

## Functional connectivity during top-down modulation of visual short-term memory representations

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### ARTICLE INFO

#### Article history:

Received 10 August 2010

Received in revised form

21 December 2010

Accepted 30 December 2010

Available online 15 January 2011

#### Keywords:

Functional connectivity

Event-related functional magnetic

resonance imaging

Attention

Top-down control

Visual short-term memory

### ABSTRACT

Recent evidence has revealed that short-lived internal representations held in visual short-term memory (VSTM) can be modulated by top-down control via retrospective attention which impacts subsequent behavioral performance. However, the functional inter-regional interactions underlying these top-down modulatory effects are not fully characterized. Here we used event-related functional magnetic imaging to investigate whether the strength of functional connectivity between the frontal cortex and posterior visual areas varies with the efficacy of top-down modulation of memory traces. Top-down modulation was manipulated by the timing of retro-cueing (early or late) in a VSTM task. Univariate analyses revealed that more effective top-down modulation (early cueing vs. late cueing) increased activity in early visual areas. Importantly, coherency analyses revealed that top-down modulation produced stronger functional connectivity between frontal and posterior occipital regions. Also, participants with stronger functional connectivity exhibit better memory performance. These results suggest that augmented functional connectivity between frontal and posterior visual areas strengthens the VSTM representations of importance to behavioral goals.

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### 1. Introduction

The short-lived internal representations in visual short-term memory (VSTM) are highly flexible and can be modulated by top-down control mechanisms (e.g. Griffin & Nobre, 2003; Jiang, Olson, & Chun, 2000; Kuo, Rao, Lepsien, & Nobre, 2009; Makovski & Jiang, 2007; Makovski, Sussman, & Jiang, 2008; Matsukura, Luck, & Vecera, 2007; Nobre et al., 2004; Nobre, Griffin, & Rao, 2008; Schmidt, Vogel, Woodman, & Luck, 2002). Although the neural mechanisms underlying VSTM are not fully understood, it is proposed that an ensemble of cortical regions, especially the prefrontal cortex (PFC), sustain these internal representations in an active state for maintaining task-relevant information according to behavioral goals and expectations (D'Esposito, Postle, & Rypma, 2000; Fuster, 2000).

Previous findings reveal that several aspects of stimulus-driven bottom-up visual processing – including the gain (Chawla, Rees, & Friston, 1999; Luck, Chelazzi, Hillyard, & Desimone, 1997), tuning (Haenny & Schiller, 1988; Murray & Wojciulik, 2004; Serences, Saproo, Scolari, Ho, & Muftuler, 2009), synchronization (Womelsdorf et al., 2007), and temporal properties of evoked sensory signals (Gazzaley et al., 2008) – may be modulated by top-down biasing signals that modify incoming sensory inputs in a goal-directed and context-driven fashion (Ester, Serences, & Awh, 2009; Harrison & Tong, 2009; Serences, Ester, Vogel, & Awh, 2009; Stokes, Thompson, Cusack, & Duncan, 2009). Via these mechanisms, it is proposed that PFC can exert top-down modulatory control of perceptual inputs (Curtis & D'Esposito, 2003; Miller & D'Esposito, 2005; Miller & Cohen, 2001; Passingham & Sakai, 2004). Accumulating evidence has also revealed that these top-down signals arise from functional interactions between frontal and posterior cortical regions (Barcelo, Suwazono, & Knight, 2000; Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008; Gregoriou, Gotts, Zhou, & Desimone, 2009; Miller, Fegen, Vytlačil, Pradhan, & D'Esposito, 2011; Moore & Armstrong, 2003; Ruff et al., 2006). However, it remains unclear whether the efficacy of top-down modulation of actively maintained task-relevant representations is reflected in the strength of

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functional connectivity between frontal cortex and posterior brain regions.

In this study, we used event-related functional magnetic resonance imaging (fMRI) to measure changes in neural activity while performing a variant of a VSTM task (Luck & Vogel, 1997). Top-down modulation in the early phase of retention can enhance activity in early visual cortex which is associated with improved later memory judgment (Ruff, Kristjánsson, & Driver, 2007; Sergent, Ruff, Barbot, Driver, & Rees, *in press*). In contrast, top-down modulation in a relatively later phase of retention does not improve memory performance (Sergent et al., *in press*; but different results have been observed by Nobre et al., 2004, 2008). We manipulated the efficacy of top-down modulatory signals by varying the timing (early vs. late) of a spatial retroactive cue during the VSTM retention interval of the task. The retro-cue indicated where VSTM information would be probed during the test period. Recent behavioral and imaging findings have revealed that attention can be oriented to a specific item held in VSTM and improve VSTM performance for cued relative to uncued items (Griffin & Nobre, 2003; Landman, Spekreijse, & Lamme, 2003; Makovski & Jiang, 2007; Makovski, Shim, & Jiang, 2006; Makovski et al., 2008; Matsukura et al., 2007; Nobre et al., 2008; Schmidt et al., 2002; Sligte, Scholte, & Lamme, 2008; Sligte, Vandenbroucke, Scholte, & Lamme, 2010). When a late cue is presented (e.g. 100 ms prior to the test probe), top-down attention cannot function as effectively given that it takes about 100–125 ms to process a spatial cue (Eriksen & Collins, 1969). Thus, we predict that only early cues can enhance VSTM representations to a level

that will impact performance. More importantly, we predict that this top-down modulatory effect of early cue, as compared to late-cues, will manifest as increased functional connectivity between frontal cortex and visual areas.

## 2. Materials and methods

### 2.1. Participants

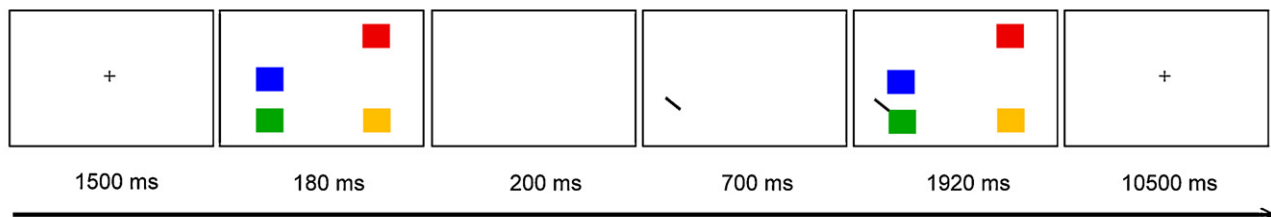
Fourteen participants (age range 19–30 years, half female) volunteered to take part in the fMRI study. The participants were recruited from the undergraduate and graduate students at National Taiwan University and National Taiwan University of Science and Technology. All participants in this study were right-handed, according to the Edinburgh handedness inventory (Oldfield, 1971). All participants were healthy and without any neurological or psychiatric history. Informed written consent was obtained from all participants prior to the study. The study was approved by the local ethics committee.

### 2.2. Behavioral task

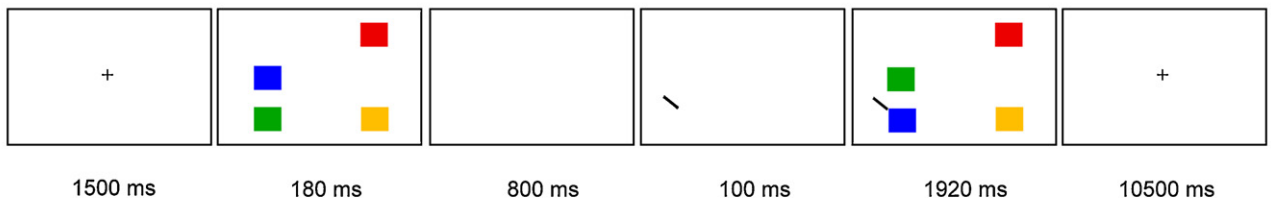
The experimental design followed a 2 (retro-cue onset time: early and late)  $\times$  2 (response type: match and non-match) factorial design. Participants viewed two stimulus arrays (an initial memory array and later a test array, with four items, respectively) on each trial, separated by a short retention interval (900 ms; see Fig. 1a and b). When the test array was shown, participants were instructed to indicate whether the cued item was identical (in match trials) or different (in non-match trials) from the initial one. A spatial retro-cue was presented during the retention interval that indicated the location where matching should be performed. Top-down modulatory effects were manipulated by the timing the retro-cue occurred, either early or late in the retention interval.

In each trial, a fixation cross was presented for 1500 ms, followed by an initial stimulus display for 180 ms. The test array was presented after a delay period of

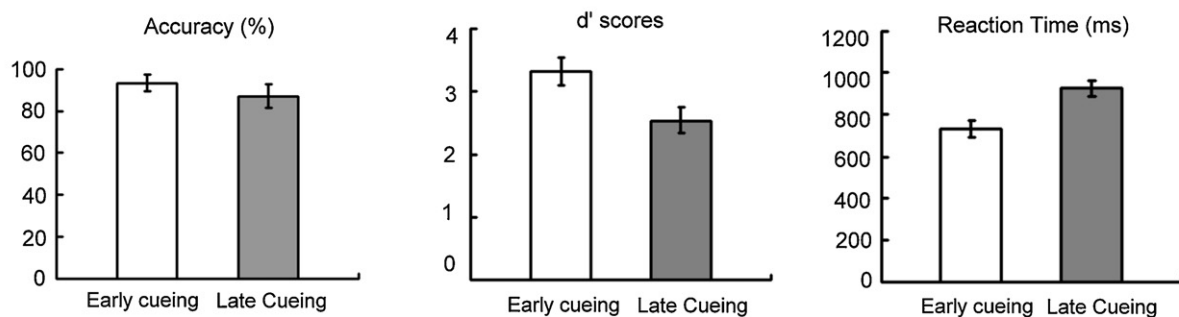
#### (a) Early-cueing condition



#### (b) Late-cueing condition



#### (c) Behavioral performance



**Fig. 1.** Schematics of experimental trials of behavioral task for the: (a) early-cueing condition (match trial) and (b) late-cueing condition (no-match trial). Top-down modulation was varied by retro-cue onset time during retention, with an interval of 700 ms in the early-cueing condition and an interval of 100 ms for the late-cueing condition prior to the test. (c) Behavioral performance: mean accuracy (percent correct) (left panel), mean  $d'$  scores (middle panel) and reaction time (RT in ms) (right panel) of correct responses in each condition. Error bars represent standard errors.

900 ms. In the early-cueing condition, a spatial retro-cue was presented 200 ms after the offset of the initial stimulus array. In the late-cueing condition, the spatial retro-cue was presented 800 ms after the offset of the initial stimulus array and 100 ms prior to the presentation of the test array. Finally, the test array was presented for 1920 ms. Responses were made using right and left thumbs counterbalanced across participants. Participants were instructed to respond as accurately and as quickly as possible. After offset of test array, a blank was shown for 10,500 ms so that the inter-trial interval was long enough to isolate the hemodynamic responses of individual trials (Friston et al., 1998).

### 2.2.1. Stimuli

Stimulus arrays were composed of four colored squares with the colors randomly selected from a set of six colors: red, green, yellow, blue, cyan, and magenta. Each stimulus subtended approximately  $0.52^\circ \times 0.52^\circ$  (edge-to-edge) and was positioned randomly in one of eight possible peripheral locations of an invisible  $3 \times 3$  matrix that subtended approximately  $6.2^\circ \times 6.2^\circ$ . In the match trials (50%), all color squares in the test array were identical to the ones in the initial array. In the non-match trials (50%), two colored squares in the test array were different from the ones in the initial memory array. Either two new colors that were not used in the memory array replaced the old ones or two stimuli switched position. A gray background was used throughout the whole experiment.

A white line pointed to the upper left corner of a stimulus location during the retention interval for spatial cueing and remained on screen until the participants responded. When the two stimulus arrays were identical, this cued position was randomly selected from the four stimulus locations. When the two stimulus arrays were different, the cued position was randomly selected from the two locations where changes would occur. Participants were told that the spatial cue indicated the location where a change would occur in the non-match trials and were encouraged to use the cue.

### 2.2.2. Behavioral analyses

Behavioral measurements included accuracy, a sensitivity score for match/no-match discrimination ( $d'$  score; Green & Swets, 1966), and reaction times (RTs). The  $d'$  score was calculated using the following equation:  $d' = Z(\text{hit rate}) - Z(\text{false alarm rate})$ . Hit rate was defined as the conditional probability that the participants responded “match” given that the test array matched to the memory array, and the false-alarm rate was defined as the conditional probability that the participants responded “match” when the test array did not match to the memory array. Only correct responses were included for RT analyses.

### 2.2.3. Procedure

Each participant was instructed on the experimental procedure and went through 40 practice trials prior to fMRI scanning to reduce anxiety and ensure high accuracy in task performance. Twenty practice trials contained an early cue and 20 trials contained a late cue, with half being the match trials and half being the non-match trials. All the practice trials were randomized.

The experiment consisted of twelve runs (6 runs of early-cueing and 6 runs of late-cueing) with 20 trials in each run. The two retro-cueing conditions were manipulated across runs. The order of early-cueing and late-cueing runs was randomized for each participant. In each run, half of the trials were no-match trials and the other halves were match trials. The response types (match and no-match) were randomized within a run so that participants could not predict the trial type until the test array was shown. Without knowing whether a non-match test array would occur or the nature of the changes, the participants must compare the cued test item with the cued representation.

## 2.3. Functional MRI acquisition and data analysis

### 2.3.1. Functional MRI scanning parameters

MRI data was collected on a Bruker MedSpec 3 T system (Bruker, Ettlingen, Germany) at National Taiwan University with a quadrature birdcage head coil. A single-shot T2\*-weighted gradient echo-planar imaging (EPI) sequence (TR = 1500 ms, TE = 30 ms, flip angle =  $90^\circ$ ) was used to measure blood-oxygen-level-dependent (BOLD) signal. Functional images were obtained from 16 contiguous axial-oblique slices (thickness = 5 mm and gap = 1 mm), which were acquired parallel to the anterior commissure–posterior commissure (AC–PC) line and in plane resolution of  $3.75 \times 3.75$  mm. The experiment was divided to 12 runs, each with 212 volumes. The start of a run was triggered by scanner pulses. The trials were presented with Presentation software (Neurobehavioral Systems) which was synchronized with EPI pulses. The stimuli were visually presented on a goggle display system (Resonance Technology Inc., CA, USA). Both eyes were corrected to normal visual acuity with lenses during the experiment. Behavioral responses were recorded using an in-house modified MRI-compatible fiber-optic light-sensitive response buttons held in the participant's hands. After functional scanning, high resolution anatomical images were also acquired by the RARE sequence (matrix size =  $256 \times 256$  and FOV =  $30 \times 30$  cm).

### 2.3.2. fMRI image preprocessing

The fMRI data were analyzed using the SPM2 software (Wellcome Department of Cognitive Neurology, London, UK) in MATLAB 6.5 (MathWorks, Inc., Natick, MA,

USA). The first eight scans in each run were discarded to account for saturation effects, and the remaining scans were corrected for each participant's movement artifact and differences in slice acquisition timing, and normalized into the standard SPM/MNI reference brain. We smoothed activity using a Gaussian filter of 8-mm full-width at half-maximum (FWHM) to accommodate for anatomical variability across subjects (Hopfinger, Buchel, Holmes, & Friston, 2000; Worsley et al., 1996).

### 2.3.3. Univariate analyses

Standard univariate analyses were first performed to identify brain regions with task-related activity. The data of each participant was analyzed using the general linear model by fitting the time series data with the canonical hemodynamic response function (HRF) modeled at the relevant event onset time points. Only the correct responses were analyzed. The time series data were then high-pass filtered with a frequency cut-off at 128 s. We computed the contrast of early-cueing trials with late-cueing trials and the resulting contrasts were entered into a second-level analysis in which the subjects were treated as a random variable using a one-sample  $t$  test. We used a threshold of  $p < .05$ , correcting for multiple comparisons using family-wise error.

### 2.3.4. Coherency analyses

To evaluate functional connectivity between brain regions, we performed a seed-basis coherency analysis (Curtis, Sun, Miller, & D'Esposito, 2005; Sun, Miller, & D'Esposito, 2005). Coherency measures how well one time-series signal can be represented by a linear transformation of another, computing the coherence between a seed region and all other voxels in the brain. We also estimated the coherence phase delays from the phase spectrum, which is derived from the phase component of coherence calculation. Coherency phase delay measures shifts in activation timing between two coherent time-series and reflects the temporal lead or lag between them (see Sun et al., 2005 for mathematical detail).

We generated coherence magnitude and phase delay maps of functional connectivity by computing the condition-specific coherency between a reference seed region and all other regions in the brain. Seed voxels within the left ( $x, y, z = -32, -88, -1$ ) and right ( $x, y, z = 27, -94, -4$ ) occipital cortex of each participant were selected as our regions of interest (ROIs) based on univariate statistics and the prior hypothesis (Postle, Awh, Jonides, Smith, & D'Esposito, 2004). We identified the most significant voxels within a 3 mm radius. The time-series data in each run were then concatenated to generate into condition-specific time-series (i.e. early-cueing and late-cueing, respectively). The condition-specific time-series was then mean-centered, windowed using a 4-point split-cosine bell function to reduce spectral leakage due to edge effects.

To estimate the condition-specific coherency of the seed ROIs with all other voxels, we used Welch's averaged periodogram method (using a 64-point discrete Fourier transform, Hanning window, and overlap of 32 points) in Matlab 6.5 (<http://www.mathworks.com>). The measure of the band-averaged low frequency (0–0.15 Hz) was used to generate condition-specific coherence magnitude and phase delay maps of each seed ROI with that of all other voxels in the brain (Curtis et al., 2005; Sun et al., 2005). Because coherency maps were generated separately for each of the cueing conditions and with each of two seed ROIs, four coherence maps and four phase-delay maps were produced for each subject (left and right occipital ROIs under early-cueing and late-cueing, respectively). We then applied an arc-hyperbolic tangent transform to the coherency maps for each subject. Thus, the coherence magnitudes and phase estimates approach a zero-centered normal distribution. The coherency maps for each seed region during the early-cueing condition could be contrasted with the late-cueing condition and applied to a parametric random-effects analysis. Group level random-effects analyses of the contrasts (e.g. early coherency map in contrast to late coherency map) under each seed ROI were then performed across subjects using a one-sample  $t$  test. A voxel-wise intensity threshold ( $p < .001, t > 4.0$ ) and a spatial extent threshold (cluster size greater than 10 voxels) were combined to control for multiple comparisons.

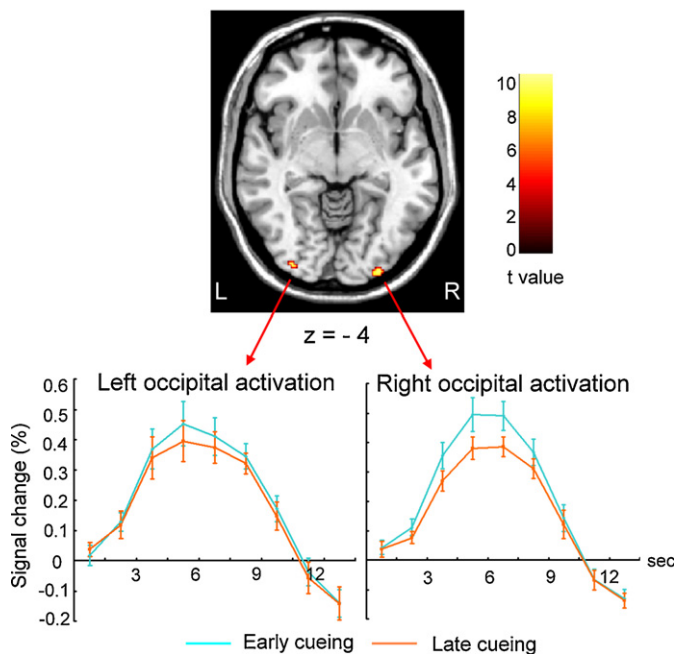
All significantly activated areas were then transformed into the Talairach space using a modified version of the mni2tal MATLAB script ([www.harvard.edu/~slotnick/scripts.htm](http://www.harvard.edu/~slotnick/scripts.htm)). Anatomical localizations were performed with Talairach Daemon software (Research Imaging Center, Health Science Center, San Antonio, TX).

## 3. Results

### 3.1. Behavioral results

A paired  $t$  test was conducted for analyzing behavioral performance (retro-cue onset: early vs. late). Fig. 1c presents the results in each condition. Participants showed more accurate and higher mean  $d'$  scores in the early-cueing (accuracy:  $93.27 \pm 3.98\%$ ;  $d'$  score:  $3.32 \pm 0.86$ ) than in the late-cueing condition (accuracy:  $87.32 \pm 5.69\%$ ;  $d'$  score:  $2.54 \pm 0.76$ ) [accuracy:  $t(13) = 3.59, p < .005$ ;  $d'$  score:  $t(13) = 2.8, p < .05$ ]. Similarly, the RTs of correct responses showed a significant effect of retro-cue onset

## Early cueing vs. Late cueing



**Fig. 2.** Univariate analyses revealed areas of significant activation associated with the cueing effect. Early cueing increased activation in bilateral inferior occipital gyrus [peak coordinates in Talairach space: left ( $x, y, z = -32, -88, -1$ ) and right ( $x, y, z = 27, -94, -4$ )]. The time course plots demonstrate the fMRI signal evoked by the early-cue trials (blue) and late-cue trials (orange). Error bars indicate standard errors.

time [ $t(13) = 8.45, p < .005$ ], with faster RTs in the early-cueing condition ( $731.58 \pm 151.43$  ms) than in the late-cueing condition ( $927.34 \pm 143.75$  ms). These results confirmed that participants were able to direct their attention toward the item for strengthening its memory representation. As a result, early cues benefited behavioral performance relative to late cues.

### 3.2. Functional MRI results

#### 3.2.1. Univariate analyses

Fig. 2 shows the univariate results. All participants showed greater activity bilaterally in the inferior occipital gyrus [Brodmann's area (BA) 18] under early cueing than under late cueing. No significant difference in activation was observed under late-cueing in contrast to early-cueing.

#### 3.2.2. Coherency analyses

**Coherence magnitude:** To demonstrate how functional connectivity was altered by top-down modulation of VSTM representations, we performed a coherence analysis for each participant using the left and right occipital ROIs as the seed regions and generated group-averaged coherence maps for each of the early- and late-cueing conditions (see Fig. 3). We then compared the right and left occipital ROI group-averaged coherence maps for the early-cueing condition with late-cueing condition. When the right occipital ROI was the seed region, the right middle frontal gyrus (MFG, BA 9) and frontal eye field (FEF) showed higher coherence magnitude during the early-cueing condition compared to the late-cueing condition. Similarly, the left occipital ROI also exhibited higher coherence magnitude with the right MFG and FEF during the early-cueing condition compared to the late-cueing condition. Fig. 3b shows the mean coherence magnitudes between each occipital seeds and right MFG and FEF ROIs.

Increased coherence during the early-cueing condition compared to late-cueing was also observed in other brain regions (see Table 1), including left superior parietal lobule and inferior occipital gyrus with right visual ROI seed; and anterior cingulate gyrus, right postcentral gyrus, right superior parietal lobule, bilateral inferior temporal gyrus, left fusiform gyrus, and bilateral middle occipital gyrus with left occipital seed. No significant increased coherence was observed during the late-cueing condition compared to the early-cueing condition for either the left or right occipital seeds.

**Coherence phase delay:** Coherence phase delay values indicate the temporal lead or lag between the seed regions and all other brain regions. To determine whether a phase delay between the frontal cortex (e.g. MFG and FEF) and posterior occipital seeds was consistently observed across subjects, we computed group averaged coherence phase delay maps based on the phase delay estimate of left and right occipital seeds in each of the early and late-cueing conditions. No significant difference in the phase delay estimates between early cueing condition and the late cueing condition was found in either the group-level result or ROI results (MFG and FEF) ( $p > .1$ ; Fig. 3c). However, as shown in Fig. 3c, there was a significant effect for activation within the frontal cortex to be earlier than right occipital cortex in both cueing conditions [early cueing condition (FEF:  $p = .035$ ; MFG:  $p = .031$ ); late cueing condition (FEF:  $p = .034$ ; MFG:  $p = .038$ )].

#### 3.2.3. Brain-behavior correlations

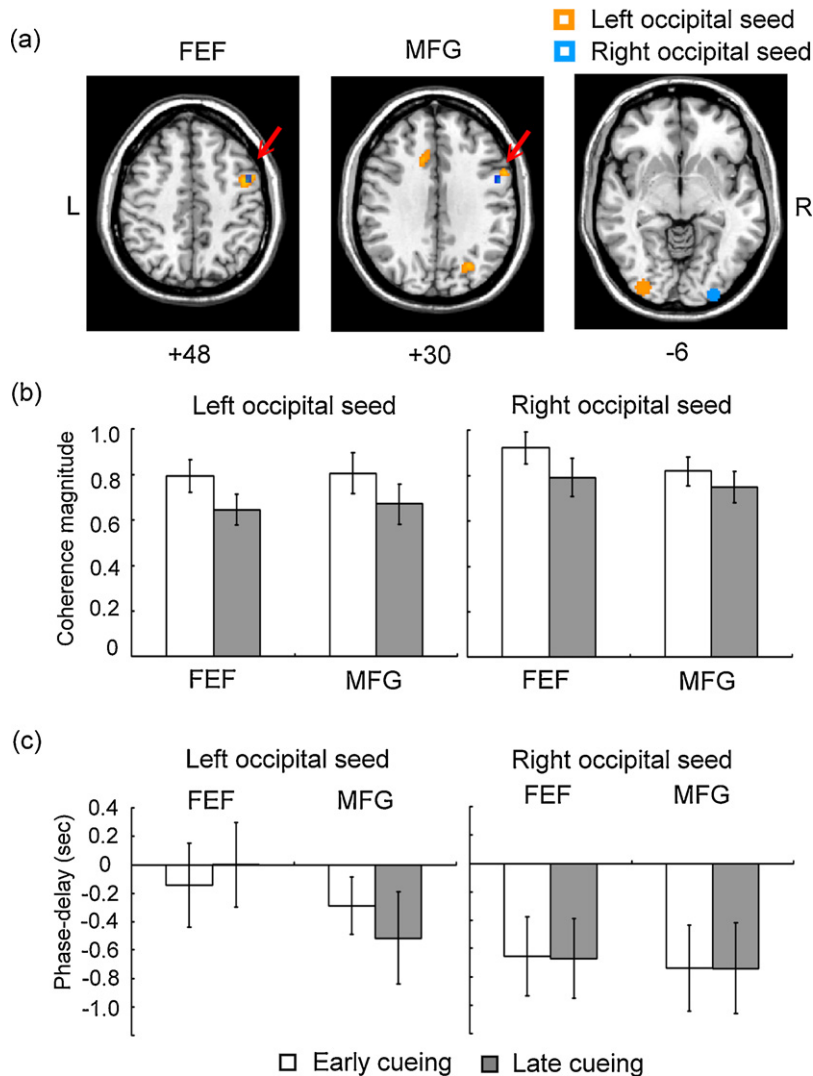
To test for a link between the strength of functional connectivity of visual and frontal regions and VSTM task performance, we also examined the correlation between the change in coherence magnitudes and the change in behavioral measures ( $d'$  score and RT) in early- vs. late-cueing conditions. A significant positive correlation was found between the change in coherence magnitude in frontal regions (FEF:  $r = 0.62, p < .05$ ; MFG:  $r = 0.52, p < .05$ ; Fig. 4) and the change in  $d'$  scores. Also, a significant negative correlation was found between the change in coherence magnitude in FEF ( $r = -0.51; p < .05$ ) and the change in RT. These correlations indicate that participants with stronger functional connectivity between frontal cortex and visual areas exhibit better memory performance. In contrast, no significant correlation was observed between the change in magnitude of univariate activity in the occipital ROIs and any behavioral measure ( $p > .1$ ).

### 4. Discussion

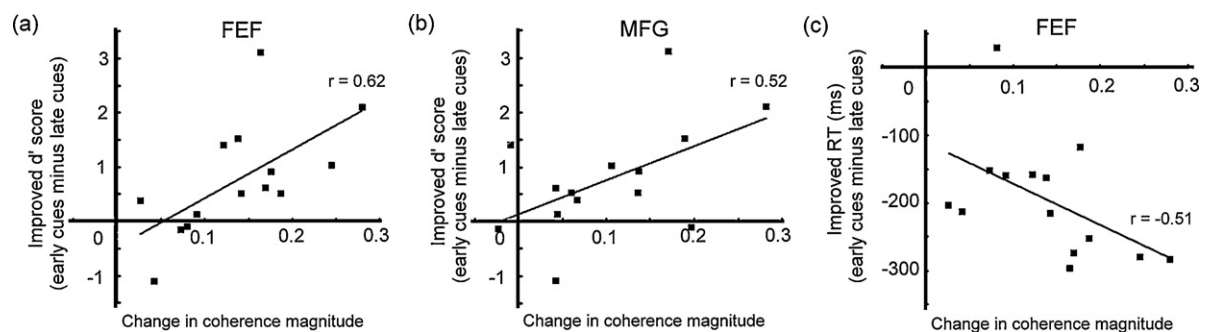
In this fMRI study, we investigated the effects of top-down modulation of VSTM representations on functional interactions between frontal cortex and posterior visual areas. Top-down modulation was varied by manipulating the onset time of a retro-cue during the retention period of a VSTM task (Yeh, Kuo, & Liu, 2007; Yeh, Yang, & Chiu, 2005). With early-cueing (i.e. 200 ms poststimulus offset) there is presumably sufficient time prior to the test phase for top-down modulatory signals to be deployed to enhance task-relevant VSTM representations. When a late cue is presented (e.g. 100 ms prior to the test probe), the same top-down modulatory signal cannot function as effectively given the time it takes to process the cue itself. In addition, early vs. late-cues likely act on memory representations at different levels of activation. Early retro-cues likely act on iconic memory representations which are stronger than representations later in the retention period that have decayed over time (Chow, 1986; Landman et al., 2003; Sligte et al., 2008; Sligte, Scholte, & Lamme, 2009; Sligte et al., 2010; Sperling, 1960). Thus, we predicted that early top-down modulatory signals would boost the strength of the memory representation of the cued item to a higher level than those representations acted on by a later top-down signal. In this way, a stronger memory representation should



## Early cueing vs. Late cueing



**Fig. 3.** Coherency analyses. (a) The left and right occipital seed coherence magnitude maps for the early-cueing condition were compared to the late-cueing condition (left occipital seed shown in orange; right in blue). For both seeds, the right middle frontal gyrus (MFG) and frontal eye fields (FEF) (indicated by red arrow) showed higher coherence magnitude during early cueing in contrast to late cueing. (b) The mean coherence magnitude between each occipital seed and right MFG/FEF ROIs were computed. Stronger coherence magnitude during early cueing in contrast to late cueing was found in all ROI pairs [right occipital seed-FEF:  $t(13)=3.14, p<.05$ ; MFG:  $t(13)=2.25, p<.05$ ; left occipital seed-FEF:  $t(13)=6.02, p<.005$ ; MFG:  $t(13)=4.80, p<.005$ ]. (c) The mean coherence phase delay between each occipital seed and right MFG/FEF ROIs were computed. Negative coherence phase delay values were found between the right occipital and frontal ROIs indicating that MFG and FEF activity preceded occipital activity in both the early and late cueing conditions. Error bars indicate standard errors.



**Fig. 4.** The correlation between the change in coherence magnitude and the change in participant's  $d'$  scores in (a) frontal eye field (FEF) and (b) middle frontal gyrus (MFG). The correlation between the change in coherence magnitude and the change in RT in (c) FEF.

**Table 1**  
Brain regions and their peak Talairach coordinates in which significantly coherence differences were observed during early cueing in contrast to late cueing with right and left occipital seeds.

Brain regions		BA	x	y	z	t
<i>Coherent with right occipital seed</i>						
Frontal eye fields	R	6	48	6	43	4.68
Middle frontal gyrus	R	9	52	3	29	4.27
Superior parietal lobule	L	7	−15	−69	58	5.35
Inferior occipital gyrus	L	18	−33	−89	−15	4.22
<i>Coherent with left occipital seed</i>						
Frontal eye fields	R	6	44	6	43	6.88
Middle frontal gyrus	R	9	58	11	30	6.35
Anterior cingulate gyrus	L	32	−9	28	24	5.26
Postcentral gyrus	R	2	50	−27	60	8.32
Superior parietal lobule	R	7	24	−57	65	4.37
Inferior temporal gyrus	L	37	−51	−68	1	5.07
	R	20	52	−52	−11	4.80
Fusiform gyrus	L	19	−39	−69	−17	5.64
Middle occipital gyrus	R	19	40	−72	7	7.03
	L	19	−35	−85	22	6.98
	L	18	−29	−84	7	6.70

Note: Broadmann area: BA; left hemisphere: L; right hemisphere: R; t: t-score.

be more readily available for later retrieval when the test display is presented, leading to improved performance.

Contrasting the early-cueing condition with the late-cueing condition, we found enhancement of activity in posterior visual areas. Although this finding is consistent with other studies (e.g. Nobre et al., 2004; Postle et al., 2004; Ruff et al., 2007; Sergent et al., *in press*), it is possible that it reflects both bottom-up and top-down effects since the presence of the early cue lasted longer than the late-cue. However, we also found that the strength of functional connectivity between these visual regions and other brain regions engaged by the task (e.g. frontal and parietal cortex) differed between early vs. late-cues. Specifically, functional connectivity between posterior visual areas and frontal cortex (and other areas) was augmented when top-down modulation was more effective (e.g. with early-cues). Also, the coherence phase delay estimate of activity between these coupled regions suggested that frontal regions were active earlier than posterior regions, which is a temporal profile consistent with a role as a source of top-down signals. Since coherence magnitude and phase can change independently, it is not surprising that an earlier response in frontal cortex relative to occipital regions would be observed in both early and late-cue trials, but only the magnitude of connectivity was greater when the top-down signal occurred earlier in the retention period.

Top-down modulatory signals can bias incoming perceptual stimuli and short-lived memory representations, favoring those aspects of the most relevant information based on intentions and goals (see Desimone & Duncan, 1995). Previous studies have revealed that neural activity in posterior visual association cortex is enhanced if attention is oriented toward a location or a stimulus that the neurons represent (Chawla et al., 1999; Lamme & Roelfsema, 2000; Moran & Desimone, 1985). Lepsien and Nobre (2007) reported in an fMRI study that top-down signals that reflect immediate task demands can modulate neural responses in functionally specialized posterior cortical areas during memory maintenance. Increased memory-related activity in the fusiform and parahippocampal areas was found when attention was oriented toward respectively a face or a scene stimulus held in visual working memory. In the current study, similar top-down modulatory effects were observed. Moreover, we demonstrated that effective top-down modulation leads to increased functional connectivity.

Few studies have examined the effects of top-down modulation on functional connectivity between frontal and visual areas (e.g. Gazzaley et al., 2007; Lauritzen, D'Esposito, Heeger, & Silver, 2009; Zanto, Rubens, Bollinger, & Gazzaley, 2010). Gazzaley et al. (2005,

2007) demonstrated that visual association cortex activity can be enhanced above or suppressed below a passive-viewing baseline depending on whether scene (or face) stimuli were attended or ignored during memory encoding. PFC exhibited strong functional connectivity with visual areas during all task conditions. The strength of this connectivity was greater when scene (or face) stimuli were attended and less correlated when the stimuli were ignored (Gazzaley et al., 2007). Also, the strength of this functional connectivity correlated with the magnitude of enhancement and suppression of visual association cortex activity (Zanto et al., 2010). Our functional connectivity findings are consistent with these results.

Our coherence analyses revealed stronger functional connectivity between occipital regions and two different frontal regions, lateral PFC (specifically MFG) and FEF with more effective top-down modulation. Abundant evidence exists that lateral PFC is a source of top-down signals (see Miller & D'Esposito, 2005 for a review). Interestingly, we found that only the right MFG show stronger connectivity with both occipital regions. In another fMRI study with a visuospatial selective attention task where auditory cues were presented before or shortly after the visual display, right MFG was more active during post- than pre-cue trials (Ruff et al., 2007). Also, similar lateralized PFC activity has been observed when an individual must select a particular spatial location being maintained in working memory (Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000). However, the possibility of laterality differences in PFC top-down signals is intriguing but additional work will be necessary to determine the precise role of the right versus left PFC in top-down modulation.

The FEF has also been identified as critical node in attentional control networks (Corbetta & Shulman, 2002; Hopfinger, Buchel, et al., 2000; Hopfinger, Buonocore, & Mangun, 2000; Kastner & Ungerleider, 2000). Specifically, FEF is involved when a spatial cue is used for guiding attention (see Kastner & Ungerleider, 2000 for a review). FEF is also involved in the maintenance of prospective codes of saccade intention that reflect the organization of a visual saliency map for locating candidate targets (Curtis, Rao, & D'Esposito, 2004; Curtis et al., 2005; Ruff et al., 2006).

Parietal cortex also exhibited stronger functional connectivity with occipital regions during early-cues in contrast to late-cues. This finding is consistent with other evidence implicating parietal cortex as a source of top-down signals (Corbetta & Shulman, 2002; Hopfinger, Buonocore, et al., 2000; Kastner & Ungerleider, 2000). Top-down parietal signals involved in visuospatial attention have recently been characterized as topographically specific

(Silver & Kastner, 2009; Silver, Ress, & Heeger, 2005; Szczepanski, Konen, & Kastner, 2010). For example, in a fMRI study Lauritzen et al. (2009) demonstrated that sustained allocation of spatial attention induces persistent activity in portions of early visual areas that retinotopically represent the attended location. Moreover, attention increased the coherence magnitude between parietal and occipital regions and coherence phase estimates revealed that attention-related activity in parietal cortex led activity in occipital regions, consistent with transmission of top-down attentional signals from parietal to early visual cortex. The differential role of parietal vs. frontal regions in attentional control is still underspecified. Determining the precise nature of these modulatory signals emanating from each region should be a high priority for further research.

In conclusion, using a bivariate coherence method, we demonstrated that top-down modulation of VSTM representations increases functional coupling between posterior visual areas and more anterior regions of frontal and parietal cortex and improves behavioral performance. These and previously published results (e.g. Armstrong, Fitzgerald, & Moore, 2006; Barcelo et al., 2000; Bressler et al., 2008; Capotosto, Babiloni, Romani, & Corbetta, 2009; Gregoriou et al., 2009; Lauritzen et al., 2009; Miller et al., 2011; Moore & Armstrong, 2003; Ruff et al., 2006; Zanto et al., 2010) suggest that frontal and parietal cortex support top-down modulation across many different levels of processing – from perceptual to mnemonic.

## Acknowledgements

B.-C. Kuo was supported by the awards for Ph.D. thesis in humanity and social science from the National Science Council, Taiwan (NSC-97-2420-H-002-186-DR). The research was supported by a grant from the National Science Council, Taiwan (NSC 95-2413-H-002-003, NSC 96-2413-H-002-007-MY3) to Y.-Y. Yeh and grants from the National Institutes of Health (MH63901 and NS40813) to M. D'Esposito. We thank J.-H. Chen (Interdisciplinary MRI/MRS Laboratory, Department of Electrical Engineering, National Taiwan University, Taipei, Taiwan) for his technical support. We also thank anonymous reviewers for their well informed and constructive comments and suggestions.

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