



## Complex span tasks and hippocampal recruitment during working memory

Carlos Cesar Faraco<sup>a,\*</sup>, Nash Unsworth<sup>b</sup>, Jason Langley<sup>c</sup>, Doug Terry<sup>b</sup>, Kaiming Li<sup>d</sup>, Degang Zhang<sup>d</sup>, Tianming Liu<sup>d</sup>, L. Stephen Miller<sup>a,b</sup>

<sup>a</sup> Biomedical Health Sciences Institute, Division of Neuroscience, University of Georgia, Psychology Building, Athens, GA., 30602, USA

<sup>b</sup> Department of Psychology, University of Georgia, Psychology Building, Athens, GA., 30602, Athens, GA., USA

<sup>c</sup> Department of Physics and Astronomy, University of Georgia, Physics Building, Athens, GA., 30602, USA

<sup>d</sup> Department of Computer Science, University of Georgia, 415 Boyd Graduate Studies Research Center, Athens, GA., 30602, USA

### ARTICLE INFO

#### Article history:

Received 7 May 2010

Revised 6 December 2010

Accepted 9 December 2010

Available online 21 December 2010

#### Keywords:

Working memory

Hippocampus

Complex span

fMRI

Executive control

### ABSTRACT

The working memory (WM) system is vital to performing everyday functions that require attentive, non-automatic processing of information. However, its interaction with long term memory (LTM) is highly debated. Here, we used fMRI to examine whether a popular complex WM span task, thought to force the displacement of to-be-remembered items in the focus of attention to LTM, recruited medial temporal regions typically associated with LTM functioning to a greater extent and in a different manner than traditional neuroimaging WM tasks during WM encoding and maintenance. fMRI scans were acquired while participants performed the operation span (OSPAN) task and an arithmetic task. Results indicated that performance of both tasks resulted in significant activation in regions typically associated with WM function. More importantly, significant bilateral activation was observed in the hippocampus, suggesting it is recruited during WM encoding and maintenance. Right posterior hippocampus activation was greater during OSPAN than arithmetic. Peristimulus graphs indicate a possible specialization of function for bilateral posterior hippocampus and greater involvement of the left for WM performance. Recall time-course activity within this region hints at LTM involvement during complex span.

© 2010 Elsevier Inc. All rights reserved.

### Introduction

Working memory (WM) is thought of as a system in which information currently in the focus of attention can be maintained and manipulated. It is also seen as a gateway through which sensory information can enter into long term memory (LTM) or through which information can be recruited from LTM into the focus of attention (Atkinson and Shiffrin, 1968; Baddeley and Hitch, 1974; Cowan, 1988; Engle et al., 1999a; Unsworth and Engle, 2007b). A properly functioning WM system enables an individual to keep attention on a desired goal while preventing other environmental or cognitive stimuli from interfering with the completion of the desired goal. Furthermore, WM is crucial when attempting to override our automatic responses through a set of cognitively salient processes (Unsworth and Engle, 2007b), thus making it critical for the performance of a variety of everyday tasks.

Atkinson and Shiffrin (1968) and Baddeley and Hitch (1974) espoused the idea that the process of WM is that by which information

is at some point stored in a location, LTM, from where it can later be retrieved by another system, short term memory (STM). The information is then manipulated, updated, and maintained in accordance with the aim of the present goal state. Of importance is also the idea that the information held in STM does not have to be retrieved from LTM, but maybe newly acquired information that has been linked with other information in LTM. Linking, or relational encoding, is necessary in order to attach meaning to the newly acquired information.

Many of the current discussions on WM have emphasized the concept of capacity limits. To describe this concept, Cowan's (1988, 1999, 2005) embedded processes model examines three states of memory: the information residing in LTM, recently perceived or accessed information that is in an easily accessible (activated) state in LTM, and a sub-portion of that information which we are consciously aware of, known as the focus of attention. WM capacity differences are believed to arise from the ability to keep the focus of attention on the task at hand while suppressing interference from environmental stimuli or irrelevant cognitions caused by the activation of other memory traces in LTM. Much in the same way, Unsworth and Engle (2006, 2007b) suggest that differences in WM capacity arise from an individual's ability to actively maintain information in primary memory (i.e., the focus of attention) while also performing a controlled search of the information residing in secondary memory (i.e., LTM).

Several tasks have traditionally been used to assess WM capacity. For example, the typical digit span task assesses capacity by

\* Corresponding author. Fax: +1 706 542 5285.

E-mail addresses: [cfaraco@uga.edu](mailto:cfaraco@uga.edu) (C.C. Faraco), [nunswor@uga.edu](mailto:nunswor@uga.edu) (N. Unsworth), [impulse@physast.uga.edu](mailto:impulse@physast.uga.edu) (J. Langley), [dpterry@uga.edu](mailto:dpterry@uga.edu) (D. Terry), [likaiming@gmail.com](mailto:likaiming@gmail.com) (K. Li), [lczhdgm@gmail.com](mailto:lczhdgm@gmail.com) (D. Zhang), [tliu@cs.uga.edu](mailto:tliu@cs.uga.edu) (T. Liu), [lsmliller@uga.edu](mailto:lsmliller@uga.edu) (L.S. Miller).

determining the maximum length of numbers that an individual can serially recall. More involved tests, such as the digits backwards and letter-number sequencing tasks, assess capacity while also requiring the ability of mental double-tracking, meaning that memorizing and reversing/ordering operations must be performed simultaneously (Lezak et al., 2004, pp. 359–363). Other tasks like Daneman and Carpenter's (1980) reading span task and Turner and Engle's (1989) operation span (OSPAN) task are complex working memory span (CWMS) tasks that require the participant to engage in a processing activity that is irrelevant to the to-be-remembered information. They involve encoding, maintenance, storage, and processing of various types of information. Proper performance on CWMS tasks requires a high degree of executive attentional-control (Conway et al., 2003; Engle et al., 1999a; Kane et al., 2007a) to switch between tasks and maintain attention on the task at hand. Of critical importance, the irrelevant task is often thought to force the to-be-remembered information to be temporarily displaced from the focus. If the to-be-remembered information is properly encoded, it may be placed into and retrieved from LTM as required (Kane et al., 2007a). The displacement of task relevant information from the focus occurs because the irrelevant task usually requires controlled, effortful processing (Conway and Engle, 1996; Engle et al., 1999b); it is of sufficiently high cognitive load that it may occupy the whole of the focus of attention, thereby displacing any information which exceeds the individual's immediate WM capacity (Bunting, 2006; McCabe, 2008). It is this type of complex processing, and the resultant interactions of items coming into and going out of the focus, that make CWMS tasks invaluable for the cognitive study and neuroimaging of WM.

#### *Neuroanatomical regions traditionally associated with WM tasks*

Functional neuroimaging experiments of WM have typically used tasks such as the Sternberg (1966) or the n-back (Gevins et al., 1990); we will refer to these types of tasks as traditional neuroimaging WM (TNWM) tasks. During the Sternberg task subjects are presented with a set of stimuli and are asked if the target stimulus matches any of the stimuli presented in the previous set. The n-back task is more complex in that there is a continuous presentation of stimuli; on target trials subjects are asked either if the target stimulus matches a stimulus presented *n* trials back (usually 1 to 3) or to identify how many trials back the target stimulus was shown. Generally speaking, most neuroimaging investigations of WM have associated a core of regions with WM functioning.

The prefrontal cortex (PFC) is believed to be integral to WM and executive control (D'Esposito et al., 2000; Owen et al., 2005; Wager and Smith, 2003). Sub-sections of the PFC, such as the ventrolateral prefrontal cortex (VLPFC) and dorsolateral prefrontal cortex (DLPFC), have been said to be involved in object and spatial domain specific processing (Courtney et al., 1998; Smith and Jonides, 1999), respectively. However, an extensive review of the neuroimaging literature by Wager and Smith (2003) indicated that PFC sub-regions were not so much domain specific as they were process specific. The DLPFC being involved in executive processes, such as attentional control or the monitoring of complex information (Cabeza and Nyberg, 2000), while the VLPFC is involved in storage-related processes such as the maintenance of spatial information (Toepfer et al., 2010) or the rehearsal of verbal information (Cabeza and Nyberg, 2000). Bor et al. (2006) showed activation of the VLPFC during a task where spatial information had to be kept online without aid of a spatial strategy; when spatial strategies for remembering the target stimuli were given, activation was only exhibited in the DLPFC. Further involvement of the VLPFC in storage processes has been demonstrated in proactive interference tasks where the left inferior frontal gyrus has shown significant activation during a recent negative condition (Jonides et al., 2000; Jonides and Nee, 2006). This activity

has been shown to occur specifically during the retrieval stage of the recent negative condition (D'Esposito et al., 1999) and is linked to the resolution of interference. A more recent review by Blumenfeld and Ranganath (2007) has further indicated the VLPFC's role in the resolution of interference by noting that it is consistently recruited when controlled selection of items is required. The DLPFC's roles in executive processing are further confirmed by demonstrating it is highly recruited for the organizational processing of information. Blumenfeld and Ranganath (2007) have also summarized the roles of VLPFC and DLPFC in LTM, suggesting VLPFC supports the formation of LTMs through the process of controlled item selection, while the DLPFC aids in building associations between items in LTM and those in the focus of attention. Another key region in the frontal lobes, the anterior cingulate cortex (ACC), is also believed to be necessary for proper WM function and is thought to be involved in conflict monitoring and error detection (Bernstein et al., 1995; Botvinick et al., 2001; MacDonald et al., 2000). Both of these are attentional control processes and as such the ACC is believed to be critical to cognitive control (Smith and Jonides, 1999; Osaka et al., 2003). Furthermore, Kaneda and Osaka (2008) suggest that the ACC may play a greater role in executive functioning than the DLPFC.

The parietal lobes are thought to function as associative centers and be involved in higher level cognitive processes. They are also believed to be crucial to WM processes and serve as storage regions (Hamidi et al., 2008; Postle, 2006; Postle and D'Esposito, 1999; Rowe et al., 2000; Srimal and Curtis, 2008). More specifically, the superior parietal lobule (SPL) and the precuneus (Brodmann area 7) are believed to be crucial in maintaining and organizing items held in the WM store (Wager and Smith, 2003; Wendelken et al., 2008), while the supramarginal gyrus (part of the inferior parietal lobule) is thought to retrieve the temporal ordering of items that have been displaced from the focus of attention through serial scanning (Öztekin et al., 2008). Parietal cortex is also thought to select the appropriate response for a specific stimulus, known as stimulus-response mapping (Corbetta and Shulman, 2002; Miller, 2000; Miller and Cohen, 2001).

The medial temporal lobes (MTL) have traditionally been associated with the encoding and maintenance of declarative LTMs. For example, Scoville and Milner's (1957) classic study demonstrated that bilateral lesions to the hippocampal formation produced an extremely detrimental impact on the retention of new memories. More recently, neuroimaging studies have challenged this limited conception of MTL regions by demonstrating hippocampal recruitment during various types of WM tasks, and specifically, during the maintenance phases of some of these tasks. Öztekin et al. (2009) found the hippocampus was active during item recognition trials of a serial position task and that activity increased for earlier items rather than the last item on a judgment of recency task. Using neurosurgically implanted electroencephalograph (EEG) electrodes, Axmacher et al. (2007) detected significant load dependent negative DC potential shifts and increases in synchronized gamma band activity in the rhinal cortex during the maintenance of multiple items during a visual Sternberg task. The negative DC shift likely indicating membrane potential depolarization and increased firing and/or synaptic activation of rhinal cortex neurons, while synchronized gamma band activity further indicated recruitment of the rhinal cortex. Van Vugt et al. (2010) furthered these findings by demonstrating a local load dependent gamma oscillatory power increase in the hippocampus during Sternberg task maintenance. Additionally, this increase was greater for non-verbal items (faces) than for verbal items (letters).

#### *What makes CWMS tasks valuable neuroimaging tools?*

Even though item recognition tasks such as the n-back and the Sternberg have proven to be valuable in dissociating many of the brain regions involved in WM functioning, there are reasons to

explore the use of CWMS tasks in neuroimaging settings. For example, the n-back has been shown to account for variability in general fluid intelligence (Gf), but it has done so only under a 3-back condition, and this variance in Gf is separate than that accounted for by WM span (Kane et al., 2007b). WM span, as measured by a CWMS task though, has been shown to account for up to half the variability in Gf (Conway et al., 2003; Kane et al., 2005). A CWMS task like the OSPAN has been shown to possess high levels of reliability and internal consistency as compared to other measures of WM capacity (Klein and Fiss, 1999). An automated version of the OSPAN has also demonstrated high levels of reliability and internal consistency, and shown high levels of correlation with other measures of WM (Unsworth et al., 2005). Moreover, more recent work has demonstrated correlations between complex WM span tasks and traditional measures of LTM (Unsworth et al., 2009; Unsworth, 2010) at sub-span levels, unlike TNWM tasks. Such correlations make the case for the use of CWMS tasks in neuroimaging WM research, especially when attempting to decipher the possible interplay of WM and LTM.

Unfortunately, CWMS tasks have seen little use in neuroimaging studies. In one of the few, Kondo et al. (2004) found the OSPAN elicited activation in regions usually activated during the n-back (e.g., PFC, ACC, and SPL), while the high-span group also exhibited significant activation in the inferior temporal cortex. Kondo et al. (2004) was limited, however, in that they mainly restricted their analysis to the functional connectivity differences of the cingulo-frontal network between high-span and low-span individuals. Recently Chein et al. (2010) examined domain general mechanisms during encoding and maintenance, and examined MTL activity during recall for verbal and spatial complex span tasks. They found activity in areas typically associated with WM during encoding and maintenance, and found the posterior hippocampus and immediately inferior portion of the parahippocampal gyrus were involved in the recall portion of the task. However, they did not specifically examine MTL recruitment during encoding and maintenance. Therefore, a more in depth neuroimaging exploration of CWMS tasks and the roles of MTL ROIs during encoding and maintenance is warranted.

### *The current study*

In this study we aimed to elucidate whether significant differences exist between the neural resources required for the performance of CWMS and TNWM tasks. More precisely, we wanted to determine if the encoding and maintenance phase of a CWMS task results in significantly greater recruitment of areas typically associated with LTM functioning than might occur during a TNWM task. As previously stated, Axmacher et al. (2007) and Van Vugt et al. (2010) demonstrated hippocampal activity during a Sternberg task maintenance, a TNWM task. To examine this, we compared functional magnetic resonance (fMRI) activity observed during the OSPAN task (complex span; letter span + equation verification) with that of an arithmetic task (traditional type of neuroimaging WM task; equation verification).

The goal of the OSPAN task is to recall the to-be-remembered items (letters) in serial order. During the OSPAN, equation verification is presented as the irrelevant, cognitively demanding task. As a result, participants should often not have sufficient cognitive resources available to rehearse the to-be-remembered letters while performing equation verification. In other words, the equation verification should occupy the focus of attention causing a displacement of the to-be-remembered letters from the focus to LTM. If the to-be-remembered items have been displaced from the focus and properly stored in LTM, they can later be retrieved from LTM as needed. By contrasting the OSPAN and Arithmetic conditions we hoped to control for the common activation patterns resulting from equation verification in order to demonstrate that the OSPAN task forces recruitment of regions associated with LTM binding and retrieval, and that

recruitment occurs during the encoding and maintenance phase of the task.

We hypothesized that 1) the OSPAN encoding and maintenance phase and Arithmetic task would yield activation in regions commonly associated with WM and the resolution of interference during on-going retrieval, such as VLPFC, DLPFC, ACC, SPL, and inferior parietal lobule (IPL), 2) activations in these regions would be greater during the OSPAN since CWMS tasks should require greater executive control than a typical neuroimaging WM task, 3) due to the nature of the OSPAN, activation would also be evidenced in areas typically associated with LTM binding and retrieval, specifically the hippocampus, and 4) the nature of CWMS tasks would be sufficiently different from TNWM tasks, resulting in unique patterns of activity within LTM associated regions such as the hippocampus. This would be the first instance where such activity would be demonstrated for a CWMS task during maintenance and encoding. We also aimed to explore what pattern of brain activity during a CWMS task is correlated with correct and incorrect recall. In other words, we explored what patterns of brain activation are associated with WM capacity and proper storage and retrieval. Edin et al. (2009) indicates we may find correct recall is associated with heightened DLPFC activity which modulates parietal activation.

## **Materials and methods**

### *Participants*

Twenty-five young adults from the University of Georgia were recruited for this study through the university's research participant pool and through word of mouth; 17 females and 8 males, average age =  $24.8 \pm 2.8$ . Exclusion criteria included self-report of previous head injury, history of loss of consciousness, current drug abuse, evidence of neurodegenerative processes, and an estimated below average IQ. Participants could also not have a history of, present clinical signs of, or currently be under treatment for, any major psychiatric symptoms or disorders. The exception to the latter exclusion criteria was a past history of depression, since a significant portion of the population may have at one point presented with clinically diagnosable symptoms (Pratt and Brody, 2008). Incompatibility with the MRI environment (e.g., metallic implants, pacemakers, stents, etc.) was assessed through a standardized screening form and participants were excluded given any signs of incompatibility.

### *Measures*

Participants were made aware of the exclusion criteria before participating in the study. Upon meeting with the investigator, participants were fully screened. Screening included completing the MRI screening form, answering questions from the psychotic symptoms screening portion of the Structured Clinical Interview for DSM-IV (SCID-I; First et al., 1997), and being asked the exclusion criteria questions described earlier. Additionally, female participants were asked to take a pregnancy test; even though the MRI environment has been shown to have no adverse side-effects, this was taken as a precautionary measure. If screening was successful, participants were given a brief IQ estimate, the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) to rule out below average IQ.

### *Task and stimuli*

Participants performed the OSPAN task in a similar fashion to Kondo et al. (2004). The full presentation of the task lasted 6 m and 45 s, with fixed alternating conditions of OSPAN, Arithmetic, and Baseline; there were 3 OSPAN, 3 Arithmetic, and 6 Baseline epochs, each lasting 30 s. The OSPAN epochs were always followed by 15 s Response epochs (Fig. 1). Each run was preceded by a set of visual

instructions and contained a total of 15 epochs; 3 OSPAN+3 Response+3 Arithmetic+6 Baseline. The OSPAN, Arithmetic, and Baseline conditions were structured so that participants received similar amounts of visual input and gave the same amount of motor output (Fig. 1).

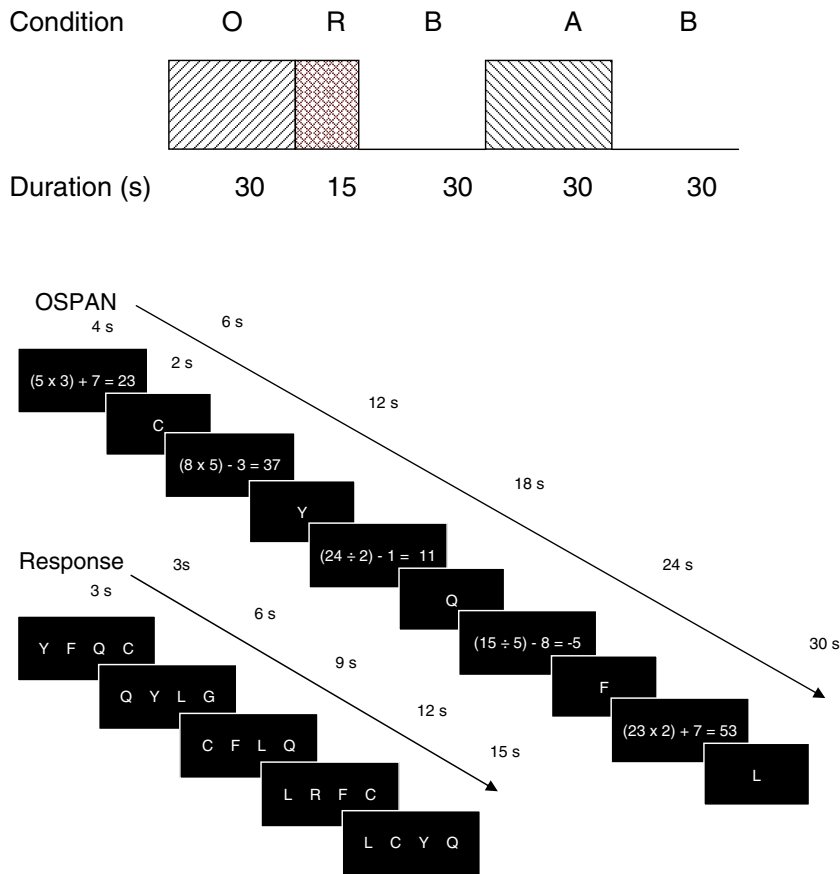
During the Baseline condition participants were presented with arrows pointing either left or right (4 s) and responded by indicating which direction the arrow was pointing with the appropriate button press. Presentation of arrows alternated with the presentation of asterisks (2 s). During the Arithmetic condition participants were presented with an equation (4 s) consisting of two operations, multiplication or division and addition or subtraction. Their task was to judge whether the equation was correct or incorrect and to respond by pressing the appropriate button on the response pad. In between the presentation of the equations they were shown an asterisk (2 s). During the OSPAN task participants also had to judge equations (4 s), but instead of asterisks they were presented with letters (2 s) which they were instructed to remember in serial order. Within all these block types, the sequences repeated five times. After each OSPAN block, there was a response block in which participants identified which letters were previously presented. They were shown 5 separate arrays, each consisting of 4 letters, for 3 s each. They were to identify the letters presented with the appropriate button presses. For the first array the participant identified which of the letters was first presented, for the second array they identified which was presented second, and so on. For any of the epochs, if the participants responded to a prompt after the allotted time, the response was considered incorrect.

### Procedure

Participants initially practiced the task by viewing it on a computer monitor and tapping their finger to the appropriate response as they would with the response pads in the MRI unit. On average, participants required 3 min before the investigator acknowledged they were performing the task appropriately. After practice, participants were placed in the MRI scanner. During the structural scan participants performed a practice run of the task in order to further become acquainted with the task and scanner environment. Participants then performed 2 runs while fMRI data was acquired. The task was designed in E-Prime, version 1.2 (Psychology Software Tools, 2006), stimuli were presented through MRI compatible goggles (Resonance Technology Inc.), participants responded through Cedrus LUMINA MRI compatible response pads by using their index and middle fingers, and responses and reaction times (RTs) were recorded by E-Prime. Behavioral data was acquired during all 3 (1 practice, 2 experimental) runs in the scanner.

### MRI acquisition

3D structural scans were acquired using a fast spoiled gradient recalled echo (FSPGR) protocol; TE = min full, TR = 7.5 ms, flip angle = 20°, 154 axial slices, slice thickness = 1.2 mm, and FOV = 256 × 256 mm. These images covered from the top of the head to the brainstem and acquisition took approximately 6 m and 20 s. Functional scans were acquired using a T2\*-weighted single shot echo planar imaging (EPI) sequence and were aligned to the



**Fig. 1.** Stimulus presentation. Top: Block design for stimuli; this sequence was repeated 3 times per run. O: OSPAN, R: word recognition, B: baseline, and A: Arithmetic condition. Bottom: Progression of OSPAN block and the preceding Response block where participants identify the letters presented during the OSPAN block in serial order. For the Arithmetic blocks, participants were presented with equations, as in the OSPAN, but asterisks were presented instead of letters. During Baseline participants were presented with either left or right pointing arrows instead of equations, and asterisks instead of letters.

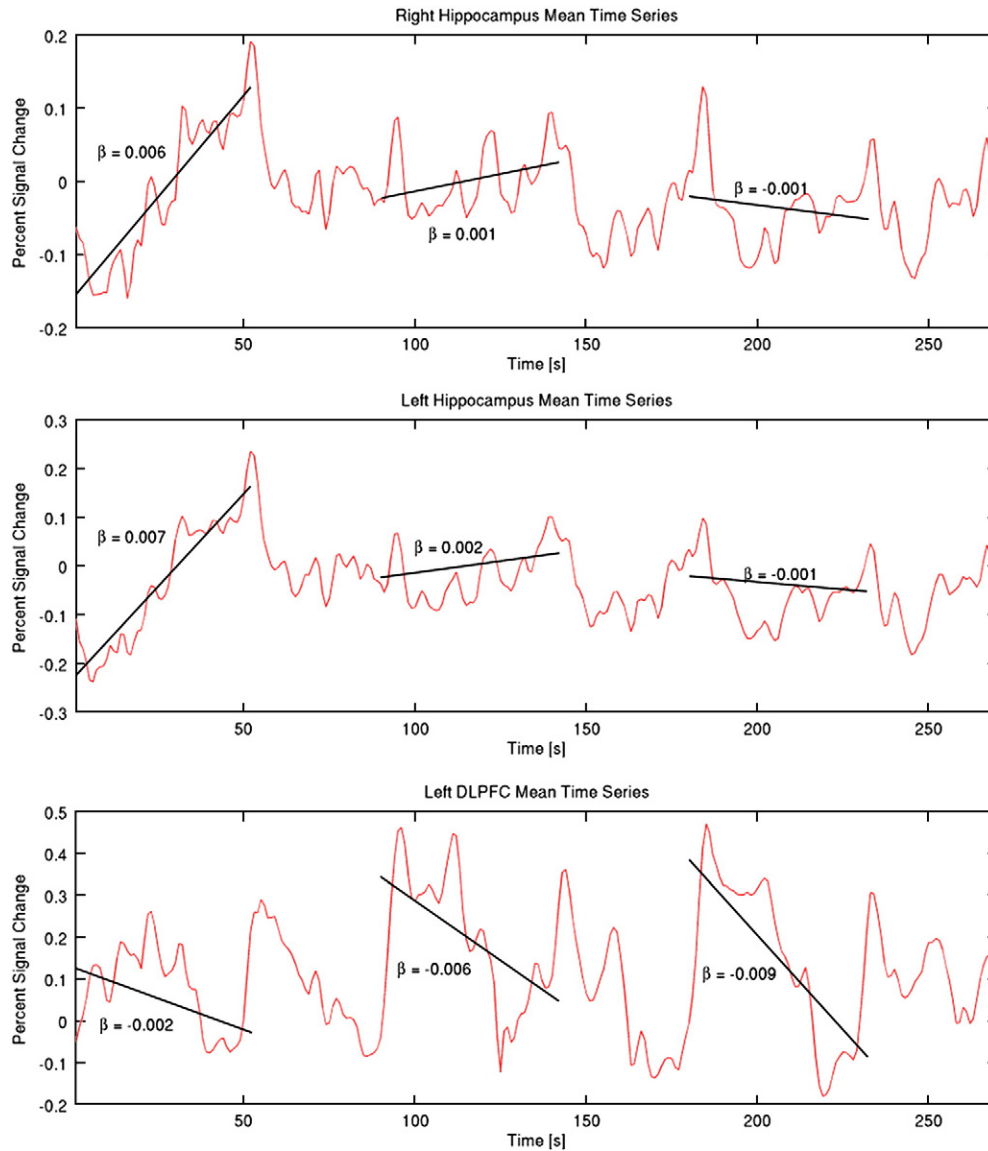
intercommisural line (AC–PC line); TE = 25 ms, TR = 1500 ms, 90° RF pulse, 30 interleaved slices, acquisition matrix = 64 × 64, spacing = 0 mm, slice thickness = 4 mm, FOV = 240 × 240 mm, and ASSET factor = 2. Functional images covered the entire cortical surface and a portion of the cerebellum. Each run consisted of 270 volumes and 10 dummy samples were discarded during the initial acquisition.

#### Data analysis

All data were processed using the FMRIB Software Library (FSL; Smith et al., 2004; Woolrich et al., 2009). Before MRI data sets were analyzed using the FMRI Expert Analysis Tool (FEAT), they were converted from their native GE DICOM format to NIFTI format using the dcm2nii conversion tool (Rorden, 2007). Each participant's fMRI data was motion corrected using the Motion Correction FMRIB Linear Registration Tool (MCFLIRT; Jenkinson et al., 2002). The images were then slice time corrected to account for the interleaved acquisition and then brain extracted using the Brain Extraction Tool (BET; Smith,

2002). Images were smoothed using a 6.875 mm isotropic FWHM Gaussian smoothing kernel, twice the voxel dimensions in the x and y planes. A high-pass temporal filter, calculated at 135 s (OSPAN + Response + Baseline + Arithmetic + Baseline times), was applied. The data were prewhitened to remove inter-voxel auto-correlation. Head motion parameters estimated from MCFLIRT were added as confound/regressor variables to the design. A standard hemodynamic response function was convolved with each run's time course. All results were warped to the 91 × 109 × 91 mm MNI standard brain using a 12-degree affine transform.

We contrasted the OSPAN and Arithmetic blocks with Baseline, and the OSPAN to the Arithmetic blocks. Comparing the task blocks to Baseline allowed us to determine the regions recruited for each task and also gave us a qualitative indication of how similar or distinct these regions were. The OSPAN > Arithmetic contrast yielded regions likely associated with the high degree of attentional control required during CWMS tasks and the storage and retrieval of information to and from LTM. Between-subjects voxel-wise analyses were performed



**Fig. 2.** Depiction of linear trend which created a bias in the hippocampal signals. The top two averaged time series depict the linear trend that occurred for the first 53 volumes of acquisition within the hippocampus; this included the initial OSPAN, baseline, and Arithmetic blocks. The lower figure depicts the time-series for the left DLPFC. This region was randomly chosen from our list of ROIs to determine whether this trend was global or localized to the hippocampi. The linear least squares lines of best fit are plotted on the graphs to further emphasize the linear trend within the hippocampus for the first 53 volumes.

using a mixed-effects model. Whole brain group results were thresholded using FSL's cluster thresholding,  $Z > 4.0$  and  $p = 0.05$ . Even at this high threshold, results for the task minus baseline contrasts were still extremely robust. We increased the Z threshold for these contrasts to 4.5 in order to parcellate some of the clusters into more meaningful regions. Increasing the threshold did not cause any activation areas of interest to become non-significant.

For hippocampal ROI analysis, FMRIB's Integrated Registration Tool (FIRST; Patenaude et al., 2007) was implemented for subcortical

segmentation. A mask was then made for each subject's hippocampi from the respective segmentation results. Hippocampus analysis in FEAT followed the standard procedure outlined above, except that at the first level each subject's brain was only registered to their respective 3D anatomical scans. The affine transformations from FIRST, optimized for subcortical alignment to the standard MNI brain, were then convolved with the EPI to 3D transformations in order to optimize the EPI to MNI registration for hippocampal alignment between subjects. A smaller 5 mm isotropic FWHM Gaussian smoothing kernel was applied to the

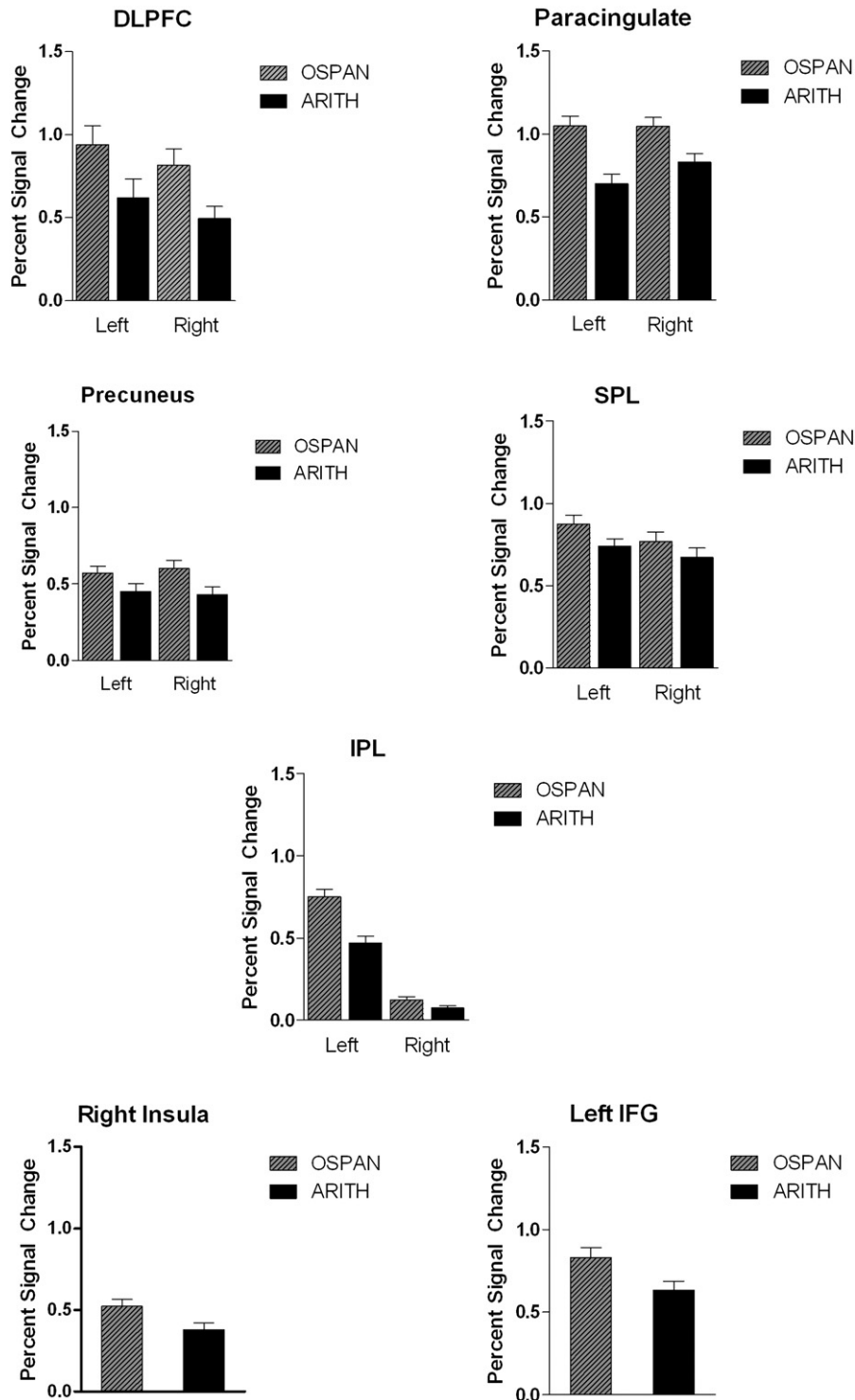


Fig. 3. Percent signal change values for ROIs. Graphs represent percent signal changes for activated ROIs with the S.E.M. OSPAN and Arithmetic conditions are presented with bilateral measures where appropriate.

hippocampal EPI data due to the restricted area of analysis. Group-wise ROI hippocampal analysis used a group modal mask of the hippocampi dilated by one voxel in every direction.

Persitstimulus plots for the hippocampi were calculated by taking the mean values of the hippocampi for each time point across participants, using the modal mask mentioned above, and averaging these values across blocks and then runs. Percent intensity change (PIC) plots were calculated by taking the PIC values for each subjects' runs and averaging them across time, resulting in a scalar value for each subject. These values were then averaged across subjects. Additionally, PIC and persitstimulus plots were calculated from voxels falling within the top 10% intensity range within the ROI. Baseline values were calculated by averaging the last two volumes of each baseline block. Mean hippocampal PIC values used baseline values from the entire hippocampus, while the top 10% used the baseline values from the top 10% voxels. Task and baseline values were calculated separately for each hemisphere.

Notably, plots of the entire mean and top 10% time-series depicted linear increases in voxel intensity through approximately the first 53 volumes of each run. This trend greatly affected the resulting statistics and persitstimulus plots because intensity values for the initial OSPAN blocks start below baseline values and increase linearly, through the initial baseline, until the third or fourth volume of the initial Arithmetic blocks (Fig. 2). A time series plot was also calculated for another region, the left DLPFC, to examine whether the linear trend was global or localized to the hippocampi. This trend was not observed for the DLPFC (Fig. 2). Thus we present hippocampus results calculated from 200 volumes of data per run, or 80 volumes of data for both the OSPAN and Arithmetic conditions. These results excluded the first 70 volumes, or the first OSPAN (TRs 1–30), baseline (TRs 31–50), and Arithmetic (TRs 51–70) blocks. The hippocampal ROI voxel-wise group analysis was thresholded at  $Z > 2.3$  and  $p = 0.05$ .

An uncorrected, voxel threshold of  $p = 0.005$ , whole brain group analysis was performed on the OSPAN > Arithmetic contrast using the average number of correct letter identification responses (demeaned) as a regressor. This was done to preliminarily identify regions whose activity during the encoding and maintenance might be significantly correlated with correct and incorrect letter identification during the recall period. Given the drawbacks associated with uncorrected voxel-wise analysis, a cluster threshold of 20 voxels was chosen in order to extract clusters with a higher likelihood of truly significant activation. Peak activated voxels from the identified clusters were dilated by an 8 mm sphere to use as masks for a more stringent cluster thresholded voxel-wise ROI analysis,  $Z > 2.3$  and  $p < 0.05$ , correlating these regions with correct and incorrect letter identification responses, respectively.

## Results

### Behavioral results

All participants completed both functional runs; answering the equations during the OSPAN and Arithmetic conditions at 87% ( $M = 13$ ,  $SD = 2.35$ ) and 85% ( $M = 12.8$ ,  $SD = 2.93$ ) accuracy, respectively, and recalling the letters in serial order during the OSPAN at 87% ( $M = 13.04$ ,  $SD = 3.43$ ) accuracy. Average RTs for the equations were 2371.29 ms ( $SD = 169.31$ ) for the OSPAN blocks and 2458.11 ms ( $SD = 175.39$ ) for the Arithmetic blocks. Paired sample  $t$ -tests revealed a significant effect for equation verification RT,  $t(24) = 4.15$ ,  $p < 0.001$ , with RTs during the OSPAN blocks occurring faster; no significant effect was found for number of correct equations  $t(24) = 0.661$ ,  $p < 0.515$ . These RT results are in accordance with those in Kondo et al. (2004).

### fMRI results

The OSPAN and Arithmetic blocks were contrasted against Baseline ( $Z > 4.5$ ,  $p = 0.005$ ), controlling for the visual input and

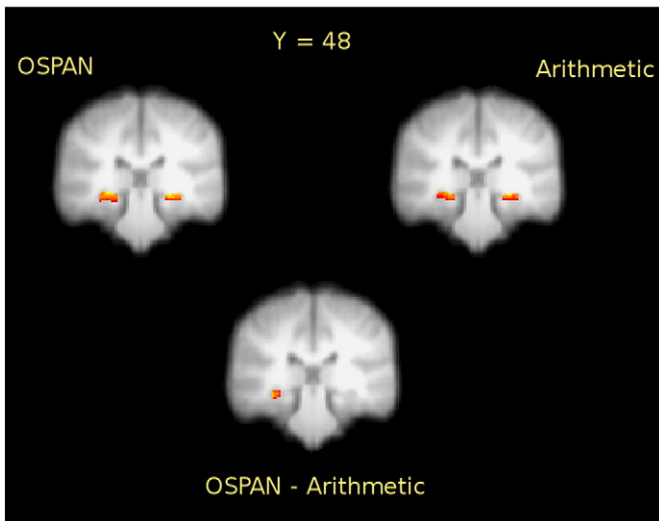
motor output that occurs during the OSPAN and Arithmetic blocks. Since participants performed well on both tasks, volumes spanning incorrect equation judgment or letters incorrectly recalled during the Response block were not excluded from the analysis. Activation sites for the OSPAN and Arithmetic blocks were similar with more robust activation occurring during the OSPAN. Activity in frontal regions was detected in the DLPFC, frontal orbital cortex, frontal operculum, middle frontal gyrus, precentral gyrus, superior frontal gyrus, supplementary motor area (SMA), and VLPFC. In parietal regions, this included the precuneus, the IPL (supramarginal and angular gyri), and the SPL. Activation was also evidenced in the ACC, paracingulate gyrus, posterior cingulate gyrus, and the anterior insular cortex. Percent signal changes for the main ROIs are displayed in Fig. 3. Activity detected in occipital regions included the lingual gyrus, occipital fusiform gyrus, and the occipital pole. In general, both tasks elicited bilateral activation in areas typically associated with WM functioning.

Of greater interest, was that the whole brain group analysis gave indication that OSPAN recruited some hippocampal areas by demonstrating activation in regions bordering, or encompassing parts of, bilateral hippocampus (Table 1). The Arithmetic task also appeared to recruit some hippocampal regions as indicated by an area of activation bordering around the left hippocampus. ROI voxel-wise analysis of the hippocampi (task > baseline;  $Z > 2.3$ ,  $p = 0.05$ ) resulted in strong activation encompassing the dentate gyrus, posterior portions of the subiculum, and posterior/mid-posterior cornu ammonis regions of the hippocampi for both tasks as compared to baseline (Fig. 4). The ROI results further demonstrate that MTL regions are recruited during CWMS tasks, but also demonstrate that they are recruited at least during more traditional types of neuroimaging WM tasks such as arithmetic.

**Table 1**  
MTL regions of activation.

Region	Coordinates in mm, MNI			Z-score
	x	y	z	
<b>Whole brain analysis</b>				
<i>OSPAN &gt; Baseline</i>				
L thalamus	-10	-20	16	6.66
L caudate	-14	2	16	5.90
L hippocampus/lateral GENICULATE	-24	-32	-2	5.10
R thalamus	18	-14	8	4.73
R hippocampus	30	-30	-4	4.73
<i>Arithmetic &gt; Baseline</i>				
L hippocampus/lateral geniculate	-24	-28	-4	5.3
<b>ROI analysis</b>				
<i>OSPAN &gt; Baseline</i>				
R hippocampus, DG/CA	28	-30	-6	6.58
R hippocampus, DG/CA	26	-34	0	5.88
R hippocampus, CA/DG	36	-26	-10	5.37
L hippocampus, DG/CA	-24	-34	-2	7.46
L hippocampus, DG	-26	-26	-10	7.06
<i>Arithmetic &gt; Baseline</i>				
R hippocampus, DG/CA	28	-28	-8	6.04
R hippocampus, DG/CA	26	-34	0	5.02
R Hippocampus, CA/DG	36	-26	-12	4.63
R hippocampus, CA	18	-40	2	2.5
L hippocampus, DG/CA	-26	-30	-8	8.25
L hippocampus, DG	-22	-32	-6	7.13
L hippocampus, DG/CA	-24	-34	-2	6.68
<i>OSPAN &gt; Arithmetic</i>				
R hippocampus, CA/DG	36	-26	-12	4.3

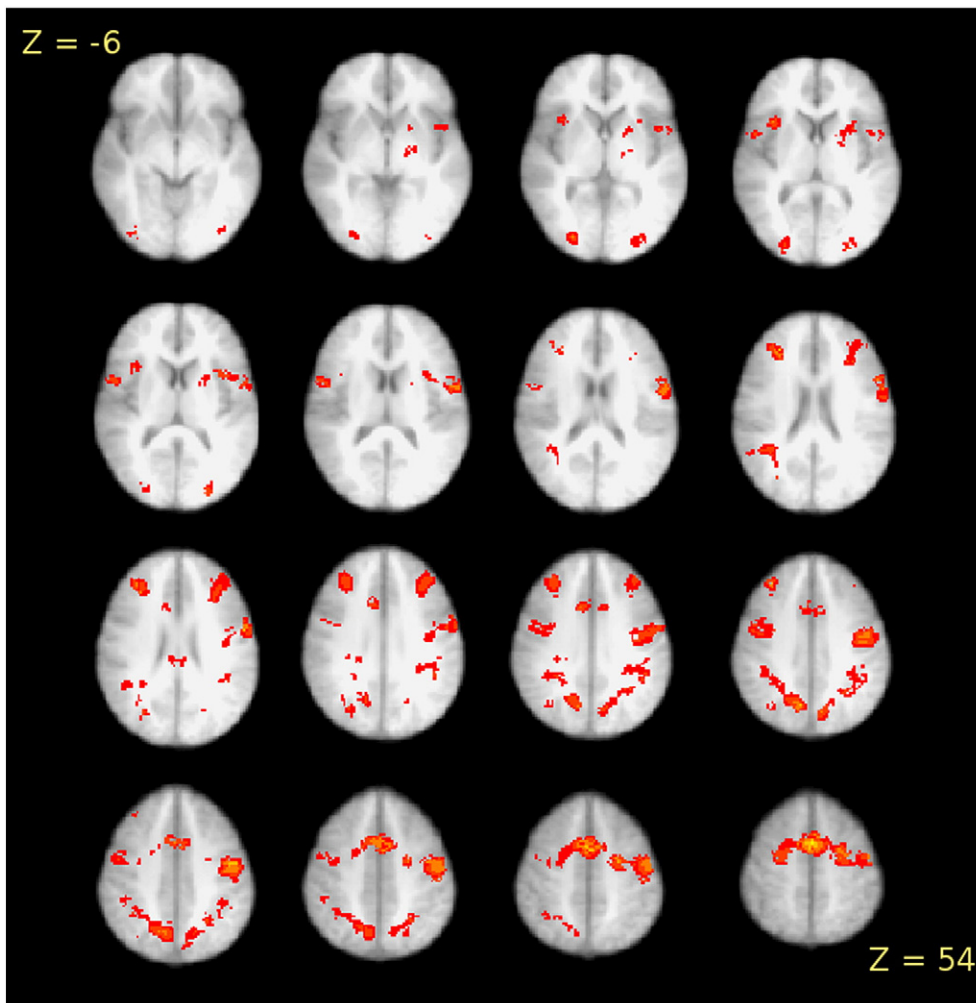
Regions of MTL activity for the Task > Baseline and OSPAN > Arithmetic contrasts. The top half presents activity detected for the whole brain contrast, while the bottom half presents the hippocampus ROI analysis results. Whole brain thresholded at  $Z > 4.5$ ,  $p < 0.05$ ; ROI thresholded at  $Z > 2.3$ ,  $p < 0.05$ .



**Fig. 4.** Activation map for hippocampal ROI analysis. The top two figures represent activation for OSPAN (left) and Arithmetic (right) as compared to Baseline, cluster thresholded at  $Z > 2.3$ ,  $p < 0.05$ . Activation covers a portion of the subiculum and part of the cornu ammonis regions. B) OSPAN>Arithmetic activation demonstrating significantly greater right posterior hippocampus activation, cluster thresholded at  $Z > 2.3$ ,  $p < 0.05$ .

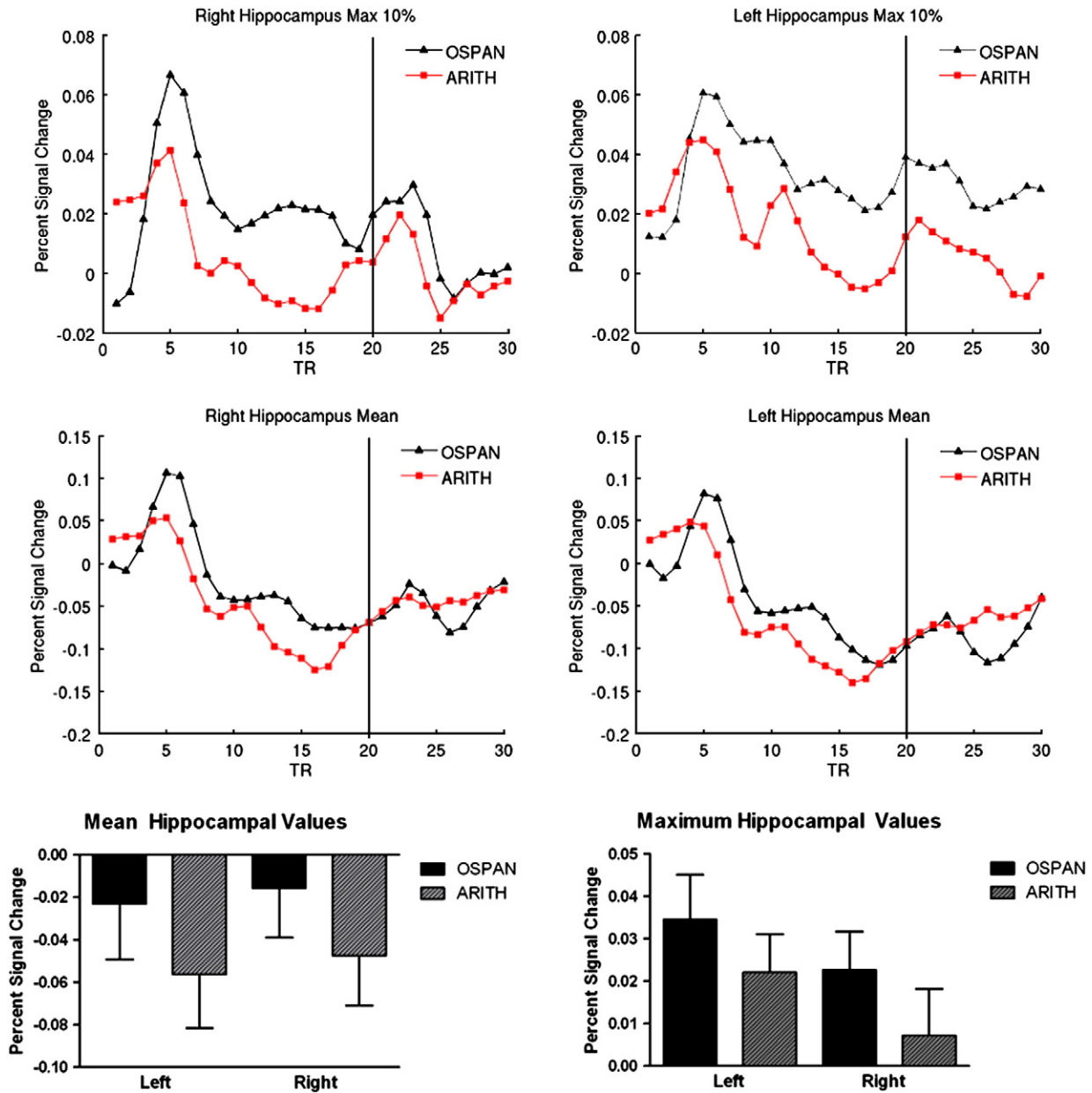
Even though our initial OSPAN>Baseline results were encouraging, our main goal was to demonstrate neural activation supporting the idea that during encoding and maintenance CWMS tasks recruit areas traditionally associated with LTM (i.e., the hippocampus) to a greater extent than TNWM tasks. The whole brain, OSPAN>Arithmetic, group activation map ( $Z > 4.0$ ,  $p = 0.05$ ; Fig. 5) revealed robust, bilateral differences in a variety of regions. Areas of increased activation for the OSPAN>Arithmetic contrast are listed in Table 3. Results demonstrated that the areas typically associated with WM tasks are much more active during complex than TNWM tasks. For example, in the frontal lobes greater activation was observed in the superior and middle frontal gyri, the paracingulate gyri, ACC, IFG, pars opercularis, DLPFC, precentral gyri. In the parietal cortex, greater activation was observed in the SPL, IPL, and precuneus. The supplementary motor cortex and the precentral gyrus exhibited the greatest differences, as the largest, most robust activation clusters encompassed these regions. Differences were also observed in regions less commonly reported in past studies, such as the right insula and left posterior cingulate cortex.

The hippocampus ROI voxel-wise analysis ( $Z > 2.3$ ,  $p = 0.05$ ) revealed a cluster of 110 voxels with significantly greater activation in the posterior right hippocampus for OSPAN>Arithmetic (Fig. 4, Table 1). The Arithmetic>OSPAN contrast did not yield any significant hippocampal differences. Mean and upper 10% values



**Fig. 5.** Activation map for the OSPAN>Arithmetic contrast. Cluster thresholded,  $Z > 4.5$ ,  $p < 0.05$ . The contrast image shows greater activation in cortical regions typically associated with working memory, this is likely due to the higher level of executive attentional control required during the OSPAN task. Images are in radiological convention, from inferior to superior.





**Fig. 6.** Peristimulus graphs and percent signal change graphs for the hippocampi. Peristimulus graphs are presented for the upper 10% and mean values of both hippocampi. Values were taken from an a-priori modal mask of the hippocampus that was dilated by one voxel in every direction. Differences between values in each of the graphs are significant across time. Peak and mean peristimulus graphs are drawn with a line at the 20 TR mark signaling the end of the OSPAN encoding and maintenance phase, and the end of the Arithmetic task. Following the OSPAN encoding and maintenance phase is the recall portion of the task. The initial peak in the mean graphs likely signals the retrieval of task relevant instructional sets, while a similar peak is evidenced after termination of the blocks, likely indicating retrieval of the instructional set for the next task. The mean peristimulus graph shows a deactivation of overall hippocampus function. This is in contrast to the upper 10% graphs which show above baseline levels of activity. Voxels falling within the upper 10% were in the posterior hippocampus across all subjects. Overall, these graphs indicate a possible specialization of function within the posterior hippocampus for working memory encoding and maintenance. Additionally, the increased activation in the posterior left hippocampus during OSPAN retrieval hints that items may have been displaced to LTM during complex span encoding and maintenance.

for the hippocampi (Fig. 6) were significantly greater for OSPAN across time between conditions; mean: left,  $t(39) = 2.573, p < 0.014$  and right,  $t(39) = 3.594, p < 0.001$ ; upper 10%: left,  $t(39) = 3.796, p < 0.001$  and right,  $t(39) = 3.124, p < 0.003$ . Values were also significantly different across hemispheres within conditions, with mean values greater on the right and upper 10% greater on the left; mean: OSPAN,  $t(39) = 6.330, p < 0.000$  and Arithmetic,  $t(39) = 3.995, p < 0.000$ ; upper 10%: OSPAN,  $t(39) = 3.068, p < 0.004$  and Arithmetic,  $t(39) = 2.534, p < 0.015$  (refer to Table 2 for a summary of these results). These results support our hypothesis and suggest a few possibilities in regards to specialization of function within the hippocampus: 1) posterior hippocampus may be critical to immediate memory functioning; 2) complex arithmetic (semantic fact-retrieval) and CWMS tasks do involve access to LTM through the hippocampus, but for different reasons; and 3) anterior hippocampal regions may specifically be part of the default/resting state network.

Group analyses using the average number of correct serially identified letters per participant as a regressor, thresholded at an uncorrected  $p = 0.005$  with a cluster size threshold  $\geq 20$ , yielded regions that could be positively and negatively correlated with the correct and incorrect recall (Table 4). Regions positively correlated with letter identification included left paracingulate/ACC, left medial temporal gyrus, right frontal pole, and pars opercularis of the right

Group analyses using the average number of correct serially identified letters per participant as a regressor, thresholded at an uncorrected  $p = 0.005$  with a cluster size threshold  $\geq 20$ , yielded regions that could be positively and negatively correlated with the correct and incorrect recall (Table 4). Regions positively correlated with letter identification included left paracingulate/ACC, left medial temporal gyrus, right frontal pole, and pars opercularis of the right

**Table 2**  
Paired differences.

Paired%-sc <i>t</i> -test differences for the hippocampus	Mean % Diff.	SD	S.E.M.	95% C.I.		<i>t</i>	df	Sig. (2-tailed)
				Lower	Upper			
<i>Differences in mean hippocampal signal change</i>								
Left hippocampus (Arithmetic-OSPAN)	0.0197	0.0484	0.0077	0.0421	0.0352	2.573	39	0.014
Right hippocampus (Arithmetic-OSPAN)	0.0257	0.0453	0.0072	0.0113	0.0402	3.594	39	0.001
Arithmetic (right-left)	0.0151	0.0238	0.0038	0.0227	0.0074	3.995	39	0.000
OSPAN (right-left)	0.0211	0.0211	0.0033	0.0278	0.0143	6.330	39	0.000
<i>Differences in upper 10% hippocampal signal change</i>								
Left hippocampus (Arithmetic-OSPAN)	0.0176	0.0293	0.0082	0.0082	0.0269	3.796	39	0.001
Right hippocampus (Arithmetic-OSPAN)	0.0156	0.0315	0.0050	0.0055	0.0256	3.124	39	0.003
Arithmetic (left-right)	0.0246	0.0246	0.0039	0.0020	0.0177	2.534	39	0.015
OSPAN (left-right)	0.0244	0.0244	0.0039	0.0040	0.0197	3.068	39	0.004

Paired *t*-test differences for percent signal values from the right and left hippocampi under the OSPAN and Arithmetic conditions. All *t*-test were significantly different across comparisons. Values were tested across time and the means of each individuals mean time points were supplied in the analysis.

inferior frontal gyrus. Regions negatively correlated with letter identification included left superior parietal lobule, right lateral occipital/cuneal cortex, left parietal operculum cortex, right post-central gyrus, and left angular gyrus. Masks from these regions were then used for ROI analysis of positive and negative correlation with correct recall using a more stringent cluster threshold ( $Z > 2.3$ ;  $p = 0.05$ ). Of the positively correlated regions used as masks, a cluster encompassing the anterior cingulate and the frontal pole was found to be significant. For negatively correlated regions, a cluster encompass-

**Table 3**  
Regions of significant differences; OSPAN>Arithmetic.

Cluster	Region	Brodmann area	Coordinates in mm, MNI			Z-score
			x	y	z	
1	R and L supplementary motor cortex	6	0	0	62	7.62
	L precentral gyrus	3/4	-50	-6	42	6.41
	L superior/middle frontal gyrus	6	-24	-4	52	6.26
	R and L paracingulate gyrus	32	0	14	46	5.95
	R anterior cingulate gyrus	24	8	12	46	5.71
	L inferior frontal gyrus, pars opercularis	44	-54	12	22	5.59
2	R precuneus	7	10	-66	38	6.24
	R angular	39	44	-48	24	5.13
	R superior parietal lobule/supramarginal	7/40	38	-48	42	4.80
3	L precuneus	7	-8	-72	38	5.45
	L supramarginal	40/39	-44	-40	34	5.41
	L superior parietal lobule	7	-26	-56	46	5.2
4	L DLPFC-middle frontal gyrus	9	-38	34	26	5.38
5	R DLPFC-middle frontal gyrus	9	34	38	38	6.24
6	R cerebellum, anterior		26	-64	-28	4.96
7	L lateral occipital cortex, inferior	18	-28	-88	4	5.47
8	R precentral gyrus	44/6	54	6	12	5.52
9	R lateral occipital cortex, superior	18	28	-84	2	5.45
10	R insula/frontal operculum	13	38	18	6	5.45
11	R lateral occipital cortex, superior	19	30	-72	28	4.98
12	R lateral occipital cortex, inferior	18	38	-82	-8	5.02
13	L thalamus		-16	-4	0	4.25
14	R white matter, adjacent to supramarginal		24	-28	30	4.53
15	L posterior cingulate cortex	23	-4	-28	26	4.34

OSPAN>Arithmetic.  $Z > 4.0$ ,  $p = 0.05$ . Here we present the results of the whole brain voxel-wise analysis for the OSPAN>Arithmetic contrast.

ing parts of the post-central and supramarginal gyri was found to be significant (Table 4). The apparent ceiling effect with regards to number of correct responses (87%) may partly explain why few cortical regions were found to be positively and negatively correlated with the encoding, maintenance, and possible displacement of items to WM under the ROI analysis.

**Table 4**  
Regions correlated with correct letter serial recall.

Cluster size	Region	Brodmann area	Coordinates in MNI, mm			Z-score
			x	y	z	
Whole brain						
<i>Positively correlated</i>						
49	L paracingulate/anterior cingulate cortex	32	-2	54	6	3.16
45	L middle temporal gyrus		-52	-46	-8	4.28
38	R occipital pole	17	12	-92	-6	4.21
27	R DLPFC	9	2	60	12	4.16
24	R inferior frontal gyrus, pars opercularis	44	60	14	18	4.09
<i>Negatively correlated</i>						
102	L superior parietal lobule	5	-22	-44	60	3.21
94	R precentral gyrus	6	20	-18	62	4.18
84	R lateral occipital cortex/cuneal cortex	7/19	14	-82	42	4.18
64	L parietal operculum cortex	40	-54	-38	22	4.19
58	R post-central gyrus	3	34	-34	66	3.11
50	L angular gyrus	39	-40	-60	18	4.27
31	L superior parietal lobule/lateral occipital cortex	7	34	-58	62	4.05
25	L superior frontal gyrus, premotor cortex	6	-16	-6	74	3.05
ROI analysis						
<i>Positively correlated</i>						
112	Bilateral paracingulate	10	0	54	6	3.45
	R paracingulate	10	-2	50	4	2.27
	L frontal pole	9	2	58	10	2.92
<i>Negatively correlated</i>						
106	R post-central gyrus/spl	5/7	32	-38	70	2.30

Regions from the OSPAN>Arithmetic contrast positively and negatively correlated with correct letter responses. Top half is from the whole brain, uncorrected voxel threshold analysis,  $p < 0.005$ , cluster threshold  $\geq 20$ . The bottom half is the ROI analysis performed using the regions detected in the whole brain analysis; cluster thresholded at  $Z > 2.3$ ;  $p < 0.05$ .

## Discussion

In this study, we used fMRI in conjunction with a CWMS task, the OSPAN, and a task resembling TNWM tasks, equation verification. Our aims were to 1) examine how brain activity differs between CWMS and TNWM tasks; 2) determine whether the hippocampus, typically associated with the retrieval and formation of LTMs, is significantly more active during the encoding and maintenance phase of a CWMS task than during a TNWM task; and 3) explore how activity during OSPAN encoding and maintenance may be correlated with later correct and incorrect recall.

LTM access during CWMS tasks is supported by the embedded processes (Cowan, 1988, 1999) and active maintenance (Unsworth and Engle, 2007b) models of WM and the limited capacity of the focus of attention (Cowan, 2001). For example, during the OSPAN task participants may be forced to access LTM in order to store and retrieve to-be-remembered letters (task relevant), as they are also asked to perform equation verification (task irrelevant) while trying to serially encode the to-be-remembered letters. That is to say, equation verification is a complex process which, when combined with the increasing list length, will likely occupy the limited capacity of the focus of attention. As such, the to-be-remembered letter sequence may be displaced from the focus of attention and stored in LTM. Consequently, this memory trace likely resides in an activated state (above threshold) and, depending on the individual's level of overall attentional control, can be retrieved back into the focus as needed (Oberauer, 2002).

Recently, neuroimaging studies have begun to show hippocampal activity during TNWM tasks. Typically, this activity has been shown to increase along with load. Unsworth and Engle (2007a) indicate that simple WM span tasks, such as TNWM tasks, may access LTM as long as a supra-span load is presented; a supra-span load would cause some items to be displaced from the focus, possibly into LTM. Even though there is strong evidence supporting the latter, we have chosen to examine the possible access of LTM associated regions during a CWMS task because these tasks require an added degree of executive control not required for the performance of simple WM span tasks, they have been shown to exhibit a higher level of ecological validity than typical WM tasks, and because the neuroimaging literature on popular CWMS tasks is scarce and deserves further exploration.

### *Shared cortical resources between CWMS and TNWM tasks in this study*

Cortical areas of activation during the OSPAN and Arithmetic conditions were similar (Fig. 3), with the OSPAN exhibiting more robust activation in regions common to both tasks. This similar pattern would be expected given both tasks require the verification of a complex equation, a cognitively demanding task; it also consistent with the dual task literature which states that dual tasks will have similar but more intense and dispersed regions of activity (Adcock et al., 2000; Bunge et al., 2000). Cortical regions seen to be active in both conditions and commonly associated with WM are DLPFC (BA 9 and 46), inferior frontal gyrus (IFG; BA 44), middle frontal gyrus (MFG; BA 6 and 9), precuneus cortex (BA 7), SPL (BA 7), IPL (BA 39 and 40), and ACC (BA 24/32). Additionally, one of the largest clusters of activation for both tasks encompassed the SMA and precentral gyrus.

DLPFC has typically been associated with overall executive functioning (Wager and Smith, 2003), but more recent evidence suggests that it is specifically involved in focusing attention on task relevant info in LTM (Abe et al., 2007). It is also reported to be involved in information source-monitoring (Wood et al., 2008). Kong et al. (2005) indicated that complex arithmetic procedures are supported by bilateral MFG and ACC activation. It has also been suggested that the ACC may play a greater role in executive functioning than the DLPFC (Kaneda and Osaka, 2008). Common to both tasks in our paradigm is that participants must be aware of

present task demands and must retrieve the appropriate response-set from LTM. Both tasks also require sub-vocal rehearsal; one of the largest clusters of activation during both tasks encompassed the SMA and precentral gyrus, areas believed to be responsible for verbal production and which may also contribute to executive functioning (Koelsch et al., 2009; Ridderinkhof et al., 2004).

Parietal regions are reported to be active during a number of different cognitive processes. A review of the precuneus by Cavanna and Trimble (2006) indicated that this region is involved in a diverse array of highly integrated functions, consistent with its role as an associative region and its high level of cortico-cortical connectivity. Wager and Smith (2003) indicate that BA7 is the most significantly activated region during the executive processes of updating, ordering, and manipulation. During equation verification, which involved two arithmetic calculations in our paradigm, these processes were necessary as participants decided how to approach the equations, manipulated the calculations within the equations, and updated portions of the equation with the proper solutions. Fehr et al. (2007) have also reported precuneus activation during both simple and complex arithmetic tasks, further supporting the idea that the precuneus is highly responsible for updating and manipulating information.

IPL activation during these two tasks likely relates to a few functions specifically associated with the IPL. Firstly, the supramarginal gyrus contributes to reading regardless of task demands (Stoekel et al., 2009). Arithmetic computation is a verbally based skill and should therefore have elicited activation in regions associated with reading since the equations were visually presented. Secondly, activity in the IPL is thought to increase as responses are made under uncertainty (Vickery and Jiang, 2009), possibly indicating it may additionally contribute to the error monitoring/checking roles typically assigned to the ACC and other frontal regions. During both tasks, participants had a limited amount of time, 4 s, to respond to a complex arithmetic equation. Therefore, it is likely that under various instances they were unsure of their responses by the time they were required to respond, at times resulting in incorrect responses. Lastly, the IPL, specifically the angular gyrus, is recruited during arithmetic fact retrieval (Dehaene and Cohen, 1997; Wood et al., 2008). Another possibility for IPL activation is that it forms part of the structural core of the human brain (Hagmann et al., 2008). Therefore it likely serves a facilitative, associative role during complex cognitive operations such as the ones performed in these tasks.

### *Differences in cortical activation between CWMS and TNWM tasks*

We contrasted the OSPAN and Arithmetic blocks to examine how encoding, maintenance, and the possible storage and retrieval of information to and from LTM manifest neurally during a CWMS task as compared to a TNWM task. The contrast revealed that, as expected, differences in neural recruitment between CWMS and equation verification were significant (Fig. 5). However, both tasks appear to recruit the same, or similar, cortical regions since differences were mainly evident in regions common to both tasks. This supports the idea that WM processes, regardless of their complexity, stem from a common network (e.g., Anurova et al., 2003; Cabeza and Nyberg, 2000; Linden, 2007). It is also possible that some of the regions within this network may assume further roles, e.g., aiding in the storage and retrieval of items to and from LTM as task complexity and interference increase.

During the OSPAN participants require a higher degree of executive control in order to switch between serial encoding and the additional processing task of equation verification, while also keeping track of an increasing number of task relevant items in WM. Participants also assumed WM loads for the to-be-remembered items that surpassed the average limit of WM capacity, currently thought to average around four items (Cowan, 2001). Under these conditions, it is evident that participants would benefit from increased WM

capacity. The DLPFC is thought to boost visuospatial WM capacity through top-down excitation of intraparietal sulcal circuits (Edin et al., 2009). This function of the DLPFC is thought not to be limited to visuospatial WM and likely occurs for a variety of cognitive functions. DLPFC activity has also been shown to be predictive of LTM formation through the binding of related items residing in WM (Blumenfeld and Ranganth, 2006). Bunge et al. (2001) found that DLPFC activity in the MFG, among other regions typically associated with WM, was significantly correlated with resolving task interference. More recent studies (e.g., Blumenfeld and Ranganath, 2007) have demonstrated that even more critical to the resolution of interference is the VLPFC. VLPFC is thought to aid in the controlled selection of items, and similarly, is thought to aid the formation of LTMs through controlled selection. These functions are critical during the OSPAN as the formation of proper LTMs becomes more crucial as set sizes increase.

In the previous section we outlined the possible role of parietal regions during both the OSPAN and Arithmetic tasks. We indicated that parietal regions are mainly involved in updating and manipulating the information currently in the focus of attention. A review by Koenigs et al. (2009) indicated that the SPL in particular may be responsible for these operations. The increased involvement of the SPL during CWMS provides further evidence for this role of SPL, as participants must update and possibly manipulate the retrieved to-be-remembered letter sets as more letters are presented. Successful updating will rely on the accuracy of the order in which the letters are kept in WM and retrieved from LTM. If participants make a discrepancy judgment and believe the ordering of the retrieved items is incorrect, the SPL may be recruited to rearrange the set based on an alternative representation.

#### *Hippocampal recruitment in CWMS and TNWM tasks*

We were particularly interested in the involvement of the hippocampus during CWMS, since the hippocampus has been traditionally associated with the formation and retrieval of long term memories (e.g., Davachi et al., 2006; Eichenbaum et al., 2007). Recent WM neuroimaging studies have indicated the involvement of the hippocampus during WM encoding, maintenance and, retrieval (e.g., Axmacher et al., 2009a, 2009b; Fletcher et al., 2003; Öztekin et al., 2009; Schon et al., 2009). Using intracranial EEG, Axmacher et al. (2007) demonstrated reduced hippocampus/MTL gamma power during maintenance of a single item, but increased power during maintenance of multiple items; fMRI data concurred with their intracranial EEG recordings. Later, Axmacher et al. (2009a, 2009b) also found MTL activation under low load visual WM conditions. However, one must take into account that even under “low load” conditions, complex visual stimuli, such as the faces used in the latter study, likely incur a high WM/attentional load due to the numerous features present in such stimuli. Öztekin et al., 2009 used an item recognition and judgment of recency task to show that the hippocampus, along with DLPFC and IFG, collectively support WM retrieval. Additionally, their data support the distinction between items maintained within and outside of the focus of attention, and argue that the mechanisms responsible for these distinctions are closely intertwined.

On the contrary, Zarahn et al. (2005) have argued that hippocampus activity is independent of WM load, or functioning, for familiar stimuli. They have argued this point based on a hippocampal activity pattern that follows an inverted-U in relation to WM load. However, an inverted-U shape is often shown for different regions of the brain in relation to WM load and is considered a standard aspect of proper WM functioning. For example, the inverted-U characteristic of brain function in relation to WM load is thought to be shifted in schizophrenia and is believed to explain their relatively poorer performance on measures of WM (e.g., Callicott et al., 2003). In a different vein, Meyer-Lindenberg et al. (2005) argue that hippocam-

pal formation activity is negatively correlated to that of DLPFC as WM load increases and therefore conclude that hippocampal formation activity is not necessary for WM. Additionally, they show that hippocampal formation activity deficiency in WM performance in schizophrenia patients may in part be due to functional decoupling between the hippocampus and DLPFC as WM load increases. Critical to the interpretation of these results is the fact that a 2-back n-back task was used rather than a CWMS task. Even though the n-back task is designed as a cognitively demanding task requiring high levels of attentional control and the updating of mental representations, it may more accurately represent an individual's immediate memory capacity rather than their WM capacity (Conway et al., 2005).

For our study, hippocampal voxel-wise ROI analysis indicated posterior bilateral hippocampal activity during the OSPAN. We also found similar bilateral hippocampal activity during the Arithmetic task. These findings indicate that Arithmetic and CWMS tasks both recruit the hippocampus for WM performance and at first glance suggest that hippocampus may be recruited for immediate memory functioning. However, studies of hippocampotomized patients have either shown no deficits, or deficits only at supra-span levels, on simple WM span tasks (e.g., Milner, 1972; Owen et al., 1996). Therefore, it is possible that some arithmetic operations recruit additional processes not required during sub-span simple WM span or TNWM tasks. There are indications that during more complex arithmetic problems, such as the large number multiplication or division problems found in our study, back up strategies are used to retrieve solutions to problems that are similar to the ones in question (Jost et al., 2009; Smith-Chant and LeFevre, 2003). For example,  $7 \times 9$  can be solved by retrieving the solution to  $7 \times 10$  and subtracting 7. For other problems, various back-up strategies may be used to retrieve or calculate information, and are cycled through while trying to identify the correct answer. Furthermore, even though it has traditionally been argued that the hippocampus is not necessary for semantic-fact retrieval from LTM, such as that required during arithmetic, recent studies suggest its involvement (e.g., Burianova et al., 2010; Hoscheidt et al., 2010; Ryan et al., 2008; Whatmough and Chertkow, 2007). Consequently, hippocampal activity during complex arithmetic operations may signal a role for the hippocampus as part of a temporary WM storage buffer for items retrieved from LTM not currently in the focus of attention. Axmacher et al. (2009a, 2009b) recently arrived at a similar conclusion and this idea is akin to Cowan's embedded processes model where items retrieved from LTM not currently in the focus reside in an activated, easily accessible state within LTM.

Support for the hypothesis that the hippocampus is involved in the maintenance of items during a CWMS task to a greater extent than during a TNWM task came from our OSPAN > Arithmetic contrast. This yielded a cluster of significantly greater activation in the right posterior hippocampus (Fig. 4). Mean peristimulus plots (Fig. 6) for the hippocampal ROIs indicate an initial bilateral peak after task onsets, possibly indicating a retrieval of task specific instructional sets, and a decrease in activity below baseline for the remainder of the tasks (30 s; 20 TRs). Peristimulus plots for voxels with intensity values in the upper 10% show above baseline activity levels for bilateral posterior hippocampi during OSPAN and Arithmetic (Fig. 6), with significantly greater activation in left posterior hippocampus versus right (Table 2).

These results indicate that the left hippocampus plays at least an equivalent or greater role than the right during WM encoding, maintenance, and updating. The difference between peak activity occurring in posterior hippocampi and mean activity for the whole hippocampi suggests a specialization of WM functioning within the posterior hippocampus. The overall decrease in mean bilateral hippocampal activation below baseline for both tasks may suggest possible resting state functions for anterior regions of the hippocampus. Recent studies of the brain's resting state networks have

implicated the hippocampus as part of some of these networks, specifically the default mode network (Buckner et al., 2008; Fransson and Marrelec, 2008; Frings et al., 2009). It is thought that the hippocampi and surrounding medial temporal structures play a key role in providing associational and relational information from memory to aid in mentalizing (Addis and Schacter, 2008; Buckner et al., 2008.)

Possible direct evidence for the idea that the hippocampus may be associated with LTM access during WM encoding and maintenance is seen in persitimus plots of the left hippocampus during OSPAN retrieval (time points 21–30). Mean hippocampus signal maintains an intensity similar to the signal during maintenance and encoding, while voxels in the upper 10% range decrease for the right hippocampus, and initially decrease then increase for the left hippocampus. Therefore, it is plausible that the developing signal within the hippocampus indicates increasing access to LTM for items displaced from the focus. Alternatively, this may indicate that the hippocampus is cycling through items in immediate memory, but the intact immediate memory performance in hippocampectomized patients suggests otherwise.

In general, these results provide support for the hippocampus' role in WM maintenance during a CWMS task above and beyond that in TNWM tasks. Given the coupling between hippocampal activity and LTM functioning, our findings are also suggestive of LTM functioning during WM maintenance of a complex WM span task. Pattern and intensity differences between the hippocampus as a whole and posterior regions suggest a specialization of function, such that posterior regions are directly involved in WM functioning. Lastly, the hippocampus may act as part of a temporary storage buffer by helping to hold information outside of the focus of attention in an activated state.

#### *Further support for the active maintenance and embedded processes models of WM*

The fronto-parietal network is often mentioned in the context of WM (e.g., Bledowski et al., 2009; Champod and Petrides, 2007; Colom et al., 2007; Vincent et al., 2008). Regressing the number of correct letter responses on the OSPAN > Arithmetic contrast gave us a further indication of the roles that frontal and parietal regions, along with the ACC, may play during WM encoding and storage of to-be-remembered items and indicated support for the embedded processes (Cowan, 1999, 2005) and active maintenance models (Unsworth and Engle, 2007b) of WM. Together, these models propose that frontal and parietal regions are highly interconnected during WM processes and the effectiveness of their interactions dictates WM capacity limits. Specifically, they suggest that the PFC is involved in monitoring and directing the attentional resources required during WM functioning and that IFG functioning in particular is critical to the retrieval of information in the face of interference (Jonides and Nee, 2006). Information storage and processing tasks, however, are not relegated to PFC regions, but rather information currently in the focus of attention is stored and manipulated in parietal regions. Additionally, it is suggested that the ACC acts a secondary monitor by biasing the degree of executive control exerted by the IFG.

Our preliminary, exploratory results indicated that activity in frontal/cingulate regions, including the DLPFC, IFG (pars opercularis), and the ACC, during WM encoding and maintenance, tended to positively correlate with number of correct letter identification responses, and that areas mainly in the parietal lobe, including the SPL, IPL, cuneal cortex, parietal operculum, and post-central gyrus, tended to negatively correlate with correct responses. If frontal and cingulate regions are involved in regulating the influence of interfering information it is probable they are working at a heightened level in individuals who are successfully filtering this information compared to those who are not. An effective, dual fronto-cingulate filter would then limit the amount of information entering into the

focus of attention and would help to reduce the information load parietal regions may have to engage or manipulate, thereby reducing parietal activation.

A similar view of frontal and parietal interaction was also recently espoused by Edin et al. (2009). Through a computational model, verified by analysis of actual fMRI data, they demonstrated that DLPFC boosts the visuospatial WM capacity of parietal regions through increased functional coupling between the regions. The middle and superior frontal gyri, which are thought to play a regulatory role in relation to the DLPFC, also evidenced activation consistent with a boosting function. Taken together, our findings and those of Edin et al. (2009) support the embedded processes and active maintenance models of WM. They indicate that frontal and cingulate regions play a role in attentional regulation/control, or enhancing WM capacity in parietal regions, while parietal regions play a role in storing and manipulating the contents in the focus of attention. Therefore, an individual's WM capacity can be said to be limited by the degree of interaction, or coupling, between frontal/cingulate and parietal regions.

To further constrain our exploratory analysis we performed a cluster-thresholded ROI analysis on these regions. This analysis yielded a bilateral cluster overlapping part of the ACC and the frontal pole was positively correlated with correct recall, while a cluster overlapping the right post central gyrus and SPL was negatively correlated with correct recall. Such findings are very promising because they suggest that an interaction between two of the regions believed to be most responsible for attentional control (ACC) and updating, ordering, and manipulation processes (SPL) may be most linked to the appropriate maintenance of information resulting in correct recall. The promising nature of our exploratory results warrant further investigation into the nature of successful encoding and maintenance during CWMS paradigms.

## **Conclusion**

Our fMRI results demonstrated that as expected, the OSPAN yielded greater activation than Arithmetic in regions typically associated with WM. Of greater consequence, the OSPAN recruited bilateral posterior hippocampi to a greater extent than Arithmetic while overall hippocampal activation decreased below baseline levels of activity during performance of both tasks. This suggests posterior hippocampal specialization during WM performance and further supplements the evidence presenting the hippocampal formation as part of the brain's default mode network. A rise in intensity signals from the left hippocampus during retrieval hint at the idea that LTM access occurs during encoding and maintenance of items presented in CWMS tasks. Such evidence calls for more in depth examination of CWMS tasks through neuroimaging, as they may provide crucial insight into the role of the hippocampus during WM functioning. High resolution neuroimaging studies have already alluded to the idea of encoding and retrieval specificity between the dentate gyrus, cornu ammonis regions, and the subiculum (Eldridge et al., 2005; Preston et al., 2010; Zeineh et al., 2003). Lastly, the linear increase in activity during the initial blocks of each run also warrants further exploration. We are not aware of any cognitive or physiological findings that may explain these trends, but can only speculate that they may be due to some form of habituation or task detection function exhibited by the hippocampi.

## **Acknowledgments**

We would like to thank the University of Georgia's BioImaging Research Center for providing the necessary imaging acquisition hours. We would also like to thank Kim Mason and Devin Smith for their assistance in acquiring MRI and behavioral data, and Brett Clementz, Jennifer McDowell, Chris Rorden, Dean Sabatinelli, and Nathan

Yansak for their excellent advice throughout the writing of this manuscript.

## References

- Abe, M., Hanakawa, T., Takayama, Y., Kuroki, C., Ogawa, S., Fukuyama, H., 2007. Functional coupling of human prefrontal and premotor areas during cognitive manipulation. *J. Neurosci.* 27, 3429–3438.
- Adcock, R.A., Constable, R.T., Gore, J.C., Goldman-Rakic, P.S., 2000. Functional neuroanatomy of executive processes involved in dual-task performance. *Proc. Natl Acad. Sci. USA* 97, 3567–3572.
- Addis, D.R., Schacter, D.L., 2008. Constructive episodic simulation: temporal distance and detail of past and future events modulate hippocampal engagement. *Hippocampus* 18, 227–237.
- Anurova, I., Artchakov, D., Korvenoja, A., Ilmoniemi, R., Aronen, H.J., Carlson, S., 2003. Differences between auditory evoked responses recorded during spatial and nonspatial working memory tasks. *Neuroimage* 20, 1181–1192.
- Atkinson, R.C., Shiffrin, R.M., 1968. Human memory: a proposed system and its control processes. In: Spence, K.W., Spence, J.T. (Eds.), *The Psychology of Learning and Motivation* (Volume 2). Academic Press, New York.
- Axmacher, N., Mormann, F., Fernández, G., Cohen, M., Elger, C., Fell, J., 2007. Sustained neural activity patterns during working memory in the human medial temporal lobe. *J. Neurosci.* 27, 7807–7816.
- Axmacher, N., Elger, C.E., Fell, J., 2009a. Working memory related hippocampal deactivation interferes with long-term memory formation. *J. Neurosci.* 28, 1052–1060.
- Axmacher, N., Haupt, S., Cohen, M.X., Elger, C.E., Fell, J., 2009b. Interference of working memory load with long-term memory formation. *Eur. J. Neurosci.* 29, 1501–1513.
- Baddeley, A.D., Hitch, G.J., 1974. Working memory. In: Bower, G.A. (Ed.), *Recent Advances in Learning and Motivation* (Vol. 8). Academic Press, New York, pp. 47–89.
- Bernstein, P.S., Scheffers, M.K., Coles, M.G., 1995. “Where did I go wrong?” A psychophysiological analysis of error detection. *J. Exp. Psychol. Hum. Percept. Perform.* 21, 1312–1322.
- Bledowski, C., Rahm, B., Rowe, J., 2009. What “works” in working memory? Separate systems for selection and updating of critical information. *J. Neurosci.* 29, 13735–13741.
- Blumenfeld, R.S., Ranganath, C., 2007. Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. *Neuroscientist* 213, 280–291.
- Blumenfeld, R.S., Ranganath, C., 2006. Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. *J. Neurosci.* 26, 916–925.
- Bor, D., Duncan, J., Lee, A.C., Parr, A., Owen, A.M., 2006. Frontal lobe involvement in spatial span: converging studies of normal and impaired function. *Neuropsychologia* 44, 229–237.
- Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S., Cohen, J.D., 2001. Conflict monitoring and cognitive control. *Psychol. Rev.* 108, 624–652.
- Buckner, R.L., Andrews-Hanna, J.R., Schacter, D., 2008. The brain's default network. *Anatomy, function, and relevance to disease.* *Ann. NY Acad. Sci.* 1124, 1–38.
- Bunge, S.A., Klingberg, T., Jacobsen, R.B., Gabrieli, J.D., 2000. A resource model of the neural basis of executive working memory. *Proc. Natl Acad. Sci. USA* 97, 3573–3578.
- Bunge, S.A., Ochsner, K.N., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 2001. Prefrontal regions involved in keeping information in and out of mind. *Brain* 124, 2074–2086.
- Bunting, M., 2006. The role of processing difficulty in the predictive utility of working memory span. *Psychon. B Rev.* 13, 998–1004.
- Burianova, H., McIntosh, A.R., Grady, C.L., 2010. A common functional brain network for autobiographical, episodic, and semantic memory retrieval. *Neuroimage* 49, 865–874.
- Cabeza, R., Nyberg, L., 2000. Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J. Cogn. Neurosci.* 12, 1–47.
- Callicott, J.H., Mattay, V.S., Verchinski, B.A., Marenco, S., Egan, M.F., Weinberger, D.R., 2003. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *Am. J. Psychiatry* 160, 2209–2215.
- Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* 129, 564–583.
- Chamod, A.S., Petrides, M., 2007. Dissociable roles of the posterior parietal and the prefrontal cortex in manipulation and monitoring processes. *Proc. Natl Acad. Sci. USA* 104, 14837–14842.
- Chein, J.M., Moore, A.B., Conway, A.R., 2010. Domain-general mechanisms of complex working memory span. *Neuroimage* 54, 550–559.
- Colom, R., Jung, R.E., Haier, R.E., 2007. General intelligence and memory span: evidence for a common neuroanatomic framework. *Cogn. Neuropsychol.* 24, 867–878.
- Conway, A.R., Engle, R.W., 1996. Individual differences in working memory capacity: more evidence for a general capacity theory. *Memory* 4, 577–590.
- Conway, A.R., Kane, M.J., Engle, R.W., 2003. Working memory capacity and its relation to general intelligence. *Trends Cogn. Sci.* 7, 547–552.
- Conway, A.R., Kane, M.J., Bunting, M.F., Hambrick, D.Z., Wilhelm, O., Engle, R.W., 2005. Working memory span tasks: a methodological review and user's guide. *Psychon. Bull. Rev.* 12, 769–786.
- Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. *Nat. Rev. Neurosci.* 3, 201–215.
- Courtney, S.M., Petit, L., Haxby, J.V., Ungerleider, L.G., 1998. The role of prefrontal cortex in working memory: examining the contents of consciousness. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 353, 1819–1828.
- Cowan, N., 1988. Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information-processing system. *Psychol. Bull.* 104, 163–191.
- Cowan, N., 1999. An embedded-processes model of working memory. In: Miyake, A., Shah, P. (Eds.), *Models of Working Memory*. Cambridge University Press, Cambridge, pp. 62–101.
- Cowan, N., 2001. The magical number 4 in short-term memory: a reconsideration of mental storage capacity. *Behav. Brain Sci.* 24, 87–185.
- Cowan, N., 2005. *Working Memory Capacity*. Psychology Press, New York.
- Daneman, M., Carpenter, P.A., 1980. Individual-differences in working memory and reading. *J. Verbal Learn. Verbal Behav.* 19, 450–466.
- Davachi, L., Maril, A., Wagner, A.D., 2006. When keeping in mind supports later bringing to mind: neural markers of phonological rehearsal predict subsequent remembering. *J. Cogn. Neurosci.* 13, 1059–1070.
- Dehaene, S., Cohen, L., 1997. Cerebral pathways for calculation: Double dissociation between rote verbal and quantitative knowledge of arithmetic. *Cortex* 33, 219–250.
- D'Esposito, M., Postle, B.R., Jonides, J., Smith, E., 1999. The neural substrate and temporal dynamics of interference effects in working memory as revealed by event-related functional MRI. *Proc. Natl Acad. Sci. USA* 96, 7514–7519.
- D'Esposito, M., Postle, B.R., Rypma, B., 2000. Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. *Exp. Brain Res.* 133, 3–11.
- Edin, F., Klingberg, T., Johansson, P., McNab, F., Tegner, J., Compte, A., 2009. Mechanism for top-down control of working memory capacity. *Proc. Natl Acad. Sci. USA* 106, 6802–6807.
- Eichenbaum, H., Yonelinas, A.P., Ranganath, C., 2007. The medial temporal lobe and recognition memory. *Annu. Rev. Neurosci.* 30, 123–152.
- Eldridge, L.L., Engel, S.A., Zeineh, M.M., Bookheimer, S.Y., Knowlton, B.J., 2005. A dissociation of encoding and retrieval processes in the human hippocampus. *J. Neurosci.* 25, 3280–3286.
- Engle, R.W., Kane, M.J., Tuholski, S.W., 1999a. Individual differences in working memory capacity and what they tell us about controlled attention, general fluid intelligence, and functions of the prefrontal cortex. In: Miyake, A., Shah, P. (Eds.), *Models of Working Memory*. Cambridge University Press, Cambridge, pp. 103–134.
- Engle, R.W., Tuholski, S.W., Laughlin, J.E., Conway, A.R., 1999b. Working memory, short-term memory, and general fluid intelligence: a latent-variable approach. *J. Exp. Psychol. Gen.* 128, 309–331.
- Fehr, T., Code, C., Herrmann, M., 2007. Common brain regions underlying different arithmetic operations as revealed by conjunct fMRI-BOLD activation. *Brain Res.* 1172, 93–102.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B., 1997. *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)*, Clinical Version. American Psychiatric Publishing, Inc., Arlington, VA.
- Fletcher, P.C., Stephenson, C.M., Carpenter, T.A., Donovan, T., Bullmore, E., 2003. Regional brain activations predicting subsequent memory success: an event-related fMRI study of the influence of encoding tasks. *Cortex* 39, 1009–1026.
- Fransson, P., Marrelec, G., 2008. The Precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. *Neuroimage* 42, 1178–1184.
- Frings, L., Schulze-Bonhage, A., Spreer, J., Wagner, K., 2009. Remote effects of hippocampal damage on default network connectivity in the human brain. *J. Neurol.* 256, 2021–2029.
- Gevins, A.S., Bressler, S.L., Cutillo, B.A., Illes, J., Miller, J.C., Stern, J., Rex, H.R., 1990. Effects of prolonged mental work on functional brain topography. *Electroencephalogr. Clin. Neurophysiol.* 76, 339–350.
- Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., Wedeen, V.J., Sporns, O., 2008. Mapping the structural core of human cerebral cortex. *PLoS Biol.* 6, e159.
- Hamidi, M., Tononi, G., Postle, B.R., 2008. Evaluating frontal and parietal contributions to spatial working memory with repetitive transcranial magnetic stimulation. *Brain Res.* 1230, 202–210.
- Hoscheidt, S.M., Nadel, L., Payne, J., Ryan, L., 2010. Hippocampal activation during retrieval of spatial context from episodic and semantic memory. *Behav. Brain Res.* 212, 121–132.
- Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage* 17, 825–841.
- Jonides, J., Nee, D.E., 2006. Brain mechanisms of proactive interference in working memory. *Neuroscience* 139, 181–193.
- Jonides, J., Marshuetz, C., Smith, E.E., Reuter-Lorenz, P.A., Koeppe, R.A., Hartley, A., 2000. Age differences in behavior and PET activation reveal differences in interference resolution in verbal working memory. *J. Cogn. Neurosci.* 12, 188–196.
- Jost, K., Khader, P., Burke, M., Bien, S., Rösler, F., 2009. Dissociating the solution process of small, large, and zero, multiplications by means of fMRI. *Neuroimage* 46, 308–318.
- Kane, M.J., Hambrick, D.Z., Conway, A.R., 2005. Working memory capacity and fluid intelligence are strongly related constructs: comment on Ackerman, Beier, and Boyle (2005). *Psychol. Bull.* 131, 66.
- Kane, M.J., Conway, A.R., Miura, T.K., Colflesh, G.J., 2007a. Working memory, attention control, and the N-back task: a question of construct validity. *J. Exp. Psychol. Learn. Mem. Cogn.* 33, 615–622.
- Kane, M.J., Conway, A.R., Hambrick, D.Z., Engle, R., 2007b. Variation in working memory capacity as variation in executive attention and control. In: Conway, A.R., Jarrold, C., Kane, M.J., Miyake, A., Towse, J. (Eds.), *Variation in Working Memory*. Oxford University Press, New York, pp. 21–48.
- Kaneda, M., Osaka, N., 2008. Role of anterior cingulate cortex during semantic coding in verbal working memory. *Neurosci. Lett.* 436, 57–61.

- Klein, K., Fiss, W.H., 1999. The reliability and stability of the Turner and Engle working memory task. *Behav. Res. Methods Instrum. Comput.* 31, 429–432.
- Koelsch, S., Schulze, K., Sammler, D., Fritz, T., Müller, K., Gruber, O., 2009. Functional architecture of verbal and tonal working memory: an fMRI study. *Hum. Brain Mapp.* 30, 859–873.
- Koenigs, M., Barbey, A.K., Postle, B.R., Grafman, J., 2009. Superior parietal cortex is critical for the manipulation of information in working memory. *J. Neurosci.* 29, 14980–14986.
- Kondo, H., Morishita, M., Osaka, N., Osaka, M., Fukuyama, H., Shibasaki, H., 2004. Functional roles of the cingulo-frontal network in performance on working memory. *Neuroimage* 21, 2–14.
- Kong, J., Wang, C., Kwong, K., Vangel, M., Chua, E., Gollub, R., 2005. The neural substrate of arithmetic operations and procedure complexity. *Cogn. Brain Res.* 22, 397–405.
- Lezak, M.D., Howieson, D.B., Loring, D.W., 2004. *Neuropsychological Assessment*, Fourth Edition. Oxford University Press, New York, pp. 359–363.
- Linden, D.E., 2007. The working memory networks of the human brain. *Neuroscientist* 13, 257–267.
- MacDonald, A.W., Cohen, J.D., Stenger, V.A., Carter, C.S., 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* 288, 1835–1838.
- McCabe, D.P., 2008. The role of covert retrieval in working memory span tasks: evidence from delayed recall tests. *J. Mem. Lang.* 58, 480–494.
- Meyer-Lindenberg, A.S., Olsen, R.K., Kohn, P.D., Brown, T., Egan, M.F., Weinberger, D.R., Berman, K.F., 2005. Regionally specific disturbance of dorsolateral prefrontal-hippocampal functional connectivity in schizophrenia. *Arch. Gen. Psychiatry* 62, 379–386.
- Miller, E.K., 2000. The neural basis of top-down control of visual attention in the prefrontal cortex. In: Monsell, S., Driver, J. (Eds.), *Attention and Performance*. Massachusetts Institute of Technology Press, Cambridge, MA, pp. 511–534.
- Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* 24, 167–202.
- Milner, B., 1972. Disorders of learning and memory after temporal lobe lesions in man. *Clin. Neurosurg.* 19, 421–446.
- Oberauer, K., 2002. Access to information in working memory: exploring the focus of attention. *J. Exp. Psychol.* 28, 411–421.
- Osaka, M., Osaka, N., Kondo, H., Morishita, M., Fukuyama, H., Aso, T., Shibasaki, H., 2003. The neural basis of individual differences in working memory capacity: An fMRI study. *NeuroImage* 18, 789–797.
- Owen, A.M., Morris, R.G., Sahakian, B.J., Polkey, C.E., Robbins, T.W., 1996. Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Brain* 119, 1597–1615.
- Owen, A.M., McMillan, K.M., Laird, A.R., Bullmore, E., 2005. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum. Brain Mapp.* 25, 46–59.
- Öztekin, I., McElree, B., Staresina, B.P., Davachi, L., 2008. Working memory retrieval: contributions of the left prefrontal cortex, the left posterior parietal cortex, and the hippocampus. *J. Cogn. Neurosci.* 21, 581–593.
- Öztekin, I., McElree, B., Staresina, B.P., Davachi, L., 2009. Working memory retrieval: contributions of the left prefrontal cortex, the left posterior parietal cortex, and the hippocampus. *J. Cogn. Neurosci.* 21, 581–593.
- Patenaude, B., Smith, S., Kennedy, D., Jenkinson, M., 2007. FIRST – FMRIB's integrated registration and segmentation tool. *Human Brain Mapping Conference*.
- Postle, B.R., 2006. Working memory as an emergent property of the mind and brain. *Neuroscience* 139, 23–38.
- Postle, B.R., D'Esposito, M., 1999. "What"–Then–"Where" in visual working memory: an event-related fMRI study. *J. Cogn. Neurosci.* 11, 585–597.
- Pratt, L.A., Brody, D.J., 2008. *Depression in the United States Household Population, 2005–2006*. U.S. Department of Health and Human Services. DHHS Publication (PHS) 2008–1209, Hyattsville, MD.
- Preston, A.R., Bornstein, A.M., Hutchinson, B., Gaare, M.E., Glover, G.H., Wagner, A.D., 2010. High-resolution fMRI of content-sensitive subsequent memory responses in human medial temporal lobe. *J. Cogn. Neurosci.* 22, 156–173.
- PST, 2006. E-Prime (Version 1.2.1.845). Psychology Software Tools, Pittsburgh.
- Ridderinkhof, K.R., Ullsperger, M., Crone, E.A., Nieuwenhuis, S., 2004. The role of the medial frontal cortex in cognitive control. *Science* 306, 443–447.
- Rorden, C., 2007. DCM2NII (Version October 7) [Computer software].
- Rowe, J.B., Toni, I., Josephs, O., Frackowiak, R.S., Passingham, R.E., 2000. The prefrontal cortex: response selection or maintenance within working memory? *Science* 288, 1656–1660.
- Ryan, L., Cox, C., Hayes, S.M., Nadel, L., 2008. Hippocampal activation during episodic and semantic memory retrieval: comparing category production and category cued recall. *Neuropsychologia* 46, 2109–2121.
- Schon, K., Quiroz, Y.T., Hasselmo, M.E., Stern, C.E., 2009. Greater working memory load results in greater medial temporal activity at retrieval. *Cereb. Cortex* 19, 2561–2571.
- Scoville, W.B., Milner, B., 1957. Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatr.* 20, 11–21.
- Smith, S.M., 2002. Fast robust automated brain extraction. *Hum. Brain Mapp.* 17, 143–155.
- Smith, E.E., Jonides, J., 1999. Storage and executive processes in the frontal lobes. *Science (New York, N.Y.)* 283, 1657–1661.
- Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 23 (Suppl 1), S208–S219.
- Smith-Chant, B.L., LeFevre, J., 2003. Doing as they are told and telling it like it is: self-reports in mental arithmetic. *Mem. Cogn.* 31, 516–528.
- Srimal, R., Curtis, C.E., 2008. Persistent neural activity during the maintenance of spatial position in working memory. *Neuroimage* 39, 455–468.
- Sternberg, S., 1966. High speed scanning in human memory. *Science* 153, 652–654.
- Stoeckel, C., Gough, P.M., Watkins, K.E., Devlin, J.T., 2009. Supramarginal gyrus involvement in visual word recognition. *Cortex* 45, 1091–1096.
- Toepfer, M., Gebhardt, H., Beblo, T., Thomas, C., Driessen, M., Bischoff, M., Blecker, C.R., Vaitl, D., Sammer, G., 2010. Functional correlates of distractor suppression during spatial working memory encoding. *Neuroscience* 165, 1244–1253.
- Turner, M.L., Engle, R.W., 1989. Is working memory capacity task dependent. *J. Mem. Lang.* 28, 127–154.
- Unsworth, N., 2010. On the division of working memory and long-term memory and their relation to intelligence: a latent variable approach. *Acta Psychol.* 134, 16–28.
- Unsworth, N., Engle, R.W., 2006. Simple and complex memory spans and their relation to fluid abilities: evidence from list-length effects. *J. Mem. Lang.* 54, 68–80.
- Unsworth, N., Engle, R.W., 2007a. On the division of short-term and working memory: an examination of simple and complex span and their relation to higher order abilities. *Psychol. Bull.* 133, 1038–1066.
- Unsworth, N., Engle, R.W., 2007b. The nature of individual differences in working memory capacity: active maintenance in primary memory and controlled search from secondary memory. *Psychol. Rev.* 114, 104–132.
- Unsworth, N., Heitz, R.R., Schrock, J.C., Engle, R.W., 2005. An automated version of the operation span task. *Behav. Res. Methods* 37, 498–505.
- Unsworth, N., Redick, T.S., Heitz, R.P., Broadway, J.M., Engle, R.W., 2009. Complex working memory span tasks and higher-order cognition: a latent-variable analysis of the relationship between processing and storage. *Memory* 17, 635–654.
- Van Vugt, M.K., Schulze-Bonhage, A., Litt, B., Brandt, A., Kahana, 2010. Hippocampal gamma oscillations increase with memory load. *J. Neurosci.* 30, 2694–2699.
- Vickery, T.J., Jiang, Y.V., 2009. Inferior parietal lobule supports decision making under uncertainty in humans. *Cereb. Cortex* 19, 916–925.
- Vincent, J.L., Kahn, I., Snyder, A.Z., Raichle, M.E., Buckner, R.L., 2008. *J. Neurophysiol.* 100, 3328–3342.
- Wager, T.D., Smith, E.E., 2003. Neuroimaging studies of working memory: a meta-analysis. *Cogn. Affect. Behav. Neurosci.* 3, 255–274.
- Wechsler, D., 2001. *Wechsler Test of Adult Reading*. The Psychological Corporation, San Antonio, TX.
- Wendelken, C., Bunge, S.A., Carter, C.S., 2008. Maintaining structured information: an investigation into functions of parietal and lateral prefrontal cortices. *Neuropsychologia* 46, 665–678.
- Whatmough, C., Chertkow, H., 2007. rCBF of the hippocampal complex covaries with superior semantic memory retrieval. *Behav. Brain Res.* 181, 262–269.
- Wood, G., Nuerk, H.-C., Moeller, K., Geppert, B., Schnitker, R., Weber, J., Wilmes, K., 2008. All for one but not one for all: how multiple number representations are recruited in one numerical task. *Brain Res.* 1187, 154–166.
- Woolrich, W.M., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M., Smith, S.M., 2009. Bayesian analysis of neuroimaging data in FSL. *Neuroimage* 45, S173–S186.
- Zarahn, E., Rakitin, B., Abela, D., Flynn, J., Stern, Y., 2005. Positive evidence against human hippocampal involvement in working memory maintenance of familiar stimuli. *Cereb. Cortex* 15, 303–316.
- Zeineh, M.M., Engel, S.A., Thompson, P.M., Bookheimer, S.Y., 2003. Dynamics of the hippocampus during encoding and retrieval of face-name pairs. *Science* 299, 577–580.