

Domain-general mechanisms of complex working memory span

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ABSTRACT

A new fMRI complex working memory span paradigm was used to identify brain regions making domain-general contributions to working memory task performance. For both verbal and spatial versions of the task, complex working memory span performance increased the activity in lateral prefrontal, anterior cingulate, and parietal cortices during the Encoding, Maintenance, and Coordination phase of task performance. Meanwhile, overlapping activity in anterior prefrontal and medial temporal lobe regions was associated with both verbal and spatial recall from working memory. These findings help to adjudicate several contested issues regarding the executive mechanisms of working memory, the separability of short-term and working memory in the verbal and spatial domains, and the relative contribution of short-term and long-term memory mechanisms to working memory capacity. The study also provides a vital bridge between psychometric and neuroimaging approaches to working memory, and constrains our understanding of how working memory may contribute to the broader landscape of cognitive performance.

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Introduction

Given its importance in so many mental aptitudes – reasoning, language comprehension, spatial visualization, problem solving, etc. – it is unsurprising that there exists a large neuroimaging literature focused on the nature of working memory (WM) and its neural underpinnings. By many accounts, this work has greatly informed current thinking regarding the structure and function of WM, and its position in the general architecture of human cognition (Kane and Engle, 2002; Owen et al., 2005; Postle, 2006; Smith, 2000). However, certain factors may limit the relevance of this large body of work to an understanding of WM's role in complex cognition. In the current paper we present a new fMRI WM paradigm designed to address these limitations. This paradigm replicates standard behavioral and imaging results, and yields novel fMRI findings regarding the domain-general processes involved in WM.

The neuroimaging and behavioral literatures on WM are disjointed for several reasons. First, prior neuroimaging studies have often utilized tasks that require only the passive storage of information in short-term memory (STM), and not the coordination of storage with additional processing demands. Yet it is the ability to maintain and

manipulate information in coordination with ongoing processing that is the very hallmark of WM (Baddeley and Hitch, 1974; Miller et al., 1960) and that distinguishes the complex working memory span (CWMS) tasks that yield the strongest correlations with complex cognition from other measures of short-term memory (Engle et al., 1999). Second, although a handful of prior neuroimaging studies has employed CWMS tasks (Bunge et al., 2000; Kondo et al., 2004; Osaka et al., 2003, 2004; Smith et al., 2001), all were conducted in only the verbal domain, thus leaving it indeterminate whether the observed brain activity reflected domain-specific or domain-general processing. It is important to make this distinction because psychometric data (based on individual differences in WM capacity) indicate that domain-general mechanisms of WM are most predictive of complex cognition (Kane et al., 2004). Third, many prior neuroimaging studies of WM have relied on item-recognition tasks, such as the Sternberg memory search task (Jonides et al., 1998) and the *n*-back task (Braver et al., 1997; Owen et al., 2005). Although a relatively small number of studies have required recall rather than recognition (Gilbert and Fiez, 2004; Osaka et al., 2004), very few studies have also included an analysis of neural activity during the recall period (cf. Chein and Fiez, 2001). This emphasis on recognition tasks, and on trial periods that precede retrieval, is unfortunate in light of recent work indicating that an important mechanism underlying individual differences in WM capacity is the ability to select and use retrieval cues to optimally focus memory search during recall (Unsworth and Engle, 2007a,b). The requirement for recall also more realistically reflects the complex cognitive behavior exhibited in such tasks as reading, reasoning, and problem solving, which all require the rapid recall of recently acquired knowledge. The present study reflects an effort to bridge the divide

Abbreviations: WM, working memory; STM, short-term memory; CWMS, complex working memory span; fMRI, functional magnetic resonance imaging; PFC, prefrontal cortex; ACC, anterior cingulate cortex; PPC, posterior parietal cortex; MTL, medial temporal lobe.

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between the neuroimaging and psychometric/behavioral literatures by addressing these earlier limitations.

The measurement of WM capacity

Variation in WM capacity across individuals correlates strongly with performance on a range of complex cognitive tasks (e.g., verbal SAT, Ravens Matrices, etc.). Through nearly 30 years of careful investigation, we and others (Bayliss et al., 2005; Conway et al., 2005; Engle et al., 1999; Miyake, 2001) have concluded that the most valid and reliable measures of WM capacity are CWMS tasks, such as reading span (Daneman and Carpenter, 1980) and operation span (Turner and Engle, 1989). In CWMS tasks, subjects remember a short stimulus list for later recall, and must simultaneously engage in a secondary “processing” task. CWMS tasks differ from traditional STM tasks, such as digit span and word span, in that they require the subject to shift attention away from each successive to-be-remembered stimulus in order to perform some other task. These tasks are thought to be a realistic reflection of WM in everyday cognition because they require maintenance of information in the face of, or in the service of, concurrent processing; the very definition of WM proposed by Miller et al. (1960) and Baddeley and Hitch (1974). Consistent with this view, CWMS tasks account for a very large proportion of the variation in individuals’ fluid intelligence and performance across a very wide range of complex cognitive tasks (for a meta-analysis, see Kane et al., 2005). Although other WM tasks involving the manipulation and updating of stored information have been used to explore the neural correlates of WM in prior research (e.g., N-back, tasks that require mental reordering of stimuli, etc.), few of these alternative WM assessments have been tested as predictors of individual differences in higher cognitive ability, and when tested, these tasks generally explain substantially less variance than do CWMS tasks (Kane et al., 2007). CWMS tasks are thus highly reliable and valid measures of WM capacity, ecologically valid, predictive of many other cognitive abilities, and consistent with the original definition of WM.

The demands of CWMS task performance can be decomposed into two phases: the first involving the period in which successive stimuli are encoded and maintained in coordination with the requirements of the secondary processing task – we refer to this as the Encoding, Maintenance, and Coordination, or EMC, phase; the second involving the period in which to-be-remembered items are retrieved and reported, typically through recall – we refer to this as the Recall phase.

Neuroimaging of CWMS

There have been only five published papers involving imaging of CWMS. The small size of this literature is surprising given the vast number of papers that have used these types of tasks in the psychometric literature to establish the relationship between WM and complex cognition. One of the few labs to administer CWMS in an imaging environment (Smith et al., 2001) noted this juxtaposition:

“...by and large the WM tasks used in neuroimaging are not the kinds of tasks that correlate with higher-level cognition. Thus, much of what we know about the neural bases of WM may not bear on the way in which WM is used in higher-level cognition” (p. 2095).

Neuroimaging studies using CWMS tasks, which *do* correlate with higher-level cognition, may thus be especially important in connecting the behavioral and neuroscientific findings on WM.

Unfortunately, it is somewhat difficult to summarize even the small body of prior CWMS imaging work due to fundamental differences in methodology. To begin, prior studies involving imaging

of CWMS have used somewhat varied measures of verbal CWMS (i.e., reading span, listening span, and operation span). Another problem is that the key fMRI contrasts have differed considerably across studies. For example, one approach (which we favor) is to contrast a CWMS condition (combined storage and processing) first with a processing-only condition, then separately with a storage-only condition, and to then take the conjunction of the two contrasts (Bunge et al., 2000). Another approach (Kondo et al., 2004; Osaka et al., 2003; Osaka et al., 2004) is to simply contrast the CWMS task with processing-only, but this necessarily confounds activity specific to the CWMS task with activity due to the storage component. Yet another approach (Smith et al., 2001) involves a contrast of the WM span condition with an average of the processing and storage components, but this approach may be flawed when regions active in storage- or processing-only do not reach threshold in averaging.

Another difference across experiments has been the response requirements, with different studies requiring serial recall (Osaka et al., 2003), cued serial recall (Bunge et al., 2000), order recognition (Smith et al., 2001), and forced-choice recognition (Kondo et al., 2004; Osaka et al., 2004). Also, the studies that did require recall did not analyze the data from the recall period.

Despite these differences in methodology, some consistencies have emerged. One universal finding is increased activity in lateral prefrontal cortex (PFC) in the CWMS condition relative to other conditions. Although some experiments have also implicated the anterior cingulate cortex (ACC) in CWMS (Kondo et al., 2004; Osaka et al., 2003, 2004), others have not (Bunge et al., 2000; Smith et al., 2001). Likewise, some experiments have found activity in posterior parietal cortex (PPC) in CWMS (Kondo et al., 2004; Osaka et al., 2004; Smith et al., 2001), while others have not (Bunge et al., 2000; Osaka et al., 2003). Despite the use of different tasks (listening span, reading span, and operation span), different response requirements (e.g., recall, cued recall, and recognition), different contrasts, and possible statistical power limitations, this set of findings does yield the basic prediction that the EMC phase of CWMS conditions should recruit lateral PFC, and possibly ACC and PPC areas.

Domain-general vs. domain-specific contributions of WM

The brain regions identified in neuroimaging studies using CWMS – lateral PFC, ACC, and PPC – are widely discussed as constituents of a domain-general cognitive control system that guides the selection and processing of mental representations and thus scaffolds controlled cognitive performance (Chein and Schneider, 2005; Duncan and Owen, 2000; Miller and Cohen, 2001; Schneider and Chein, 2003). Domain-general, as used in the neuroimaging and psychometric literatures, refers simply to involvement in tasks with varying material types. Despite the use of exclusively verbal tasks, activity in these regions during CWMS task performance has been interpreted as reflecting the engagement of domain-general, or executive, WM mechanisms. This interpretation is broadly consistent with psychometric data showing that shared variance across verbal and spatial measures of CWMS is highly predictive of individual differences in various measures of reasoning and fluid intelligence (Conway et al., 2003).

However, two contested issues in the psychometric literature are relevant to this interpretation, and to the present study. First, although much prior work (Conway et al., 2002; Daneman and Carpenter, 1980; Engle et al., 1999; Kane et al., 2004) establishes that verbal CWMS tasks more strongly predict cognitive ability than do verbal STM tasks, this distinction is less well established in the spatial domain. While some researchers have found spatial CWMS tasks to be more predictive than spatial STM tasks (Kane et al., 2004), others have not (Miyake et al., 2001). Second, the presumed domain-generality of “executive” WM resources has also been brought into question by conflicting psychometric findings. One hypothesis is that there is

indeed a unitary, domain-general component of WM, explaining why individual differences in spatial WM are strongly correlated with individual differences in verbal WM (Conway and Engle, 1996; Kane et al., 2004; Turner and Engle, 1989). By this account, one would expect that verbal and spatial CWMS tasks should engage overlapping (domain-general) neural resources. An alternative hypothesis is that there are separate executive WM resources for different types of information (MacDonald and Christiansen, 2002; Shah and Miyake, 1996). According to this latter view, which rejects the basic notion of domain-generality, one would expect distinct cortical regions to be activated by verbal and spatial versions of a CWMS task.

Short-term and long-term memory mechanisms underlying WM capacity

A further development in our current view of WM regards the relative contribution of short-term and long-term memory mechanisms to CWMS. While the terms “working memory” and “short-term memory” have often been used interchangeably, many recent studies indicate that WM and long-term memory tasks (e.g., episodic retrieval) tap into common neural mechanisms (Cabeza et al., 2002; Nee and Jonides, 2008; Ranganath et al., 2004; Talmi et al., 2005). These neuroimaging findings have motivated several memory theorists to revisit their assumptions regarding the relationships between short-term, long-term, and working memory (Baddeley, 2000; Cowan, 2008; Healey and Miyake, 2009; Unsworth and Engle, 2007a). Of direct relevance to the present work, Unsworth and Engle (2007a,b) have argued that there are two dissociable domain-general mechanisms that influence WM capacity; (1) a dynamic attention component that maintains a small amount of information in a transiently more accessible state (i.e., in STM), and (2) a search component, responsible for guiding a search through information that has been lost from the focus of attention and thus displaced into secondary (long-term) memory. According to this perspective, as a subject performs a CWMS task, the dynamic attention component is necessary during the EMC phase, to coordinate the processing and storage demands of the task and to maintain the to-be-remembered items in an active and accessible state. The search component is necessary during the Recall phase to support recovery of to-be-remembered items that have been lost from the focus of attention. While Unsworth and Engle do not provide a neural model, the dynamic attentional mechanisms described in their account are consistent with neuroanatomically motivated computational models of WM implicating the lateral PFC and ACC as regions involved in the active maintenance, updating, and monitoring of information in WM (Miller and Cohen, 2001; O'Reilly and Frank, 2006). The engagement of this active maintenance system is thus consistent with the reported increases in PFC and ACC activities in association with CWMS performance.

Unsworth and Engle further speculate that the medial temporal lobes (MTL) should be important for CWMS performance. Historically, the MTL has been associated specifically with long-term memory, in large part because damage to the MTL is associated with profound long-term memory deficits but typically leaves short-term memory intact (Squire and Schacter, 2002). Most neuroimaging studies of short-term and working memory have, consistent with this interpretation of the neuropsychological findings, failed to elicit activation of the MTL (Chein et al., 2002; Owen et al., 2005; Wager and Smith, 2003). There is evidence, however, that MTL structures may play a role in supporting WM encoding and maintenance when the memoranda are unfamiliar, complex, or require relational processing (Cabeza et al., 2002; Olson et al., 2006; Ranganath and D'Esposito, 2001). Unsworth and Engle's view further implicates the MTL in WM recall, even with simple and familiar stimuli, when the task demands exceed the limitations of active maintenance processes; as is the case for CWMS tasks. Specifically, Unsworth and Engle argue that the cue-

dependent search process elicited during recall relies on coordinated activity between PFC and MTL areas. This speculation is again consistent with computational models that explain both neural and behavioral findings by simulating the interaction between PFC and MTL in a variety of memory tasks (Polyn et al., 2009). These claims lead us to the previously untested prediction that the hippocampus and neighboring medial temporal cortices should be more strongly recruited during the recall period of a CWMS task than during the recall period of an STM span (storage-only) task (so long as the number of to-be-remembered items does not exceed the limited capacity of attention).

Novel CWMS paradigm for fMRI

To address the aforementioned limitations, and to support investigation of domain-general and long-term memory contributions to CWMS performance, we developed a novel CWMS paradigm adapted for use with fMRI. Beyond its incorporation of both verbal and spatial CWMS conditions and a recall procedure, our implementation involves two further important departures from prior neuroimaging studies. First, our paradigm used a fully crossed design which included both *same-domain* CWMS conditions (e.g., verbal storage combined with verbal processing) as well as *cross-domain* CWMS conditions (e.g., verbal storage combined with spatial processing). A few behavioral studies have manipulated and crossed both the storage and processing domains of WM span tasks (Bayliss et al., 2003; Shah and Miyake, 1996). The key behavioral result in these studies, which we used as a benchmark to validate our paradigm, was that interference effects were stronger in the same-domain tasks than in the cross-domain tasks (i.e., recall accuracy was lowest when the storage and processing were conducted in the same-domain).

Second, our CWMS conditions included an important change from prior implementations of the pacing of the processing component. A complication with prior neuroimaging studies of CWMS is that they have always presented the processing component for a fixed amount of time between each to-be-remembered item. For example, a single sentence in reading span was presented for 4 s (Osaka et al., 2004). The problem inherent with this approach is that subjects who process quickly have excess time to devote to the storage component of the task. Such fixed-pacing has been shown to undermine the strong correlation between CWMS performance and complex cognition in psychometric studies (Conway et al., 2005; Friedman and Miyake, 2004), likely because it encourages the engagement of domain-specific maintenance strategies (e.g., subvocal rehearsal). We addressed this dilemma by requiring subjects to make as many rapid forced-choice decisions as they could in each 4 s epoch of the processing task component. Designed this way, the processing components were still of fixed overall duration (4 s), which accommodates fMRI design considerations, but a subject's attention was continuously occupied for the entire duration of the processing component. Barrouillet, Camos, and colleagues have recently shown that CWMS tasks with this type of repetitive processing component are as predictive of cognitive ability as are traditional CWMS tasks (Lepine et al., 2005). By deploying a novel CWMS task tailored to the pragmatic constraints of fMRI experimentation, with both verbal and spatial materials and a recall procedure, the present study extends a small but promising foundation of prior neuroimaging work on the neural mechanisms underlying CWMS task performance.

Materials and methods

Subjects

Twelve right-handed, native English speaking, subjects (age range 19–24 years, 7 females) selected from the Princeton University

community took part in the fMRI experiment after providing written consent.

Behavioral procedures

Design

Two independent variables were manipulated, both within subjects: (1) processing component (spatial, verbal, and control), and (2) storage component (spatial, verbal, and control). This resulted in 8 different task conditions, with control/control being an empty cell in the design. The order of presentation of task conditions was pseudo-randomized across subjects.

Processing components

There were two processing tasks, lexical decision (LEX) and symmetry decision (SYM). Decisions in each task were indicated by button presses on an MRI compatible response unit held in the subject's left hand. In lexical decision, a string of letters was presented and the subject was asked to indicate whether the string formed a word or not by pressing the designated button. A pool of 200 letter strings, half of which were words, was sampled without replacement throughout the task. In the symmetry decision condition, cells of an 8×8 matrix were colored either black or white and the subject had to indicate whether or not the matrix was symmetrical about the vertical axis by pressing the designated response button. A pool of 200 matrices, half of which were symmetrical, was sampled without replacement throughout the task.

Storage components

There were two storage conditions, letters (LET) and locations (LOC), in which subjects attempted to maintain a sequence of 4 items for later recall. In the letter condition, a lowercase letter was presented in 24 point, white Geneva font, shown in the center of a black screen. The pool of sampled letters consisted of 16 consonants (b, c, d, f, g, j, k, l, m, n, p, s, t, v, x, and z). In the locations condition, one cell in a 4×4 matrix was highlighted in red. A given letter or location was never repeated within a given trial.

Trial conditions

There were 8 trial conditions involving various combinations of the processing and storage components (Fig. 1a). Four conditions were dual-task CWMS conditions (LEX-LET, LEX-LOC, SYM-LET, and SYM-LOC), and the other four were baseline conditions, involving either the processing component with no storage requirement (LEX, SYM) or the storage component with no processing requirement (LET, LOC).

Run and trial sequences

The entire session consisted of 8 "runs", with each run involving 8 trials. Each trial lasted 52 s, and included (Fig. 1b): an instruction period (2 s), four repetitions of the processing (4 s) and storage (1 s) elements ($4 \times (4 + 1) = 20$ s total), a recall period (8 s), feedback (2 s), and finally, a resting baseline period (20 s). Subjects recalled the to-be-remembered stimuli for each trial by selecting the appropriate cells in a 4×4 matrix using an MRI compatible mouse held in the right hand (resting on a lap desk positioned on the subject's lower abdomen). For LOC items, the locations in the 4×4 recall grid corresponded to the to-be-remembered locations. For LET items, the 16 letters used as possible stimuli throughout the experiment were re-presented in the 4×4 matrix (one letter per cell). The locations of the letters within the matrix shifted from trial to trial so that subjects could not adopt a spatial strategy to aid verbal recall. In both storage tasks, the subject had to click on the appropriate items in correct serial order.

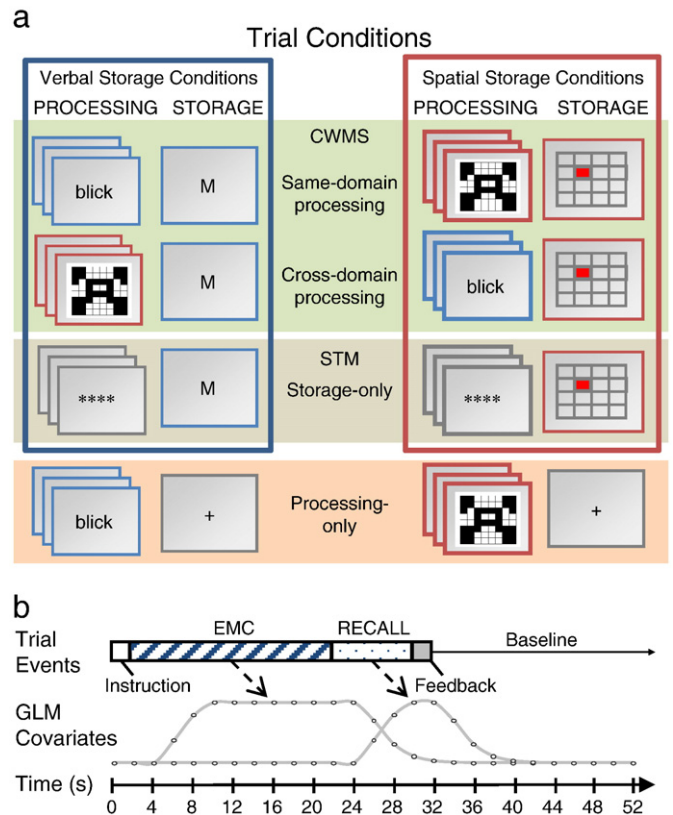


Fig. 1. (a) Schematic representation of the 8 trial types included in the fMRI design, and (b) timeline of trial events and the corresponding GLM model regressors.

fMRI procedures

fMRI data acquisition

Scanning was conducted on a 3-Tesla head-only Siemens Allegra magnet equipped with a standard transmit/receive head coil. Subjects lay supine, and stimuli were projected onto a visual display positioned inside the magnet's bore (viewed through a mirror placed above the subjects' eyes).

Prior to functional scanning, a high-resolution 3D structural volume (Siemens MPRAGE, 1 mm cubic voxels) was collected from each subject. Subsequent functional series were acquired using a T2*-weighted echo-planar imaging (EPI) sequence (TE = 30 ms, TR = 2 s, FOV = 200 mm, slice-thickness = 4.0 mm, flip angle = 90, in-plane resolution = 3.125 mm). Functional MRI data were collected in 8 separate runs corresponding to sequential runs of the cognitive paradigm.

fMRI data analysis

Data analysis was conducted off-line using AFNI (Cox, 1996). A series of preprocessing steps was employed to correct for artifacts and individual subject differences. Slice scan time correction using sinc interpolation was first applied to compensate for variation in acquisition timing. Then, images were adjusted for subject motion through a six-parameter rigid-body automated registration algorithm. Next, temporal high-pass filtering (.01 Hz cutoff) and 3D isotropic Gaussian smoothing (8 mm FWHM) were applied. In order to obtain group composite results, structural images from each subject were transformed into the space of the MNI stereotaxic atlas (Mazziotta et al., 2001), and the resulting transformation was applied to each subject's functional data.

Statistical analysis of the functional data employed least-squares estimation based on the general linear model (GLM), allowing fMRI BOLD signal changes occurring during particular temporal stages of

each trial to be assessed. The full model included separate covariates associated with the 20 s EMC period, and with the 8 s Recall period, for each of the eight trial conditions (Fig. 1b).

As detailed in the Results section, several statistical contrasts based on this full model were conducted. Each contrast was conducted via a whole-brain, voxel-wise, random-effects test based on the coefficients obtained from the GLM model. To reduce noise variance, individual subject runs producing outlier (>2 standard deviations) coefficient estimates were censored from further analysis. EMC regions were identified by using a conjunction approach in which the relevant CWMS condition (EMC regressor) was contrasted with its processing-only counterpart, then with its storage-only counterpart, and then a conjunction of the two independent contrasts was formed. Recall regions were identified by contrasting the relevant CWMS condition to its storage-only counterpart, using the recall period regressors. For each individual contrast, a voxel-wise False Discovery Rate (FDR) threshold of $q < .05$ was used, followed by the removal of small clusters ($<135 \text{ mm}^3$). A gray matter mask, which excluded voxels from outside of the brain, voxels in large white matter regions, and voxels from inside ventricles, was also applied.

Results

Behavioral results

Analysis of performance focused on recall accuracy (Fig. 2, see online supplementary material for complementary results obtained from analysis of accuracy and reaction time data associated with processing judgments). All null hypothesis significance tests were non-directional with $\alpha = .05$. Effect sizes for ANOVA results were calculated using the formula for partial eta-squared, η^2 , and for pairwise comparisons using Cohen's d . The numbers of stimuli correctly recalled per trial were averaged within condition (max. of 4, min. of 0). Recall accuracy means were then submitted to a 2×3 repeated measures ANOVA with 2 levels of storage (LET and LOC) and 3 levels of processing (LEX, SYM, and control). This analysis revealed a marginally significant main effect of storage condition, $F(1,11) = 4.44$, $p = .06$, $\eta^2 = .29$, a significant main effect of processing condition, $F(2,22) = 25.26$, $p < .05$, $\eta^2 = .70$, and a significant interaction, $F(2,22) = 15.51$, $p < .05$, $\eta^2 = .59$. The slight main effect of storage reflects the fact that average recall was slightly better in the dual-task LET conditions than in the dual-task LOC conditions. However, there were no differences between the verbal and spatial storage-only tasks, suggesting that they were equally demanding. The main effect of processing condition is unsurprising and reveals the fact that recall was better on trials with no processing decisions than with either SYM or LEX decisions ($p < .05$ for both pairwise comparisons to control; the pairwise comparison between SYM and LEX was not

significant, $p > .05$). The key predicted behavioral result is the significant interaction, which demonstrates greater interference when the processing and storage domains matched than when they were different. In order to test this prediction more directly, we conducted a planned contrast comparing average interference in same-domain conditions to average interference in cross-domain conditions. This contrast was significant, $t(11) = 4.08$, $p < .05$, $d = 1.18$, with greater same-domain interference ($M = .72$) than cross-domain ($M = .30$).

The behavioral results replicate previous experiments on cross-domain WM span, in which subjects experienced greater interference when processing and storage domains matched than when they were different. These results are reassuring because they suggest that our CWMS paradigm, developed to be compatible with the fMRI environment, is valid and produces the same signature behavioral results as traditional CWMS tasks. The behavioral effects also support more detailed interpretation of brain activation patterns, as we discuss below.

Imaging results

Separate analyses focused on two segments of task performance: 1) the EMC period, during which participants alternated between the processing and storage task components, and 2) the Recall period, during which participants attempted to serially recall the earlier presented storage items.

Encoding, Maintenance, and Coordination in WM

We identified EMC regions by using a conjunction approach in which the relevant CWMS condition (verbal or spatial) was contrasted with its processing-only counterpart, then with its storage-only counterpart, and then a conjunction of the two independent contrasts was formed (Bunge et al., 2000). This conjunction can be described as $[(\text{CWMS-P}) \cap (\text{CWMS-S})]$ and is consistent with the conjunction methodology suggested by Nichols et al. (2005). Each contrast was conducted via a whole-brain, voxel-wise, random-effects test based on the coefficients obtained from each subject for the EMC covariates in the GLM model. Regions showing significantly increased activity for the same-domain verbal CWMS condition (LET–LEX) relative to both verbal processing alone (LEX) and verbal storage alone (LET) are shown in Fig. 3a (left), and partially detailed in Table 1 (see Table 2, included in the online supplement, for a listing of domain-specific verbal CWMS sites).

As can be seen, the verbal CWMS condition was associated with increased activation in the bilateral PFC (BA 9/46), bilateral PPC (BA 7), and ACC (BA 32), among other regions. This pattern of activation essentially replicates the findings from prior neuroimaging studies of CWMS, all having used a same-domain verbal CWMS task (Bunge et al., 2000; Kondo et al., 2004; Osaka et al., 2003, 2004; Smith et al., 2001).

Results from the contrast of the analogous spatial CWMS condition (LOC–SYM) relative to its counterpart storage-only (LOC) and processing-only (SYM) conditions are also shown in Fig. 3a (right) and Table 1. While this conjunction identified some brain regions not detected in the verbal contrast (see Table 2, included in online supplement, for a detailing of domain-specific spatial CWMS sites), the overall pattern of activity was highly consistent with verbal CWMS; with bilateral PFC, bilateral PPC, and ACC regions again exhibiting increased engagement in the spatial CWMS task.

A central aim in analyzing the EMC period was to evaluate the domain-general nature of PFC, PPC, and ACC contributions to CWMS. In the independent analyses of the verbal and spatial CWMS conditions described above, each of these regions was found to exhibit significantly increased activity (see Table 1). While the exact clusters of activation differed slightly across the verbal and spatial CWMS tasks, in every case the peak of activation was within 15 mm (Euclidean distance) of the analogous activation peak, and the identified clusters were mostly overlapping across domains (i.e.,

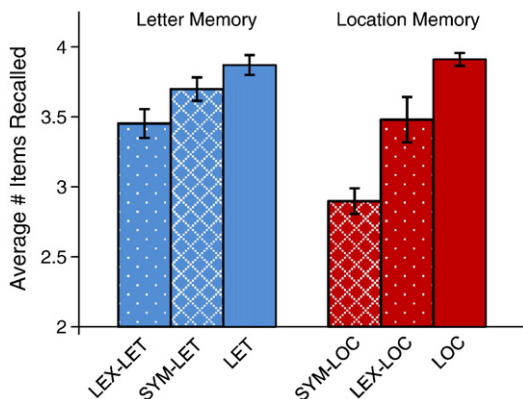


Fig. 2. Average number of letters or location recalled in the same-domain CWMS (LEX–LET and SYM–LOC), cross-domain CWMS (SYM–LET and LEX–LOC) and storage-only (LET and LOC) conditions.

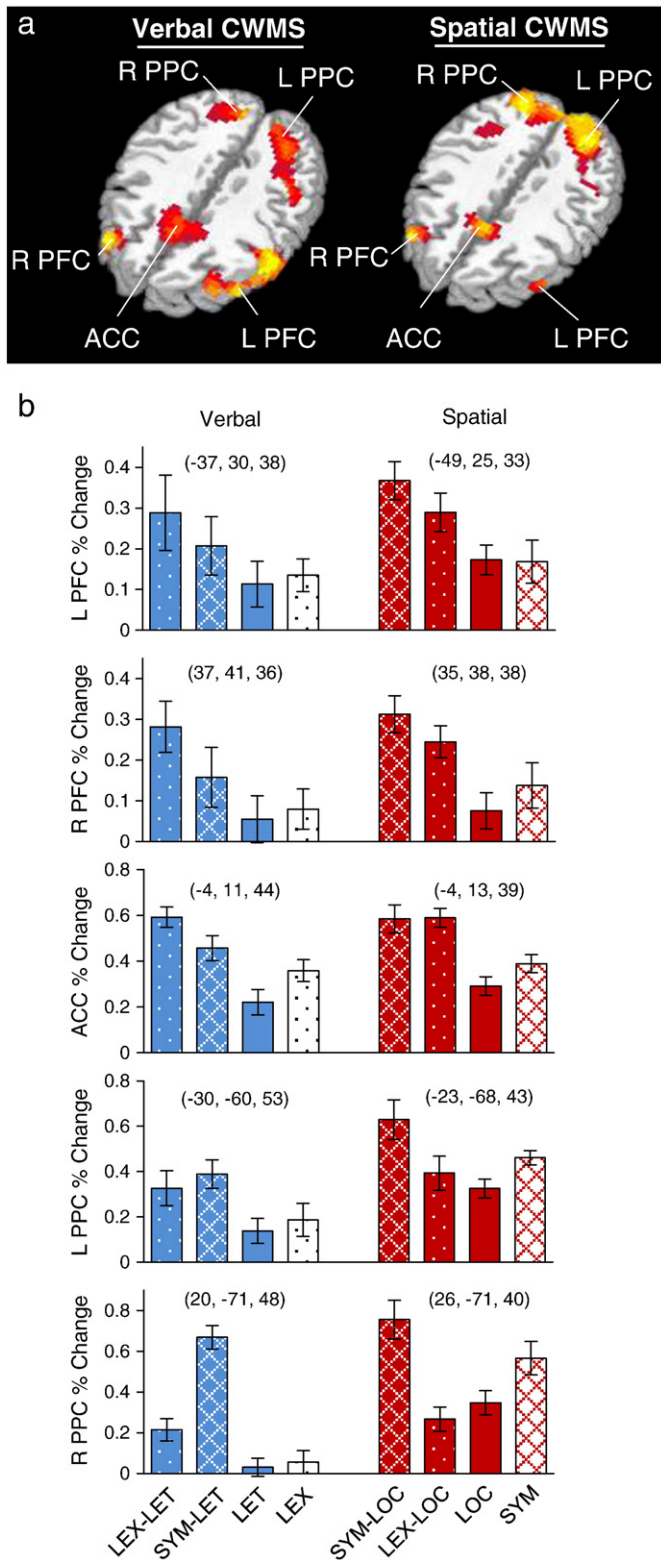


Fig. 3. (a) Regions exhibiting significantly increased activity during the Encoding, Maintenance, and Coordination (EMC) phase for same-domain verbal and spatial CWMS conditions, relative to the corresponding storage-only and processing-only controls, and (b) the patterns of signal change observed in each domain-general (overlapping) region across the 8 trial types.

included common voxels). Beyond these *a priori* regions, only the medial frontal gyrus (medial BA 6), left precentral gyrus (lateral BA 6) and left anterior insula (BA 13) exhibited common and significant

recruitment in both the verbal and spatial CWMS conditions during the EMC period.

To further elucidate the involvement of these brain areas, we examined average estimated percent signal change during the EMC period for the same-domain CWMS (LET–LEX and LOC–SYM), cross-domain CWMS (LET–SYM and LOC–LEX), processing-only (LEX and SYM), and storage-only (LET and LOC) conditions; shown in Fig. 3b. These activation patterns show that the PFC and ACC are most strongly engaged for same-domain CWMS conditions, but also exhibit significant recruitment in cross-domain CWMS, regardless of whether the to-be-remembered materials are verbal (letters) or spatial (locations). Overall, the general pattern of activity observed in PFC and ACC regions is entirely consistent with a domain-general interpretation of their involvement in CWMS task performance.

Activity in the PPC partially paralleled that observed in anterior regions, by again revealing increased engagement for same-domain CWMS relative to the corresponding processing- and storage-only controls. However, the right PPC was substantially more activated in the cross-domain SYM–LET condition (relative to LEX–LET), and strong recruitment of bilateral PPC regions was also apparent for the spatial control conditions (LOC and SYM). Moreover, the crossed LEX–LOC condition did not increase activity beyond the level observed for location memory alone (LOC). Thus, although the PPC shows significant involvement in CWMS for both the verbal and spatial domains, the interpretation of PPC activity must also account for additional sensitivity to spatial processing demands, as evidenced by the contribution that this region makes to single-task spatial storage (LOC), and non-mnemonic visuo-spatial processing (SYM).

Controlled retrieval from LTM

As discussed above, recent studies indicate that CWMS performance may be mediated not only by dynamic attentional processes, but also by controlled retrieval mechanisms used to recall information that has been displaced from active memory, but that can be recovered from LTM. To identify candidate regions involved in this putative controlled retrieval process, we contrasted recall period activity for the verbal and spatial CWMS conditions with their storage-only controls (LET–LEX vs. LET, LOC–SYM vs. LOC). Since subjects had nothing to recall in the processing-only conditions (LEX, SYM), these conditions were not included in the analysis of recall period activity.

Unsworth and Engle (2007b) predicted that recall in CWMS tasks might involve interactions between PFC and MTL mechanisms. These regions could thus be considered *a priori* regions of interest in our analysis of recall activity. Once again, the primary focus of analysis was to identify regions making a similar contribution to recall for both verbal and spatial domains (since the controlled retrieval process under investigation is presumably used to support recall regardless of content). Accordingly, active clusters were first identified by independent contrasts conducted within each domain, and then common sites of recall-related activity were identified. Regions exhibiting activity consistent with a domain-general contribution to recall (see Table 1) included bilateral PFC areas (BA 46/10, anterior and inferior to the loci implicated in active maintenance), the left posterior MTL, and few other regions. An analogous right lateralized MTL region displayed significant activity increases for verbal CWMS, but fell just below the statistical threshold for spatial CWMS (for a full list of domain-specific activations associated with the recall period, see Table 2 in the online supplement).

To further investigate MTL involvement in CWMS recall, and to determine the consistency of its recruitment across subjects, we inspected the position and pattern of MTL activity on a subject-by-subject basis. While this approach revealed some inter-individual variation in the position of activation, almost every individual (10 out of 12) exhibited significant MTL recruitment during CWMS recall, and the most common localization was in the posterior hippocampus and

Table 1
Peak coordinates and descriptive statistics for regions exhibiting domain-general engagement during the Encoding, Maintenance, and Coordination (EMC) and Recall phases of CWMS task performance.

| EMC Regions | Verbal conjunction | | | | | | Spatial conjunction | | | | | | Δ | |
|---------------------------|--------------------|-----|-----|-----|-----------------|-----------------|---------------------|-----|-----|-----|-----------------|-----------------|----------|-----------------|
| | BA | x | y | z | mm ³ | Z-score | Z-score | x | y | z | mm ³ | Z-score | | Z-score |
| | | | | | | LET–LEX vs. LET | LET–LEX vs. LEX | | | | | LOC–SYM vs. LOC | | LOC–SYM vs. SYM |
| L mid. frontal (L PFC) | 9/46 | −37 | 30 | 38 | 594 | 3.29 | 2.65 | −49 | 25 | 33 | 216 | 2.62 | 2.95 | 13.9 |
| R mid. frontal (R PFC) | 9 | 37 | 41 | 36 | 1350 | 2.51 | 2.11 | 35 | 38 | 38 | 864 | 2.85 | 3.09 | 4.1 |
| Ant. cingulate (ACC) | 32 | −4 | 11 | 44 | 1620 | 3.09 | 2.70 | −4 | 13 | 39 | 864 | 3.09 | 3.09 | 5.4 |
| L sup. parietal (L PPC) | 7 | −30 | −60 | 53 | 5535 | 3.67 | 2.88 | −23 | −68 | 43 | 5697 | 3.61 | 3.02 | 14.6 |
| R sup. parietal (R PPC) | 7 | 20 | −71 | 48 | 2565 | 2.44 | 3.09 | 26 | −71 | 40 | 2862 | 3.84 | 3.73 | 10.0 |
| L med. frontal | 6 | −2 | 2 | 52 | 3429 | 3.71 | 3.27 | −1 | 2 | 51 | 1728 | 3.73 | 2.62 | 1.4 |
| L precentral | 6 | −31 | −10 | 56 | 837 | 3.29 | 2.62 | −31 | −14 | 57 | 702 | 3.70 | 2.97 | 4.1 |
| L ant. insula | 13 | −31 | 19 | 9 | 540 | 3.35 | 3.29 | −32 | 17 | 11 | 135 | 3.55 | 2.42 | 3.0 |
| Recall regions | Verbal recall | | | | | | Spatial recall | | | | | | Δ | |
| | BA | x | y | z | mm ³ | Z-score | Z-score | x | y | z | mm ³ | Z-score | | Z-score |
| | | | | | | LET–LEX vs. LET | LET–LEX vs. LEX | | | | | LOC–SYM vs. LOC | | LOC–SYM vs. SYM |
| L mid./inf. frontal (PFC) | 46 | −41 | 41 | 9 | 162 | 3.15 | 2.90 | −42 | 45 | 13 | 2349 | 3.90 | 3.93 | 5.7 |
| R mid./inf. frontal (PFC) | 46 | 47 | 44 | 3 | 135 | 2.90 | 2.90 | 44 | 47 | 13 | 3780 | 3.93 | 3.93 | 10.9 |
| L hipp./parahipp. (MTL) | | −29 | −41 | 3 | 1539 | 3.89 | 3.89 | −26 | −43 | 3 | 189 | 3.02 | 3.02 | 3.6 |
| L ant. insula | 13 | −29 | 20 | −1 | 216 | 3.26 | 3.26 | −36 | 20 | −4 | 1863 | 3.89 | 3.89 | 7.6 |
| Thalamus | | 2 | −20 | 3 | 297 | 3.7 | 3.7 | 2 | −17 | 3 | 2295 | 3.22 | 3.22 | 3.0 |
| Midbrain/cerebellum | | 2 | −37 | −31 | 567 | 2.98 | 2.98 | −2 | −34 | −34 | 999 | 3.31 | 3.31 | 4.2 |

Notes: BA = Brodmann Area; x, y, z = MNI coordinates; Δ = Euclidean distance between verbal CWMS and spatial CWMS peaks.

immediately inferior portion of the parahippocampal gyrus. Left MTL activation sites from illustrative individual subjects are shown in Fig. 4, together with an averaged time-course of activity in this recall-related MTL site.

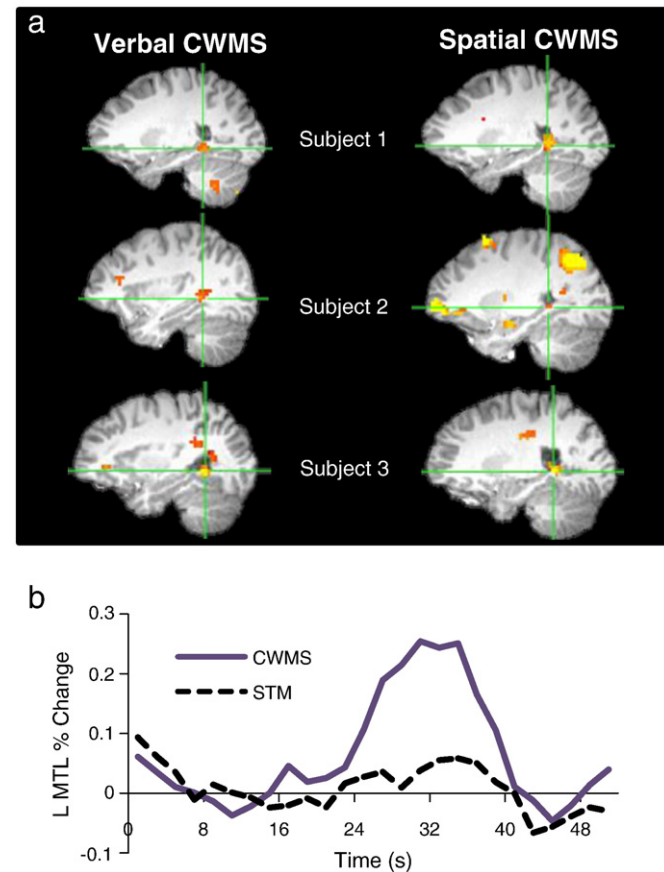


Fig. 4. (a) Significant regions of activity in the left posterior MTL during the recall period for verbal and spatial CWMS conditions relative to their corresponding storage-only controls, for 3 illustrative subjects, and (b) The average activation profile for recall-related activity in the left MTL for CWMS and storage-only (STM) conditions.

Discussion

Working memory is a central construct in cognitive neuroscience because it plays a critical role in such a wide range of cognitive behaviors, and because it is dependent upon the function of the prefrontal cortex (PFC), an area of the brain that has traditionally held a prominent position in neuroscientific accounts of why humans and non-human primates exhibit superior cognitive abilities relative to other species (Fuster, 1995; Goldman Rakic, 1998). The findings from the current experiment (1) replicate and extend previous neuroimaging results on verbal CWMS, (2) generalize these earlier findings into the spatial domain – thus demonstrating that the implicated brain regions support domain-general mechanisms of WM, and (3) provide a novel discovery with respect to the role of the MTL in CWMS – thus informing recent theoretical claims regarding the involvement of both short-term and long-term memory mechanisms in mediating the relationship between WM and other measures of cognitive function. Taken together, the findings provide a number of important insights regarding the nature of WM and the neural mechanisms underlying the predictive validity of CWMS tasks (i.e., why CWMS tasks are so successful in predicting individual differences across a wide range of cognitive tasks).

The finding of increased activity in the PFC and ACC during verbal CWMS replicates previous imaging studies (Kondo et al., 2004; Osaka et al., 2003, 2004). As well, we found significantly greater behavioral interference for same-domain than for cross-domain CWMS conditions, providing a replication of prior behavioral studies (Bayliss et al., 2003; Shah and Miyake, 1996). These replications give assurance that our novel CWMS paradigm affords a valid measure of WM that shares its essential features with the CWMS tasks used more broadly in the psychometric literature.

The inclusion of cross-domain CWMS conditions is also novel among neuroimaging studies, and affords unique insights into the specific mechanisms that link CWMS tasks and measures of higher cognitive function. In PFC (bilaterally) and ACC regions, activity for both same-domain verbal CWMS (LEX–LET) and cross-domain verbal CWMS (SYM–LET) conditions was significantly greater than in either control condition. Without data from the cross-domain condition (as was the case for all prior neuroimaging studies of CWMS), activity in these regions could be interpreted as a neural response to conflict produced when to-be-remembered information must compete for

representation with the products of the secondary processing task. For instance, the phonological representations of to-be-remembered letters (words in some prior studies) may compete directly with the phonological representations that underlie lexical decisions (verbal representations of sentences or equations in prior studies), thus producing a high conflict situation that elicits an increase in the recruitment of cognitive control areas (Botvinick et al., 2001). However, the observation that these regions are also significantly recruited when storage and processing involve highly disparate representations (as in the case of verbal storage with visuo-spatial processing) suggests that direct representational conflict may not be the principle source of PFC or ACC activity. Instead, we interpret increased PFC and ACC activities during CWMS conditions as indicating the engagement of attention control and selection mechanisms that directly support active maintenance in WM.

Moreover, while both verbal CWMS conditions produced significant increases in activity for these regions, stronger magnitude increases were consistently observed for the same-domain, relative to the cross-domain, condition.¹ This pattern provides still further traction in explaining PFC and ACC contributions to CWMS. Specifically, the pattern shows that the degree of activation in these regions is dependent on the magnitude of behavioral interference produced by the secondary task, not simply by the demand for dual-tasking or the coordination of task-switching (between storage and processing tasks). These findings inform an ongoing debate regarding the basis for the predictive validity of CWMS tasks. While we and others hold that CWMS tasks are predictive because they place strong demands on the domain-general attention control mechanisms that maintain information in an accessible state (Hudjetz and Oberauer, 2007; Kane et al., 2001), an alternative theory is that CWMS tasks are predictive because they index the ability to execute and coordinate task-switching operations (Towse et al., 2000). The finding that activity in these regions is contingent on the degree of interference produced by the secondary task, despite similar demands for task-coordination, seems to favor the controlled attention view over the task-coordination view.

A somewhat different pattern of activation was observed in the PPC, where the cross-domain SYM-LET task condition produced stronger bilateral PPC activity than did the same-domain LEX-LET condition (though again, both were significantly active above the storage-only and processing-only control conditions). This pattern of PPC engagement can be more fully understood in light of the findings from spatial CWMS conditions, which we consider next.

One of the central goals of the present study was to extend previous results by testing whether the brain regions implicated in verbal CWMS performance are also engaged by spatial CWMS tasks. By examining verbal and spatial CWMS activity using a common methodology, we hoped to demonstrate that regions previously implicated in only verbal CWMS performance in fact mediate domain-general WM processes. Consistent with this aim, we found that during the active maintenance phase, PFC, ACC, and PPC regions again exhibited increased activity when same-domain spatial CWMS (SYM-LOC) was contrasted with its counterpart storage-only (LOC) and processing-only (SYM) control conditions. While there was some variation in the precise set of voxels activated in the analogous verbal and spatial CWMS contrasts, the verbal and spatial CWMS clusters were in very close proximity to one another, included overlapping voxels, and evinced nearly identical patterns of activity across the conditions belonging to each domain. We believe that this overall

pattern of results strongly supports a domain-general interpretation of activity in these regions, and converges with psychometric data indicating that verbal and spatial WM tasks tap into shared underlying cognitive processes (Kane et al., 2004).

These results are generally *inconsistent* with the idea that WM supports cognition through primarily domain-specific mechanisms (MacDonald and Christiansen, 2002), or the idea that there are separate pools of executive resources for verbal and spatial WM (Shah and Miyake, 1996). Admittedly, one could still defend these latter domain-specific WM positions by looking beyond apparent commonalities and instead emphasizing observed differences between the verbal and spatial CWMS contrasts (e.g., the right PFC is more strongly active in spatial contrasts, the obtained clusters have slightly disparate peak locations and contain non-overlapping voxels, there are other regions that appear active in the contrast for only one domain). However, differences of this type would be expected even when attempting a replication of the identical task condition, due to the inherent noisiness of fMRI (Manoach et al., 2001; Noll et al., 1997), and taking this position necessitates that one ignore the overwhelmingly parallel findings from the verbal and spatial domain in *a priori* regions.

The data from the spatial CWMS conditions may also help adjudicate a further contested issue arising from conflicting psychometric studies. While there is general agreement that verbal CWMS tasks are typically more predictive of complex cognition than are traditionally used verbal STM tasks (e.g., digit span), there is less consensus regarding the dissociability of spatial CWMS from spatial STM span measures. In showing that spatial CWMS is distinguished neurally from spatial STM in much the same fashion as verbal CWMS is distinguished from verbal STM (i.e., stronger PFC and ACC activity in the contrast of CWMS to STM for both domains), the current findings seem to support models that dichotomize CWMS and STM in both the verbal and spatial domains (Kane et al., 2004). However, it is interesting and potentially informative that in at least one region implicated in domain-general WM processing, the PPC, spatial STM (LOC) and processing-only (SYM) conditions evoked activity increases that were similar (if not greater) in magnitude to those observed for the same-domain verbal CWMS condition (LEX-LET) and the cross-domain spatial CWMS condition (LEX-LOC). By contrast, verbal STM (LET) and processing-only (LEX) conditions evinced very little response from the PPC. These findings suggest the possibility that common recruitment of PPC mechanisms in both spatial STM and CWMS contexts may explain a higher degree of shared variance between these spatial conditions than is observed between the analogous verbal conditions.

Perhaps the most novel aspect of the current findings pertains to the observation of greater activity in the MTL in CWMS conditions relative to storage-only conditions during recall. This result was explicitly predicted by Unsworth and Engle (2007a) but had not been tested. Bilateral PFC activations (anterior to those observed for the active maintenance period) were similarly found to exhibit domain-general involvement in CWMS recall. These are important findings in that they suggest a key distinction between CWMS tasks and other WM tasks that have previously been used in imaging studies (and which typically do not show MTL activity). The findings are consistent with the proposal of a controlled search mechanism that is supported by interactions between lateral PFC and MTL processes, and are compatible with lesion and neurophysiology studies indicating that these same regions are critically involved in reactivating information from long-term memory (Ranganath and Rainer, 2003). Although information can be lost from its activated state over the course of CWMS performance, the surviving cues in primary memory may be sufficient to guide search through recent LTM representations, allowing for recovery of to-be-remembered traces. This guided search process appears to be orchestrated by domain-general MTL and anterior PFC mechanisms.

¹ Though not discussed in the Results section, we note that stronger PFC and ACC activations in the same-domain conditions (relative to the cross-domain conditions) were observed even when the clusters were defined by a conjunction contrast of the cross-domain CWMS conditions with their counterpart storage-only and processing-only conditions. In general, the cross-domain clusters identified in these regions comprised a sub-set of the voxels revealed in association with the same-domain CWMS contrasts.

Minimal engagement of the MTL in the storage-only (STM) conditions is addressed within this account by assuming that active maintenance processes (e.g., the focus of attention) offer sufficient capacity to maintain the integrity of the four presented items in an accessible form, thus obviating the need to conduct controlled search of LTM during recall. According to this explanation, one might predict that if the number of to-be-remembered items exceeds the capacity of the focus of attention (i.e., too many items are presented and the capacity of active maintenance is exceeded), or if the task design somehow discourages the utilization of active maintenance processes (e.g., speeded presentation, use of materials that are too complex or novel to actively maintain), then the MTL–PFC retrieval path would be necessary to recover items regardless of whether the task involves storage and processing (CWMS) or storage-only (STM). Indeed, consistent with these predictions, others have reported retrieval-based MTL involvement in short-term storage-only tasks that have these relevant characteristics, including the recall of primacy items from a long-list (12-item) recognition task (Talmi et al., 2005), the recognition of earlier serial items (the first 2 of 3) in a rapidly presented item-recognition test (Nee and Jonides, 2008), and the short-term recognition of complex visual scenes (Schon et al., 2009). These results, together with the present findings, thus lend support to the view that WM often involves controlled retrieval from long-term memory, as portayed in Unsworth and Engle's (2007a,b) framework.

In conclusion, neuroimaging research has greatly informed current theoretical accounts of WM and its place in cognition. However, several factors have limited the relevance of neuroimaging work for the question of how WM contributes to complex cognition. Here we present a new experimental procedure that addresses several of these limitations, replicates previous behavioral and imaging results, and provides novel data on the involvement of the PFC, ACC, and PPC in both verbal and spatial WM, and on the role of the MTL in WM. Future work will be needed to explore the relative importance of different brain regions for the performance of various types of WM tasks, and to explore how activity in these brain regions gives rise to individual differences in cognitive ability.

The following are the supplementary materials related to this article. Supplementary Material.

Table 2. Peak coordinates for regions exhibiting domain-specific engagement during the Encoding, Maintenance, and Coordination (EMC) and Recall periods of CWMS task performance.

Supplementary materials related to this article can be found online at [doi:10.1016/j.neuroimage.2010.07.067](https://doi.org/10.1016/j.neuroimage.2010.07.067).

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