Top–down flow of visual spatial attention signals from parietal to occipital cortex

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Given the complexity of our visual environment, the ability to selectively attend to certain locations, while ignoring others, is crucial for reducing the amount of visual information to manageable levels and for optimizing behavioral performance. Sustained allocation of spatial attention causes persistent increases in functional magnetic resonance imaging (fMRI) signals in portions of early visual cortex that retinotopically represent the attended location, even in the absence of a visual stimulus. Here we test the hypothesis that topographically organized posterior parietal cortical areas IPS1 and IPS2 transmit top–down spatial attention signals to early visual cortex. We employed fMRI and coherency analysis to measure functional connectivity among cortical areas V1, V2, V3, V3A, V3B, V7, IPS1, and IPS2 during sustained visual spatial attention. Attention increased the magnitude of coherency for many pairs of areas in occipital and parietal cortex. Additionally, attention-related activity in IPS1 and IPS2 led activity in several visual cortical areas by a few hundred milliseconds. These results are consistent with transmission of top–down spatial attention signals from IPS1 and IPS2 to early visual cortex.

Keywords: attention, top–down, fMRI, visual cortex, occipital cortex, parietal cortex

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Introduction

In humans, allocation of attention to a portion of the visual field increases accuracy and decreases reaction time for detecting targets within the attended region (Bashinski & Bacharach, 1980; Posner, Snyder, & Davidson, 1980). Neural correlates of this enhancement of perception by attention have been described in human visual cortex using fMRI (Pessoa, Kastner, & Ungerleider, 2003) as well as in animals using electrophysiological measures (Reynolds & Chelazzi, 2004). We have previously shown that sustained attention to a location in the visual field causes persistent increases in fMRI responses in human early visual cortex in the absence of visual stimulation (Silver, Ress, & Heeger, 2007). These attention signals are restricted to the portions of visual cortex that represent the attended visual field locations (Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Silver et al., 2007).

Previous electrophysiological (Colby & Goldberg, 1999), neuropsychological (Mesulam, 1999), and neuroimaging (Corbetta & Shulman, 2002) studies have demonstrated the importance of parietal cortex in the control of visual spatial attention. In particular, IPS1 and IPS2 are cortical areas in human intraparietal sulcus that, like early visual cortical areas, contain topographic maps of visual spatial attention signals (Silver, Ress, & Heeger, 2005). However, unlike early visual cortex, IPS1 and IPS2 respond poorly to passive viewing of visual stimuli (Silver et al., 2005). The fact that attention signals are organized into visual field maps in IPS1 and IPS2 raises the possibility that these areas transmit spatially specific top–down attention signals to early visual cortex.

To test this possibility, we employed fMRI and coherency analysis (Sun, Miller, & D'Esposito, 2004, 2005) to measure functional connectivity among IPS1, IPS2, and six retinotopic visual cortical areas during sustained visual spatial attention. Coherency analysis generates values for magnitude, corresponding to the strength of coupling

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between two time series, and phase, corresponding to the temporal latency difference between the two time series. We compared coherency measures from two conditions to characterize functional connectivity specifically associated with top–down spatial attention. The baseline condition was sustained fixation in the absence of visual stimulation and explicit attentional demands. Coherency magnitude and phase values during fixation reflect anatomical connectivity, differences in neurovascular coupling between areas, and other aspects of connectivity not directly related to attention. The second condition was a period of sustained visual spatial attention in the absence of visual stimulation. A measure of attention-specific functional connectivity was derived by subtracting coherency magnitude and phase values during fixation from those during sustained attention.

Analysis of coherency magnitudes revealed that sustained attention was accompanied by increased coupling for many pairs of parietal and occipital cortical areas. Coherency phase values were used to determine which areas led or lagged other areas and demonstrated that attention-related activity in IPS1 and IPS2 led activity in several occipital cortical areas by a few hundred milliseconds. This finding is evidence for a top–down flow of attention signals from IPS1 and IPS2 to early visual cortex. These results are the first steps in developing a "circuit diagram" of functional connectivity that describes the flow of top–down visual spatial attention signals in human parietal and occipital topographic cortical areas.

Methods

Subjects

Four healthy subjects participated in the study, all of whom had extensive experience as subjects in psychophysical and fMRI experiments. All subjects provided written consent, and the experiments were carried out in compliance with safety guidelines for MR research. The experimental protocol was approved by the human subjects institutional review board of Stanford University.

Visual detection task

This task has been previously described (Silver et al., 2007) and will only be summarized here. The visual target was a plaid annulus with inner diameter 1.5 and outer diameter 4.5 degrees of visual angle (Figure 1). The spatial frequency of the component gratings was 1 cycle/deg, and the target was presented for 250 ms. The target contrast was smoothly ramped on and off (contrast modulated by one half cycle of a 2-Hz temporal sinusoid). The target contrast varied across subjects and corresponded to individual detection thresholds as determined by behavioral testing before fMRI scanning commenced.

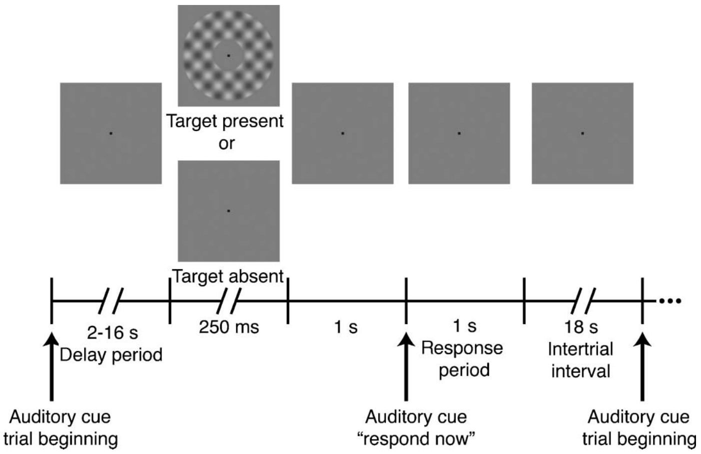

Figure 1. Sustained visual attention task. Each trial began with an auditory cue followed by a delay period of variable duration. On half of the trials, a threshold-contrast target was shown at the end of the delay period. A second auditory cue instructed the subjects to respond whether they had seen the target. Each trial was followed by a long fixation period.

Each trial began with a brief auditory stimulus, followed by a variable (2–16 seconds) delay period. On approximately half of the trials, selected randomly, the target was presented at the end of the delay period, and the screen remained uniform gray for the remaining trials. A second auditory stimulus instructed the subject to report whether the target had been presented or not. A 1-second interval was inserted between the detection period and the response period to allow any visual iconic memory or visual aftereffects of target presentation to dissipate. Subjects were required to maintain attention during the entire delay period to correctly detect the target, and they could not simply report their current perceptual state when prompted to generate a behavioral response. Each trial was followed by a long (18 seconds) intertrial interval. Subjects were instructed to simply fixate during the intertrial interval, and there were no explicit demands on attention during this time. The stimulus protocol was written in MATLAB (The MathWorks, Inc., Natick, MA) using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997). A 0.125-deg square fixation point was presented continuously to encourage stable eye position.

Experimental sessions typically included 10 approximately 5-minute runs, corresponding to a total of about 70 trials of the sustained attention task per subject, collected with a sampling rate (TR) of 1.5 seconds. The time series for each voxel was high-pass filtered with a cutoff frequency corresponding approximately to the longest interval between trial onsets (35 seconds, or 0.03 Hz). Finally, each voxel's time series was divided by its mean intensity to convert the data from arbitrary image intensity units to percent signal modulation and to compensate for the decrease in mean image intensity as a function of distance from the radio frequency coil.

Although eye position was not monitored in the present study, all of the subjects in this study also participated in another study involving covert attention in which eye position was measured during fMRI scanning (Silver et al., 2005). In that study, subjects were cued to attend to a single peripheral location, and they performed a visual detection task at that location. Under these conditions, subjects showed only a very slight bias in eye position towards the cued location (Silver et al., 2005). The present study, by comparison, cued subjects to attend to an annulus surrounding the fixation point, making it much easier for subjects to maintain fixation.

Defining regions of interest (ROIs)

The boundaries of visual areas V1, V2, V3, V3A, V3B, and V7 were defined using well-established retinotopic mapping methods (Engel et al., 1994). A visual localizer was then used to retinotopically restrict each visual area. Subjects passively viewed a stimulus annulus that had the same size and shape as the visual target in the sustained attention experiments. The annulus was a checkerboard (100% contrast, 3 cycle/deg, 4-Hz contrast reversal) presented for blocks of 9 seconds in alternation with 9-second blocks of a uniform gray field. Each visual cortical area was restricted to those voxels that exhibited a positive BOLD response to the checkerboard stimulus (for details, see Silver et al., 2007).

A spatial attention mapping task was used to define cortical areas IPS1 and IPS2 in the intraparietal sulcus (Silver et al., 2005). Subjects performed a visual target detection task in which attention was directed to one of a series of peripheral visual field locations. The focus of attention systematically traversed the visual field, generating traveling waves of activity in cortical areas containing topographic maps of spatial attention. The attended locations in the mapping task comprised an annulus that was the same shape and size as the target annulus used in the sustained attention task described in the present study. Therefore, the IPS1 and IPS2 ROIs corresponded to the attended portion of the visual field during the sustained attention task.

Coherency analysis theory

Correlation measures the simultaneous coupling between two time series, while coherency can be thought of as a spectral analog of correlation and is defined as

$$R_{xy}(\nu) = \frac{\langle f_{xy}(\nu)\rangle}{\langle f_x(\nu)\rangle\langle f_y(\nu)\rangle}, \qquad (1)$$

where $\langle f_x(\nu)\rangle$ and $\langle f_y(\nu)\rangle$ are the means of the power spectra of segments of time series x and y at frequency ν (see Coherency calculations section below), and $\langle f_{xy}(\nu)\rangle$ is the mean of the cross spectrum of segments of x and y (Sun et al., 2004). $R_{xy}(\nu)$ is a complex quantity ($a + ib$). In polar coordinates, the absolute value (modulus) is the length of the vector $R_{xy}(\nu)$, $\sqrt{a^2+b^2}$, and this corresponds to the magnitude of coupling between x and y (taking a value between 0 and 1). The complex argument, or polar angle, of $R_{xy}(\nu)$ defines the phase spectrum. Dividing this phase spectrum by a given temporal frequency yields the delay between x and y in units of time (taking positive or negative values, depending on the direction of the delay between the time series). Thus, coherency analysis allows the measurement of both the strength of functional coupling between two time series (magnitude) as well as the direction of signal transmission (phase). A more detailed description of coherency analysis and its application to neural signals can be found in Rosenberg, Amjad, Breeze, Brillinger, and Halliday (1989).

Coherency analysis overcomes a significant problem in interpreting functional connectivity patterns based on correlation-type measurements in the time domain. The hemodynamic response function (HRF) is the transfer function that relates neural activity to the blood oxygenation level-dependent (BOLD) signals measured with fMRI, and the shape of the HRF varies significantly across cortical areas of individual subjects (Handwerker, Ollinger, & D'Esposito, 2004). Because of this, two areas with very similar temporal patterns of neural activity can have substantially different fMRI time courses, resulting in artifactually low levels of correlation. Because coherency magnitudes are computed in the frequency domain and not in the time domain, they are largely unaffected by differences in HRF shape across cortical areas (Sun et al., 2004).

Extracting time series for coherency analysis

For each trial, segments of the fMRI time series corresponding to fixation and to sustained attention (delay period activity) were excised for each ROI. Attention segments began at the onset of sustained attention (beginning of the delay period) and ended at the offset of attention (end of delay period). These excised segments were then concatenated to generate a single sustained attention time series for each subject/ROI combination. Only attention trials with a delay period longer than 3 seconds were used. A fixation time series for each subject and ROI was generated using the same procedures. Each excised fixation segment had the same length as the attention segment excised from the previous delay period. Thus, the fixation and sustained attention concatenated time series had the same total duration, number of trials, and distribution of lengths of excised segments. With a TR of 1.5 seconds, discontinuities resulting from concatenation of time series segments introduce temporal frequencies far outside of the range used for coherency calculations. As a result, performing temporal windowing on the concatenated time series segments was not required, as this procedure would only have reduced power at these higher temporal frequencies. We verified this by applying temporal windowing to the segments and found that this did not alter the results reported here (not shown). The average total length of the concatenated time series was approximately 1500 time points for each subject.

Coherency calculations

Condition-specific coherency was computed using Welch's periodogram-averaging method with a 64-point discrete Fourier transform (DFT) Hanning window (Sun et al., 2004) with 32-point overlap between windows. Coherency was analyzed for frequency bands 0.0625–0.15 Hz. The lower bound of this frequency range was determined by the longest periods of sustained attention (16 seconds) in our task. The upper bound was chosen based on the fact that the frequency content of temporal fluctuations in fMRI brain signals is limited by low-pass filtering by the HRF (Cordes et al., 2001; Sun et al., 2004). Coherency was computed for nine frequency bands centered around 0.0625, 0.0729, 0.0833, 0.0938, 0.1042, 0.1146, 0.125, 0.1354, and 0.1458 Hz.

Coherency phase delays for pairs of cortical areas were converted to units of time by dividing by the frequency for each of the nine bands and then averaging the time delays across the frequency bands. An alternative method for computing temporal delays between areas would be to compute the slope of the coherency phase versus frequency plot (Sun et al., 2005). A delay in time between two areas that is equally present for all measured frequencies will result in a linear relationship between coherency phase and frequency. We decided to convert the phase value for each frequency to units of time and to then average these temporal delays instead of estimating the temporal delay from the slopes of the phase versus frequency plots. Although we did not observe stark differences in attention-related temporal differences in the various frequency bands, if attention-specific temporal relationships were not identical across the large range of frequencies analyzed in this study (0.0625–0.15 Hz), a linear fit of the phase difference versus frequency plots would not be appropriate. For example, spontaneous BOLD signal fluctuations have been reported to be highly synchronized across multiple cortical areas in low-frequency bands (0–0.1 Hz, Cordes et al., 2001; 0.009–0.08 Hz, Fox et al., 2005). If these synchronized fluctuations were similar for fixation and attention in our data, the resulting phase differences would be near zero for these frequency bands. This would result in an increase in the slope of the phase versus frequency plot (overestimating the latency in units of time) and a non-zero *y*-intercept, possibly leading to false positive errors in estimates of attention-specific inter-areal temporal latencies.

In contrast, when computing temporal latency by averaging across frequencies, as we did in the present study, this kind of low-frequency synchronized oscillation would tend to simply reduce the estimate of the temporal delay. That is, the method of averaging time delays across frequency bands is a conservative approach to the problem of heterogeneity of the BOLD signals in different frequency bands. Unlike the slope of the phase versus frequency plot approach, our method is unlikely to generate false positive results in the presence of large-scale low-frequency synchronized oscillations. Nevertheless, we also computed the slopes of the linear fits of the phase versus frequency plots shown in Figure 4 (Supplementary Figure 1). Of the 14 pairs of areas that demonstrated significant negative coherency phase differences (top–down connections), 10 of them had negative phase versus frequency slopes, and the mean of these slopes was significantly less than zero ($p < 0.05$).

The maximum possible temporal differences for any pair of areas were 16 to 6.67 seconds for frequencies 0.0625–0.15 Hz. Most temporal differences between cortical areas in this study were a few hundred milliseconds. However, because phase is a circular variable, these temporal differences could also be on the order of several seconds in the opposite direction. Given that temporal latencies between activity in cortical areas are unlikely to be several seconds long, we defined the direction of temporal difference direction as that corresponding to the smaller delay.

Coherency magnitude and time difference matrices were created by subtracting fixation from sustained attention matrices. This assumes a linear relationship between the functional connectivity underlying attention and fixation. If this relationship were sublinear, our measurements of attention-specific coherency magnitudes and phases (attention coherency − fixation coherency) would underestimate the actual values.

Statistical analysis

Conventional statistical analyses that assume normally distributed data are not appropriate for coherency analysis, since coherency magnitude values are bounded between 0 and 1 and coherency phase values are bounded between $-\pi$ and π radians. We therefore employed a bootstrap procedure (Efron & Tibshirani, 1993) to test whether coherency magnitude and phase differences between attention and fixation were significantly different from zero. For each pairwise combination of cortical areas in each subject, one thousand bootstrap data samples of the coherency magnitude difference values were sampled with replacement over the nine frequency bands. This bootstrap procedure was repeated for phase difference values. Note that this analysis assumes statistical independence of the coherency magnitude and phase values across frequency bands, an assumption that may not be strictly correct. A non-parametric rank test was employed to determine statistical significance of the mean coherency magnitude and phase differences for each pair of cortical areas. For analysis of the average of the four subjects, samples were drawn from data pooled across all subjects and frequency bands. We corrected for multiple comparisons using the false discovery rate (FDR) method (Genovese, Lazar, & Nichols, 2002) with 28 values in each coherency difference matrix, comprising all possible pairwise comparisons between the eight cortical areas. All analysis code was written in MATLAB (The MathWorks, Inc., Natick, MA).

Results

Sustained attention task

Subjects performed a target detection task with a variable-duration delay period (Figure 1). Prior to fMRI scanning, subjects practiced the task extensively so that they became familiar with the size, shape, location, and appearance of the target annulus. Threshold contrasts for target detection were measured for each subject before the first fMRI session (for behavioral data and detailed task description, see Silver et al., 2007). At the beginning of each trial, an auditory cue signaled subjects to begin attending in anticipation of target presentation. This was followed by a 2- to 16-second delay period during which there was no visual stimulation. The target was then presented on 50% of the trials. When it was shown, the target was always presented at the end of the delay period. As a result, subjects had to maintain attention throughout the delay period at the visual field locations corresponding to the target while maintaining fixation at the center of the attended region. Each trial concluded with an 18-second intertrial interval during which the subjects simply fixated the central point. For the remainder of this paper, the delay period segments are referred to as "sustained attention" and the intertrial intervals as "fixation."

We previously reported that attention signals in cortical areas V1, V2, and V3 during performance of this task were sustained for the duration of the delay period (Silver et al., 2007). In the present study, we performed additional analyses of fMRI time series from portions of areas IPS1 and IPS2 that represented attended visual field locations. These analyses indicated that IPS1 and IPS2 also exhibit sustained activity during maintenance of attention in the absence of visual stimulation (Supplementary Figure 2).

Functional connectivity associated with attention

Functional connectivity between pairs of cortical areas depended on the task (sustained attention versus fixation). We employed coherency analysis (Sun et al., 2004, 2005) to measure functional connectivity for every pairwise combination of cortical areas V1, V2, V3, V3A, V3B, V7, IPS1, and IPS2. Coherency was measured both for periods of sustained spatial attention and for periods of fixation without explicit demands on attention. Topographic cortical areas were defined in each subject using a combination of stimulus-based (Engel et al., 1994) and spatial attention (Silver et al., 2005) phase-encoded fMRI mapping procedures. Each area was then restricted to the portion of the visual field map that represented the attended visual field locations.

Initially, segments of the fMRI time series from the fixation period were excised and then concatenated into a single time series for each cortical area. Coherency analysis was then performed on each pairwise combination of these fixation time series for each subject to provide a baseline measure of functional connectivity (Figures 2A and 2D). The magnitude of the resulting coherency described the strength of the coupling between two time series, and the phase corresponded to temporal differences between the time series. The sign of the phase indicated whether a given time series was leading or lagging the time series to which it was being compared. The same procedure was then applied to segments of the fMRI time series from the sustained attention periods (Figures 2B and 2E). Coherency matrices for fixation were subtracted from those for sustained attention, resulting in coherency magnitude and phase differences that were specific to top–down visual spatial attention (Figures 2C and 2F).

In addition to serving as a control for task selectivity, this subtraction procedure eliminated functional connectivity based purely on anatomical connectivity (for example, X projects to Y, so whenever X is active, Y is active). Finally, this method controls for possible differences in the shape or latency of the hemodynamic response function (HRF) across brain areas (Handwerker et al., 2004). The shape of the HRF is believed to be a property of the tissue in a given cortical area and hence unlikely to differ for attention and fixation. Therefore, subtraction of coherency phase measurements associated with fixation from those associated with sustained attention isolated temporal differences specific to attention without contamination from areal differences in HRF shape.

Functional connectivity of top–down spatial attention signals

Coherency magnitude differences were positive for many pairs of occipital and parietal cortical areas, indicating that correlations for these pairs of areas were enhanced during sustained attention relative to fixation. This pattern was observed in three of four subjects (Figure 2C; Figures 3A and 3B). The remaining subject had a large "off response" at the end of the sustained attention period (Jack, Shulman, Snyder, McAvoy, & Corbetta, 2006; Silver et al., 2007). This off response was synchronized across cortical areas and therefore increased coherency magnitude values for the

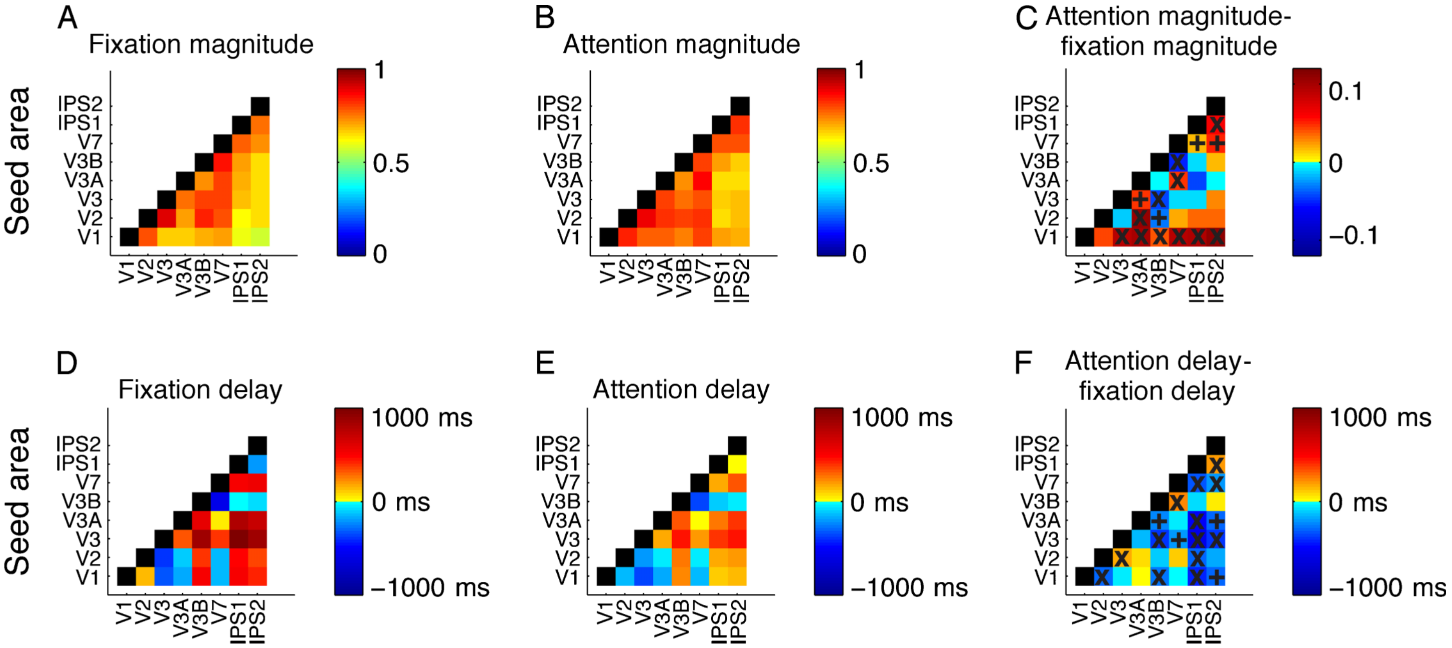

Figure 2. Coherency magnitude and phase matrices for fixation and for sustained attention. Data are shown for Subject 1. Left column, functional connectivity associated with fixation. Middle column, functional connectivity associated with sustained attention. Right column, differences in values between the first two columns, i.e., attention-specific connectivity. Top row, coherency magnitudes. Bottom row, coherency phase values (converted to units of time). Colored squares indicate coherency magnitude (A, B), phase (D, E), or differences in magnitude (C) or phase (F) for each pairwise combination of areas. Positive values (yellow-red) of coherency phase indicate temporal differences consistent with feedforward progression from areas earlier in the visual processing hierarchy to later areas, and negative values (cyan-blue) correspond to top–down signal transmission. The attention-specific delays in panel (F) are mainly negative, suggesting a top–down flow of attention signals for many pairs of cortical areas. x, $p < 0.01$; +, $p < 0.05$ (corrected for multiple comparisons).

subsequent fixation periods, resulting in negative values of attention-specific coherency magnitude differences for this subject (Figure 3C).

Coherency phase differences between IPS1 and IPS2 and visual cortical areas were generally negative, suggesting a top–down flow of information during sustained attention, with IPS1 and IPS2 leading visual cortical areas located earlier in the processing hierarchy (Figure 2F; Figures 3D–3F). In addition to the subject whose data are displayed in Figure 2, complete sets of coherency matrices for fixation and for sustained attention for the remaining subjects are presented as supplementary material (Supplementary Figures 3–5).

For the average of four subjects, attention increased correlations (difference in coherency magnitudes for attention and fixation) for the following pairs of areas: IPS2 and V1, IPS2 and V3, IPS2 and V3A, V7 and V1, and V3A and V1 (Figure 4C). Coherency magnitudes were decreased for attention relative to fixation for IPS1 and V3B and for IPS1 and V7. These coherency magnitude differences undoubtedly represent an underestimate of the effects of attention due to the off-response artifact present in Subject 4 (Figure 3C and Supplementary Figure 5). To examine the effects of attention on coherency magnitudes in the absence of this off-response artifact, we averaged functional connectivity measures for Subjects 1–3, excluding Subject 4. For the average of Subjects 1–3, attention significantly increased coherency magnitude relative to fixation in 13 pairs of cortical areas (including connections between IPS2 and all the other cortical areas) and did not decrease coherency magnitude for any pair of areas (Supplementary Figure 6).

Analysis of coherency phase indicated that for both fixation (Figure 4D) and sustained attention (Figure 4E), activity in early visual cortical areas V1, V2, and V3 led activity in visual cortical areas higher in the processing hierarchy. Because these temporal differences between areas could have resulted from a combination of neural, neurovascular, and/or vascular factors, it is difficult to interpret fMRI latency differences in a single task condition (fixation or sustained attention) in terms of underlying neural activity. However, the difference between coherency phase values for attention and fixation isolates functional connectivity specific to sustained attention. Fifteen pairs of areas exhibited significant differences in coherency phase between sustained attention and fixation (Figure 4F and Table 1). Fourteen of these were negative differences, including 8 of the 12

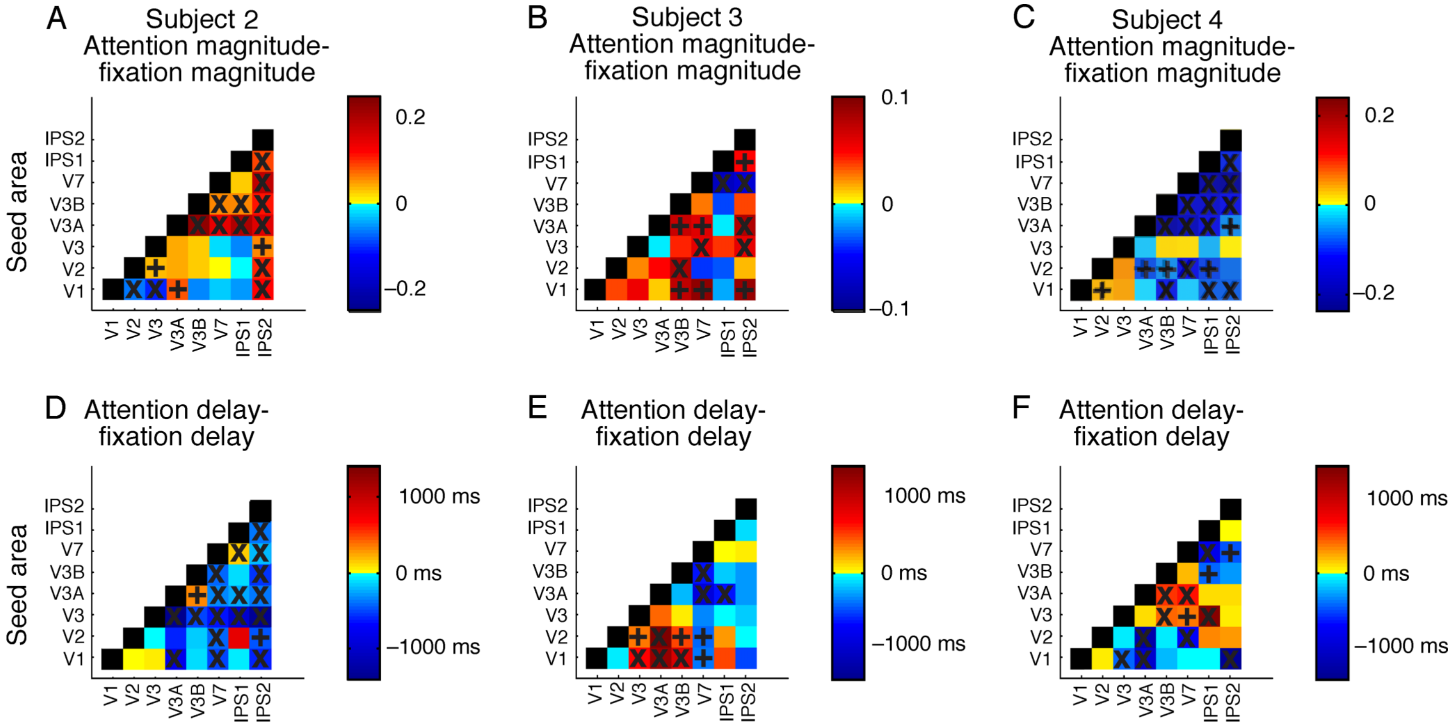

Figure 3. Coherency magnitude (A–C) and phase differences (D–F) between attention and fixation for Subjects 2 (A, D), 3 (B, E), and 4 (C, F). Coherency magnitude differences were generally consistent with attention increasing functional connectivity for Subjects 2 and 3. Attention reduced coherency magnitudes relative to fixation for Subject 4, and this was due to a large synchronized off-response at the end of the sustained attention period (see text for details). x, $p < 0.01$; +, $p < 0.05$ (corrected for multiple comparisons).

connections between parietal (IPS1 and IPS2) and visual cortical areas, consistent with a top–down flow of attention signals from posterior parietal to visual cortex. The mean temporal difference for these 14 pairs of areas was 225 ms, ranging from 87 to 482 ms. Exclusion of the subject with the off-response artifact (Subject 4) had minimal effects on coherency phase differences (compare Figure 4F and Supplementary Figure 6F).

Our procedure of task subtraction removes any source of coupling between fMRI time series in two areas that does not modulate as a function of task condition (fixation versus attention). This increases the likelihood that the task-specific functional connectivity patterns we have observed are related to neural activity. However, there are a number of physiological signals that also exhibit strong fluctuations at the frequencies used in our coherency analysis, including arterial carbon dioxide concentration (Wise, Ide, Poulin, & Tracey, 2004) and changes in respiratory rate (Birn, Diamond, Smith, & Bandettini, 2006).

To directly test whether more global fluctuations could contribute to our results, we conducted coherency analysis for portions of V1, V2, and V3 that contained peripheral visual field representations that were far from the attended region (about 10 degrees eccentricity; Silver et al., 2007). This analysis allowed the comparison of functional connectivity patterns in attended and unattended regions in early visual cortex. Exactly the same procedures were employed for analysis of time series from attended and unattended regions of interest. For peripheral, unattended V1, V2, and V3, coherency magnitudes tended to be higher during fixation than during sustained attention (Supplementary Figure 7), although this difference was statistically significant only for the connection between V1 and V3. This is distinct from the overall pattern of coherency magnitude differences obtained for attended portions of the same areas, in which coherency magnitudes tended to be higher for attention than for fixation (Figure 4C). The fact that different patterns of task-specific connectivity were obtained for attended and unattended portions of the same cortical areas strongly suggests that global fluctuations in physiological signals did not make a substantial contribution to the attention-specific patterns of functional connectivity we observed.

We interpret negative values in the phase difference matrix (Figure 4F) as indicating a top–down flow of attention signals from parietal to occipital visual cortex. However, negative phase differences could also have occurred if there were a bottom–up flow of signals that was more pronounced during fixation than during attention. Such a bottom–up pattern could be associated with the presentation of a low-contrast target on half of the trials, the perceptual decision regarding the presence or absence of the target, and/or the motor response made by the subject. All of these events occur at the end of the trial and would therefore be expected to influence fMRI signals

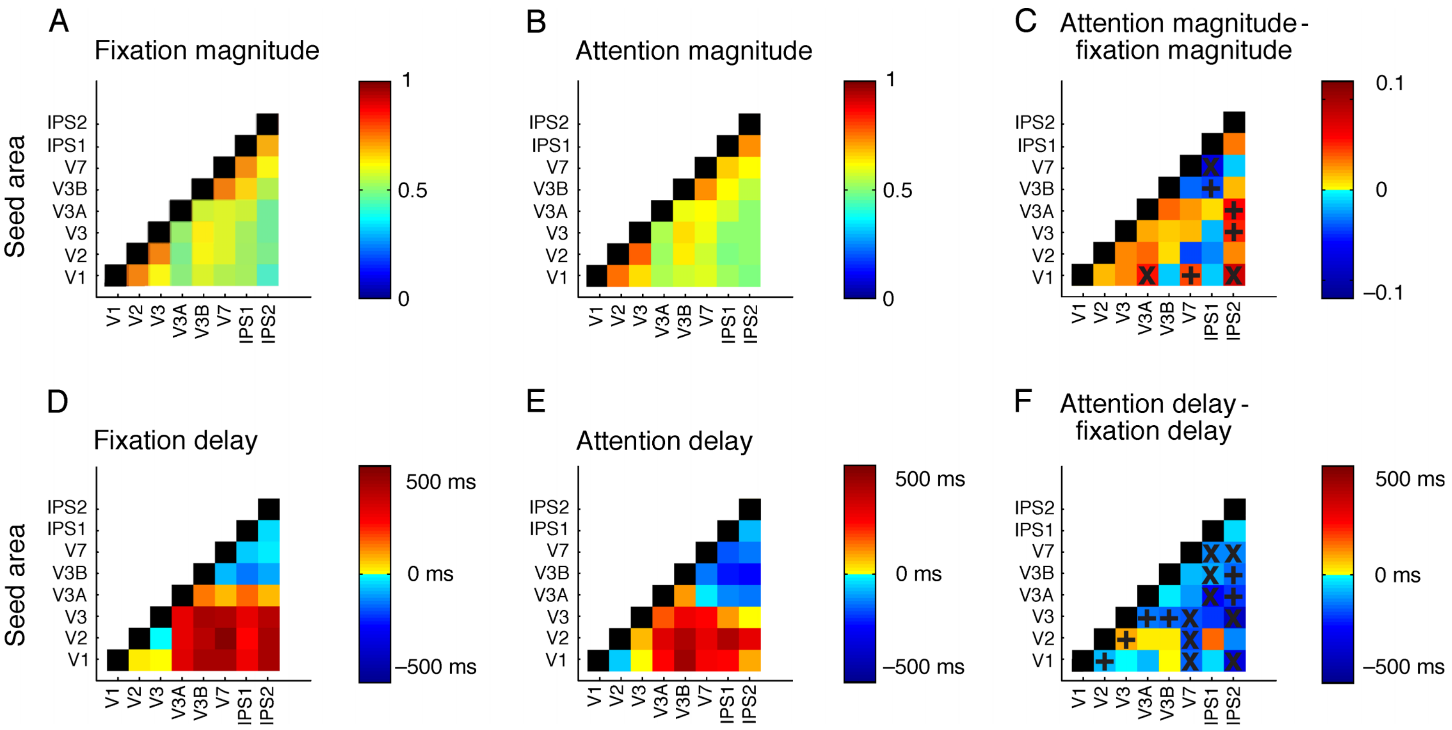

Figure 4. Mean coherency magnitudes, delays, and magnitude and delay differences between sustained attention and fixation for the group of four subjects. Same format as Figure 2. Colored squares indicate coherency magnitude (A, B), phase (converted to units of time) (D, E), or differences in magnitude (C) or phase (F) for each pairwise combination of areas. Coherency phase differences were generally negative, consistent with a top–down flow of attention signals. x, $p < 0.01$; +, $p < 0.05$ (corrected for multiple comparisons).

in the subsequent fixation period. However, if any of these events evoked significant feedforward coupling between cortical areas, we would expect larger coherency magnitudes associated with fixation compared to attention. In fact, the opposite result was obtained: coherency magnitudes were more likely to be larger for attention than for fixation (Figure 4C and Supplementary Figure 6C). This supports the conclusion that any significant values in the phase difference matrix are likely to be due to signals specific to visual spatial attention and not to signals related to other components of the task. All statistically significant attention-specific temporal differences between pairs of cortical areas are shown schematically in Figure 5. However, differences in timing between areas do not necessarily reflect direct transmission from one area to another. Temporal differences between two areas could also arise from a third area that projects to both of them.

These results demonstrate that a combination of objective identification of cortical regions representing attended visual field locations, coherency analysis, and subtraction of a baseline fixation condition can isolate patterns of functional connectivity associated with a cognitive operation, in this case, sustained visual spatial attention. The temporal precision attainable with this method allows measurement of temporal differences between areas on the order of hundreds of milliseconds and provides information regarding the directionality of flow of attention signals through the cortical areas in the

	V1	V2	V3	V3A	V3B	V7	IPS1	IPS2
IPS2								
IPS1								−47 ± 44
V7							**−150 ± 56**	**−147 ± 62**
V3B						−88 ± 60	**−112 ± 49**	**−190 ± 86**
V3A					−30 ± 73	−127 ± 84	**−335 ± 66**	**−255 ± 100**
V3				**−165 ± 141**	**−187 ± 62**	**−203 ± 69**	−238 ± 135	**−482 ± 139**
V2			**101 ± 47**	26 ± 153	23 ± 78	**−233 ± 74**	192 ± 153	−142 ± 118
V1		**−87 ± 35**	−4 ± 62	−83 ± 125	18 ± 74	**−197 ± 48**	−45 ± 86	**−406 ± 119**

Table 1. Mean ± *SEM* of coherency delay differences (ms) for the group of four subjects, as plotted in Figure 4F. Significant attention-specific delays are printed in bold.

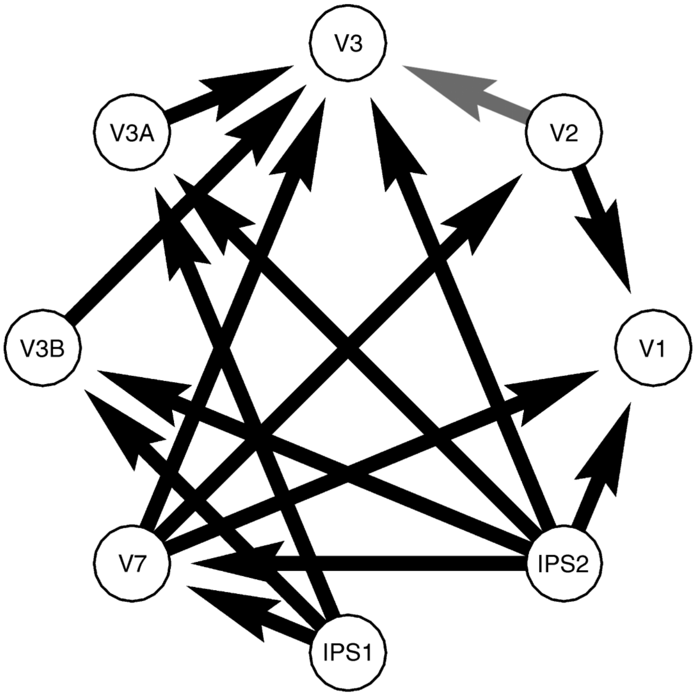

Figure 5. Temporal differences in attention-related activity for pairs of cortical areas. Arrows indicate significant differences in functional connectivity between attention and fixation. Black arrows represent top–down flow of attention signals, and the gray arrow indicates a bottom–up relationship between V2 and V3.

network. In particular, the attention-specific functional connectivity data are consistent with a top–down flow of attention signals from IPS1 and IPS2 to visual cortical areas with inter-areal latencies of a few hundred milliseconds.

Discussion

Our results show that sustained visual spatial attention in the absence of visual stimulation is accompanied by widespread increases in coherency magnitude for many pairs of parietal and occipital cortical areas and that attention-related activity in IPS1 and IPS2 leads that in the visual cortex by a few hundred milliseconds. These findings imply a top–down flow of information from IPS1 and IPS2 to earlier areas in the visual cortical processing hierarchy during sustained attention and support the hypothesis that IPS1 and IPS2 transmit attention signals from higher brain areas to visual cortex.

Possible neural substrates of attention-related functional connectivity

The observed effects of attention on functional connectivity could be due to three distinct (though not mutually exclusive) neural mechanisms. First, the measured coherency magnitude and phase differences might reflect ongoing neural interactions between cortical areas throughout the period of sustained attention. Spatially selective and persistent increases in fMRI responses during sustained attention in the absence of visual stimulation have been found in early visual cortex (Kastner et al., 1999; Silver et al., 2007) and in IPS1 and IPS2 (Supplementary Figure 2). Similar results were obtained with magnetoencephalographic (MEG) measures of visual spatial attention in the absence of sensory stimulation in human visual and parietal cortex (Siegel, Donner, Oostenveld, Fries, & Engel, 2008). If these responses in visual cortex are driven by sustained inputs from IPS1 and IPS2, this would result in a sustained (ongoing) increase in functional connectivity between parietal and visual cortical areas. In support of this conjecture, sustained attention caused persistent increases in coherency magnitude (in the 10- to 35-Hz frequency band) between parietal and visual cortex in monkey local field potential (LFP) recordings (Saalman, Pigarev, & Vidyasagar, 2007). Although this is a much higher frequency range than that measured with fMRI in the current study, we summarize evidence below for a link between low-frequency fMRI fluctuations and gamma band oscillations.

Second, the timing of activity at the onset of a period of sustained attention might differ between cortical areas. Given the sluggishness of the hemodynamics, even a transient change in neural activity will continue to influence the fMRI time series for many seconds, a time scale commensurate with the durations of sustained attention in our experiment. Much longer epochs of sustained attention and fixation would be required to definitively separate fMRI measurements of transient and sustained changes in functional connectivity associated with top–down visual spatial attention.

Third, attention might accelerate the feedforward progression of neural signals through the visual processing hierarchy. We found that attention-related activity in IPS1 and IPS2 leads that in early visual cortical areas by a few hundred milliseconds. However, this result was only obtained when the coherency values associated with fixation were subtracted from those associated with sustained attention. Before this subtraction, V1, V2, and V3 led higher order areas by a few hundred milliseconds both for fixation (Figure 4D) and attention (Figure 4E), consistent with a feedforward progression of activity during both task conditions. Subtraction of coherency phase values associated with fixation from the corresponding attention values resulted in negative phase differences for many pairs of areas (Figure 4F). This is consistent with a model in which attention accelerates feedforward processing relative to fixation. This model also receives support from magnetoencephalographic (MEG) experiments in which the latency of visual responses is reduced when stimuli are attended (Noguchi, Tanabe, Sadato, Hoshiyama, & Kakigi, 2007).

Temporal precision of BOLD signals

Given the sluggishness of the hemodynamics and the typically slow sampling rate (1.5 seconds in this experiment) of fMRI time series, one might be surprised that fMRI measurements have the necessary temporal resolution to detect the small temporal differences between brain areas (a few hundred milliseconds) reported here. While the temporal resolution of fMRI signals is indeed low, the time course of these signals can exhibit very high temporal precision. Temporal aliasing is not a concern, since the low-pass hemodynamics precede the low rate of temporal sampling of the signals. As a result, fMRI has been used to estimate changes in cortical activity of about 100 ms (Formisano & Goebel, 2003; Lee, Blake, & Heeger, 2005; Menon, Luknowsky, & Gati, 1998). Our results, along with those of Sun et al. (2005), further demonstrate that temporal differences between brain areas can be accurately measured with a precision much greater than the sampling rate of the fMRI time series.

Previous studies of fMRI functional connectivity of visual attention

A number of methods have been used to measure functional connectivity of fMRI attention signals in human cerebral cortex, including structural equation modeling (Büchel & Friston, 1997), nonlinear modeling of effective connectivity (Friston & Büchel, 2000), dynamic causal modeling (Haynes, Tregellas, & Rees, 2005), and Granger causality (Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008). These studies did not topographically define IPS1 and IPS2 but nevertheless provide evidence for attentional modulation of visual cortex by posterior parietal cortex and/or an attention-related increase in coupling among early visual cortical areas. However, no information regarding the temporal relationships among attention signals in occipital and parietal cortex is available from these studies. In contrast, we report estimates of temporal delays of the underlying neural signals specifically associated with visual spatial attention, for all pairs of retinotopically identified cortical areas, including IPS1 and IPS2.

Relationships between slow fMRI signal fluctuations and electrophysiological measurements

Our conclusions are based on task-specific coherency differences in the frequency range 0.0625 to 0.15 Hz, but how can these relatively low frequencies be related to the much faster temporal frequencies associated with neural activity? A number of experimental findings provide a link between slow fluctuations in fMRI signals and in electrophysiological recordings. LFP recordings from macaque visual cortex exhibit slow (0.05–0.1 Hz) fluctuations of the envelope of the power of the gamma frequency band (30–100 Hz) (Leopold, Murayama, & Logothetis, 2003). These correlated slow fluctuations in gamma-band power in the LFP are, in turn, temporally coupled with fluctuations in BOLD signals as measured with fMRI (after correcting for the hemodynamic delay) (Shmuel & Leopold, 2008). Taken together, these studies suggest a relationship between slow fluctuations in BOLD signal and slow modulations in power of the gamma frequency band. This relationship appears to extend to functional connectivity. Spontaneous fluctuations in fMRI responses are correlated between widely separated cortical areas while subjects are at rest, i.e., in the absence of stimulation (Cordes et al., 2001; Fox et al., 2005), and spontaneous fluctuations in spike rates and gamma-band power from LFP and electrocorticography (ECoG) recordings in human sensory cortex exhibit similar long-range (interhemispheric) correlations in the same low-frequency band (<0.1 Hz) (Nir et al., 2008).

Electrophysiological studies in the macaque monkey have documented effects of visual spatial attention on neuronal oscillations in the gamma frequency band. Microelectrode recordings in macaque area V4 have shown attentional modulation of gamma-band LFPs and spike-field coherence (Fries, Reynolds, Rorie, & Desimone, 2001). In addition, the correlation between slow fluctuations in the gamma-band power of LFPs and those in the BOLD signal suggests that the increase in LFP power during visual spatial attention may be related to the elevated fMRI responses that we observed in human visual cortex during sustained spatial attention (Silver et al., 2007). Paired recordings of single-unit activity and LFPs in the macaque monkey revealed increased coherency magnitudes (in the 10- to 35-Hz frequency band) between the lateral intraparietal area (LIP) and area MT following the allocation of visual attention, with the phase of the coherency implying that LIP activity was leading MT activity (Saalman et al., 2007). This is analogous to our observation of increased coherency magnitudes and phase differences between IPS1 and IPS2 and visual cortical areas. However, electrophysiological studies of attention have been limited by the difficulty of recording signals simultaneously in many different brain areas.

Previous studies of the time course of top–down visual spatial attention signals

Electroencephalography (EEG) has been used to infer timing differences between cortical areas associated with attentional modulation of a stimulus-evoked response, and studies have reported that the effects of attention are first observed in extrastriate cortex and only later in V1, consistent with a top–down flow of visual spatial attention signals to cortical area V1 (Di Russo, Martínez, &

Hillyard, 2003; Martínez et al., 2001). More recent studies have demonstrated attentional modulation of the earliest recorded response to the visual stimulus (EEG: Kelly, Gomez-Ramirez, & Foxe, 2008; MEG: Poghosyan & Ioannides, 2008). As all of these studies measured attentional modulation of a stimulus-evoked response, it is difficult to compare their findings to our own study of sustained fMRI attention signals in the absence of visual stimulation.

We used low contrast (barely visible) targets along with temporal uncertainty (a variable delay of 2–16 seconds) to measure sustained attention signals independent of the cortical activity related to stimulus presentation, perceptual decision, and behavioral response. We have previously reported that there was no sustained fMRI activity in early visual cortex when there was no uncertainty as to when or where a high contrast (easily visible) target was shown (Offen, Schluppeck, & Heeger, 2009). If a target is easily visible and/or appears at a predictable time, then subjects can apparently adopt a strategy in which they simply wait for it to appear. In this case, there would be a confound of top–down flow of attention control and bottom–up attentional modulation of sensory signals.

Presentation of a cue that directs voluntary attention to a peripheral visual field location decreases reaction time for target detection for cue-target onset asynchronies that are shorter (200 ms; Posner, Cohen, & Rafal, 1982) than the temporal differences in attention signals between IPS2 and early visual cortex reported here (406 ms for IPS2 and V1 and 482 ms for IPS2 and V3). These discrepancies call into question the accuracy of estimates of temporal differences in top–down attention fMRI signals as measured with coherency. However, although cueing effects on reaction time can be detected for very brief cue-target intervals, the magnitude of the cueing effects continues to increase for intervals as long as 500 ms (Posner et al., 1982), indicating additional top–down attentional modulation can occur at these longer intervals. Moreover, the reaction time measurements indicate the time course of shifts of attention immediately following cue onset, while our coherency phase differences are based on fMRI attention signals that are sustained for many seconds following presentation of the cue (Silver et al., 2007). Previous studies have described differences between the neural substrates of shifts of spatial attention and those associated with maintenance of attention at a peripheral location (Kelley, Serences, Giesbrecht, & Yantis, 2008; Yantis et al., 2002).

Thus, the available measurements of the time course of attentional modulation of EEG, MEG, and behavioral responses are based on stimulus onsets and/or shifts of attention, in contrast to our estimates of temporal differences associated with steady-state sustained attention in the absence of visual stimulation. Future physiological studies that measure temporal differences between brain areas during sustained attention are needed to confirm the accuracy of the absolute values of the temporal differences reported here. In any case, the temporal differences we have measured with fMRI provide evidence for a directionality of the flow of signals for pairs of brain areas during sustained visual spatial attention.

Conclusions

We have used a combination of topographic mapping to objectively identify cortical areas, retinotopic restriction of these areas to voxels representing attended visual field locations, coherency analysis, and a task subtraction procedure to measure functional connectivity associated with sustained top–down visual spatial attention. In addition, we measured temporal latencies of attention signals in parietal and occipital cortex on the order of hundreds of milliseconds. The results provide evidence for top–down transmission of attention signals from parietal areas IPS1 and IPS2 to visual cortex and enable the first steps in constructing a "circuit diagram" of functional connectivity that illustrates the flow of top–down visual spatial attention functional signals through these cortical areas (Figure 5). It should be noted that functional coupling between two areas does not necessarily indicate a direct anatomical connection between the areas.

Identification of additional topographic areas in parietal (Konen & Kastner, 2008; Swisher, Halko, Merabet, McMains, & Somers, 2007) and frontal (Hagler & Sereno, 2006; Kastner et al., 2007) cortex raises the possibility that the approach employed in the present study could be extended to higher levels of the attention control system. In addition, allocation of attention to a region of visual space causes impaired behavioral performance (Bashinski & Bacharach, 1980; Posner et al., 1980) and a reduction in fMRI signals at ignored visual field locations (Müller & Kleinschmidt, 2004; Silver et al., 2007). Defining regions of parietal and occipital cortex corresponding to ignored visual field locations would allow our methods to be applied to the study of functional connectivity of suppression as well as enhancement by attention.

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