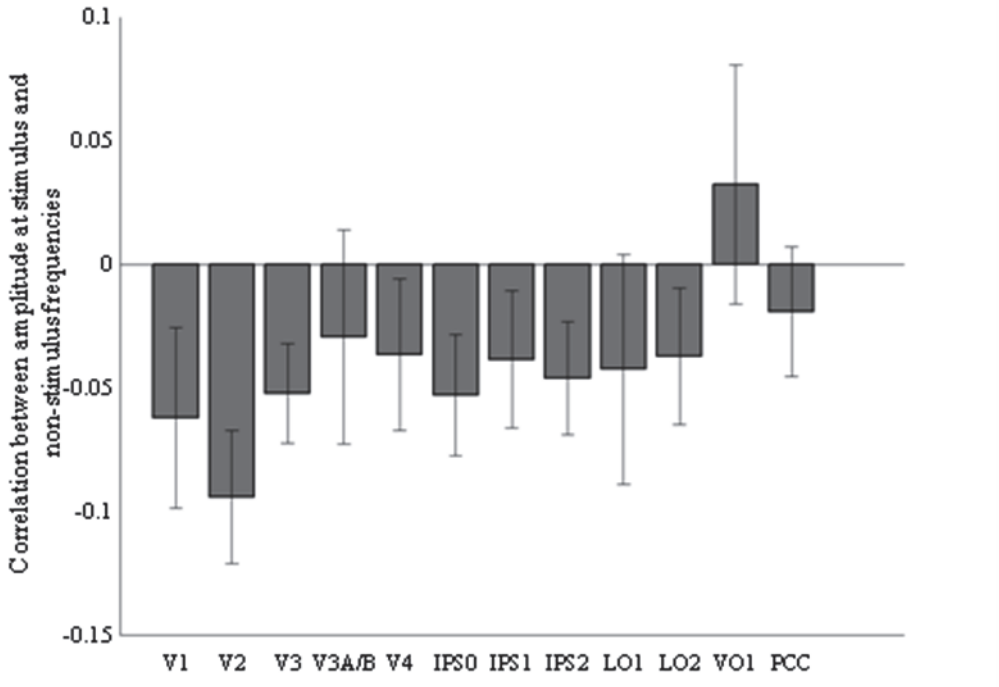

Figure 11. **Correlation coefficients between normalized amplitude at the stimulus frequency and amplitude of non-stimulus frequencies.** Normalized amplitude at the stimulus was computed by subtracting the mean of the amplitude at non-stimulus frequency bands on either side of the stimulus frequency. In each area, there was no significant correlation between the normalized stimulus amplitude and the average amplitude at non-stimulus frequencies.

Effects of spatial attention on strength of fluctuations in fMRI signals at stimulus and non-stimulus frequencies

The rotating wedge evoked periodic modulation in any brain location that exhibited a spatially-specific response to the stimulus, and the frequency of this modulation was equal to the frequency of wedge rotation (0.0293 Hz). A Fourier transform was computed for each voxel's time series to quantify the amplitude of the evoked response at the stimulus frequency (0.0293 Hz) and at non-stimulus frequencies between 0 and 0.1 Hz. We measured attentional modulation of both of these quantities and found that, relative to attending to fixation, attending to the wedge significantly increased the amplitude of the stimulus-evoked response in cortical areas V1, V2, V3, V3A/B, hV4, IPS0, and VO1 ($p<0.05$, two-tailed t-test, FDR corrected) but not in posterior parietal (IPS 1/2) or lateral occipital (LO 1/2) cortex (Figure 8A). Attending to the wedge significantly decreased the amplitude of slow endogenous fluctuations at non-stimulus frequencies in all eleven tested cortical areas ($p<0.05$, two tailed t-test, FDR corrected, Figure 8B).

Examination of power spectra of attentional modulation in individual cortical areas indicates that attentional suppression was confined mostly to the lowest frequencies (approximately <0.03 Hz; Figure 9), although this suppression extended to higher frequencies for some cortical areas (for example, IPS0; Figure 9C).

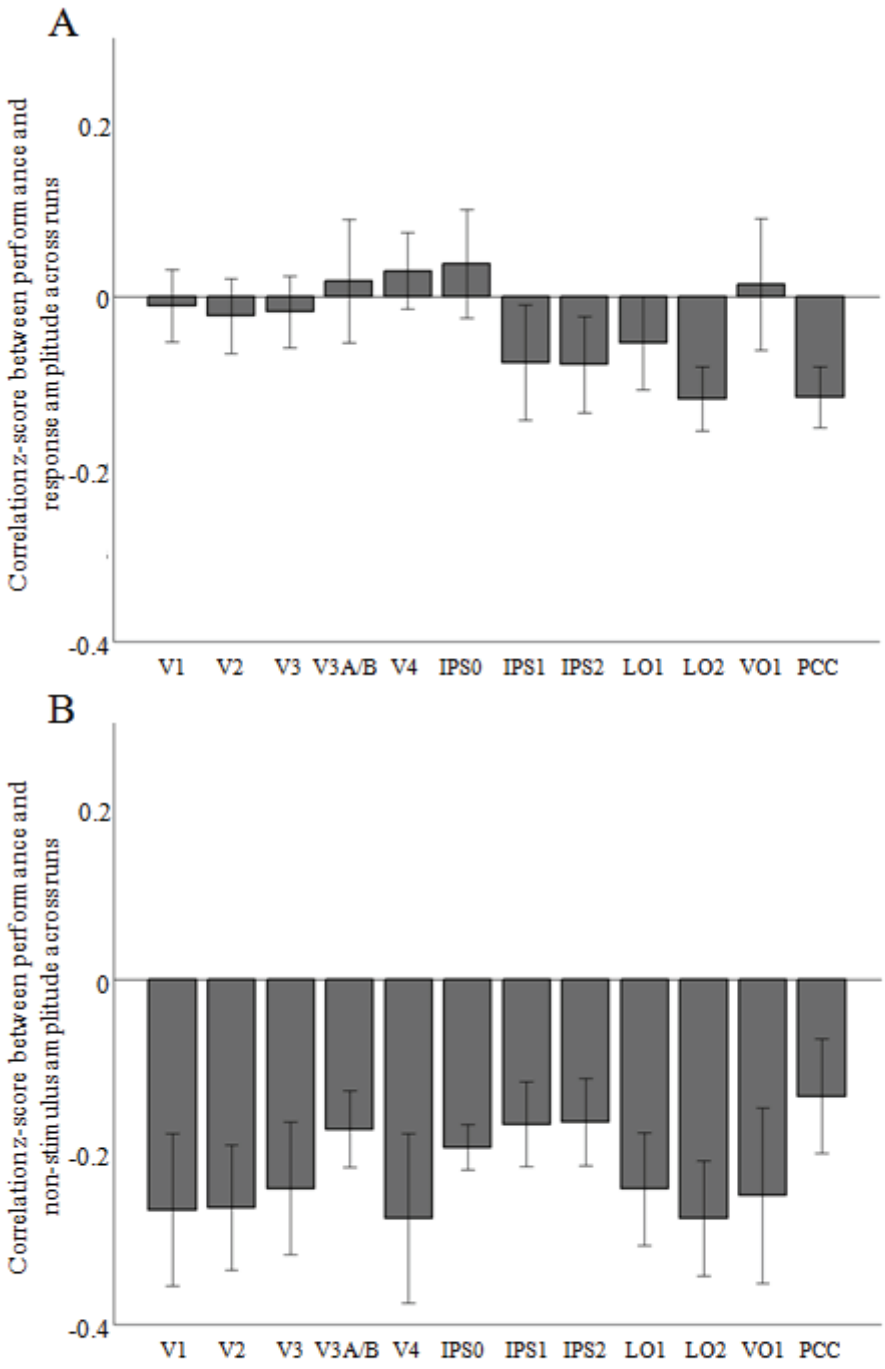

Figure 12. **Correlation between performance and fMRI amplitude at stimulus and non-stimulus frequencies.** A: No topographic area showed a significant correlation between fMRI amplitude at the stimulus frequency and percentage of targets correctly detected across runs. B. Performance was significantly negatively correlated with amplitude of fMRI fluctuations at non-stimulus frequencies.

Relative contributions of attentional enhancement and suppression to improved response reliability vary across topographic cortical areas

We previously showed in chapter 2 that directing attention to the rotating wedge increased the reliability of the fMRI response to the wedge in many topographically-organized areas in occipital and parietal cortex. This improved response reliability by attention could be due to increased amplitude of the stimulus-evoked response and/or suppression of activity unrelated to the representation of the stimulus. To determine the relative contributions of attentional enhancement and suppression to improved response reliability, we directly related the amount of attentional enhancement at the stimulus frequency to the amount of attentional suppression at non-stimulus frequencies across topographic cortical areas. This analysis revealed that lateral occipital and posterior parietal areas generally showed the strongest suppression and weakest enhancement by spatial attention, ventral visual areas had the strongest enhancement and weakest suppression, and early visual areas exhibited both enhancement and suppression (Figure 10).

To test if these inter-areal differences were significant, we grouped our visual regions into three groupings corresponding to placement in the visual hierarchy: 1) a ventral area grouping (hV4 and VO1), 2) an early area grouping (V1, V2, and V3), and 3) a grouping covering dorsal (V3A/B), lateral-occipital (LO1 and LO2), and intra-parietal (IPS0, IPS1, and IPS2) areas. We then ordered these groupings from ventral to early to dorsal and fit a linear function to the plot of attentional modulation versus grouping for each subject and each run. This analysis revealed that the magnitude of the attentional enhancement of the stimulus-evoked response decreased moving up the visual hierarchy from ventral to early to dorsal regions (i.e. slope was significantly less than zero; $p<0.05$, two-tailed t-test). In contrast, the magnitude of the attentional suppression of non-stimulus fluctuations increased moving up the visual hierarchy from ventral to early to dorsal regions (i.e. slope was significantly greater than zero; $p<0.05$, two-tailed t-test).

This analysis revealed an inverse relationship across cortical regions between the amount of signal enhancement and suppression of endogenous frequencies by spatial attention ($r = -0.66$; $p < 0.05$; Figure 10). To determine whether periods of strong attentional enhancement were associated with weaker suppression, and vice versa, for each voxel we correlated across runs the amplitude of the evoked response at the stimulus frequency with the amplitude of endogenous frequencies at non-stimulus frequencies. These correlation coefficients were uniformly high in all cortical areas (Fisher transformed correlation z-score = 0.15 – 0.3). However, some of this large positive correlation between amplitudes at stimulus and non-stimulus frequencies is due to the fact that endogenous fluctuations of fMRI signal occur at many frequencies (Zarahn, et al., 1997), including the stimulus frequency. To remove this factor, we subtracted the mean of the amplitude at non-stimulus frequency bands on either side of the stimulus frequency from the amplitude at the stimulus frequency on each run, resulting in a normalized amplitude at the stimulus frequency that better reflects the amplitude of the stimulus-evoked response. We then recomputed correlation coefficients between this normalized amplitude at the stimulus frequency and the mean amplitudes of the remaining non-stimulus frequencies. None of the cortical areas produced a significant correlation between amplitudes at stimulus and non-stimulus frequencies across runs (Figure 11; $p>0.05$, two-tailed t-test, FDR corrected), indicating that for a given cortical area, greater enhancement of the stimulus-evoked response over the course of a 5-minute fMRI run is not necessarily accompanied by greater suppression of endogenous fluctuations, and vice versa.

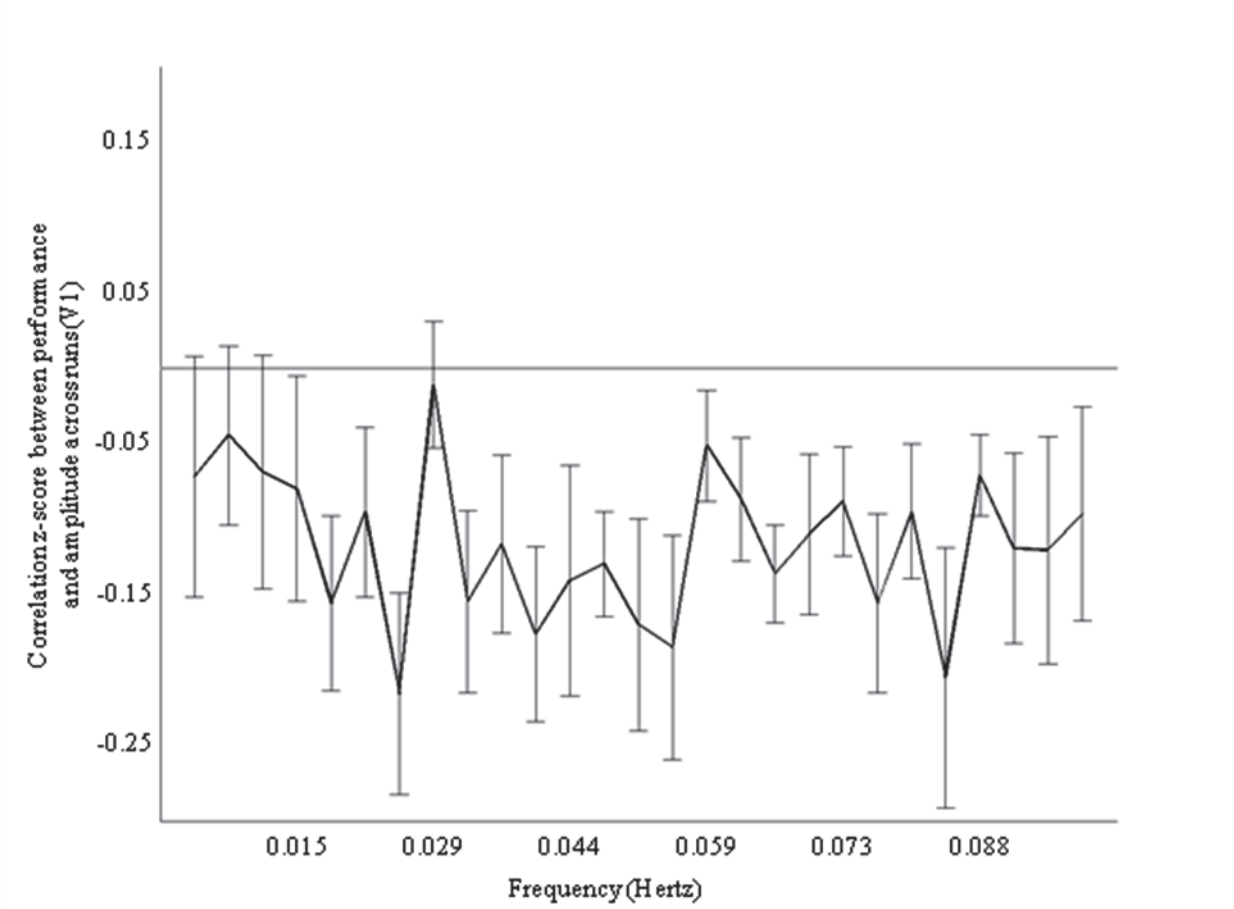

Figure 13: **Correlation between performance and amplitude of fluctuation at different frequencies (V1)**. In all topographically-organized areas, the correlation between performance and the attention-induced change in fluctuation strength is weakest at the slowest non-stimulus frequencies and stronger in higher non-stimulus frequencies.

Target detection is negatively correlated with amplitude of endogenous fluctuations but not with amplitude of the stimulus-evoked response

We correlated behavioral performance on the attention-to-wedge task with fMRI amplitude at both stimulus and non-stimulus frequencies. Each 5-minute fMRI run generated a single behavioral measure (percentage of targets correctly detected) and fMRI measures of the amplitude of both the stimulus-evoked response and endogenous fluctuations at non-stimulus frequencies. Surprisingly, target detection performance across attention-to-wedge runs was not correlated with stimulus-evoked response amplitude in any cortical area (Figure 12A; $p>0.05$, two-tailed t-test, FDR corrected). That is, stronger responses to an attended visual stimulus were not associated with enhanced target detection performance. On the other hand, behavioral performance across attention-to-wedge runs was significantly negatively correlated with the amplitude of non-stimulus frequencies in all topographic areas ($p<0.05$, two-tailed t-test, FDR corrected). Therefore, suppression of slow endogenous fluctuations that were unrelated to the stimulus significantly predicted target detection performance (Figure 12B).

The frequency distribution of the correlation between behavioral performance and suppression of slow endogenous fluctuations was generally strongest at frequencies above 0.02 Hz and often extended to 0.1 Hz, the highest frequency we analyzed (Figure 13).

Lack of effects in a control cortical region: PCC/precuneus

The consistent attentional suppression of fMRI activity fluctuations at non-stimulus frequencies across all the cortical areas we studied raises the possibility of a global effect of allocation of spatial attention to the wedge. Fluctuations in arterial carbon dioxide concentration (Wise, Ide, Poulin, & Tracey, 2004) and respiratory rate (Birn, Diamond, Smith, & Bandettini, 2006) occur within the 0-0.1 Hz range that we used to measure non-stimulus frequencies, and these non-neural fluctuations would be expected to influence BOLD signals. Although task difficulty was equated in the attention-to-fixation and attention-to-wedge conditions for every participant in our study, it is still possible that allocating covert spatial attention to the wedge resulted in a global reduction in the amplitude of endogenous BOLD fluctuations across the brain.

To control for this possibility, we anatomically defined an ROI in the posterior cingulate cortex (PCC) / precuneus (Greicius, et al., 2003) of each participant (see Methods). The PCC/precuneus is part of a network of regions that exhibits reduced activity during attention-demanding cognitive processing (Greicius, et al., 2003) and whose spontaneous activity is negatively correlated with activity in visual cortical regions (Fox, et al., 2005; Fransson, 2006). Relative to the attention-to-fixation condition, attending to the wedge did not have a significant effect on either the amplitude of the stimulus-evoked response (Figure 8A) or endogenous fluctuations at non-stimulus frequencies (Figure 8B) in the PCC/precuneus ($p>0.05$, two-tailed t-test, FDR corrected) (see also Figure 10). Moreover, attentional enhancement of the stimulus-evoked response was significantly greater in all topographic regions (except LO1) than in PCC ($p<0.05$, two-tailed paired t-test, FDR corrected for 11 statistical tests), and attentional suppression at non-stimulus frequencies was significantly greater in all topographic regions (except hV4, IPS2, and VO1) than in PCC ($p<0.05$, two-tailed paired t-test, FDR corrected). In addition, there was no significant correlation between behavioral performance in attend-to-wedge runs and response amplitude (Figure 12A) or amplitude at non-stimulus frequencies (Figure 12B) in the PCC/precuneus ($p>0.05$, two-tailed t-test, FDR corrected). However, direct statistical comparisons of PCC/precuneus correlation values with those of individual topography areas revealed no significant differences for either stimulus or non-stimulus frequencies ($p>0.05$, paired two-tailed t-test, FDR corrected).

Discussion

Allocation of spatial attention to a visual stimulus improves the reliability of the BOLD response to that stimulus. In the present study we show that this increase in reliability is due to a reduction in the strength of slow endogenous fluctuations, unrelated to the visual stimulus, in every topographic cortical area we studied. In addition, an increase in the amplitude of the stimulus-evoked response when attending the wedge also contributed to increased response reliability in early and ventral visual cortical areas. However, while the magnitude of the stimulus-evoked response was not predictive of the subjects' ability to detect targets within the wedge, suppression of slow endogenous fluctuations was highly correlated with successful target detection.

Attentional enhancement of stimulus-evoked responses

We found that allocating spatial attention to the rotating wedge stimulus enhances the BOLD response evoked by the wedge. This enhancement was strongest in ventral areas hV4 and VO1, moderate in early visual areas V1, V2, and V3, small but significant in dorsal areas V3A/B and IPS0, and not significant in posterior parietal cortical areas IPS1/2 and lateral occipital areas LO1/2. The lack of attentional modulation of the stimulus-evoked response in IPS areas is consistent with that reported in (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000) and does not necessarily contradict previous studies showing robust attentional modulation of BOLD activity in this region (Serences & Yantis, 2007; Silver, et al., 2005; Yantis, et al., 2002), as these studies did not directly compare IPS responses to attended and unattended visual stimuli. Finally, we found no attentional enhancement of the stimulus-evoked response in LO1/2, consistent with a previous study showing a similar lack of attentional enhancement of LO visual responses for stimuli with greater than 30% contrast (Murray & He, 2006).

Attentional suppression of slow endogenous fluctuations

We found attentional suppression of slow (< 0.1 Hz) endogenous fluctuations in every topographic cortical area we studied. This suppression was strongest in dorsal (V3A/B and IPS0/1) and lateral occipital (LO1/2) areas, moderate in early visual areas (V1, V2, V3) and VO1, and weakest in hV4 and IPS2. Previous studies have used various levels of visual stimulation to study endogenous fluctuations in fMRI activity, ranging from eyes closed in darkness (Logothetis, et al., 2009), eyes open in darkness (Horovitz, et al., 2008; Mennes, et al., 2010), eyes closed not in darkness (McAvoy, et al., 2008), eyes open viewing a gray screen (Fransson, 2006; Raichle, et al., 2001; Shmuel & Leopold, 2008), eyes open in low level illumination (Fox, et al., 2005; Zarahn, et al., 1997), and during high-contrast visual stimulation (Bianciardi, et al., 2009; Fox, Snyder, et al., 2006). In Bianciardi et al. (2009) and the present study, the use of a periodic stimulus limits evoked activity to a specific frequency band. This enables the measurement of endogenous fluctuations in visual cortex in other frequency bands during high-contrast visual stimulation. There is evidence that endogenous fluctuations are largely unaffected by visual stimulation compared to a blank screen condition (Bianciardi, et al., 2009) and that stimulus-evoked activity linearly combines with endogenous fluctuations (Fox, et al., 2007; Fox, Snyder, et al., 2006; Scholvinck, et al., 2012). In the present study, we also equated the visual stimulus and task difficulty in the two attention conditions, allowing us to attribute changes in the magnitude of slow fluctuations primarily to changes in the locus of spatial attention.

How do changes in the magnitude of slow endogenous fluctuations in fMRI signals relate to neural activity? BOLD signal amplitude in a given cortical location is correlated with levels of single-unit spiking, LFP power across many frequency bands, and multi-unit activity in the local neural population, with LFP gamma power showing the strongest correlation with BOLD responses (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Mukamel, et al., 2005; Niessing, et al., 2005; Viswanathan & Freeman, 2007). Moreover, endogenous fluctuations in the power of many LFP bands (especially gamma), as well as fluctuations in single and multi-unit activity (Scholvinck, et al., 2010; Shmuel & Leopold, 2008) and EEG gamma (Scheeringa, et al., 2011), are correlated with slow fluctuations in BOLD activity over large areas of cortex (including the opposite hemisphere). Therefore, the decrease in amplitude of slow BOLD fluctuations in our study likely reflects a reduction in fluctuations in neural activity (especially in gamma-band power) at those frequencies.

Differential amounts of attentional enhancement of stimulus-evoked responses and attentional suppression of endogenous fluctuations across cortical areas

We found that the relative levels of attentional enhancement of the visually-evoked response and suppression of endogenous fluctuations varied across areas. In early and ventral visual cortical areas, an increase in the strength of the evoked response contributed to enhanced response reliability, but this effect was not observed in posterior parietal cortical areas IPS1 and IPS2 or in lateral occipital cortical areas. In contrast, every topographic cortical area we studied exhibited a decrease in non-stimulus endogenous fluctuations that contributed to enhanced response reliability. That is, attentional suppression of endogenous activity not related to the stimulus contributes more broadly to the effect of attention on fMRI response reliability than attentional enhancement of the stimulus-evoked response.

Ventral cortical areas hV4 and VO1 exhibited the strongest increases in stimulus-evoked response and the weakest reductions in the strength of ongoing fluctuations. In contrast, dorsal areas V3A/B, IPS0, and IPS1, as well as lateral occipital areas LO1 and LO2, showed little or no increase in evoked response and the strongest reduction in endogenous fluctuations. Previous studies have suggested that the ventral attention network may be particularly involved in transient orienting to unexpected or salient stimuli (Corbetta & Shulman, 2002), whereas the dorsal attention network (including IPS and FEF) may be particularly important for sustained top-down attention (Fox, Snyder, et al., 2006). Therefore, attentional enhancement of the evoked response in ventral cortical areas may be important for rapid orienting to salient stimuli, whereas attentional suppression of endogenous fluctuations in activity in dorsal areas may be more important for sustained attention. Additionally, ventral cortical areas have an over-representation of inputs from central visual field locations, whereas dorsal areas have a relative under-representation of inputs from these locations (Baizer, Ungerleider, & Desimone, 1991); if attention processes are fundamentally different in near and far periphery (Roberts, Delicato, Herrero, Gieselmann, & Thiele, 2007), this could also contribute to differences across areas that we observed.

Effects of attention on enhancement, suppression, and response reliability

Response reliability can be represented as a signal-to-noise ratio. For neural representations of sensory stimuli, enhanced response reliability can result from increased evoked response and/or reduction of endogenous activity not related to the stimulus. Although there is an inverse relationship between levels of attentional enhancement of the response to the stimulus and attentional suppression of endogenous fluctuations across cortical areas, these two effects of attention do not covary across fMRI runs within a cortical area. That is, the amplitude of the stimulus-evoked response and the amplitude of slow endogenous fluctuations of non-stimulus frequencies were not significantly correlated, suggesting that they may reflect dissociable mechanisms, at least at the time scale studied here (5-minute fMRI runs).

A common metric for measuring response reliability of single neurons is the ratio of the mean response to the variance of this response across trials (Fano factor) (McAdams & Maunsell, 1999). At the population level, response reliability can be increased by pooling the responses of multiple neurons (Zohary, Shadlen, & Newsome, 1994). However, trial-to-trial fluctuations in response amplitude tend to be shared by many neurons within a local population (Cohen & Kohn, 2011; Kohn & Smith, 2005; Smith & Kohn, 2008; Zohary, et al., 1994), and

these correlations extend to the very long timescales we have studied using fMRI (Nir, et al., 2008). These correlated fluctuations in activity can therefore impose serious limitations on the reliability with which a neural population can represent a visual stimulus. Spatial attention can increase neuronal response reliability, both by increasing the evoked response amplitude (McAdams & Maunsell, 1999; Reynolds, et al., 1999) and by decreasing intertrial response variability (Cohen & Maunsell, 2009; Mitchell, et al., 2007, 2009). Attention can also enhance response reliability by decorrelating fluctuations in firing rate within neuronal populations (Cohen & Maunsell, 2009; Mitchell, et al., 2009). These studies describe attentional suppression of correlated activity on much shorter timescales than those for which we have demonstrated attentional suppression of endogenous fluctuations of fMRI signals. However, the level of correlation of firing rates within a population of neurons has been associated with the amount of BOLD activity (Niessing, et al., 2005; Nir, et al., 2007).

The effects of attention on stimulus-evoked responses and endogenous fluctuations we report here are not uniformly present across the brain. Attentional enhancement of the stimulus-evoked response was significantly greater in all topographically-defined regions (except LO1) than in a control non-topographic cortical region (PCC). In addition, attentional suppression of endogenous fluctuations was significantly greater in all topographically-defined regions (except hV4, IPS2, and VO1) than in PCC. However, the distinction between topographic areas and PCC was less clear for the correlation between behavior and strength of endogenous fluctuations. Although every topographically defined region had a negative correlation value that was numerically greater than that in PCC, these differences were not statistically significant. These results suggest that the relationship between behavioral performance and the strength of slow endogenous fluctuations may be more widespread across cortex than the effects of attention on the strength of slow endogenous fluctuations. In addition, attentional suppression of endogenous fluctuations was strongest at very low temporal frequencies (< 0.03 Hz), while the negative correlation between target detection performance and the amplitude of endogenous fluctuations was more evident at higher temporal frequencies (> 0.02 Hz).

Relationships among behavioral performance, stimulus-evoked responses, and endogenous fluctuations

A stronger response of individual neurons in a number of cortical areas predicts correct detection of a threshold-level stimulus (Cook & Maunsell, 2002; Dubner, Kenshalo, Maixner, Bushnell, & Oliveras, 1989). In EEG and LFP studies, greater gamma synchrony (Meador, Ray, Echauz, Loring, & Vachtsevanos, 2002; Palva, Palva, & Kaila, 2005; Womelsdorf, Fries, Mitra, & Desimone, 2006) and lower alpha power (Babiloni, Vecchio, Bultrini, Luca Romani, & Rossini, 2006) predict better performance. In fMRI, the BOLD response to an attentional cue (Ress, Backus, & Heeger, 2000; Sapir, d'Avossa, McAvoy, Shulman, & Corbetta, 2005; Sylvester, Jack, Corbetta, & Shulman, 2008; Sylvester, Shulman, Jack, & Corbetta, 2007) or to a visual stimulus (Pessoa & Padmala, 2005; Pins & Ffytche, 2003; Ress & Heeger, 2003) is greater for detected compared to undetected threshold targets. In contrast to many of these prior studies, we found that successful target detection was not correlated with the amplitude of stimulus-evoked responses in any topographic cortical area we studied. Instead, improved behavioral performance was predicted by suppression of slow endogenous fluctuations.

Other studies have demonstrated relationships between spontaneous neural activity and behavior in visual perception tasks. Both synchronization of pre-stimulus spontaneous correlated

firing between V1 neurons and overall spontaneous firing level (Super, et al., 2003) predict subsequent performance in a visual task. Stronger pre-stimulus gamma power following an attention cue predicts better detection of subsequent threshold stimulus (Wyart & Tallon-Baudry, 2009). In addition, the phase of ongoing oscillations predicts detection of a threshold stimulus for oscillations in the infra-slow (Monto, et al., 2008), alpha (Busch, et al., 2009; Mathewson, et al., 2009) and theta (Busch, et al., 2009) range, and pre-stimulus connectivity between distant sites predicts subsequent performance (Hanslmayr, et al., 2007; Hipp, Engel, & Siegel, 2011; Ploner, Lee, Wiech, Bingel, & Tracey, 2010). Within the extremely slow frequency range we have studied, spontaneous slow negative cortical shifts in EEG signal (which index greater cortical excitability (Birbaumer, Elbert, Canavan, & Rockstroh, 1990)) predict better detection of threshold stimuli (Devrim, et al., 1999). In fMRI, greater spontaneous BOLD activity predicts detection of threshold stimuli (Boly, et al., 2007; Hesselmann, Kell, & Kleinschmidt, 2008; Scholvinck, et al., 2012).

In all of these previous studies, behavior was related to instantaneous pre-stimulus measures of spontaneous activity. In contrast, we show that the magnitude of endogenous fluctuations in fMRI signals over very long timescales is inversely related to task performance in every topographic cortical area we studied. The fact that the strength of stimulus-related fluctuations did not predict performance in any area suggests that spontaneous changes in endogenous activity may be more important for certain types of perception than the strength of the response to an external stimulus. Various theories of the role of slow endogenous fluctuations in cortical function have been proposed, including self-regulation of cortical excitability to avoid overactivation and insensitivity (Birbaumer, et al., 1990), generation of predictive internal models of the environment (Berkes, Orban, Lengyel, & Fiser, 2011), providing a substrate for top-down expectation signals (Ringach, 2009), and integrating information across wide regions of cortex necessary for consciousness (He & Raichle, 2009). It is possible that slow endogenous fluctuations are important for coordinating neural activity across distant regions of cortex to perform non-perceptual functions but that they also divert resources from performance of specific perceptual tasks and/or interfere with representations of sensory signals.

Conclusion

We show that in addition to increasing the strength of visually-evoked BOLD responses, sustained visual spatial attention reduces the strength of endogenous BOLD fluctuations. This reduction substantially contributes to improved response reliability and behavioral performance in every topographic cortical area we studied. In contrast, attention's effect on visually-evoked BOLD responses contributed to improved response reliability only in early and ventral cortical areas and did not predict behavioral performance in any area. Therefore, our results provide evidence that suppression of endogenous fluctuations in brain activity is important for neural representations and perception of sensory information.

Chapter 4

Introduction

Visual attention allows us to manage the vast amounts of visual input that constantly bombards our eyes. In the spatial domain, visual target detection is improved at attended locations and impaired at unattended locations (Bashinski & Bacharach, 1980; Posner, et al., 1980). Attention can also counteract the reduction in target detection performance caused by visual noise surrounding the target (Lu, et al., 2002; Zenger, et al., 2000). Physiologically, these effects are mirrored by an increase in activity in portions of visual cortex that represent the attended location (Gandhi, et al., 1999; Kastner, et al., 1999) and a suppression of neural activity in cortex that represents unattended locations (Muller & Kleinschmidt, 2004; Silver, et al., 2007).

However, visual processing varies widely across the visual field. Spatial resolution, contrast sensitivity, detection speed, and detection accuracy are significantly worse for peripheral compared to central vision (Carrasco, Ptalgar, & Cameron, 2001). In contrast, temporal processing is better (Hartmann, Lachenmayr, & Brettel, 1979) and surround suppression is stronger (Xing & Heeger, 2000) for peripheral compared to central vision. These psychophysical effects are mirrored by differences in cortical representation for central and peripheral visual field locations. The receptive field size of visual cortical neurons scales with eccentricity, and the amount of visual cortex representing each degree of visual angle decreases approximately linearly with eccentricity (Carrasco, 2011). Although appropriately scaling the size of visual stimuli for peripheral locations eliminates some eccentricity-dependent psychophysical effects, many of these effects remain (Kitterle, 1986).

Surprisingly, despite large differences in visual processing between central and peripheral vision, few studies have reported eccentricity-dependent effects of spatial attention. Performance on visual search tasks is worse for peripheral compared to central vision, but appropriate scaling of stimulus size eliminates this difference (Carrasco & Frieder, 1997). Exogenous attention improves performance on a texture segmentation task at far eccentricities and worsens it at near eccentricities, but this eccentricity dependence can be accounted for by a decrease in neuronal receptive field size across all eccentricities (Yeshurun & Carrasco, 1998, 2000). Specifically, reduced receptive field size impairs performance at near eccentricities where spatial filters were already too narrow to optimally perform the task, but it improves performance at far eccentricities where spatial filters were too broad. In addition, endogenous attention improves texture segmentation performance at all eccentricities (Yeshurun, Montagna, & Carrasco, 2008). In tasks that benefit from improved spatial resolution at all eccentricities, there is evidence that attention enhances performance more for larger than smaller eccentricities (Carrasco, Williams, & Yeshurun, 2002).

One way that attention could sharpen spatial resolution is by contracting neuronal receptive fields around the attended object. Numerous studies have shown that when multiple visual stimuli fall within a neuron's receptive field, the receptive field shrinks (Luck, et al., 1997; Moran & Desimone, 1985) and moves towards the attended stimulus (Womelsdorf, Anton-Erxleben, et al., 2006). Functional MRI results are compatible with shrinking of receptive fields by spatial attention (Fischer & Whitney, 2009; Kastner, et al., 1999)). In V1, receptive fields are typically too small to allow single-unit measures of these phenomena, as it is difficult to fit multiple stimuli within a single receptive field. However, a recent study reported the effects of attention on length tuning of individual V1 neurons, a 1-D measure of receptive field size, and

found that directing spatial attention to a stimulus reduces optimal stimulus length at near eccentricities and increases it at far eccentricities (Roberts, et al., 2007).

In this study, we analyzed the effects of visual spatial attention the amplitude and spatial extent (an indirect measure of spatial resolution) of visual responses in many topographically-organized cortical areas in human occipital and parietal cortex. We found that the effects of attention on these measures were eccentricity-dependent and differed across cortical areas. Early visual areas showed greater attentional enhancement of response amplitude at near compared to far eccentricities, possibly highlighting the importance of resolving fine detail of an attended object at fixation. Visual regions involved in the dorsal visual stream (dorsal occipital, temporal-occipital, and parietal cortical areas) showed greater attentional enhancement of spatial resolution at far compared to near eccentricities, perhaps reflecting the importance of detecting behaviorally relevant objects in the periphery for planning of motor responses. Finally, ventral regions showed attentional effects consistent with a role in integrating bottom-up visual input with top-down feedback.

Materials and Methods

Subjects

Nine healthy subjects (2 males, 7 females) participated in the study, all of whom had extensive experience as participants in psychophysical and fMRI experiments. One subject (F.C.F.) was also an author of the study. All participants provided written informed consent, and the experimental protocol was approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley. Each subject participated in one session to acquire high-resolution whole-brain anatomical MRI images and in one retinotopic mapping fMRI session. Prior to the retinotopic mapping session, each subject practiced the target detection task for a total of two hours in a behavioral testing room, allowing subject performance to reach asymptotic levels. In addition, behavioral data from the practice sessions were used to determine the target sizes for each subject that resulted in equivalent performance across eccentricities in the fMRI experiment.

Visual stimuli and task

Stimuli were presented using an LCD projector (Avotec, Stuart, FL). A circular grid was visible on the screen at all times during fMRI scanning (Figure 1). The grid was divided into 12 wedges, each of which subtended 30 degrees, and 6 rings, each of which was 3 degrees of visual angle wide, for a total of 72 patches. The 6 rings were centered at eccentricities of 0.5-3, 3-6, 6-9, 9-12, 12-15, and 15-18 degrees of visual angle. A fixation point with radius of 0.2 degrees of visual angle was located at the center of the grid.

At any point in time, each patch was either ON (containing colored checks that flickered at 5 Hz) or OFF (isoluminant gray). For each trial, one patch in the left visual field and one patch in the right visual hemifield were ON, and the rest of the patches were OFF. Stimulus contrast was always at least 65%. The actual luminance values varied slightly, as checks were randomly assigned either dark or light colors (Figure 1), with the constraint that no check could be either white or black (Swisher, et al., 2007). The size of the checks in the pattern was scaled according to the cortical magnification factor in human V1 (Slotnick, et al., 2001). The checkerboard pattern was presented only in patches within the four inner rings, for a total of 48 patch locations

(2 visual hemifields x 6 angles x 4 eccentricities) that were visually stimulated over the course of each scan.

The beginning of each scan started with 3 seconds (1 TR) of blank screen, followed by 9 seconds during which only the grid was visible on the screen. For each of the following 192 TRs (576 seconds), the checkerboard pattern appeared in two patch locations (one in the left and one in the right visual field). Each scan ended with 18 seconds during which only the grid was visible on the screen, for a total of 606 seconds (202 TRs) per run. A given patch contained a visual stimulus once every 72 seconds on average, for a total of 8 stimulus presentations for each run. A pseudo-random sequence of ON and OFF states for each patch was used to minimize temporal correlations between spatial patterns of visual stimulation. At the beginning of each 'activation' TR, the fixation point briefly increased luminance for 100 ms to remind subjects to maintain central fixation. After an additional 300 ms (during which only the grid was visible on the screen), the checkerboard pattern was presented in two patch locations for 2600 ms.

On a given run, subjects were instructed to detect targets in either the left or right visual field while maintaining fixation at a central point. The target was a briefly presented (200 ms) gray annular segment of zero contrast with mean luminance equal to the mean luminance of the checkerboard stimulus. The target appeared with 50% probability within each ON patch and could appear either towards the left or right side of the patch with an onset 400-2400 ms after the onset of the patch. To equate sensory stimulation in the attend-left and attend-right conditions, contrast decrement targets were presented in both attention conditions (although the temporal sequence of presentation in the left and right visual hemifields were independent and were based on a 50% probability of presentation for each patch activation). Subjects immediately pressed a button when they detected the target in the attended visual field.

If necessary, the sizes of the targets were adjusted during the fMRI experiments to maintain approximately equivalent performance for each of the eccentricity rings. The attend-left and attend-right runs always occurred in sequential pairs, and any changes to the target sizes were applied to both runs in the pair. In addition, the sequence of patch activation was identical for a given pair of scans, so that identical visual stimuli were shown for attend-left and attend-right conditions. Thus, the only difference between the two attention conditions was the side of the stimulus that subjects attended. Five subjects attended to the left visual field during the first scan, and the remaining four subjects attended to the right visual field during the first scan. Eye movements were not recorded during the fMRI experiments. However, all participants were highly trained in maintaining fixation through participation in numerous prior psychophysical experiments.

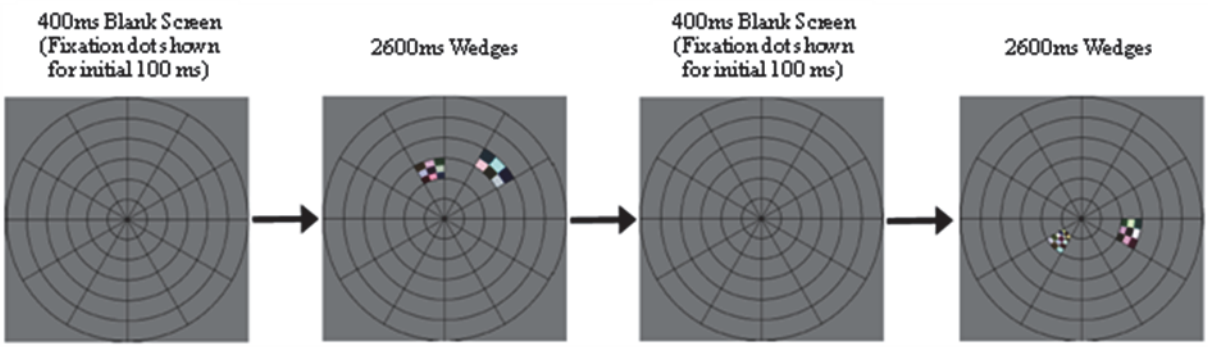

Figure 14: **Trial Sequence.** Subjects maintained fixation while viewing a grid of 72 patches. During each 3000ms trial, a contrast-reversing colorful checkerboard pattern appeared in one patch on the left side of the grid and in one patch on the right side of the grid. Subjects attended to the patches on the right or left side on alternating runs, and attempted to detect low-contrast annular-segment targets presented within the stimulated patch by pressing a button.

fMRI data acquisition

Functional MRI experiments were conducted with a 3 Tesla Siemens Trio MR scanner. A transmit/receive surface radiofrequency coil was used to maximize contrast-to-noise ratio in posterior cortex. Functional echo-planar images were acquired using a gradient-echo EPI sequence. The field of view was 200 x 200 mm, and the matrix size was 78 x 78, resulting in an inplane voxel resolution of 2.6 x 2.6 mm. The repetition time (TR) was 3000 ms, and the echo time (TE) was 24 ms. 27 slices were prescribed with an interslice gap of 0.25 mm and a slice thickness of 2.5 mm. The slices were angled between the coronal and axial planes to provide coverage of occipital and posterior parietal cortex. A set of T1-weighted anatomical images that were coplanar with the EPI images was acquired at the beginning of every imaging session.

fMRI data preprocessing

Each run lasted 606 s (202 TRs), and each subject completed either 8 or 10 runs. Head movements were corrected offline using a 3D image registration algorithm (MCFLIRT; (Jenkinson, et al., 2002)). Each run was classified as attend-left or attend-right. The time series from each run were concatenated across runs of a given attention condition, so that a voxel's concatenated time series for a given attention condition was either 808 TRs (4 runs) or 1010 TRs (5 runs) long. Each of these two concatenated time series for each voxel was divided by its mean intensity to convert the data from arbitrary units to percent signal modulation and to compensate for the decrease in mean image intensity as a function of distance from the surface coil. Finally, both time series were high-pass filtered above 0.014 Hz in each voxel.

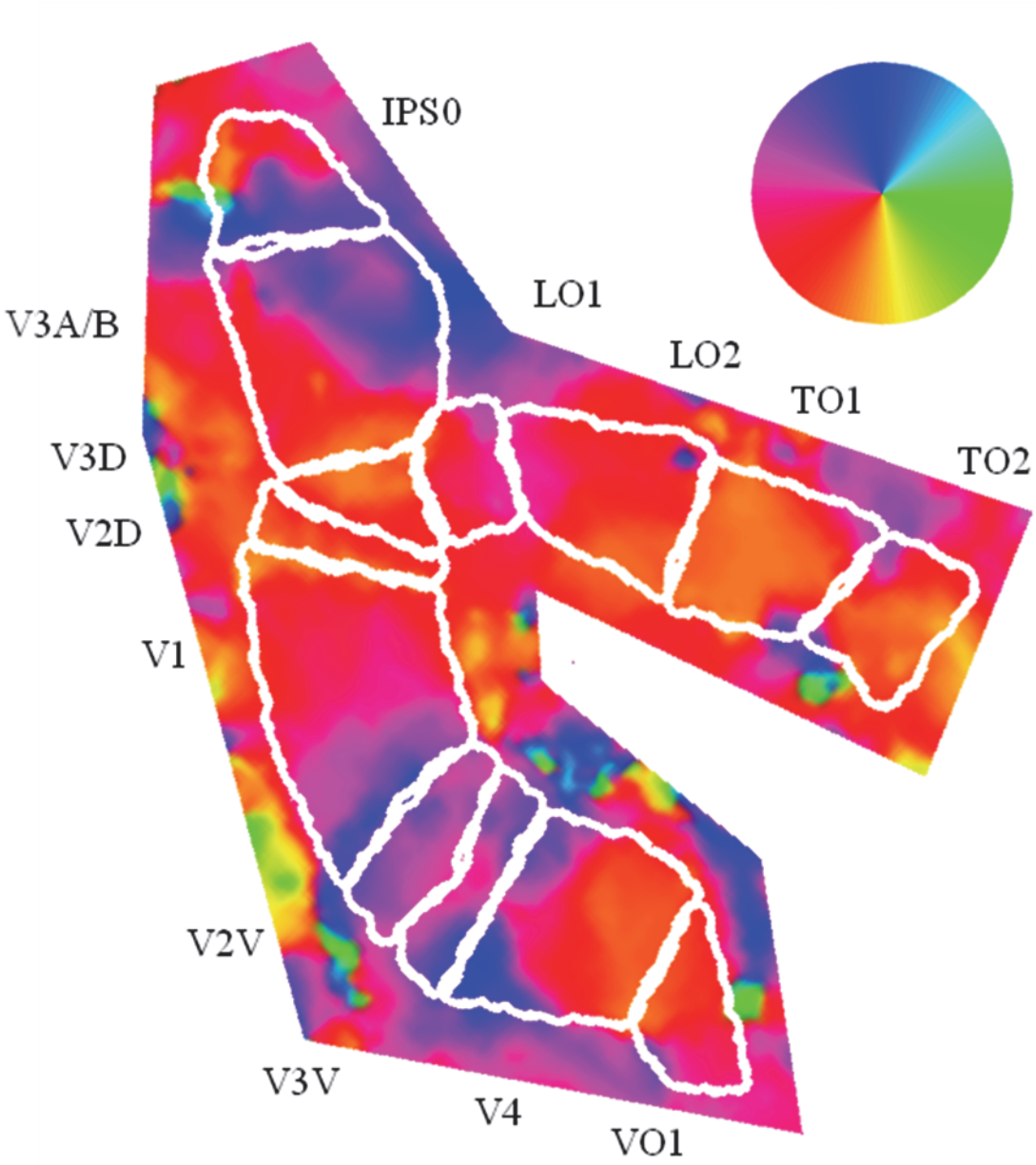

Figure 15: **Visual field representations of response angle.** For each voxel, an equal number of attend-left and attend-right time series were averaged together. Using reverse correlation, a spatial profile of the portions of the visual field that produced a significant positive response in the voxel was determined. The center of this positive response profile was transformed into polar coordinates to determine the angle and eccentricity in visual space to which the voxel was most sensitive. The color wheel indicates the one-to-one mapping between a cortical location and the angular component of the visual field location. In this computationally-flattened patch of right occipital and parietal cortex (Subject #4), each topographic area represents the contralateral visual field.

Estimation of visual fMRI responses for each patch location

To determine the locations and boundaries of topographically-organized cortical areas, we averaged the BOLD response at each voxel across the attend-left and attend-right conditions (the sequence of visual stimulation was identical for these two conditions). For each voxel, we used reverse correlation to estimate its BOLD response to visual stimulation at each patch location (Hansen, David, & Gallant, 2004). The kernel BOLD response, h(τ), is the cross-correlation of a particular voxel's fMRI time-series data R(t) and the time-offset stimulus sequence at a particular patch S(t-τ):

$$h(\tau) = \frac{1}{\sigma_S^2 T}\sum_{t=1}^{T} R(t)(S(t-\tau) - \bar{S}$$

Here, t is time (in units of TR), $\sigma_S^2 T$ is the variance of the stimulus sequence, T is the total number of TRs, τ is the time lag between the stimulus and the hemodynamic response, S takes values of either 1 (stimulus-ON) or 0 (stimulus-OFF), and $\bar{S}$ is the mean value of the stimulus sequence. h(τ) is in units of % change in BOLD signal (same units as R(t)). The response of a voxel to a given patch was defined as the average of the kernel response between 3 and 6 s after stimulus onset. We chose this temporal lag window (associated with the rise and peak of the estimated hemodynamic responses) because we observed that it resulted in more consistent responses across voxels than other lag windows.

For each voxel, we performed permutation testing to identify the stimulus locations that evoked a significant positive or negative response at the voxel. The sequence of each patch's ON and OFF stimulus time series was randomized, and we computed the cross-correlation between this randomized sequence of stimulus presentation and the voxel's fMRI time series. This procedure was repeated 500 times for each voxel and each patch's stimulus time series, and the significance threshold for a positive response was defined as the response amplitude greater than 95% of the values produced by this randomization procedure. Similarly, we defined the significance threshold for a negative response as the response value less than 95% of the response values produced by the randomization procedure. The resulting spatial layout of patch locations that generated a significant positive or negative response in a given voxel is the spatial response profile for that voxel.

We next computed the center of the positive spatial response profile for each voxel (in polar visual field coordinates) to determine the location in visual space to which each voxel was most responsive. For each voxel, the angle value of the response to each patch was calculated by generating a vector with an angle equal to that of the patch location in visual space and a length scaled by the strength of the response generated by that patch. The length of vectors for patches that fell below the positive significance threshold was set to zero. This resulted in 48 vectors per patch, and the center of the spatial response profile for each voxel was defined as the angle of the sum of these vectors. A similar procedure was used to compute the eccentricity of the center of the positive response spatial profile. We first scaled the eccentricity of each patch by its positive response amplitude (setting the response amplitude of nonsignificant patches to zero), then summed these scaled values across all 48 locations, then divided by the sum of all significant response amplitudes. The resulting weighted-average eccentricity value assigned to each voxel was a continuous variable bounded by the center of the most foveal patch location (1.5 degrees) and the center of the most peripheral patch location (10.5 degrees) in the stimulus array.

We used the angle and eccentricity values computed from the average of the attend-left and attend-right time series to define visual field boundaries for early (V1, V2, V3), ventral (hV4,

VO1), lateral occipital (LO1, LO2), temporal occipital (TO1/TO2), and dorsal (V3A/B, IPS0) cortical areas. The boundaries of VO2 and of posterior parietal topographic areas beyond IPS0 were not clearly defined in many hemispheres, so we have excluded these areas from our analyses. For all further analyses, we only considered those voxels that represented contralateral visual space (for example, voxels in left hemisphere that represent locations in the right visual field).

For every stimulus patch, there were some runs during which spatial attention was focused on the patch and other runs in which spatial attention was directed to the opposite hemifield. For each voxel, we computed an "attended" spatial response profile (based on responses to patches when they were attended) as well as an "unattended" response profile (based on responses to patches when they were unattended). For each attention condition, we next used the positive response profile to compute three quantities for each voxel: 1) response size, 2) response spread, and 3) response amplitude. To determine response size, we summed the total area (in squared degrees of visual angle) of the patches that evoked a significant positive response in the voxel. Response spread was defined as the average distance (in degrees of visual angle) for all pairwise combinations of these patches, and response amplitude corresponded to the mean evoked response across these patches. We also computed these three values for the negative response profile for each voxel. Attentional modulation (attended – unattended) was then calculated for each of these values. However, in order to measure effects of attention on response amplitude that were independent of attentional modulation of spatial extent, the patch locations used to compute response amplitude were those that evoked significant positive (or negative) responses in the average of the attend-left and attend-right time series.

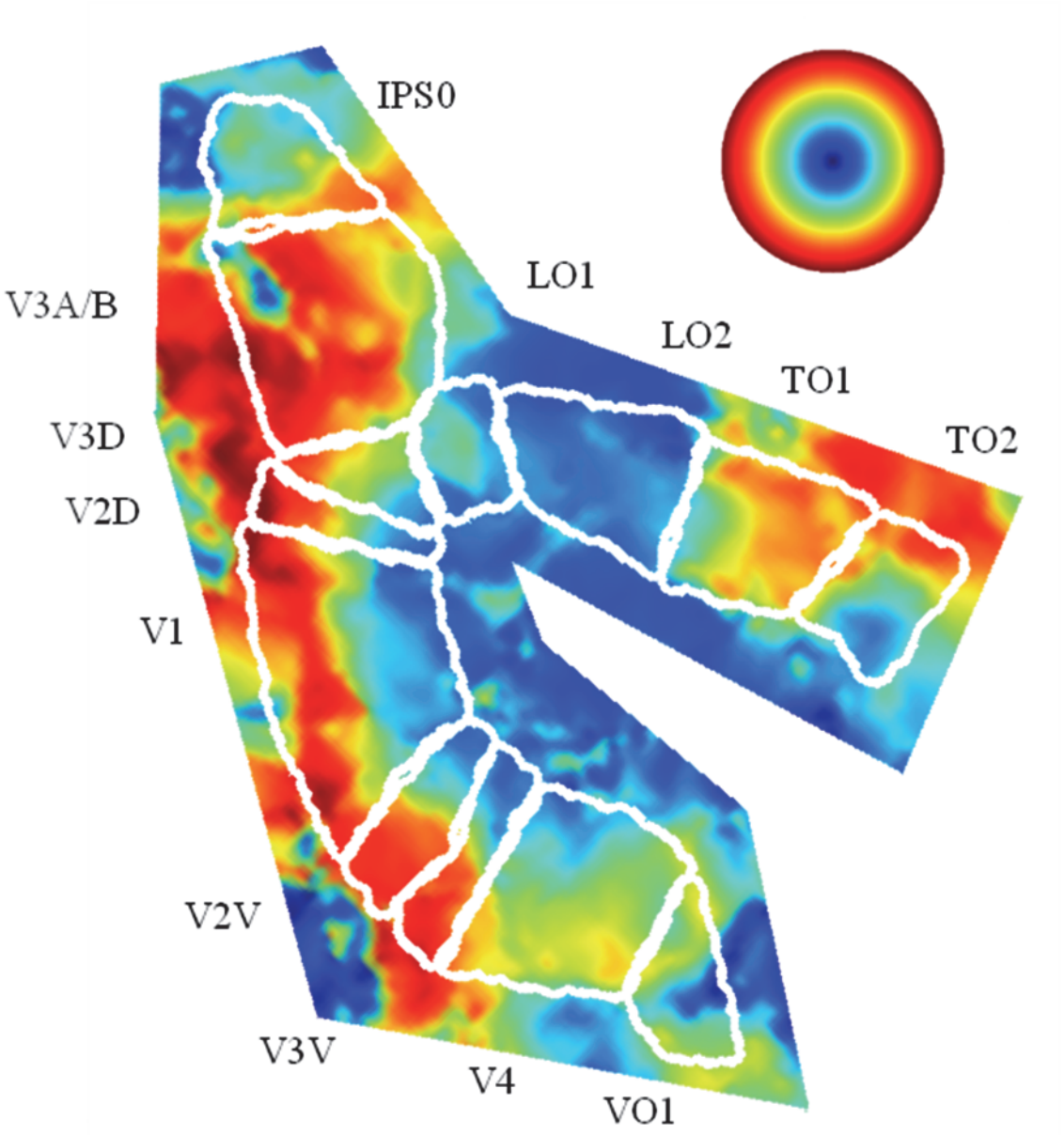

Figure 16: **Visual field representations of response eccentricity.** For each voxel, an equal number of attend-left and attend-right time series were averaged together. Using reverse correlation, a spatial profile of the portions of the visual field that produced a significant positive response in the voxel was determined. The center of this positive response profile was transformed into polar coordinates to determine the angle and eccentricity in visual space to which the voxel was most sensitive. The color wheel indicates the one-to-one mapping between a cortical location and the eccentricity component of the visual field location. In this computationally-flattened patch of right occipital and parietal cortex (Subject #4), each topographic area represents the contralateral visual field.

Results

Behavioral results

Subjects maintained fixation while checkerboard stimuli were simultaneously presented within single patches in the left and right sides of a stimulus array. Gray targets were unpredictably presented in the stimulated patches, and subjects were instructed on alternating runs to detect the targets within the patch in either the left (attend-left condition) or right (attend-right condition) visual field. Target sizes were selected to produce equivalent (approximately 70% correct) behavioral performance for targets at each eccentricity.

There was no significant group difference in overall performance (% targets correctly detected) for the attend-left and attend-right conditions ($p=0.14$, two-tailed paired t-test, $n=9$ subjects). In addition, there was no significant group difference in performance between attend-left and attend-right conditions at any eccentricity band (0.5-3 degrees: $p=0.19$; 3-6 degrees: $p=0.28$; 6-9 degrees: $p=0.10$; 9-12 degrees: $p=0.85$, two-tailed paired t-test, $n=9$ subjects). The fact that performance was equivalent for attend-left and attend-right conditions controls for a number of possible confounds, including differences in fMRI responses due to task difficulty, attentional effort, and/or arousal. Although there was significant variance in performance across eccentricity (mean performance for each eccentricity band=[59%, 75%, 65%, 73%], $F(3,6)=4.85$, one-way analysis of variance, $df=3$, $n=9$ subjects), performance averaged across the two most foveal eccentricity bands was not significantly different than performance averaged across the two most peripheral eccentricity bands ($p=0.55$, paired two-tailed t-test, $n=9$ subjects), suggesting that there was no overall difference in task difficulty for more central and more peripheral eccentricities.

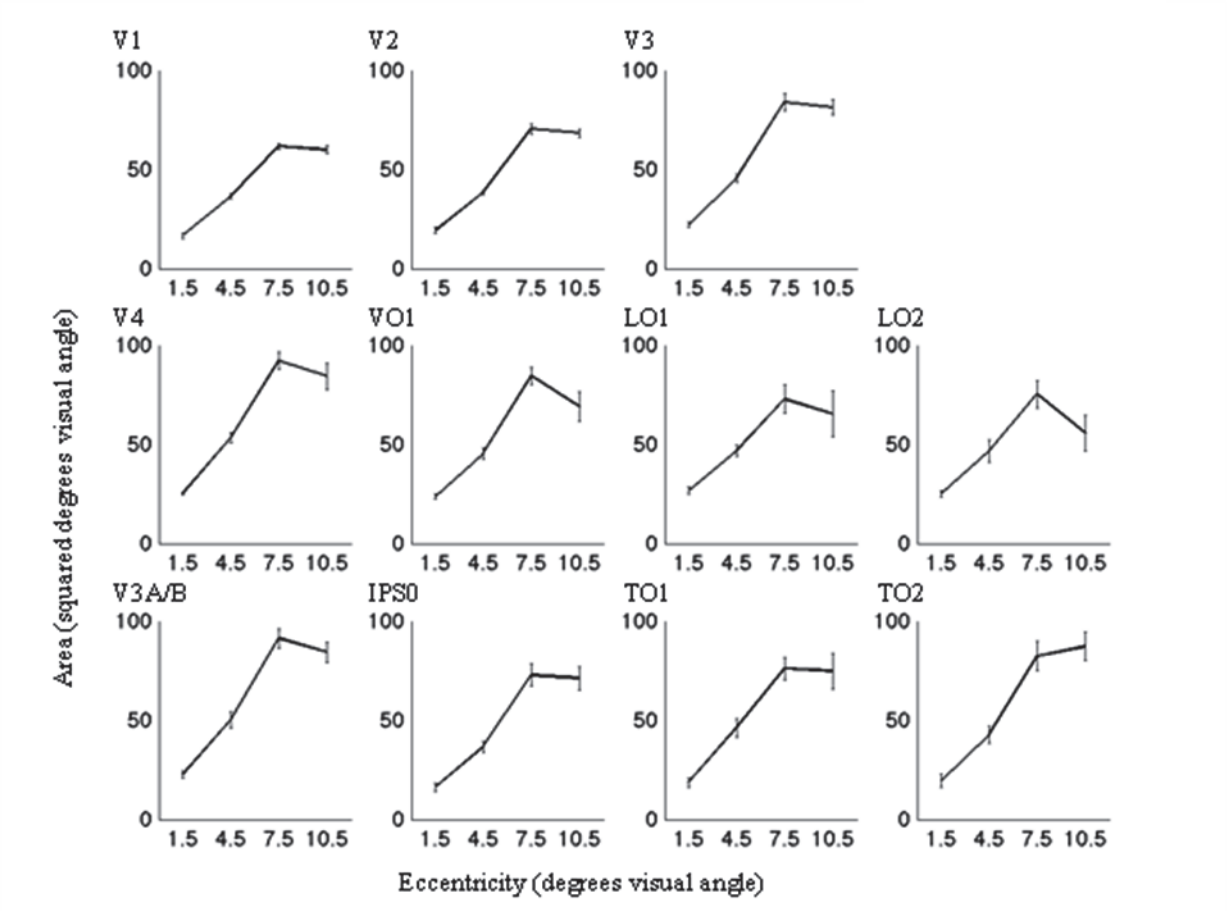

Figure 17: **Summed area of positive response profile.** The total area (in squared degrees of visual angle) of all patches that evoked a significant positive response in a given voxel increases as a function of eccentricity.

Retinotopic mapping

For each voxel, we determined the spatial profile of positive fMRI responses to visual stimulation at all patch locations across the visual field. The center of the positive response profile (in visual field coordinates; based on the average of attend-left and attend-right conditions) was computed for each voxel and used to generate angle (Figure 2) and eccentricity (Figure 3) maps of visual field locations. Based on these maps, we defined the boundaries of topographically-organized areas V1, V2, V3, hV4, VO1, TO1, TO2, V3A/B, IPS0, LO1, and LO2 in both hemispheres in each subject. We also measured the total area (in squared degrees of visual angle) of all patches that evoked a significant positive response in a given voxel. This measure of response size increased with eccentricity in all studied cortical areas except LO1 (i.e. slope greater than zero; $p<0.05$, two-tailed t-test, n=9 subjects) (Figure 4).

Spatial attention increases positive and negative response amplitudes in an eccentricity-dependent manner

For each voxel in each cortical area, we calculated the average response amplitude separately for unattended and attended response profiles. Positive responses were averaged

across all patch locations that evoked a significant positive response in the averaged time series, and negative responses were averaged across all patch locations evoking a significant negative response. Attending to a given location increased overall positive response amplitude for each region except IPS0 (Figure 5A; $p<0.05$, two-tailed t-test, n=9 subjects, FDR-corrected for multiple comparisons). However, the magnitude of attentional enhancement of positive response amplitude strongly varied as a function of eccentricity and cortical area. We quantified these effects by fitting a linear function to the plot of attentional modulation versus eccentricity in each cortical area and each subject. In early visual cortical areas (V1, V2, V3), attention enhanced response amplitude more for near than for far eccentricities (i.e., slope of linear fit was significantly less than zero; $p<0.05$, two-tailed t-test, n=9 subjects, FDR-corrected) (Figure 6A). This same general pattern was evident in ventral and lateral occipital areas but only reached significance in hV4, LO1, andLO2 ($p<0.05$, two-tailed t-test, n=9 subjects, FDR-corrected). In contrast, attention tended to enhance response strength more for far than for near eccentricities in dorsal regions; this pattern reached significance only in TO2 (i.e., slope of linear fit was significantly greater than zero; $p<0.05$, two-tailed t-test, n=9 subjects, FDR-corrected).

Attention also enhanced the amplitude of the negative fMRI response (made the response more negative) in all cortical areas ($p<0.05$, two-tailed t-test, n=9 subjects, FDR-corrected) (Figure 7A). The eccentricity dependence of attention modulation of negative fMRI responses was less consistent and more variable than the effects of attention on positive fMRI response amplitude. In early, ventral and lateral occipital areas, eccentricity tended to show greater effects of attention for near than far eccentricities; however, this pattern was only significant in V3 (i.e., slope of the linear fit was significantly more than zero; $p<0.05$, two-tailed t-test, n=9 subjects, FDR-corrected) (Figure 8A). No clear relationship between attentional modulation of negative fMRI response amplitude and eccentricity was observed in dorsal and temporal occipital areas.

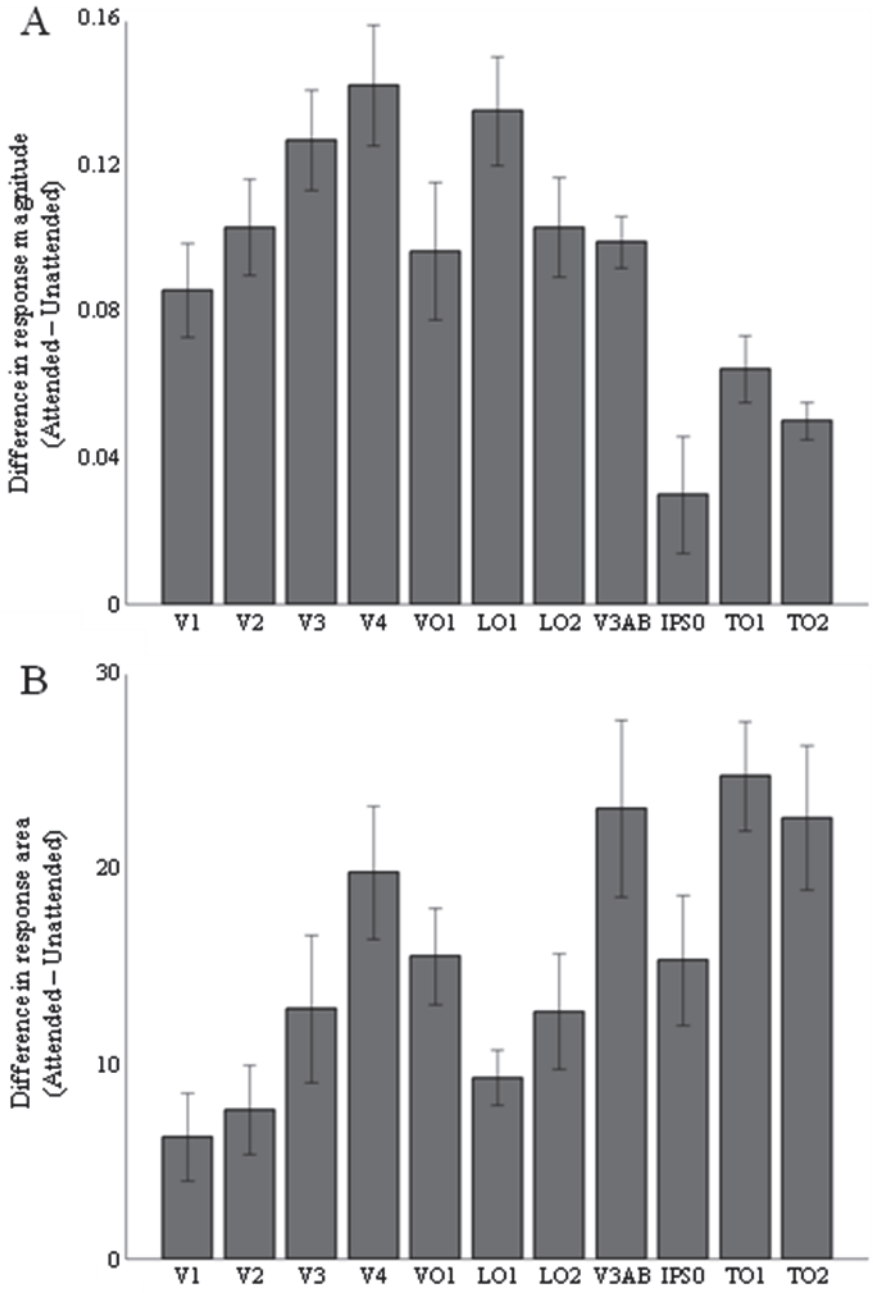

Figure 18: **Attention-induced changes in positive response amplitude and area.** Attending to the visual stimulus significantly increases the amplitude (percent BOLD modulation) of the positive visual response in every measured topographically-organized area except IPS0 (A), and significantly increases the area (squared degrees of visual angle) of visual space that positively activates a given voxel (B).

Attention affects spatial extent of positive and negative responses as a function of eccentricity

For each voxel in each cortical area, we calculated the area (squared degrees of visual angle) of visual space that evoked a significant positive response. The response area was computed separately for attended and unattended conditions. In all regions, attention significantly expanded the region of visual space that positively activated a given cortical

location ($p<0.05$, two-tailed t-test, n=9 subjects, FDR-corrected) (Figure 5B). This expansion was greater for far eccentricities compared to near eccentricities for ventral cortical areas hV4 and VO1, lateral occipital area LO2, dorsal regions (V3A/B, IPS0), and temporal-occipital regions (TO1, TO2) (i.e., slope was significantly positive; $p<0.05$, two-tailed t-test, n=9 subjects, FDR-corrected) (Figure 6B). In all other regions, the attentional expansion did not differ across eccentricities. For each subject, we compared the strength of attention's effect on positive response magnitude in a given area to its effect on the spatial extent of the response profile, and found no significant correlation ($p>0.05$, two-tailed t-test, n=9 subjects) between the strength of the attention-induced amplitude increase and the strength of the spatial extent expansion (Figure 9).

For each voxel, we also calculated the area of visual space that evoked a significant negative response in attended and unattended conditions (Figure 7B). In every region, attention expanded the portion of the visual field that induced a negative response ($p<0.05$, two-tailed t-test, n=9 subjects, FDR-corrected). Moreover, in every region except for IPS0 and TO1 this effect was stronger for near compared to far eccentricities (i.e., slope was significantly negative; $p<0.05$, two-tailed t-test, n=9 subjects, FDR-corrected) (Figure 8B).

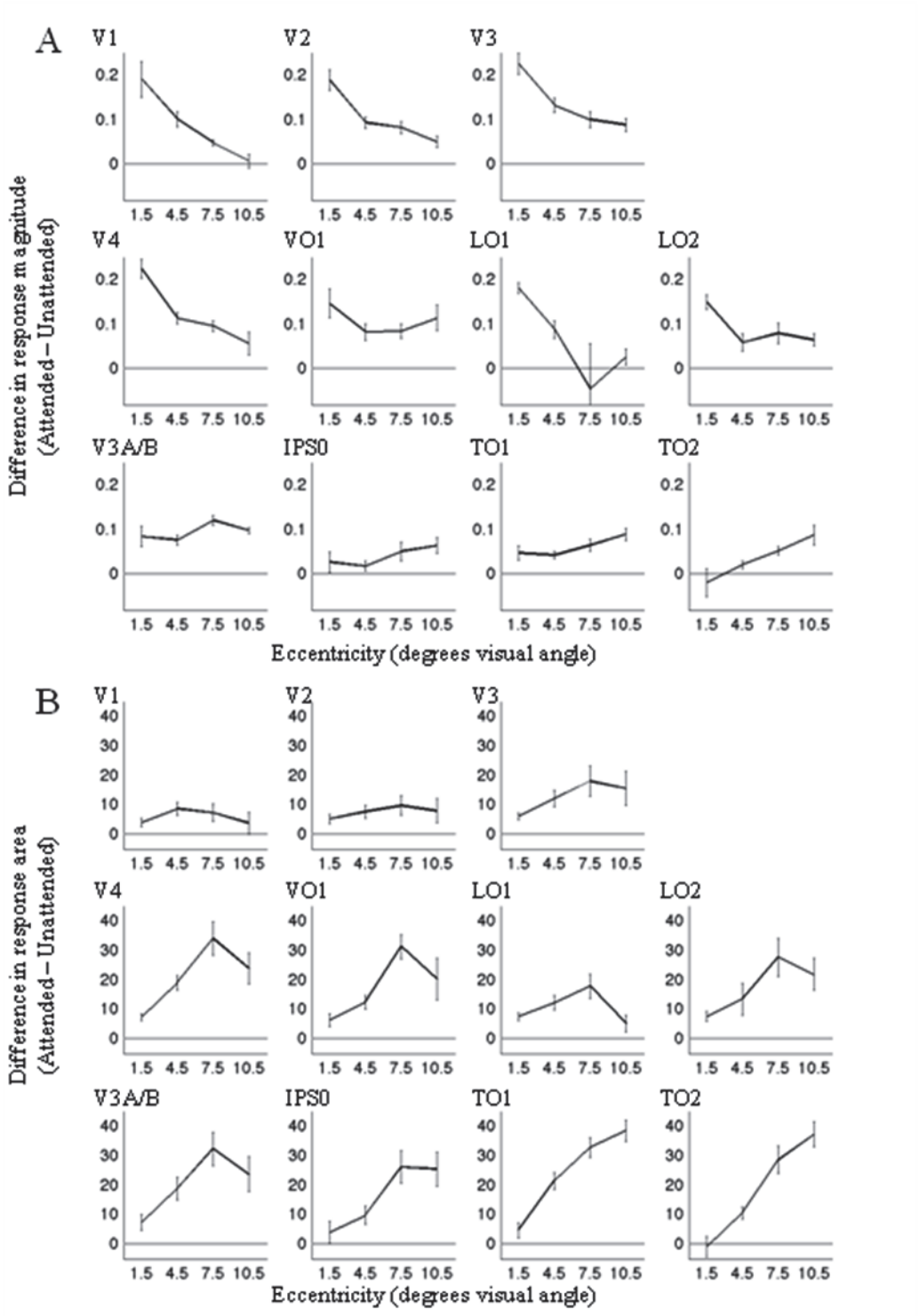

Figure 19: **Eccentricity modulation of attention-induced changes in positive response amplitude and area.** Attention's effect on response amplitude (percent BOLD modulation) is greater for near compared to far eccentricities in V1, V2, V3, V4, LO1, and LO2, and greater for far compared to near eccentricities in TO2 (A). Attention's effect on response area was greater for far compared to near eccentricities for V4, VO1, LO2, V3A/B, IPS0, TO1, and TO2 (B).

Discussion

Effects of attention on strength and spatial extent of responses to visual stimuli

In our experiment, we found that attention enhanced positive response strength in every visual cortical region that we identified. This matches several studies showing that spatial attention typically increases the amplitude of visual cortical responses to attended stimuli. This has been shown with single-unit (McAdams & Maunsell, 1999) and LFP (Chalk, et al.) recordings and with fMRI (Buracas & Boynton, 2007; Murray, 2008). Previous studies have revealed differences across visual areas in the strength of attentional modulation. For example, attention increases the response of individual neurons in extrastriate areas but not in V1 (Luck, et al., 1997), although BOLD studies show a robust attentional enhancement in V1 (Buracas & Boynton, 2007; Murray, 2008). In general, the influence of spatial attention (compared to passive visual stimulation) progressively increases from early visual areas to higher dorsal areas (Serences & Yantis, 2006; Silver, et al., 2005). There is also ample evidence of stronger attentional modulation for ventral visual cortical areas compared to earlier visual areas (Brefczynski & DeYoe, 1999; Hansen, et al., 2007; Kastner, et al., 1999; Serences & Yantis, 2007).

We also found that in each visual area attention increased the total area of visual space that evoked a significant positive response in a given voxel. The most direct analog of this measure in single-unit electrophysiology studies is the excitatory receptive field size of visual cortical neurons. Estimates from fMRI recordings of the extent of visual space that positively activates a given voxel (the "population receptive field", or PRF) are proportional to corresponding estimates of receptive field sizes of individual neurons (Dumoulin & Wandell, 2008). However, PRF sizes are systematically larger than receptive field sizes of corresponding individual neurons. This is presumably due to the fact that the PRF is a measure of the aggregate receptive fields of the neurons within a voxel and therefore reflects both neuronal RF size and the spatial scatter of RF locations of individual neurons in a given voxel. Nevertheless, BOLD PRF sizes are consistent with those estimated from macaque LFP recordings (Victor, Purpura, Katz, & Mao, 1994), and the relative PRF sizes across eccentricities and across visual areas closely matches known relative differences in receptive field sizes from neurophysiological recordings (Dumoulin & Wandell, 2008).

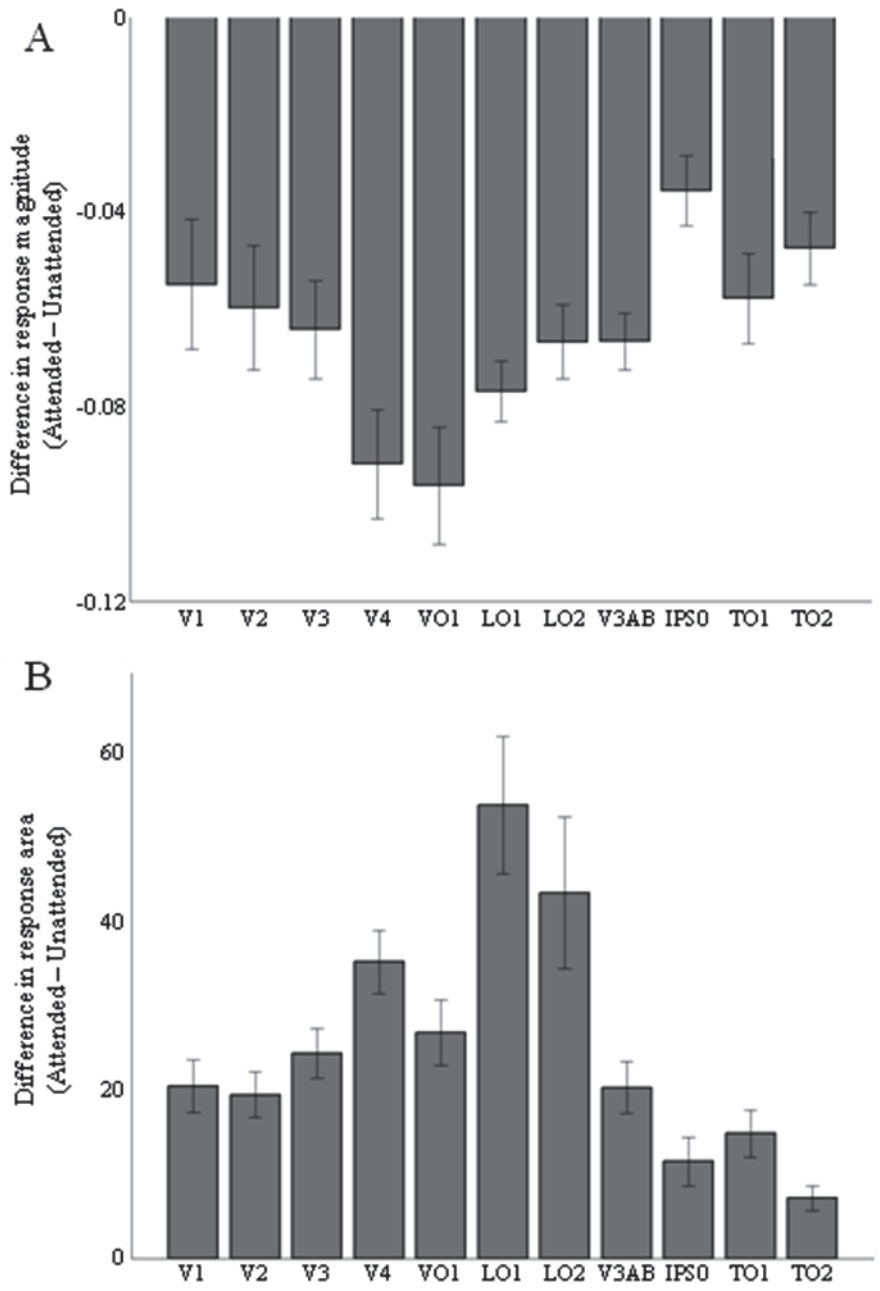

Figure 20: **Attention-induced changes in negative response amplitude and area.** Attending to the visual stimulus significantly decreases the amplitude (percent BOLD modulation) of the negative visual response in every measured topographically-organized area (A), and significantly increases the area (squared degrees of visual angle) of visual space that negatively activates a given voxel (B).

In our experiment, we also found that attention enhanced negative response strength and widened the total area of visual space that negatively activated each voxel. Visual stimulation at a given location will increase neural activity at some cortical locations and decreases it at other cortical locations (Shmuel, Augath, Oeltermann, & Logothetis, 2006). Likewise, a given visual neuron will increase firing to visual stimulation at some visual locations and decrease firing for

stimulation at other locations (Womelsdorf, Anton-Erxleben, et al., 2006; Womelsdorf, Anton-Erxleben, & Treue, 2008). The "negative BOLD" response likely reflects this cortical decrease in neural firing rates (Bressler, Spotswood, & Whitney, 2007; Shmuel, et al., 2006) rather than "stealing" of hemodynamic resources by nearby positively activated cortex. In early visual cortex, negative BOLD reliably occurs surrounding positive BOLD activity in response to presentation of visual stimuli (Silver, Shenhav, & D'Esposito, 2008) and may therefore reflect center-surround organization of visual cortical neuronal RFs (Zuiderbaan, Harvey, & Dumoulin). In addition, negative BOLD responses contain precise information about the spatial locations of visual stimuli (Bressler, et al., 2007). Sustained spatial attention, even in the absence of visual stimulation, also induces retinotopically precise negative BOLD activity in cortical locations that represent unattended visual space (Silver, et al., 2007). Progressing up the visual hierarchy from V1 to hV4, the size of the region of enhancement and of the suppressive surround increases, and the distance of the suppressive surround from the locus of enhancement also increases (possibly reflecting larger receptive fields) (Muller & Kleinschmidt, 2004; Slotnick & Yantis, 2003).

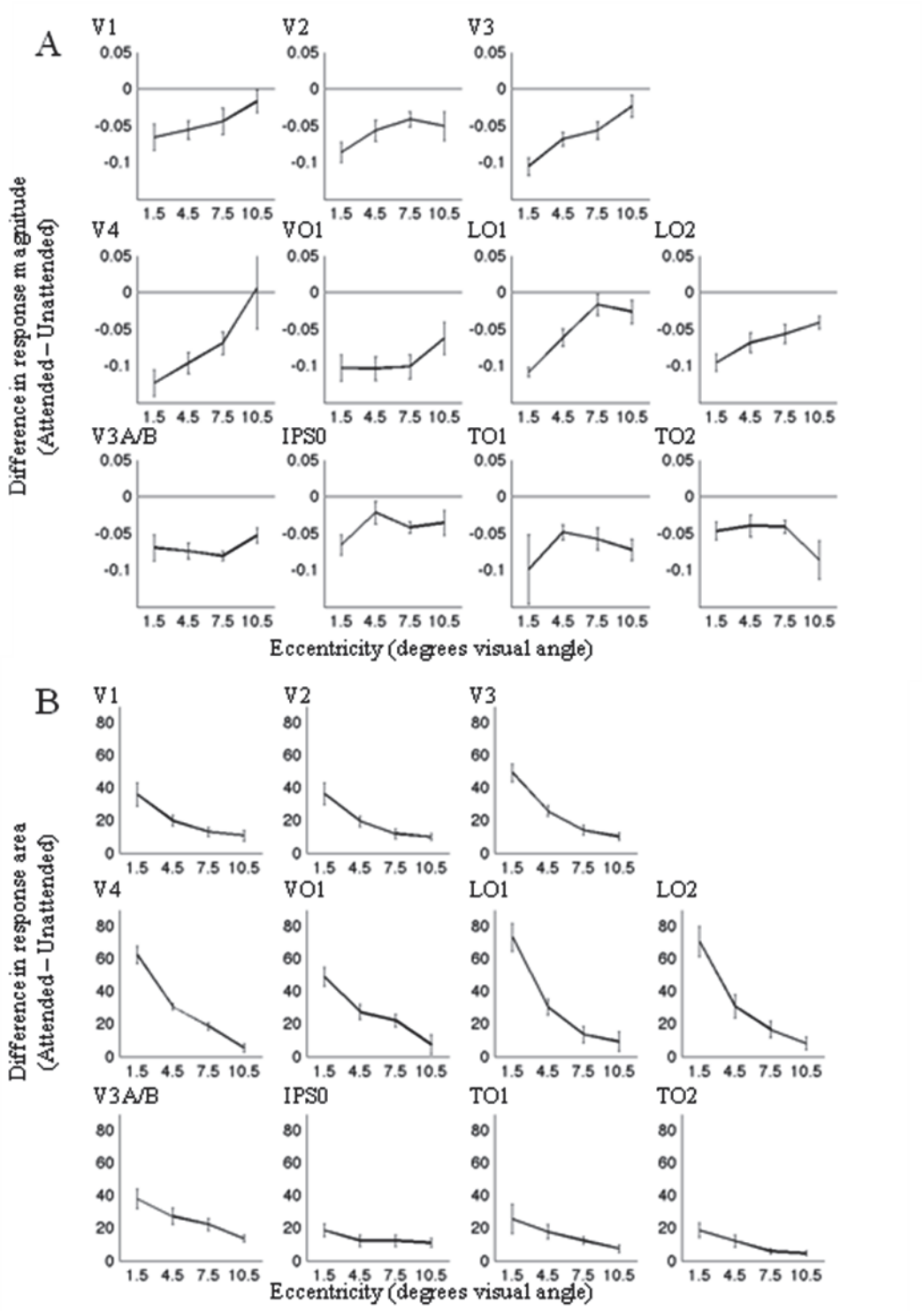

Figure 21: **Eccentricity modulation of attention-induced changes in negative response amplitude and area.** Attention's effect on negative response amplitude (percent BOLD modulation) is greater for near compared to far eccentricities in V3 (A). Attention's effect on negative response area was greater for near compared to far eccentricities in every topographically-organized region except IPS0 and TO1 (B).

Numerous studies have shown that attention can change the shape and location of a neuron's receptive field and its suppressive surround region. Attending to a location outside the receptive field can shift the receptive field center towards the attended location (Connor, Preddie, Gallant, & Van Essen, 1997; Womelsdorf, Anton-Erxleben, et al., 2006; Womelsdorf, et al., 2008), even if the attended location is in the opposite hemifield. In addition, attention can shift a receptive field's suppressive surround region towards the attended location, so that both excitatory gain and surround suppression are stronger near the attended location (Womelsdorf, et al., 2008). Directing attention inside a receptive field moderately shrinks the receptive field size (Anton-Erxleben, Stephan, & Treue, 2009; Womelsdorf, Anton-Erxleben, et al., 2006; Womelsdorf, et al., 2008) when using single small stimuli, but directing attention immediately outside a receptive field can expand it (Anton-Erxleben, et al., 2009).

What neural changes could underlie an increase in the area of visual space that positively activates a given voxel? The most straightforward explanation is that the size of the underlying receptive fields expanded, but other mechanisms are possible. For instance, it is possible that the response of a voxel's neurons to an unattended surround location is positive, but too small to be significantly detected. In this case, attention could increase the gain of the response enough for there to be adequate signal to noise, changing the response from insignificant to significant. If this was the case, there should be a strong relationship between attention's effect on the magnitude and extent of the positive response profile. We found there was no significant correlation between these attention effects across areas, so changes in response magnitude cannot fully explain changes in the width of activation. However, for negative responses these effects were strongly correlated, so attention's effects on the strength of the suppressive response may partially explain the change in its spatial extent. Another possibility is that a neuron's receptive field and surrounding summation area may be located outside the surround location in the unattended condition, but shift into the location in the attended condition (Womelsdorf, Anton-Erxleben, et al., 2006). This possibility also holds true for the negative response profile; the surround suppressive area of a voxel's neurons may have spatially shifted into the stimulated region due to attention, which has been demonstrated for MT neurons (Anton-Erxleben, et al., 2009).

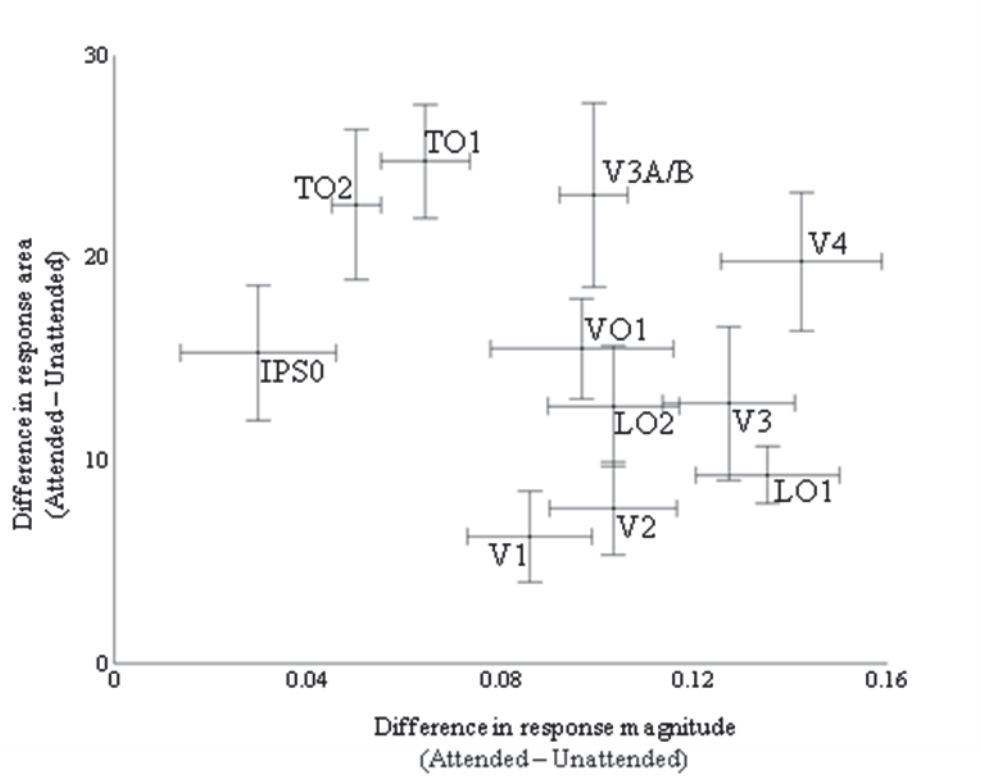

Figure 22: **Relationship between attention effects on positive response magnitude and area.** Plotting attention-induced enhancement of visual response magnitude versus attention-induced expansion of response area. Across visual regions, there was no correlation between these effects.

Attention's effects as function of eccentricity

To our knowledge, only one previous experiment has studied the effects of attention on neural responses as a function of eccentricity. Roberts (Roberts, Delicato, Herrero, Gieselmann, & Thiele, 2007) measured the optimal stimulus length for individual V1 neurons at near (2-3 degrees) and far (6-7 degrees) eccentricities. In addition to increasing response amplitude for all neurons, attention reduced optimal stimulus length for near eccentricities but increased it for far eccentricities. In addition, attention increased the strength (but not size) of the inhibitory surround for far but not near eccentricities. However, since the inhibition area extended beyond the maximal stimulus size tested, it is possible that there are additional attention effects that were not detected in this study.

We found that eccentricity modulated attention's effects on the strength and spatial profile of the BOLD response to a visual stimulus and that this modulation differed across cortical areas. First, in nearly every cortical region we studied, attention enhanced the area of visual space that negatively activated cortex. This effect was more pronounced for voxels that represented central visual locations than for voxels representing the periphery. Suppression of signals from a wider region of visual space (with either a decrease or no change in the extent of positively-activating space) means that more cortical locations reduce their spontaneous neural firing, and therefore there is less "noise" in the response to a visual stimulus. . This expansion of the width of the suppressive region was significantly modulated by eccentricity in most regions, whereas in almost every region the change in suppressive strength was not significantly

modulated by eccentricity. These results suggest that attention enhances perception across the entire visual field by enhancing the strength of suppression, but particularly enhances central vision by suppressing inputs from a larger portion of surrounding cortex.

In early visual cortex, receptive field sizes within the eccentricities stimulated in the current experiment are relatively small, facilitating perception of fine spatial resolution. In these areas, attention enhanced both positive and negative response strength more for near than far eccentricities. Moreover, attention increased the area that exhibited a negative fMRI response in early visual cortical voxels more for near than for far eccentricities. Increasing the gain of both the central excitatory response and the surrounding inhibitory response increases the 'contrast' between the attended location and surrounding distracters (Anton-Erxleben, et al., 2009; Cutzu & Tsotsos, 2003). Therefore, our results show that in early visual cortex, attention enhances response amplitude and spatial resolution the most in visual field locations where perceptual spatial resolution is the finest (near eccentricities). Where perceptual resolution is poor (far eccentricities), attention has smaller effects in early visual cortex.

In our experiment, the effects of attention were similar in temporal-occipital (TO1, TO2) and dorsal (V3A, IPSO) areas. Human TO1 and TO2 are thought to be the homologue of monkey MT (Amano, Wandell, & Dumoulin, 2009), which is an important node in the dorsal visual stream that brings spatial information to the parietal lobe (Rizzolatti & Matelli, 2003), and at rest is strongly correlated with the dorsal visual attention network (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). In the in dorsal-stream regions we measured in our experiment, attention enhanced positive response strength and spatial response area more for far than near eccentricities. Dorsal regions are important for identifying spatial locations as targets for subsequent shifts in voluntary attention and eye position (Corbetta & Shulman, 2002). Therefore, the larger effects of attention that we observed for peripheral representations may underlie the dorsal attention system's ability to accurately shift voluntary attention. In addition, the expansion of the positive response profile for peripheral representations may promote more effective detection of behaviorally relevant peripheral objects that can then be brought into foveal vision for detailed analysis.

Finally, ventral regions exhibited attention-induced increases in positive response amplitude more for near than far eccentricities, but expanded positive response profile more for far than near eccentricities. Therefore, attentional effects in ventral regions are similar to those of early visual areas for near eccentricities but resemble those of dorsal areas at far eccentricities. This functional pattern matches anatomical connectivity; only foveal hV4 receives direct input from V1 (Nakamura, Gattass, Desimone, & Ungerleider, 1993), whereas peripheral hV4 receives feedback from dorsal areas (Baizer, et al., 1991). Moreover, it has been suggested that the primary function of hV4 is to integrate bottom-up input (from early areas) and top-down feedback (from dorsal areas), to allow selective extraction of behaviorally relevant features or spatial locations (Roe, et al., 2012). For example, for ventral visual cortical neurons representing the fovea, attention may primarily enhance the strength of feedforward visual input and thereby allow successful extraction of complex forms from the visual scene. For peripheral ventral neurons, attention may primarily enhance top-down feedback from dorsal regions, allowing accurate selection of a spatial location. The pattern of results in lateral occipital regions was very similar to those in ventral regions: attention enhanced positive response amplitude more for near than far eccentricities, but expanded positive response profile more for far than near eccentricities. These results are consistent with other functional similarities between ventral and

lateral occipital regions, such as their involvement in representation of complex shape (Roe, et al., 2012). Future studies should further explore differences between these regions in eccentricity-dependent attention modulations.

It is important to point out a significant methodological difference between our study and others that have studied attention's effects on receptive field location and size. Many previous studies direct attention to a specific spatial location and then map out a cell's receptive field by recording the cell's response to unattended visual stimuli presented at numerous locations across the visual field (Anton-Erxleben, et al., 2009; Connor, Gallant, Preddie, & Van Essen, 1996; Connor, et al., 1997; Womelsdorf, et al., 2008). This procedure is then repeated with attention directed to another visual location (usually inside versus outside the receptive field). In contrast, our study compares attended and unattended responses to visual stimulation at many locations across the visual field.

This distinction implies that our experimental design is not optimal to detect shrinkage in receptive field size. Whereas previous studies measured receptive field size when surround stimulation was unattended, our study measures spatial response profiles when the surround was attended. It is possible that the receptive fields of neurons in a given voxel shifted towards the surround locations when they were stimulated and attended, resulting in an apparent expansion of the PRF. This may explain why in our study the region of visual space that positively activated a voxel mostly expanded with attention, whereas most previous studies have described a shrinkage of receptive field size with attention (Anton-Erxleben, et al., 2009; Womelsdorf, et al., 2008). Second, the influence of surround stimulation may be enhanced when it is attended (Sundberg, Mitchell, & Reynolds, 2009), so our experiment potentially activates stronger surround suppressive influences than previous studies. Thus, whereas other experiments study changes in receptive fields (computed from unattended visual stimulation) due to shifts in spatial attention, our experiment mainly studies the effects of surround stimulation when it is attended versus when it is not.

Conclusion

We have shown that attentional modulation of both the strength and extent of fMRI responses to visual stimuli is strongly dependent on eccentricity. In addition, these types of attentional modulation differ significantly across cortical areas. These findings provide neural correlates for behavioral results showing that visual perception is fundamentally different for foveal and peripheral vision. Moreover, our results provide new evidence for functional distinctions between the ventral and dorsal attention systems and suggest possible mechanisms underlying these functional differences.

Chapter 5

Visual spatial attention induces substantial changes to the brain's response to visual stimulation. In the second chapter, we demonstrated that attention improves the reliability of retinotopically-organized representations of visual stimuli in every cortical region we measured. In chapter three, we demonstrated that this improvement resulted not only from an increase in the strength of the neural response evoked by the attended stimulus but also from a suppression of the strength of very slow fluctuations in BOLD activity unrelated to the visual stimulation. Moreover, it was the magnitude of this suppression, rather than the enhancement of response strength, that predicted subjects' performance on a detection task. In the fourth chapter, we showed that among early, ventral, and dorsal regions, attention has significantly different effects on response strength and the spatial resolution of cortical responses.

These projects show that attention improves cortical processing at all levels of the visual hierarchy. Chapter 2 shows that attention enhanced response signal-to-noise in every visual region we measured. This enhancement of response reliability was the greatest in lateral-occipital and intra-parietal cortical regions, where retinotopic mapping is most difficult to detect. These findings suggest attentional enhancement of response reliability is cortically widespread, more so than even the attentional enhancement of response strength (which chapters 3 and 4 showed was not detectable in dorsal and lateral occipital regions).

However, there are a number of different mechanisms through which attention could enhance perception, and our experiments showed that these mechanisms differed across visual areas. One way that attention could enhance response reliability is by increasing the strength of the BOLD response to visual stimulation. In chapter 3, we showed that attention does in fact increase the strength of fluctuations in BOLD activity at the frequency of visual stimulation. This effect was strongest in ventral regions, robust in early visual areas, and weakest in dorsal and lateral occipital regions. Notice, however, that an increase in strength of fluctuation at the stimulus frequency could result from a stronger positive response to the attended stimulus (a higher peak), as well as a stronger suppression when the attended stimulus was elsewhere (a lower trough).

The third experiment helped to disentangle these possibilities. This analysis showed that in ventral cortical regions, attention both strongly enhanced the response when the visual stimulation was at a voxel's preferred spatial location and strongly suppressed the response to visual stimuli at other spatial locations. Early visual areas showed a strong attentional enhancement of the positive response but a relatively weak suppression of the negative BOLD response. In contrast, dorsal areas showed little to no attentional enhancement of positive response, but a moderate suppression of negative BOLD responses. Therefore, the differences between regions in BOLD fluctuation strength at the stimulus frequency likely resulted from differences across areas in attentional effects on positive and negative BOLD responses.

In addition to changes in positive and negative BOLD response strength due to attention, we discovered a new mechanism: attention enhances response reliability by suppressing endogenous BOLD fluctuations at slow frequencies unrelated to the visual stimulation. This effect was also very cortically widespread; it was significant in every visual region we were able to define. Nevertheless, the effect was strongest in dorsal and lateral-occipital regions, of moderate strength in early regions, and weakest (but still significant) in ventral visual regions. This effect of attention may improve perception by making neural representations more closely

match visual inputs over time; indeed, performance on a visual detection task was predicted by the strength of this effect.

Finally, visual attention can improve perception by changing the extent of visual space to which a given cortical location responds. For example, perception of fine detail could be improved by shrinking the visual region that a cortical location responds to. On the other hand, detection of salient peripheral visual objects could be enhanced by expanding the visual region that a cortical location responds to. In chapter 4, we found the former effect in early visual areas and the latter effect in dorsal visual areas.

In sum, we found that spatial attention improved visual representations in the brain and that this improvement was widespread across many cortical areas. In all regions, attentional enhancement of neural representations was supported by a suppression of non-stimulus BOLD fluctuations, which caused changes in neural activity over time to more closely match the sequence of visual stimulation. In most but not all regions, attention also enhanced the strength of positive and negative BOLD responses, so that the magnitude of changes in neural activity due to visual stimulation was also larger. Finally, the effects of attention on the extent of visual space that activated a cortical location varied across the visual field and across visual regions, suggesting specific functional roles for different visual regions.

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