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Spatial attention influences trial-by-trial relationships between response time and functional connectivity in the visual cortex

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ABSTRACT

Variations of response time (RT) in selective attention tasks are often associated with variations of activity and functional connectivity in sensory cortices that process relevant stimuli. Here, we investigated whether such relationships are influenced by spatial attention. To investigate this hypothesis, we asked fourteen healthy adults to perform a covert spatial attention task, which made use of bilateral stimulus displays, while we recorded their brain activity using functional magnetic resonance imaging (fMRI). As expected, activity in the middle occipital gyrus increased when spatial attention was directed to the contralateral (versus the ipsilateral) visual field. Surprisingly, variations of RT were not associated with variations in the magnitude of this attentional enhancement. As predicted, however, they were linked to opposing variations of functional connectivity between middle occipital regions contralateral (but not ispilateral) to the attended visual field and the left fusiform gyrus, which is thought to figure prominently in the perceptual processing of visually presented letters. These findings suggest that trial-by-trial variations of RT reflect, at least partially, trial-by-trial variations in the extent to which spatial attention enhances functional connectivity between sensory regions that process relevant stimuli.

Somewhat paradoxically, one of the most stable aspects of human performance is its variability across time. For example, when a person is asked to identify a given stimulus on multiple occasions, response time (RT) varies appreciably across trials (Gilden, 2001). Such fluctuations are often assumed to reflect, at least partially, variations in the efficiency of cognitive and neural processes underlying behavioral performance (Bellgrove et al., 2004; Gilbert et al., 2006; Hahn et al., 2007; Weissman et al., 2006). Consistent with this view, excessive across-trial RT variability in tasks requiring executive control has been noted following damage to the frontal lobes (Stuss et al., 2003), in persons with attention-deficit and hyperactivity disorder (ADHD) (Castellanos et al., 2005), in sleep-deprived populations (Chee et al., 2008), and in older adults (West et al., 2002). Critically, such fluctuations may also have adverse consequences in unimpaired populations. For example, even a small increase in the time it takes to react to changing road conditions while driving could lead to a serious accident (Beede and Kass, 2006). Thus, advancing our understanding of the cognitive and neural underpinnings of trial-by-trial variations of RT has tremendous theoretical, clinical, and practical relevance.

To further this objective, we have begun using fMRI to investigate whether variations of attention contribute to variations of RT in selective attention tasks (Chee et al., 2008; Prado et al., in press; Weissman et al., 2006, 2009). In our studies, participants were instructed to identify a relevant stimulus as quickly as possible without making mistakes while ignoring a simultaneous irrelevant stimulus. Thus, we hypothesized that increases of RT across trials might, to some extent, reflect reductions of attention to the relevant stimulus and/or failures to suppress the processing of the irrelevant stimulus. We reasoned that if our hypothesis was correct, then we might observe a number of effects that follow straightforwardly from current neurological models of attention. Such models posit that attention aids performance by enhancing activity (Corbetta et al., 2008; Corbetta and Shulman, 2002; Desimone, 1998; Hopfinger et al., 2000; O'Craven and Kanwisher, 1999) and functional connectivity (Bressler et al., 2008; Friston and Büschel, 2000; Haynes et al., 2005; Lauritzen et al., 2009) that is related to the sensory processing of relevant stimuli as well as by limiting activity that is related to the sensory processing of irrelevant stimuli (de Fockert et al., 2001). Thus, we predicted that if reductions of attention contributed to increases of RT in our tasks, then increases of RT should be linked to decreased activity and functional connectivity in sensory regions that processed relevant stimuli and enhanced activity in sensory regions that processed irrelevant stimuli.

Consistent with this prediction, we found that increases of RT across trials were linked to reductions of both activity (Weissman

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et al., 2009) and functional connectivity (Prado et al., in press) in sensory regions that processed relevant stimuli. For example, when participants were instructed to identify a visual letter while ignoring a simultaneous auditory distractor, increases of RT were linked to reductions of (a) activity in middle occipital gyrus (MOG) regions that likely processed the relevant visual letter and (b) functional connectivity between the right MOG and the left fusiform gyrus (FFG), a region that is thought to play an important role in visual letter processing (James et al., 2005; Polk et al., 2002; Vinckier et al., 2007). Furthermore, increases of RT were linked to increases of activity in superior temporal gyrus (STG) regions of the auditory cortex that likely processed the irrelevant auditory letter, consistent with a failure to inhibit the processing of the irrelevant auditory distractor. Interpreting our findings in light of current models, we concluded that variations of attention likely contributed to variations of RT in our cross-modal selective attention task, such that reductions of attention were associated with increases of RT.

The present study had two objectives. First, we wished to investigate whether effects analogous to those described previously could be observed in a covert visual spatial attention task that involved different stimuli and responses. Such a result would support the view that variations of attention contribute to variations of RT in spatial as well as non-spatial attention tasks. Second, we wished to more explicitly manipulate attention than we did in our prior studies. In those studies, the visual aspect of the cross-modal stimulus was always relevant and the auditory aspect was always irrelevant. Thus, it is unclear whether the effects we observed in the sensory cortices reflected (a) different levels of attention to the relevant and irrelevant stimuli or (b) attention-independent differences in the way that distinct sensory regions (e.g., visual and auditory cortex) respond to increases of RT.

To investigate our hypotheses, we asked participants to perform a covert spatial attention task while we recorded their brain activity using fMRI (Fig. 1). At the start of each block, participants were cued to attend either to the left visual field (LVF) or to the right visual field (RVF). Then, in each of several trials, participants discriminated the orientation of a target-colored letter, which usually appeared in the attended visual field, while ignoring a simultaneous non-target-colored distractor letter, which always appeared in the opposite visual field. Given that the cued direction of attention (left or right) alternated across blocks, the letter presented in each visual field (e.g., the LVF) was sometimes attended (left cue) and sometimes not attended (right cue). Thus, we were able to identify the regions of the visual cortex in which overall activity varied with the direction of spatial attention. We then determined whether and how activity and functional connectivity involving these regions varied with trial-by-trial measures of RT. We hypothesized that if reductions of attention contributed to increases of RT in our task, then increases of RT should be linked to (1) reductions of activity in the MOG contralateral (but not ipsilateral) to the direction of spatial attention and/or (2) reductions of functional connectivity between the MOG contralateral (but not ipsilateral) to the direction of spatial attention and the left FFG, a region that is thought to make an important contribution to visual letter processing (James et al., 2005; Polk et al., 2002; Vinckier et al., 2007).

Materials and methods

Participants

Seventeen healthy adults participated in the study. All were right-handed and had normal hearing, normal or corrected-to-normal vision, and no history of neurological or psychiatric disorders. Each participant gave informed written consent before the experiment and was paid $20 per hour. Two participants were excluded due to excessive head movement (i.e., greater than 3 mm). Data from a third participant were excluded due to unusable eye-tracker recordings. Fourteen participants were thus included in our final analyses (5 men, 9 women; age range, 18–22 years; mean age, 20 years). All experimental procedures were approved by the University of Michigan Biomedical and Health Sciences Institutional Review Board.

Task and procedure

In each of six runs, participants performed a covert spatial orienting task (Fig. 1). Specifically, across six 68 s blocks, they alternated between covertly attending to stimuli in the LVF and covertly attending to stimuli the RVF. The nature of the first block in each run (attend left or attend right) was counterbalanced across participants. Specifically, half of the participants started the experiment with an "attend left" block, while the other half began with an "attend right" block. A symbol (< or >; size, 1.70° × 1.55°) cued the direction of spatial attention (left or right) throughout each block. Eye position was monitored and trials in which subjects broke fixation or blinked were excluded (see Eye tracking section).

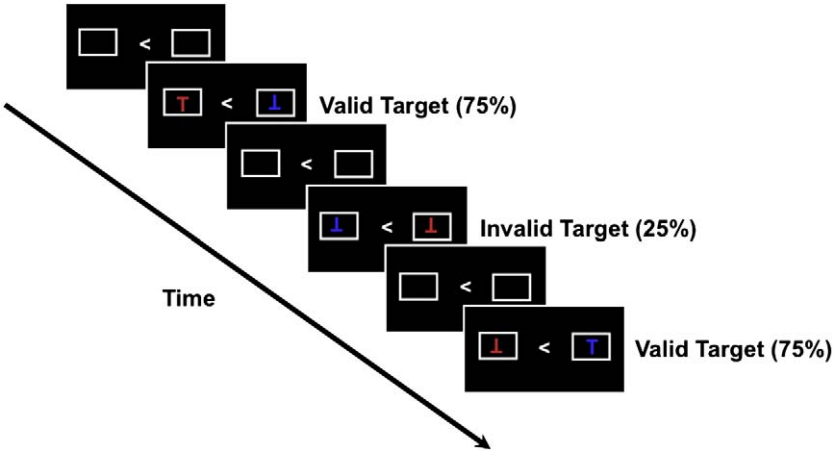

Fig. 1. Illustration of the covert visual spatial attention task. At the beginning of each 68 s block, a cue (< or >) instructed participants to direct their spatial attention either to the left or to the right visual field. In each of 12 subsequent trials (duration, 3750 ms), participants identified the orientation (i.e., upright or inverted) of the "T" that appeared in a predetermined color (e.g., red; duration, 100 ms) while ignoring a simultaneous "T" that appeared in an irrelevant color (e.g., blue; duration, 100 ms) in the opposite visual field. In valid trials (75%), the relevant letter (e.g., red) appeared in the visual field indicated by the cue (< or >). In invalid trials (25%), the relevant letter appeared in the other visual field. Variable periods of visual fixation were inserted between the cue and the first trial and between all subsequent trials (ranging from 0 ms to 3750 ms, in units of 1250 ms). Trials were presented in a pseudo-random order, such that each invalid trial was preceded and followed by a valid trial. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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There were 12 trials in every block. In each 3.75 s trial, two "Ts" were presented simultaneously (duration, 100 ms; size 2.1°×2.9°): one 8° to the left of fixation and the other 8° to the right. Visual stimuli were generated using Presentation software (Neurobehavioral Systems, www.neurobs.com) and projected onto a translucent screen that was viewed by the participants through a mirror attached to the head-coil. One of the Ts was red while the other was blue. Participants discriminated the orientation of the T that appeared in a pre-specified color (e.g., red; counterbalanced across subjects) by using the index or middle finger of their right hand to press a key on an MR-compatible keypad. In valid trials (75%), the T in the relevant color appeared in the cued visual field (e.g., the LVF) while in invalid trials (25%) it appeared in the uncued visual field (e.g., the RVF). We varied the orientation of the Ts (i.e., upright or inverted) independently in the two visual fields across trials. Moreover, trials were presented in a pseudo-random order such that, within every block, an invalid trial was always preceded and followed by a valid trial.

The timing between different events in our task varied as follows. First, 15 s of fixation occurred prior to the first block and 30 s of fixation occurred after the last block. Second, the time between the onset of the cue at the beginning of each block and the first trial was jittered in units of the 1.25 s repetition time (TR) that was used during fMRI scanning. In particular, this interval varied between 0 and 3 TRs (i.e., 0 and 3.75 s) following a roughly exponential distribution that favored short ITIs (Ollinger et al., 2001a,b). Third, the time between trials within each block was jittered in exactly the same way.

Behavioral analyses

Mean RT and mean error rate were analyzed using *t*-tests (2-tailed, unless otherwise noted) and repeated-measures analyses of variance (ANOVAs) as noted in the Results section.

Eye tracking

Eye position and pupil size during the scanning session were recorded monocularly at 60 Hz with an MR-compatible infrared video eye-tracker (NordicNeuroLab, Bergen, Norway). Before each run, the eye tracker was calibrated at a central position as well as at 8 eccentric points. Analyses of the eye movement data were performed off-line. For each trial, we analyzed the eye position traces from −100 to +400 ms post-stimulus onset. Trials in which subjects broke fixation were detected by calculating the derivative of the horizontal eye-position trace, i.e., saccade velocity. Trials in which subjects blinked were identified by measuring pupil size. When either saccade velocity exceeded 30°/s or pupil size equaled zero, a trial was excluded from further analysis (see Macaluso et al., 2002 for similar exclusion criteria). For two of the fourteen participants, one run was excluded from the fMRI analyses because more than 30% of the trials were rejected due to eye movements.

Imaging procedures

Images were collected using a 3-T GE Signa scanner (General Electric, Milwaukee, WI) equipped with a standard quadrature head coil. The fMRI blood oxygenation level dependent (BOLD) signal was measured with a reverse spiral imaging sequence (repetition time [TR] = 1250 ms, echo time [TE] = 30 ms). Twenty-seven contiguous axial slices were acquired in each functional image (4.50-mm thick, field of view, 22 cm; in-plane resolution, 3.44×3.44 mm). In each run, we collected 351 functional images. The first six images contained no trials and were discarded to allow for T1 equilibration effects.

Following functional image acquisition, a 3D spoiled gradient echo (SPGR), high-resolution, T1-weighted anatomical image was collected for each subject (TR = 10.5 ms, TE = 3.4 ms, FOV = 24 mm, flip angle = 25°, slice thickness = 1.5 mm).

FMRI data analysis

A number of preprocessing steps were performed on the fMRI data before trial-related activity was estimated. First, physiologic fluctuations were corrected using waveforms of respiration and cardiac cycles that were collected while participants performed the task in the scanner (Hu et al., 1995). Second, using SPM5 software (Wellcome Department of Cognitive Neurology, London, UK, www.fil.ion.ucl.ac.uk), the functional images were corrected for slice acquisition delays, spatially realigned to the first image of the first run to correct for head movements, normalized to the Montreal Neurological Institute (MNI) template (normalized voxel size, 3.75×3.75×4.5 mm), and spatially smoothed with an isotropic Gaussian filter (8-mm full width at half maximum). Due to head movements greater than 3 mm, one run of functional images was not further analyzed in each of two participants.

Event-related regression analyses (conducted separately in each participant) were performed using a version of the general linear model in which the fMRI signal in each trial is modeled with a standard hemodynamic response function (Josephs et al., 1997). In each run, correct trials with RTs more than three standard deviations from the mean of their corresponding trial type were excluded from behavioral and fMRI analyses (1.5% of all trials). Errors (2.5% of trials) were also excluded from the analysis. Correct trials were sorted by trial type (attend LVF cue, attend RVF cue, valid LVF target, valid RVF target, invalid LVF target, and invalid RVF target), yielding six event-related regressors of interest per run. Regressors of no interest were also included in the model. These regressors coded for trials that were excluded from the analysis (i.e., incorrect trials and trials in which the subjects broke fixation or blinked) and head motion.

Finally, the time series data from each run was high-pass filtered (1/128 Hz), and serial correlations were corrected using an autoregressive AR(1) model. Random effects analyses on the beta values from each participant were used to account for between-participants variance and to ensure that our findings would generalize to the population.

RT regressors

For each voxel, the brain response (y) was modeled by a general linear model of the form: $y = \alpha_0 + (RT - \overline{RT})\alpha_1 + \beta_0 + \varepsilon$. In this equation, the coefficient α_0 models the average response to each trial type (irrespective of variations of RT) and the coefficient α_1 models the linear (first-order) contribution of RT to the average hemodynamic response of each trial type. Since no response was required for attend LVF cues and attend RVF cues, only the average response was modeled for each of these two trial types. β_0 represents the y-intercept term (a column of ones), while ε represents the residual error term after each component has been fitted to the data. Our choice to parametrically model only linear effects of RT on activity was justified by several prior findings indicating a paucity of non-linear effects. Specifically, we have found in similar paradigms that stimulus-evoked BOLD responses vary with RT in a predominantly linear fashion (i.e., that little variance is explained by second-, third- and fourth-order effects), both when a canonical hemodynamic response shape is assumed (Prado et al., in press) and when it is not assumed (Chee et al., 2008).

As in our prior studies (Chee et al., 2008; Prado et al., in press; Weissman et al., 2006, 2009), RT regressors for each of the four target types were created by mean-centering the RT in each correct trial. Specifically, we subtracted the mean RT (i.e., $\overline{RT}$ in the equation described previously) for all correct trials of the corresponding trial type (i.e., valid LVF target, valid RVF target, invalid LVF target, or invalid RVF target) in the same functional run. The parameter estimate, or beta weight, for each RT regressor was calculated in units of *change in parameter estimate per second of increased RT*.

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Functional connectivity analyses

We tested our hypotheses about functional connectivity using psychophysiological interaction (PPI) analyses (Friston et al., 1997). PPI analyses assess whether interactions between brain regions vary with an experimental parameter. More specifically, they identify brain regions whose activity varies with activity in a seed region differently as a function of a psychological factor (Friston et al., 1997; Gitelman et al., 2003). Our analyses determined whether functional connectivity changed as a function of mean-centered RT (as defined in RT regressors section earlier), the direction of spatial attention (left or right), or with an interaction involving both of these factors. To implement these analyses, we extended the standard PPI algorithm in SPM5 to include all of these psychological factors and their interactions.

We defined seed regions in the MOG for the PPI analyses in the following manner. First, we created a mask in the right MOG ($x=38$, $y=-83$, $z=-14$), which was a sphere that had a 15 mm radius centered around right MOG coordinates from our prior study of functional connectivity in the visual cortex (Prado et al., in press). Second, we created another 15 mm radius mask centered in the analogous region of the left MOG ($x=-38$, $y=-83$, $z=-14$). Within each of these masks, we identified the voxel that exhibited the maximal effect of spatial attention on activity (i.e., the maximal *t*-value) in each individual participant. This procedure was motivated by prior findings indicating inter-subject variability with regard to the location of spatial attention effects in the visual cortex (Mangun et al., 1998). In the right MOG mask, we identified the voxel that showed the greatest increase in activity for valid LVF (versus valid RVF) targets. In the left MOG mask, we identified the voxel that showed the greatest increase in activity for valid RVF (versus valid LVF) targets. The exact locations of these "peak" voxels for each participant (and the average coordinates and standard deviations for the group as a whole) are listed in Table 1.

PPI analyses in each participant were conducted as follows. To begin, we extracted the first eigenvariate time series from a sphere that was 6 mm in radius and centered around each participant's "peak" voxel in (a) the right MOG and (b) the left MOG. Each of these regional time series served as the first regressor in a different PPI analysis (i.e., the "physiological" part of the PPI). Next, we entered the mean-centered RT and direction of spatial attention (1 or −1) values in each valid trial, after they had each been convolved with a synthetic HRF, as the second and third regressors (the "psychological" parts of the PPI). Lastly, we entered regressors reflecting interactions between the physiological and psychological factors (i.e., the "interaction" part of the PPI). To compute these interaction regressors, we multiplied various combinations of the RT, direction of spatial attention, and deconvolved seed activity regressors (Gitelman et al., 2003). These multiplications yielded a "psychological" interaction term – RT × direction of spatial attention – as well as three "psychophysiological" interaction terms for each seed: seed × RT, seed × direction of spatial attention, and seed × RT × direction of spatial attention. These interaction terms were then convolved with a synthetic HRF. After conducting each PPI analysis, one or more contrasts involving the resulting beta values from each participant were entered into standard random effects analyses.

Table 1
Coordinates of the left and right MOG seed regions in each participant.

Subject	Left MOG seed			Right MOG seed		
	x	*y*	*z*	*x*	*y*	*z*
01	−28	−89	−22	31	−72	−14
02	−28	−76	−9	45	−82	−14
03	−38	−86	−14	52	−79	−14
04	−45	−86	−9	48	−76	−9
05	−34	−82	0	38	−76	−22
06	−41	−76	−9	45	−79	−9
07	−31	−82	−18	41	−86	0
08	−41	−76	−22	28	−72	−14
09	−31	−89	−9	48	−79	−4
10	−41	−72	−18	31	−79	−4
11	−38	−93	−4	34	−79	−27
12	−34	−79	−27	38	−82	−22
13	−31	−86	−22	41	−79	−14
14	−38	−72	−22	28	−79	−4
Mean	−36	−82	−15	39	−78	−12
SD	5	7	8	8	4	8

Notes. Coordinates are in mm according to the Montreal Neurological Institute system; SD., standard deviation.

Voxelwise analyses

Given our *a priori* focus on the left FFG and bilateral regions of the MOG, we created an anatomical mask that included only these regions using the Wake Forest University (WFU) Pick Atlas (http://www.fmri.wfubmc.edu/download.htm). To control for false positive activations inside this mask, we used a voxel height threshold of $p<0.005$ with a cluster extent of at least 5 contiguous voxels. These thresholds reduced the voxelwise probability of false positives to $P<0.05$ within the anatomical mask, as determined by a Monte Carlo simulation (5000 iterations over the search space of the *a priori* mask) that we conducted using the 'AlphaSim' program (http://afni.nimh.nih.gov/afni/docpdf/alphasim.pdf).

Whole-brain analyses were conducted with a voxel height threshold of $p<0.005$ and a cluster extent of at least 25 contiguous voxels. These thresholds reduced the voxelwise probability of false positives to $p<0.05$ over the whole-brain, as determined by a Monte Carlo simulation (5000 iterations over the whole-brain) using the 'AlphaSim' program (http://afni.nimh.nih.gov/afni/docpdf/alphasim.pdf). All coordinates are reported in MNI space.

Region of interest analyses

Region of interest (ROI) analyses were conducted using the SPM toolbox Marsbar (http://marsbar.sourceforge.net/). ROIs included all voxels within a 6 mm radius of each coordinate of interest. In each participant, we calculated the average activity for each trial type within an ROI by averaging the fMRI signal across all voxels within that ROI. Unless otherwise noted, two-tailed *p* values were reported. *p* values less than 0.05 were considered significant.

Results

Overall behavior

Mean error rates were quite low (2.47%). A repeated-measures ANOVA on mean error rates with the factors direction of spatial attention (left or right) and validity (valid or invalid) revealed no significant main effects or interactions.

An analogous ANOVA on mean RT indicated no main effect of direction of spatial attention, $F(1,13)=0.19$, $p>0.6$. However, as expected (Posner, 1980), there was a main effect of validity because mean RT was significantly longer in invalid trials (631 ms) than in valid trials (594 ms), $F(1,13)=29.69$, $p<0.0015$. Although not important for present purposes, there was also a significant interaction between direction of spatial attention and validity, $F(1,13)=5.99$, $p<0.029$. This interaction occurred because the increase in RT observed in invalid compared to valid trials was larger when attention was directed to the left visual field (639 ms versus 585 ms) than when it was directed to the right visual field (623 ms versus 604 ms). Nonetheless, the validity effect was significant in both visual fields (LVF: $t(13)=6.06$, $p<0.001$; RVF: $t(13)=1.89$, $p=0.0407$; in these comparisons, we used one-tailed *t*-tests because we had an *a priori* hypothesis that RT should be longer in invalid than in valid trials).

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Eye movements

We excluded trials from the fMRI analyses if they contained one or more eye movements between 100 ms before and 400 ms after stimulus onset. However, it is also important to verify that eye movements did not differ for the valid LVF target and valid RVF target trials that *were* included in the fMRI analyses. Thus, we determined whether (a) eye position or (b) eye velocity differed in valid LVF target and valid RVF target trials using a relatively large temporal window around stimulus onset (−3000 to +3000 ms). First, we decomposed the eye movement data into 12 successive time bins, each of which lasted 500 ms. Second, we analyzed (a) the average eye position data (Fig. 2A) and (B) the average eye velocity data (Fig. 2B) from each of these 500 ms time bins in separate repeated-measures ANOVAs. Each ANOVA contained two within-participants factors: (1) direction of attention (left or right) and (2) time (0–500 ms). Of importance, none of the resulting 24 ANOVAs revealed (1) a significant main effect of direction of attention (all $p>0.05$) or (2) a significant interaction between direction of attention and time (all $p>0.05$). Thus, we observed no evidence to suggest that eye movements differed for valid LVF and valid RVF targets.

fMRI

Spatial attention modulates mean activity in the right and left MOG seed regions

Before testing our main hypotheses, we wished to confirm that spatial attention did indeed modulate mean activity in the left and right MOG seed regions (Fig. 3A). Recall that these seeds were defined separately in each participant by creating a spherical ROI around the voxel in each hemisphere that exhibited the largest increase of activity when spatial attention was directed to the contralateral (versus the ipsilateral) visual field. For this reason, it is not surprising that ROI analyses revealed a highly significant interaction between seed region (right MOG or left MOG) and direction of spatial attention (LVF or RVF), $F(1, 13)=39.38$, $p<0.0001$ (Fig. 3B). As expected, tests of simple effects in the left MOG seed indicated greater activity in *valid RVF target* than in *valid LVF target* trials, $t(13)=3.34$, $p<0.006$. Also as expected, analogous tests in the right MOG seed revealed greater activity in *valid LVF target* than in *valid RVF target* trials, $t(13)=2.90$, $p<0.02$. These findings confirmed that activity in our seed regions was highly sensitive to the direction of spatial attention. Thus, we concluded that these particular seed regions were appropriate for testing our main hypotheses.

Spatial attention does not influence relationships between RT and activity in the visual cortex

Our first hypothesis was that increases of RT would be linked to reductions of activity in the MOG contralateral (but not ipsilateral) to the direction of spatial attention. Contrary to this prediction, ROI analyses revealed that activity did not vary with RT in the MOG. First, we did not observe a main effect of RT in either the left MOG, $t(13)=-0.81$, $p>0.40$, or the right MOG, $t(13)=-1.30$, $p>0.20$. More generally, whole-brain voxelwise analyses failed to reveal *any* regions of the visual cortex in which activity varied with RT. Second, we did not observe an interaction between RT and direction of spatial

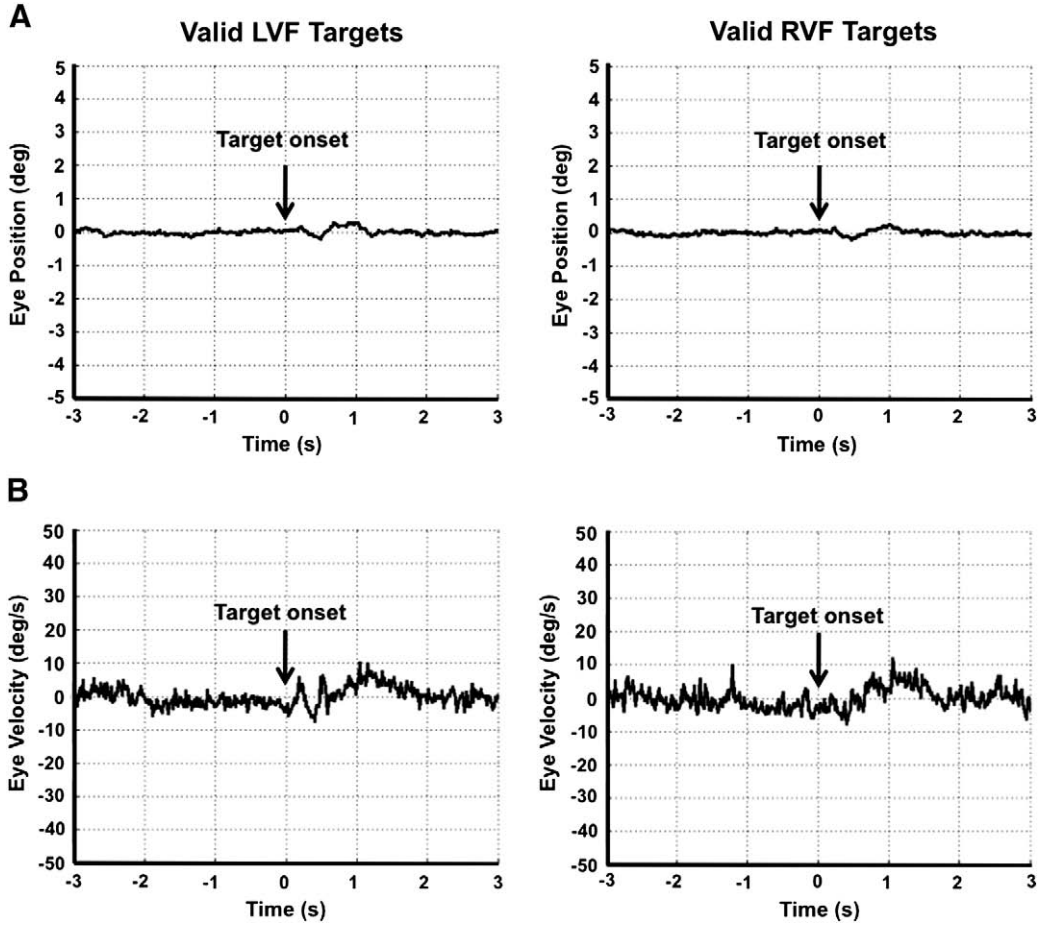

Fig. 2. Average eye movement data from −3000 ms to +3000 ms after stimulus onset. (A) Average horizontal eye position in trials with valid LVF targets (left) and valid RVF targets (right). (B) Average horizontal eye velocity in trials with valid LVF targets (left) and valid RVF targets (right). Analyses of the eye movement data revealed no significant differences between trials with valid LVF targets and trials with valid RVF targets.

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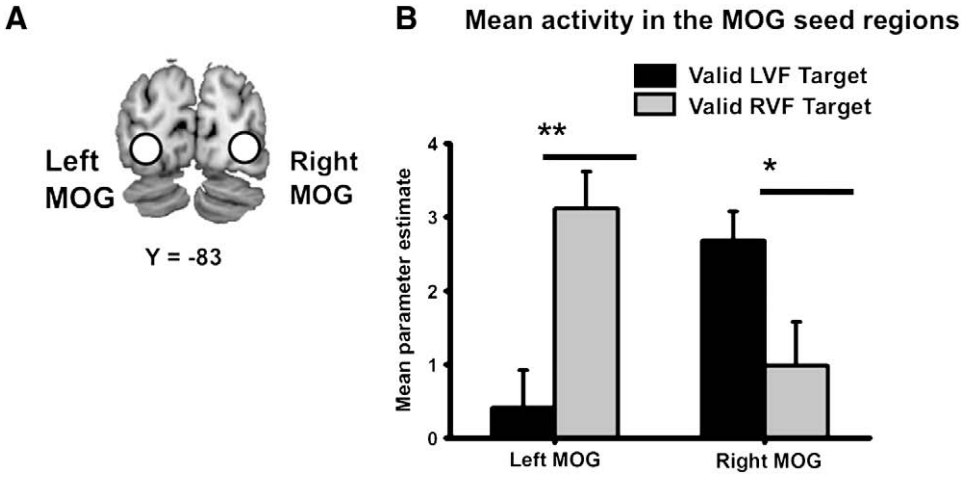

Fig. 3. Seed regions for the PPI analyses in the middle occipital gyrus (MOG). (A) Anatomically defined masks in the left MOG and the right MOG overlaid on a slice of the MNI-normalized anatomical brain. Within each of these masks, a spherical seed region (6-mm radius) centered on the voxel that showed the greatest spatial attention effect (i.e., greater activity for contralateral versus ispilateral targets as indicated by a maximal *t*-value) was defined independently in each participant. (B) Across participants, the left MOG seed exhibited significantly greater activity in *valid RVF target* than in *valid LVF target* trials (**, $p<0.01$), while the right MOG seed exhibited the opposite effect (*, $p<0.05$).

attention in either the left MOG, $t(13)=0.37$, $p>0.70$, or the right MOG, $t(13)=-1.03$, $p>0.30$. Third, we did not observe a three-way interaction between RT, direction of spatial attention, and ROI (left MOG or right MOG), $F(1,13)=0.89$, $p>0.35$. In sum, contrary to our first hypothesis, increases of RT were not linked to reductions of activity in MOG regions that were contralateral to the direction of spatial attention.

Spatial attention does influence relationships between RT and functional connectivity in the visual cortex

Our second hypothesis was that increases of RT would be linked to reductions of functional connectivity between the MOG contralateral (but not ipsilateral) to the direction of spatial attention and the left FFG. Using functional connectivity as the dependent measure in a voxelwise analysis, we did not observe a significant interaction between seed region (right MOG or left MOG) and direction of spatial attention (attend LVF or attend RVF) in any regions of the visual cortex. Consistent with predictions, however, we observed a significant three-way interaction between RT, seed region (right MOG or left MOG), and direction of spatial attention (attend LVF or attend RVF) in the left FFG. As predicted, the location of the peak functional connectivity effect within the left FFG ($x=-34$, $y=-55$, $z=-14$) was proximal to a left FFG region that has been implicated in the perceptual processing of visually presented letters (Polk et al., 2002) (Fig. 4A). To evaluate the precise nature of this three-way interaction in the left FFG, we next analyzed its simple effects using ROI analyses.

Of importance, the simple effects confirmed our prediction that increases of RT would be linked to reductions of functional connectivity between the MOG seed region contralateral (but not ipsilateral) to the visual target and the left FFG (Fig. 4B). First, increases of RT were linked to larger reductions of functional connectivity between the left MOG and the left FFG in *valid RVF target* than in *valid LVF target* trials, $t(13)=3.11$, $p<0.009$ (Fig. 4B, left). In particular, increases of RT were linked to reductions of functional connectivity between these regions in *valid RVF target* trials, $t(13)=2.86$, $p<0.007$ (one-tailed, *a priori* hypothesis), but not in *valid LVF target* trials, $t(13)=0.09$, $p=0.90$. Second, increases of RT were linked to larger reductions of functional connectivity between the right MOG seed region and the left FFG in *valid LVF target* than in *valid RVF target* trials, $t(13)=4.26$, $p<0.001$ (Fig. 4B, right). More specifically, increases of RT were linked to reductions of functional connectivity between these regions in *valid LVF target* trials, $t(13)=2.12$, $p<0.03$ (one-tailed, *a priori* hypothesis), but to increases of functional connectivity between these regions in *valid RVF target* trials, $t(13)=2.30$, $p<0.04$. Consistent with current models of selective attention, this latter effect suggests that increases of RT were associated with failures to suppress communication between sensory regions that process irrelevant stimuli. In sum, confirming our

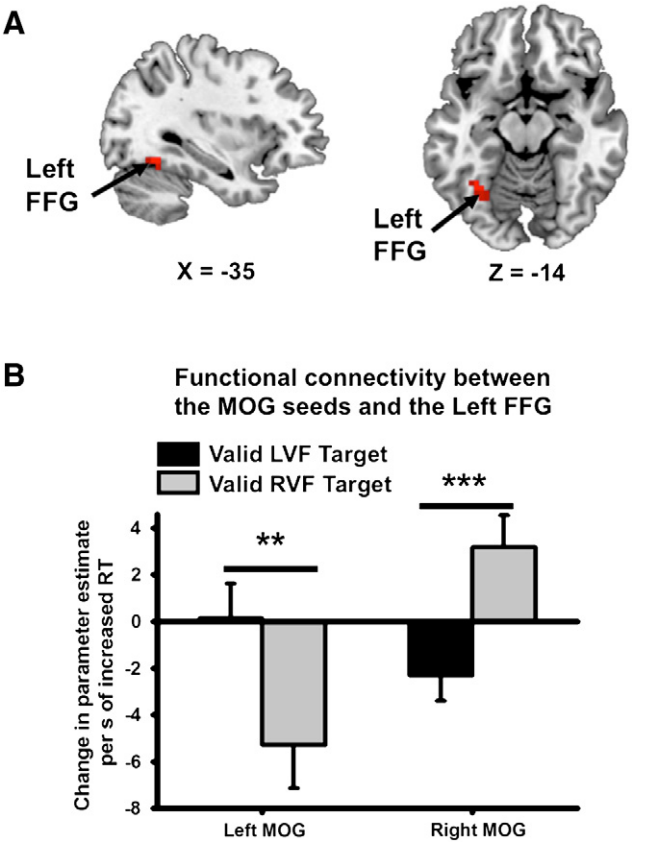

Fig. 4. Covert visual spatial attention modulates relationships between RT and functional connectivity in the visual cortex. (A) Increases of RT were linked to reductions of functional connectivity between the MOG seed region contralateral (but not ipsilateral) to the direction of spatial attention and a region of the left fusiform gyrus (FFG), which is overlaid on two slices of the MNI-normalized anatomical brain. (B) For the left MOG seed region, increases of RT were linked to larger reductions of functional connectivity with the left FFG in *valid RVF target* than in *valid LVF target* trials (**, $p<0.01$). For the right MOG seed region, the exact opposite pattern was observed (***, $p<0.001$).

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second hypothesis, increases of RT were linked to reductions of functional connectivity between the MOG seed region contralateral (but not ipsilateral) to the direction of visual spatial attention and the left FFG.

Earlier, we reported that variations of RT were not linked to variations of activity in the visual cortex in a voxelwise analysis. Given the functional connectivity effects above, however, we performed a supplementary ROI analysis to investigate whether activity varied with RT in the left FFG. Consistent with the voxelwise analyses, increases of RT were not associated with variations of activity in the left FFG in either (a) contralateral valid RVF target trials, $t(13) = 0.95$, $p = 0.36$ or (b) ipsilateral valid LVF target trials, $t(13) = 0.60$, $p = 0.56$ Thus, similar to the left and right MOG, activity did not vary with RT in the left FFG.

Discussion

In several prior studies of attention, we found that trial-by-trial variations of RT were systematically related to trial-by-trial variations of activity (Prado et al., in press; Weissman et al., 2006, 2009) and functional connectivity (Prado et al., in press) in sensory regions that processed relevant stimuli. Here, we investigated whether such relationships are influenced by spatial attention. To investigate this hypothesis, we determined whether and how increases of RT in a covert visual spatial attention task were related to activity and functional connectivity in sensory regions that processed (a) relevant stimuli and (b) irrelevant stimuli. Consistent with prior findings (Indovina and Macaluso, 2007), bilateral visual stimuli evoked greater activity in the MOG contralateral (versus ipsilateral) to the direction of spatial attention. Contrary to our first hypothesis, however, increases of RT were not associated with reductions of activity in these (or any other) regions of the visual cortex. Rather, in line with our second hypothesis, they were linked to reductions of functional connectivity between the MOG contralateral to the direction of visual spatial attention and the left FFG, a region that is thought to make an important contribution to the perceptual processing of visual letter stimuli (James et al., 2005; Polk et al., 2002; Vinckier et al., 2007). In sum, variations of RT were associated with variations in the magnitude of some, but not all, neural signatures of covert visual spatial attention.

Spatial attention does not modulate relationships between RT and activity in the visual cortex

Our first hypothesis was that increases of RT across trials would be associated with reductions of activity in regions of the visual cortex that processed relevant stimuli. However, we did not observe *any* relationships between activity and RT in the visual cortex. This result is surprising given that increases of RT were linked to reductions of activity in the relevant-modality visual cortex in three of our prior fMRI studies of attention (Prado et al., in press; Weissman et al., 2006, 2009). Although it is always difficult to diagnose a null effect, we now consider how fundamental differences between the covert spatial attention task used here and our prior tasks (Prado et al., in press; Weissman et al., 2009) might explain this discrepancy.

Two fundamental differences are immediately apparent. First, while our prior studies employed foveal stimuli, the present study made use of peripheral stimuli. A greater number of neurons represent foveal than peripheral locations (Rovamo and Virsu, 1979). Thus, it may simply be easier to observe subtle relationships between activity and RT when relevant stimuli are presented foveally than when they are presented peripherally. Moreover, this may be particularly true when the number of participants is relatively low as in the present study ($n = 14$). Second, while our prior studies involved non-spatial attention, the present study employed a covert visual spatial attention task. Thus, our prior findings may have been specific to non-spatial attention. This possibility is broadly consistent with prior data indicating that partially distinct cognitive/neural resources enable spatial and non-spatial attention (Egly et al., 1994). As we mentioned earlier, it is always difficult to diagnose a null effect. Therefore, at present, we merely conclude that variations of RT in our covert visual spatial attention task were not associated with variations in the magnitude of one well-accepted neural signature of visual spatial attention: visual cortex activity contralateral to the location of a behaviorally relevant stimulus.

Spatial attention influences relationships between RT and functional connectivity in the visual cortex

Our second hypothesis was derived from models in which attention aids performance by enhancing functional connectivity between sensory regions that process relevant stimuli (Bressler et al., 2008; Friston and Büschel, 2000; Haynes et al., 2005; Lauritzen et al., 2009). Specifically, we hypothesized that if increases of RT reflect, at least to some extent, reductions of attention, then increases of RT should be associated with reductions of functional connectivity between sensory regions that process relevant, but not irrelevant, stimuli. Consistent with this prediction, increases of RT were linked to selective reductions of functional connectivity between early regions of the visual cortex (i.e., the MOG) contralateral (but not ipsilateral) to the direction of spatial attention and the left FFG, a region that is thought to play an important role in processing of visual letter stimuli (James et al., 2005; Polk et al., 2002; Vinckier et al., 2007). These findings suggest that variations of RT in our attentional task reflected, to some extent, variations in the degree to which spatial attention enhanced functional connectivity between sensory regions that processed relevant stimuli.

Our findings also suggest that variations of RT reflected, at least in part, variations in the degree to which spatial attention limited functional connectivity between sensory regions that processed *irrelevant* stimuli. Specifically, in the Attend RVF condition, increases of RT were linked to increases of functional connectivity between the right MOG and the left FFG. Given that irrelevant stimuli were located in the LVF (i.e., contralateral to the right MOG) and given that selective attention is thought to limit the sensory processing of irrelevant stimuli (de Fockert et al., 2001; Desimone, 1998), this result further suggests that increases of RT were linked to reductions in the efficiency of selective attention. Interestingly, we did not observe an analogous effect in the left MOG. This result is consistent with prior work indicating that although the right hemisphere attends to both sides of space, the left hemisphere attends mainly to the right side (Mesulam, 1981). Thus, the left hemisphere should be relatively uninvolved in the processing of irrelevant LVF stimuli, as we observed. Nonetheless, the functional connectivity effects involving the right MOG suggest that variations of RT in our task reflected, at least partially, variations in the degree to which spatial attention limited the processing of irrelevant stimuli.

Relation of the present findings to prior work

Our findings add to a growing literature indicating that trial-by-trial variations of behavioral performance are tightly coupled with variations of communication between brain regions. First, variations of RT during attentional tasks have been linked to variations of functional connectivity between fronto-parietal regions that are thought to enable attentional control (Prado et al., in press) and between sensory regions that are thought to process relevant stimuli (Prado et al., in press). Second, variations of RT during a semantic object classification task have been linked to variations of functional connectivity between prefrontal and temporal regions which, respectively, likely implement semantic selection and object identification

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processes (Ghuman et al., 2008). Third, variations of accuracy in a perceptual decision-making task have been linked to variations of functional connectivity between the prefrontal cortex and various sensory regions, the nature of which suggests that prefrontal regions make decisions about object identity by comparing the outputs of sensory regions that are specialized for processing different types of objects (Heekeren et al., 2004). Together with these prior findings, the present results suggest that moment-to-moment fluctuations of behavioral performance are associated with variations of functional connectivity between brain regions. Critically, for selective attention tasks like the one used in the present study, our findings also suggest that variations of attention contribute to these variations of behavioral performance.

Broader relevance of the present work

Our findings are broadly relevant to the functional neuroimaging literature because they constitute a rare example in which a difference in functional connectivity between two conditions *cannot* be attributed to a difference in time on task. First, mean RT did not significantly differ in our two attentional conditions (i.e., attend to the LVF versus attend to the RVF). Second, and more fundamentally, the distinct variations of functional connectivity that we observed in our two attentional conditions were associated with *identical* variations in time on task, a control that was enabled by the parametric nature of regression-based PPI analysis (Friston et al., 1997). Similarly, we have previously employed parametric regression methods to show that distinct variations of *activity* in different experimental conditions can be associated with identical variations in time on task (Chee et al., 2008; Weissman et al., 2006, 2009). In contrast, most researchers compare mean levels of activity or functional connectivity in two conditions that differ with respect to mean response time. In such cases, any observed differences in brain activity or functional connectivity may stem from differences in (a) the recruitment of a cognitive process, (b) time on task, or (c) both (Yarkoni et al., 2009). The present work is therefore broadly relevant because it illustrates a method for distinguishing variations in activity and functional connectivity that are related to variations in (a) the recruitment of a cognitive process versus (b) time on task.

The present work also indicates that estimating trial-by-trial relationships between functional connectivity and RT can reveal effects of attention that would otherwise go unnoticed in conventional analyses of functional neuroimaging data. Indeed, functional connectivity involving the MOG seed regions and the left FFG varied with an interaction between RT and the direction of spatial attention even though, on average, it did not vary with the direction of spatial attention. Thus, certain effects of attention may be visible *only* when trial-by-trial measures of RT are directly incorporated into the analysis of functional neuroimaging data.

Limitations

Variations of RT across trials may stem from a large number of sources, including variations of attention (Castellanos et al., 2005), repetition priming (Buckner et al., 1998), and speed-accuracy tradeoffs (Van Veen et al., 2008). Thus, it is important to consider whether the present findings might be better explained by one or more of these factors than by spatial attention. Although this possibility may seem plausible at first glance, it is highly unlikely. Indeed, we contrasted the neural substrates of variations of RT in two conditions that differed only with respect to the direction of spatial attention (i.e., attend to the LVF versus attend to the RVF). Thus, other sources of RT variability (e.g., repetition priming, speed-accuracy tradeoffs, etc.), which were likely equated in these two conditions, probably cannot account for the distinct relationships between functional connectivity and RT that we observed.

Conclusions

The present findings make several important contributions to the literature on attention.

First, they suggest that variations of RT are linked to variations in the extent to which spatial attention enhances functional connectivity between sensory regions that process relevant stimuli. Second, they indicate that certain relationships between attention and functional connectivity may be revealed only when trial-by-trial measures of RT are explicitly incorporated into analyses of functional neuroimaging data. And third, they illustrate how one can distinguish variations of functional connectivity that are related to variations in (a) the recruitment of a cognitive process like attention from (b) time on task. Future studies that include trial-by-trial measures of RT in analyses of functional neuroimaging data will likely continue to advance our understanding of trial-to-trial variability in the deployment of attentional processes.

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