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Research Report

Reward modulation of prefrontal and visual association cortex during an incentive working memory task

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ABSTRACT

Cognitive performance differs with motivation, but little direct evidence exists regarding the neural mechanisms of the influence of reward motivation on working memory (WM). We tested the effects of motivation on the top-down control in visual WM. Encoding relevant stimuli for maintenance, while suppressing inappropriate inputs is considered a core process in cognition. Prior functional magnetic resonance imaging (fMRI) results demonstrated that stimulus-specific visual association cortex serves as a marker of activation differences for task-relevant and task-irrelevant inputs, such that enhanced activity occurs when attention is directed to relevant stimuli and suppressed activity occurs when attention is directed away from irrelevant stimuli [Gazzaley, A., Cooney, J., McEvoy, K., Knight, R.T., and D'Esposito, M. J. *Cogn. Neurosci.* 17, 507–517]. We used fMRI to test whether differential WM performance, indexed by lowered response times on a delayed-recognition task, was associated with amplification of enhancement and suppression effects during stimulus encoding within visual association cortex. Our results indicate that enhancement and suppression are amplified for trials with the highest reward level relative to non-rewarded trials for a scene-selective cortical region. In a face-selective region, similar modulation of enhancement for the highest reward level relative to non-rewarded trials was found. Prefrontal cortex also showed enhanced activity during high reward trials. Overall these results reveal that reward motivation can play a pivotal role in driving performance through top-down signaling in frontal regions involved in WM, as well as visual association regions selective to processing the perceptual inputs of the items to be remembered.

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1. Introduction

There is a rich literature linking reward motivation and working memory (WM); however, it has largely consisted of single-cell recording in non-human primates. This evidence suggests that reward motivation and WM processes overlap and interact. Despite this linkage, there has been little direct

investigation of the interaction between reward motivation and WM in humans.

Much of the research aimed at understanding the neural basis of reward processing has focused on the responsivity of the midbrain dopaminergic system and limbic cortex in the anticipation and receipt of reward. For example, numerous studies have emphasized the involvement of both the nucleus

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Abbreviations: WM, working memory; PFC, prefrontal cortex; IT, inferior temporal; ROI, region of interest

accumbens (Breiter et al., 2001; Knutson et al., 2001) and ventral striatum (Elliott et al., 2000; Delgado et al., 2003) in reward processing. Additionally, the orbital sector of the prefrontal cortex (PFC) has been emphasized in representing reward value (O'Doherty et al., 2001; Delgado et al., 2003; Rolls, 2004; Izquierdo et al., 2004, Simmons et al., 2005). Several recent studies have also begun to probe the influence of cognitive aspects and how they modulate reward-related brain regions. Tricomi et al. (2004) showed that fMRI response in the caudate nucleus was dependent upon the need to perform an action to obtain reward. Zink et al. (2004) have presented similar evidence showing that modulation of the caudate and nucleus accumbens is dependent upon task-related action contingency when compared to the passive receipt of money.

Further investigations of the linkage between midbrain activation and memory formation have been recently reported. In a long-term memory study for object pictures Wittmann et al. (2005) reported greater dopaminergic mid-brain activation associated with items that predicted monetary rewards and that these items were recalled later at a higher degree and were associated with greater hippocampal activation. A recent study by Adcock et al. (2006) demonstrated that long-term memory for scenes was influenced by monetary rewards and that the ventral tegmental area showed greater connectivity with the hippocampus suggesting a midbrain reward-related role in facilitating learning. These studies indicate that rewards can affect brain areas involved in facilitating the storage of information when reward-based information processing occurs.

In this study, we sought to investigate the effects of reward motivation on neural systems supporting higher levels of cognitive control. Recent neuronal recording studies from non-human primates have reported that neurons within the lateral PFC show firing to both reward motivation and abstract task demands. Hikosaka and Watanabe (2000) characterized the lateral PFC as being a site for the integration of cognition and reward and Watanabe et al. (2002a,b) have reported evidence of cognitive control and reward in the firing characteristics of lateral PFC neurons. Leon and Shadlen (1999) reported evidence of reward facilitation of lateral PFC neurons involved in a WM task. In this experiment task-related neurons showed a further amplification of firing rate when a desirable food trial-outcome was cued relative to when a less-desirable trial-outcome was cued. Similar results in non-human primate lateral PFC come from Kobayashi et al. (2002), who reported increases in neuronal firing rates to reward trials, but these investigators also reported populations of neurons tuned to the combination of target maintenance and non-reward. Additionally, Tsujimoto and Sawaguchi (2004) reported cells within the lateral PFC that appeared to represent response outcome in a WM task. Overall these results indicate that task-relevant PFC neurons can be enhanced or suppressed by the influence of the reward contingency of a WM trial.

Functional MRI evidence of reward motivation influencing performance has been reported recently in WM, attention, and motor tasks. Taylor et al. (2004) found an interaction within the PFC between WM for shapes and reward motivation. Greater activation has also been reported within frontopolar

cortex (BA 10), when reward motivation interacts with performance on a WM n-back task (Pochon et al., 2002) and in verbal maintenance regions when reward is offered for performance on task requiring WM for words (Gilbert and Fiez, 2004). In a spatial attention task, parietal regions associated with the allocation of spatial attention in visual cueing task were enhanced by the presence of reward incentives for speeded performance (Small et al., 2005). Visual cortex also showed enhancement of signal when reward was present in that spatial-attention task. Lastly, motor response preparation was linked with reward by Ramnani and Miall (2003), who reported greater activation within the left parahippocampal gyrus when reward was present in their motor task. In summary, these prior studies demonstrate that cortical areas associated with cognitive performance can show enhanced BOLD responses when performance-based rewards can be obtained.

In the current study, we investigate the influence of reward on cognitive control in WM by examining modulatory responses in visual association cortex. Monkey studies of inferior temporal (IT) cortex during delayed-match-to-sample (DMS) tasks have demonstrated support for the modulatory influences of task goals on activity in this region during behavior. For example, Miller and Desimone (1994) trained monkeys to perform a DMS task in which they had to maintain and make match judgments about picture stimuli. In addition to finding IT neurons associated with the active maintenance of pictorial information, they also noted that a subset of the population of neurons showed enhancement of spiking activity at the time of match judgment when a previously shown image was repeated. Also, other neurons suppressed their firing rate when the test picture was a match. These neuronal tuning characteristics indicate that IT neurons are sensitive to task demands and may participate actively in the judgment process, possibly via connections with the lateral PFC (Fuster et al., 1985; Miller et al., 1993; Knight et al., 1999).

Mounting evidence from human studies also indicates that the lateral PFC exerts control over visual association areas (Barcello et al., 2000; Miyashita and Hayashi, 2000; Ranganath et al., 2004; Rose et al., 2005). For example, Gazzaley et al. (2005a,b) used a delayed recognition task in which pictures of faces and scenes were presented serially at encoding and subjects were instructed to attend to one category and ignore the other. Both fMRI and ERP results supported a modulation of stimulus-relevant activity within IT visual association cortex. For scene stimuli, regions within the parahippocampal gyrus showed significant activation for the perception of scene stimuli. Activation within these regions was enhanced when scenes were to be attended relative to a perceptual baseline condition and suppressed relative to baseline when scenes were to be ignored. A similar modulation was reported for face-selective visual association cortex. The current experiment will build upon these findings by testing the effect of increased reward motivation on top-down modulation using this WM paradigm.

In this study, we present results from an fMRI experiment that pairs reward and WM using a variant of the task described by Gazzaley et al. (2005a,b) in which pictures of faces and scenes are presented at encoding with the requirement that one category be attended to for later memory after a delay,

while the other category is ignored. We investigated whether the top-down modulatory patterns of enhancement and suppression described previously in scene-selective parahippocampal gyrus and in a face-selective area of fusiform cortex are modified by reward motivation. Furthermore, we tested whether task-relevant regions of the PFC would also show this modulatory pattern with reward and WM. Additionally, we attempted to determine the extent to which either of these modulatory patterns influences performance of the task relative to non-rewarded task conditions.

2. Results

2.1. Behavioral data

Overall accuracy on all trials was relatively high across all reward levels. Accuracy was uniformly high in the passive view trials (99.47% for low reward and 100.00% for high and non-reward), thus all analyses of mean accuracy included comparisons of the remember faces/ignore scenes and remember scenes/ignore faces only. We had predicted that rewards would potentially influence accuracy rates leading to higher accuracy when a reward was possible. Means for accuracy were analyzed with a 3 (reward) \times 2 (stimulus condition) \times 2 (match or non-match response) repeated-measures ANOVA. Results revealed a main effect of stimulus to be remembered, $F(1,15)=13.79$, $p<0.01$, such that remember scenes/ignore faces trials resulted in higher accuracy than remember faces/ignore scenes trials. Additionally, there was a significant main effect of response type, $F(1,15)=7.24$, $p<0.05$, where match trials resulted in higher accuracy than non-match trials. No other effects were statistically significant. Thus, reward did not have an impact on accuracy overall, despite an apparent numerical trend toward improved accuracy when rewards were possible. Table 1 shows mean accuracy percentages for each of the trial categories. A d' analysis was conducted to determine whether reward value significantly altered response biases, but this analysis failed to show reliable differences.

We hypothesized that rewarded trials would result in an improvement in efficiency as indexed by faster response times for correct trials. A 3 \times 2 \times 2 repeated-measures ANOVA com-

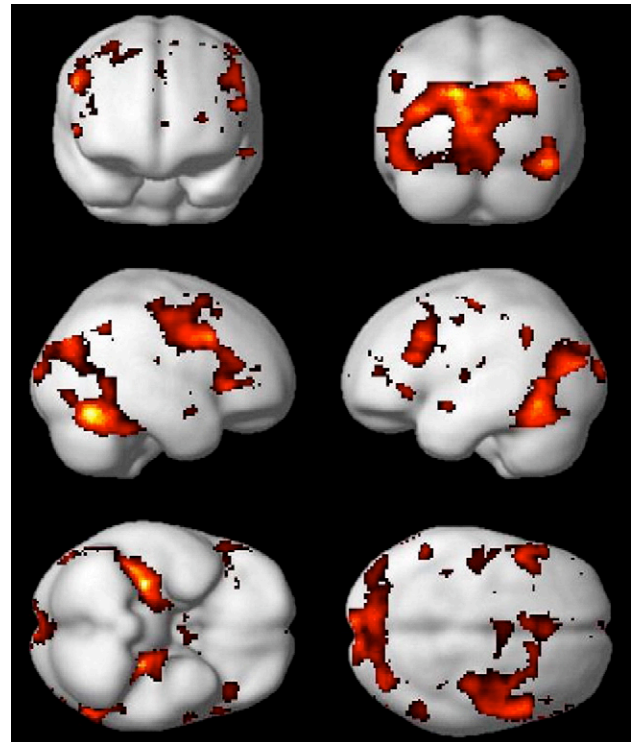


Fig. 1 – (A) Group whole-brain map of the significant effects (False Discovery Rate $p<0.05$) over the 4 s encoding period collapsing across all reward conditions. Significant regions of activation within this group map included bilateral prefrontal cortex (dorsal and ventrolateral), medial prefrontal cortex, premotor cortex, cerebellum, bilateral striatum, bilateral ventral and superior temporal cortex, bilateral occipital cortex, and right posterior cingulate cortex. It should be noted that we did not obtain complete coverage of the ventral prefrontal cortex or the posterior parietal cortex due to our oblique axial slice orientation.

paring response times of correct trials for each reward level collapsed across each condition revealed a significant effect of reward, $F(2,30)=4.79$, $p<0.05$. Bonferroni-corrected post hoc tests ($p<0.05$) revealed that mean response time for high-reward trials and low-reward trials were each faster than that

Table 1

	Remember faces/ignore scenes match	Remember scenes/ignore faces non	Remember faces/ignore scenes non	Remember scenes/ignore faces match
<i>Mean accuracy</i>				
Non-reward	75.19%	84.28%	64.81%	74.06%
Low reward	72.12%	81.83%	67.25%	86.13%
Hi reward	77.91%	65.22%	69.38%	89.44%
<i>Mean response time</i>				
Non-reward	842.65	670.13	649.00	692.33
Low reward	676.33	620.75	608.00	695.17
Hi reward	639.25	619.38	654.00	673.00

non = non-match trial.

for non-reward trials (see Table 1 for mean response times). This analysis also revealed a significant effect of response-type, $F(1,15)=4.79$, $p<0.05$, indicating that non-match trials were completed significantly faster than match trials. Reward magnitude and response-type also interacted significantly, $F(2,30)=4.41$, $p<0.05$. This interaction was carried predominantly by differences among the match and non-match trials at the low reward levels and the differences between the match trials in the high compared to non-reward trials (refer to Table 1 for means). Overall these data indicate that rewards significantly reduced response time for correct trials compared to instances in which rewards were not available. Furthermore, the match trials took longer to complete than non-match trials.

2.2. Imaging data

Fig. 1 shows the overall group effects during the encoding period collapsed across reward levels (reported at False Discovery Rate, $p<0.05$). Consistent with previous studies using a similar WM task, there were several regions of significant activation across the brain during this task period including bilateral prefrontal cortex (dorsal and ventrolateral), medial prefrontal cortex, premotor cortex, bilateral parietal cortex, cerebellum, bilateral striatum, bilateral ventral and superior temporal cortex, bilateral occipital cortex

extending dorsally toward the parietal cortex, and right posterior cingulate cortex.

To test for specific effects within ROIs, we performed a 3 (reward level) \times 3 (stimulus condition) ANOVA on mean parameter estimates from the left scene-selective ROI (see Fig. 2A). This same region was previously reported to show significant enhancement above passive view baseline when scenes are to be remembered, as well as suppression below passive view baseline when scenes are to be ignored (Gazzaley et al., 2005a,b). As such, we hypothesized that this region would be modulated by task demands with higher activation when scenes were to be attended and lower activation when scenes were to be ignored. Further, we predicted that the opportunity to win monetary rewards would amplify these patterns within this region. This analysis revealed a significant main effect of stimulus-type, $F(2,28)=19.24$, $p<0.01$. Bonferroni-corrected post hoc comparisons ($p<0.05$) revealed that the remember scenes/ignore faces condition showed higher activation than the passive view condition and the remember faces/ignore scenes condition. The passive view condition showed marginally higher activation than the remember faces/ignore scenes, but this comparison was non-significant ($p<0.09$). These results are consistent with the previous study indicating that the scene-selective ROI is sensitive to detecting attentional modulation during the encoding period.

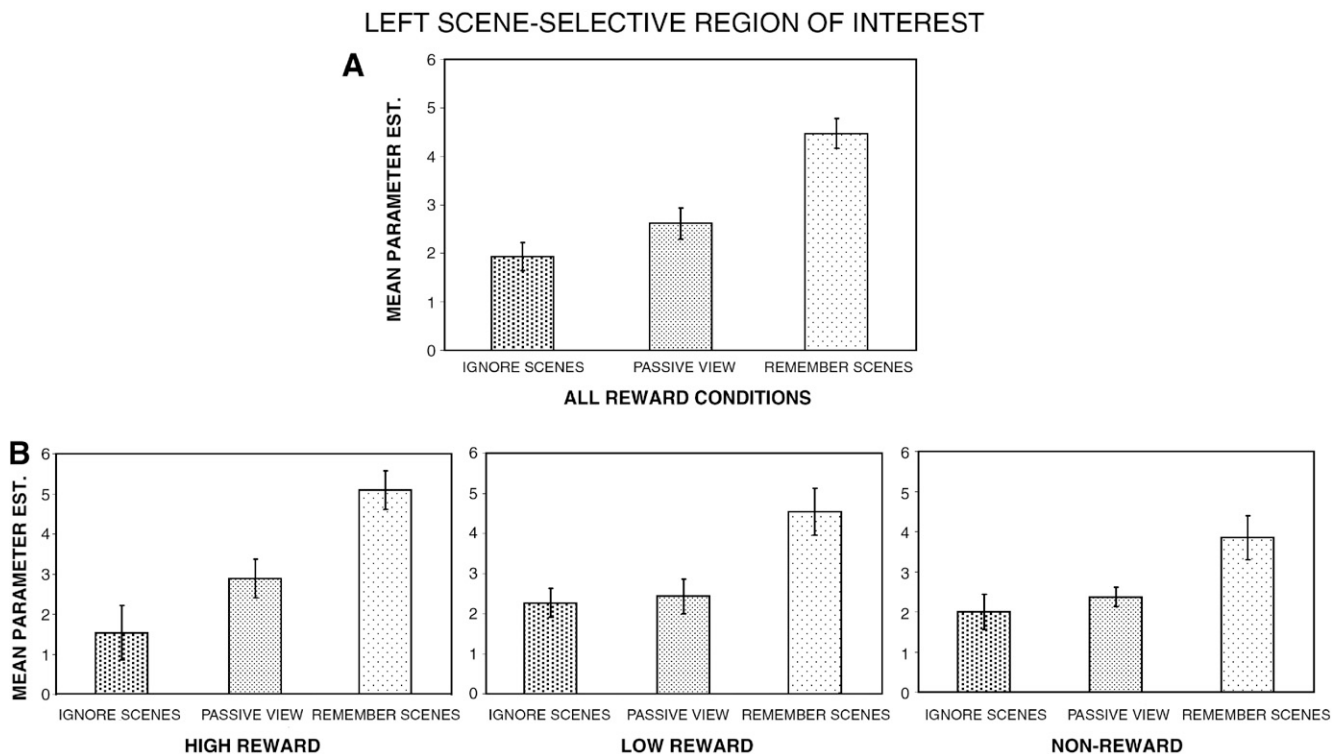


Fig. 2 – (A) Group mean parameter estimates for each condition (e.g. remember faces/ignore scenes, passive viewing, remember scenes/ignore faces) in the left hemisphere scene-selective ROI during the encoding period of the task. (B) Group mean parameter estimates for each condition from the left scene-selective ROI during the encoding period for the high reward, low reward, and non-reward trials. Significant enhancement (remember scenes/ignore faces minus passive viewing) was found for both high and low reward conditions, but not for the non-reward condition. Furthermore, significant suppression below baseline (remember faces/ignore scenes minus passive viewing) was found for the high reward condition. Error bars denote standard error of the mean.

To directly test our hypothesis regarding the influence of reward on BOLD signal change, we computed an *overall modulation index* by subtracting BOLD signal parameter estimates from all remember scenes/ignore faces trials minus the parameter estimates from all remember faces/ignore scenes trials. This value was calculated for high reward trials (as this condition had showed a performance difference for remember scenes/ignore faces trials) and for all non-reward trials. Comparisons of these scores indicated that high reward trials showed a greater modulation index ($M=3.55$) than non-reward trials ($M=1.88$); $t(14)=1.86$, $p<0.05$). This supports the hypothesis that the highest level of reward motivation modulated activity of posterior visual areas involved in WM.

We also compared the magnitudes of enhancement and suppression for each reward level to determine the extent to which rewards influenced modulation. Fig. 2B shows that a similar overall pattern was replicated across reward levels. Analyses of the degree to which each reward level showed significant enhancement and suppression of remember scenes/ignore faces and remember faces/ignore scenes values relative to baseline were compared separately in each of the reward value trial sets. Significant enhancement above passive view baseline was found for both high ($t(14)=2.97$, $p<0.01$) and low reward conditions ($t(14)=3.00$, $p<0.01$), but not for the non-reward condition. Furthermore, significant suppression below baseline was found for the high reward condition ($t(14)=2.38$, $p<0.05$). We interpret these results as showing a greater strength of enhancement and suppression when a high reward was present. There was a clear trend in the expected directions of enhancement and suppression in the non-reward trials. Dividing the trials into these categories likely reduced the power to show significant enhancement and suppression in all conditions despite the pattern being consistent within each.

Data from the face-selective ROIs were analyzed using 3 (reward) \times 3 (condition) ANOVAs. These regions were hypothesized to also show attentional modulations with greater activation when faces were to be remembered and we predicted that they might also be modulated further by the presence of rewards. The ANOVA revealed no significant differences in the right face-selective ROI. In the left face-selective ROI we found a significant main effect of reward, $F(2,28)=4.15$, $p<0.05$. Means for this interaction did not survive corrected post hoc comparisons, but revealed a trend toward greater activation with higher rewards (high reward $M=1.56$, low reward $M=1.43$, non-reward $M=1.01$). Additionally, reward interacted with stimulus type, $F(4,56)=3.17$, $p<0.05$. This effect was carried by the fact that rewarded trials yielded higher activation values for both remember faces/ignore scenes and remember scenes/ignore faces conditions, while rewards yielded lower activation for passive view trials within this ROI. These results indicate that the left face-selective ROI was modulated by reward in the enhancement direction. Unlike the left scene-selective ROI, suppression was not found in the face-selective regions.

To further probe the extent of reward enhancement within the face-selective ROIs, we conducted comparisons

of the mean parameter estimates for the overall modulation index (remember faces/ignore scenes trials relative to passive view baseline minus remember scenes/ignore faces trials relative to baseline) with planned comparisons. These comparisons revealed that the high reward ($M=1.79$) and non-reward ($M=0.71$) conditions were significantly different within this right face-selective ROI $t(14)=2.77$, $p<0.05$. Further, the low reward ($M=1.70$) condition was also significantly higher than the non-reward condition $t(14)=2.38$, $p<0.05$. Similar analyses within the left face-selective ROI revealed that the low reward condition ($M=-0.16$) was significantly more active relative to the non-reward condition ($M=-0.94$) $t(14)=2.18$, $p<0.05$. These results also support the hypothesis that greater enhancement occurs when rewards are possible relative to the non-reward conditions.

We hypothesized that our frontal ROI would also show reward-based modulation based on the prior evidence of reward-related enhancement within PFC neurons (Leon and Shadlen, 1999). Analysis of the frontal ROI data involved conducting a 3 (reward) \times 3 (condition) ANOVA. This analysis revealed a significant linear trend across the three reward conditions, $F(1,15)=6.32$, $p<0.05$, indicating that relative parameter estimates increased with the level of reward overall (see Fig. 3). It should be noted that we consider the PFC to be subserving similar executive functions during both the remember scenes/ignore faces and remember faces/ignore scenes conditions. When these sets of trials were separated and compared using repeated measures ANOVAs, similar results were obtained. For the remember scenes/ignore faces condition, a significant linear trend was also obtained, $F(1,15)=5.11$, $p<0.05$. For the remember faces/ignore scenes condition, this analysis reached marginal significance, $F(1,15)=3.46$, $p=0.08$. The greater strength of the result for the remember scenes/ignore faces condition may reflect the fact that remember scenes/ignore faces trials were performed more accurately than remember faces/ignore scenes trials.

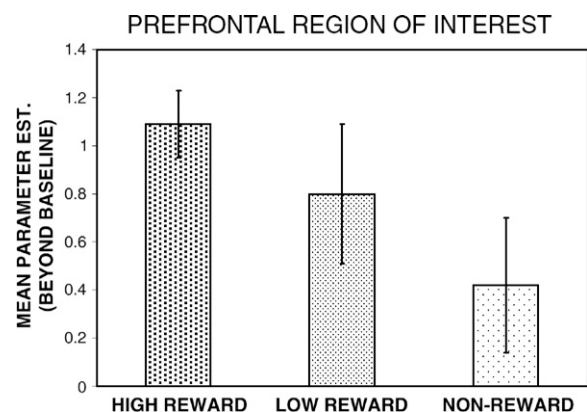


Fig. 3 – Data from PFC areas active at the encoding period. The three reward conditions are shown plotted as activation level for memory encoding relative to passive viewing. The high reward condition showed greater relative activation compared to the non-reward condition and a significant linear trend was also present. Error bars denote standard error of the mean.

3. Discussion

We present evidence that reward motivation can influence a task that requires top-down attentional signaling to perform at optimal levels. Specifically, we found that incentives influence top-down attentional signals, that is, when rewarding goals are available, top-down modulation can be driven to higher levels, due to both increased ability to enhance task-relevant inputs and to suppress competing irrelevant perceptual inputs. This finding adds to a growing body of research emphasizing the idea that human cognitive control relies heavily upon directing attention toward relevant stimuli to be maintained, as well as selectively suppressing irrelevant stimuli to be ignored (Fuster et al., 1985; Rowe and Passingham, 2001; Fuster, 2003; Gazzaley et al., 2005a,b).

At the behavioral level, the presence of reward incentives for accurate performance reduced response times during a delayed recognition task. This finding is consistent with the monkey electrophysiology literature, as faster response times are one of the classic markers of improved performance due to the presence of an incentive (Watanabe et al., 2002a,b). It is important to note that while accuracy did not significantly improve with the presence of reward, it did not decline, and in fact remained at a numerically higher level overall than the accuracy for non-rewarded trials. This is notable, as it indicates that subjects did not emphasize speed over accuracy, but rather, emphasized both speed and accuracy in accord with task instructions. It is also noteworthy that both mnemonic conditions (e.g. faces and scenes) showed reliably faster response times in high versus non-reward conditions, but that the low reward condition showed an asymmetry in which it was faster for remember faces/ignore scenes but not remember scenes/ignore faces trials. This difference between conditions at the low reward level indicates that the low rewards may have been motivating in general, but lacked the overall significance to influence task performance the same manner that high reward trials did. This difference also highlights the possibility that remembering faces and visual scenes may involve the use of different mnemonic strategies leading to the asymmetry of the relative response times for low reward trials. It is likely that with greater numbers of trials this difference between the two conditions may disappear.

At the neural level, we found modulation from baseline in scene-selective visual association cortex, replicating our previous studies (Gazzaley et al., 2005a,b). This region showed significant enhancement from passive view baseline toward scenes when subjects were directed to remember scenes and a trend in the predicted direction of significant suppression below passive view baseline for scenes that were to be ignored. A similar effect was found in face-selective association cortex. The lack of robustly significant suppression in our data differs somewhat from prior findings (Gazzaley et al., 2005a,b); however, this task was made more challenging than the version employed previously, through shorter presentation times of the stimuli at encoding. This may have resulted in a reduction in suppression due to increases in WM resources necessary to correctly perform the task.

Trials with the possibility of obtaining the highest possible rewards for correct responses demonstrated greater modula-

tion from baseline compared to non-rewarded correct trials for stimulus-selective regions of visual cortex. This finding demonstrates a greater overall magnitude of change supported by both the enhancement and suppression of correct and incorrect information for scene-selective cortex and magnitude of change by enhancement in the face-selective cortex. When further examined at each reward level, despite a lowered statistical power due to many fewer analyzed trials, the scene-selective data were sufficiently robust to support both significant enhancement and suppression in high-reward trials. Low-reward trials showed robust enhancement with a non-significant pattern of suppression, while non-rewarded trials showed non-significant patterns toward enhancement and suppression. We interpret this as evidence that high rewards boosted the overall enhancement and suppression to a greater degree than non-rewarded trials, with low-reward trials in between. We also found that a right face-selective region showed greater enhancement relative to baseline for high and low reward remember face trials relative to non-reward trials, while a left face-selective region showed similar modulation. Suppression was not robust in these face-relevant data, but this may have been due to the low presentation times compared to the prior study (Gazzaley et al., 2005a,b) and possibly because faces are a biologically relevant class of stimuli that may be more difficult to ignore. Critically, this study shows that reward need not influence behavior merely through general and diffuse increases in arousal, but rather, reward specifically influencing core processes of attentional control.

Although our experiment cannot directly determine the source of top-down signals, it is likely that such signals arise from lateral PFC. We demonstrated that the task-relevant regions of PFC were modulated by reward with greater signal for high reward over non-reward correct trials. Several lines of evidence support the link between PFC and top-down control (Miller and D'Esposito, 2005). In non-human primates, Fuster et al. (1985) demonstrated that neuronal responses in inferior temporal cortex were attenuated in a WM delay task when lateral PFC was deactivated. Furthermore, Tomita et al. (1999) reported evidence that inferior temporal neurons are activated by a top-down influence from the PFC in the absence of any bottom-up stimulus. In humans, PFC lesions have been shown to impair the ability to enhance relevant inputs and suppress irrelevant ones (Chao and Knight, 1998; Knight et al., 1999; Barcello et al., 2000). Moreover, in the same task used in this study, a suppression deficit was found in normal elderly subjects, also consistent with a frontal source of top-down signals (Gazzaley et al., 2005a,b).

Having provided evidence that reward motivation can influence top-down control, an important goal for future research is to determine how reward system neural circuitry influences lateral PFC systems thought to mediate top-down control. There are numerous possible sources of reward influence upon cognitive control, but perhaps the most likely regions responsible for translating potential value into attentional enhancement are the orbitofrontal cortex and striatum. Both of these regions have been implicated in processing reward value (O'Doherty et al., 2001; Schultz, 2002; Rolls, 2004). While we did not get adequate orbital coverage in the current study. Additionally, neuronal firing patterns within these

regions have been reported to show sensitivity to both task-related response and reward value (Leon and Shadlen, 1999; Kobayashi et al., 2002; Hollerman et al., 1998; Hassani et al., 2001). Anatomical evidence indicates that the lateral PFC shares direct connections with the orbitofrontal cortex and primate neurophysiological studies indicate that the orbitofrontal cortex may relay motivationally significant information to the lateral PFC (Watanabe et al., 2002a,b; Wallis and Miller, 2003). Another possibility is that dopamine neurons in the midbrain may have a direct influence upon the top-down system through connections to the lateral PFC. This view is supported by reports from non-human primate studies in which alterations of dopamine levels of input to lateral PFC (BA 46) have been shown to affect WM performance (Sawaguchi and Goldman-Rakic, 1991, 1994). In the current task, it is possible that dopaminergic signaling is intensified when potential rewards may be obtained and this may have a direct influence on frontal regions thought to influence top-down attention when encoding stimuli.

These results extend upon our knowledge of how reward motivation can increase performance and activation within brain regions not linked directly to the representation of reward. Prior studies have reported that regions in lateral PFC and premotor cortex can be enhanced when rewards are offered for performance (Pochon et al., 2002; Taylor et al., 2004; Ramnani and Miall, 2003). Furthermore, Small et al. (2005) showed evidence of enhancement within a posterior parietal area related to the efficient allocation of spatial attention when rewards are possible. Also, relevant are results from Adcock et al. (2006) and Wittmann et al. (2005) who reported long-term memory facilitation through monetary reward and regions related to reward anticipation. Our study complements these findings by demonstrating that scene and face-

selective regions of visual association cortex show differential modulation of attentional enhancement with rewarded trials over non-rewarded ones. Lastly, this modulation may be linked to the PFC, which showed reward-related modulation for all WM trials at the encoding phase.

Our results suggest that theories of cognitive control should be extended to integrate the effects of both reward motivation and cognition rather than focusing purely on reward processes (Damasio, 1996) or purely on WM without motivational modulations (Wood and Grafman, 2003). This study highlights the existence of important connections between these two domains.

4. Experimental procedure

4.1. Subjects

Sixteen volunteer subjects (6 females) from the University of California participated after providing informed consent. Age ranged from 19 to 37 ($M=22.22$, $S.D.=3.86$). All subjects had normal or corrected vision, were free of neurological disorders, and were not taking any medications having a psychoactive, cardiovascular, or homeostatic effect. Fifteen subjects were right-handed and one was predominantly, but not exclusively left-handed as reported in our consent protocol.

4.2. Cognitive task and procedure

A WM delay recognition task was used and each trial was assigned a point value that could be earned if the trial was performed correctly. Points were worth money that was paid as bonus after the experiment was completed and subjects

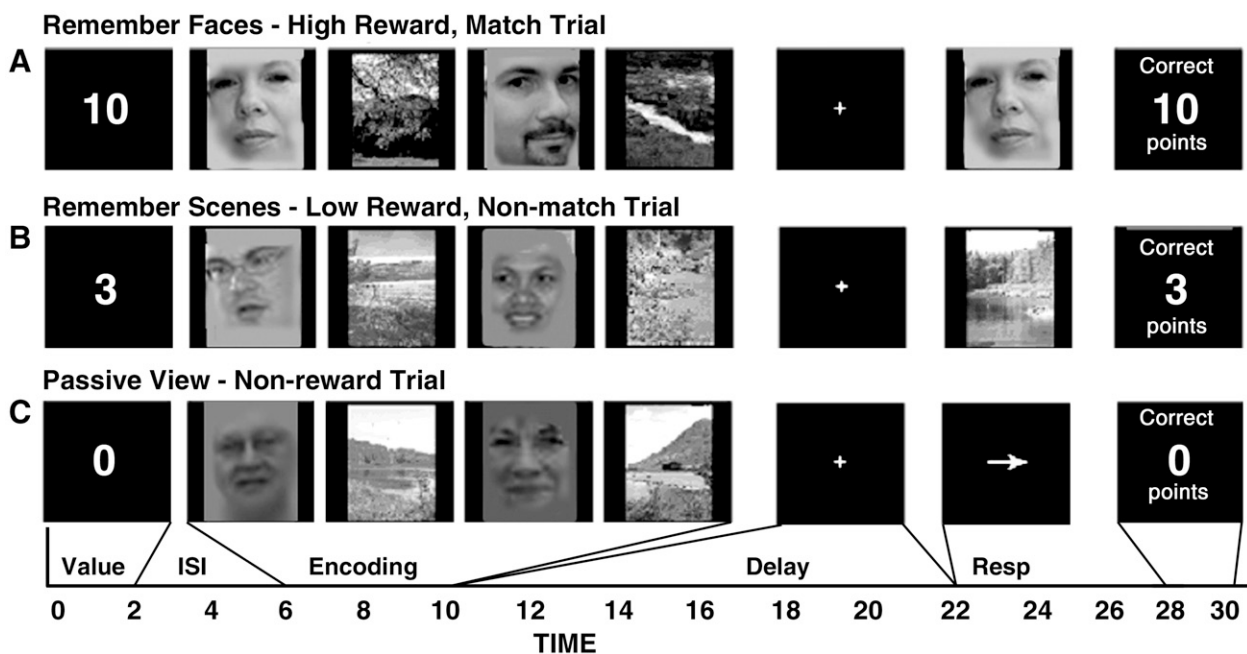


Fig. 4 – Illustration of the three task conditions with examples of the reward cue presentation for each level. (A) A remember faces/ignore scenes trial with the high reward cue presented. (B) A remember scenes/ignore faces trial with a low reward cue. (C) A passive view trial with a non-reward cue and response period requiring a button press only as directed by the arrow.

were informed that they could earn up to \$40.00 extra for points earned. Three conditions were included: remember faces/ignore scenes, remember scenes/ignore faces, and passive viewing (see Fig. 4). Three blocks of 16 trials were presented for the remember faces/ignore scenes and remember scenes/ignore faces conditions and 2 blocks of 16 trials were presented for the passive viewing condition. The subject was informed about the instructional condition of each block prior to the first trial. For six subjects two remember scenes/ignore faces sets were completed and for two subjects two remember faces/ignore scenes sets were completed due to time limitations.

The trial structure was the same in all conditions. Each trial began with the presentation of a point value (10 points for high reward, 3 points for low reward, 0 points for no reward) in green print for 2 s and was followed by a fixation cross for 4 s. A 4 s encoding period followed in which 2 pictures of faces and two pictures of scenes were presented for 400 ms per image with a 600 ms inter-stimulus interval consisting of a blank screen. All pictures were 225 pixels wide by 300 pixels tall and subtended approximately 5 to 6 degrees of visual angle. Each face image was cropped with blurred edges to include only the facial features and each face had a neutral expression. *Remember faces/ignore scenes* blocks required participants to remember the pictures of faces at encoding and to ignore pictures of scenes, while the *remember scenes/ignore faces* trials required them to do the opposite and remember scenes and ignore faces. In *passive viewing* trials subjects viewed each picture with no mnemonic goals. A jittered delay period lasting 8, 10, or 12 s followed. A probe period began with the presentation of a test picture for 2 s (a face in remember faces, a scene in remember scenes) or an arrow in passive view. In the remember faces/ignore scenes and remember scenes/ignore faces conditions, subjects were instructed to judge if they had seen the picture in the encoding phase of that trial and to make a button press with the right thumb on a keypad if they had and a button press with the left thumb if they had not. In the passive viewing condition, a right arrow prompted a right thumb press and a left arrow prompted a left thumb press. Subjects were required to respond within 1 s of probe stimulus onset in order to get a correct answer and earn points for the trial. After a 4 s fixation cross presentation, a 2 s feedback screen was presented indicating whether the subject's response had been correct, incorrect, or had exceeded the 1 s response window. If correct, a feedback statement indicating a gain of the point value earned for that trial was presented in green numerical type for 2 s. If incorrect, a statement that zero points were gained was presented in red type for 2 s. A fixation cross appeared for 4 s followed by a jittered inter-trial interval of 4, 6, or 8 s.

Additional counterbalancing measures were employed in order to minimize the differences between the conditions. Point values were pseudorandomly distributed throughout each block with the constraint that an equal number of high, low, and no reward trials were included in each condition, except the passive viewing condition, which contained 2 additional low reward trials due to the fact that only 32 trials of this type were presented. The presentation of images in the encoding period was counterbalanced for order of presentation. Gender of the face was held constant such that the two

encoding pictures in any given trial were always the same gender. The probe stimulus contained an equal number of correct and incorrect trial types for the remember faces/ignore scenes and remember scenes/ignore faces conditions, as well as an equal number of left and right arrows in the passive viewing condition. Order of block presentation was pseudorandomized as well. Data were acquired in 8 runs of 16 trials lasting 9 min 45 s each yielding a total of 128 trials.

Subjects performed a functional localizer task prior to the WM task that allowed us to functionally define ROIs for use in our group analyses. The functional localizer consisted of seven 16 s blocks of grayscale faces, grayscale scenes, or a fixation cross. In order to insure that subjects were attentive during the localizer task, they were instructed to make simultaneous right and left button presses with the thumbs if they saw an image repeat. This localizer task has previously been shown to reliably activate scene and face-selective regions of inferior temporal cortex (Ranganath et al., 2004; Gazzaley et al., 2005a,b). Subjects were in the scanner for approximately 105 min, with the experimental task taking approximately 90 min to complete.

4.3. MRI data acquisition

Images were acquired using a 4 T Varian INOVA scanner using a gradient echoplanar sequence (TR=1000 ms, TE=28 s, 64 × 64 matrix, FOV=24 cm) sensitive to BOLD contrast. Each volume consisted of 18 tilted axial slices (5 mm thick, 0.5 mm slice gap) that provided nearly whole brain coverage. Anatomical T1-weighted images (TR=200 ms, TE=5) were also acquired in the same space. Head motion was limited using foam head padding.

4.4. Functional MRI data analysis

Detailed descriptions of the procedure used for analyzing activation within trials have been published previously (Zarahn et al., 1997, 32) and are summarized below. Activation of each phase of the trials was assessed using multiple regression (Zarahn et al., 1997; Postle et al., 2000). Preprocessing stages included correction for slice timing differences using a sync-interpolation method, and interpolation of the data to 1 s temporal resolution by combining each shot of half k-space with the bilinear interpolation of the two flanking shots. Subsequent analyses were conducted using SMP2 run in Matlab 6.5 (<http://www.mathworks.com>). EPI images were realigned to the first volume of acquisition and then smoothed with an 8 mm 3D Gaussian kernel.

Separate regressors were used to model three phases of the task: encoding (6–10 s into the trial), delay (14–15 s into the trial) and response (1 s covariate capturing the first second of the response window). Note that the delay period regressor was placed 4 s after the delay period had begun in order to prevent contamination of the delay period activity from remaining signal associated with the encoding period. Only correct trials were included in the analysis. Incorrect trials and those in which the subject exceeded the response window were modeled separately and excluded from group analyses. Each regressor was convolved with a canonical hemodynamic response function (HRF) provided in SPM2 and entered into the

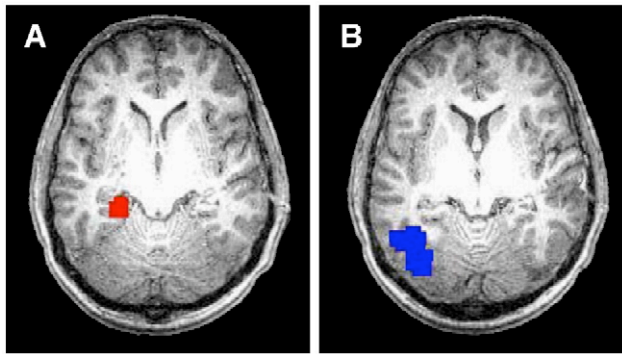


Fig. 5 – (A) A representative ROI for the left scene-selective cortical region within the parahippocampal gyrus. This ROI was defined with a 5 mm sphere centered upon the most active cluster from a scene minus face contrast from the perceptual viewing task. (B) A representative left face-selective ROI comprised of all active voxels centered upon the fusiform gyrus from a face minus scene contrast performed on the perceptual viewing task.

modified general linear model of SPM2. A high-pass filter (cutoff 128 s) was applied to the data to remove frequency effects. Parameter estimates (e.g. β values) were extracted from this GLM analysis for the regressors modeling the encoding period of the task and averaged within functionally defined regions of interest (ROIs). As our hypotheses centered on the encoding period, our group analyses were restricted to this task phase regressor. Planned comparisons were conducted on these data using paired-samples *t*-tests ($p < 0.05$) to test our a priori hypotheses regarding regional activation. Data from all subjects were coregistered to the MNI template brain and normalized for a group analysis of the encoding period data.

Regions of interest (ROIs) were chosen to test for differences in top-down modulation of visual areas, as well as reward modulation of these regions, the PFC and primary motor cortex. A scene-selective ROI was based on the localizer task GLM using a scene minus face contrast to obtain regions responsive to scene perception. Activation was restricted to the parahippocampal gyrus by masking the most active cluster with a spherical mask (5 mm radius) centered upon the voxel with the highest *t*-value. This procedure yielded either 8 or 9 voxels for each ROI chosen. ROI masks for scene selective areas were obtained for 15 subjects in the left hemisphere (see Fig. 5A) as it has been demonstrated previously to be the most sensitive region for detection of stimulus-specific attentional modulation differences using face and scene stimuli (Gazzaley et al., 2005a,b). Face-selective ROIs were obtained bilaterally by conducting a face minus scene contrast on the localizer task GLM data. For these analyses all voxels within the right or left fusiform gyrus were included in the lateralized ROI, as the face-sensitive regions typically did not form spherical clusters. The left face-selective ROI (see Fig. 5B) was localized in 15 subjects and was comprised of a mean of 60.80 voxels, while the right face-selective ROI was localized in 13 subjects and was comprised of a mean of 96.85 voxels. ROIs were defined in the PFC and primary motor/premotor cortex for each subject by running a

GLM contrast on the data from the experimental runs to obtain regions active for the encoding period collapsed across task conditions and reward levels. The PFC ROIs were anatomically restricted in all subjects to include only those voxels within the lateral PFC including middle and inferior frontal gyrus (anterior to primary motor cortex and superior to the orbital gyrus) falling into the following MNI coordinate ranges ($x = -70$ to 70 , $y = 5$ to 70 , $z = -10$ to 70). Frontal ROIs were bilateral in 15 subjects and right-sided in one subject. These ROIs were comprised of a mean of 92.14 voxels. The ROIs within primary motor/premotor cortex were defined in a similar way by defining regions that were posterior to the PFC ROIs (for each individual subject) and fell within either primary motor cortex or premotor cortex defined based on the cortical geography of each individual subject. These ROIs consisted of a mean of 508.13 voxels with foci of activation bilaterally in all subjects and within a medial portion of the motor regions in 15 of the subjects.

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