

FACTORS CONTROLLING NEURAL ACTIVITY DURING DELAYED-RESPONSE TASK PERFORMANCE: TESTING A MEMORY ORGANIZATION HYPOTHESIS OF PREFRONTAL FUNCTION

B. RYPMA*

Rutgers University, Psychology Department, Smith Hall, 101 Warren Street, Newark, NJ 07102, USA

Abstract—Understanding the role of prefrontal cortex in delayed-response task performance has been a central focus of neuroimaging research. The first part of this review will emphasize consistent observations of memory-load-related effects on prefrontal cortex activity that have led me and my colleagues to propose a “memory-organization hypothesis” of prefrontal cortex function. The second part examines how predictions of this hypothesis have borne up to empirical testing. The final part of this review suggests that there is important information contained in between-study variance in the anatomical locus and temporal sequence of neural activity. I will examine how subtle variations in task-structure affect subjects’ strategies, producing meaningful variability in neuroimaging data. Systematic manipulation of these variables in future research can assist in elucidating the role of prefrontal cortex in delayed response task performance. © 2005 IBRO. Published by Elsevier Ltd. All rights reserved.

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The structure of working memory (WM) has been characterized a number of different ways (e.g. Kane and Engle, 2002; Cowan, 2001; Baddeley, 2001, 2003; Verhaegnen et al., 2004; Oberauer, 2002) but there is near universal consensus about its central role in a broad range of cognitive tasks including planning (Prabhakaran et al., 2000), reasoning (e.g. Goel and Grafman, 1995) and problem-solving (Duncan et al., 2000; Prabhakaran et al., 1997). The importance of understanding the neural structures that underlie this ubiquitous cognitive mechanism is similarly well understood, as reflected by the number of studies investigating its neural basis using neuroimaging, neuropsychological, human, and animal behavioral methods (see e.g. Curtis and D’Esposito, 2003; Wager and Smith, 2003).

The most influential WM model has been that proposed by Baddeley (e.g. 1986, 2001; Baddeley and Hitch, 1974). In the basic form of this model, WM serves to permit the maintenance and manipulation of information in the service of higher order tasks such as reasoning, planning, and problem-solving. In this formulation, “slave-system”

components operate in the service of maintaining information over delay intervals. An executive component controls allocation of attention and coordinates information held in the slave-system buffers.

Neuroimaging research has focused on the role of prefrontal cortex (PFC) in supporting these WM subcomponents. The basis for this anatomical focus comes from early lesion, tracing and metabolic imaging studies with infrahuman primates performing delayed response tasks (DRTs). Briefly, these studies have demonstrated the importance of PFC in WM by showing WM-specific sensitivity to PFC lesions, and persistent PFC activity during encoding and/or delay periods of delayed match to sample tasks. Among the first of these researchers was Jacobsen (1935) who demonstrated dramatic delayed-match-to-sample performance deficits following large frontal lobe lesions in monkeys. More recent work has demonstrated greater anatomical specificity of this PFC-dependent ability. Funahashi et al. (1993) demonstrated that when lesions are made to Walker’s areas 9, 10 and 46 in macaque, performance accuracy drops nearly to chance. Similar deficits are observed when lesions are made with cortical cooling and electric current methods (e.g. Quintana and Fuster, 1993).

Since the time of these landmark studies, primate research and human neuroimaging research have continued to focus on PFC but have otherwise taken different paths. Primate WM research has focused on subsequent findings of persistent delay-period activity in PFC neurons during DRT performance (e.g. Goldman-Rakic, 1987). These findings are taken as evidence of on-line maintenance of sensory representations that guide behavior in the absence of environmental cues. This seminal work has led to research programs aimed mainly at defining the neurochemical substrate and precise nature of these representations (see e.g. Arnsten, 1998; Rao et al., 1997).

Human neuroimaging studies have mostly focused on defining the functional roles that sub-regions of PFC play in supporting the hypothesized subcomponents of WM. While some researchers are compelled by the continuity of results in monkey and human neuroimaging work, the weight of the evidence suggests that human PFC mediates much more than mere mnemonic maintenance (see e.g. Curtis and D’Esposito, 2003; Wager and Smith, 2003; D’Esposito et al., 2000; Smith and Jonides, 1999; Postle et al., 1999; Rypma et al., 1999; Courtney et al., 1997; Braver et al., 1997; Kimberg et al., 1997). This review will focus on the role of human PFC in WM and will otherwise be limited as outlined below.

*Tel: 973-353-5440 x234; fax: 973-353-1171.

E-mail address: rypma@psychology.rutgers.edu (B. Rypma).

Abbreviations: BA, Brodmann’s area; DRT, delayed response task; fMRI, functional magnetic resonance imaging; PFC, prefrontal cortex; WM, working memory.

Scope of review

Although studies of the neural basis of WM components have relied on a number of behavioral paradigms, the present analysis will focus mostly on studies of WM in humans performing DRTs. Studies using other paradigms will be considered to the extent that they inform speculation about the neural and psychological mechanisms that might be employed during verbal DRT performance. The reasons for this focus are (1) the DRT has been used in both animal and human literature and thus provides some basis for continuity between them, (2) the DRT has provided well-replicated behavioral results upon which to base speculation of underlying neural mechanisms and (3) where neuroimaging is concerned, its design is most clearly aimed at experimental dissociation of WM components (i.e. encoding, maintenance and retrieval).

Although studies of the neural basis of WM have used a number of different stimulus domains (i.e. verbal, object, spatial), this review will focus on the verbal domain. The reasons for this focus are that (1) evidence suggests that distinct neural systems underlie verbal and spatial WM, and (2) they have been used most extensively in WM behavioral research and thus provide the firmest footing for interpretation of neuroimaging data. Thus, the studies considered here can be said to be those that rely on tasks most closely resembling those first studied by Sternberg (e.g. 1969).

This review will cover studies that have formed the foundation of a basic model of the role of PFC in verbal

WM function during DRT performance. It will illustrate how between-study variations in temporal task parameters and WM demand structure influence subjects' strategies, and contribute to variability in neuroimaging data.

A basic model of PFC function in human DRT performance: the memory organization hypothesis

The neural substrate underlying the short-term retention of information remains to be precisely specified. Important clues, however, come from DRT studies that have *explicitly* manipulated task demands through instruction (i.e. requirements to repeat letters, alphabetize them, or remember their list-position) and *implicitly* manipulated task demands by variations in both the *extent* of memory-load (i.e. the quantity of items that must be maintained over the delay) and the *number* of memory loads (i.e. "extreme" conditions such as 1 letter and 6 letters or a parametric range of conditions such as 3, 4, 5, and 6 letters; see Table 1). Together these results suggest a precise organization of WM PFC function in which a capacity limited buffer exists for storage (estimated to be around 4 ± 1 items; Cowan, 2001; other estimates have also been made; e.g. Verhaegan et al., 2003; McEree and Doshier, 1993; Glanzer and Razel, 1974; Tulving and Colotla, 1970; Murdock, 1967; Miller, 1956), or *maintenance*, a function mediated by ventral PFC (possibly in concert with parietal cortex). The capacity limitation of this buffer requires, under conditions of high memory demand, that to-be-remembered information be consolidated, that is, *organized*, a function

Table 1. Summary of verbal delayed response tasks

Number of memory loads			Extent of memory loads	Study
a. Block-design studies				
1			4	Letters Awh et al., 1996
1			4	Letters Reuter-Lorenz et al., 2000
1			6	Letters Paulesu et al., 1993
1		a	5	Letters Marshuetz et al., 2000 ^b
2			3	Letters Rypma et al., 1999
2		a	6	Letters Rypma et al., 1999
b. Event-related studies with a single memory-load condition				
1		D	5	Words Chein and Fiez, 2001
1			5	Digits Manoach et al., 2003
c. Event-related studies with multiple memory-load conditions				
2	E		2, 5	Letters Postle et al., 1999
2	E		2, 6	Letters Rypma and D'Esposito, 1999
3	—	D	1, 3, 6	Letters Zarahn et al., 2004
4	E ^c	D	3–6	Letters Narayanan et al., 2005
4	E	D	3–6	Letters Eldreth et al., 2005 ^b
4	E		2, 4, 6, 8	Letters Cairo et al., 2004
6	E	—	2–7	Letters Veltman, et al., 2003
8	E ^d	D	1–8	Letters Rypma et al., 2002

Summary of verbal DRT studies included in this paper, their design type (block or event-related), the number and extent of memory loads used in the study design, and the stimulus type. Part a lists block design studies. Footnote ^a indicates which of those reported dorsal PFC activation. Parts b and c list event-related studies and the task-period in which dorsal PFC activity was reported. E, encoding; D, Delay; R, retrieval.

— Results not available or not reported for this task period.

^a Dorsal PFC activity observed.

^b Order-maintenance tasks.

^c Reanalysis indicates the possibility of load effects at encoding (Fig. 5a).

^d Reanalysis indicates load effect between one- and six-letter conditions (Fig. 4).

mediated by dorsal PFC. These organization processes are conceptually similar to those referred to as “chunking” or “intelligent grouping” by researchers like Miller (1956), Gobet and Simon (1998) and Baddeley (1986). They are conceptually distinct from these notions insofar as proposing that, when subjects must maintain long lists in memory, such processes may be carried out “on-the-fly,” so to speak, by grouping, or binding, of adjacent list items (e.g. Bower and Springston, 1970; Bower and Winzenz, 1969). In summary, the hypothesis is that ventral PFC subserves the maintenance of verbal information. Dorsal PFC is recruited when organization of information is needed to store supracapacity information loads.

In the first part of this review, I will show analyses of neuroimaging data collected during verbal DRT performance that support the memory-organization hypothesis (see Table 1). Further, this analysis indicates that the functional structure of PFC varies with task-demand, possibly reflecting differences in how subjects organize information in different kinds of tasks. Evidence from which the memory-organization hypothesis was formulated will be reviewed presently.

Localization of maintenance functions

Initial studies using the DRT paradigm in combination with functional magnetic resonance imaging (fMRI) block designs (Table 1a) have identified putative WM slave-system components with inferior PFC regions. In one PET study, for instance, Paulesu and his colleagues (1993) demonstrated that brief retention of verbal information (as compared with visuospatial information) resulted in activation believed to be associated with subvocal rehearsal in left inferior frontal cortex, identified as Brodmann’s area (BA) 44. These results were consistent with information from neuropsychology suggesting that Broca’s area, a region identified closely with BA 44, was vitally involved in a “phonological loop” that involved other regions, including parietal cortex (see e.g. McCarthy and Warrington, 1990; Vallar and Shallice, 1990). It can be observed in Table 1 that Paulesu et al.’s (1993) study employed a relatively high WM load (six letters). The baseline comparison in this study involved retention of six nonsense characters. This baseline permitted these researchers to assess activity due to phonological (as opposed to visuospatial) retention. It did not permit them to assess activity due to a high (as opposed to low) memory demand. As a result it is not possible to assess what activity (if any) may be uniquely associated with high memory-load retention.

Two other studies listed in Table 1a, those of Awh et al. (1996) and Reuter-Lorenz et al. (2000), varied the amount of time over which subjects were required to maintain four letters. While the memory-demand was lower in these tasks than Paulesu et al.’s (1993), these studies were similar in that the experimental and control conditions involved the same level of memory-demand. Awh et al. (1996) and Reuter-Lorenz et al. (2000) compared PET activation in a condition in which subjects were required to maintain the letters over 3000 ms to one in which they were required to maintain them over 200 ms (Awh et al.,

1996) or 300 ms (Reuter-Lorenz et al., 2000) PFC activity appeared prominently in area 44 of the left hemisphere, similar to the results observed by Paulesu et al. (1993).

Localization of organization functions

The memory-organization hypothesis of the neural locus of chunking operations has come from neuroimaging studies using executive WM tasks (mainly self-ordering, reordering, and dual tasks). Consistent with the more varied functions that have been attributed to the WM executive component (e.g. Miyake et al., 2000) studies using diverse behavioral methods have converged on the notion that, whereas relatively ventral (and left-lateralized) PFC regions mediate maintenance WM functions, relatively dorsal (and bilateral) PFC regions mediate executive functions.

Among the first studies to suggest this dorsal/ventral subdivision was one that used a “self-ordered pointing task,” a task in which PFC-lesioned monkeys and PFC-damaged humans have shown performance deficits, compared with healthy monkeys and humans (Petrides et al., 1993a,b; Petrides, 1995, 1996). In one study, humans were shown a series of cards with an array of eight abstract figures printed on them over 60-s PET scan periods. In the first condition they were required to locate the position of one of the designs, determined by the experimenter prior to scanning (an “externally-ordered” task). In a second condition, subjects were required to point to a different design each time they were presented with a card (a “self-ordered” task). This latter task is believed to tap executive functions because it requires subjects to monitor, and order their performance on the basis of their recollection of which designs they had previously pointed to. Consistent with the monkey- and human-lesion studies, PET activation differences between the externally-ordered and self-ordered conditions were reliably observed in dorsal regions of PFC corresponding to BAs 9 and 46. These results were consistent with the idea that dorsal PFC regions mediate executive WM processes, associated with behavioral guidance based on internal representations.

Another function attributed to WM executive has been allocation of attentional resource to concurrent task-processing. Accordingly, dual-task paradigms have been exploited for the purpose of locating the neural correlates of the executive component of WM. In one landmark study, D’Esposito and his colleagues (1995) used fMRI to compare neural activity when subjects performed a single task to that when subjects performed two tasks concurrently. The results of this study indicated above-baseline dorsal-PFC activation only during dual-task performance. On the basis of these data these researchers suggested that dorso-lateral PFC mediates WM executive functions.

The idea that dorsal PFC mediates executive WM received support from subsequent work with *reordering* tasks (Wagner et al., 2001; D’Esposito et al., 1999; Postle et al., 1999). In this kind of task, subjects are required to mentally shuffle to-be-remembered list items (e.g. alphabetizing letters, or ordering words according to some metric like desirability). Activation in reordering conditions can

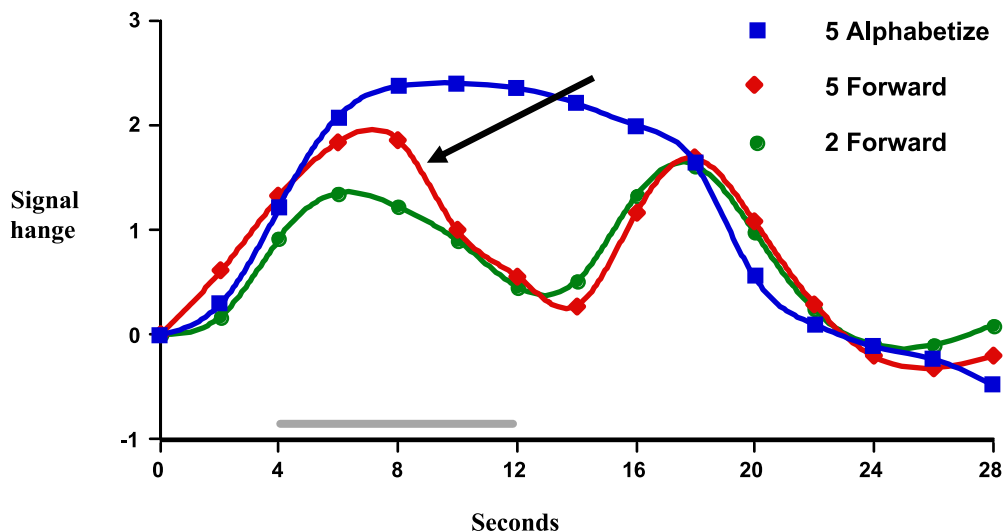


Fig. 1. Results from Postle et al., 1999. Dorsal PFC activation was associated with the requirement to reorder (i.e. "alphabetize") the letters. Memory-load effects associated with the encoding period in the two-letter (green line) and five-letter (red line) order-maintenance (i.e. "forward") conditions were observed (Postle, personal communication).

then be compared with conditions in which the subject is required to maintain the given list order. The results of these kinds of studies consistently indicate greater dorsal PFC activation during reordering than order maintenance conditions (see Fig. 1).

Evidence that the requirement to reorder information, and the requirement to maintain supracapacity amounts of information (i.e. more than four items; evidence that will be reviewed below) both elicit relatively greater dorsal PFC activity than non-manipulation or subcapacity conditions has been taken to indicate that it is this region that mediates the additional processing requirements of high-load WM retention.

The results of the studies reviewed above, DRT studies showing mainly ventral PFC activation with increases in WM demand, and self-ordering and dual-task studies showing mainly dorsal PFC activation with increased processing demand, have been important for several reasons. First, they support a broad distinction in WM between subsystems devoted to maintenance (functions that are attributed to WM storage buffers), and those subsystems devoted to a range of other management and organization processes that facilitate storage (functions that are attributed to WM executive), given known limits on the amount of information that can be maintained in WM (Baddeley, 1986; Cowan, 2001). Second, they suggest a precise organization of PFC in which WM storage buffers are ventrally instantiated in PFC regions (corresponding to BAs 44, 45, and 47) while WM executive functions are dorsally instantiated in PFC regions (corresponding to BAs 9 and 46).

Based upon this model of PFC function, the memory-organization hypothesis supposes that the increased dorsal PFC activation observed during self-ordering, reordering and dual tasks reflects a kind of information-processing that is similar to that employed when subjects must carry out WM organization operations. These organization pro-

cesses are aimed at reducing the amount of to-be-remembered information so as to accommodate the known capacity limits of WM maintenance buffers. Testing this hypothesis has required observation of neural activity changes over a range of memory loads in the DRT. An expanding set of studies has undertaken this enterprise (see Table 1).

Systematic investigation of the effect of WM-load on PFC activity during DRT performance supports the idea of a single organizational framework wherein ventral PFC mediates WM storage buffers and dorsal PFC mediates WM executive functions. In one study, Rypma and his colleagues (1999) observed prefrontal activation during a DRT in which participants were required to maintain one, three or six letters for 5 s. When participants were required to maintain three letters in WM, relative to one letter, activation in frontal regions was limited to left ventral PFC corresponding to BA 44, similar to the PET results observed by Awh, et al. (1996) and Paulesu et al. (1993). When participants were required to maintain six letters, relative to one letter, additional activation of bilateral dorsal PFC, corresponding to BAs 9 and 46 was observed, similar to results observed by Postle and colleagues (see Fig. 2).

This pattern of results supports the idea of a single framework of PFC function in which ventral PFC mediates WM storage while dorsal PFC mediates a diverse set of executive processes, possibly including those aimed at optimizing memory performance. They further indicate that the nature of PFC organization may vary with the extent of task demand. Under low-demand WM conditions, ventral PFC activation has been consistently observed in left hemisphere, a region associated mainly with verbal information processing, as in Rypma et al.'s three-letter condition and Awh et al.'s four-letter condition. Evidence for the material-specificity of this system comes from studies showing ventral PFC activation in the right hemisphere when subjects were required to

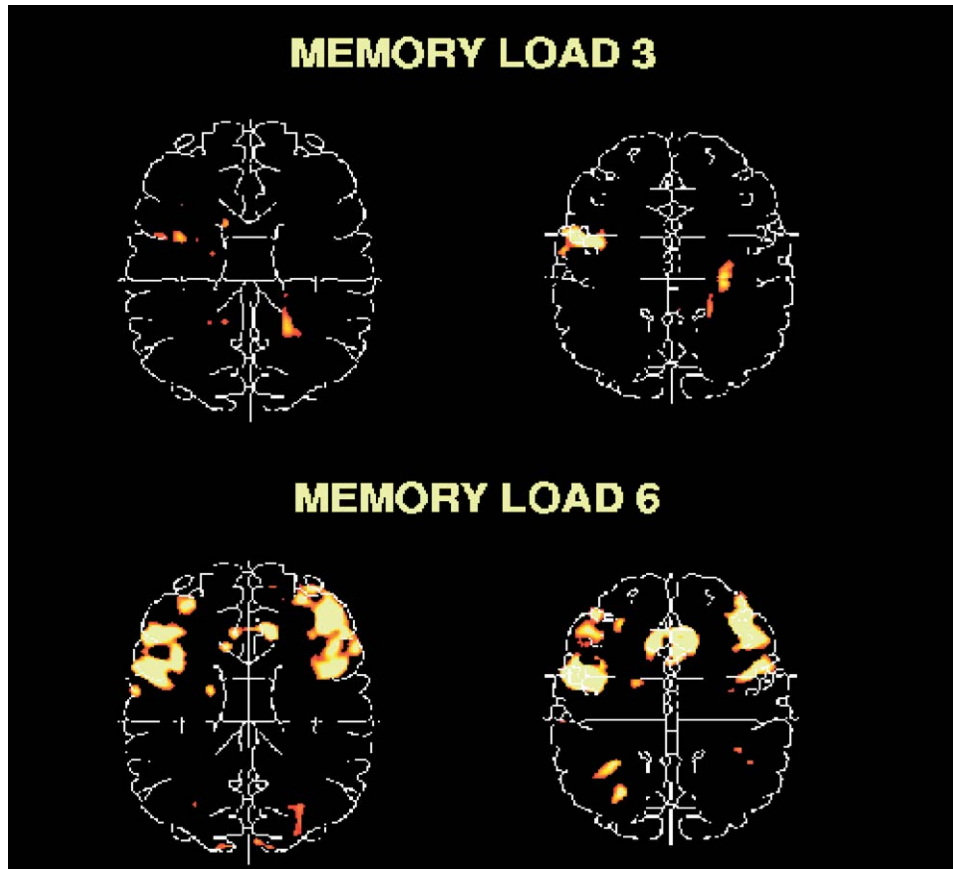


Fig. 2. Results from Rypma et al., 1999. Memory-load effects associated with the six-letter memory-load condition were observed in dorsal PFC in this block-design study.

remember the locations of three dots (Jonides et al., 1993). These results suggest that requirements to remember relatively small numbers of items may lead to the enlistment of one kind of functional network specialized for WM processing of specific kinds of material. When WM demand increases, however, a different organization system may prevail, one that involves bilateral and more dorsal PFC regions similar to those observed in Petrides' self-ordering task, D'Esposito et al. (1999), Wagner et al. (2001), and Postle et al.'s (1999) reordering tasks and dual-tasks. The addition of these regions may reflect a strategic shift to memory mechanisms that are necessary for successful maintenance of these larger memory loads, regardless of material type.

The variation in load-dependent activation observed by Rypma et al. (1999) demonstrated that dorsal PFC is active not only when tasks overtly require WM manipulation but also when the demands of maintenance exceed the capacity of short-term storage. Estimates of the capacity of short-term storage have varied but a broad review of studies aimed at determining WM storage capacity has suggested a "magic number" of 4 ± 1 items (e.g. Cowan, 2001) when no chunking or reorganization is permitted. When this WM capacity is exceeded, as in Rypma et al.'s six-letter condition, strategic processes may need to be employed to maintain items in WM (e.g. Waugh and Nor-

man, 1965; Baddeley and Hitch, 1974). These strategic processes are similar to other conceptions of WM manipulation (e.g. ordering, reordering, alphabetization, dual-tasking) in that they seem to be aimed at *reorganization* of to-be-remembered information. They are distinct from these conceptions to the extent that they are aimed specifically at *consolidation* of information for efficient storage and retrieval.

TESTING PREDICTIONS OF THE MEMORY-ORGANIZATION HYPOTHESIS

Subsequent studies have tested a number of predictions that follow from the memory-organization hypothesis. These predictions were (1) that greater dorsal PFC activity should be observed early in the DRT trial sequence (i.e. at encoding), (2) that continuous increases in memory-load should produce continuous increases in dorsal, but not ventral, PFC activity, and (3) that overt manipulation demand increases (e.g. requirements to reorder increasing numbers of letters) and more covert demand increases (i.e. of requirements to maintain various numbers of letters) should produce relatively equivalent changes in dorsal PFC activity. A number of studies, involving systematic variations of WM load, in combination with event-related fMRI paradigms, have tested these predictions. These

studies are represented in Table 1b and c and are reviewed presently.

Prediction 1: load-related dorsal PFC activation during DRT encoding

Rypma and D'Esposito (1999) tested a key prediction of the memory-organization hypothesis, that load-related activation increases would occur during DRT encoding, by using event-related fMRI methodology that permitted observation of neural activity in each of the task-periods of a DRT. In their experiment, subjects were required to (1) encode either two or six letters during a 4-s encoding period, (2) maintain them over an unfilled delay interval lasting 12-s, and (3) determine if a subsequently-presented single letter was or was not part of the memory set. They reasoned that if load-dependent activation increases reflected organization of to-be-maintained information, then memory-load-dependent effects should be observed early in the DRT sequence. Consistent with the memory-organization hypothesis, they observed load-dependent activation changes only during the encoding period (no load-related increases were observed in the maintenance or retrieval periods) in dorsal PFC but not in ventral PFC (see Fig. 3). These results are consistent with the idea that manipulation functions, mediated by dorsal PFC, operate at encoding to compress or “chunk” large amounts of to-be-remembered information to accommodate the se-

vere limits of WM storage capacity (e.g. Rypma and D'Esposito, 1999; Rypma and Gabrieli, 2000). Further support for the claim that successful maintenance of large lists depends on encoding-related dorsal PFC activity, comes from a follow-up study showing significantly greater encoding-related dorsal PFC activity only on trials in which subjects subsequently responded correctly. No such effects were observed in any other task periods or in ventral PFC (Rypma and D'Esposito, 2003).

The claim that load-related dorsal PFC changes are tied to encoding, and not maintenance DRT periods has been controversial. Nonetheless, other event-related fMRI studies show load-dependent activation early in the trial-sequence, consistent with the memory-organization hypothesis (e.g. Narayanan et al., 2005). As will be discussed further below, variance in results between different studies may be due to at least two factors, (1) extent, and (2) number, of memory loads. Table 1b and c shows that these factors have varied across DRT studies.

Prediction 2: continuous load-related dorsal PFC activation during DRT encoding

The second prediction of the memory-organization hypothesis of PFC function is that continuous increases in WM demand should produce continuous increases in dorsal PFC activity whereas load-dependent activity should appear relatively limited in ventral PFC function. The present hypothesis specifically postulates monotonic changes in PFC activity with changes in memory-load. This hypothesis supposes that the nature of the relationship between memory-load and neural activity is linear (e.g. Boynton et al., 1996) and varies with factors that influence the capacity limit at any one time. Factors such as inherent differences between individuals (e.g. Rypma and D'Esposito, 1999, 2000), strategy differences (Rypma et al., 2002; Speer et al., 2003; Cowan, 2001; McLean and Gregg, 1967), the extent to which stimulus lists afford associations to long-term memory (Gobet and Simon, 1998), available encoding time, and stimulus configuration can all lead to variations in capacity limits (Chase and Simon, 1973, McLean and Gregg, 1967). Given that these factors could be expected to cause capacity decreases (down to, say, 3 items) in some cases but increases (up to, say, 5 items) in other cases, one would expect to see, on average, gradual shifts in the extent and locus of neural activity with changes in memory rather than step-wise changes as has sometimes been assumed.

Neuroimaging studies that have tested the relationship between neural activity and memory-load have produced different patterns of results. In the context of a “sequential letter memory task” (an *n*-back task), memory-load has been varied by requiring subjects to respond when a briefly presented letter had also occurred either 1, 2, or 3 presentations earlier. In one study, Cohen and his colleagues (1997) observed sustained, or “step-wise” load-dependent changes in dorsal PFC. Another study, however, that employed a similar design showed more gradual, monotonic load-dependent changes in PFC (Braver et al., 1997). These results suggest that, even in apparently similar stud-

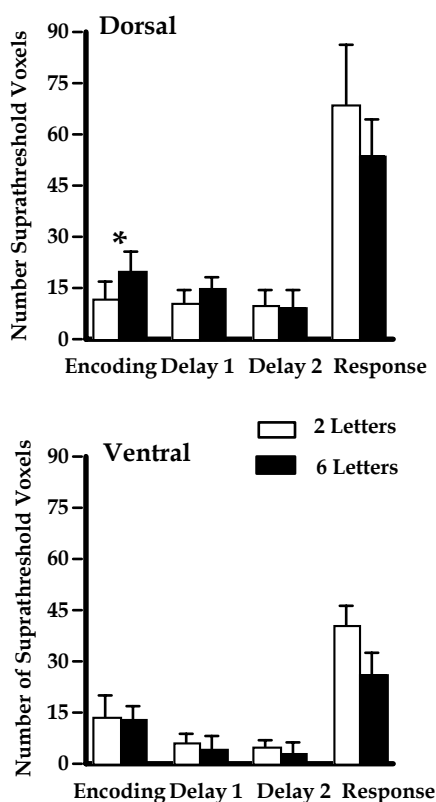


Fig. 3. Results from Rypma and D'Esposito, 1999. Memory-load effects associated with the six-letter memory-load condition were observed in dorsal PFC only during the encoding period in this event-related study.

ies, subtle differences in procedure, stimuli, or subject composition can lead to between-study variability in results.

Rypma et al. (2002) tested the prediction of monotonic load-related PFC activation increases in the context of a DRT. They observed that previous DRT studies were limited to “extreme-conditions” designs. That is to say these studies relied on one subcapacity (i.e. 1 or 2 letters) and one supracapacity (i.e. 6 letters). They reasoned that such studies could limit the effects of memory-load on PFC activity by limiting, for instance, the demand to vary encoding strategies across memory loads.

In their study, subjects were required to encode between 1 and 8 letters for 4-s. After a 12-s delay period, they determined whether a subsequently-presented single let-

ter was or was not part of the memory set. When they plotted PFC activation against the number of to-be-remembered letters, significant monotonic activation increases were not observed over the entire range of eight memory-load conditions during encoding. However, monotonic activation increases between 1 and 6 letter memory-loads were observed (see arrow in Fig. 4), consistent with earlier observations. To emphasize the point, Fig. 4 shows a zoom-view of the dorsal PFC encoding activity for memory-load conditions 1–6. Analysis of the continuous activation changes between memory-load conditions 1 through 6, using Page’s distribution-free test for ordered alternatives (Hollander and Wolfe, 1999), indicated monotonic activation increases ($P < 0.0005$). Compared with the relatively high level of dorsal PFC activation observed in the

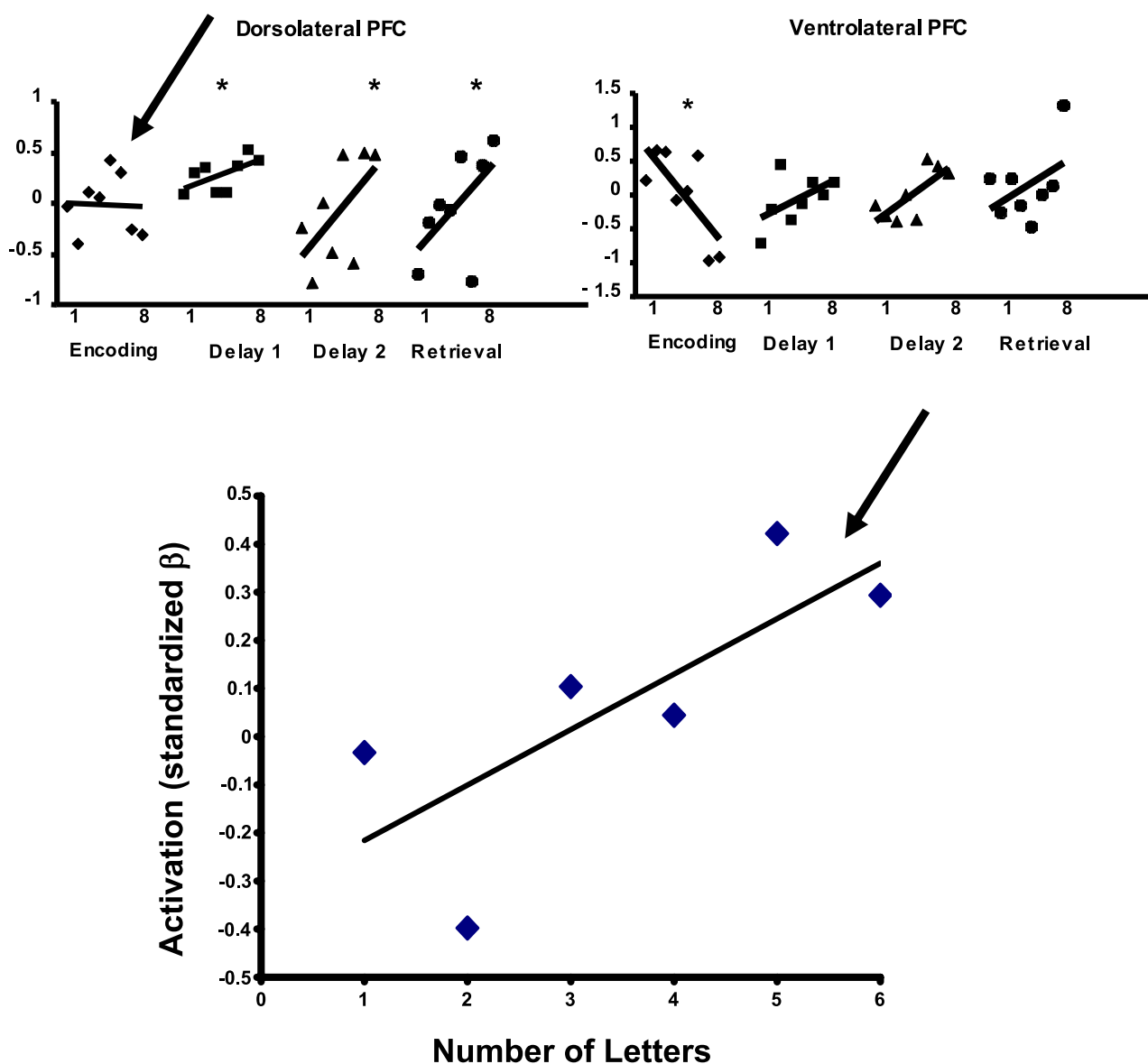


Fig. 4. Results from Rypma et al., 2002. Memory-load effects were observed between the one- and six-letter conditions (arrow and zoom-view; note remarkable similarity to those data shown in Fig. 5) in dorsal PFC during encoding. In higher memory load conditions, encoding-related activation decreased. It increased however in the delay and retrieval task periods.

6-letter condition, activation in the 7-letter and 8-letter conditions declined to roughly those of the 1-letter condition, suggesting a fundamental shift in strategy at very high memory loads (though these effects were mediated by individual performance differences).

Other event-related studies using similar parametric designs (Table 1c) have found similar group-level results, though substantial differences in temporal dynamics between these studies limit the extent to which comparisons between them can be made. In one study, Veltman et al. (2003) reported load-dependent encoding-period activity when subjects encoded 2 to 7 letters over a relatively long 8-s period, followed by a 2-s delay prior to retrieval. The length of the encoding period makes it difficult to link this load-dependent activity with either the encoding or the delay DRT task periods (e.g. Postle et al., 2000; Zarahn et al., 1997; Narayanan et al., 2005) but it is certainly plausible that the load-related activity they observed originated at encoding. Narayanan et al. (2005) also reported PFC activation during encoding with a relatively short 2.16 s encoding period, followed by a 6.48 s delay period prior to retrieval. While they did not report load-related activation changes during DRT encoding, they make clear that unambiguous interpretation of their results is difficult given the considerable time over which encoding may occur, and that the considerable temporal lag of hemodynamic activity can cause closely-spaced, boxcar-shaped, covariates to become unduly collinear (Zarahn et al., 1997; Postle et al., 2000; Jha and McCarthy, 2000). Given the narrow spacing of covariates, the load-dependent pattern observed in their results may indicate WM-load sensitivity in dorsal PFC sensitivity during encoding. Indeed, analysis of their time-series data from BA 9 shows load-related activity increases where they would be expected if there was load-related activation associated with encoding (i.e. 6–8 s following stimulus onset), given known properties of the hemodynamic response following neural activity (see Fig. 5a). Tests of the monotonic activation increases in the 6–8 s period following stimulus presentation indicate good fit to a linear function ($F(1, 11)=11.7, P<0.007, MSe=.002$). In fact, the results, when analyzed this way bear striking resemblance to the corresponding conditions in the Rypma et al.

(2002) results (Fig. 4) and the results of a similar study from our laboratory (Eldreth et al., unpublished observations; Fig. 5b).

Another important feature of the Rypma et al. (2002) results is the dramatic reduction in dorsal PFC encoding activation at the highest memory-loads (seven and eight letters). These results force some modification of the original hypothesis. One possibility is that this change in the relationship between memory-load and activation reflects some fundamental shift in subjects' letter-encoding strategies. It has been known for some time that chunking strategies are used to overcome the capacity limitations of short-term memory (Ericsson and Chase, 1982). Indeed, another feature of the results, consistent with a strategy-shift explanation was that load-dependent effects were also observed during the maintenance period in the Rypma et al. (2002) study, unlike those in the Rypma and D'Esposito (1999) extreme-conditions design study, but similar to the parametric-design studies of Veltman et al. and Narayanan et al.

To test this strategy-shift explanation, Rypma et al. (2002) compared results in "high-performance" subjects (i.e. those subjects whose performance was above the group median) and "low-performance" subjects (i.e. those subjects whose performance was below the group median), they observed load-dependent activation in DRT delay only in high-performers, in both dorsal and ventral PFC.

These results suggested that individual subjects' performance varied on the basis of different strategies. Comparison of dorsal PFC activation between high- and low-performing subjects indicated that, in high performers, activation increased over the course of high memory-load trials (5 to 8 letters) but decreased over the course of low memory-load trials (1 to 4 letters). No such effect was observed in the low performers. This pattern of results suggests that high-performers, more than low performers, distinguished between high and low memory-demand conditions and applied different strategies accordingly. It is worth noting that a strict maintenance-based account of dorsal PFC function cannot account for this pattern of results.

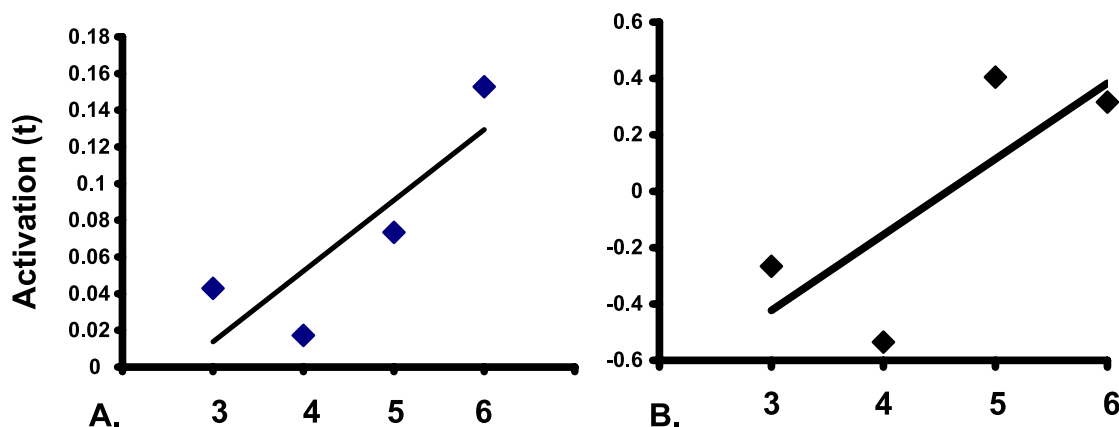


Fig. 5. Part a shows time-series data averaged over 6-s and 8-s time points following trial-onset for each memory-load condition from Narayanan et al., 2005. Part b shows 4-s encoding-period data for each memory-load condition from Eldreth et al., unpublished observations.

What might be the nature of the strategy patterns reflected in load-dependent activation changes? Evidence suggests that individuals have at their disposal a number of chunking strategies (McLean and Gregg, 1967). One possibility, suggested by differences in PFC activation differences between low and high memory-load conditions (even when the number of memory-loads is held constant; Speer et al., 2003) is that, as memory-load increases and chunking becomes more important for successful task performance, strategies that involve long-term memory come more into play. Such load-related activation changes may also reflect a priority-ordering of lower perceptual encoding of to-be-remembered information and higher-level organization of such information. It may be that successful retention of long lists requires that subjects strategically defer higher-level operations until lower-level operations have approached completion (Rypma et al., 2002).

Strategy-shift accounts of load-dependent changes in activation patterns await further empirical tests. Other studies have observed changes in PFC activity when strategy shifts are explicitly manipulated (e.g. Speer et al., 2003). Whatever load-dependent PFC activity changes may mean, one assumption upon which the memory-organization hypothesis rests is that, when subjects are confronted with the high WM demand of long lists, they implicitly manipulate information in a way that is qualitatively similar to explicit manipulations (e.g. reordering; Wagner et al., 2001; D'Esposito et al., 1999; Postle et al., 1999) that have been used in WM manipulation studies.

Prediction 3: similar load-related dorsal PFC activation during encoding of to-be-manipulated and to-be-maintained information

In one experiment, we (Eldreth et al., unpublished observations) tested the hypothesis that explicit and implicit manipulation processes are qualitatively similar by directly comparing them within the same study, within the same subjects and with WM-demand parametrically varied. This study design allowed comparison of load-related activation changes under conditions in which WM-demand was varied explicitly by reordering requirements and when it was varied implicitly by maintenance requirements. In this study there were two encoding conditions. In one condition, subjects were required to remember the order in which letters appeared in a list. In the second condition, subjects were required to alphabetically reorder letters. The length of letter lists varied between 3 and 6. Subjects were scanned during eight trial blocks (half of which required alphabetization encoding, while the other half required item-order coding). Each trial began with a 4-s encoding period, during which subjects viewed a set of 3, 4, 5, or 6 phonetically dissimilar consonants, presented simultaneously in a single string.

Reaction time data indicated that subjects were slower in the Alphabetical than in the Chronological condition [$F(1, 12)=9.2, P<0.01, MSe=41807.5$]. Reaction time increased with increasing memory set-size [$F(1, 12)=19.5, P<0.0001$] in both encoding conditions. The Task×Set-size interaction was not significant, $F<1$. Accu-

racy data indicated that subjects performed with equivalent accuracy in the Alphabetical and Chronological conditions $F<1$. Accuracy decreased with increasing memory set size [$F(1, 12)=19.5, P<0.0001$]. The Task×Set-Size interaction was not significant [$F(1, 12)=2.6, P<0.14, MSe=.001$].

To assess differential memory-load effects in each task conditions, we conducted 2 (Task) × 4 (Memory-load) ANOVAs on activation data from dorsal regions of PFC. Results of analyses for these purposes are presented below and in Fig. 5B. In the Chronological-task condition there was a linear trend indicating a monotonic activation increase $F(1, 11)=3.34, P<0.1, MSe=1.3$. No such effect was observed in the Alphabetical Task condition. Similarly we observed effects implicating qualitative processing differences in the reordering and order-maintenance conditions in the maintenance period (where we observed a significant Task-type×Memory-load interaction, $F(1, 11)=12.8, P<0.01, MSe=1.57$) and in the retrieval period ($F(1, 11)=9.05, P<0.012, MSe=2.35$).

Qualitatively different PFC activation patterns were observed with different task demands in the Eldreth et al. (unpublished observations) results. Load-related activity patterns differed between item-order maintenance and item-reordering conditions. Thus these results do not support the assumption of the memory-organization hypothesis that dorsal PFC activity related to reordering is qualitatively similar to that observed during maintenance of long lists. Further, these results suggest that the nature of load-related activation effects depends critically on the task; increases in operational demand appear to be associated with PFC activation increases under some circumstances (order-maintenance in this case) and to decreases under other circumstances (reordering in this case). These results again force some modification of the original hypothesis. They suggest that, while dorsal PFC is important for both kinds of operations, reordering and strategic-grouping are qualitatively different cortical operations.

The distinction between these two kinds of WM manipulation operations is consistent with research reviewed above indicating the diversity of functions that can be attributed to PFC. A number of mechanisms by which list items may be grouped have been proposed. The classic formulation of such operations involves contact between short-term and long-term memory structures (e.g. Gobet and Simon, 1998). Others have proposed that rehearsal operations are vital to achieve data reduction through chunking (Cowan, 2001). For instance it may be that subsets of list items may be grouped by rehearsing them together quickly (McLean and Gregg, 1967), a process that may be associated with dorsal PFC (Raye et al., 2002).

One kind of operation that may be more similar to that reflected in dorsal PFC activity during large-list retention is inter-item binding, that is, binding of list items on the basis of their proximity in the list. There is evidence that one common chunking strategy is to bind adjacent list items (Bower and Springston, 1970; Bower and Winzenz, 1969). It may that, in the absence of other mnemonic devices (e.g.

availability of government, corporate or academic abbreviations), subjects group adjacent list items “on the fly” into approximately three-item chunks (e.g. Bower and Springston, 1970). Evidence exists to support this speculation. Spatial binding task-requirements have been uniquely associated with dorsal PFC activity (Prabhakaran et al., 2000; Mitchell et al., 2000), as have requirements to maintain item order (e.g. Marshuetz et al., 2000; but see Henson et al., 2000). Finally, spatially overlapping suprathreshold activity has been observed in comparisons of binding and large-list maintenance tasks (Prabhakaran et al., 2000).

We (Eldreth et al., unpublished observations) have begun testing the idea that subjects may implement inter-item binding strategies by exploiting two known properties of alphabet memory. The first property is that subjects mentally represent the alphabet in chunks based on the alphabet-song (e.g. Jou and Aldridge, 1999; Klahr et al., 1983). Thus, when alphabetic sequence is important to the task, processing may reflect this chunk structure. The second property is that alphabetic positions of individual letters are coded in memory. The closer two letters are, the more similar they appear to be. Thus, relatively proximal letters may be better remembered together than relatively distal letters.

Further exploratory analyses suggest support for the idea that dorsal PFC activity may reflect these different strategic operations. When we categorized individual letter lists, not by number of letters, but by the number of alphabet-song chunks, a monotonically increasing activation trend was observed in the encoding period of Alphabetic reordering trials (slope = .83; $r^2 = .67$; $t = 2.1$; $P = 0.06$). We did not observe similar effects in other task periods or in ventral PFC. No such effect was observed in the Chronological task data. Importantly, no such effects were observed in the Order-maintenance task data.

When we categorized individual letter lists, not by number of letters, but by the alphabetic distances between letters, a monotonically increasing activation trend was observed in the encoding period of order maintenance trials (slope = .78; $r^2 = .6$; $t = 1.9$, $P = 0.09$). We did not observe similar effects in other task periods or in ventral PFC. Importantly, no such effects were observed in the Alphabetic-reordering task data. These studies represent our initial efforts to understand the cognitive grouping mechanisms that may be reflected in the increases in dorsal PFC neural activity observed during high-demand DRT performance. The results of these analyses are important because they suggest intriguing clues about the nature of interactions between WM and long-term memory in PFC. Future research involving manipulations of task, stimulus type (e.g. object and spatial), and list composition will be necessary to illuminate the cognitive processes reflected by load-dependent changes in PFC activity.

Conclusion: the effects of task-related variables on PFC activity during DRT performance

In this report, I have detailed the basis for positing a memory-organization hypothesis of PFC function. Primate,

neuropsychological, neuroimaging, and behavioral research suggests support for the idea that load-related dorsal PFC activity observed during WM encoding reflects organization operations aimed at consolidation of information for efficient storage and retrieval. This hypothesis has been useful in generating predictions that have been tested in our laboratory and in the laboratories of others.

A key prediction of this hypothesis is that load-related dorsal PFC activity should be observed early in the DRT task sequence when subjects are encoding and presumably organizing incoming information. This prediction has endured empirical scrutiny thus far. Analysis of methods in different studies suggests that apparent variance in results between studies could be due to, among other things, variation in temporal dynamics between studies. Variation in the time available for encoding, the nature of the regressors used to model HRF-neural activation coupling (i.e. convolved boxcars or spike-trains), and regressor-spacing have all contributed to apparent variations in results.

Table 1 suggests two other task-related variables that could contribute to inter-study variance. One factor suggested by Table 1 is the one most extensively considered in verbal DRT neuroimaging studies, memory-load. Table 1a indicates that the block design studies considered here consistently show dorsal PFC activity when the memory-load exceeds five letters (the Paulesu et al., 1995 result is exceptional due the nature of the baseline condition, see above). This result is also present in the event-related studies in sections b and c of Table 1. A second factor that has varied between studies is the number of different memory load conditions. It can be observed in Table 1b and c that number and extent of memory-loads jointly influence the task periods in which memory-load effects are observed. This between-study variation could affect the strategies that subjects employ in these different contexts. Strategy-switching is known to add executive demand to cognitive tasks. Additionally, it is known to affect neural activity in dorsal PFC. A number of studies by now indicate that strategic organization and strategy-shifting processes are mediated by dorsolateral PFC (Bor et al., 2003; Prabhakaran et al., 1997, 2001; Smith et al., 2001; Jenkins et al., 1994; Deiber et al., 1991). Further research is needed to elucidate the interactive effects of the number and extent of memory loads on PFC neural activity during DRT performance.

The second prediction of the memory-organization hypothesis is that continuous load-related dorsal PFC activation during DRT encoding should be observed across memory-load conditions. Results of studies testing this prediction have been more equivocal. Reanalysis of Rypma et al.'s (2002) results indicate, consistent with our earlier results and results of other studies, that memory-load effects in dorsal PFC during encoding may be limited to memory loads ranging up to 6 letters. This result is important as it indicates boundary conditions for the memory-organization hypothesis and suggests that other strategies or mechanisms may prevail when memory demand gets very high. One interpretation of these results is that beyond this memory load, subjects implement a funda-

mental strategy change. Future research using high memory-demand conditions could elucidate the meaning of these PFC activation changes at very high memory-loads.

The third prediction of the memory-organization hypothesis was that similar load-related dorsal PFC activation patterns should be observed in item-reordering and item-maintenance conditions. We tested this hypothesis by directly comparing reordering and order-maintenance tasks within the same subjects, across a range of memory load conditions (Eldreth et al., unpublished observations). The results suggested that qualitatively different operations are performed in these two types of task. Subsequent analyses suggested that order-maintenance tasks may depend on inter-item binding and that reordering may depend on alphabetic chunking. This result also places important boundaries on the memory-organization hypothesis. It suggests that speculation about the nature of early DRT processing cannot rest on findings from reordering tasks as I have assumed. They suggest that the neural basis of WM chunking operations should focus on their possible relationship to binding operations such as those investigated by Mitchell et al. (2000) and Prabhakaran et al. (2000).

Research that endeavors to understand the nature of the relationships between task-demands and neural activity must pay careful attention to the nature of subtle task variables such as list composition. For instance, our analyses suggest that the letter sequence MLPN may place relatively minimal demands on manipulation mechanisms as these letters are contained within the same alphabetic chunk. The letter sequence BKPV may place relatively greater demand on manipulation mechanisms because these letters are contained in different alphabetic chunks.

Examination of between-study variances conducted in this report suggests that there are a number of important factors to which attention must be paid to meaningfully interpret results of PFC neural activity during DRT performance. One set of factors is technical in nature. These include the temporal characteristics of DRT tasks (i.e. how much time is permitted for encoding, maintenance and retrieval task components, cf. Jha and McCarthy, 2000), the nature of the covariates (e.g. box-cars, spike trains), and their spacing (Postle et al., 2003; Zarahn et al., 1997). A second set of factors is psychological in nature. These include variations in task demand, such as instructions to maintain letters, to maintain their order, or to reorder them; the number of memory-loads used in the DRT and the extent of memory-load. There has been a growing recognition of the importance of task factors in WM performance (e.g. Postle, 2003). The analyses of the present study indicate that these factors comprise a subset of subtle task variations that can affect PFC neural activity. Further study, and systematic manipulation, of these variables in future research can assist in elucidating the role of PFC in DRT performance.

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