Cerebral Cortex July 2008;18:1618-1629
doi:10.1093/cercor/bhm195
Advance Access publication November 13, 2007

Dynamic Adjustments in Prefrontal, Hippocampal, and Inferior Temporal Interactions with Increasing Visual Working Memory Load

Jesse Rissman[1,2], Adam Gazzaley[1,3,4] and Mark D'Esposito[1,2,3]

[1]Henry H. Wheeler, Jr. Brain Imaging Center, University of California-Berkeley, Berkeley, CA 94720, USA, [2]Department of Psychology, University of California-Berkeley, Berkeley, CA 94720, USA [3]Helen Wills Neuroscience Institute, University of California-Berkeley, Berkeley, CA 94720, USA and [4]Current address: Departments of Neurology and Physiology, University of California-San Francisco, San Francisco, CA 94158, USA

The maintenance of visual stimuli across a delay interval in working memory tasks is thought to involve reverberant neural communication between the prefrontal cortex and posterior visual association areas. Recent studies suggest that the hippocampus might also contribute to this retention process, presumably via reciprocal interactions with visual regions. To characterize the nature of these interactions, we performed functional connectivity analysis on an event-related functional magnetic resonance imaging data set in which participants performed a delayed face recognition task. As the number of faces that participants were required to remember was parametrically increased, the right inferior frontal gyrus (IFG) showed a linearly decreasing degree of functional connectivity with the fusiform face area (FFA) during the delay period. In contrast, the hippocampus linearly increased its delay period connectivity with both the FFA and the IFG as the mnemonic load increased. Moreover, the degree to which participants' FFA showed a load-dependent increase in its connectivity with the hippocampus predicted the degree to which its connectivity with the IFG decreased with load. Thus, these neural circuits may dynamically trade off to accommodate the particular mnemonic demands of the task, with IFG–FFA interactions mediating maintenance at lower loads and hippocampal interactions supporting retention at higher loads.

Keywords: beta series correlation analysis, fMRI, functional connectivity, medial temporal lobe, short-term memory

Introduction

Theories of visual working memory (WM) postulate that the prefrontal cortex (PFC) provides top-down signals to high-level visual processing regions in the inferior temporal cortex (ITC) in order to keep neural representations of behaviorally relevant sensory information activated when it is no longer present in the external environment (Petrides 1994; Knight et al. 1999; Fuster 2000; Miller and D'Esposito 2005; Postle 2005a). Single-unit recordings in primates have identified neurons exhibiting sustained firing during the delay period of visual WM tasks in both PFC (Fuster and Alexander 1971; Miller et al. 1996; Rainer et al. 1998) and ITC (Mikami and Kubota 1980; Fuster and Jervey 1982; Miller et al. 1993). Functional magnetic resonance imaging (fMRI) has given researchers the opportunity to measure the blood oxygenation level–dependent (BOLD) signal (Ogawa et al. 1990), a correlate of neural activity (Logothetis et al. 2001), when human participants engage in a WM task. A number of event-related fMRI studies, which separately assess activity levels during the cue, delay, and probe stages of a visual delayed recognition task (Zarahn et al. 1997), have identified delay period activity in the PFC (for a review, see Curtis and D'Esposito 2003; Courtney 2004) and ITC (Postle et al. 2003; Ranganath et al. 2004; Yoon et al. 2006). Interactivity between PFC and ITC is suggested by anatomical tract tracing studies, which have demonstrated their reciprocal connectivity (Ungerleider et al. 1989; Webster et al. 1994; Petrides and Pandya 2002) and by several elegant lesion/electrophysiological studies, which document alterations in ITC activity resulting from a loss of PFC-mediated top-down control (Fuster et al. 1985; Tomita et al. 1999; Barcelo et al. 2000).

A growing body of evidence also indicates that medial temporal lobe (MTL) regions, which show extensive reciprocal connections with ITC (Yoshida et al. 2003), contribute to visual memory even over very brief delays. MTL regions, such as the hippocampus, have not traditionally been considered a component of the WM system because patients with MTL damage typically perform normally on tests requiring only the short-term maintenance of information, while exhibiting pronounced long-term memory impairments (Squire et al. 2004). However, in a recent review of the neuropsychological literature on short-term memory, Ranganath and Blumenfeld (2005) concluded that although MTL-damaged patients do well on short-term memory tasks involving simple overlearned materials such as letters, words, or digits, they are often impaired on tasks requiring the maintenance of complex novel visual objects. These impairments exist even with retention delays as short as 2–10 s (Holdstock et al. 1995, 2000; Owen et al. 1995; Buffalo et al. 1998). In fact, recent studies found MTL-damaged patients to be significantly impaired on a visual delayed recognition task requiring the maintenance of a single face stimulus across delays as short as 4 s (Olson, Moore, et al. 2006) and 7 s (Nichols et al. 2006). A study by Aggleton et al. (1992) found MTL-damaged patients were most impaired at a visual delayed recognition task when the task required the retention of multiple items.

These data on the effects of naturally occurring lesions in humans are corroborated by the results of well-controlled lesion studies in rats and monkeys that demonstrate deficits in spatial and/or object short-term memory following MTL ablations (Olton and Feustle 1981; Olton et al. 1982; Zola-Morgan and Squire 1986; Raffaele and Olton 1988; Murray et al. 1989; Wan et al. 1994; Lee and Kesner 2003). Further evidence for MTL involvement in WM tasks comes from neurophysiological findings of sustained delay period firing of hippocampal neurons in rats (Wible et al. 1986; Hampson et al. 1993) and monkeys (Watanabe and Niki 1985; Cahusac et al. 1989). fMRI studies with humans have also revealed hippocampal activity during the delay period of WM tasks requiring the maintenance of novel visual stimuli (Ranganath and D'Esposito 2001; Park et al. 2003; Ranganath et al. 2004; Schon et al. 2004; Ranganath, Cohen, Brozinsky 2005; Nichols et al. 2006) but not during the maintenance of highly familiar faces (Ranganath and D'Esposito 2001) or verbal stimuli, such as letters (Zarahn et al. 2005).

Despite the suggestive evidence that the PFC and hippocampus interact with ITC in the service of visual WM, the differential contributions of these structures to the maintenance of novel visual representations are unclear. Studying task-dependent changes in the functional interactions between these regions could yield valuable insights into the role they play in WM. In recent years, researchers have begun to take advantage of the fact that fMRI records an index of neural activity virtually simultaneously throughout the entire brain to explore how anatomically disparate brain areas interact during cognitive tasks. Such interactions have typically been characterized by identifying regions that show correlated fluctuations in their fMRI time series data, with the assumption that temporal correlations in BOLD signal reflect synchronous neural firing in communicating or "functionally connected," regions. Early fMRI studies of functional connectivity used blocked designs involving the continuous performance of a single task across an extended block of time (e.g., Lowe et al. 2000). In order to study functionally connectivity during a particular stage of a multicomponent task, such as the delay period of a delayed recognition task, it is necessary to have a method capable of obtaining stage-specific measures of interregional correlations in event-related fMRI designs.

A major limitation in using functional connectivity analysis techniques to probe delay period connectivity in event-related fMRI designs has been the challenge of generating delay period connectivity data that are uncontaminated by the slowly evolving hemodynamic signal evoked during the preceding cue period or ensuing probe period. To address this limitation, we recently developed and validated a new bivariate analysis method designed specifically to characterize functional connectivity in event-related fMRI data and measure interregional correlations during the individual stages of a multistage cognitive task (Rissman et al. 2004). The method, "beta series correlation analysis," employs a general linear model (GLM) approach (Friston, Holmes, et al. 1995), as do most univariate analyses for estimating stage-specific activity, but adapts the model such that distinct parameter estimates (beta values) are computed for each trial and then used as the dependent data in a correlation analysis. Whereas standard univariate analyses inherently treat trial-to-trial variability as noise, beta series correlation analysis explicitly measures and capitalizes on this variability. If 2 areas of the brain are functionally interacting with each other during a particular stage of WM, then fluctuations in the amount of activity that the 2 areas exhibit during that stage should be correlated across trials. The method can be implemented either by selecting a region of interest (ROI), or "seed," and determining the network of regions that correlate with it, or by defining a set of regions and assessing their correlations with each other. Several studies have now successfully employed the beta series correlation analysis method to yield novel insights into the interregional interactions occurring during the delay period of WM tasks (Gazzaley et al. 2004; Buchsbaum et al. 2005; Ranganath, Heller, et al. 2005; Fiebach et al. 2006).

In a recent study, we sought to characterize the WM maintenance network by using beta series correlation method to analyze data from a face WM task, in which participants had to maintain a single face stimulus across a 7 to 8 s delay period (Gazzaley et al. 2004). Participants also performed an independent "localizer" task, in which the fusiform face area (FFA), a focal ITC region that exhibits a high degree of selectivity for faces (Puce et al. 1995; Kanwisher et al. 1997), was functionally defined in each participant's right fusiform gyrus. Given the FFA's important role in face processing, it was of interest to determine which cortical regions interact with the FFA to facilitate the short-term maintenance of face representations. Using the beta series correlation analysis method, the functional connectivity between each participant's FFA seed and every voxel in the brain was computed separately for the cue, delay, and probe stages of the task. The group-level delay period correlation map revealed a robust network of regions that correlated significantly with the FFA seed, including the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), dorsal premotor cortex, and hippocampus.

In the present experiment, we seek to refine our understanding of the interregional interactions facilitating WM maintenance by examining how this system adapts to accommodate increasing mnemonic demands. By assessing how frontal and hippocampal regions differentially strengthen, sustain, or weaken the strength of their functional coupling with ITC as a function of increasing WM load, we hope to gain valuable insights into the nature of each region's contribution to the short-term retention of task-relevant visual representations. To this end, we performed a functional connectivity analysis on an existing fMRI data set in which participants performed a visual WM task that involved a parametric manipulation of memory load. The data set has been previously analyzed with univariate methods, and these results have been published elsewhere (Druzgal and D'Esposito 2001, 2003; Landau et al. 2004). In the experiment, participants were presented with 1–4 face stimuli on each trial, which they were then required to remember across an 8 s delay interval. Applying beta series correlation analysis to this data set allows us to examine how the strength of connectivity between brain regions that functionally interact with the FFA during the delay period of a face WM task changes as a function of the number of faces being maintained.

Materials and Methods

A complete description of the experimental design and scanning protocol can be found in Druzgal and D'Esposito (2003); the critical details are summarized below.

Participants

Ten right-handed participants (age range 22–27 years) were recruited from the University of Pennsylvania Medical Center and gave written informed consent prior to their participation. All participants were screened against medical, neurological, and psychiatric illnesses and were not currently taking any prescription medications. Due to reasons expounded upon below (see ROI Analysis), the data from 1 participant were excluded from all analyses.

Experimental Task

Participants performed 8 runs of 12 delayed recognition trials for a total of 96 trials (Fig. 1). At the start of each trial, participants viewed 4 serially presented gray scale images, which were a combination of intact and scrambled faces. Each image was displayed for 1 s, and participants were instructed to remember all of the intact faces. On any given trial, 1–4 of the stimuli were intact faces and the remainder (if any) were scrambled faces. The inclusion of scrambled faces was

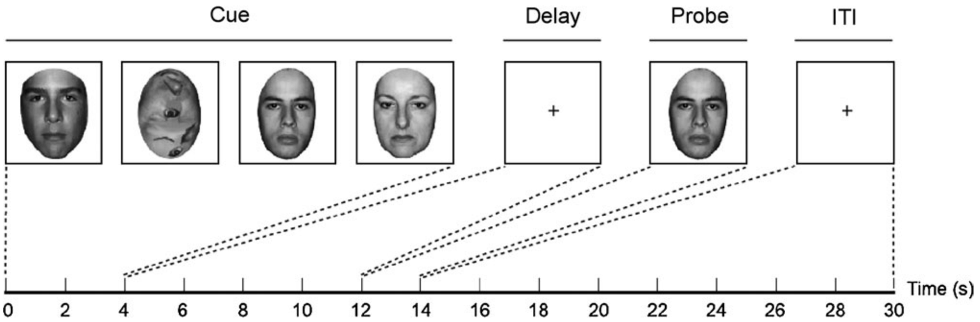

Figure 1. Structure of the behavioral task. On each trial, 4 cue stimuli were serially presented for 1 s each. The stimulus set contained 1, 2, 3, or 4 intact faces, with the remainder of the images (if any) composed of scrambled faces. A trial with a memory load of 3 faces is illustrated here. Participants were instructed to remember all of the intact faces across an 8 s delay period. Following the delay, a probe face appeared for 2 s, and participants made a button press response indicating whether or not the probe face matched any of the cue faces. After responding, participants were instructed to fixate on a crosshair during a 16 s intertrial interval.

intended to equate the overall amount of bottom-up visual stimulation across all 4 load conditions. Both the mnemonic load of each trial and the order in which intact face and scrambled face stimuli were presented were randomized so that the participants did not know how many faces they would have to remember until the end of the encoding period. After the 4 stimuli were presented, a fixation cross appeared for an 8 s delay period. Finally, a probe face appeared for 2 s, and participants made a key press indicating whether the probe face matched any of the previously presented face stimuli. A 16 s intertrial interval elapsed between trials.

All face stimuli were unfamiliar to the participants at the onset of the experiment and were cropped to an ovoid shape so that their external features, such as hair and head shape, were not visible. Over the course of the experiment, each face was presented as a cue stimulus an average of 2.5 times.

Prior to performing the WM task in the scanner, participants performed a localizer task in which they passively viewed blocks of face and object stimuli to identify face-sensitive regions of the fusiform cortex (FFA) (Kanwisher et al. 1997). None of the face stimuli presented in this task were also used in the main experiment.

fMRI Acquisition and Processing

All functional images were acquired on a 1.5-T General Electric scanner with a gradient-echo echo-planar imaging sequence (time repetition [TR] = 2000 ms, time echo = 50 ms, matrix size = 64 × 64, field of view = 24 cm^2). Each functional volume consisted of 21 contiguous 5-mm-thick axial slices. fMRI data processing included sinc interpolation in time to correct for between-slice timing differences in image acquisition, motion correction using a 6-parameter, rigid-body transformation algorithm (Friston, Ashburner, et al. 1995), normalization of the time series of each voxel by its mean signal value, and spatial smoothing with an 8-mm full-width half-maximum Gaussian kernel.

fMRI Data Analysis

BOLD responses during the cue, delay, and probe stages of the task were modeled as brief epochs of neural activity convolved with an in-house canonical hemodynamic response function (HRF), obtained by averaging the empirically derived HRFs (Aguirre et al. 1998; Handwerker et al. 2004) across a group of participants who performed fMRI experiments on this scanner. The onsets of temporally adjacent covariates were spaced at least 4 s apart (Zarahn et al. 1997) to minimize the contamination of the delay period covariate by residual cue period activity. This approach has been used to successfully model delay period activity in numerous published studies (Postle et al. 2000; Barde and Thompson-Schill 2002; Pessoa et al. 2002; Druzgal and D'Esposito 2003; Curtis et al. 2004; Ranganath et al. 2004). Prior to convolution with the HRF, the cue period covariate modeled the first 2 TRs of each trial, the delay period covariate modeled the fourth and fifth TR, and the probe period covariate modeled the seventh TR.

Functional connectivity analyses were conducted using the beta series correlation analysis method (Rissman et al. 2004). Because this approach requires that separate parameter estimates (beta values) be computed for each component of each individual trial, the cue, delay, and probe stages of each individual trial were coded with a unique covariate. This resulted in a total of 288 covariates of interest being entered into the GLM (3 task stages × 4 memory load conditions × 24 trials per condition). The GLM also included covariates of no interest to model the effects of shifting signal levels across runs. Band-pass filters were used to attenuate frequencies above 0.25 Hz and below 0.02 Hz. The GLM was run for each participant using the VoxBo analysis package (http://www.voxbo.org). The least squares solution of the GLM yielded a unique set of 288 beta values for each voxel in the brain. For each voxel, these beta values were sorted by the memory load condition as well as by the task stage from which they were derived to form 12 distinct "beta series" for that voxel. Each beta series thus reflects the voxel's estimated activity during a particular task stage of each experimental trial of a given memory load condition. Only beta values from trials for which the participant produced the correct response were included in the beta series. The extent to which brain regions interact during a particular task stage and memory load condition is quantified by the extent to which their respective beta series from that stage/condition are correlated.

The 7 contiguous voxels in each participant's right fusiform gyrus that exhibited the strongest response preference to faces versus objects in the localizer task, as assessed by a *t*-test, were defined as that participant's FFA (Kanwisher et al. 1997) and used as seeds in the subsequent correlation analyses. By defining the FFA seed based on an independent fMRI task rather than a contrast within the WM experiment itself, we ensure that our subsequent analyses are not biased toward showing a particular pattern of results. Our choice of seed size was somewhat arbitrary but based on our observations that seeds of this size are more robust to noise than those based on a single peak voxel and more selective to the activity profile of the FFA than larger clusters. We chose to use a right-lateralized FFA seed because lesion, electrophysiological, neuroimaging, and behavioral studies have shown the right hemisphere to play a dominant role in the perceptual analysis and recognition of faces (Hillger and Koenig 1991; Bentin et al. 1996; Kanwisher et al. 1997; Rossion et al. 2003). Stage-specific seed correlation maps were obtained by calculating the correlation of the FFA seed's beta series (averaged across the 7 seed voxels) with that of all brain voxels. Separate beta series, and hence separate correlation maps, were derived for each of the 4 WM loads in addition to being subdivided by task stage.

To allow statistical conclusions to be made based on the correlation magnitudes, we applied an arc-hyperbolic tangent transform (Fisher 1921) to the correlation coefficients of all brain voxels. Because the correlation coefficient is inherently restricted to range from −1 to +1, this transformation serves to make its null hypothesis sampling distribution approach that of the normal distribution.

In addition to the functional connectivity analysis, a standard univariate analysis was also conducted using the same placement scheme for the cue, delay, and probe covariates described above. However, for this analysis, rather than using a unique set of covariates to model the activity from each individual trial, a single set of covariates was used to model the activity across all of the trials of each load condition.

ROI Analysis

The general strategy of our ROI analysis was to identify the regions of the PFC and hippocampus that showed the strongest delay period functional connectivity with the FFA seed, averaged across all mnemonic loads, and then to probe how the functional connectivity of these regions changed as a function of load. In this way, we ensured that our procedure for defining the ROIs was not biased toward finding load effects. We based our ROI definition on the delay period in an effort to keep our investigation focused on the neural mechanisms subserving visual information processing in the absence of bottom-up sensory input. Although maintenance processes are initiated during the cue period of the task, these processes are confounded with load-dependent changes in the overall amount of visual attention/processing (because the scrambled face stimuli do not need to be richly encoded). Likewise, connectivity during the probe period is difficult to interpret because of the multiple cognitive operations that must be implemented to process the probe stimulus, make a memory-guided decision, and implement the appropriate motor response. Moreover, we do not have a sufficient number of trials to separately assess interregional interactions during the probe period of match and nonmatch trials, which have been shown to evoke different profiles of brain activity (Druzgal and D'Esposito 2001).

We began by averaging the arc-hyperbolic tangent-transformed delay period FFA correlation maps from all 4 load conditions to create a mean delay correlation map for each participant. ROIs in each participant's right and left inferior frontal gyrus (IFG), middle frontal gyrus (MFG), dorsal premotor cortex (chosen to approximately correspond to the frontal eye fields [FEF]), and hippocampus were defined as the cluster of 7 contiguous voxels within each region exhibiting the highest average delay period correlation with the FFA seed. Although not technically considered a "pre"-frontal region, FEF was included as an ROI given the documented role that FEF signals play in the goal-directed attentional modulation of neural activity in the ventral stream (Moore and Armstrong 2003; Armstrong et al. 2006; Ruff et al. 2006; Taylor et al. 2007). Seven voxel ROIs were defined so that the correlations would be computed between identically sized regions (because the FFA seed was also defined as a 7 voxel cluster). In order to ensure that a complete set of 8 ROIs were obtained for each participant, a lower bound threshold was not applied to the mean correlation maps. Occasionally, it was not possible to isolate a 7 voxel cluster simply by titrating the threshold until 1 emerged because sometimes narrow "bridges" formed between adjacent clusters. When this occurred, a mask was drawn around the cluster with the strongest mean correlation level. When multiple clusters were observed within a large anatomical region, such as the IFG, an effort was made to select the cluster that represented the most consistent anatomical location of that cluster across participants (in this case, the more ventral aspect of the IFG). Explicit anatomical masks were used, when necessary, to restrict the functionally defined ROIs to the specific anatomical regions being interrogated. For the hippocampal ROIs, these anatomical masks were limited to the anterior two-thirds of the hippocampus because the anterior portion of the hippocampus has previously been implicated as playing a role in visual WM (Ranganath and D'Esposito 2001; Ranganath, Heller, et al. 2005). Given the voxel size and smoothing kernel used in this study, we are unable to definitively rule out the possibility that these hippocampal ROIs include some signal contributions from adjacent MTL cortical regions.

By defining our ROIs separately for each participant based on their native space correlation map, we sought to maximize the power of our group analysis, given our small sample size. However, because our functionally defined, anatomically constrained ROIs varied slightly across participants in their localization, the regional effects we report cannot be mapped onto precise atlas coordinates. In an effort to provide an approximation of the atlas-based localization of our ROIs, we warped each participant's ROI mask images into standard Montreal Neurological Institute atlas space using the normalization routine from SPM2 (http://www.fil.ion.ucl.ac.uk/spm). Because these mask images consist of 1's at all locations included in the ROI and 0's at all other locations, summing the spatially normalized mask images across participants yields a mask overlap map. In such a map, the value of each voxel indicates the number of participants whose normalized ROI mask included that voxel. From these maps, we determined a coordinate of maximal overlap for each of our 8 ROIs (in brackets), as well as the number of participants whose ROI included this coordinate (in braces): right IFG [52, 30, 8] {6}; left IFG [−45, 48, 8] {5}; right MFG [38, 50, 28] {5}; left MFG [−32, 56, 18] {5}; right FEF [28, 14, 48] {4}; left FEF [−24, 6, 48] {4}; right hippocampus [26, −12, −18] {6}; left hippocampus [−22, −20, −14] {7}.

For each of the 8 ROIs, the mean beta series (averaging across the 7 voxels) was extracted for each task stage and load. These beta series were then correlated across trials with the corresponding beta series of the FFA to produce a set of stage-specific correlation values for each memory load condition. Load-dependent changes in each ROI's delay period correlation with the FFA were then assessed statistically using linear contrast analyses (*F*-tests) across all load conditions and pairwise comparisons (2-tailed paired sample *t*-tests) between the 2 endpoint conditions ("1 face" [1F] vs. "4 faces" [4F]), with participants as random factor.

During the process of defining individual participant ROIs based on the mean delay period FFA connectivity map, it became apparent that the correlation data from 1 participant was substantially different from that of the other 9 participants. Specifically, the participant's FFA seed correlated strongly with virtually the entire brain volume; 68% of all his brain voxels had a correlation of $r > 0.5$ with the FFA seed during the delay period (and correlations were similarly high and nonselective during the cue and probe stages). Given that this value is 6 standard deviations above that of the other 9 participants (who showed an average of 13% of voxels exceeding an $r > 0.5$ correlation level) and likely indicates the presence of a global colored noise component, we elected to exclude this participant's data from all analyses.

Results

Behavioral Data

Group-averaged behavioral data are presented in Figure 2. One participant was excluded from the behavioral analysis due to a hardware problem that prevented the collection of behavioral data. Participants' accuracy declined significantly as a function of increasing memory load (1F vs. 4F: $t_7 = 11.91$, $P < 0.0001$; linear contrast: $F_{1,7} = 71.35$, $P < 0.0001$). On trials in which participants responded correctly, reaction time increased with mnemonic load (1F vs. 4F: $t_7 = -5.09$, $P < 0.001$; linear contrast: $F_{1,7} = 23.94$, $P < 0.005$).

Functional Connectivity Analysis

Of the 6 frontal ROIs tested (right and left IFG, MFG, and FEF), only the right IFG showed a significant effect of memory load on its delay period correlation with the FFA (Fig. 3). Specifically, this region's correlation with the FFA decreased significantly from the 1F condition to the 4F condition, and there was a significant linear component to this decline (1F vs. 4F: $t_8 = 3.15$, $P < 0.05$; linear contrast: $F_{1,8} = 7.10$, $P < 0.05$). In contrast, both the left and the right hippocampus ROIs revealed a pattern of increasing correlations with the FFA with increasing load. However, this effect achieved statistical significance only in left hippocampus ROI (1F vs. 4F: $t_8 = -2.77$, $P < 0.05$; linear contrast: $F_{1,8} = 8.55$, $P < 0.05$) (Fig. 3). The right hippocampus ROI showed a marginally significant load-related increase in its correlation with the FFA (1F vs. 4F: $t_8 = -1.88$, $P = 0.097$), but the linear trend analysis was not significant ($P = 0.24$) (data not shown). The differential effect of load on the functional connectivity patterns of the right IFG and left

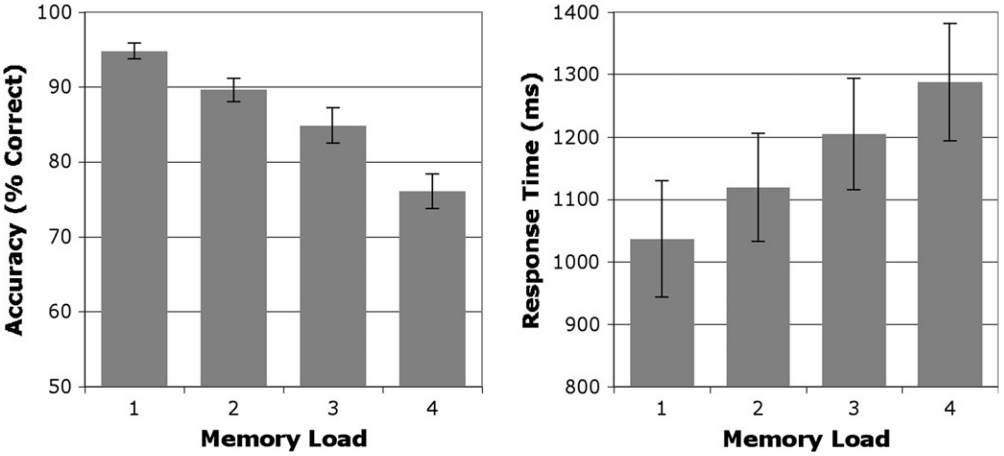

Figure 2. Mean accuracy and reaction time for each of the 4 load conditions. Error bars represent standard error of the mean.

hippocampus was further supported by a significant ROI × load interaction ($F_{3,24} = 3.19$, $P < 0.05$).

To illustrate how this changing functional connectivity profile manifests itself in the context of the beta series correlation analysis method, a set of correlation scatter plots taken from a representative participant are shown in Figure 4. In these scatter plots, each data point represents the estimated activity level (beta value) from a single trial for the FFA (x axis, both charts) and either the right IFG (y axis, left-side chart) or the left hippocampus (y axis, right-side chart). To emphasize the load-dependent changes in correlations, the lowest load (1F; open diamonds, gray regression line) and the highest load (4F; filled circles, black regression line) are plotted. Mirroring the pattern of results observed at the group level, this participant's FFA is more strongly correlated with the right IFG during the delay period of the 1F condition and more strongly correlated with the left hippocampus during the delay period of the 4F condition.

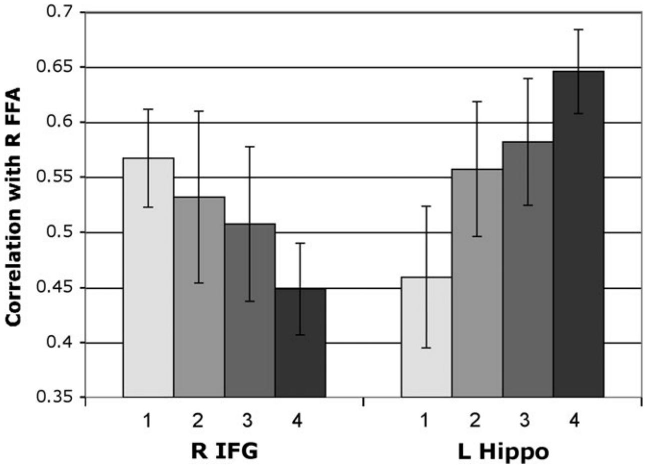

Figure 3. FFA delay period correlations as a function of mnemonic load. The mean correlation (Pearson's r) of the right FFA's delay period beta series with that of the right IFG and left hippocampus ROIs is depicted for each face load condition (load is indicated by the numbers below each bar). The FFA shows a linear decrease in its correlation with the right IFG and a linear increase in its correlation with the left hippocampus; the pairwise differences between the "1 face" and "4 faces" conditions are also significant for both ROIs (all Ps < 0.05). Error bars indicate standard error of the mean.

To assess whether the load-dependent connectivity increases with the left hippocampus were systematically related to the load-dependent connectivity decreases with the right IFG, we evaluated load-dependent changes in these correlations across participants. Indeed, these 2 effects were found to be inversely correlated ($r = -0.68$, $P < 0.05$), such that the more a participant's right IFG showed a load-dependent decrease in its correlation with the FFA, the more their left hippocampus showed a load-dependent increase in its correlation with the FFA (Fig. 5). This inverse relationship between the load-dependent connectivity of frontal and hippocampal regions with the FFA suggests that increased hippocampal correlations may attempt to compensate for decreased frontal correlations at high loads. The fact that some participants showed this trade-off more than others suggests that there may be individual differences in the extent to which participants adapt their maintenance circuitry to cope with increasing mnemonic load.

Next, we wished to assess whether the connectivity effects observed between these ROIs were accompanied by load-dependent changes in the mean BOLD signal level (univariate activity) with the ROIs during the delay period, as has been reported in other studies. The right IFG was the only ROI that showed a significant influence of load on its delay period univariate activity. In this region, we observed a significant linear increase in delay period activity with increasing load ($F_{1,8} = 5.87$, $P < 0.05$). However, the direct contrast between the 1F and 4F conditions was only marginally significant ($t_8 = -2.20$, $P = 0.059$). Univariate load effects were not found in the other PFC or hippocampal ROIs, nor were they found in the FFA seed.

The fact that the right IFG ROI showed increasing univariate activity as a function of load implies that this region must serve an important role during the delay period of high load trials, despite its decreased coupling with the FFA. Although a detailed examination of this region's functional interactions with the rest of the brain is beyond the scope of the present investigation, we decided to test the hypothesis that the right IFG increases its connectivity with the hippocampus at high loads. Interactions between VLPFC and MTL regions are thought to play a critical role in the control of long-term memory processes (Simons and Spiers 2003). Given our supposition that long-term memory-like mechanisms in the MTL can contribute to the retention of visual information even

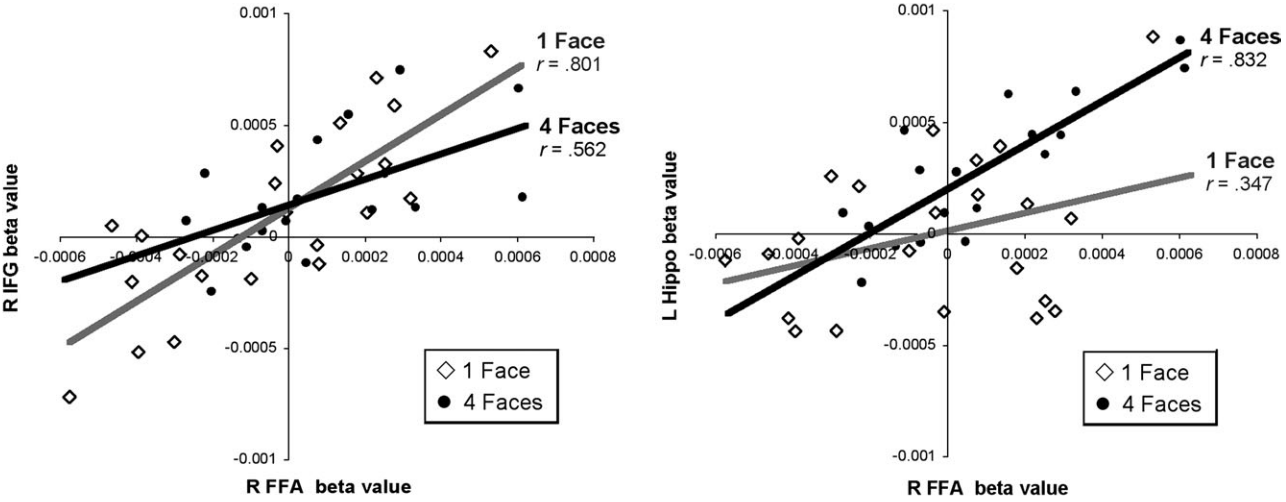

Figure 4. Example of load-dependent functional connectivity changes in an individual participant. In these scatter plots, each data point represents the estimated delay period activity (beta value) from a single trial, taken either from the "1 face" condition (open diamonds) or "4 faces" condition (filled circles). The beta values obtained from the right FFA (*x* axis, both charts) are plotted against those obtained in the right IFG (*y* axis, left-side chart) and left hippocampus (*y* axis, right-side chart) across all trials for which this participant made a correct response. The degree to which regions show correlated fluctuations in their delay period activity across trials is taken as a measure of their functional connectivity.

over short delays (Ranganath and Blumenfeld 2005), we reasoned that increased frontal–hippocampal coupling might guide or supplement increased hippocampal–FFA coupling at high loads. To test this hypothesis, we used the same hippocampal and right IFG ROIs we had already defined for each participant based on their strong delay period connectivity with the FFA (averaged across loads) and assessed how connectivity between them changed as a function of load. Indeed, the right IFG ROI's correlation with both the left and right hippocampus ROIs increased with load. For the left hippocampus ROI, this effect was significant for the 1F versus 4F contrast ($t_8 = -2.35$, $P < 0.05$) but did not achieve significance for the linear contrast ($P = 0.112$). For the right hippocampus ROI, this effect was significant for both the 1F versus 4F contrast ($t_8 = -2.77$, $P < 0.05$) and the linear contrast ($F_{1,8} = 7.41$, $P < 0.05$). A summary of these load-dependent changes in frontal, hippocampal, and inferotemporal connectivity is presented in Figure 6. Note that this schematic depiction of the pattern of interregional correlations does not constitute a path analysis of the causal relationship or directionality of these interactions.

Given that our ROIs were defined based on their delay period connectivity with the FFA, our analysis procedure was not optimally structured for assessing load effects on connectivity during the cue and probe stages of the task. However, it is worth noting that while all 8 ROIs exhibited statistically significant connectivity with the FFA seed during all task stages and loads, none of these ROIs showed significant load-dependent increases or decreases in their connectivity with the FFA during the cue and probe stages of the task.

Discussion

In the present study, we applied a recently developed functional connectivity analysis procedure (Rissman et al. 2004) to an event-related fMRI data set to investigate how the interregional interactions subserving visual WM change as function of mnemonic load. Our ROI analyses yielded several

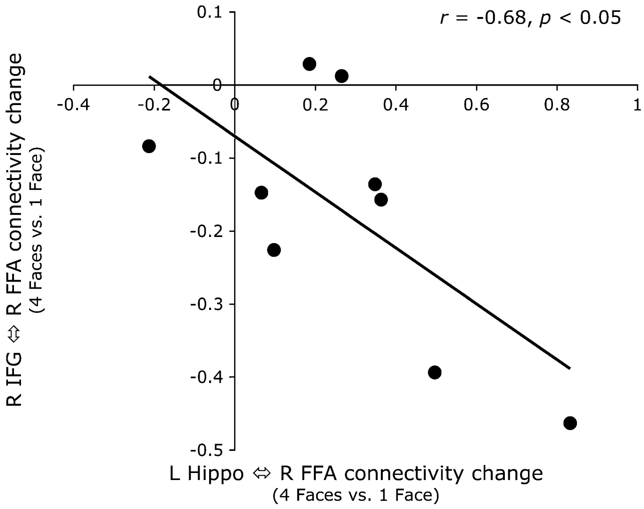

Figure 5. Load-dependent trade-off between prefrontal and hippocampal connectivity with the FFA. The amount that each participant's delay period correlation between the right FFA and right IFG changed as a function of load (*y* axis) is plotted against the corresponding change in the correlation between the right FFA and left hippocampus (*x* axis). The values of each axis correspond to the difference between the arc-hyperbolic tangent-transformed correlation coefficients of the "4 faces" condition and "1 face" condition. A significant negative correlation was observed between these connectivity change measures.

novel and important results. First, we observed that while the right IFG interacted strongly with the FFA when participants were required to maintain a single face stimulus, functional connectivity between these regions linearly decreased as the number of to-be-maintained faces increased. Second, we found that the hippocampus, an MTL region traditionally thought to be involved only in long-term memory processes, exhibited the opposite load-dependent connectivity profile—a linearly increasing degree of functional connectivity with the FFA. Third, these complementary neural circuits supporting visual WM appeared to dynamically trade off as load increased, such that the amount that a participant's IFG–FFA connectivity decreased

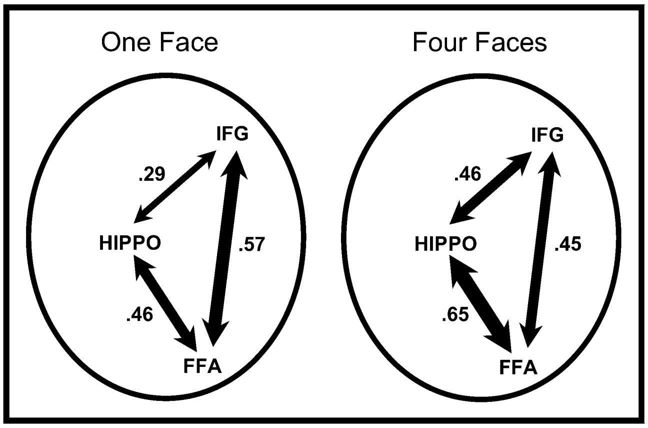

Figure 6. Schematic summary of interregional connectivity at low and high loads. These diagrams depict the mean correlation level between the right FFA, right IFG, and left hippocampus ROIs during the delay period of the "1 face" and "4 faces" conditions. The mean correlation coefficient (r value) between each pair of nodes is indicated alongside each arrow, and the thickness of the arrows is scaled proportionally to this value. All 3 node pairs show significant changes in their correlation between these load levels (all Ps < 0.05). This schematic depiction of the interregional correlations observed in our study does not constitute a path analysis of the causal relationship or directionality of these interactions.

with load was significantly correlated with the amount that their hippocampus–FFA connectivity increased with load. Fourth, this altered pattern of regional interactions was further reflected in the finding that the connectivity between the right IFG and the hippocampus increased significantly from low to high loads. Thus, when faced with increased mnemonic load, the IFG and FFA interacted less with each other, while these regions mutually strengthened their degree of functional coupling with the hippocampus.

Prefrontal Interactions with the FFA

We interpret the strong functional connectivity observed between the IFG and FFA during the maintenance of a single face stimulus as reflecting the presence of a modulatory signal originating in the IFG that serves to sustain the activity of a sparse ensemble of neurons in the FFA in an effort to keep the stimulus representation active across the delay period (Gazzaley et al. 2004). Although this functional relationship must be predominantly top-down in nature because there is no bottom-up visual stimulation during delay period, the active maintenance of the relevant sensory information likely involves reverberant interactions between reciprocally connected IFG and FFA neurons (Fuster 2000). Because our measure of interregional coupling is inherently correlational, we cannot make claims about the causal relationship or directionality of these modulatory interactions. Although the specific neural mechanisms of these interactions remain to be elucidated, it is our view that the functional connectivity between IFG and FFA is a neural instantiation of the persistent allocation of attention to the to-be-maintained face representations in the service of WM. In fact, we consider the essential element of WM maintenance to be the sustained attention to relevant preexisting cortical representations, rather than assuming a dedicated WM storage buffer. This perspective of short-term memory as the PFC-guided attention-based activation of long-term memory representations has recently been articulated by others (Cowan 1993; Ruchkin et al. 2003; Postle 2005b).

To the extent that IFG–FFA connectivity during the delay period represents a neural correlate of active maintenance, one might have expected that the strength of this coupling would increase, or at least remain constant, as a function of WM load because higher loads inherently require the retention of more visual information. However, our data revealed a pattern of decreasing functional connectivity between the right IFG and right FFA as the load increased. This result raises the possibility that IFG–FFA connectivity is not the principle mechanism by which face representations are maintained when the task requires the retention of multiple unique face stimuli. In fact, this finding suggests that this circuit is progressively less utilized for maintenance as the load increases. One plausible explanation for this load-related connectivity decrease is that the maintenance demands of the task exceed the capacity of visual WM at loads greater than a single face. The visual WM system is severely limited in the amount of information that can be simultaneously maintained in an active state (Phillips 1974; Luck and Vogel 1997; Cowan 2001; Alvarez and Cavanagh 2004; Marois and Ivanoff 2005). Indeed, the human capacity for maintaining complex visual objects, such as faces, has been estimated to be only 1–2 items, even over very brief delay periods (~1 s) in the absence of any distraction (Jackson and Raymond 2004; Eng et al. 2005; Xu and Chun 2006). Such capacity estimates are thought to reflect the number of integrated chunks of information that can be maintained within the focus of attention at a time. Given the longer delay period (8 s) of the present study, along with the potentially distracting effect of the scrambled face stimuli that were intermixed with the memoranda, it is possible that participants were only able to effectively engage in active attention-based maintenance on trials in which a single face was presented. As the load increases, the IFG–FFA circuit is engaged to a lesser extent, potentially because its limited capabilities accomplish the maintenance of a progressively smaller percentage of the total amount of to-be-remembered information, thus decreasing its utility. This account of the IFG–FFA connectivity findings presumes that an alternative neural circuit becomes involved at higher loads to compensate. The putative role of the hippocampus in this process will be discussed in more detail below.

Of the PFC ROIs we queried, only the right IFG (roughly corresponding to Brodmann's Area 45) showed a significant load effect on its delay period functional connectivity with the FFA. The emergence of this effect in this VLPFC region is logical given the functional and anatomical properties of this region. VLPFC regions are known to have direct long-range projections to and from posterior visual association cortices (Ungerleider et al. 1989; Webster et al. 1994; Petrides and Pandya 2002) and are thought to play a predominant role in visual object processing, whereas more dorsal PFC regions are thought to be more critical for spatial processing (Wilson et al. 1993; Sala et al. 2003). Indeed, face-selective neurons have been found in the primate VLPFC but not the DLPFC, and these neurons receive direct projections from the ITC (O'Scalaidhe et al. 1997). In addition, several functional imaging studies have associated activity in the right IFG with the processing and maintenance of faces (Haxby et al. 1995; Courtney et al. 1997; Ungerleider et al. 1998; Sala et al. 2003). Right IFG regions are thought to play a greater relatively greater role in visuospatial WM than their left IFG counterparts, which are preferentially involved in the rehearsal of verbal materials (Postle and D'Esposito 2000; Reuter-Lorenz et al. 2000; Braver et al.

2001). The right hemisphere lateralization of the IFG load effect may also be partly attributable to our use of a right-lateralized FFA seed, given that PFC projections to posterior visual regions are predominantly intrahemispheric (Eacott and Gaffan 1992; Chao and Knight 1998; Barcelo et al. 2000). Lastly, our association of IFG–FFA connectivity with maintenance-related processes is consistent with theories of functional specialization in the PFC that have proposed that the VLPFC is preferentially involved in the maintenance of information whereas DLPFC regions are recruited when cognitive tasks require higher level executive control processes such as manipulation or monitoring (D'Esposito et al. 1999; Owen et al. 1999).

Load-dependent connectivity changes were not observed in the left IFG ROI or the 2 MFG ROIs. Given that these ROIs were specifically defined based on their having a high delay period correlation with the FFA (averaged across loads), a null effect of load should not be taken as strong evidence that these regions showed equivalently high correlations with the FFA at all loads. That said, the MFG–FFA correlations at all loads were of similar magnitude to those seen in the right IFG in the 1F condition. This suggests that communication between the MFG and FFA, while most likely polysynaptic (Petrides and Pandya 1999), may make a functional contribution to the task in a load-independent manner. One speculative explanation is that top-down signals emanating from MFG regions tag face representations in the FFA as task relevant, regardless of the mnemonic load, which serves to facilitate task-set maintenance (Fassbender et al. 2006). Load-dependent connectivity changes were also not observed in the FEF ROIs. Top-down modulatory signals from the FEF to posterior visual regions have been related to the allocation of spatially directed attention (Moore 2006), but there is little evidence that FEF signals modulate high-level nonretinotopic object representations in ITC. Because our face WM task predominantly taxes object- and feature-based visual attention, rather than spatial attention, it is perhaps unsurprising that FEF–FFA connectivity levels do not scale with mnemonic load.

Hippocampal Interactions with the FFA

In contrast to the load-related decreases in the delay period functional connectivity between the FFA and IFG, the strength of the interaction between the FFA and hippocampus increased linearly as a function of increasing mnemonic load. Indeed, the effect of load on hippocampus–FFA connectivity was inversely correlated with the effect of load on IFG–FFA connectivity. That is, the participants who showed the largest load-related increase in their hippocampus–FFA connectivity also showed the largest load-related decrease in their IFG–FFA connectivity. Thus, increased hippocampal connectivity at high loads may reflect a shift in neural processing away from PFC-mediated maintenance as it becomes increasingly difficult for participants to actively allocate attentional resources to the cortical representations of multiple face stimuli. The maintenance of the face stimuli may have been particularly challenging in the high load trials because each successive face that is presented to the participant at the start of the trial requires mnemonic encoding and essentially distracts the participant from maintaining a mental image of the previous face. Given this challenge, along with the extremely limited capacity of WM for faces (Eng et al. 2005), most participants reported that on the high load trials they resorted to recognizing the probe faces based on their subjective familiarity. Functional connectivity between the hippocampus and FFA during the delay period may have served to strengthen the mnemonic traces of the face stimuli in a way that would make them more recognizable when the probe stimulus was presented and a match/nonmatch decision was required. The neural circuitry of the hippocampus, particularly the sparse representations of the dentate gyrus and CA3, afford it the unique ability to assign distinct pattern-separated representations to stimuli, facilitating rapid learning with minimal interference from similar stimuli (O'Reilly and Norman 2002; Leutgeb et al. 2007). Increased MTL–FFA connectivity during the delay period of the high load trials may have also served to reactivate the representations of the first few faces in the series after their attempted maintenance had been disrupted by the need to encode the subsequently presented faces (Sakai et al. 2002; Sakai and Passingham 2004).

Previous studies suggesting that the hippocampus is not critically involved in WM tasks have utilized tasks in which highly overlearned stimuli can be readily rehearsed during the delay period (Cave and Squire 1992; Zarahn et al. 2005). Our findings suggest that hippocampal processing resources may only be utilized when the number (or complexity) of to-be-remembered stimuli exceeds the capacity limits of short-term memory. In other words, when a WM task cannot be accomplished using attention-based maintenance or verbal rehearsal, individuals may form and utilize hippocampus-dependent mnemonic representations. These representations are likely similar to those that support long-term memory. However, the fact that task performance worsened as a function of load suggests that increased hippocampal connectivity cannot fully compensate for the putatively decreased efficacy of the IFG–FFA circuit at high loads.

In the present experiment, participants were only tested on their memory for face stimuli after an 8 s delay interval. Thus, we do not have the behavioral data to determine whether the increased hippocampus–FFA connectivity at high loads reflects the formation of new long-term memory traces that would lead to successful face recognition if participants were tested after a longer interval. Data from several recent studies suggest that hippocampal involvement during the delay period of visual WM tasks can lead to improved subsequent long-term memory for the stimuli being maintained. Ranganath, Heller, et al. (2005) employed the beta series correlation analysis method to examine functional connectivity in a WM task requiring the maintenance of complex novel objects. Using the left hippocampus as a seed, they determined that its delay period functional connectivity with a network of cortical regions, including ITC, was significantly greater on trials in which the participants subsequently remembered the stimuli on a surprise postscan recognition memory test versus trials in which they subsequently failed to recognize the stimuli. Other studies have demonstrated that univariate activity levels in the hippocampus during the delay period of visual WM tasks also predict subsequent long-term recognition memory performance (Schon et al. 2004; Ranganath, Cohen, Brozinsky 2005; Nichols et al. 2006).

Some investigators have noted that hippocampal damage produces a particularly severe impairment in the memory for the relations between multiple items (Ryan et al. 2000). One recent experiment testing patients with hippocampal amnesia on task requiring the memory for the relations between faces and scenes or objects within a scene demonstrated significant impairments at delay lags as short as 3 s (Hannula et al. 2006). Another recent experiment found that patients with MTL lesions showed severely impaired recognition memory for object-location conjunctions at 8 s delays (Olson, Page, et al. 2006). Although the present experiment did not probe participants' memory for the order of, or relations between, the sequentially presented face stimuli, it is possible that some of the hippocampal involvement at high loads may reflect implicit relational processing. Additional studies will be needed to examine the degree to which hippocampal connectivity with posterior sensory cortices scales with the demand for relational processing.

One neural mechanism that has been hypothesized to mediate the long-range communication between the hippocampus and ITC is synchronous oscillatory activity in the theta (4–12 Hz) range (Bastiaansen and Hagoort 2003; Kirk and Mackay 2003; Guderian and Duzel 2005). Recent evidence in monkeys suggests that theta phase locking may be particularly robust during the WM delay period (Lee et al. 2005). It is important to note that our measure of functional connectivity only demonstrates that activity is correlated across a given pair of regions; it does not imply that these regions are monosynaptically connected. Because processing in the hippocampus proper is channeled through a polysynaptic circuit, and hippocampal input and output are relayed through the entorhinal cortex, the functional coupling we observe between the hippocampus and FFA most likely reflects indirect neural communication.

It is unclear why the most robust load-dependent hippocampus–FFA connectivity increase emerged in the left hippocampus ROI. Some studies have suggested that the left hippocampus is particularly important for verbal encoding, whereas visual encoding tends to engage the hippocampus bilaterally, albeit with a right-hemispheric bias for face stimuli (Powell et al. 2005). However, a recent review exploring the nature of memory-related MTL activations found only a slight trend toward these material-specific lateralization effects (Henson 2005). It is interesting to note that fMRI studies utilizing visual WM tasks have documented a strong relationship between the delay period activity/connectivity of the left hippocampus and subsequent long-term recognition memory performance (Ranganath, Cohen, Brozinsky 2005; Ranganath, Heller, et al. 2005). However, given that our right hippocampus ROI also showed a marginally significant load-dependent increase in its connectivity with the FFA, we are hesitant to place too much weight on the fact that our strongest load effects were found in the left hippocampus. It is possible that with more statistical power, we might have observed equivalent load-dependent connectivity increases between our right-lateralized FFA seed and the left and right hippocampi. Moreover, it is worth noting that our right IFG ROI showed significant load effects on its connectivity with both hippocampal ROIs. Further research will be needed to better differentiate the contributions of right and left hemisphere MTL regions to visual memory over short delays.

Interpreting PFC Activity and Connectivity Increases

We have speculated that the load-related decreases in PFC–FFA connectivity reflect a diminished reliance on active attention-based maintenance at higher loads. This finding, which at first glance implies reduced prefrontal involvement with increasing load, may seem surprising in the context of the extant fMRI literature on WM load effects. Most event-related fMRI studies of WM that have included load manipulations have documented load-related increases in PFC activation during the delay period (Jha and McCarthy 2000; Rypma et al. 2002; Druzgal and D'Esposito 2003; Linden et al. 2003; Cairo et al. 2004; Leung et al. 2004; Habeck et al. 2005; Zarahn et al. 2005). Indeed, Druzgal and D'Esposito (2003), working with the same data set used in the present study, reported greater PFC activity during the delay period of high load trials. Our reanalysis of this data set also documented a load-related increase in univariate delay period activity in our right IFG ROI, even though this ROI was defined based on its connectivity with the FFA during the delay period and not on univariate activity levels. The fact that the right IFG increased its delay period activity with load suggests that this region still makes important contributions to task-related processes at high loads, despite its diminished connectivity with the FFA.

Our finding that this right IFG region shows a load-dependent increase in its connectivity with the right and left hippocampi provides suggestive evidence for some potential roles that this prefrontal region may be playing at high loads. Because active PFC-guided maintenance of the detailed visual representations held in the FFA may be inadequate at supra-capacity loads, the IFG's shift toward increased functional coupling with the hippocampus may indicate increased reliance on MTL representations. This increased frontal–hippocampal communication could signal the need for a shift away from attention-based maintenance toward a retention process that maximally exploits the mnemonic codes of the MTL memory system. According to this view, top-down input from the IFG might orient the hippocampus toward the need to strengthen its processing of the decaying sensory representations in the FFA, thus triggering increased connectivity between the hippocampus and FFA. Alternatively, the IFG may establish reverberant communication with the MTL at high loads in a similar manner to its relationship with the FFA at low loads, in both cases with the goal of modulating and sustaining activity in a specific neural population containing task-relevant codes. Given the substantial intercorrelation of all nodes in our simplified network, we are unable to discern whether the increased IFG–hippocampus connectivity at high loads causes or supplements the increased hippocampus–FFA connectivity. Moreover, it is likely that PFC–MTL interactions are mediated via multiple intermediary connections. Further research will be needed to determine how the frontal–hippocampal interactions observed in the present study relate to those thought to play a critical role in the control processes regulating the encoding and retrieval of long-term memories (Simons and Spiers 2003).

Funding

NSF Graduate Research Fellowship, the National Institutes of Health (NIH) National Research Service Award to J.R.; the NIH to A.G. and M.D.; the Veterans Administration Research Service to M.D.

Notes

The authors thank T. Jason Druzgal for use of this fMRI data set and David Badre for helpful comments on an earlier version of the manuscript. *Conflict of Interest*: None declared.

Address correspondence to Jesse Rissman, Department of Psychology, Stanford University, Jordan Hall, Building 420, Stanford, CA 94305-2130, USA. Email: jesse.rissman@stanford.edu.

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