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Eldreth, Dana A.; Patterson, Michael D.; Porcelli, Anthony J.; Biswal, Bharat B.; Rebbeschi, Donovan; and Rypma, Bart, "Evidence for Multiple Manipulation Processes in Prefrontal Cortex" (2006). *Psychology Faculty Research and Publications*. 86.

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Evidence for Multiple Manipulation Processes in Prefrontal Cortex

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Abstract

The prefrontal cortex (PFC) is known to subserve working memory (WM) processes. Brain imaging studies of WM using delayed response tasks (DRTs) have shown memory-load-dependent activation increases in dorsal

prefrontal cortex (PFC) regions. These activation increases are believed to reflect manipulation of to-be-remembered information in the service of memory-consolidation. This speculation has been based on observations of similar activation increases in tasks that overtly require manipulation by instructing participants to reorder to-be-remembered list items. In this study, we tested the assumption of functional equivalence between these two types of WM tasks. Participants performed a DRT under two conditions with memory loads ranging from 3 to 6 letters. In an “item-order” condition, participants were required to remember letters in the order in which they were presented. In a “reordering” condition, participants were required to remember the letters in alphabetical order. Load-related activation increases were observed during the encoding and maintenance periods of the order maintenance condition, whereas load-related activation decreases were observed in the same periods of the reordering condition. These results suggest that (1) the neural substrates associated with long-list retention and those associated with reordering are not equivalent, (2) cognitive processes associated with long-list retention may be more closely approximated by item-order maintenance than by reordering, and (3) multiple forms of WM manipulation are dissociable on the basis of fMRI data.

Keywords

Working memory, Prefrontal cortex, Delayed response task, fMRI

1. Introduction

Working memory (WM) refers to the ability to maintain information on-line over brief periods of time (Baddeley, 1986). Delayed response tasks (DRTs) have been used in combination with in vivo recording and imaging techniques to isolate the role of prefrontal cortex (PFC) in monkeys' and humans' WM task performance. Evidence from these studies suggests that PFC subserves working memory (e.g., Awh et al., 1996, D'Esposito et al., 1995, D'Esposito et al., 1998, D'Esposito et al., 1999a, D'Esposito et al., 1999b, Fuster and Alexander, 1971, Goldman-Rakic, 1987, Goldman-Rakic, 1995, Kubota and Niki, 1971, Manoach et al., 1997, Manoach et al., 2003, Narayanan et al., 2005, Petrides, 1996, Rypma and D'Esposito, 1999, Rypma et al., 1999, Rypma et al., 2002, Rypma et al., 2005, Cairo et al., 2004, Wiegiersma et al., 1990) and other higher cognitive processes (e.g., Duncan et al., 2000, Goel and Grafman, 2000, Just and Carpenter, 1992, Prabhakaran et al., 2001) that may depend on working memory.

Results from behavioral studies suggest that WM can be divided into separate components, including “slave-system” buffers for the short-term retention of small amounts of information and a supervisory attentional system or central executive that controls allocation of attention and coordinates information held in the slave-system buffers (Baddeley, 1986, Norman and Shallice, 1980). Behavioral research suggests that, whereas only slave-system buffers mediate low memory load (i.e., “subcapacity”) performance, both slave-system and executive processes mediate high memory load (i.e., “supracapacity”) performance. Baddeley and Hitch (1974), for instance, required participants to comprehend prose passages while holding zero, three, or six letters in WM. When they compared comprehension in the zero- and three-letter memory load conditions, performance did not change (73% and 70% accuracy, respectively). Significant decrements in prose comprehension were observed, however, when participants were required to hold six items in WM (60% accuracy). This result suggests that, when participants must carry out a complex task while retaining a subcapacity memory load, resources can be devoted to the more demanding task. When, however, memory loads approach the capacity of short-term storage (i.e., 4 items \pm 1; Cowan, 2001, Morey and Cowan, 2005), executive involvement is required.

Neuroimaging research in humans suggests that PFC may be subdivided to support slave-systems, mediated by ventral PFC, and executive systems, mediated by dorsal PFC. For instance, brief retention of small numbers of items (e.g., 2–3 letters) has consistently evoked ventral PFC activity (e.g., Paulesu et al., 1993, Awh et al., 1996, Rypma et al., 1999) in fMRI and PET studies. Retention of larger numbers of items evokes additional dorsal

PFC activity (e.g., D'Esposito et al., 1995; Petrides, 1996; Rypma et al., 1999; Rypma and D'Esposito, 1999; Rypma and D'Esposito, 2003).

The cognitive processes that may be reflected by these load-dependent neural activity changes are not yet known. Rypma et al. (2002) have speculated that such activation may be related to organization of supracapacity memory loads that permit efficient maintenance and retrieval of to-be-remembered information. Specifically, manipulation functions, mediated by dorsal PFC, operate at encoding to compress or “chunk” large amounts of information to accommodate the severe limits of WM storage capacity (Cowan, 2001; Miller, 1956; Rypma and D'Esposito, 1999; Rypma et al., 1999; Rypma and Gabrieli, 2001). This idea has received support from studies showing the regional specificity of load-dependent effects in a number of working memory studies (e.g., Braver et al., 1997; Rypma et al., 1999; Rypma et al., 2002; Rypma and D'Esposito, 1999; Cairo et al., 2004; Narayanan et al., 2005). Event-related studies suggest that such dorsal PFC activity occurs early in the DRT trial sequence (i.e., during encoding; Rypma, 2006; Rypma and D'Esposito, 1999; but see Narayanan et al., 2005; Veltman et al., 2003; Woodward et al., 2006).

Further support for the idea that dorsal PFC mediates covert manipulation of to-be-remembered information has been based on studies in which subjects are overtly instructed to reorder letters alphabetically (D'Esposito et al., 1999a; D'Esposito et al., 1999b; Postle et al., 1999). In one such study, participants encoded 5 letters in an initial 3-second encoding period. Participants were then given a cue, either to reorder or to maintain the order of a letter string over a delay interval. After the delay, participants verified whether or not a single letter–number pair veridically represented a list item in its correct position according to the cue. The results of these studies indicated delay-related dorsal PFC activation both when participants were required to alphabetize and when they were required to maintain the letters.

The common dorsal PFC activation observed in alphabetical reordering and high-load maintenance tasks have been taken to indicate that this region mediates the covert chunking processes necessary for long-list retention (e.g., Postle et al., 1999; Rypma, 2006). In this view, manipulation is regarded as a unitary construct that mediates both chunking and reordering. The validity of this inference would receive support if it were shown that similar load-related slope functions occurred in the same task periods (i.e., at encoding) in which they have been observed in maintenance-only DRTs. There are two limitations to the above-cited studies that obviate observation of such across-task similarities. First, load-related slope-effects have not been examined in these studies. Second, participants were only informed about the manipulation or maintenance requirement of any given trial at the onset of the delay period. Thus, it is not possible to assess precisely when in the trial sequence load-related manipulation effects might have occurred. While reordering is an important executive process, it is not thought to play a central role in WM organization mechanisms *per se* that people use to retain large amounts of information (e.g., Cowan, 2001).

Although the role of reordering in WM is unclear, order information does appear to play a central role in organization mechanisms that people use to retain large amounts of information. The cognitive processes related to item-order coding of to-be-remembered lists have been the focus of study over many years (Anderson and Matessa, 1997; Bower and Springston, 1970; Henson et al., 2000; Hitch et al., 1996; McElree and Doshier, 1993; Sternberg, 1967). Bower and Springston (1970), for instance, suggested that, when attempting to remember long lists of letters, individuals may chunk items according to their relative proximity. It may be that, in the absence of other mnemonic devices (e.g., government, corporate, or academic abbreviations), participants bind adjacent list items into approximately 3-item chunks (e.g., Bower and Springston, 1970). One implication of these results is that chunking, in the service of remembering long lists, may preserve item-order.

Studies of the neural basis of item-order coding have supported the notion of functional equivalence between chunking and item-order maintenance. Using a blocked DRT, Marshuetz et al. (2000) observed equivalent dorsal

PFC activation when subjects maintained the order of 5 letters and when they simply maintained their identity. Similarly, Henson et al. (2000) required subjects to view a 6-item list of serially presented letters. In a “sequence-probe condition,” subjects viewed letter strings immediately after list presentation and determined if they represented the same letters in the same order as those seen at the beginning of the trial. In a “letter probe condition,” subjects viewed a single letter after list presentation and determined if it represented one of those seen at list presentation. Similar to the Marshuetz et al. (2000) study, comparison of activation between these two conditions indicated equivalent dorsal PFC activation in sequence-probe and letter-probe conditions. These null findings lend some support to the idea of functional equivalence between item-identity maintenance and item-order maintenance. The relative similarity of the two kinds of tasks, however, may have encouraged the use of similar strategies in both tasks.

In the present study, we sought stronger evidence that item-order maintenance more closely approximates the processes associated with long-list retention. Our strategy was to compare neural activity during item-order maintenance and reordering. Based on our literature review, we expected to see patterns of PFC activation in item-order maintenance that were similar to those observed during simple maintenance, but different from those observed during reordering.

We hypothesized that load-related PFC activity changes during verbal DRT performance (such as those observed by Rypma and D'Esposito, 1999) are more closely related to chunking of adjacent list items than they are to reordering of stored items. To test this hypothesis, we parametrically varied WM load (cf. Braver et al., 1997, Kane and Engle, 2003, Sternberg, 1966) while subjects performed item-order and reordering DRTs. We predicted that task and memory load would differentially affect neural activity. Specifically, we predicted that activation during order maintenance would show WM load-related increases only in dorsal PFC activation during early portions of the task. Such load-related effects, we hypothesized, reflect chunking operations, not reordering. Thus, we did not expect load-related activation increases at encoding in the reordering task. To test these predictions, we used event-related methodology (unlike the previous studies) to allow for observation of the temporal dynamics of brain activity associated with item-order coding and reordering.

In the present study, participants performed DRTs under two conditions. In the “Item-order” condition, participants were required to encode letter lists in the order in which they appeared. During the probe period, they were asked to verify if a single letter–number combination veridically indicated a letter that appeared at encoding and its list position. In the “Reordering” condition, participants were required to alphabetize letter lists. During the probe period, they were asked to verify if a single letter–number combination represented a letter that appeared at encoding and its alphabetical list position (see Fig. 5; Postle et al., 1999). With this procedure, we directly compared PFC activity related to order maintenance (i.e., the “Item-order” condition) and that related to reordering (i.e., the “Reordering” condition) to ascertain whether task and memory load would show interactive effects on neural activity.

2. Results

2.1. Behavioral data

Reaction time (RT) data, shown in Fig. 1A, indicated that participants were slower in the Reordering than in the Item-order condition [$F(1,12) = 9.2, p < 0.01, \text{MSE} = 41807.5$]. RT increased with increasing memory set-size [$F(1,12) = 19.5, p < 0.0001$]. A 2 (Task-type) \times 4 (Memory-load) interaction was not significant, $F < 1$. Accuracy data, shown in Fig. 1B, indicated that participants performed with equivalent accuracy in the Reordering and Item-order condition, $F < 1$. Accuracy decreased with increasing memory set size [$F(1,12) = 19.5, p < 0.0001$]. The Task-type \times Memory-load interaction was not significant [$F(1,12) = 2.6, p < 0.14, \text{MSE} = 0.001$]. Participants were more accurate on match trials (86%) than catch trials (68%) in the Item-order condition (according to Mann–

Whitney, $p = 0.0007$). Participants' accuracy on match trials (81%) and catch trials (77%) in the Reordering condition was not different. RT data indicated that subjects performed match trials (1665.10 s) faster than catch trials (2137.18 s) for the Item-order condition $p = 0.002$ and participants were also faster on match trials (1785.61 s) than catch trials (2061.18 s) for the Reordering condition $p = 0.04$. Thus, performance data showed no Task-type \times Memory-load interactions. The same patterns were not observed, however, in the fMRI data.

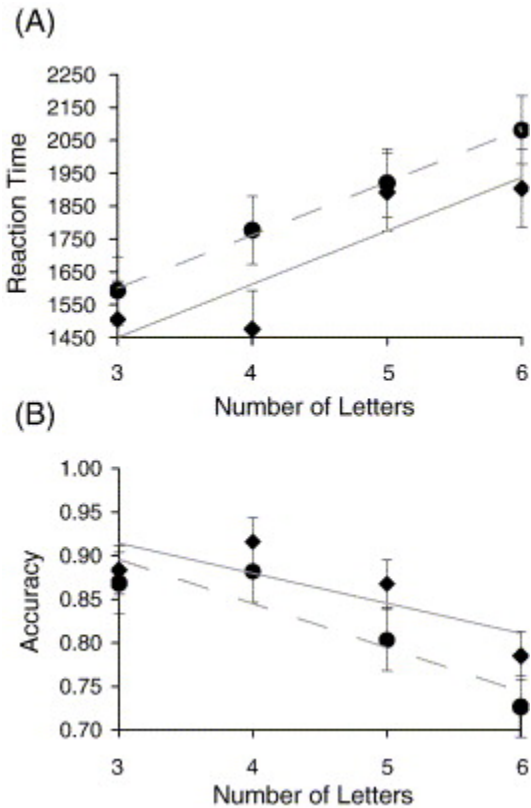


Fig. 1. (A) Mean RT for the retrieval period for each memory load, correct trials only. (B) Mean accuracy for the retrieval period for each memory load. Item-order condition results are represented in diamonds and solid lines, and the Reordering condition results are represented in circles and dotted lines.

2.2. fMRI data

2.2.1. Task- and load-dependent activity differences

Random effects analyses of map-wise data yielded activation in regions where they have been observed before (e.g., Curtis and D'Esposito, 2003, Rypma et al., 1999, Rypma and D'Esposito, 2000 Table 1A, Table 1B). Figs. 2A and B show medians of individual subjects' activation across WM load conditions in PFC ROIs during the Item-order and Reordering tasks. The results in Fig. 2 indicate the presence of substantial variability between subjects. Indeed, standard errors across these conditions ranged from 0.25 to 0.59. Fig. 2 also reveals individual differences in both positive and negative activation. The functional properties of negative activation are poorly understood, but connectivity studies suggest that patterns of both positive and negative activity are critical for understanding the neural architecture of cognitive task performance (Shmuel et al., 2006). This variability is due to subject-dependent activity differences (Rypma et al., 2002) that we will analyze after we examine task- and load-related variability. In order to minimize the influence of this intersubject variability in each region, we converted each subject's t -values to z -scores (separately for each load condition and task period) by subtracting the subject's within-region mean and scaling that difference by the subject's within-region standard deviation. This linear transformation reduced the range of standard errors across conditions to 0.20, maintained ordinal differences between load conditions and subjects, and permitted comparisons between memory load conditions

within each task period. This enabled us to answer the principal questions of the present report regarding task- and load-dependent effects. Because we hypothesized task differential memory load effects, we conducted planned comparisons to test for interactions between Task-type and Memory-load in each PFC ROI. Results are presented in Figs. 3A–F.

Table 1A. Regions of significant activation in each task period of Reordering task

Lobe	Hemisphere/Brodmann area	Activation region
<i>Encoding</i>		
Frontal	LR6	Precentral, middle, medial
	LR8	Superior, medial
	LR9, L10, L46	Superior, middle
	LR44, LR45, LR47	Inferior
Insula	LR	
Parietal	LR7	Superior
	LR39	Angular, inferior parietal lobule
	LR40	Supramarginal, inferior
Temporal	L21	Inferior
Occipital	LR17	Cuneus, inferior
	LR18	Lingual, middle
	LR19	Fusiform, lingual, superior, inferior
Cingulate	LR23, 24	Middle
Subcortical		LR caudate, L hippocampus, LR globus pallidus, R thalamus, LR putamen
<i>Maintenance</i>		
Frontal	LR6	Precentral
	LR10	Superior
	L44	Inferior
	R9, R46	Middle
Parietal	LR7	Superior
	LR40	Inferior
<i>Retrieval</i>		
Frontal	LR6	Precentral
	LR8, LR10, LR11	Superior, medial
	LR9, LR46	Middle
	LR44, LR45, LR47	Inferior
Parietal	LR7	Superior
	LR39	Angular, inferior
	LR40	Supramarginal, inferior
Temporal	LR20, L21, LR37	Inferior, middle
	L38	Superior
Occipital	LR17	Cuneus, inferior
	LR18	Lingual, middle
	LR19	Lingual, inferior, superior
	LR31	Precuneus
Cingulate	LR32	Anterior
Subcortical		LR caudate, LR thalamus

Table 1B. Regions of significant activation in each task period of Item-order task

Lobe	Hemisphere/Brodmann area	Activation region
<i>Encoding</i>		
Frontal	LR4, LR6	Postcentral, precentral
	LR9	Middle
	LR10	Superior
	LR44, L45, LR47	Inferior
Insula	LR	
Parietal	LR7	Superior
	L39	Angular, inferior
	LR40	Supramarginal, inferior
Temporal	L21	Middle
	L22	Superior
Occipital	LR17	Lingual, inferior
	LR18, LR19	Cuneus, fusiform, superior, inferior, middle
Cingulate	LR32	Anterior
	LR23, LR24	Middle
	L31	Posterior
Subcortical		LR caudate, L hippocampus, LR globus pallidus, LR thalamus, LR putamen
<i>Maintenance</i>		
Frontal	LR6	Precentral
	LR9, LR46	Middle
	L8, L10	Superior
	L44, R47	Inferior
Parietal	LR7	Superior
	L39	Angular, inferior
	LR40	Inferior
Temporal	L22, L42	Superior
Occipital	L18	Lingual
Subcortical		LR caudate, LR thalamus, L putamen
<i>Retrieval</i>		
Frontal	LR4, LR46	Postcentral, precentral
	LR9	Middle
	LR8, LR10	Superior, medial
	LR44, LR45, LR47	Inferior
Parietal	LR7	Superior
	LR39	Angular, inferior, middle
	LR40	Supramarginal, inferior
Temporal	L21, LR37	Middle
	LR22, L42	Superior
Occipital	LR17	Cuneus, inferior
	LR18	Lingual, middle
	LR19	Lingual, inferior, superior
	LR31	Precuneus
Cingulate	LR32	Anterior
	R23, LR24	Middle

	R29, R30	Posterior
Subcortical		LR caudate, L hippocampus, LR globus pallidus, LR thalamus

Note. Listed regions are those that were significant at $p < 0.01$, uncorrected.

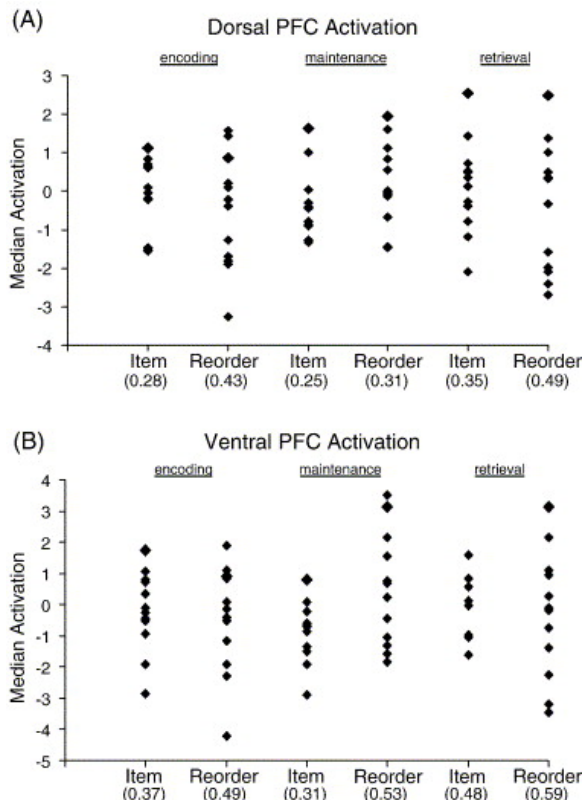


Fig. 2. (A–B) Median activation (t -values) for individual subjects in (A) dorsal PFC and (B) ventral PFC. Item-order has been abbreviated as “Item” and Reordering has been abbreviated as “Reorder.” Regional standard errors of the mean are in parentheses below each abbreviation.

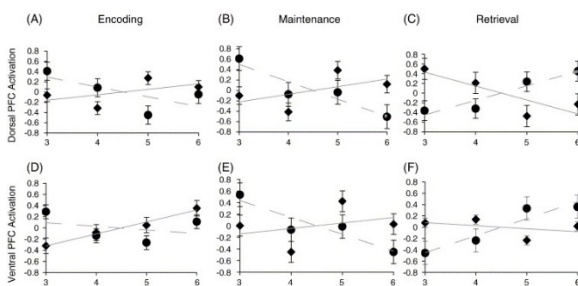


Fig. 3. (A–F) Z-standardized fMRI signal (t -values) from dorsal and ventral PFC during encoding, maintenance, and retrieval periods for each memory load (3–6) in the Item-order condition (diamonds, solid line) and the Reordering condition (circles, dotted line). Regression lines have been fit to the data points to illustrate interactions. (A) Dorsal PFC activation at encoding, (B) dorsal PFC activation at maintenance, (C) dorsal PFC activation at retrieval, (D) ventral PFC activation at encoding, (E) ventral PFC activation at maintenance, (F) ventral PFC activation at retrieval.

2.2.2. Dorsal PFC

In dorsal PFC, Encoding period activity increased with increasing Memory-load in the Item-order task, but decreased with increasing Memory-load in the Reordering task. The planned test consisted of a 2 (Task-type) \times 4 (Memory Load) ANOVA. The planned test indicated a significant Task-type \times Memory Load interaction $F(1,11) = 5.4$, $p < 0.04$, $MSE = 1.01$. Distribution-free tests for one-sample location indicated

significant activation differences between tasks in the 5-letter memory load condition (Hollander and Wolfe, 1999). Delay period activity showed similar patterns to that of the Encoding period, and the Task-type \times Memory-load interaction was similarly significant $F(1,11) = 10.31, p < 0.004, MSE = 0.78$. Distribution-free tests located significant activation differences between tasks in the 3-letter and 5-letter memory load conditions. Retrieval period activity showed the opposite pattern. Activation increased with increasing Memory-load during the Reordering task but decreased during the Item-order task. The planned test was significant, $F(1,11) = 8.2, p < 0.02, MSE = 0.83$. Distribution-free tests located significant activation differences between tasks in the 3-, 4-, 5-, and 6-letter memory load conditions. Thus, the prediction of differential task and memory load effects was supported (Figs. 3A–C).

2.2.3. Ventral PFC

In ventral PFC, Encoding period activity increased with increasing Memory-load in the Item-order task but not in the Reordering task. The Task-type \times Memory-load interaction was not significant $F(1,11) = 2.2, p < 0.16, MSE = 1.03$. Delay period activity decreased in the Reordering condition but not in the Item-order condition. The interaction of Task-type and Memory-load was significant, $F(1,11) = 5.2, p < 0.04, MSE = 0.85$. Distribution-free tests located significant activation differences between tasks in the 5-letter Memory-load condition. Retrieval period activity increased with increases in Memory-load in the Reordering task but not in the Item-order task. The interaction of Task-type and Memory-load was not significant $F(1,11) = 3.5, p < 0.09, MSE = 1.1$. Thus, counter to our prediction, differential task and memory load effects were observed during the maintenance period in ventral PFC (Figs. 3D–F).

2.2.4. Subject-dependent activity differences

We observed considerable subject-dependent variability in these data. In previous studies, this variability has been effectively accounted for by individual subject performance (e.g., Rypma et al., 2002). In order to examine subject-dependent activity differences, we conducted tests to determine the extent to which subjects' processing speed accounted for neural activity. These tests involved regression of individual subjects' RT slopes on their non-standardized fMRI activation data. Table 2A, Table 2B show the normalized regression coefficients that characterize the relationship between each subject's RT slope and regional activation in the Item-order and Reordering conditions. In the Item-order condition, regression analyses indicated a strong correlation between retrieval activity and RT slope that accounted for 61% of the variance. In the Reordering task, regression analyses indicated a marginally significant relationship between RT slope and activation in the Delay period but it accounted for relatively modest proportions of the variance.

Table 2A. Parameters and statistical tests from regression of RT slope and regional mean *t*-value across memory load conditions in the Item-order task

Task period	Slope	Regression parameter		
		r^2	t	p
Encoding				
Dorsal	0.33	0.11	1.0	0.33
Ventral	0.48	0.23	1.6	0.13
Maintenance				
Dorsal	0.45	0.20	1.5	0.16
Ventral	0.52	0.28	1.9	0.10
Retrieval				
Dorsal	0.78	0.61	3.7	0.005
Ventral	0.78	0.61	3.8	0.004

Table 2B. Parameters and statistical tests from regression of RT slope and regional mean *t*-value across memory load conditions in the Reordering task

Task period	Slope	Regression parameter		
		r^2	t	p
Encoding				
Dorsal	0.38	0.15	1.5	0.25
Ventral	0.25	0.06	0.78	0.45
Maintenance				
Dorsal	0.58	0.26	2.2	0.06
Ventral	0.61	0.38	2.4	0.04
Retrieval				
Dorsal	0.02	0.00	0.05	0.96
Ventral	0.06	0.004	0.18	0.86

2.2.5. Exploratory analysis

The patterns of decreasing activation during Reordering task encoding and maintenance were unexpected and warranted further investigation. To more closely examine the processes involved in the Reordering task, we tested the idea that semantic representation of the alphabet may influence neural activity in this task. The alphabet appears to be mentally represented on the basis of chunks in the alphabet song (i.e., (ABCD) (EFG) (HIJK) (LMNOP) (QRS) (TUV) (WXYZ); e.g., Klahr et al., 1983). It may be that the alphabetization-related neural activity varies more with the number of alphabetic chunks represented in letter lists than the number of letters. To test this hypothesis, we calculated the number of alphabet song chunks that were contained within each letter list (e.g., DBZ, has two chunks, B and D from the ABCD chunk, and Z from the WXYZ chunk).

When we regressed activation against individual letter lists grouped by number of alphabet song chunks, a monotonically increasing activation trend was observed only in the Encoding period of Reordering task trials (slope = 0.83; $r^2 = 0.67$; $t = 2.1$; $p = 0.06$; see Fig. 4). We did not observe similar effects in ventral PFC. No such effect was observed in the Item-order task data. Because this test was exploratory, alphabet song chunks were not equally represented in all load conditions. We therefore performed a weighted regression in which error terms were weighted by the number of instances of each chunk size. That is to say, chunk sizes with greater representation received greater weight than those with less representation. The results were similar to those of the unweighted regression. Specifically, during Reordering task encoding, there was a monotonically increasing activation trend ($p < 0.10$) only in dorsal PFC.

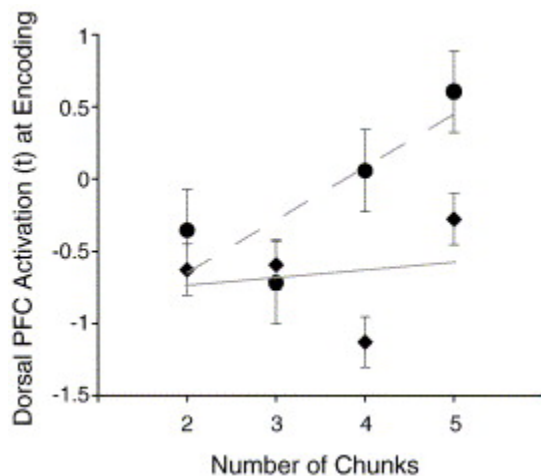


Fig. 4. Mean fMRI signal from the dorsal PFC during the encoding period for each chunk load (2, 3, 4, 5).

3. Discussion

In this study, behavioral performance was consistent with that observed in previous studies. RT increases were observed with increasing WM load in both task conditions, whereas accuracy decreases were observed with increasing WM load in both conditions. These results indicated that higher WM loads were associated with increases in WM demand. RT data indicated that participants were slower in the Reordering task condition compared to the Item-order task condition. Accuracy was not significantly different between tasks. Although there were similar behavioral patterns for the Item-order and Reordering tasks, task differential PFC activation patterns were observed in each task period and ROI.

One hallmark of dissociable systems in behavioral research has been the statistical interaction. Despite equivalence of the behavioral results between the 2 tasks, results from dorsal PFC indicated significant interactions between task and memory load in the encoding and maintenance periods. Specifically, Item-order activation significantly increased with increasing WM load while Reordering activation decreased. Interactions between task and WM load also occurred in the retrieval period wherein Item-order activation decreased with increasing WM load while Reordering activation increased with increasing WM load. These results suggest that PFC-based manipulation processes associated with item-order coding and those associated with reordering are not functionally equivalent as behavioral data suggest and has been assumed in neuroimaging literature. These results suggest that there are multiple dissociable WM manipulation processes that are mediated by dorsal PFC (see also Wagner et al., 2001).

In ventral PFC, the only significant interaction between task-type and WM load occurred during the Delay period wherein activity decreased with increasing WM load in the Reordering task but not in the Item-order task. This result suggests a more complex role for ventral PFC in WM maintenance than has been previously thought. For instance, it may be that ventral PFC specifically mediates the retention of consolidated order information. Future research is needed to understand how ventral PFC activity interacts with variations of task and WM load.

Observations of load-related dorsal PFC activation increases during the encoding and maintenance periods in the Item-order task suggest that item-order coding is intimately related to retention of long lists. Across subjects, regression coefficients of activation as a function of WM load were positive, indicating activation increases with WM load. One sample *t*-tests on these coefficients confirmed this observation ($p < 0.05$). These results resemble activation patterns observed in previous DRT studies (Rypma et al., 1999, Rypma et al., 2002, Veltman et al., 2003) in which no overt manipulation instructions were given to subjects. Veltman et al. (2003), for instance, observed load-dependent activation increases during the encoding and retrieval periods in the dorsal and ventral PFC when WM load was varied from 2 to 7 letters. Similarly, Rypma et al. (2002) found activation increases with WM load increases during maintenance and retrieval periods in the dorsal and ventral PFC when load was varied from 1 to 8 letters. Together, these results are consistent with the idea that item-order coding may model the encoding and maintenance processes people use during DRT performance. They suggest that item-order coding is related to the memory-consolidation operations individuals utilize to remember long lists over brief maintenance intervals.

It may be that, in the absence of obvious mnemonic relationships between items (e.g., availability of government, corporate, or academic abbreviations), participants segment the items into smaller units or “chunks” to maximize their performance (Bower and Springston, 1970, Bower and Winzenz, 1969). These chunks may be formed between adjacent items by some inter-item binding process mediated by dorsal PFC. Chunk boundaries may be formed between items that are spatially or temporally separated at encoding (cf. Bower and Winzenz, 1969). Bower and Winzenz (1969) tested this idea by varying the location of temporal pause-boundaries in the presentation of 12-letter strings. Their results indicated that participants' immediate recall was more accurate when letters were grouped into 3-item sets than when they were not grouped or when they

were grouped in other ways. They suggested that these pauses facilitated inter-item grouping of 3-letter sets. When they analyzed participants' errors, they observed that, when there were no pauses in list presentation, participants appear to spontaneously group items into sets of 3. Clearly more research needs to be done to elucidate the effects of stimulus configuration parameters on neural activity.

Although reordering and order maintenance requirements did not interact with memory load behaviorally, interactions between these two task types at the neural level support the hypothesis that Item-order and Reordering constitute qualitatively distinct cognitive processes despite similar patterns of performance. Our conclusions regarding the meaning of these statistical interactions presuppose additive models of brain–behavior relationships. Approximate linearity of BOLD data has been supported in prior studies (Boynton et al., 1996). Another possible explanation for these interactions is that subjects' activation in the two conditions may be negatively correlated. That is to say, those subjects who showed relatively greater activation in one task showed less activation in the other task. However, plots of each subject's Item-order activation against their Reordering activation did not show any such negative relationship.

These results are consistent with other fMRI studies in suggesting that brain–behavior relationships are complex and vary with both task and subject factors (e.g., Rypma et al., 2002). Indeed, across studies, fMRI activation increases are sometimes associated with fast and accurate performance (e.g., Gray et al., 2003) but are sometimes associated with slow and inaccurate performance (Rypma et al., 2002, in press(a),(b); Rypma, 2006, Rypma and D'Esposito, 1999). These differences appear to vary between populations (i.e., younger and older; Rypma and D'Esposito, 2001, Eldreth et al., 2004, Springer et al., 2005) and between brain regions (Rypma et al., in press(a), Rypma et al., in press(b)). The present results suggest that the type of task subjects are required to perform is another factor that affects the nature of brain–behavior relationships.

3.1. Individual differences—task dependent effects

In the Item-order and Reordering task conditions, we observed considerable between-subjects variability in overall activation. These analyses indicated that, in the Item-order task, retrieval-related dorsal PFC activation was greater for subjects who performed more slowly and less accurately than for subjects who performed faster and more accurately. In the Reordering task, there were trends toward a similar activation-performance pattern in the maintenance period, but they accounted for relatively modest amounts of the variance. These results are consistent with other studies showing that the presence or absence of subject-dependent effects depends on the nature of the task (Rypma et al., 2002). Additionally, these results are similar to previous DRT study results. Thus, they lend further support to the idea that mnemonic processes employed during the retention of long lists more closely approximate those employed during item-order maintenance than reordering of to-be-remembered information.

Previous studies have shown that intersubject activation differences are systematically related to performance. In one study for instance, Rypma and D'Esposito (1999) regressed individual subjects' dorsal and ventral PFC neural activity against their performance on a DRT with separate low (2 letters) and high (6 letters) memory load conditions. Similar to the Item-order task results, neural activity was higher for slower as compared to faster subjects, only during the retrieval period of the task. Unlike the present results, this activation-performance pattern only occurred in dorsal PFC. This discrepancy in results may be related to relative differences in difficulty between the two tasks. Indeed, in a study that employed 8 different memory loads (1–8 letters), monotonic relationships between neural activity and subject-performance were observed in both dorsal and ventral PFC (Rypma et al., 2002). Nonetheless, these results are consistent with a model of neural efficiency that we have proposed and tested elsewhere (Rypma and D'Esposito, 1999, 2000, 2001, Rypma et al., in press(a),(b)). In this model, cognitive processes may be neurally instantiated as “sigmoid activation” functions in which optimal ranges of neural activity result in optimum performance (as with the faster performers in the current study).

Performance decrements occur when neural activity deviates above this optimal activity level (as with the slower performers in the current study; e.g., Rypma and D'Esposito, 2001).

3.2. Exploratory analyses—task dependent interactions between long-term and working memory

The patterns of decreasing activation during Reordering task encoding were unexpected and led us to conduct additional exploratory analyses. We tested the idea that semantic representation of the alphabet influenced neural activity during this task. The results from our exploratory analyses provide support for the idea that dorsal PFC activity may reflect different operations in different tasks. When we categorized individual letter lists by the number of alphabet song chunks, a monotonically increasing activation trend was observed in the encoding period of alphabetic reordering trials, in contrast to the decreasing activation in the initial memory load analysis. No such effect was observed in the Item-order maintenance task data. These data suggest that participants may utilize long-term memory structures to optimize performance on some WM tasks (Bor et al., 2003, Chase and Simon, 1973, Veltman et al., 2003). They may rely on stimulus configuration in other WM tasks. It is unclear why the memory load and alphabet song analyses yielded such divergent results. Nonetheless, the present findings give further evidence that different strategic operations are performed in order maintenance and reordering. Interactions between long-term and short-term memory systems certainly require further research.

Where (i.e., in which brain region) and when (i.e., in which DRT period) load-dependent activation is observed have been a source of variance and controversy between studies. When participants have been required to encode 2 or 6 letters, load-dependent activation patterns were observed in dorsal PFC only during encoding (Rypma and D'Esposito, 1999). The present study and other studies have shown load-dependent activation during maintenance and retrieval in the dorsal and ventral PFC. Veltman et al. (2003; using a relatively long 8 s encoding period) reported load-dependent encoding and retrieval period PFC activity when participants encoded 2–7 letters. Narayanan et al. (2005; using a relatively short 2.16 s encoding period) also reported load-dependent PFC activation only during the maintenance period. Differences between task designs such as the amount of time participants were allotted during the encoding, maintenance, and retrieval periods may explain some of this between-study variance (Rypma, 2006, Narayanan et al., 2005). Our data provide evidence that instructional manipulation affects where and when load-dependent activation occurs.

In summary, strategies employed during the maintenance of long lists appear to be more closely approximated by item-order maintenance than by mental reordering of list items as has been assumed (e.g., Rypma, 2006, D'Esposito et al., 1999a, D'Esposito et al., 1999b, Postle et al., 1999). During long-list maintenance, mnemonic chunks may be formed on the basis of stimulus configuration by an inter-item binding process mediated by dorsal PFC. During alphabetical reordering, subjects may rely on long-term memory structures like the alphabet song. Our exploratory analysis supported this hypothesis. Indeed, a number of neuropsychological memory tasks (e.g., California Verbal Learning Test; Hopkins Verbal Learning Test; Rey Auditory Verbal Learning Test) explicitly test subjects' ability to exploit long-term memory structures to increase WM capacity. Future studies involving careful calibration of these stimulus parameters will be needed to more thoroughly explore how the involvement of long-term memory structures (e.g., chunks formed from the alphabet song) affects WM performance and PFC neural activity.

The results of the present study suggest that, despite their behavioral equivalence, PFC mediates multiple forms of WM manipulation processes, as indicated by fMRI data. They further suggest that cognitive processes associated with long-list retention may be more closely approximated by manipulation processes associated with order maintenance than those associated with reordering.

4. Experimental procedures

4.1. Research participants

Twelve right-handed (aged 18–34, 7 male) participants were recruited from the Rutgers University undergraduate campus through posted flyers. Participants were excluded if they reported or received treatment for any major medical, psychiatric (i.e., anxiety, depression), and neurological disorders (i.e., epilepsy, loss of consciousness > 30 min) including taking prescription medication. The Rutgers University and University of Medicine and Dentistry of New Jersey Institutional Review Boards approved this study. All participants gave informed consent and were remunerated for their time.

4.2. Task structure

The DRT in the present study consisted of two encoding conditions (see Fig. 5). One condition was an “Item-order” condition, in which participants were instructed to remember letters in the order they appeared in the list (that is, exactly as presented on the screen). The second condition was a “Reordering” condition, in which participants were instructed to alphabetically reorder the letters. Participants were given encoding instructions (either “Chronological” for the Item-order condition or “Alphabetical” for the Reordering condition) at the beginning of each block and at the beginning of each trial. Participants were scanned during 8 blocks of trials (4 blocks of Reordering and 4 blocks of Item-order) consisting of 20 trials. Trials were 16 s long and were separated by an inter-trial interval (ITI) of 10 s. This design allowed measurement of unique neural activity for each task period.

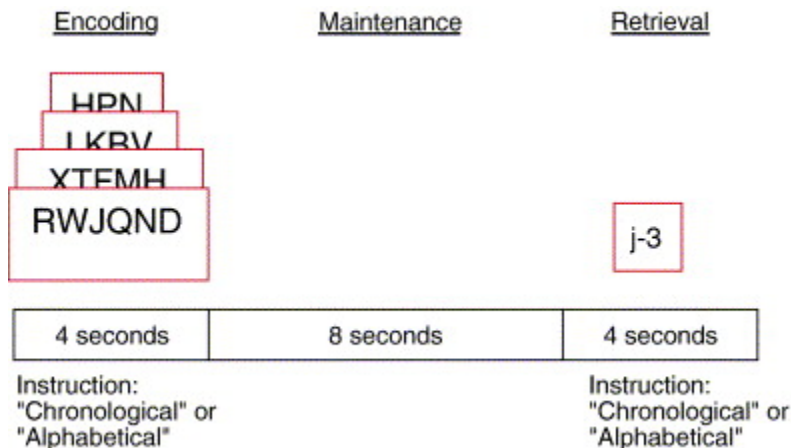


Fig. 5. Delayed response task. At each 4 s encoding period, subjects viewed between 3 and 6 phonologically dissimilar consonants and instructions to maintain them in the order in which they appeared in the list or to reorder them alphabetically. During the 8 s maintenance period, subjects were required to maintain the list in the order they were instructed to remember it. At the time of the 4 s retrieval period, participants viewed a probe consisting of a single lowercase consonant and a number. Below the letter and the number, an instruction word, appropriate for the scanning run, appeared reminding participants of the order in which they were to recall the list. Subjects responded by button press to indicate whether or not the letter occurred in the list and if the number indicated the correct position that was appropriate to the task instructions.

Each trial was composed of a 4 s encoding period in which participants viewed a string of 3–6 uppercase phonologically dissimilar consonants along with the instruction word appropriate for each scanning run. Following this period, participants viewed a blank screen for an 8 s maintenance period. In the retrieval period, participants viewed a probe consisting of a single lowercase consonant and a number. The probe remained on the screen for 4 s. Below the letter and the number, an instruction word, appropriate for the scanning run, appeared reminding participants of the order in which they were to recall the list. In the Item-order task,

participants responded “no” with their left thumb if the letter was not present in the list seen at encoding or if the number did not indicate the correct item-order position (i.e., indicating its original list order); otherwise they responded “yes” with their right thumb. In the Reordering task, participants responded “no” if the letter did not match any of those seen at encoding or if the number did not indicate the position the letter would be in if the list was rearranged alphabetically; otherwise they responded “yes.” Half of the foils were incorrect because the letter was in the incorrect position, and half were incorrect because they contained a letter not present in the list seen at encoding.

4.3. Catch trials

Because we were concerned that participants could adopt a deferral strategy (Rypma et al., 2002)¹, especially during the Reordering trials, we implemented a catch-trial system to ensure that participants performed the encoding strategies as instructed. Occasionally (on 20% of trials), participants were surprised by an instruction word printed in red in the probe period that did not match the trial-block instruction. During these “catch trials,” participants were asked to recall the list in a different way than they originally encoded it (i.e., instructed to encode the list “chronologically,” but asked to retrieve the letter in alphabetical order). Participants were informed of these catch trials in the instructions, and they were included in practice sessions. Our reasoning was that, if participants were performing encoding strategies as instructed, performance should be relatively poor on these trials.

A total of 260 echo-planar images were collected for each slice in each 8 min 40 s run. There were a total of 2080 observations for all 8 blocks allowing for considerable power to determine within-subject effects. Stimuli were presented through a backlit projection screen. Participants were able to view the stimuli via mirror lenses attached to the head coil. Participants responded using their thumbs by pressing a button on a magnet compatible response system. Stimuli were presented on, and RT and accuracy were recorded on, a Dell PC.

4.4. Data collection

Testing was completed in two sessions. During the first session, participants received 30 min of practice on the computerized behavioral task. In the second session, participants completed the fMRI scan.

4.5. MRI technique

Imaging data were collected on a Siemens 3 T Allegra head-only MR system equipped with a fast gradient system for echo-planar imaging. A radiofrequency head coil was used to record MR signal. High-resolution (TR = 564 ms, TE = 9.1 ms) T1-weighted images (32 slices acquired) were collected in the axial plane for every subject at the beginning of the fMRI session. Functional data were collected using a gradient echo, echo-planar sequence (TR = 2000 ms, TE = 50 ms) sensitive to the BOLD signal. Image resolution was 3.4375 × 3.4375 mm in plane, and 4.0000 mm between planes (32 slices acquired). Eighteen seconds was added to the beginning of each block of data collection to ensure that brain tissue had reached steady-state magnetization.

4.6. Regions of interest

To examine activity in specific regions of PFC, dorsal regions of interest (ROIs) were drawn on T1 axial slices of each subject to include middle and superior frontal gyri (BAs 9 and 46 according to the Talairach and Tournoux atlas, 1988). A similar procedure was used to draw ventral PFC ROIs to include inferior frontal gyrus (BAs 44, 45, and 47).

4.7. Data analysis

Off-line data processing was performed using Voxbo software on Linux workstations. Data were motion corrected using a slice-wise motion compensation method to remove spatially coherent signal changes using a partial correlation method and by applying a 6-parameter rigid-body, least-squares realignment routine. fMRI

signal changes that occurred during particular temporal periods of the behavioral trials were modeled with covariates comprised of time-shifted, BOLD hemodynamic response functions (HRFs) derived from each subject individually (Aguirre et al., 1998).

fMRI data were analyzed using the general linear model modified to account for serially correlated error terms that result from the temporal correlations in fMRI data. A time-domain representation of the 1/F power structure of MRI signal and a filter that removes frequencies below 0.025 and above 0.25 were placed in the model to account for low frequency confounds and artifacts at the Nyquist Frequency. Additionally, trial-effect covariates were included in the model to account for mean signal associated with each trial (Zarahn et al., 1997a, Zarahn et al., 1997b).

4.7.1. Group analyses

Relationships with each task period and the ITI were assessed by contrasts yielding t -statistics (with ~ 1195 df) involving the parameter estimates and error terms that corresponded to the covariates that modeled each task period. Two covariates modeled each 4 s of the Maintenance period. Given temporal estimates of the HRF, the covariate modeling the first 4 s of the Maintenance period would be expected to be contaminated by hemodynamic activity originating in the Encoding period. Thus, only the second 4-s Maintenance period is considered in the analyses (Zarahn et al., 1997a, Zarahn et al., 1997b). Because we observed significant overall signal differences between individuals, parameter estimates for the spatially averaged time series (derived from each ROI and averaged separately for dorsal and ventral PFC for each subject), scaled by their respective least-squared error term, were z -standardized. Random effects tests were then used to compare activation (t) between task type, for each task period and PFC ROI across participants. There were not sufficient numbers of error trials to conduct separate analyses of correct and incorrect trials. Thus, trials associated with correct and incorrect responses were included in the analysis to maximize statistical power. Note that our procedure did not depend upon thresholds for determination of neural activity.

4.7.2. Individual differences analyses

To account for variability between subjects, we regressed individual subjects' performance against their non-standardized neural activity. We determined for each subject the magnitude of activation in each task period, independent of memory load, using a contrast involving the sum of the coefficients of the task period covariates in each of the memory loads in each PFC ROI. Next, we performed a linear regression of subjects' RT slope and activation at each task period. Thus, we sought to characterize the relationship between memory-retrieval rate and regional cortical activity across each region of interest.

Acknowledgments

Supported by NIH grant MH61636 (BR). We thank staff at the UMDNJ-Rutgers Advanced Imaging Center who contributed to this project. We especially thank our research assistants Catherine Rypma, Elizabeth Bukowski, Eric Zaccone, and Jacquelyn Witham for their assistance in data collection and data analysis.

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