The Spatial Attention Network Interacts with Limbic and Monoaminergic Systems to Modulate Motivation-Induced Attention Shifts

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How does the human brain integrate information from multiple domains to guide spatial attention according to motivational needs? To address this question, we measured hemodynamic responses to central cues predicting locations of peripheral attentional targets (food or tool images) in a novel covert spatial attention paradigm. The motivational relevance of food-related attentional targets was experimentally manipulated via hunger and satiety. Amygdala, posterior cingulate, locus coeruleus, and substantia nigra showed selective sensitivity to food-related cues when hungry but not when satiated, an effect that did not generalize to tools. Posterior parietal cortex (PPC), including intraparietal sulcus, posterior cingulate, and the orbitofrontal cortex displayed correlations with the speed of attentional shifts that were sensitive not just to motivational state but also to the motivational value of the target. Stronger functional coupling between PPC and posterior cingulate occurred during attentional biasing toward motivationally relevant food targets. These results reveal conjoint limbic and monoaminergic encoding of motivational salience in spatial attention. They emphasize the interactive role of posterior parietal and cingulate cortices in integrating motivational information with spatial attention, a process that is critical for selective allocation of attentional resources in an environment where target position and relevance can change rapidly.

Keywords: amygdala, fMRI, inferior parietal sulcus, posterior cingulate, posterior parietal cortex

Introduction

The term "spatial attention" designates interrelated sensory, motor, and cognitive processes that collectively enable the selective allocation of neural resources to motivationally relevant parts of the environment. A key aspect of this process is the compilation of a salience map that combines the spatial coordinates of an event with its perceptual and motivational relevance (Fecteau and Munoz 2006; Gottlieb 2007). How the human brain integrates information from sensory, motor, cognitive, and motivational domains to dynamically guide spatial attention is not fully understood.

Spatial attention is supported by a large-scale network consisting of interacting cortical components in posterior parietal cortex (PPC), including intraparietal sulcus (IPS), lateral frontal cortex, including the frontal eye fields (FEF) and the cingulate gyrus, including its posterior segment (PC) (Mesulam 1981; Corbetta et al. 1993; Nobre et al. 1997; Gitelman et al. 1999; Kim et al. 1999; Mesulam 2000). It is likely that these components support spatial attention by mediating dynamic interactions between spatial orienting and more abstract cognitive functions such as motivational and emotional

evaluation. This possibility has been examined via a few single-unit recording studies in nonhuman primates (Platt and Glimcher 1999; Coe et al. 2002; Sugrue et al. 2004), but remains to be examined in humans.

Motivational encoding of stimuli is mediated by subcortical, limbic, and paralimbic structures, including the amygdala (LaBar et al. 2001; O'Doherty et al. 2002; Gottfried et al. 2003), orbitofrontal cortex (OFC) (Rolls et al. 1981; Tremblay and Schultz 1999; Small et al. 2001), and ascending mono-aminergic pathways arising from the substantia nigra (SN) and nucleus locus coeruleus (LC) (Foote et al. 1980; Aston-Jones et al. 1997; Schultz et al. 1997). Effective motivational modulation of spatial attention most likely depends on accurate real-time assessment of motivational salience mediated via these regions. However, the involvement of limbic and mono-aminergic areas in the encoding of motivational salience of cues that predict locations of relevant attentional targets is relatively understudied.

The present study was designed to explore the motivational modulation of the spatial attention network in a task that manipulated the motivational properties of the attentional target, the motivational state of the participant and the location of the target. To that end, we used a covert attentional shift paradigm to examine the effect of alterations in motivational states (hunger and satiety) on attentional biasing to peripheral locations where motivationally relevant (food) and irrelevant (tools) targets were expected to appear. We expected participants to respond faster to food-related targets when hungry than when full and that this effect would not be present for tools. We hypothesized that hunger would selectively increase neural responses in limbic regions and pontomesen-cephalic monoaminergic nuclei to food- but not tool-related directional cues. Finally, we examined the possibility that components of the spatial attention network, including PPC and posterior cingulate cortex would mediate motivational modulation of anticipatory spatial attention in a material-specific manner reflecting the current motivational value of the attentional target rather than the nonspecific effects of arousal.

Materials and Methods

Participants

Nine right-handed volunteers (4 women; mean/SD age = 27/5.25 years) participated in the study. Participants were screened for a history of psychiatric and neurologic illness or contraindications for functional magnetic resonance imaging (fMRI) and gave written informed consent prior to participation. Participants were also screened to ensure that they liked the food stimuli, that is, donuts and danishes and were not restrictive eaters or diabetics. The study was approved by the Northwestern University Institutional Review Board. Two participants were excluded due to fMRI related artifacts resulting in a final N of 7.

Procedure

Participants were asked to perform a modification of the task developed by Posner for examining covert shifts of spatial attention (Posner 1980) while undergoing fMRI in hungry and satiated states which were counterbalanced across participants. While performing the task, participants were asked to fixate on a central diamond (1° wide) that remained on the screen for the complete duration of the task. They were instructed to respond to the onset of peripherally presented donuts or hex-nuts (targets) and danishes or screws (foils) by pressing a button (Fig. 1). To ensure that participants attended to the stimuli, they were instructed to press the left-hand button for foils and the right-hand button for target images. All food and tool stimuli were obtained from commercially available images, and were formatted to the same resolution and size. Each trial began with a darkening of one side or the entire central diamond, which provided an alerting directional or nondirectional cue respectively (Fig. 1). This cue remained on the screen until the appearance of the target stimulus to avoid engaging working memory. Three different lengths of delay (or stimulus asynchrony, SOA of 200, 400, and 800 ms) between cue and target presentation were employed to maximize attentional demands and prevent temporal predictability. Following this delay, targets or foils appeared in 1 of 2 peripheral squares (on the right and left of the diamond, each 1.5° wide) centered at 7.5° from the central diamond for 100 ms, on the side indicated by the directional cue (valid trial), on the opposite side (invalid trial), and on either side of the nondirectional cues (nondirectional trial). The total intertrial interval varied as a function of SOA such that each trial totaled 2200 ms (i.e., 2000, 1800, and 1600 ms). Null events or time periods when the screen remained blank, were interspersed with target events to allow deconvolution of the hemodynamic response function (HRF) (Burock et al. 1998). Null events lasted 1000 ms and up to 3 could occur consecutively. Half of the trials in each run were comprised of null events.

Each participant was imaged as they performed the task in 2 experimental sessions, once while hungry and once while satiated on donuts. The 2 experimental sessions were held 1 week apart and their order was counterbalanced across subjects. All participants were instructed not to eat food for at least 8 h prior to the fMRI session. Ratings of hunger and appetitiveness of all target stimuli were obtained prior to each experimental session. To manipulate the motivational salience of the food stimuli, subjects were informed that they would be given 1 donut following testing in the hunger condition and were allowed to consume as many donuts as they could before testing in the satiated condition. In the scanner, the participants viewed the task via a mirror attached to the head coil. Using a liquid crystal display projector attached to the stimulus presentation computer, stimuli were back-projected onto translucent screen that the participants viewed through a mirror.

Participants performed a total of 6 randomly presented runs in each experimental session. Within each run, the task was implemented as a mixed event-related design by presenting the food and tool trials in separate blocks. This was done in order to avoid introducing the additional factor of deciding whether the stimuli were foods or tools. An image saying "FOOD" or "TOOLS" appeared at the beginning of each block for 1000 ms to cue subjects on the block type. Each run consisted of 6 randomly presented blocks, 3 food blocks and 3 tool blocks. Overall, each experimental run consisted of 216 trials (90% targets and 10% foils) out of which, 60% were valid trials, 15% were invalid trials, and 25% were nondirectional trials.

Image Acquisition

Functional images were acquired with a 3-Tesla Siemens Trio whole-body MRI system using a birdcage head coil. Participants lay supine within the scanner. Their heads were immobilized with a vacuum pillow (Vac-Fix, Bionix, Toledo, OH) and the restraint calipers built into the head coil. A vitamin E capsule was taped to the left temporal region to mark laterality for image processing. Participants were given 2 nonmagnetic button boxes, which enabled recording of their reaction time (RT) data.

In each of the 6 runs/session, 227 images were acquired using echo-planar T_2-weighted sequence (time repetition = 2.1 s, time echo = 20 ms; flip angle 90°, field of view = 220 cm, matrix = 64 × 64 voxels). Each image consisted of 40 contiguous axial slices (slice thickness 3 mm, in-plane resolution 3 × 3 mm) acquired parallel to the anterior and posterior commissures. Six dummy images were collected at the beginning of each functional run to allow the blood oxygen–dependent (BOLD) signal to reach a steady state and were excluded from further processing and analysis. After the fMRI acquisition, a 160-slice magnetization-prepared rapid gradient echo structural sequence was acquired (spatial resolution 1 × 1 × 1 mm) in each session and was used to register the participant's functional data into standard space.

Data Analyses

Behavioral Analyses

Trials with RTs less than 100 ms or greater than 1000 ms were discarded. Mean RT was calculated for valid, invalid, and nondirectional trials separately for hungry and satiated experimental sessions. An overall repeated-measures analysis of variance (ANOVA) with 3 factors, motivational state (hungry and full), target type (food and tools), and directional nature of cue (valid, invalid and nondirectional) was performed to evaluate the impact of alterations in hunger and satiety on the RT for validly, invalidly, and nondirectionally cued food and tool targets. To compute the degree to which a valid directional cue benefited performance, a cue benefit score was calculated using equation (1).

$$\frac{\overline{RTN} - RTV_i}{\sigma_{RTN}} \tag{1}$$

$\overline{RTN}$ is the mean RT for the nondirectional trials, RTV_i is the RT for each validly cued trial, and σ_{RTN} is the standard deviation of the nondirectional trials. The cue benefit scores were calculated separately for the hungry and satiated sessions using the mean and standard deviation nondirectional RT for that particular session. The cue benefit scores, which are measures of the speed of attentional shifts to the food or tool-related targets, were used to predict variations in the HRF during the validly cued trials.

Image Processing and Analyses

fMRI data were analyzed using the SPM2 software (Wellcome Department of Cognitive Neurology, London, UK) running under the MATLAB environment (Mathworks, Inc., Sherborn, MA). Functional images for each participant were corrected for slice timing, realigned for correction of motion artifacts, coregistered to that participant's high-resolution anatomical T_1 image, spatially normalized, using the EPI template provided in SPM2, into a standard anatomical space (Montreal Neurological Institute [MNI-305]) that approximately conforms to the atlas of Talairach and Tournoux (1988) and smoothed with an isotropic Gaussian kernel (full width half maximum = 7 mm). Runs with more than 1 voxel of scan-to-scan movement were excluded from further analysis.

For each subject, a canonical HRF approximating the temporal course of the BOLD HRF to valid, invalid, and nondirectionally cued food and tool targets was modeled separately for the hungry and satiated sessions. The temporal derivative of the HRF was included to accommodate temporal variability in the HRF function across brain areas and participants. This model yielded a per-voxel parameter estimate (β) map representing the magnitude of activation associated with each trial type. Null trials were not modeled explicitly and contributed to the implicit baseline. The design also included a 128 sec high-pass filter and an AR(1) model to account for temporal non-sphericity due to autocorrelations.

The fMRI data were first examined to determine brain regions that are involved in encoding motivational salience (level 1). These regions were expected to show selective sensitivity to food-related cues when hungry but not when satiated, an effect that would not generalize to tools. For each subject, statistical comparisons between different trial types were conducted by comparing the corresponding β maps using linear contrasts. To contrast activation for food versus tool targets in the hungry versus satiated state, corresponding β maps from validly cued trials were subjected to a double subtraction procedure resulting in a [(hungry food − full food) − (hungry tools − full tools)] statistical parameter (SPM) t map for each subject. This procedure is statistically
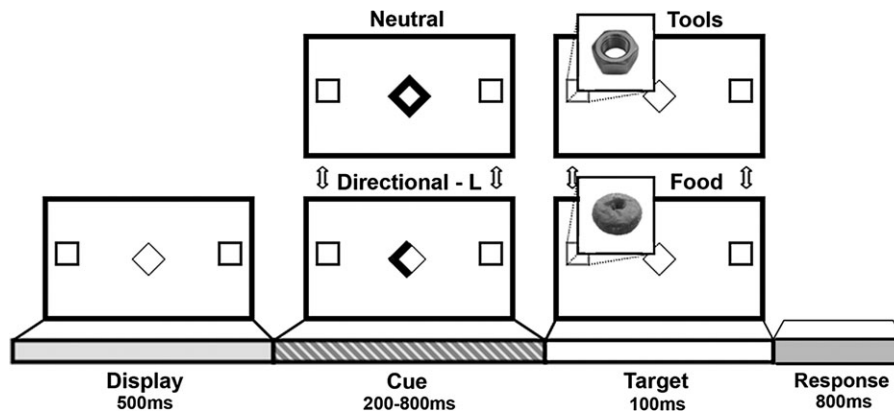
Figure 1. Stimuli and timelines used in the experimental task. Participants were instructed to respond to the onset of peripherally presented targets (donuts or hex-nuts) and foils (danishes or screws) by pressing the right and left button respectively. A cue that preceded target onset by 200, 400, or 800 ms indicated that the target would appear on the side indicated by the directional cue (valid trial), on the opposite side (invalid trial), and on either side of the nondirectional cues (nondirectional trial). Each participant was imaged as they performed the task in 2 experimental sessions, once while hungry and once while satiated on donuts.

equivalent to motivational state by target type, within-subject interaction. Finally, the [(hungry food – full food) – (hungry tools – full tools)] linear contrast images computed at the individual subject level were forwarded to a second-level random-effects analysis to examine the effect of motivational state (hungry and full) on neural responses to directional cues indicating food- and tool-related targets.

Next, we examined brain regions that mediate motivational modulation of anticipatory spatial attention in a material-specific manner (level 2). For this purpose, another model was estimated to examine brain areas whose activity was associated significantly with cue benefit scores. This model was identical to the one outlined above except for the addition of a condition specific regressor that modeled the benefit scores derived from the cues as a continuous factor. This regressor allowed us to identify voxels that specifically show a significant correlation with cue benefit scores on validly cued trials. The calculation of the cue benefit scores is described in the behavioral analyses section above. To examine how motivational state altered the correlation between neural activity and the speed of attentional shifts differentially to food versus tool targets we subjected the β maps denoting correlation between cue benefit scores and brain activity for validly cued trials to the double subtraction procedure outlined above. This double subtraction procedure resulted in a [(hungry food – full food) – (hungry tools – full tools)] SPM t map for each subject. These maps were forwarded to a second-level random-effects analysis to examine the effect of motivational state (hungry and full) on the correlation between cue benefit scores and neural responses to directional cues indicating food- and tool-related targets.

Because we had specific a priori hypotheses regarding the role of limbic regions (e.g., amygdala and PC) in encoding of motivational valence (level 1) and the role of spatial attention network (e.g., PC, PPC/IPS, FEF) in biasing spatial attention (level 2), we conducted a region of interest (ROI) analyses. Search volumes for the ROI analyses were restricted within a 6–10 mm radius of coordinates for amygdala (±21, –3, –27), PC (±21, –39, 36; ±9, –39, 24), PPC/IPS (±21, –60, 51; ±27, –60, 57), FEF (±27, –6, 42; ±51, 0, 36), medial OFC (MOFC) (±18, 25, –18), and lateral OFC (LOFC) (±41, 34, –19) that were derived from earlier studies conducted in our labs, from contrasts most relevant to the present study (Gitelman et al. 1999; LaBar et al. 2001; Small et al. 2001, 2003, 2005). For these ROIs small volume correction was applied to P-values and only regions that were activated above a $P < 0.05$, false discovery rate (FDR) corrected threshold are reported. In addition, to examine regions other than those identified by the ROI analyses, we conducted an exploratory whole-brain analyses by using a statistical threshold of $P \leqslant 0.005$, uncorrected and a cluster threshold of greater than 6 voxels. Finally, the pattern of activation in regions identified as being above threshold in the ROI and whole-brain analyses outlined above was examined in greater detail. This was done by extracting signal time courses and calculating the spatially averaged percent signal change or parameter estimate for each condition from each activation

cluster using the Marsbar toolbox (http://marsbar.sourceforge.net/). SPSS was then used to examine the simple effects driving the interaction confirmed by whole-brain and ROI analyses.

Finally, we examined the task-dependent changes in connectivity that linked the 2 levels using psychophysiological interaction (PPI) analyses. The PC, which has been shown to be involved in anticipatory biasing of spatial attention to motivationally relevant events (Small et al. 2003, 2005), served as a seed region from the first level. For PPI, the deconvolved time-series data for PC was extracted from each participants normalized data, based on a sphere of radius 6 mm around the peak activation voxel from the group analyses. The product of this activation time-series data and the psychological vector of interest (hungry food – full food) resulted in the PPI term. New SPMs with the physiological variable (PC activity), psychological variable, and their interaction as regressors were computed for each subject. These subject level PPI SPMs were then entered into a random-effects group analyses using a t-test within functional parietal and OFC ROIs where motivational state differentially altered the relationship between neural activity and speed of attentional shifts toward food compared with tool-related targets and results were thresholded at $P < 0.05$ (uncorrected) with a cluster size of >6 contiguous voxels.

Results

Motivational modulation of spatial attention was examined by asking participants (in the fasting or satiated state) to perform an event-related fMRI task in which central cues signaled locations of motivationally relevant (food) and motivationally irrelevant (tool) attentional targets that were presented peripherally. Thus, the present study implemented a motivational state (hungry and full) by attentional target type (food and tools) factorial design. One aim was to reveal areas that were selectively responsive to motivationally relevant targets. The second aim was to examine whether regions of the spatial attention network mediate motivational modulation of anticipatory spatial attention in a material-specific manner.

Behavioral

Behavioral ratings of hunger level showed that participants rated themselves as significantly more hungry prior to performing the task in the hungry condition compared with the satiated condition (Fig. 2A; $t_6 = 10.07$, $P < 0.05$). Participants also rated food stimuli as less appetizing when fed than when hungry, whereas this effect did not generalize to the tools (Fig. 2B). A repeated-measures ANOVA with motivational state and target type as factors showed a significant interaction ($F_{1,6} = 31.11$,
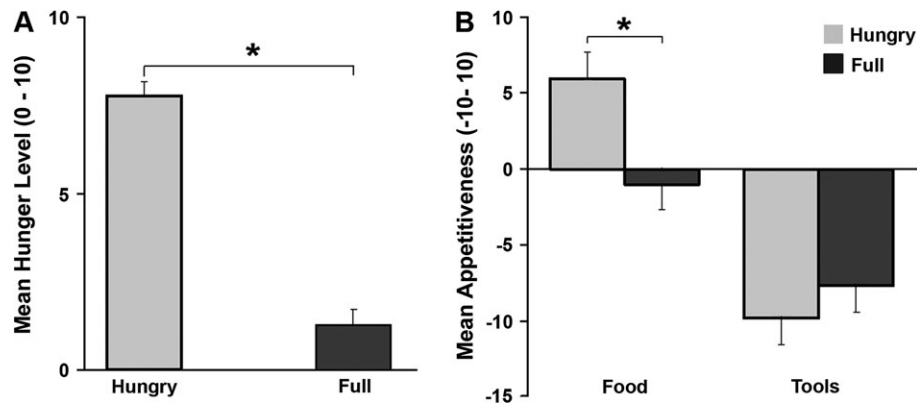
Figure 2. (A) Mean ratings of hunger level at pre- and postsatiety. (B) Mean ratings of appetitiveness for food and tool target stimuli at pre- and postsatiety. Error bars represent 1 SEM.

$P = 0.001$) and a main effect of target type ($F_{1,6} = 31.11$, $P = 0.001$). Simple-effects tests showed that food stimuli were rated as more appetizing during the hungry than the satiated condition ($P < 0.05$) whereas appetitiveness ratings for tools remained unaffected by motivational status.

A 3-way repeated-measures ANOVA with motivational state, target type, and cue type (valid, invalid, and nondirectional) as factors showed a significant main effect of the cue type ($F_{2,5} = 6.32$, $P = 0.043$). Planned comparisons showed a faster mean RT for validly cued than invalid and nondirectional trials and a faster mean RT for nondirectional than invalidly cued trials ($F_{1,6} = 15.18$, $P = 0.008$) indicating that we were able to effectively modulate spatial biasing of attention. Because the present study proposed specific hypotheses regarding selective enhancement of attentional biasing toward motivationally relevant targets, we used a 1-tailed, paired t-test to examine whether participants showed faster RT for food-related targets that were motivationally relevant. Results showed a trend toward significance with marginally faster mean RT's to validly cued food-related targets when hungry than when full ($t_6 = -1.59$, $P = 0.083$). This effect did not generalize to validly cued tool targets or nondirectionally cued food- and tool-related targets, indicating that it reflects a relatively specific effect of hunger-related motivation on spatial attention directed to edible objects.

Functional MRI

#### Encoding of Motivational Salience (Level 1)

The first aim of the present study was to reveal areas that are selectively responsive to the motivational value of targets. For this purpose, a random-effects analysis was used to examine the effect of motivational state (hungry and full) on neural responses to directional cues indicating food- and tool-related targets (Methods). ROI analyses showed a motivational state by target type interaction in a priori defined ROIs in the PC and amygdala (Fig. 3A, Table 1). The pattern of percent signal change in both ROIs indicated that the interaction was driven primarily by hunger-related increases in neural responses to food- but not tool-related cues (Fig. 3B). Repeated-measures ANOVAs on the mean percent signal change extracted from these ROIs confirmed the motivation state by target type interaction in the PC ($F_{1,6} = 5.58$, $P = 0.056$) and the amygdala

($F_{1,5} = 17.83$, $P = 0.008$). Simple-effects tests examining the interaction in both ROIs showed that activity for tool-related cues when hungry did not differ from tool-related cues when full and food-related cues when hungry (all Ps were nonsignificant). In both PC and amygdala, the interaction was driven by increased activity for cues indicating food-related targets when hungry than when full (Ps < 0.05). In addition, the amygdala showed significant difference between food and tool-related cue activity in the satiated condition ($P < 0.05$).

Analyses of the whole brain showed a motivational state by target type interaction in parahippocampal gyrus, peristriate cortex, and in areas of the pontomesencephalic brainstem region consistent with the location of the LC and SN (Fig. 3A, Table 1). The representative pattern of percent signal change in these clusters indicates that the interaction was driven by hunger-related increases in neural responses to food- but not tool-related cues (Fig. 3B). A repeated-measures ANOVA on the percent signal change confirmed a motivational state by target type interaction in parahippocampal gyrus ($F_{1,6} = 22.52$, $P = 0.003$), peristrate cortex ($F_{1,6} = 5.60$, $P = 0.056$), SN ($F_{1,6} = 38.78$, $P = 0.001$), and LC ($F_{1,6} = 19.90$, $P = 0.004$), indicating that these regions responded differentially to food- and tool-related cues based on motivational state. Simple-effects tests showed greater activity for food-related cues when hungry than food-related cues when full and tool-related cues when hungry (all Ps < 0.05). Simple effects comparing tool-related cue activity when full to tool-related activity when hungry and food-related activity when full were nonsignificant. Thus, the interactions were primarily driven by changes in food-related cue activity for hungry and satiated condition. Although the spatial resolution provided by fMRI does not allow for a precise identification of smaller structures such as brainstem nuclei, the locations of the activations in the present study are compatible with locations reported for LC and SN in earlier imaging studies (O'Doherty et al. 2002; Wittmann et al. 2005; Sterpenich et al. 2006; Germain et al. 2007; Murray et al. 2007).

Motivational Modulation of Spatial Attention (Level 2)

Next we examined whether regions of the spatial attention network mediate motivational modulation of anticipatory spatial attention in a material-specific manner. We identified brain areas where motivational state altered the correlation between neural activity and speed of attentional shifts toward
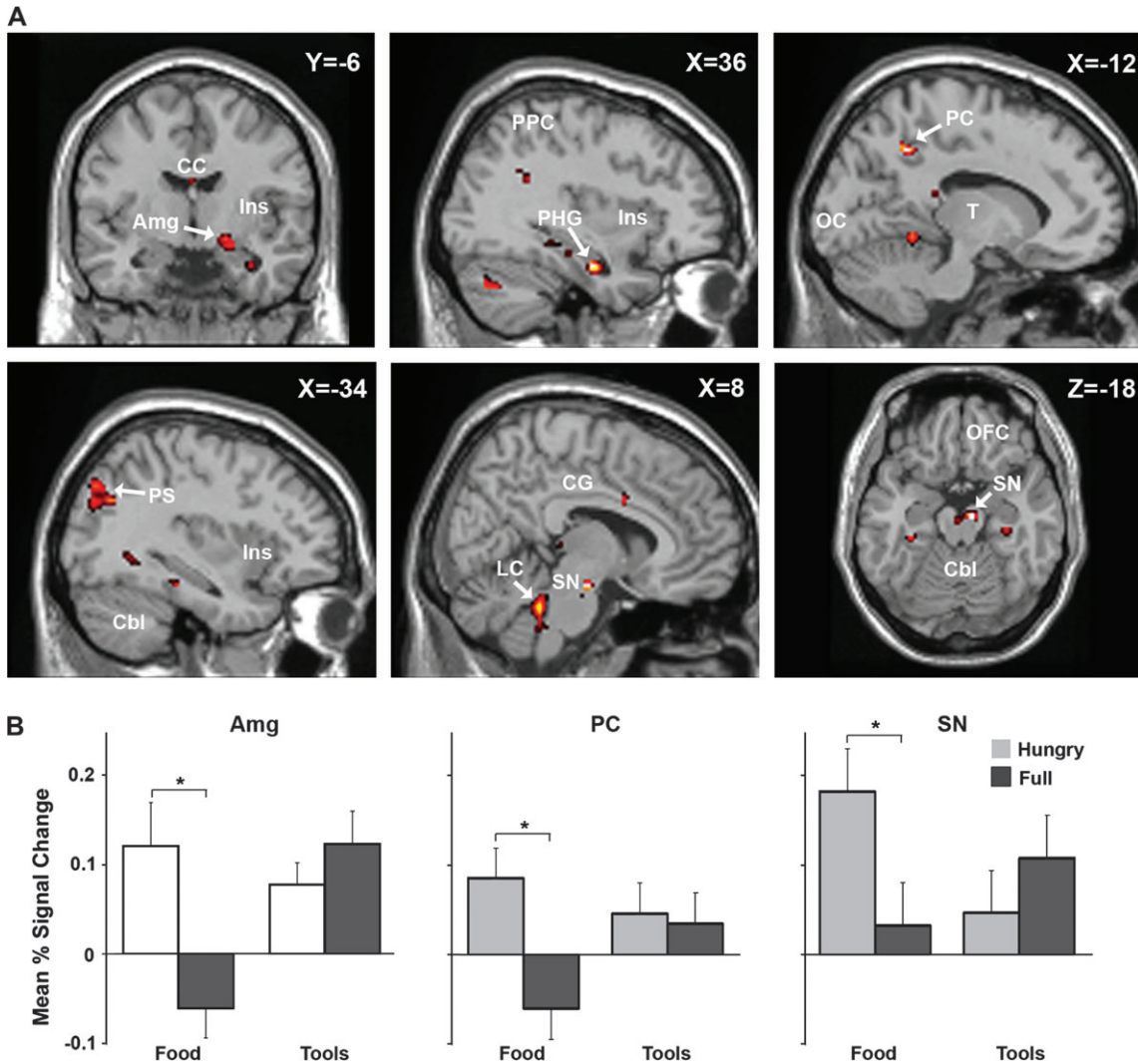
Figure 3. (A) Modulation of neural responses to food and tool-related directional cues by hunger and satiety. Images from the group random-effects analysis depict regions that responded differentially to food versus tool-related directional cues in the hungry versus satiated conditions. The images are thresholded at $P < 0.05$, uncorrected, for display purposes. Top coronal and sagittal sections show activity in amygdala (Amg), parahippocampal gyrus (PHG), and posterior cingulate (PC); sagittal and axial sections below display peristriate (PS), LC, and SN activity; corpus callosum (CC), insula (INS), PPC, occipital cortex (OC), thalamus (T), cerebellum (Cbl), cingulate gyrus (CG), and OFC. (B) Selective increase in neural responses to directional cues predicting food- but not tool-related targets in the hungry versus satiated condition. Bar plots show the mean percent BOLD signal change (± 1 SEM) in the Amg, PC and SN (B) for food and tool stimuli in hungry and satiated condition.

food versus tool-related targets differentially (Methods). ROI analyses using a priori ROIs identified in spatial attention experiments conducted in our lab show a motivation state by target type interaction in IPS/PPC and PC (Fig. 4A, Table 1). The pattern of mean parameter estimates extracted from these regions indicates a stronger positive correlation between brain activity and benefits derived from cues signaling food-related targets when hungry versus food targets when full, whereas an inverse pattern is present for tool-related targets (Fig. 4B). This interaction was confirmed by repeated-measures ANOVA conducted on mean parameter estimates extracted from IPS/PPC ($F_{1,5} = 20.22$, $P = 0.006$) and PC ($F_{1,5} = 6.92$, $P = 0.046$). Simple-effects tests confirmed a stronger positive relationship between brain activity and cue benefits when expecting food-related targets in the hungry condition versus food targets in the full condition and tool-related targets in the hungry condition ($P < 0.05$), whereas an opposite pattern seen for tools was marginally significant ($P < 0.08$).

We also conducted ROI analyses with MOFC and LOFC coordinates because OFC subdivisions have been shown to be differentially recruited based on the reward value of a food item. Results showed a motivation state by target type interaction in the MOFC and LOFC (Fig. 4C, Table 1). Further examination revealed a differential pattern of results in the 2 OFC subdivisions with increased MOFC activity associated with greater cue benefits for food-related targets while hungry and increased LOFC activity associated with less cue benefits while hungry and greater cue benefits for food-related targets while full (Fig. 4D).

Finally, whole-brain analyses showed an interaction in PPC/ IPS (upper axial sections in Fig. 4A), temporoparietal junction (TPJ), and parahippocampal gyrus (lower axial section in Fig. 4A, Table 1). A repeated-measures ANOVA on the parameter estimates confirmed the motivational state by target item interaction in the TPJ ($F_{1,5} = 29.50$, $P = 0.003$) and parahippocampal gyrus ($F_{1,5} = 6.92$, $P = 0.046$), indicating that these regions were

Table 1

Encoding of motivational relevance (level 1) and motivational modulation of attention (level 2)

Regions	Co-ordinates	Z	Level 1	Level 2
ROI analyses				
Amygdala	21, −6, −9	2.99	**	NS
Posterior cingulate	12, −51, 42	3.62	**	
	−9, −42, 15	2.81		**
PPC/IPS	21, −57, 48	2.95	NS	**
MOFC	21, 30, −18	2.73	NS	**
LOFC	−45, 33, −18	3.40	NS	**
Whole-brain analyses				
Parahippocampal gyrus	15, −45, −6	3.22		*
	36, −12, −24	3.59	*	
	18, −21, −21	2.94	*	
LC	9, −42, −30	3.23	*	NS
SN	9, −15, −18	4.55	*	NS
	3, −15, −6	3.34	*	
	−3, −24, −6	3.20	*	
Peristriate cortex	−33, −69, 30	3.18	*	NS
TPJ	39, −48, 18	3.20	NS	*
PPC/IPS	21, −57, 45	3.01	NS	*
	27, −54, 54	2.74		*

Note: *Significant at a mapwise threshold of $P \leq 0.005$, uncorrected and **significant at a $P < 0.05$, FDR corrected using small volume correction, NS = nonsignificant.

differentially involved in spatial attention based on motivational state. Simple-effects tests confirmed a stronger positive relationship between brain activity and cue benefits when expecting food-related targets in the hungry condition versus food targets in the full condition and tool-related targets in the hungry condition, whereas an opposite pattern was seen for tool-related targets ($P < 0.05$).

We also examined PC's role as a putative neural link between motivation and spatial attention using PPI analysis (Friston et al. 1997). This analysis allowed us to examine context-specific changes in functional integration between PC and IPS or OFC during spatial biasing of attention toward motivationally relevant compared with irrelevant targets. PPI analysis was conducted using functional ROIs where motivational state differentially altered the correlation between neural activity and speed of attentional shifts toward food compared with tool-related targets (Methods). Results revealed a cluster of voxels in the IPS ROI that showed motivational state specific increments in functional integration with PC such that functional coupling between IPS and PC for food-related stimuli increased when the stimuli were motivationally relevant (hungry state) versus when they were irrelevant (full state). Thus, the functional coupling between PC and IPS increased during spatial biasing of attention to motivationally relevant stimuli compared with irrelevant stimuli. Although a similar pattern of results was seen for the functional coupling between OFC and PC, the findings were marginally significant ($P < 0.08$).

Summary of Results

Subjects rated themselves hungrier and the donuts as more appetizing after the fast; hunger caused a shortening of RT to foods but not tools; the SN, LC, amygdala, parahippocampal gyrus, and peristriate cortex were more strongly activated by foods than tools when hungry but not when full; activation in components of the spatial attention network such as the PPC, banks of the IPS, TPJ, and PC was more positively correlated with the speed of attentional shifts to food targets when hungry than full, whereas an inverse pattern was seen for tool targets; stronger functional coupling between PC and IPS during spatial biasing of attention toward motivationally relevant stimuli; in the OFC positive correlations of neural activity with attentional shifts to foods were seen medially (MOFC) when hungry and laterally (LOFC) when full.

correlations of neural activity with attentional shifts to foods were seen medially (MOFC) when hungry and laterally (LOFC) when full.

Discussion

Earlier studies have used secondary reinforcers like money to demonstrate the influence of motivational variables on attention (Small et al. 2003, 2005; Della Libera and Chelazzi 2006; Engelmann and Pessoa 2007). The present study manipulated the motivational state of the participants and used targets with intrinsic hedonic relevance to examine the neural mechanisms involved in the motivational guidance of spatial attention. In this study, fasting or satiated participants performed an event-related fMRI task in which spatially uninformative or directional cues signaled locations of motivationally relevant (food) and motivationally irrelevant (tool) attentional targets. The trials were blocked into "food" and "tool" sessions in order to maintain a consistent set of motivational expectation. The foils ensured that subjects attended to the targets, whereas the invalid and spatially uninformative cues allowed us to quantify the effectiveness of cue-induced attentional shifts and differentiate them from the effects of temporal expectancy. We examined the influence of motivational state (hungry vs. satiated) and cues depicting targets (food vs. tools) on neural activity in order to explore how attentional shifts are modulated by motivational factors. Although we modeled neural activity for predictive cues, it is to be noted that the present experimental design does not allow clear separation of cue from target-related activity.

Limbic and Monoaminergic Encoding of Motivational Valence

Hunger selectively enhanced activity in visual peristriate cortex, limbic structures (amygdala, PC, parahippocampal gyrus), and brainstem monoaminergic nuclei (SN, LC) to food- but not tool-related directional cues. Recordings in monkeys (Nishijo et al. 1988; Ono et al. 2000), amygdala lesion studies in rats (Dwyer and Killcross 2006) and humans (Bechara et al. 1995, 1999), and fMRI studies in neurologically intact subjects (LaBar et al. 2001; O'Doherty et al. 2002; Gottfried et al. 2003) have demonstrated the importance of amygdala in mediating the motivational and visceral impact of motivationally relevant events. Similarly, noradrenergic and dopaminergic pathways have been known to regulate motivational and arousal aspects of behavior (Foote et al. 1980; Berridge 1996; Aston-Jones et al. 1997; Schultz et al. 1997). Our study further establishes their sensitivity to predictive cues that trigger an anticipatory attentional shift toward locations where motivationally relevant events are expected to occur.

Through its interconnections with peristriate areas (Aggleton 1993), the amygdala could provide a top-down modulatory influence that preferentially enhances the encoding of salient events in visual areas (Fig. 3A). Although it is unlikely that there is a one-to-one correspondence between the monoaminergic pathways and specific cognitive domains, the activation of these modulatory pathways provides a general mechanism for augmenting neural responses to salient events. The combined activation of these 2 pathways in anticipation of the food picture would be expected to enhance the hunger-induced
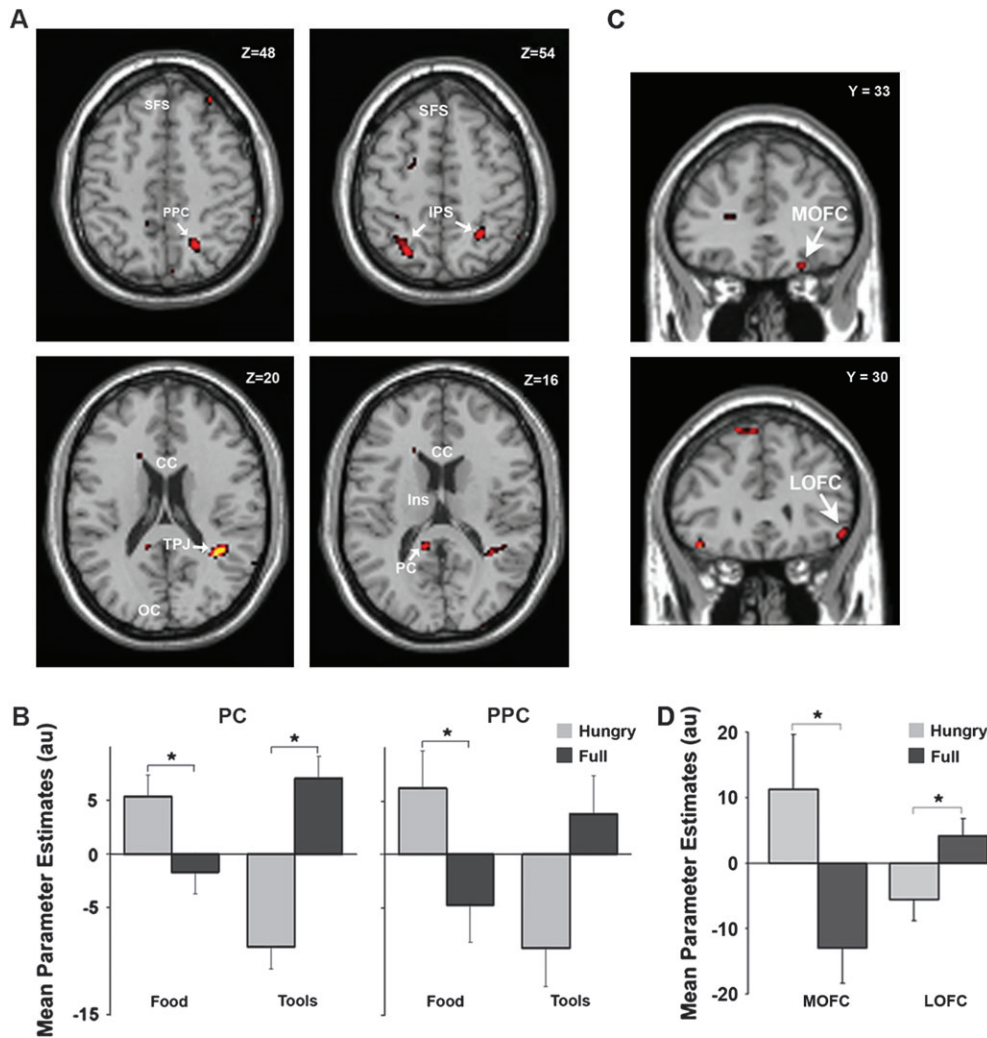
Figure 4. (A) Hunger and satiety differentially modulate the correlation between neural activity in regions involved in spatial attention and the speed of attentional shifts to food and tool targets. Images from the group random-effects analysis of the regression of cue benefit score across the whole brain show an interaction of motivation state by target type in the PPC and IPS in top axial sections and TPJ and PC in axial sections below. The images are thresholded at $P < 0.05$, uncorrected, for display purposes. (B) Hunger altered the correlation between neural activity in the attentional network and the speed of attentional shifts differentially to food versus tool targets. There was a stronger positive correlation of neural activity with attentional shifts to food targets when hungry than when satiated, whereas an inverse pattern was seen for tools. Bar plots show mean parametric estimates (± 1 SEM) of the correlation between neural activity in the PC and PPC and speed of attentional shifts to food and tool stimuli in hungry and satiated condition. (C) Modulation of correlation between neural activity and the speed of attentional shifts to food targets by hunger and satiety in the MOFC and LOFC. Images from the ROI analysis of the regression of cue benefit scores on MOFC and LOFC activity examined for an interaction of motivation state by target type. The images are thresholded at $p < 0.05$, uncorrected, for display purposes. (D) OFC subdivisions show a differential pattern of correlation between neural activity and the speed of attentional shifts towards food-related targets, with MOFC showing a stronger positive correlation when hungry and LOFC showing a stronger positive correlation when satiated. Findings indicate functional differences in medial and lateral OFC's role in motivational guidance of spatial attention.

salience of the motivationally relevant stimulus and therefore make it a more effective target for attentional shifts.

Motivational Modulation of Attentional Network

How do neurons sensitive to motivational valence influence the deployment of spatial attention? To address this question, we looked for those areas where hunger altered the correlation between neural activity and speed of attentional shifts differentially to foods versus tools. We found that in the parietal components of the spatial attention network (banks of IPS and TPJ and in the PC), activity was more positively correlated with the speed of attentional shifts to food targets when hungry than when full, whereas an opposite pattern was seen for tool targets.

The banks of the IPS may participate in the guidance of spatial attention by compiling a "salience map" (Gottlieb 2007; Molenberghs et al. 2007). An important requirement for the compilation of a saliency map is sensitivity to the motivational relevance of extrapersonal stimuli, a property that has been demonstrated for lateral intraparietal (LIP) neurons of the IPS in nonhuman primates. In monkeys placed in a foraging environment where reward values of alternative spatial targets changed, LIP neurons represented the probability that a particular region of space would serve as the endpoint of the next saccade (Sugrue et al. 2004). When animals were allowed to choose freely between alternative responses, LIP neuronal activation was correlated with the reward that the animal could

expect from each response (Platt and Glimcher 1999; Coe et al. 2002). Our results show that the human IPS region may have similar response contingencies. Analyses in Figures 3 and 4 indicate that IPS neurons do not mediate a general encoding of motivational valence but that they are sensitive to motivational relevance specifically when it guides spatial attention. These findings support the role of IPS in integrating information from multiple domains, including motivational and spatial, in forming topographical saliency representations that guide spatial attention. Another posterior parietal area with a similar response pattern was located in TPJ, a region frequently activated by spatial attention tasks and implicated in the reorientation of attentional focus (Nobre et al. 1997; Gitelman et al. 1999; Corbetta and Shulman 2002). The present study provides evidence that the involvement of TPJ in spatial attention is modulated by motivational variables.

In the present study, we also found a negative correlation between IPS/PC/TPJ activity and attentional biasing toward motivationally irrelevant (tools when hungry) and devalued (food when full) targets. This finding is consistent with another study that showed TPJ deactivation for a stream of distractors, a finding that is proposed to reflect attentional filtering of irrelevant inputs (Shulman et al. 2007). Another somewhat unexpected finding was that of positive correlation between neural activity in spatial attention regions and speed of attentional shifts to tool targets when satiated, a relationship that may be attributable to the relative preference for tool-related targets in contrast to devalued (and perhaps aversive) food targets in the satiated state. These patterns may be indicative of attentional modulation aimed at enhancing the impact of motivationally relevant stimuli and diminishing the impact of motivationally less relevant stimuli (Fenske 2006) in a dynamic fashion that is sensitive to real-time changes of context.

Present results also demonstrate that the OFC plays an important role in motivational guidance of spatial attention. MOFC and LOFC subdivisions show functional (Elliott et al. 2000; O'Doherty et al. 2001; Small et al. 2001) and anatomical (Morecraft et al. 1992) heterogeneity. MOFC is involved in processing reward value whereas LOFC is involved in processing aversive information or in suppression of previously rewarding responses (O'Doherty et al. 2001; Small et al. 2001). Our results show that MOFC activity correlates positively with attentional shifts toward motivationally relevant targets and negatively with shifts toward devalued targets. Conversely, LOFC activity correlates positively with attentional shifts toward devalued targets and negatively with motivationally relevant targets. These findings extend functional differences in medial and lateral OFC to its role in motivational guidance of spatial attention. Due to strong connectivity with PC, it is likely that the OFC provides an encoding of motivational salience that is relayed to the spatial attention network through the PC.

The Posterior Cingulate Cortex: Crossroads of Motivation and Spatial Attention

The primate cingulate gyrus is interconnected with the amygdala, parahippocampal region, insula, OFC, and inferior parietal lobule (Mesulam et al. 1977; Pandya et al. 1981; Morecraft et al. 1992; Morris et al. 2000). Furthermore, PC shows involvement in the generation of visuospatial biases to cues predicting attentional targets (Hopfinger et al. 2000; Small et al. 2003). Hence, the PC is ideally suited to serve as a neural interface between motivation, as encoded by the limbic system,

and spatial attention. We have previously found that neural activity in the PC correlates positively with anticipatory shifts of spatial attention and that this relationship is strengthened by the presence of monetary incentives (Small et al. 2003, 2005), indicating that the PC is involved in anticipatory biasing of spatial attention to motivationally relevant events. However, in these studies the target had no intrinsic hedonic relevance and became motivationally relevant only through introduction of monetary incentives. Furthermore, motivational state (desire to earn money) remained constant and the reward was postponed until the end of the session when the subject received the earnings based on performance.

The present experiment involved a more naturalistic setting where targets had ecologically relevant hedonic valence and the corresponding biological motivation could be manipulated to alter the appetitiveness of the targets. The PC neurons in our study responded differently than IPS and TPJ neurons, displaying sensitivity to the general motivational valence of an upcoming stimulus (Table 1, Fig. 3) and also mediating the motivational guidance of spatial attention shifts (Table 1, Fig. 4). These findings are consistent with monkey single-cell recording studies showing that PC neurons signal expected and actual reward outcomes associated with shifts of gaze (McCoy et al. 2003) as well as subjective preferences that guide visual orienting (McCoy and Platt 2005). Furthermore, the parahippocampal gyrus, a region that is strongly interconnected with PC (Pandya et al. 1981), shows a similar pattern of results as the PC (Table 1) which is consistent with the proposed role of PC-parahippocampal connections in visuospatial biasing (Vogt et al. 1992). Finally, the proposed role of PC as a neural interface between motivation and spatial attention was supported by findings of increased functional coupling between PC and IPS during spatial biasing toward motivationally relevant but not irrelevant attentional targets. Hence, a possible mechanism through which the posterior cingulate directs attention may involve modulation of saliency representations in the PPC such that salient locations in extrapersonal space become the preferential targets of limited attentional resources.

Effective motivational modulation of spatial attention depends on accurate real-time assessment of motivational salience. The results of the present investigation reveal conjoint limbic and monoaminergic encoding of fluctuations in motivational salience of cues predicting attentional targets. Furthermore, attentional network components such as IPS and PC show greater involvement in spatial biasing toward motivationally relevant targets and less involvement in biasing toward motivationally irrelevant targets. OFC subdivisions are differentially involved in motivational guidance of spatial attention showing positive correlations of neural activity with attentional shifts to foods medially (MOFC) when hungry and laterally (LOFC) when full. Finally, PC appears to play a pivotal role in integrating the limbic encoding of valence with the sensorimotor aspects of spatial attention, a process that is essential for directing spatial attention selectively to motivationally relevant targets in an environment where the position of targets and their relevance can undergo rapid changes.

Notes

References

Aggleton JP. 1993. The contribution of the amygdala to normal and abnormal emotional states. Trends Neurosci. 16:328-333.

Aston-Jones G, Rajkowski J, Kubiak P. 1997. Conditioned responses of monkey locus coeruleus neurons anticipate acquisition of discriminative behavior in a vigilance task. Neuroscience. 80:697-715.

Bechara A, Damasio H, Damasio AR, Lee GP. 1999. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. J Neurosci. 19:5473-5481.

Bechara A, Tranel D, Damasio H, Adolphs R, Rockland C, Damasio AR. 1995. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. Science. 269:1115-1118.

Berridge KC. 1996. Food reward: brain substrates of wanting and liking. Neurosci Biobehav Rev. 20:1-25.

Burock MA, Buckner RL, Woldorff MG, Rosen BR, Dale AM. 1998. Randomized event-related experimental designs allow for extremely rapid presentation rates using functional MRI. Neuroreport. 9:3735-3739.

Coe B, Tomihara K, Matsuzawa M, Hikosaka O. 2002. Visual and anticipatory bias in three cortical eye fields of the monkey during an adaptive decision-making task. J Neurosci. 22:5081-5090.

Corbetta M, Miezin FM, Shulman GL, Petersen SE. 1993. A PET study of visuospatial attention. J Neurosci. 13:1202-1226.

Corbetta M, Shulman GL. 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci. 3:201-215.

Della Libera C, Chelazzi L. 2006. Visual selective attention and the effects of monetary rewards. Psychol Sci. 17:222-227.

Dwyer DM, Killcross S. 2006. Lesions of the basolateral amygdala disrupt conditioning based on the retrieved representations of motivationally significant events. J Neurosci. 26:8305-8309.

Elliott R, Dolan RJ, Frith CD. 2000. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. Cereb Cortex. 10:308-317.

Engelmann JB, Pessoa L. 2007. Motivation sharpens exogenous spatial attention. Emotion. 7:668-674.

Fecteau JH, Munoz DP. 2006. Salience, relevance, and firing: a priority map for target selection. Trends Cogn Sci. 10:382-390.

Fenske. 2006. Affective influences of selective attention. Curr Dir Psychol Sci. 15:312-316.

Foote SL, Aston-Jones G, Bloom FE. 1980. Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. Proc Natl Acad Sci USA. 77:3033-3037.

Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. 1997. Psychophysiological and modulatory interactions in neuroimaging. Neuroimage. 6:218-229.

Germain A, Nofzinger EA, Meltzer CC, Wood A, Kupfer DJ, Moore RY, Buysse DJ. 2007. Diurnal variation in regional brain glucose metabolism in depression. Biol Psychiatry. 62:438-445.

Gitelman DR, Nobre AC, Parrish TB, LaBar KS, Kim YH, Meyer JR, Mesulam M. 1999. A large-scale distributed network for covert spatial attention: further anatomical delineation based on stringent behavioural and cognitive controls. Brain. 122:1093-1106.

Gottfried JA, O'Doherty J, Dolan RJ. 2003. Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science. 301:1104-1107.

Gottlieb J. 2007. From thought to action: the parietal cortex as a bridge between perception, action, and cognition. Neuron. 53:9-16.

Hopfinger JB, Buonocore MH, Mangun GR. 2000. The neural mechanisms of top-down attentional control. Nat Neurosci. 3:284-291.

Kim YH, Gitelman DR, Nobre AC, Parrish TB, LaBar KS, Mesulam MM. 1999. The large-scale neural network for spatial attention displays multifunctional overlap but differential asymmetry. Neuroimage. 9:269-277.

LaBar KS, Gitelman DR, Parrish TB, Kim YH, Nobre AC, Mesulam MM. 2001. Hunger selectively modulates corticolimbic activation to food stimuli in humans. Behav Neurosci. 115:493-500.

McCoy AN, Crowley JC, Haghighian G, Dean HL, Platt ML. 2003. Saccade reward signals in posterior cingulate cortex. Neuron. 40:1031-1040.

McCoy AN, Platt ML. 2005. Risk-sensitive neurons in macaque posterior cingulate cortex. Nat Neurosci. 8:1220-1227.

Mesulam M. 2000. Brain, mind, and the evolution of connectivity. Brain Cogn. 42:4-6.

Mesulam MM. 1981. A cortical network for directed attention and unilateral neglect. Ann Neurol. 10:309-325.

Mesulam MM, Van Hoesen GW, Pandya DN, Geschwind N. 1977. Limbic and sensory connections of the inferior parietal lobule. area PG. in the rhesus monkey: a study with a new method for horseradish peroxidase histochemistry. Brain Res. 136:393-414.

Molenberghs P, Mesulam MM, Peeters R, Vandenberghe RR. 2007. Remapping attentional priorities: differential contribution of superior parietal lobule and intraparietal sulcus. Cereb Cortex. 17:2703-2712.

Morecraft RJ, Geula C, Mesulam MM. 1992. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. J Comp Neurol. 323:341-358.

Morris R, Paxinos G, Petrides M. 2000. Architectonic analysis of the human retrosplenial cortex. J Comp Neurol. 421:14-28.

Murray GK, Corlett PR, Clark L, Pessiglione M, Blackwell AD, Honey G, Jones PB, Bullmore ET, Robbins TW, Fletcher PC. 2007. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. Mol Psychiatry. doi:10.1038/sj.mp.4002058.

Nishijo H, Ono T, Nishino H. 1988. Single neuron responses in amygdala of alert monkey during complex sensory stimulation with affective significance. J Neurosci. 8:3570-3583.

Nobre AC, Sebestyen GN, Gitelman DR, Mesulam MM, Frackowiak RS, Frith CD. 1997. Functional localization of the system for visuospatial attention using positron emission tomography. Brain. 120(Pt 3):515-533.

O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C. 2001. Abstract reward and punishment representations in the human orbitofrontal cortex. Nat Neurosci. 4:95-102.

O'Doherty JP, Deichmann R, Critchley HD, Dolan RJ. 2002. Neural responses during anticipation of a primary taste reward. Neuron. 33:815-826.

Ono T, Nishijo H, Nishino H. 2000. Functional role of the limbic system and basal ganglia in motivated behaviors. J Neurol. 247(Suppl 5):V23-V32.

Pandya DN, Van Hoesen GW, Mesulam MM. 1981. Efferent connections of the cingulate gyrus in the rhesus monkey. Exp Brain Res. 42:319-330.

Platt ML, Glimcher PW. 1999. Neural correlates of decision variables in parietal cortex. Nature. 400:233-238.

Rolls BJ, Rolls ET, Rowe EA, Sweeney K. 1981. Sensory specific satiety in man. Physiol Behav. 27:137-142.

Schultz W, Dayan P, Montague PR. 1997. A neural substrate of prediction and reward. Science. 275:1593-1599.

Shulman GL, Astafiev SV, McAvoy MP, d'Avossa G, Corbetta M. 2007. Right TPJ deactivation during visual search: functional significance and support for a filter hypothesis. Cereb Cortex. 17:2625-2633.

Small DM, Gitelman D, Simmons K, Bloise SM, Parrish T, Mesulam MM. 2005. Monetary incentives enhance processing in brain regions mediating top-down control of attention. Cereb Cortex. 15:1855-1865.

Small DM, Gitelman DR, Gregory MD, Nobre AC, Parrish TB, Mesulam MM. 2003. The posterior cingulate and medial prefrontal

cortex mediate the anticipatory allocation of spatial attention. Neuroimage. 18:633-641.

Small DM, Zatorre RJ, Dagher A, Evans AC, Jones-Gotman M. 2001. Changes in brain activity related to eating chocolate: from pleasure to aversion. Brain. 124:1720-1733.

Sterpenich V, D'Argembeau A, Desseilles M, Balteau E, Albouy G, Vandewalle G, Degueldre C, Luxen A, Collette F, Maquet P. 2006. The locus ceruleus is involved in the successful retrieval of emotional memories in humans. J Neurosci. 26:7416-7423.

Sugrue LP, Corrado GS, Newsome WT. 2004. Matching behavior and the representation of value in the parietal cortex. Science. 304:1782-1787.

Talairach J, Tournoux P. 1988. Co-planar stereotaxic atlas of the human brain. New York: Thieme Medical Publishers, Inc.

Tremblay L, Schultz W. 1999. Relative reward preference in primate orbitofrontal cortex. Nature. 398:704-708.

Vogt BA, Finch DM, Olson CR. 1992. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. Cereb Cortex. 2:435-443.

Wittmann BC, Schott BH, Guderian S, Frey JU, Heinze HJ, Düzel E. 2005. Reward-related fMRI activation of dopaminergic midbrain is associated with enhanced hippocampus-dependent long-term memory formation. Neuron. 45:459-467.