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Neural Correlates of Spatial Attention and Target Detection in a Multi-Target Environment

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Our ability to attend and respond in a multi-target environment is an essential and distinct human skill, as is dramatically demonstrated in stroke patients suffering from extinction. We performed a functional magnetic resonance imaging study to determine the neural anatomy associated with attending and responding to simultaneously presented targets. In healthy subjects, we tested the hypothesis that the right intraparietal sulcus (IPS) is associated both with the top-down direction of attention to multiple target locations and the bottom-up detection of multiple targets, whereas the temporo-parietal junction (TPJ) is predominantly associated with the bottom-up detection of multiple targets. We used a cued target detection task with a high proportion of catch trials to separately estimate top-down cue-related and bottom-up target-related neural activity. Both cues and targets could be presented unilaterally or bilaterally. We found no evidence of target-related neural activation specific to bilateral situations in the TPJ, but observed both cue-related and target-related neural activation specific to bilateral situations in the right IPS and target-related neural activity specific to bilateral situations in the right inferior frontal gyrus (IFG). We conclude that the IPS and the IFG of the right hemisphere underlie our ability to attend and respond in a multi-target environment.

Keywords: extinction, functional magnetic resonance imaging (fMRI), intraparietal sulcus (IPS), parietal, temporo-parietal junction (TPJ)

Introduction

The ability to simultaneously attend and respond to multiple sources of relevant information in our visual surroundings is a fundamental requirement in humans. It allows us to perceive and act coherently while constantly subjected to a potentially overwhelming number of sources of information. The importance of this ability is demonstrated impressively in neurological patients suffering from extinction after brain damage. These patients have lost the ability to simultaneously attend and respond to multiple sources of information, most commonly as a consequence of a right hemispheric stroke (Becker and Karnath 2007). As a result, these patients are not able to perceive and act on information presented on their left contralesional side in situations where information is concurrently presented on their right ipsilesional side. Extinction is most commonly seen as a consequence of biased competitive interactions between the ipsilesional and contralesional target stimuli and an exaggeration of the difficulty that normal subjects have while trying to attend and respond to multiple targets presented simultaneously (Desimone and Duncan 1995; Driver et al. 1997; Duncan et al. 1997; Duncan 1998), in combination with a pathologically limited attentional capacity (Driver et al. 1997; de Haan et al. 2012). Interestingly, the observation from extinction patients (and transcranial magnetic stimulation studies performed in neurologically healthy subjects, see below) that (transient) focal brain damage can selectively impair the ability to attend and respond in a multi-target environment, while leaving the ability to attend and respond in a single-target environment intact, suggests the presence of distinct neural substrates underlying our ability to attend and respond in single-target and multi-target environments.

An area of active research concerns the brain regions critically associated with this ability to simultaneously attend and respond to multiple target stimuli. Several studies have demonstrated that extinction is associated with damage to (Karnath et al. 2003; Grandjean et al. 2008; Chechlacz et al. 2013), or abnormal perfusion of (Ticini et al. 2010) the right temporo-parietal junction (TPJ). In correspondence with these findings, the results of a transcranial magnetic stimulation (TMS) study demonstrated that a temporary disruption of neural activity at the right TPJ can induce extinction-like behavior in neurologically healthy subjects (Meister et al. 2006). Several other studies have (additionally) suggested a role for the more dorsally located intraparietal sulcus (IPS) in the ability to simultaneously attend and respond to multiple targets and its failure in extinction patients. TMS studies have found that a unilateral temporary disruption of neural activity at the right (Hung et al. 2005; Koch et al. 2005) or either the left or right IPS (Pascual-Leone et al. 1994; Battelli et al. 2009) can result in extinction-like behavior in neurologically healthy subjects. Moreover, studies in monkeys have demonstrated that inactivation of the right IPS (area LIP) induces an abnormal preference for ipsilesional targets only in situations where monkeys were free to make a saccade to one of 2 targets presented bilaterally, whereas performance was unimpaired in unilateral situations (Wardak et al. 2002; Wilke et al. 2012).

Thus, both the IPS and the TPJ of particularly the right hemisphere have been associated with our ability to attend and respond to multiple targets simultaneously. The precise contribution of each of these 2 areas is, however, currently unclear. Interestingly, an influential model of attention proposed by Corbetta and colleagues (Corbetta et al. 2000, 2008; Corbetta and Shulman 2002; Shulman et al. 2003; Kincade et al. 2005) reserves a special role for these 2 areas. These authors propose that the right IPS, as part of a bilateral dorsal goal-driven attention network, is critically associated with both top-down direction of attention and bottom-up target detection (whereas the left IPS is typically associated with top-down direction of attention only) and might thus function as a "priority map" in which top-down and bottom-up information are combined to determine to focus of attentional selection, whereas the right TPJ, as part of a right-lateralized ventral stimulus-driven attention network, is critically associated with bottom-up target detection.

This model, however, is predominantly based on results obtained in single-target situations where a participant, at any

one time, directs attention to a single spatial location and ultimately detects a single target. We hypothesize that, while the IPS and the TPJ might be associated with the top-down direction of attention and the bottom-up detection of a target in single-target situations, these areas might be particularly crucial in competitive situations when multiple targets are simultaneously present. In other words, we propose that the IPS is associated with both top-down direction of attention to multiple spatial locations simultaneously and bottom-up detection of multiple target stimuli simultaneously, whereas the TPJ is specifically associated with bottom-up detection of multiple targets simultaneously. Should this be the case, we would expect a qualitative (involving distinct subregions) or quantitative (involving different levels of neural activation in the same regions) difference in neuronal activity in the IPS when comparing situations where subjects direct their top-down attention to multiple spatial locations simultaneously to situations where subjects direct their top-down attention to a single spatial location, regardless of location side (left visual field or right visual field). Likewise, we would expect a qualitative or quantitative difference in neuronal activity in the TPJ when comparing situations where subjects detect multiple target stimuli simultaneously to situations where subjects detect a single target stimulus, regardless of target presentation side. To test this hypothesis, we here conduct a functional magnetic resonance imaging (fMRI) study where subjects perform a cued target detection task based on the task used by Ciçek et al. (2007).

Materials and Methods

Participants

Twenty-seven subjects participated in this study. A single subject had to be excluded from the analyses due to a technical error during data collection. Furthermore, 3 subjects were excluded from further analysis due to failure to comply with the task instructions to lie still and fixate on the central fixation cross(see below for task). Thus, 23 subjects (18 females, mean age 25.5 years, range 21–37 years) were available for the entire set of analyses. All subjects were healthy with no history of neurological or psychiatrical disorders, were right-handed and had normal or corrected to normal vision. All subjects were volunteers and signed an informed consent approved by the ethics committee of the Medical Faculty of Tübingen. Subjects were paid 10€ per hour for their participation.

Task Design and Procedure

Subjects performed a cued target detection task based on the task used by Ciçek et al. (2007) (see Fig. 1) while lying in the bore of the magnetic resonance imaging (MRI) scanner. The software package E-prime (Psychology Software Tools Inc.) running on a PC was used to present the stimuli. Visual displays were presented with a beamer that projected these visual displays to a mirror mounted on the head coil. Each trial started with a 150 ms presentation of a centrally presented fixation cross surrounded by a diamond shape with a size of ~0.8° visual angle. Additionally, 2 peripheral target boxes subtending ~1.5° visual angle were present at an eccentricity along the horizontal midline of ~7.5° visual angle. These peripheral target boxes remained visible throughout the entire trial. Subsequently, one of 4 possible endogenous cue types was presented for 200 ms; spatial uninformative (neutral/uncued), unilateral left, unilateral right, or bilateral. Each of these 4 cue types was presented equally often. The spatially uninformative cues were included to allow us to determine whether the participants actively used the cue information (in which case performance should differ between cued and uncued trials) and introduced no change to the visual display (i.e., this cue condition was simply characterized by the absence of an informative cue stimulus). The informative cue stimulus consisted of a thickening of one (unilateral cue) or both (bilateral cue) sides of the diamond shape surrounding the central fixation cross. Following an interstimulus interval (ISI) of 1991, 2491, or 2991 ms (average duration 2491 ms, creating an average cue-onset to target-onset interval of 1 TR) in which the fixation cross surrounded by the diamond shape and the peripheral target boxes was again presented, subjects were presented with target (×) and/or distractor (+) stimuli appearing within the 2 peripheral target boxes. Both target and distractor stimuli could be presented unilaterally (either in the left or in the right visual field) or bilaterally (2 stimuli, one in each visual field) and were presented for 200 ms. Moreover, during bilateral trials either 2 target stimuli, 2 distractor stimuli or a target and a distractor stimulus could be presented. Subjects were instructed to respond only when target(s) and no distractor stimulus or stimuli were present (i.e., when either a unilaterally presented target stimulus or a bilateral trial consisting of 2 target stimuli was presented, termed "target display") by pressing a button on a MRI-compatible button box as fast as possible and to withhold response in all other cases (termed "distractor display"). These distractor displays were presented so that subjects were required to identify the stimulus presented at the potential target stimulus locations before responding. The proportion of yes to no trials was 75–25%. Target and distractor displays, when following an informative cue, always appeared on the cued location. In 33.3% of the trials, the trial ended directly after the presentation of the cue stimulus (catch trials). This high percentage of catch trials allowed us to separate the neural activation associated with processing of the cue from the neural activation associated with processing of the target or distractor display (Ollinger, Corbetta et al. 2001; Ollinger, Shulman et al. 2001). Finally, after an intertrial interval of 2491, 5182, or 7873 ms (i.e., a cue/target-onset to start of next trial interval of 1, 2, or 3 TRs with an average duration 3836.5 ms), the next trial started.

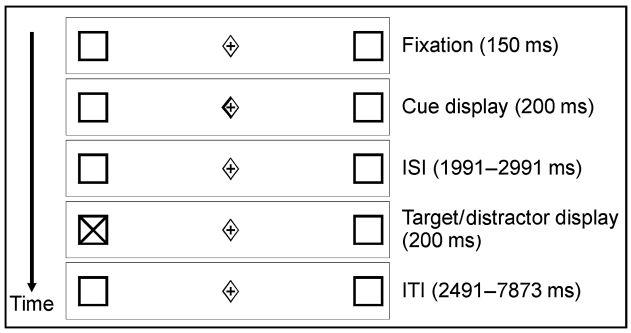

Figure 1. Illustration of events in a single-trial example. This example depicts an informatively cued unilateral left target trial.

Subjects performed 400 trials, divided over 8 runs. As a consequence, 99 trials did not contain a cue stimulus (i.e., the uncued trials) and of these 99 trials 33 trials did not contain a target/distractor display, 17 trials contained a unilateral left target display, 17 trials contained a unilateral right target display, 17 trials contained a bilateral target display, 5 trials contained a distractor left display, 5 trials contained a distractor right display, and 5 trials contained a bilateral distractor display (1 trial with distractor + distractor, 2 trials with target + distractor, and 2 trials with distractor + target). 100 trials contained a unilateral left cue and of these 100 trials 33 trials did not contain a target/distractor display, 51 trials contained a unilateral left target display and 16 trials contained a unilateral left target display. Likewise, 100 trials contained a unilateral right cue and of these 100 trials 33 trials did not contain a target/distractor display, 51 trials contained a unilateral right target display and 16 trials contained a unilateral right distractor display. Finally, 101 trials contained a bilateral cue and of these 101 trials 34 trials did not contain a target/distractor display, 51 trials contained a bilateral target display, and 16 trials contained a bilateral distractor display (6 trials with distractor + distractor, 5 trials with target + distractor, and 5 trials with distractor + target). While the subjects performed the task, both reaction times and response accuracies were recorded. Subjects were instructed to fixate on the fixation cross

and eye fixation position was continuously measured at 50 Hz with an MR-compatible eye-tracker (SensoMotoric Instruments).

Imaging and Data Analysis

All functional imaging was performed using a 3 T Siemens Magnetom Trio scanner (Erlangen, Germany). For each subject, 5 sessions of continuous fMRI data were collected (one for each task run). Each session consisted of a series of whole-brain functional T_2* EPI volumes, covering the entire task run duration. The fMRI volumes were collected axially with a flip angle of 90°, a time to echo (TE) of 40 ms and a time to repetition (TR) of 2691 ms. Each fMRI volume contained 33 slices acquired in sequential ascending order with a slice thickness of 3 mm (with no gap between slices) and an in-plane resolution of 3 × 3 mm (field of view [FOV] = 192 × 192). Additionally, we sagittally acquired a high resolution T_1-weighted anatomical volume (176 slices, 1 × 1 × 1 mm, 256 × 256) using a GRAPPA sequence with a flip angle of 8°, a TE of 2.92 ms and a TR of 2300 ms for each subject to aid normalization.

Preprocessing and statistical analyses were performed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) running under Matlab R2010b (Mathworks). The functional volumes were slice time corrected using the middle slice as the reference slice (Henson et al. 1999) and realigned to match the first volume of the first session (Friston, Ashburner et al. 1995). A failure to lie still was defined as scan-to-scan movement exceeding 1 voxel (3 mm). Subsequently, the T_1-weighted volume was coregistered with the mean functional volume obtained after realignment (Collignon et al. 1995). Transforms for warping the coregistered T_1-weighted volume to standard stereotaxic space were computed by the unified normalization–segmentation approach (Ashburner and Friston 2005). The resulting transformation parameters were used to warp the functional volumes and structural volumes into stereotaxic space. Finally, the functional volumes were spatially smoothed with an isotropic 8 mm full-width at half-maximum Gaussian filter.

For each experimental event (left cue, right cue, bilateral cue, left target, right target, bilateral target, left distractor, right distractor, and bilateral distractor), changes in blood-oxygenation level were modeled using the standard SPM8 haemodynamic response (Friston, Holmes et al. 1995; Lange 2000; Worsley 2001; Kiebel and Holmes 2003) with temporal and dispersion derivatives. Additionally, we added the time series of the mean white matter signal as a regressor of no interest to reduce global noise. The inclusion of this regressor has recently been shown to improve the sensitivity of statistical analyses without inducing artificial signal changes by itself (Linzenbold and Himmelbach 2012). To obtain the time series of the mean white matter signal, we first thresholded each individual white matter volume, obtained after segmenting the T_1-weighted volume, at a probability value of 0.9. Subsequently, we used the SPM toolbox MarsBar (Brett et al. 2002) to extract the mean signal time course within the thresholded white matter volume from the slice timed, realigned, and normalized functional volumes.

A series of comparisons was conducted designed to determine which brain regions showed event related fMRI signal changes. Within each subject, we contrasted both the fMRI signal in response to unilateral left cues and the fMRI signal in response to unilateral right cues to the fMRI signal in response to bilateral cues. Likewise, we contrasted both the fMRI signal in response to unilateral left target displays and the fMRI signal in response to unilateral right target displays to the fMRI signal in response to bilateral target displays. The resulting contrast images of these 4 comparisons were subsequently passed on to second-level random effects analyses (Holmes and Friston 1998). We performed 2 one-sample *t*-tests on the results of the comparison of either unilateral left cues or unilateral right cues from bilateral cues while including the mean-centered reaction time difference between either unilaterally left cued target displays or unilaterally right cued target displays and bilaterally cued target displays as a covariate to control for potential effects of task difficulty between unilateral and bilateral situations. In a similar vein, we also performed 2 one-sample *t*-tests on the results of the comparison of either unilateral left target displays or unilateral right target displays from bilateral target displays while including the mean-centered reaction time difference between either unilateral left or unilateral right target displays and bilateral target displays as a covariate. Finally, we binarized the volume containing the significantly activated voxels for each of the 4 one-sample *t*-test and calculated 2 conjunction maps to isolate the voxels specifically associated with either bilateral cue presentations or bilateral target display presentations. Thus, we obtained 1 conjunction map containing voxels where ([bilateral cue > unilateral left cue] AND [bilateral cue > unilateral right cue]) and one conjunction map containing voxels where ([bilateral target display > unilateral left target display] AND [bilateral target display > unilateral right target display]). As we were solely interested in assessing the areas of the brain specifically associated with either bilateral cue or bilateral target display presentations, distractor display presentations were not included in the statistical comparisons. For all statistical analyses a cluster-based threshold of $P < 0.05$ (Bonferroni FWE corrected for multiple comparisons) based on a feature-inducing voxel threshold of $t > 3$ (roughly equivalent to $P < 0.001$ uncorrected for multiple comparisons) was applied to determine which clusters were significantly activated at each comparison. Where possible, the results of the statistical analyses were anatomically interpreted with the aid of the stereotaxic probabilistic cytoarchitectonic atlas (Schleicher et al. 2000; Amunts and Zilles 2001) using the SPM Anatomy Toolbox (Eickhoff et al. 2005, 2006, 2007). Results that could not be assigned to cortical areas included in the stereotaxic cytoarchitectonic atlas were anatomically interpreted with the aid of the LONI Probabilistic Brain Atlas (Shattuck et al. 2008). Additionally, we used the SPM toolbox MarsBar (Brett et al. 2002) to extract the mean percent signal change evoked by the different events for each statistically significant cluster to further describe the response profiles of significant clusters. We used the default settings of MarsBar where the baseline signal of a region of interest is defined as the mean signal over time in that region of interest.

Behavioral Data Analysis

Using the program iLab (Gitelman 2002) under Matlab 2010b (Mathworks), we calculated the duration that subjects spent fixated within a 1.5° visual angle radius of the center of either the fixation cross or the peripheral target boxes as a percentage of the total experimental duration after removing eye blinks. A failure to fixate was defined as spending <90% of the total experimental duration fixated on the fixation cross and/or spending >1% of the total experimental duration fixated on either the left or the right peripheral target box.

The reaction times in response to target display presentations were analyzed using a repeated measures 2 (cue type: cued, uncued) by 3 (target display type: left, right, and bilateral) repeated-measures analysis of variance (ANOVA). Incorrect trials and trials where the reaction time exceeded 1500 ms were excluded from these analyses. Additionally, we used 2 (cue type: cued, uncued) by 3 (display type: left, right, bilateral) repeated-measures ANOVAs to analyse the response accuracies in response to both target display presentations and distractor display presentations.

Results

Behavioral Results

We were able to perform an offline analysis on the gaze fixation position data in 19 of the 23 subjects. In 3 of the 4 remaining subjects, compliance with the gaze fixation requirement was monitored online and found to be good, but due to bad data quality, offline data analysis was not possible. In 1 remaining subject, eye tracking was not possible due to technical difficulties. On average, subjects spent 98.13% (with a standard deviation [SD] of 1.65%) of the experimental duration correctly fixating the central fixation cross. Subjects spent on average 0.06% (with a SD of 0.09%) of the experimental duration incorrectly fixating the left-sided peripheral target box and 0.07% (with a SD of 0.12%) of the experimental duration incorrectly fixating the right-sided peripheral target box.

Table 1
Mean accuracy and reaction times (and the nSE in brackets) for each of the target display presentation conditions

	Cued			Uncued		
	Left	Right	Bilateral	Left	Right	Bilateral
ACC (%)	98.96 (0.50)	97.57 (0.66)	95.61 (0.84)	96.30 (1.10)	95.91 (1.04)	95.17 (1.31)
RT (ms)	582.99 (6.80)	582.00 (6.38)	622.70 (9.76)	657.01 (8.91)	639.51 (9.05)	679.02 (12.39)

Table 2
Mean accuracy (and the nSE in brackets) for each of the distractor display presentation conditions

	Cued			Uncued		
	Left	Right	Bilateral	Left	Right	Bilateral
ACC (%)	89.70 (1.66)	91.91 (1.52)	92.30 (1.35)	98.26 (1.34)	96.52 (1.68)	92.55 (2.58)

The mean percentage accuracy and normalized standard error (nSE, Loftus and Masson 1994) for each of the 6 possible combinations of cue type and target display type (unilateral left uncued, unilateral right uncued, bilateral uncued, unilateral left cued, unilateral right cued, and bilateral cued) are shown in Table 1. A 2 (cue type: cued, uncued) by 3 (target display type: left, right, and bilateral) repeated-measures ANOVA demonstrated a marginally significant main effect of cue type ($F_{1,22} = 3.62$, $P = 0.07$) with performance being slightly better for cued than for uncued target displays. Neither the main effect of target display type, nor the interaction between cue type and target display type were significant ($F_{2,44} = 1.69$, $P = 0.20$ and $F_{2,44} = 0.91$, $P = 0.41$, respectively).

The mean percentage accuracy and nSE for each of the 6 possible combinations of cue type and distractor display type (unilateral left uncued, unilateral right uncued, bilateral uncued, unilateral left cued, unilateral right cued, and bilateral cued) are shown in Table 2. A 2 (cue type: cued, uncued) by 3 (distractor display type: left, right, and bilateral) repeated-measures ANOVA demonstrated a significant main effect of cue type ($F_{1,22} = 5.42$, $P = 0.0290$) with false alarm rates being significantly lower for uncued than for cued distractor displays. Neither the main effect of distractor display type, nor the interaction between cue type and distractor display type were significant ($F_{2,44} = 0.73$, $P = 0.49$ and $F_{2,44} = 2.32$, $P = 0.11$, respectively).

The mean reaction time and nSE for each of the 6 possible combinations of cue type and target display type are shown in Table 1 and Figure 2. A 2 (cue type: cued, uncued) by 3 (target display type: left, right, bilateral) repeated-measures ANOVA showed a significant main effect of cue type ($F_{1,22} = 55.30$, $P < 0.0001$) with reaction times for cued target displays being lower than reaction times for uncued target displays. Moreover, this ANOVA demonstrated a significant main effect of target display type ($F_{2,44} = 7.32$, $P = 0.0018$) with post hoc planned comparisons showing that reaction times for bilateral target displays were significantly higher than reaction times for either unilateral left or unilateral right target displays ($t_{22} = 2.49$, $P = 0.0414$ and $t_{22} = 3.14$, $P = 0.0094$, respectively after Bonferroni correction). The interaction between cue type and target display type failed to reach significance ($F_{2,44} = 0.65$, $P = 0.5200$).

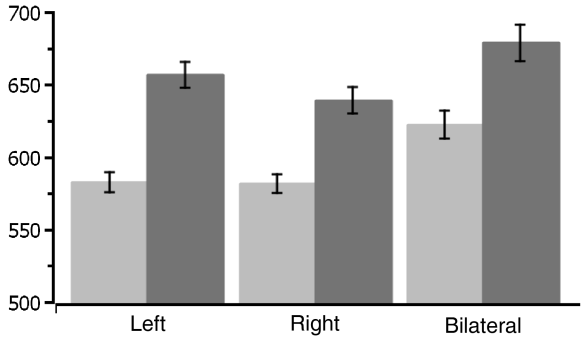

Figure 2. The mean reaction time in milliseconds and nSE for each of the 6 possible combinations of cue type and target display type. Light gray bars reflect cued target presentations and dark gray bars reflect uncued target presentations. Error bars reflect nSE of the mean.

fMRI Results

We identified 2 significant clusters specific to bilateral cue presentations (see Fig. 3*A*): 1 predominantly located on the lateral wall of the right intraparietal sulcus (latIPS) and 1 located in the left occipital gyrus. The first cluster located in the right latIPS contained 143 voxels (center of mass: Montreal Neurological Institute [MNI] 38 −55 47) and 98.3% of this cluster could be anatomically interpreted with the stereotaxic cytoarchitectonic atlas. 39.7% of the cluster was assigned to hIP3, 23.2% to hIP1, 20.3% to PGa, 14.9% to 7A and 0.2% to 7P. The cue-related mean percent signal change extracted from this cluster (Fig. 3*A*, dark gray bars) demonstrated that this cluster was selectively activated by bilateral cue presentations whereas unilateral cue presentations evoked virtually no change in the mean percent signal. A repeated-measures 1-way ANOVA on the target-related mean percent signal change extracted from this cluster (Fig. 3*A*, light gray bars) suggested that this cluster also tended to preferentially respond to bilateral target presentations, but this pattern did not reach statistical significance ($F_{2,44} = 2.00$, $P = 0.1500$). The second cluster located in the left occipital gyrus contained 33 voxels (center of mass: MNI −16 −95 6) and 73.4% of this cluster could be anatomically interpreted with the stereotaxic cytoarchitectonic atlas. 67% of the cluster was assigned to Area 17 and 6.4% to Area 18. The remaining 8.8 voxels were located in the left

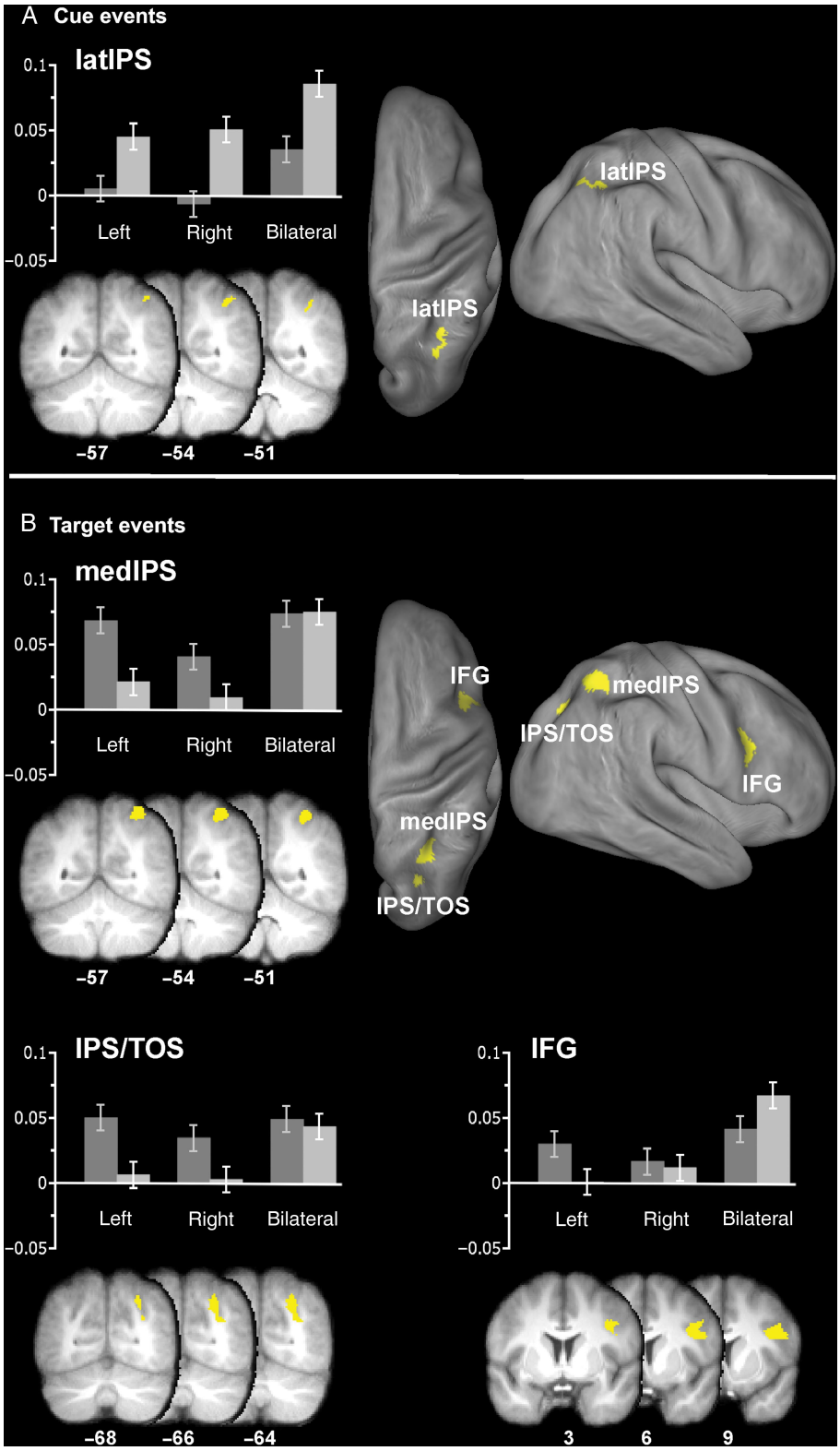

Figure 3. Results of the conjunction analyses highlighting areas of the brain where ([bilateral > left] and [bilateral > right]). (*A*) Area of the brain specifically activated in response to bilateral cue presentations and the percentage signal change extracted from this cluster. (*B*) Areas of the brain specifically activated in response to bilateral target presentations and the percentage signal change extracted from these clusters. In all bar graphs, the dark gray bars denote the percentage signal change evoked by the different cue types and the light gray bars denote the percentage signal change evoked by the different target types. Error bars reflect nSE of the mean. The program Caret was used to project the significant activation onto the average surface rendering of 12 individuals (Van Essen 2005). The significant activation is additionally shown on selected coronal slices of the mean T_1 image created by averaging of the 23 normalized T_1 images in our dataset. All images are in neurological orientation and slice numbers reflect MNI coordinates.

middle occipital gyrus directly lateral to Area 17 and Area 18. The mean percent signal change extracted from this cluster, however, revealed that this cluster was not selectively activated by bilateral cue presentations. Instead, this cluster was deactivated during unilateral cue presentations, whereas bilateral cue presentations evoked no change in the mean percent signal.

We identified 3 significant clusters specific to bilateral target presentations (see Fig. 3*B*): 1 located in the right inferior frontal gyrus (IFG), 1 predominantly located on the medial wall of the right intraparietal sulcus (medIPS) and 1 located in the right IPS/right transverse occipital sulcus (IPS/TOS). The first cluster located in the right IFG contained 461 voxels (center of mass: MNI 43 6 28) and 37.9% of this cluster could be anatomically interpreted with the stereotaxic cytoarchitectonic atlas, which assigned all these voxels to right Area 44. The remaining 286.1 voxels were located in the right IFG directly medial to Area 44 extending dorsally into the right precentral gyrus. The target-related mean percent signal change extracted from this cluster (Fig. 3*B*, light gray bars) demonstrated that this cluster was selectively activated by bilateral target presentations whereas unilateral target presentations evoked virtually no change in the mean percent signal. The second cluster located in the right medIPS contained 373 voxels (center of mass: MNI 33 −55 56) and all of them could be anatomically interpreted with the stereotaxic cytoarchitectonic atlas. 64.9% of the cluster was assigned to 7A, 19.3% to 7PC, 15.5% to hIP3 and 0.3% to Area 2. The target-related mean percent signal change extracted from this cluster (Fig. 3*B*, light gray bars) demonstrated that, whereas this cluster tended to show a mild preference for contralateral left-sided targets, it was particularly activated by bilateral target presentations. The third cluster located in the IPS/TOS contained 331 voxels (center of mass: MNI 28 −64 34) and only 0.3% of this cluster could be anatomically interpreted with the stereotaxic cytoarchitectonic atlas, which assigned that single voxel to hIP3. The remaining 330 voxels were located in the right superior parietal gyrus directly ventral to hIP3 and medial to the angular gyrus extending ventrally towards the TOS and into the superior and middle occipital gyrus. The target-related mean percent signal change extracted from this cluster (Fig. 3*B*, light gray bars) demonstrated that this cluster was also selectively activated by bilateral target presentations whereas unilateral target presentations evoked virtually no change in the mean percent signal. While these 3 significant clusters all show a significant preference for bilateral target presentations over both left and right unilateral target presentations, the cue-related mean percent signal change extracted from these clusters (Fig. 3*B*, dark gray bars) suggests that whereas the neural activation in the IFG and the IPS/TOS clusters did not differentiate between the different cue presentation conditions (IFG $F_{2,44} = 1.81$, $P = 0.1800$; IPS/TOS $F_{2,44} = 1.61$, $P = 0.2100$), the cluster in the medIPS demonstrated a marginally significant preference for contralateral cue presentation conditions regardless of whether the cue was unilateral or bilateral ($F_{2,44} = 4.36$, $P = 0.0190$; pairwise comparisons: bilateral vs. left: $t_{22} = 0.53$, $P > 0.9999$; bilateral vs. right: $t_{22} = 2.47$, $P = 0.0648$; left vs. right: $t_{22} = 2.24$, $P = 0.1074$, Bonferroni corrected for multiple comparisons).

The fact that our targets, when cued, were always validly cued, means that it is possible that differences in subject expectation between bilateral and unilateral target presentations confounded our target-related conjunction results. To address this possibility, we extracted the percent signal change separately for both cued and uncued bilateral and unilateral target presentations from the 3 regions identified in our conjunction analysis as being specifically associated with bilateral target presentations (IPS/TOS, medIPS, and IFG). Should our results indeed have been confounded by differences in subject expectations, we would expect to find target-related neural activation specific to bilateral situations for cued, but not (or to a lesser extent) for uncued target (as without cue, subject expectations should not differ between unilateral and bilateral target presentations). In other words, should our results have been confounded by differences in subject expectations, we would expect to find a significant interaction in a 2 (cue type: cued, uncued) by 3 (target display type: left, right, and bilateral) repeated-measures ANOVA in some or all of the 3 regions identified by the conjunction analysis as being specifically associated with bilateral target presentations.

This ANOVA revealed the same pattern of results for each region (Bonferroni corrected for multiple comparisons): firstly, a significant main effect of cue type with higher percent signal change for uncued than for cued target presentations (IPS/TOS: $F_{1,22} = 17.80$, $P = 0.0012$; medIPS: $F_{1,22} = 35.00$, $P = 0.0003$; IFG: $F_{1,22} = 27.80$, $P = 0.0003$). Secondly, a significant main effect of target display type with higher percent signal change for bilateral than for either unilateral left or unilateral right target displays (IPS/TOS: $F_{2,44} = 5.14$, $P = 0.0294$; medIPS: $F_{2,44} = 5.23$, $P = 0.0276$; IFG: $F_{2,44} = 9.58$, $P = 0.0012$). Thirdly and most importantly, no significant interaction between cue and target display type (IPS/TOS: $F_{2,44} = 0.03$, $P > 0.9999$; medIPS: $F_{2,44} = 0.05$, $P > 0.9999$; IFG: $F_{2,44} = 0.43$, $P > 0.9999$). These results suggest that the target-related neural activity specific to bilateral situations in the IPS/TOS, medIPS, and IFG cannot be attributed to differences in subject expectations.

Additionally, the presence of reaction time differences between bilateral target trials and unilateral target trials means that it is possible that our conjunction results are confounded by effects of task difficulty (note, however, that we did for this precise reason include these reaction time differences as covariates in our fMRI conjunction analyses). To address this possibility, we performed Pearson product-moment correlation analyses to assess the strength of the correlation between the percent signal change difference scores (bilateral vs. unilateral left and bilateral vs. unilateral right) and the associated reaction time difference scores within each of the regions highlighted by the conjunction analyses (latIPS, medIPS, IPS/TOS, and IFG). These analyses revealed no significant correlation between the percent signal change difference scores and the associated reaction time difference scores in any of the regions (latIPS bilateral vs. unilateral left: $r = 0.07$, $P > 0.9999$; latIPS bilateral vs. unilateral right: $r = -0.04$, $P > 0.9999$; medIPS bilateral vs. unilateral left: $r = -0.03$, $P > 0.9999$; medIPS bilateral vs. unilateral right: $r = -0.02$, $P > 0.9999$; IPS/TOS bilateral vs. unilateral left: $r = 0.21$, $P > 0.9999$; IPS/TOS bilateral vs. unilateral right: $r = -0.03$, $P > 0.9999$; IFG bilateral vs. unilateral left: $r = 0.09$, $P > 0.9999$; IFG bilateral vs. unilateral right: $r = 0.25$, $P > 0.9999$, Bonferroni corrected for multiple comparisons). These analyses thus suggest that our conjunction analysis results cannot be attributed to between-condition difficulty differences.

Contrary to our hypothesis, we found no evidence of target-related neural activation specific to bilateral situations in the TPJ. It has been suggested that the ventral stimulus-driven

attentional network and the TPJ in particular is especially activated when targets are presented at unattended locations (Corbetta et al. 2000; Kincade et al. 2005; Doricchi et al. 2010) and it is thus possible that we failed to find neural activation specific to bilateral situations in the TPJ simply because we averaged over cued and uncued targets. Thus, we ran an additional analysis identical to the main analyses (i.e., [{bilateral > unilateral left} AND {bilateral > unilateral right}]), this time using the subtraction of cued from uncued targets instead of the average of cued and uncued targets as input in the second-level random-effects model. Even at the extremely liberal voxelwise statistical threshold of $P < 0.05$ uncorrected for multiple comparisons, we found no significant activation specific to bilateral situations in the TPJ. When we restricted our analyses to uncued targets only, we likewise found no significant activation specific to bilateral situations in the TPJ, despite again lowering the statistical threshold to $P < 0.05$ uncorrected for multiple comparisons.

Another possible explanation for not finding target-related neural activation specific to bilateral situations in the TPJ is that, perhaps due to the long ISI between cue and target, our task might predominantly engage the dorsal goal-driven attention network. To assess whether the ventral stimulus-driven attention network was engaged in our task, we selectively compared the neural activation in uncued unilateral trials to the neural activation in cued unilateral trials which has previously been shown to be a powerful contrast to elicit neural activation in the ventral stimulus-driven network (Corbetta et al. 2000; Kincade et al. 2005; Doricchi et al. 2010). At a cluster-based statistical threshold of $P < 0.05$ FWE corrected for multiple comparisons, this analysis revealed large-scale activation in the ventral stimulus-driven attention network, in particular in the right TPJ (see Fig. 4), demonstrating that our task did engage the ventral attention network. We additionally extracted the mean percent signal change from 2 spherical regions of interest (radius 4 mm) centered on the left and the right TPJ (MNI coordinates: −53 −52 13 and 54 −42 22, respectively, indicated by the blue spheres in Fig. 4) for both cued and uncued targets. A 2 (cue type: cued, uncued) × 3 (target display type: left, right, and bilateral) repeated-measures ANOVA on the mean percent signal change from both the left and the right TPJ demonstrates an overall higher level of activity in response to uncued target presentations than cued target presentations (left TPJ: $F_{1,22} = 11.30$, $P = 0.0056$; right TPJ: $F_{1,22} = 30.80$, $P = 0.0002$, Bonferroni corrected for multiple comparisons). Neither the main effect of presentation condition, nor the interaction between cue condition and presentation condition were statistically significant. In other words, in line with the results of the whole-brain analyses reported above, neural activity in the left and the right TPJ was not particularly enhanced in response to bilateral targets, regardless of whether the targets were cued (Fig. 4, light gray bars) or uncued (Fig. 4, dark gray bars). To strengthen this conclusion, we additionally extracted the mean percent signal change from 3 spherical regions of interest (radius 4 mm) centered on the right TPJ as defined by Corbetta et al. (2000); Doricchi et al. (2010), and Kincade et al. (2005) when comparing the neural activation elicited by invalidly and validly cued unilateral targets, with MNI coordinates 59 −47 33, 60 −46 28, and 57 −50 29, respectively (original Talairach coordinates as reported by Corbetta et al. and Kincade et al. were converted to MNI coordinates using the tal2icbm transform [Lancaster et al. 2007]). Results were identical, regardless of the TPJ coordinates taken; the 2 (cue type: cued, uncued) × 3 (target display type: left, right, and bilateral) repeated-measures ANOVAs on the mean percent signal change extracted from these 3 spherical ROIs demonstrate an overall higher level of activity in response to uncued target presentations than cued target presentations in each ROI (Corbetta

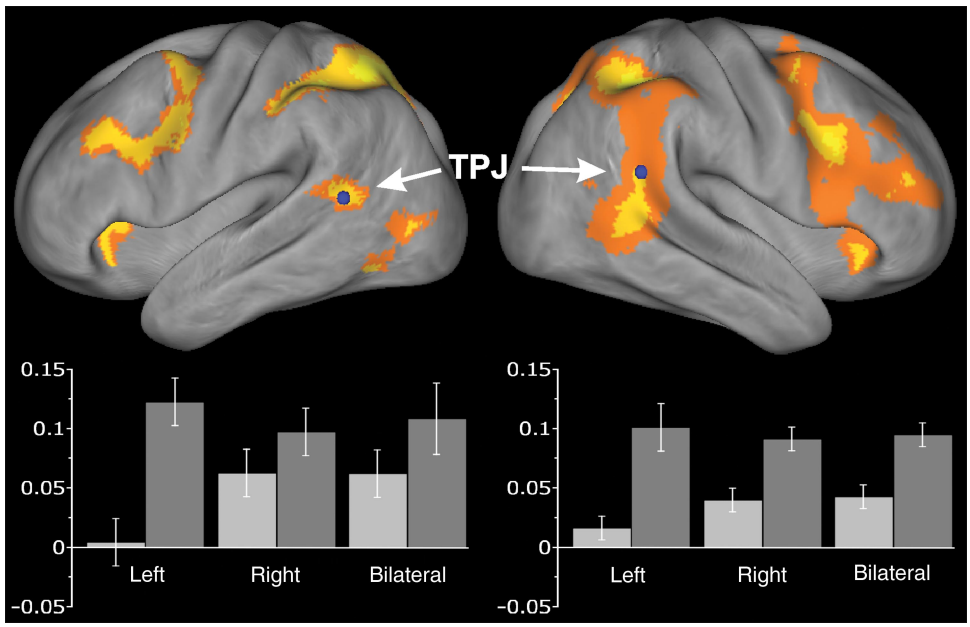

Figure 4. Results of the *t*-test highlighting areas where (uncued unilateral targets > cued unilateral targets). Bar graphs denote the percentage signal change extracted from the left and right TPJ (blue spheres) for each of the 6 possible combinations of cue type and target display type. Light gray bars reflect cued target presentations and dark gray bars reflect uncued target presentations. Error bars reflect nSE of the mean. The program Caret was used to project the significant activation onto the average surface rendering of 12 individuals (Van Essen 2005) and all images are in neurological orientation.

et al.: $F_{1,22} = 4.63$, $P = 0.043$; Doricchi et al.: $F_{1,22} = 11.50$, $P = 0.0027$; Kincade et al.: $F_{1,22} = 7.96$, $P = 0.0099$). Moreover, neither the main effect of presentation condition, nor the interaction between cue condition and presentation condition were statistically significant in any of the ROIs.

Discussion

Previous lesion/perfusion analysis and TMS studies have suggested an importance of both the right IPS and the right TPJ in our ability to attend and respond to multiple targets simultaneously and the loss of this ability in the neuropsychological disorder of extinction. The precise role of each of these 2 areas, however, is currently unclear. Inspired by the model proposed by Corbetta and colleagues (Corbetta and Shulman 2002; Corbetta et al. 2008), we hypothesized that the right IPS might be associated with both the top-down goal-driven direction of attention to multiple target locations and the bottom-up stimulus-driven detection of multiple targets simultaneously, whereas the right TPJ is solely associated with the bottom-up detection of multiple targets simultaneously.

Most previous fMRI studies investigating the neural correlates of this ability to simultaneously attend and respond to multiple sources of relevant information in our visual surroundings estimated the neural activation elicited by the presentation of one or more targets while the potential location(s) at which the target(s) could occur were known in advance and typically reported that neural activity in the IPS was correlated with the amount of locations attended (Geng et al. 2006), objects processed (Mitchell and Cusack 2008; Emrich et al. 2011) or objects encoded and maintained in visual short-term memory (Todd and Marois 2004; Xu and Chun 2006; Mitchell and Cusack 2008; Emrich et al. 2011; Gillebert et al. 2012). However, in these situations, subjects will have directed their top-down attention to (a subset of) these potential target locations prior to target presentation and the neural activation elicited by the presentation of one or more targets will thus have reflected both the top-down direction of attention to the potential target location(s) and the bottom-up detection of the target(s). To separate the contributions of top-down attention to the potential target location(s) and bottom-up detection of the target(s), 2 design characteristics are essential: firstly, a cued target detection task should be used which contains one event (the cue stimulus) that triggers the top-down direction of attention to the potential target location(s) and one event (the target stimulus) that triggers the bottom-up detection of the target(s). Secondly, the design should contain a large proportion of catch trials (trials where the cue stimulus is not followed by a target stimulus) which enables the separate estimation of the top-down neural activation associated with cue presentations and the bottom-up neural activation associated with target presentations (Ollinger, Corbetta et al. 2001; Ollinger, Shulman et al. 2001). The single previous study that did feature both these design characteristics, however, solely focused on the neuronal activity elicited by top-down direction of attention to multiple target locations simultaneously (Ciçek et al. 2007). Thus, our study is the first to separately assess both the neural activation specifically associated with top-down direction of attention to multiple potential target locations and the neural activation specifically associated with bottom-up detection of multiple targets simultaneously. This enabled us to assess, for the first time, whether the IPS is associated with both top-down direction of attention to multiple spatial locations and bottom-up detection of multiple targets simultaneously and whether the TPJ is associated with the bottom-up detection of multiple targets simultaneously.

In broad agreement with our hypothesis, our results suggest that both top-down goal-driven direction of attention to multiple target locations and bottom-up stimulus-driven detection of multiple targets simultaneously elicit neural activation in the right IPS. Goal-driven direction of attention to multiple target locations simultaneously was associated with an increase of neural activity in a single cluster located for the large part on the lateral wall of the horizontal segment of the IPS. The largest part (62.9%) of this cluster was assigned to hIP1 and hIP3 in the IPS. This cluster was located in close proximity to the "anterior IPL" peak associated with top-down direction of attention to multiple target locations simultaneously reported in the study performed by Ciçek et al. (2007), demonstrating that we were able to replicate their findings in a highly similar task. Additionally, the location of this cluster also closely agreed with the location of peaks from 2 other previous studies that assessed the areas where neural activation most likely reflected a combination of both top-down direction of attention to the potential target location(s) and bottom-up detection of the target(s) (Geng et al. 2006; Gillebert et al. 2012, "middle IPS"). Interestingly, the observation that this cluster responded selectively during bilateral cue presentations and was virtually silent during unilateral presentations supports the suggestion that distinct neural substrates underlie our ability to attend to a single spatial location and our ability to attend to multiple spatial locations simultaneously.

It has been argued that hIP1/hIP3 represents the human homolog of monkey area LIP (Vandenberghe et al. 2005; Gillebert et al. 2013). This argument is supported by the observation of functional similarities between hIP1/hIP3 and monkey LIP. In our study, hIP1/hIP3 was specifically activated during bilateral cue presentations. However, interestingly, hIP1/hIP3 also tended to be preferentially activated during bilateral target presentations when compared with unilateral target presentations (though this pattern failed to reach statistical significance). This suggests that neuronal activity in hIP1/hIP3 might be modulated by both top-down direction of attention and bottom-up detection of stimuli. Likewise, neuronal activity in monkey LIP has been shown to be modulated by both bottom-up visual inputs and top-down cognitive signals, which has led to the suggestion that monkey LIP represents a priority map that ultimately guides the direction of covert and/or overt attention to the spatial location(s) corresponding to the peak(s) in the priority map (Bisley and Goldberg 2010). Nevertheless, despite these functional similarities between hIP1/hIP3 and monkey LIP, the precise location of the human homolog of monkey area LIP is still debated with some studies arguing instead for a location more posterior (Sereno et al. 2001) or dorsomedial (Koyama et al. 2004). Moreover, the observation that hIP1/hIP3 was preferentially activated by both bilateral cue and bilateral target presentation does not necessarily mean that the same neuronal population underlies the response to both bilateral cue and bilateral target presentations. It is also possible that bilateral cue and bilateral target presentations activate different neuronal (sub)populations at a spatial scale that is inaccessible to methods like fMRI. The observation that hIP1/hIP3 preferentially responded to both bilateral cue presentations and bilateral target presentations

does, however, suggest that this area might be of particular importance for our ability to attend and respond in a multi-target environment.

Stimulus-driven detection of multiple targets simultaneously was also associated with an increase in neuronal activity in the right IPS. As previous studies either only assessed the neural correlate of top-down direction of attention or assessed the neural correlate of the combined processes of top-down direction of attention and bottom-up target detection in multi-target situations, the finding that the bottom-up detection of multiple targets simultaneously, when separately assessed, is also associated with neural activation in the right IPS, is new. This suggests that the right IPS might be critical for our ability to attend and respond to relevant information not only in a single-target environment as originally shown by Corbetta et al. (2000) see also (Shulman et al. 2003; Kincade et al. 2005), but particularly in a multi-target environment. Compared with goal-driven direction of attention to multiple target locations, stimulus-driven detection of multiple targets simultaneously was, however, associated with an increase in neuronal activation in 2 different parts of the right IPS.

The first cluster associated with the stimulus-driven detection of multiple target simultaneously was predominantly located on the medial wall of the horizontal segment of the IPS. The largest part (64.9%) of this cluster was assigned to area 7A. Despite the close proximity of this target-driven cluster to the cue-driven cluster located on the lateral wall of the IPS, there were subtle differences in the response profiles of these clusters; while the cluster on the lateral wall of the IPS showed a preference not only for bilateral cue presentations, but also a slight preference for bilateral target presentations, the cluster on the medial wall was specifically activated by bilateral target presentations, but showed no preference for bilateral cue presentations. Instead, the cluster on the medial wall of the IPS showed a significant preference for contralateral left-sided cue presentations regardless of whether the cue was unilateral or bilateral. The second cluster associated with stimulus-driven detection of multiple targets simultaneously was located more posteroventrally in the IPS in the superior parietal gyrus extending towards the TOS and into the superior and middle occipital gyrus. This cluster showed a response profile highly similar to the first cluster associated with stimulus-driven detection of multiple targets, i.e., a selective increase in neuronal activity in response to bilateral target presentations paired with a slight preference for contralateral left-sided cue presentations. This increase in neural activity specific to bilateral target presentations in the IPS is unlikely to be a mere consequence of differences in sensory stimulation between bilateral and unilateral target presentations. Increases in neural activity solely associated with increasing the amount of sensory stimulation typically occur in occipital (Todd and Marois 2004; Schwartz et al. 2005) and inferior temporal areas (Schwartz et al. 2005), areas not found in our conjunction analyses. Moreover, in the parietal cortex, increasing the amount of sensory stimulation has been shown to be associated with a decrease in neuronal activity, not with an increase (Schwartz et al. 2005). Taken together, we feel that the increase in neural activity in the IPS (and IFG) specific to bilateral target presentations is unlikely to be a consequence of differences in the amount of sensory stimulation, but instead is more likely to reflect attentional effects.

Similar to the cue-driven cluster located on the lateral wall of the IPS, the finding that these clusters responded selectively to bilateral target presentations and showed virtually no response during unilateral target presentations suggests that distinct neural substrates underlie our ability to detect a single target and our ability to detect multiple simultaneously presented targets. Moreover, the observation that both these clusters in the IPS responded to bilateral target presentations, but not to bilateral cue presentations, suggests that these clusters might serve a more selective role in the stimulus-driven selection of multiple targets simultaneously. In line with this, an area of the brain encompassing both these clusters has been associated with perceptual load, with neuronal activity increasing as a function of the number of objects simultaneously processed independently of visual working memory load (Mitchell and Cusack 2008; Emrich et al. 2011), and visual working memory load, with neural activity increasing as a function of the number of objects encoded and maintained in visual short-term memory (Todd and Marois 2004; Xu and Chun 2006). To account for our ability to encode multiple objects simultaneously, Xu and Chun (2009) proposed a 2-stage process for the encoding of multiple objects simultaneously. In the first stage objects are individuated, meaning that a fixed number of potentially relevant coarsely represented objects are selected on the basis of their spatial location. In the second stage, a subset of these individuated objects is subsequently processed in more detail to allow object identification. Interestingly, Xu and Chun (2009) proposed that object individuation is linked to the inferior IPS to an area that overlaps with our IPS/TOS cluster, whereas object identification is linked to the superior IPS to an area that overlaps with our cluster located on the medial wall of the IPS.

While our results broadly confirm our hypothesis that both top-down goal-driven direction of attention to multiple target locations and bottom-up stimulus-driven detection of multiple targets simultaneously elicit neural activation in the right IPS, our results failed to support our hypothesis that the right TPJ is associated with the bottom-up detection of multiple targets simultaneously. Specifically, we found no evidence to suggest that the TPJ was sensitive to bilateral target situations, regardless of whether targets were cued or uncued. Previous studies have suggested that a (temporary) disruption of neural function in the right TPJ is capable of eliciting extinction (Karnath et al. 2003; Meister et al. 2006; Grandjean et al. 2008; Ticini et al. 2010; Chechlacz et al. 2013), suggesting that the TPJ is critical for our ability to attend and respond to multiple targets presented simultaneously. However, fMRI studies comparing the neuronal activity between multi-target and single-target situations have typically failed to demonstrate increased neuronal activation associated with multi-target situations in the TPJ (Todd and Marois 2004; Geng et al. 2006; Xu and Chun 2006; Çiçek et al. 2007; Mitchell and Cusack 2008; Emrich et al. 2011; Gillebert et al. 2012).

How can we explain this discrepancy? One possibility is that the TPJ is not directly involved with the ability to simultaneously attend and respond to multiple targets, but that neuronal activity in the TPJ indirectly contributes to our ability to simultaneously attend and respond to multiple targets. As mentioned in the introduction section, extinction is most commonly seen as a consequence of biased competitive interactions between the ipsilesional and contralesional target stimuli in combination with

a pathologically limited attentional capacity (Driver et al. 1997; de Haan et al. 2012). Several studies have shown that a reduction of attentional capacity, for example by a concurrent visual short-term memory task, elicits a functional deactivation of the TPJ (Todd et al. 2005; Emrich et al. 2011). Moreover, this functional deactivation of the TPJ has been associated with target detection deficits (Todd et al. 2005; Emrich et al. 2011), particularly for targets presented in the left visual field and in multi-target environments (Emrich et al. 2011). These studies suggest that (temporary) damage to the TPJ might elicit extinction by reducing attentional capacity without the TPJ being directly associated with the ability to simultaneously attend to multiple targets.

While the TPJ was not sensitive to bilateral target presentations, the IFG, another node in the stimulus-driven ventral attention network as postulated by Corbetta and Shulman (2002) and Corbetta et al. (2008), was specifically associated with the stimulus-driven detection of multiple targets simultaneously. Like the clusters on the medial wall of the right IPS and the IPS/TOS, this cluster responded selectively during bilateral target presentations and was virtually silent during unilateral target presentations, again supporting the suggestion that distinct neural substrates underlie our ability to detect a single target and our ability to detect multiple simultaneously presented targets. Moreover, like these target-related clusters in the right IPS, this cluster was sensitive to the bottom-up detection of multiple targets simultaneously, but not to the cue-driven top-down direction of attention to multiple spatial locations simultaneously. Previous studies have shown that this area is sensitive to the top-down direction of attention to multiple spatial locations (Çiçek et al. 2007) and to the combined processes of top-down direction of attention to multiple spatial locations and bottom-up detection of multiple targets simultaneously (Geng et al. 2006). Moreover, the IFG has been associated with both perceptual and visual working memory load (Emrich et al. 2011). Taken together, this suggests that, like the 2 stimulus-driven clusters in the right IPS, the right IFG might be important for our ability to encode multiple objects simultaneously.

To summarize, broadly in line with our hypotheses, we found that the IPS is associated with both goal-driven direction of attention to multiple spatial locations and stimulus-driven detection of multiple targets. However, our results also suggest that different areas of the right IPS might provide different contributions to our ability to attend and respond in a multi-target environment. Our results suggest that both top-down direction of attention to multiple spatial locations and bottom-up detection of multiple target stimuli are associated with increased neural activation on the lateral wall of the IPS, suggesting that this area might be of particular importance for our ability to attend and respond in a multi-target environment. Moreover, our results suggest that, when separately assessed, bottom-up detection of multiple targets is associated with neural activation in 2 additional areas in the IPS, namely an area on the medial wall of the IPS and a more posterior area extending inferiorly towards the TOS, suggesting that these areas might serve a more selective role in the stimulus-driven selection of multiple targets simultaneously, possibly related to object individuation and identification in multi-target environments. We found no evidence for a role of the TPJ in stimulus-driven detection of multiple targets simultaneously. We did, however, find that in addition to the areas in the IPS, the right IFG is also associated with stimulus-driven target detection in a multi-target environment, suggesting a role in the ability to encode multiple objects simultaneously for this area as well. Thus, our results suggest that the IPS and the IFG of the right hemisphere underlie our ability to attend and respond in a multi-target environment.

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Notes

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