

A functional neuroimaging study of motivation and executive function[☆]

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Executive functions, such as working memory, must intersect with functions that determine value for the organism. Functional imaging work in humans and single-unit recordings in non-human primates provide evidence that PFC might integrate motivational context with working memory. With functional magnetic resonance imaging (fMRI), we addressed the question of motivation and working memory, using a trial-related design in an object-working memory task. The design permitted the analysis of BOLD signal at separate stages, corresponding to encoding, maintenance, and retrieval. Subjects were motivated by a financial incentive during the task, such that they could gain a high or a low reward. The two different levels of reward also entailed greater or lesser risk of losing money for incorrect responses. In the high, relative to the low, reward condition, subjects shifted response bias, and showed a trend to greater sensitivity. We found main effects in fMRI BOLD signal for reward, which overlapped with BOLD effects for maintenance of information, in the right superior frontal sulcus and bilateral intraparietal sulcus. We also found an interaction between reward and retrieval from working memory in the right dorsolateral prefrontal cortex. Main effects of load and reward occurred in adjacent regions of the ventrolateral PFC during retrieval. The data demonstrate that when subjects perform a simple working memory task, financial incentives motivate performance and interact with some of the same neural networks that process various stages of working memory. Areas of overlap and interaction may integrate information about value, or they may represent a general effect of motivation increasing neural effort.

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Cognitive processes occur in the context of specific motivational states and ongoing assessments of the potential value of selected responses (cf. Cohen and Blum, 2002). Executive func-

tions, which organize lower-level processing in the service of integrated behavior, must have access to neural systems in the brain that determine potential value and assign priorities among possible responses. Several different experimental approaches have begun to shed some light on the neural systems where executive function intersects value. Studies with affectively salient stimuli in a working memory task (Perlstein et al., 2002) and in working memory performed after the induction of emotional states (Gray et al., 2002) have demonstrated that function in the lateral prefrontal cortex (PFC) interacts with emotion and working memory. Hence, both groups of investigators conclude that prefrontal regions may entail a subsystem where salient emotional information can influence cognitive function.

However, studies that manipulate emotional salience may not be relevant to motivation, per se, which entails the facilitation of behavior in the anticipation of a possible reward or the avoidance of a punishment. The study of motivational influences on the human brain have occurred primarily in tasks that investigate the influence of reward (and punishment) for simple reaction time tasks (Elliott et al., 2003; Knutson et al., 2000, 2001a, 2003; Thut et al., 1997), for instrumental tasks involving stochastic decisions (Elliott et al., 2000; Paulus et al., 2002; Rogers et al., 1999), for probabilistic learning tasks (Cools et al., 2002), or for classical, appetitive conditioning (Berns et al., 2001; McClure et al., 2003; O'Doherty et al., 2003). Although findings from these investigations are not readily summarized, some consistencies have begun to emerge. For instance, several studies demonstrate that the striatum, particularly in the ventral aspect, anticipates the receipt of a reward (Knutson et al., 2001b, 2003; O'Doherty et al., 2002), and responds to changes in the predictability of a reward (Berns et al., 2001; McClure et al., 2003; O'Doherty et al., 2003). The medial orbitofrontal cortex (OBFC) and ventral-medial prefrontal cortex (PFC) respond to the receipt of a rewarding stimulus (Knutson et al., 2001b; O'Doherty et al., 2001), and the lateral OFC responds to punishment (O'Doherty et al., 2001), conflicts about anticipated payoffs (Rogers et al., 1999), and reversal learning (Cools et al., 2002; O'Doherty et al., 2001). These studies provide insight into the brain systems that calculate potential gain and loss, but generally do not address the integration of this information with an executive function, such as working memory.

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A logical hypothesis holds that prefrontal regions, generally held to play a key role in executive functioning, might also integrate motivational information, as was shown for emotional information (Gray et al., 2002; Perlstein et al., 2002). For instance, experiments in non-human primates have demonstrated that PFC neurons associated with information storage in working memory tasks also process information associated with the preference for an expected reward (Leon and Shadlen, 1999; Watanabe, 1996). Watanabe found that 50% of delay-related neurons in the lateral PFC exhibited preferences for specific types of reward (Watanabe, 1996). More generally, neurons in the lateral PFC exhibit activity correlated with motivational context, that is, the presence or absence of a reward (Watanabe et al., 2002). A recent human fMRI study by Pochon et al. (2002) examined neural responses in subjects performing an “n-back” task, in which the subject had to determine whether or not a stimulus matched another stimulus presented previously (1, 2, or 3 stimuli “back”). During the working memory task, motivation was parametrically manipulated with a performance-based financial reward over the course of the experiment. They found that motivation interacted with reward in frontal and prefrontal networks in the middle and inferior frontal gyri, along with the anterior cingulate gyrus.

The study by Pochon et al. provides some support for the hypothesis that the PFC integrates motivation and executive function, but many questions are raised by this initial work. Working memory typically consists of several distinct stages, such as encoding stimuli, maintaining storage, manipulating the information and retrieving an appropriate response. The design of the study by Pochon et al. confounded these stages. Trial-related, also called slow event–event designs (Petit et al., 1998; Zarahn et al., 1997), permit the analysis of separate processing stages, and suggest that distinct brain regions might subserve each stage. For example, the dorsolateral PFC appears to manipulate information, whereas the ventrolateral PFC appears to store and retrieve information from short-term stores (D’Esposito et al., 1998; Petrides et al., 1993, 1995; Smith and Jonides, 1999). Therefore, an investigation of the effects of motivation on working memory in a trial-related design may demonstrate where motivational processing may operate.

In the trial-related experiment described here, we selected a simple object working memory task with abstract visual shapes (Smith et al., 1995), which required maintenance, but little manipulation. Subjects were motivated by a financial incentive during the task, utilizing two levels of monetary reward, and a biased payoff matrix differentially rewarded correct responses and penalized mistakes. Based on the animal data cited above (Leon and Shadlen, 1999; Watanabe, 1996), we tested the prediction that motivation would activate the same or adjacent regions in the prefrontal cortex as those involved in the maintenance of working memory, either as a main effect of motivation or an interaction between motivation and memory load. In addition to this regional hypothesis, we also tested for effects at each stage of working memory throughout the brain.

Methods

Subjects

Twelve healthy subjects were recruited from community advertisements (six women, six men; mean age $\pm$ SD = 24.2 $\pm$ 4.2

years). The purpose and risks of the study were explained to all subjects, who gave written informed consent to participate, as approved by the local institutional review board.

Experimental design

Subjects performed an object-working memory task, in which two orthogonal factors were varied: (1) *memory load* and (2) *reward*. The experimental task required subjects to maintain three, consecutively presented, irregular polygons (Attneave and Arnoult, 1956) in memory, and then decide if a probe stimulus matched any of the three target stimuli. For *memory load*, the set of three objects was either identical (*low load*) or all different (*high load*). For *reward*, the target and probe stimuli were either red or blue, which corresponded either to low or high motivation, counterbalanced across subjects. Subjects were informed ahead of time that they would win or lose money according to a payoff schedule, which was asymmetric to induce a response bias and better differentiate the conditions. For the *high reward* color, subjects received \$1 for a hit, lost \$1 for a miss, received 1 ¢ for a correct rejection and lost 10 ¢ for a false alarm (to prevent subjects from always responding that the probe matched the target set). For the *low reward* color, subjects received 1 ¢ for a hit or correct rejection, and lost 1 ¢ for a miss or a false alarm. For convenience, we refer to the experimental manipulation as high and low *reward*, but the manipulation also included high and low *risk of penalties*. Task difficulty was set to ensure that all subjects received a net reward. Subjects were given \$10 at the beginning of the experiment, and saw an updated tally of their earnings between each run in the fMRI scanner. They received no feedback for individual trials. They were encouraged to try hard to make a good score, and were rewarded with an extra \$20 when they made \$20, and \$20 more when (if) they made \$35. The earned amount was paid to the subjects at the end of the experiment. All subjects practiced 1–3 days before the fMRI scanning session to familiarize themselves with the task.

The experiment was presented in 10 runs of 12 trials each. An experimental trial consisted of three events, plus an 8-s intertrial interval (ITI), for a total trial duration of 22 s (Fig. 1). The target set (TARGET) was displayed for 4 s (600 ms duration for each of three objects, 67 ms interstimulus interval), followed by an 8-s delay interval (DELAY), and then a 2-s interval for the probe (PROBE), when subjects responded with a button press by the right index or middle finger to indicate whether or not the probe was in the target set (0.5 probability). Stimulus presentation and recording of responses occurred using a MacIntosh PC, running PsyScope (Macwhinney et al., 1997) via back projection and an angled mirror in the head coil housing.

fMRI image acquisition

MR images were acquired on a 1.5 Tesla GE Signa Echospeed system (LX release). After initial acquisition of T1 structural images, 132 T2*-weighted, axial functional images were acquired using a gradient-echo spiral pulse sequence (Noll et al., 1995; TR = 2000, TE = 35, FA = 65, FOV = 20, 64 $\times$ 64 matrix, 28 $\times$ 3 mm slices, skip 0 mm, 4 disdags). After the collection of 10 runs, a high-resolution T1 image was acquired (3D-GRE, FA = 35, FOV = 24, 192 $\times$ 256 $\times$ 124, 1.5 mm) to aid in anatomic normalization. BOLD images were reconstructed to yield isotropic voxels, 2 mm on edge. For two of the subjects, hardware problems corrupted the

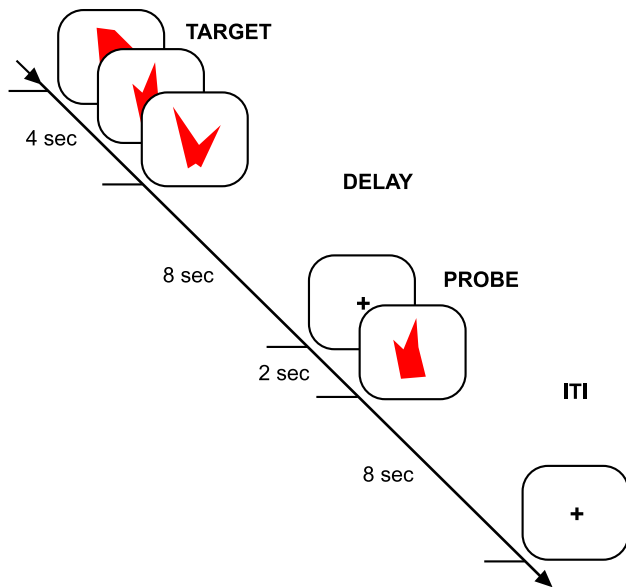


Fig. 1. The figure demonstrates the order of events in the 22-s experimental trial. TARGET consisted of the consecutive presentation of three abstract stimuli, followed by an 8-s DELAY period when subjects had to maintain information in working memory. A PROBE stimulus required subjects to respond whether or not the probe was in the previous set of three objects.

spiral acquisitions; thus, we analyzed fMRI data from only 10 subjects.

Analysis of fMRI data

Data analysis was performed within the Statistical Parametric Mapping analytic package (SPM99, Wellcome Department of Cognitive Neurology, London, UK). For each subject, the data were sinc-interpolated in time, slice-by-slice, re-aligned to the first acquired volume and co-registered with the high-resolution SPGR T1 image. This high-resolution image was then spatially normalized and the transformation parameters were then applied to the co-registered functional volumes, resliced and smoothed with a 5-mm isotropic Gaussian smoothing kernel. Each normalized image set was band pass filtered (low pass filter = canonical hemodynamic response function; high pass filter = 100 s) and analyzed with a general linear model, using 13 experimental regressors (3 events $\times$ 4 conditions per event, plus ITI), convolved with the canonical hemodynamic response function.

The planned analysis focused on the effects of working memory *load* (high minus low) and *reward* (high minus low) within each event (TARGET, DELAY, and PROBE) of the trial. Contrasts were calculated for *load* and *reward* as main effects plus interaction terms. In addition, we also tested for a non-specific effect of reward, by collapsing reward regressors for all three events in a single contrast. Contrast images were derived for each subject and smoothed with an 8-mm isotropic Gaussian kernel to stabilize variance properties and account for residual between subject anatomic variability. The smoothed contrast maps were then entered into a random effects analysis, and foci were identified with a height threshold of $P < 0.001$, uncorrected, and an extent of activation threshold with an uncorrected probability of $P < 0.05$. At the next step, corrections for multiple comparisons were performed at a probability of $P < 0.05$ for the entire brain, based on the spatial

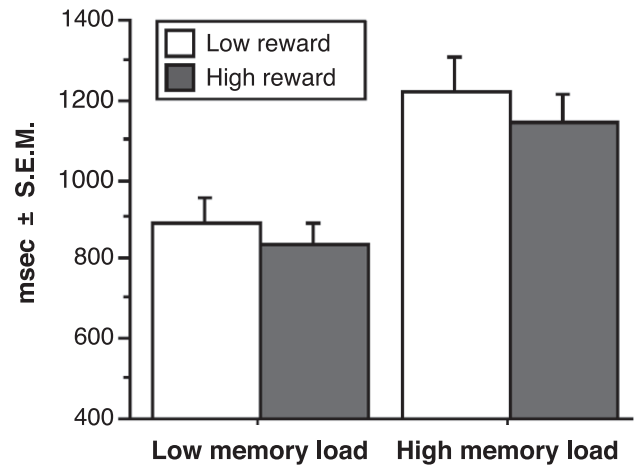


Fig. 2. The graph illustrates reaction time data for the high reward condition (filled bars) and the low reward condition (empty bars). Subjects showed similar improvements in reaction time with reward, for both high and low load conditions.

extent of each focus. However, because we were searching for brain regions that subserved working memory and motivation, we also used the activations in the memory conditions as a mask to identify voxels activated in both *load* and *reward* conditions.

Results

Behavioral results

There were clear effects of memory load on both reaction time ($F[1, 10] = 55.2$, $P < 0.000$; see Fig. 2) and accuracy ($F[1, 9] = 277$, $P < 0.000$; see Table 1). Subjects responded with a slightly faster response time for the high reward condition, compared to the low reward condition, showing a trend for a main effect of reward ($F[1, 10] = 4.61$, $P = 0.06$). In response to the asymmetric payoff matrix, subjects exhibited a significant shift in the likelihood of making an affirmative response to the presence of a target, indicated by a change in β , the response 'bias' (Table 1). The shift meant that subjects were willing to experience higher false alarms to achieve more hits and avoid missing a target. This shift was the intended result of the payoff matrix, set up to bias responses in the high reward/high risk condition. The non-parametric measure of sensitivity, A' , also showed a non-significant trend to increase with reward, indicating that subjects were also somewhat better able to detect the presence of a target, independent of their response criteria. Technical difficulties with the response

Table 1
Behavioral results

Motivation condition	Low memory load overall accuracy	High memory load overall accuracy	Sensitivity ^a (A')	Response bias ^a (β)
High reward	0.97 $\pm$ 0.03	0.71 $\pm$ 0.04	0.85 $\pm$ 0.04 ^b	0.32 $\pm$ 0.48 ^c
Low reward	0.96 $\pm$ 0.03	0.69 $\pm$ 0.08	0.78 $\pm$ 0.10	0.71 $\pm$ 0.30

^a Sensitivity and response bias calculated from high memory load trials.

^b Difference between high and low reward, $t = 1.87$, $df = 9$, $P = 0.09$.

^c Difference between high and low reward, $t = 3.17$, $df = 9$, $P = 0.01$.

Table 2
Activation foci for the TARGET event

Region (Brodmann area)	Memory load			Reward		
	Cluster size ^a	(x, y, z) ^b	Z-score ^c	Cluster size ^a	(x, y, z) ^b	Z-score ^c
R inferior frontal g (44)	96	52, 6, 32	3.83			
		46, 12, 28	4.39			
R superior parietal lobule (7)	64	36, -54, 62	3.70			
L superior parietal lobule (7)	52	-18, -60, 58	3.33			
		-22, -64, 52	3.46			
		-24, -70, 42	3.17			
R lateral occipital cortex (18/19)	163 ^d	44, -64, 16	3.61			
		46, -66, 4	3.85			
		52, -72, 6	3.91			
R superior occipital cortex (19)				80	34, -76, 32	3.85
					36, -84, 40	3.27
L superior occipital cortex (19)	181 ^e	-30, -78, 30	4.52			
		-26, -86, 22	3.85			
Precuneus (7)				408 ^f	14, -68, 68	4.32
					6, -76, 56	4.29
					-10, -76, 42	3.91
R caudate/putamen	108	18, 8, -2	3.52			

^a Number of voxels (exceeding height threshold, $P < 0.001$, uncorrected) per cluster; clusters listed for size, $P < 0.05$, uncorrected.

^b Stereotactic coordinates according to MNI atlas, right/left, anterior/posterior and superior/inferior, respectively.

^c Z-score for peak magnitude(s) within a cluster.

^d $P < 0.01$, corrected.

^e $P < 0.005$, corrected.

^f $P < 0.000$, corrected.

Table 3
Activation foci for the DELAY event

Region (Brodmann area)	Memory load			Reward		
	Cluster size ^a	(x, y, z) ^b	Z-score ^c	Cluster size ^a	(x, y, z) ^b	Z-score ^c
<i>Frontal cortex</i>						
Medial frontal/anterior cingulate cortex (6/32)	780 ^d	-2, 12, 54	4.64			
		2, 18, 46	4.81			
		-2, 28, 38	4.00			
L superior frontal sulcus and middle/inferior frontal g (6/8/9)	1036 ^d	-20, 2, 54	4.73			
		-26, 8, 60	4.64			
		-54, 10, 50	4.84			
R superior frontal sulcus and middle frontal g (6/8)	451 ^d	36, 0, 54	5.64	47	36, -2, 60	4.15 ^e
		34, 4, 42	4.75			
		24, 10, 46	3.69			
L rostral middle frontal g (10)	34	-34, 52, 6	3.91			
R inferior/middle frontal g (45/46)	156 ^f	36, 40, 26	3.64			
		44, 46, 16	3.78			
<i>Posterior cortex</i>						
Intraparietal sulcus (R 7/40/39)	1955 ^d	34, -62, 52	4.93			
		34, -74, 52	4.70			
(R 39)				34	28, -58, 36	4.27
(L 7/40/39)		-42, -54, 52	4.70			
(L 39)				119 ^g	-32, -52, 28	4.38
					-24, -58, 38	3.79
					-16, -54, 44	3.67
L superior parietal lobe (7)				85	-18, -66, 68	4.10
R superior occipital cortex (19)	33	34, -80, 38	3.76			

^a Number of voxels (exceeding height threshold, $P < 0.001$, uncorrected) per cluster; clusters listed for size, $P < 0.05$, uncorrected.

^b Stereotactic coordinates according to MNI atlas, right/left, anterior/posterior and superior/inferior, respectively.

^c Z-score for peak magnitude(s) within a cluster.

^d $P < 0.01$, corrected.

^e $P < 0.05$, small volume corrected.

^f $P < 0.01$, corrected.

^g $P < 0.05$, corrected.

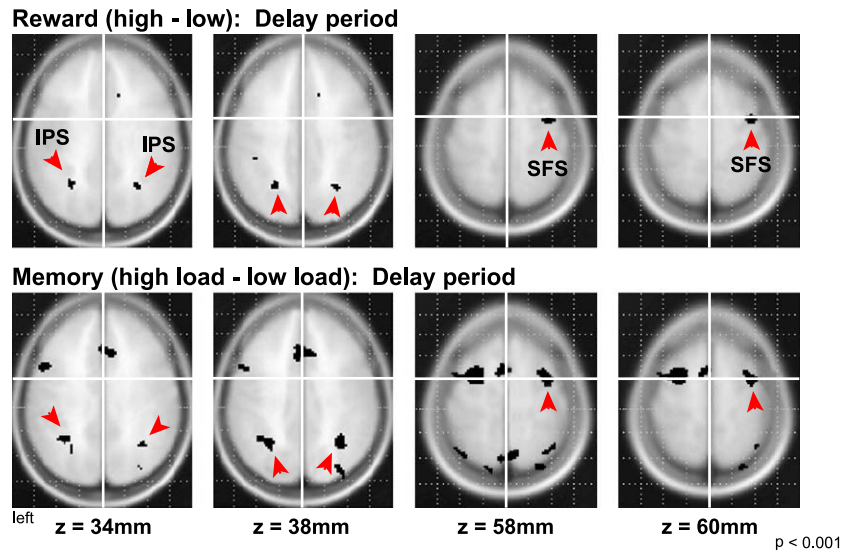


Fig. 3. Activation foci, during the DELAY period, occurred in the contrast of high–low reward (top row) in the intraparietal sulcus (IPS) and superior frontal sulcus (SFS). The bottom row shows the corresponding regions (red arrowheads) also activated during maintenance in working memory contrast (high–low load; bottom row). Activation foci are superimposed on the MNI averaged brain template, using a height threshold of $P < 0.001$.

box interfered with data collection in two subjects for accuracy and one subject for reaction time.

BOLD activation during TARGET

At the height threshold of $P < 0.001$, no overlap occurred between load and reward activations. Memory load activated posterior regions (left parietal lobe, bilateral occipital cortex), right inferior frontal gyrus and right striatum during the TARGET event (Table 2). Reward activated the precuneus, significant after corrections for multiple comparison at the cluster level. Activations also occurred in the right superior occipital cortex, although this was not significant after correction.

Interaction analysis revealed no activations that overlapped the load or reward activations during TARGET. A single focus in the midbrain exceeded the uncorrected threshold, and no activations were significant after correction for multiple comparisons.

BOLD activation during DELAY

Reward and load activations exhibited some overlap during the DELAY. For the effect of memory load, bilateral activation occurred in the frontal cortex, including superior frontal sulcus (SFS; areas 6/8), lateral prefrontal cortex (10 and 46), plus medial frontal cortex/anterior cingulate cortex (see Table 3). Within the load-activated regions of the lateral frontal cortex, one focus of activation occurred in the right SFS for the reward contrast (see Fig. 3). Because of the importance of frontal cortex in working memory, a small volume correction with Bonferroni correction was performed, using a mask to restrict the search area to the activated regions in the frontal cortex. Based on suggestions that medial and lateral cortex have differing roles in working memory tasks (Haxby et al., 2000; Smith and Jonides, 1999), two masks were created: One for the activation predicted in the medial frontal cortex/anterior cingulate area, the other for bilateral frontal cortex. With

Table 4
Activation foci for the PROBE event

Region (Brodmann area)	Memory load			Reward		
	Cluster size ^a	(x, y, z) ^b	Z-score ^c	Cluster size ^a	(x, y, z) ^b	Z-score ^c
R middle frontal g (44)	71	48, 26, 32	4.33			
L middle frontal g (10)	62	−40, 50, −6	3.83			
R inferior frontal g (45)	96	42, 28, −2	4.06			
R inferior frontal/orbitofrontal g (11/47)				57	32, 20, −12	3.94
L inferior frontal g (47)	47	−40, 18, −4	3.82			
L inferior frontal/orbitofrontal g (11/47)				104 ^d	−28, 24, −10 −30, 24, −2	3.84 3.71
R orbital g (11)	32	24, 40, −20	4.03			
Anterior cingulate cortex (32)	52	4, 36, 36	3.76			
L inferior parietal lobule (39)	38	−36, −60, 40	4.67			

^a Number of voxels (exceeding height threshold, $P < 0.001$, uncorrected) per cluster; clusters listed for size, $P < 0.05$, uncorrected.

^b Stereotactic coordinates according to MNI atlas, right/left, anterior/posterior and superior/inferior, respectively.

^c Z-score for peak magnitude(s) within a cluster.

^d $P < 0.05$, corrected.

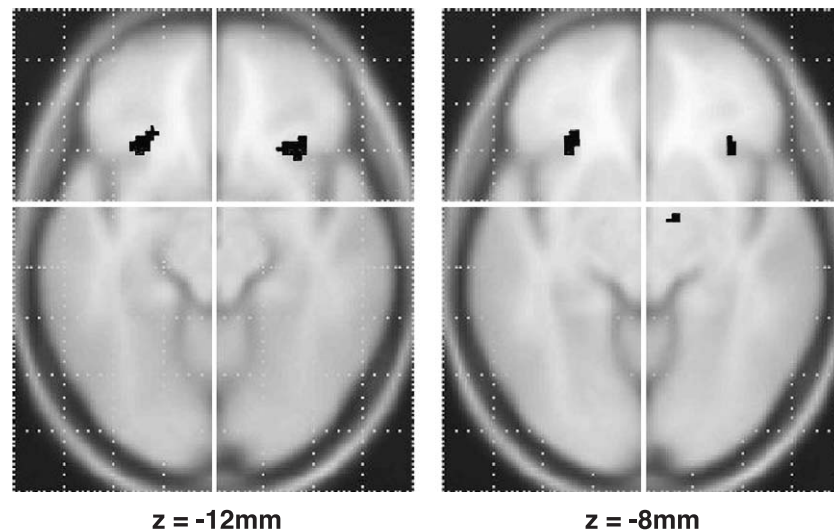


Fig. 4. Motivation (high–low reward) activates bilateral inferior frontal gyrus/lateral orbitofrontal gyrus during retrieval from working memory in the PROBE period. Activation foci are superimposed on the MNI averaged brain template, using a height threshold of $P < 0.001$.

correction, the right SFS focus showed significant magnitude of activation during the reward contrast. No reward foci appeared in the medial frontal/anterior cingulate region of interest, although a focus did appear in the right anterior cingulate, just rostral and lateral to the load-activated region (x, y, z coordinates = 14, 22, 36; $Z = 3.61$, extent = 9 voxels).

Posterior activation during load consisted of a large contiguous bilateral network in the intraparietal sulcus (IPS; areas 7/39/40), and the superior occipital cortex. Activation foci for reward occurred in more circumscribed regions, closely overlapping the

most inferior extent of the load activation in area 39 (see Fig. 3). One cluster, in the inferior extent of the left IPS survived correction for multiple comparisons (see Fig. 3). This focus was mirrored on the right by a focus of smaller extent, but similar magnitude. We also noted a peak, not significant after correction, in the left superior parietal lobe, which did not overlap activations for load.

Interaction analyses were conducted for the two possible crossings of load and reward. For the crossing, High reward [high–low load]–Low reward [high–low load], two foci of activation exceeded the uncorrected threshold in the right posterior

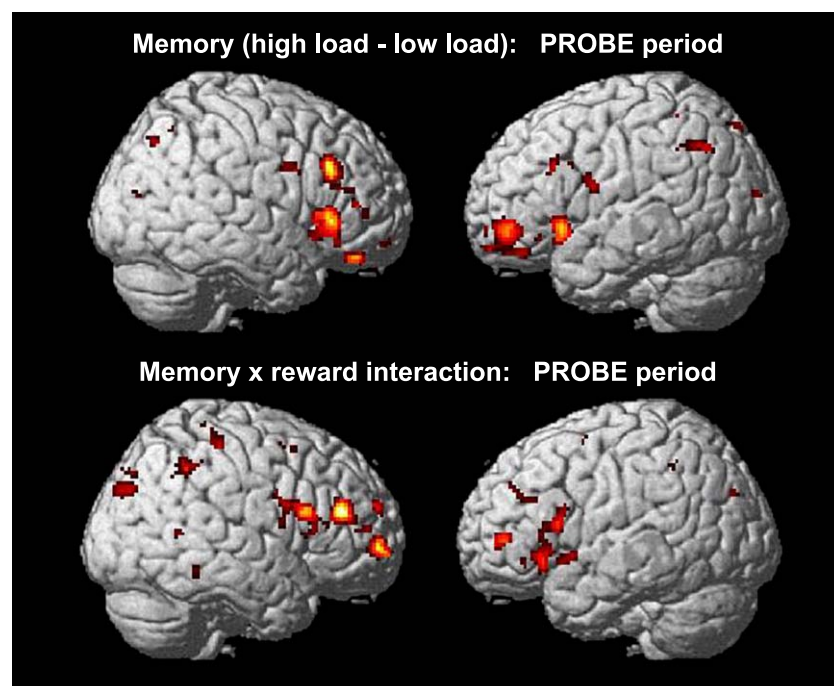


Fig. 5. Lateral PFC activation occurred during retrieval from working memory as a main effect of memory load (probe period; top row), and in the interaction of load with reward (bottom row). Activation foci projected onto a surface-rendered anatomical template image for $P < 0.005$.

central sulcus and the left posterior central gyrus. For the opposite crossing, a single focus was noted in the right lateral occipital cortex. However, none of these foci survived correction for multiple comparisons. There were no (uncorrected) foci within the load-related, frontal regions, nor did any foci overlap any of the other activations for load or reward, at the chosen threshold of $P < 0.001$. This remained true even when the threshold was set to $P < 0.01$.

BOLD activation during PROBE

During the PROBE event, memory load was associated with several foci in the right and left middle frontal gyrus, as well as the right and left inferior frontal gyrus (IFG), the anterior cingulate cortex, right orbital gyrus, and left inferior parietal lobule (Table 4). The reward manipulation was associated with activation of right and left IFG, although only the left IFG was significant after correction for multiple comparisons (Fig. 4). Both of these foci occurred in proximity to foci in the IFG for load, although the foci for reward extended in a more anterior and medial direction, extending into area 11 and the lateral orbitofrontal cortex (OBFC). At the threshold of $P < 0.001$, no overlap between the load and reward activations occurred.

The interaction analysis revealed several foci exceeding the uncorrected threshold in the contrast: High reward [high–low load]–Low reward [high–low load]. These included activations in the right IFG (area 44), right middle frontal gyrus (MFG; area 45/46, area 10), left IFG (area 44), right caudate and right IPS (area 39). One focus survived corrections for multiple comparisons, in the right MFG, Brodmann area 45/46 ($x, y, z = 48, 36, 22$; $Z = 4.30$, extent = 126, $P = 0.01$, corrected). This interaction could indicate where the effect of memory load was greater in the high reward, compared to the low reward, condition. To determine what contributed to the interaction, main effects were examined for positive and negative changes. The right MFG focus was in very close proximity to load-related activations, and when the threshold was lowered to $P < 0.005$, bilateral activity appeared for both load and the interaction (Fig. 5). No lateral frontal activations occurred in this region for the reward contrast, superior to the IFG/lateral OBFC activations. There were no negative BOLD changes, where

low reward > high reward in the lateral PFC, suggesting that the interaction derived from the greater effect of high reward on load, compared to low reward. Lastly, no significant foci (even at the uncorrected level) were noted in the opposite interaction contrast.

BOLD activation for reward, all events

For reward conditions, across all events, we found activation in some of the same regions activated in the discrete events (Table 5). Specifically, several foci in the precuneus and superior parietal lobe appeared during the TARGET and DELAY events. We also found activations in the precentral gyrus, anterior insula, and right basal ganglia, which did not appear in the discrete events. Of these, only the focus in the right basal ganglia (caudate nucleus and ventral pallidum) was significant after correction.

Discussion

This experiment set out to demonstrate brain regions where motivation might influence executive function. The results showed that a financial incentive/penalty changed cognitive performance and activated brain regions in association with a working memory task. We found main effects of reward, which overlapped with a right frontal area associated with maintenance of information in working memory. During the retrieval phase of the task, an interaction between working memory and motivation occurred in the dorsolateral PFC, thereby extending prior work suggesting that executive functions in the PFC might integrate information about value to organize behavior. We also noted main effects of load and reward that activated adjacent regions of the ventrolateral PFC, as well as regions activated by reward processing which appeared quite apart from the working memory networks, mainly during encoding. Notably, with the exception of encoding, most motivation-related activation occurred in or near the same regions associated with the working memory task. Overall, the results represent an important step towards establishing how the brain does integrate motivation and cognition, but several different interpretations of these results deserve discussion.

The trial-related design sought to break up the working memory task into three stages: encoding, maintenance, and retrieval. The goal of our study was to identify how motivation might separately influence these processing stages, since a previous report examining motivation and working memory, by Pochon et al. (2002), had used an “n-back” task that confounds these stages. Strictly speaking, the events of our trial (TARGET, DELAY, and PROBE) are not independent of one another, since they always appeared in the identical order. Hence, the design permits only tentative separation of presumed processing stages based on differential activation patterns. Nevertheless, the trial-related paradigm for working memory has been well studied (Courtney et al., 1998; D’Esposito et al., 1998; Rypma et al., 1999; Rowe et al., 2000), and our results are in close agreement with the published literature for working memory tasks, providing some information about the processing stages where motivation might influence this executive function.

During the DELAY period, subjects had to maintain representations of the abstract shapes in working memory. We noted an overlap between reward-associated and load-associated activations in the premotor SFS and intraparietal sulcus, which are both regions thought to carry out maintenance of information (Cohen

Table 5
Activation foci for reward, all events

Region (Brodmann area)	Reward		
	Cluster size ^a	(x, y, z) ^b	Z-score ^c
R caudate nucleus and ventral pallidum	293 ^d	8, 20, 0	4.45
		14, 0, –6	3.98
		4, 12, 6	3.84
R anterior insula	55	34, 22, –8	3.63
L pre-central g	37	–34, –4, 44	3.84
Precuneus/superior parietal lobe (7)	42	8, –78, 56	3.46
	235 ^d	–14, –64, 66	4.70
		–26, –68, 58	4.06
		–22, –62, 62	3.92

^a Number of voxels (exceeding height threshold, $P < 0.001$, uncorrected) per cluster; clusters listed for size, $P < 0.05$, uncorrected.

^b Stereotactic coordinates according to MNI atlas, right/left, anterior/posterior and superior/inferior, respectively.

^c Z-score for peak magnitude(s) within a cluster.

^d $P < 0.000$, corrected.

et al., 1997; Courtney et al., 1998; Jonides et al., 1998; Rowe et al., 2000). These imaging findings are consistent with single unit recordings in monkeys, showing that prefrontal neurons associated with the maintenance of information in working memory also process information about motivation (Leon and Shadlen, 1999; Watanabe, 1996) and that cells in the IPS are sensitive to potential rewards (Platt and Glimcher, 1999). The study by Pochon et al. (2002) also reported activation in the IPS, which responded both to working memory load and a financial incentive. We did not find any interactions between reward and memory load in this region, although conclusions about a negative result should be cautiously offered. Nevertheless, the lack of interaction suggests that the effect of motivation may be independent of maintenance activity, that is, that motivation is additive to the activity of maintaining information.

Participants in the study demonstrated clear behavioral changes in response to the financial incentive, which included the risk of a penalty, and several factors could have influenced their behavior. The experiment was designed to motivate interest in obtaining a reward, interest in not losing money, and a change in the response criterion (a bias to indicate that the probe was in the target set). All subjects reported that they *felt* like they tried harder for the high reward stimuli. Behaviorally, subjects showed significant shifts in the response criterion and trends to greater sensitivity and faster response latency. The regionally specific activations associated with reward may indicate where the brain integrates information about the potential value of a stimulus with storage and retrieval of that stimulus from working memory stores. Alternatively, activations might also reflect calculations to avoid a perceived punishment, or calculations about shifting the response criterion. There may have been individual differences in how subjects approached the task. For example, some subjects may have been more motivated by a fear of losing money, rather than the anticipation of gaining a reward. Along with these possible interpretations, the high reward condition may have reflected “generalized motivation,” akin to arousal or enhancement of processing by attention.

An important consideration in the interpretation of our data is that the motivated condition may have led to a general increase in neuronal activity. For example, one could posit that when a person works harder at a task, as when they are motivated by the prospect of gaining, or losing, money, they use more of their brain. Behavioral studies demonstrate that motivational state does influence performance on cognitive tasks, particularly at higher levels of difficulty (Niedenthal and Kitayama, 1994). Parametric imaging studies that systematically increase the load on working memory systems show that frontoparietal networks increase activity, apparently to meet the demand of increasing load (Braver et al., 1997; Rypma et al., 1999; Smith and Jonides, 1998). One could interpret these results to mean that with greater motivation, a person expends greater effort and activates more working memory networks. This could occur through a generalized mechanism, such as monoaminergic systems with widespread ramifications throughout the cortex (Aston-Jones et al., 2000; Gaspar et al., 1989; Goldman-Rakic et al., 1992). While we did not see widespread activation during the high motivation conditions throughout the brain, the more regionally specific activations with motivation could reflect a simple statistical artifact of low experimental power or high thresholds, which artificially define narrow regions of activity.

In contrast to the apparently additive effects of reward on memory processing in the right STS and IPS, activity in the right MFG exhibited an interaction between reward and memory load

during the retrieval period. Lowering the threshold suggested more widespread activation in the right PFC that exhibited this interaction, an area also associated with retrieval in response to working memory load. Therefore, a plausible interpretation of the interaction is that the same region that mediated retrieval also integrated information about potential rewards and losses. This interpretation finds support in the study of Pochon et al. (2002), which also noted an interaction in the right lateral PFC between motivation and working memory. Since this interaction occurred during the PROBE period, we conclude that it represents an interaction with retrieval from working memory. An integrative role for the PFC agrees with other imaging studies suggesting that emotionally salient material and cognitive function are integrated in the lateral PFC (Gray et al., 2002; Perlstein et al., 2002), as well as broader conceptions of the lateral PFC as a neural location critical to the integration of complex behavior (Fuster, 2000; Stuss and Benson, 1986).

The finding of an interaction between motivation and memory load in the right lateral PFC during retrieval may have broader implications for the analysis of neural activation patterns. Much remains to be understood about individual differences in neural activations, of which motivation is only a single component. For example, most healthy subjects who participate in functional imaging experiments come to an imaging experiment motivated to perform well and not appear incapable. Since subjects typically perform an easier, less challenging task in contrast to the more difficult task that taps a cognitive process of interest (here, working memory), they must work harder to perform well and minimize mistakes. In other words, the more difficult tasks may motivate subjects more than easier control tasks, and this motivation may interact with the neural activation, as we saw in the lateral PFC. Therefore, functional imaging studies may do well to investigate motivation and effort as one possible factor behind individual differences in activation.

Activation during the PROBE period occurred in the IFG/lateral OBFC, which was adjacent to load-related foci in the IFG. In response to load, activity in the IFG has been suggested to mediate retrieval or organization of recall (Owen et al., 1998; Petrides et al., 1995). The reward-related foci in the IFG/lateral OBFC, lying just ventral and medial to the foci for memory load, is anatomically positioned to process information about the potential value of stimuli in working memory. This IFG/lateral OBFC region has also been activated in simple reaction time tasks that contrast incentive and non-incentive conditions (Knutson et al., 2000; Thut et al., 1997). It corresponds to what Ongur and Price (2000) label area 47/12, a part of a medial network, with connections both to orbital cortex, anterior cingulate cortex and the ventral striatum (Ferry et al., 2000; Ongur and Price, 2000). The activation found for reward extended into the orbitofrontal cortex, associated with the anticipation of rewards and punishments (Elliott et al., 2000; O'Doherty et al., 2001; Rolls, 1996). Connections to the ventral striatum would also be important for processing information about potential rewards (Schultz et al., 2000). Alternative explanations for the IFG/lateral OBFC activation are certainly possible, but processing information about value does appear to recruit this region.

Several areas of the brain activated as main effects of reward. The right caudate nucleus, along with focus in the right ventral pallidum, exhibited significant activity only when we analyzed activity across all of the trial events. This finding agrees with previous reports in the literature, showing activation of the

caudate nucleus for the anticipation of reward, as well as punishment (Knutson et al., 2001a,b, 2003; O'Doherty et al., 2002). Perhaps due to the sustained nature of caudate function over the course of the trial, as subjects anticipated their gain or loss in the task, this focus only appeared when we searched for activity common to all events in the trial. We also noted superior parietal activity in the precuneus, which appeared in the encoding phase, a result reported by at least one other group (Pochon et al., 2002). While this could represent top-down modulation of visual processing, previously shown for salient visual stimuli (Lang et al., 1998; Taylor et al., 2000), such an interpretation remains speculative.

In conclusion, the data presented here demonstrate that when subjects perform a simple working memory task, financial incentives not only motivate their performance, but they interact with and recruit some of the same neural networks that process various stages of the task. Additional work should explore the effect of more specific motivational manipulations in a cognitive task, such as obtaining a greater reward versus avoiding a punishment. Also, questions remain about whether areas of overlap and interaction process information about value, or respond in a more general way to motivation increasing neural effort. In either case, these findings should have significant implications for studies of psychiatric disorders, such as schizophrenia, that exhibit both impaired motivation (Andreasen, 1982) and impaired working memory (e.g., Goldman-Rakic, 1994; Park et al., 1995). Although an important consideration for any neuroimaging study in a patient group with impaired motivation, results demonstrating an apparent effect of motivation in no way invalidate the studies that have employed neurobehavioral probes in effortful tasks. Instead, these findings should suggest new leverage points for understanding how a cognitive task might be carried out in the context of motivation and value.

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