

Maintaining structured information: An investigation into functions of parietal and lateral prefrontal cortices

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Abstract

Working memory – including simple maintenance of information as well as manipulation of maintained information – has been long associated with lateral prefrontal cortex (PFC). More recently, evidence has pointed to an important role for posterior parietal cortex (PPC) in supporting working-memory processes as well. While explanations have emerged as to the nature of parietal involvement in working-memory maintenance, the apparent involvement of this region in working-memory manipulation has not been fully accounted for. We have hypothesized that parietal cortex, through its representation of spatial information, in conjunction with dorsolateral PFC, supports organization of information (manipulation) and the maintenance of information in an organized state. Through computational modeling, we have demonstrated how this might be achieved. Presently, we consider a pair of fMRI experiments that were designed to test our hypothesis. Both experiments involved simple working-memory delay tasks with contrasts between maintenance of information in organized and unorganized states, as well as contrasts between high and low working-memory load conditions. Two different kinds of organization, associative (grouping) and relational, were employed in the two studies. Across both studies, superior parietal cortex (BA 7) demonstrated a significant increase in activity associated with maintenance of information in an organized state, over and above any increases associated with increased working-memory load. During the delay period, dorsolateral PFC (BA 9) exhibited similar increases for both organization and load; however, this region was particularly engaged by organization demand during the initial cue period. Functional connectivity analysis indicates interaction between dorsolateral prefrontal cortex (DLPFC) and superior parietal cortex, especially when organization is required.

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1. Introduction

Central to the performance of complex cognition is the ability to hold information in mind in a manner, and for a length of time, such that it can be used in some computation or cognitive operation. The mechanism that supports this *working-memory* capacity has been long associated with lateral prefrontal cortex (latPFC). Early evidence for this link has come from primate lesion studies (Butters & Pandya, 1969; Jacobsen, 1936) and from single-unit recording (Fuster & Alexander, 1971; Goldman-Rakic, Funahashi, et al., 1991). More recently,

especially with the advent of neuroimaging, evidence has accumulated that in addition to latPFC, a second brain region, posterior parietal cortex (PPC), also plays an important role in working memory; however, the nature of PPC involvement in working memory has been subject to considerable debate (for review, see Wager & Smith, 2003).

One hypothesis is that PPC is involved in working memory for certain domains of information, especially spatial information. This idea is supported by the fact that PPC, including both the superior parietal lobe (SPL, BA 7) and the inferior parietal lobe (IPL, BA 40), is frequently activated during spatial working-memory storage tasks (Courtney, Ungerleider, et al., 1996; Wager & Smith, 2003). In fact, these parietal regions are involved in a wide range of spatial tasks—not just in working memory (see, e.g. Andersen, 1995; Kesner, Farnsworth, et al., 1991). However, it has also been shown that IPL activation is strongly

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sociated with phonological working-memory tasks (Jonides, Schumacher, et al., 1998; Wager & Smith, 2003), suggesting that this region may be important for phonological storage as well.

The hypothesis about domain-specificity of PPC in working memory has its analogue with respect to latPFC: it has been proposed that dorsolateral prefrontal cortex (DLPFC) mainly subserves working memory for spatial information, while ventrolateral prefrontal cortex (VLPFC) mainly subserves working memory for object information (Wilson, Scaiaidhe, et al., 1993). Anatomical evidence lends credence to this view, insofar as VLPFC is relatively well connected to inferotemporal cortex, a region thought to be the locus of object representation, while DLPFC is better connected to PPC and its representations of spatial information (Petrides & Pandya, 1984). However, this domain-specific view has been contradicted by the demonstration of VLPFC involvement both in the maintenance of spatial formation and in the maintenance of non-spatial information (Owen, Stern, et al., 1998).

An alternative theory holds that VLPFC supports basic maintenance, or online storage, of information in any domain, while DLPFC supports higher level control processes variously referred to as updating, monitoring, or manipulation (D'Esposito, Postle, et al., 1999; Petrides, 1995). This process-specific theory was motivated by evidence that mid-VLPFC lesions in monkeys selectively impair performance on self-ordered pointing tasks (Petrides, 1995), and also by neuroimaging data showing increased DLPFC activity when subjects were asked to alphabetize a set of letters during the delay period of a working-memory task (D'Esposito et al., 1999). It has been shown that rearranging items according to preference similarly engages DLPFC (Wagner, Maril, et al., 2001), as does reversing the order of a set of items (Crone, Wendelken, et al., 2006; Sakai & Passingham, 2003).

A number of brain imaging studies have failed to show a sharp division of maintenance and manipulation processes onto VLPFC and DLPFC, respectively (Veltman, Rombouts, et al., 2003). This is perhaps not surprising, given that manipulation of items in working memory relies on their maintenance, and given the strong interconnection between VLPFC and DLPFC. And several recent studies provide additional forms of evidence for a specific role for DLPFC in manipulation processes. One study showed that increased DLPFC activity associated with manipulation is predictive of subsequent long-term memory (Lumenfeld & Ranganath, 2006). In a developmental fMRI study, children, who make disproportionately more errors than adults on trials requiring manipulation (item order reversal) relative to maintenance, exhibited an adult-like activation profile over VLPFC but failed to recruit right DLPFC during the period when manipulation was required (Crone et al., 2006). Finally, transcranial magnetic stimulation of DLPFC has been shown to specifically disrupt manipulation (Postle, Ferrarelli, et al., 2006).

Regardless of the success of the process-specific theory in explaining activity within latPFC, the theory fails to address one major relevant finding: a recent meta-analysis of working memory indicates that PPC (in particular, SPL), bilaterally, is strongly associated with the updating, order, and manipulation processes that have been linked to DLPFC (Wager & Smith, 2003). In

fact, based on evidence from the meta-analysis, the association of SPL with these high-level working-memory processes may be stronger than that of DLPFC.

1.1. Hypothesis—PPC, latPFC, and organization in working memory

What, then, is the role of PPC in working memory, and specifically of SPL in high-level working-memory processes such as manipulation? If PPC serves as a storehouse of specific kinds of information, such as spatial and phonological representations, then it is likely that this region does play a role in their maintenance, and much evidence suggests that this is indeed the case (Jonides et al., 1998; Wager & Smith, 2003). However, a role in basic maintenance does not account for the data implicating superior parietal cortex involvement in working-memory manipulation. To account for this involvement, and in consideration of evidence that this region is also involved in representation of spatial information, we propose that SPL supports working-memory manipulation – or more generally, working memory involving organized content – by virtue of its rich representation of space and spatial relationships. Specifically, we propose that while the primary role of SPL is spatial processing, in the presence or absence of working-memory demand, it is the spatial relational representations stored in SPL that are the substrate for organization of items in working memory. For example, in a task that requires one to arrange or rearrange a set of items according to some rule (e.g. alphabetize letters, arrange pictures by size or preference), spatial relational representations in SPL (e.g. concepts like *above* or *between*) provide the structure or organizational framework into which the items are placed and maintained.

Manipulation can be said to occur whenever changes are made to organizational structure; this would happen whenever a new organization is created (e.g. arranging a set of abstract pictures) or when item placement is altered (e.g. reversing words in a list). Manipulation should strongly recruit SPL. Maintenance of arbitrary structure or organization over a set of items, though not an example of manipulation, should also involve SPL; thus, neurons involved in spatial relational representations in SPL would exhibit sustained activity to support maintenance of organizational structure.

It should be noted that our hypothesis is similar to another proposal, that numerical or magnitude representations in SPL support maintenance of order information, which was put forward to explain SPL activation in a serial order working-memory task (Marshuetz, Reuter-Lorenz, et al., 2006; Marshuetz, Smith, et al., 2000). Our hypothesis can be considered a generalization of this idea, insofar as numerical representations are probably related to spatial representations and serial order is one type of organization.

Other previous studies are also relevant to the current investigation. The finding that left parietal cortex is engaged during the transformation of letter strings in an abstract symbol-manipulation task (Anderson, Qin, et al., 2004) is highly relevant, as the transformation of letter strings can be seen as an example of organization or manipulation in working memory.

Chunking – the grouping of items in order to improve memory performance – may have much in common with the organization mechanism examined here; recent evidence suggests that lateral prefrontal cortex is particularly important for chunking (Bor, Cumming, et al., 2004).

If spatial relational representations in SPL are to support organization of items in working memory, then there must be some mechanism by which maintained items are linked to these spatial representations. Establishing and maintaining this dynamic binding, we propose, is a key function of DLPFC. If VLPFC plays the major role in item maintenance, as the process-specificity theory suggests, then either VLPFC directly stores working-memory items, or more likely, it provides connections to posterior cortical representations of these items. DLPFC, which is strongly linked both to VLPFC and to PPC, is in position to create dynamic connections between VLPFC item representations and PPC spatial representations. Thus we posit that DLPFC plays a key role in setting up, and probably also in maintaining, organizational structure.

This hypothesis has been examined initially through the implementation of a connectionist model (Wendelken, 2002). The model consists of separate network modules representing VLPFC, DLPFC, SPL, and IT (inferotemporal cortex object representations)—labeled VL, DL, SP, and IT respectively, in Fig. 1. Recurrent connectivity between VL module “maintainer” nodes and nodes involved in item representation (IT) implements a form of working memory: select representations (e.g. “A”, “C”, and “D” in Fig. 1) are kept active and become accessible via nodes in VL. Circuitry of the DL module serves to dynamically bind VL nodes to spatial relational representations (e.g. “q”, “r” in Fig. 1) in the SP module. This dynamic binding

accomplished using temporal synchrony, whereby synchronous firing of item nodes with spatial relational role nodes (representing, for example, x in the relation $above(x,y)$) temporarily place the item within the relation. (In Fig. 1, color indicates temporal synchrony, and thus item “C” is depicted as the first role-filler in the relation “ $q(x,y)$.”) In this model, maintenance of one or more items involves sustained activity of nodes in VL and IT. Maintenance of items in an organized state involves these modules as well as sustained activity of nodes in DL and especially SP. The design of this implemented model is based in part on the SHRUTI model of knowledge representation and reasoning (Shastri, 1999; Shastri & Ajjanagadde, 1993); in particular, the encoding of objects and spatial relations are borrowed directly from this previous model.

1.2. Experiment motivation and overview

The model outlined above provides a detailed elaboration of the proposal, and serves to demonstrate the viability of the proposed mechanisms. It cannot, however, confirm or reject the basic hypothesis. It is necessary to test the model's predictions, particularly those that are novel or unique.

The model predicts that both SPL and DLPFC should be especially active, and interactive, whenever maintenance of items in working memory is supplemented with the need to create or maintain an organizational structure over those items. On the other hand, it predicts that VLPFC should be primarily sensitive to the number of items to be maintained (i.e. working-memory load), and should be relatively less affected by organizational demand (though not necessarily unaffected, given its close interaction with DLPFC). The differing predictions for VLPFC and DLPFC are largely consistent with those made by the process-specificity theory; however, our model predicts increased DLPFC not only for active manipulation or rearrangement of items in working memory, but more generally to support the establishment and maintenance of any organizing schema. In addition, while the process-specificity theory makes no mention of a role for SPL, our hypothesis predicts SPL activation during both the creation and maintenance of organized item sets. Furthermore, while both our proposal and that of Marshuetz et al. (2000) suggests that SPL activity should be associated with serial order memory, our hypothesis also predicts that SPL should be engaged during other kinds of organization. In fact, many studies of working-memory manipulation have focused narrowly on serial order, so a broadening of this focus to other types of organization is an important goal of the present work.

We do not assume that *all* neurons in SPL, or in any particular sub-region thereof, are involved in the representation of spatial relations. Similarly for other modeled regions, model neurons are expected to be representative of only a fraction of the neurons in a region. Thus, our model can only make predictions about relative activation for appropriate contrasts, and cannot predict overall levels of activation.

To test our hypothesis, we sought to probe neural activity in prefrontal and parietal cortices that accompanies the creation and maintenance of organized item sets. This article describes two experiments that were designed with this goal in mind.

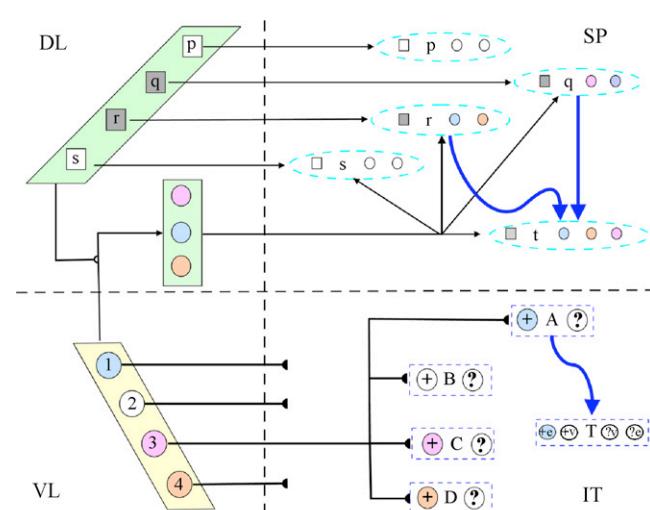


Fig. 1. Depiction of a connectionist model of working memory. Each of the four parts of the model plays a specific role in the maintenance and organization of items in working memory. Structures within IT provide for long-term representation of objects, and structures within SP provide for long-term representation of spatial concepts. These modules are meant to correspond, roughly, to inferotemporal cortex and superior parietal cortex. Nodes within the VL module (corresponding to VLPFC) connect to IT object structures and support sustained activation of these representations. Nodes within the DL module (corresponding to DLPFC) link active VL nodes to spatial representations in SP, to effect the organization of maintained items.

both of these experiments constitute working-memory delay tasks in which an organization condition was contrasted with non-organization control conditions. Two different types of organization were chosen for the two experiments: Experiment 1 involved subdivision of a set of items into groups, while Experiment 2 involved organization according to a set of relationships. In addition to the main organization contrast, we examined our assumptions about VLPFC, and sought to rule out explanations of organization as a simple load effect, by including both high and low working-memory load control conditions. For the investigation of organization as well as load, our primary focus is on delay-period activity, since both effects can be most unambiguously detected during this stage.

Materials and methods

1. Participants

For Experiment 1, 15 right-handed young adults were scanned (9 males, age = 21.2 ± 3.2). Fifteen additional right-handed adults (10 females, age = 23.9 ± 4.4) were scanned for Experiment 2. All subjects were compensated for their participation in the study. Because all subjects remained sufficiently still in the scanner (we had planned to exclude runs that contained multiple movement spikes in excess of 2 mm) and performed significantly above chance on all conditions, no subject data were excluded from analysis.

2. Task conditions

Both experiments included three variations of a delayed item-recognition task: (1) a condition that required organization of items in WM, hereafter labeled ORG, (2) a condition without organization but with a high WM load, hereafter labeled HIGH, and (3) a condition without organization and with a low WM load, hereafter labeled LOW. The items to be remembered (i.e. the target set) were alphanumeric characters: letters and single-digit numbers in Experiment 1, and consonants and single-digit numbers in Experiment 2. The experiments differed primarily with regard to the type of organization required; two different types of organization were probed in the two experiments. In Experiment 1, grouping was the mode of organization. Groups of letters were indicated by color, and subjects were instructed to remember, for each trial, which letters had appeared and how they were grouped. In Experiment 2, relational organization was examined. Items in the ORG condition were organized according to an arbitrary relational structure, which was indicated by a set of arrows.

3. Experimental procedure

Experimental paradigms are depicted in Fig. 2. In Experiment 1 (grouping), there were always six letters presented for the ORG condition, and these were divided into three groups of two letters each. Each probe consisted of two letters (at least one of which had just been presented), and subjects indicated via button press whether or not those two letters had been presented as part of the same group. For both the HIGH and LOW conditions, all letters were presented in the same color. For the HIGH conditions, as for the ORG conditions, six letters were presented, whereas for the LOW condition, only three letters were presented. For these two conditions, as for the ORG condition, the probe consisted of two letters; here, subjects were instructed to indicate whether or not both letters were included in the initial set.

In Experiment 2 (relational organization), there were always four letters present for the ORG and LOW conditions, and seven letters present for the HIGH condition. This latter number was chosen to match the total number of objects (letters plus arrows) used for the ORG condition. The organizational structure, determined by the placement of three arrows, was randomly generated for each trial, and was constrained to be a polytree (i.e. an arbitrary directed graph, without loops of any kind). Subjects were instructed to think about each arrow representing some transitive relationship, such as greater-than. The probe

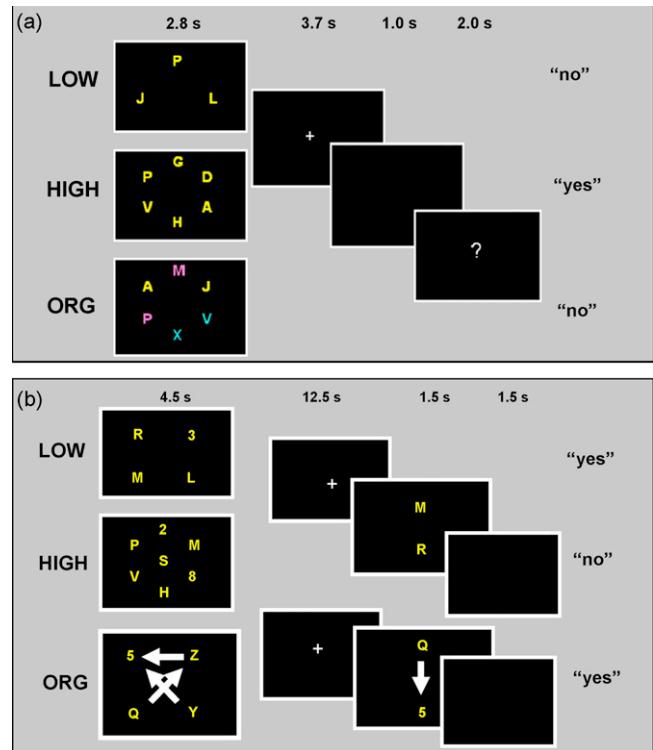


Fig. 2. Experimental paradigms. Both experiments included low-load (LOW), high-load (HIGH) and organization (ORG) conditions. In Experiment 1 (a), letters were grouped by color in the ORG condition. In Experiment 2 (b), relational organization over the set of letters was indicated by three arrows. Task timing is shown along the top for each experiment, and sample correct responses are shown on the right side.

always consisted of two letters, with one arrow added for the ORG trials. For the two non-organization conditions, the subject task was equivalent to Experiment 1. For ORG trials, subjects were instructed to respond positively if the relation represented by the probe stimulus was valid given the initial relational structure. This could be the case if the probe exactly matched one of the relations in the target set or if it represented a transitive inference from the target set. In both experiments, at least one of the two probe letters was from the memory set, and no letter appeared in successive trials.

Both experiments had the same basic trial structure. A brief prompt was followed by presentation of the cue stimulus, followed by a blank screen. After a delay, probe items were briefly presented and subjects had a short window of opportunity to make a yes or no button press response. Specific timing details of both experiments are shown in Fig. 2. Of note, the delay period was significantly longer in Experiment 2 (12.5 s) than in Experiment 1 (3.7 s). The longer delay period was used in the second experiment to allow for separation of delay-period activation from activation associated with cue and response.

Trials were presented in pseudorandom order, with jittered fixation periods of 2–12 s between each pair of trials. Each experiment included 40 trials per condition. Experiment 1 involved four 8-min scans, with 10 LOW trials, 10 HIGH trials, and 10 ORG trials per scan. Experiment 2 involved five 10-min scans, with 8 trials of each condition per scan.

2.4. fMRI data acquisition

Basic fMRI acquisition parameters were the same for both experiments. Scanning was performed on a 1.5 T MRI scanner (General Electric Signa Advantage, Medical Advances Inc., Milwaukee, Wisconsin, USA) at the University of California at Davis Imaging Research Center, using a standard whole-head coil. Visual stimuli were back-projected onto a screen that was viewed through a mirror mounted above the MRI head coil. Head motion was restricted with foam inserts that surrounded the head. Stimulus presentation and response acquisition

were controlled by the presentation software system (<http://nbs.neuro-bs.com>). Subjects held a button box in their right hand, and a microphone tube for communication in their left hand.

Functional data were acquired using a gradient-echo echo-planar pulse sequence (TR = 2.0 s, TE = 40 ms, 24 axial slices, 3.44 mm × 3.44 mm × 5 mm). Two hundred and fifty four and three hundred volumes were acquired per scan, for Experiments 1 and 2, respectively. The first four volumes of each scan were discarded to allow for T1-equilibration effects. In addition to the functional scans, high-resolution T1-weighted (SPGR) coronal anatomical images were collected, as well as coplanar anatomical images.

2.5. Data preprocessing and analysis

Data were preprocessed and analyzed with SPM2 (Wellcome Department of Cognitive Neurology, London). Functional images were corrected for differences in slice acquisition timing, and were realigned to the first volume by means of rigid body motion correction with sinc interpolation. Structural and functional images were spatially normalized to T1 and EPI templates, respectively. These templates are based on the MNI stereotaxic space (Cosoco, Kollokian, et al., 1997), an approximation of Talairach space (Talairach & Tourneaux, 1988). The normalization algorithm consisted of a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions. During normalization, the volumes were resampled to 3 mm × 3 mm × 3 mm cubic voxels. Functional images were spatially smoothed with an 8-mm full-width half-maximum isotropic Gaussian kernel. The smoothed, normalized images were then submitted to statistical analyses.

For each experiment, general linear models (GLMs) incorporating task effects, session effects, and linear trends were used to analyze each subject's data. The specific GLMs utilized were designed to identify activity during the delay period of each trial, and also to identify activation associated with the initial cue. For Experiment 1, two GLMs were tested to this end: the first modeled neural activity as an impulse function placed at the midpoint of each delay period, while the second modeled neural activity as an impulse function placed at the onset of the initial cue for each trial. For Experiment 2, a single model was utilized, which incorporated impulse functions placed at cue onset, delay-period midpoint, and response time of each trial. Separate GLMs were utilized in Experiment 1 due to the relative brevity of the delay period and resultant difficulty of separating cue-related activity from delay-related activity within a single model. It should be noted that even with the current approach, this separation is incomplete: activation for the cue analysis may in fact be somewhat influenced by delay-period activity, and vice versa, in Experiment 1. The separation of cue-related activation from delay-related activation should be much more reliable in Experiment 2, due to the considerably longer delay period. Each GLM was used to compute the least-squares parameter estimate of the height of the best fitting synthetic response function for each condition at each voxel. Only correct trials were considered for each task condition; all error trials were modeled together as a covariate of no interest. High-pass temporal filtering with an upper limit of 120 s was applied to eliminate low-frequency noise from the data. Parameter estimates associated with each experimental condition were combined to produce contrast images, and associated T-maps, for target contrasts. The T-maps were thresholded at $p < .001$ (uncorrected), with an extent threshold of five voxels, to determine regions of activation associated with each contrast. This combination of height and extent threshold was expected, on the basis of prior simulations, to correspond to an alpha of approximately .05 after correction for multiple comparisons across cortical gray matter voxels (Forman, Cohen, et al., 1995; Poline, Worsley, et al., 1997). We report this and in some cases the less conservative $p < .005$ threshold in order to facilitate comparison between the two studies. We also report cluster p -values as determined by SPM2; activation clusters that passed our general threshold but that were associated with cluster p -values in excess of .05 are reported as marginally significant.

Timecourses were extracted from selected activation clusters using Marsbar and custom MATLAB scripts. Event-related timecourse were constructed by taking the first 16 s (Experiment 1) or 26 s (Experiment 2) of data following each cue onset, and averaging across trials for each condition. This simple model-free selective averaging was deemed suitable here as a complementary method to the GLM analyses.

Functional connectivity analysis was performed using the beta-series correlation method (Rissman, Gazzaley, et al., 2004), implemented via SPM2 and

custom MATLAB scripts. SPM's canonical HRF was fit to each occurrence of each condition and the resulting parameter estimates (betas) were sorted according to condition to produce a condition-specific beta-series for each voxel. The beta-series associated with functional ROI seeds (bilateral SPL, derived from the ORG > HIGH contrast in each experiment) were correlated with voxels in frontal cortex. Contrasts between correlation images were subjected to an arc-hyperbolic tangent transform to allow for statistical inference based on the correlation magnitudes. Group-level t -tests were performed on the resulting subject contrast images to produce group correlation contrast maps (as shown in Fig. 8).

3. Results

3.1. Behavioral performance

In Experiment 1, subjects were more accurate for the LOW condition (94% correct) compared with either HIGH (84% correct; $F_{1,14} = 17.57, p < .001$) or ORG (84% correct; $F_{1,14} = 26.9, p < .001$). They also responded more rapidly to LOW trials (1.35 s) than to HIGH (1.67 s, $F_{1,14} = 18.6, p < .001$) or ORG trials (1.61 s, $F_{1,14} = 14.1, p < .01$). There were no differences in performance between HIGH and ORG trials. In Experiment 2, subjects were again more accurate for the LOW condition (95% correct) compared with either HIGH (87% correct; $F_{1,14} = 19.4, P < 0.001$) or ORG (85% correct; $F_{1,14} = 10.33, p < .01$). They responded more slowly to ORG trials (1.79 s) than to either HIGH (1.56 s, $F_{1,14} = 27.7, p < .001$) or LOW (1.47 s, $F_{1,14} = 33.5, p < .001$). Thus, as expected, across both experiments, the low memory load condition proved easier (i.e. faster, more accurate, or both) than the high-memory load and organization conditions. The addition of organization demand slowed response times in Experiment 2 relative to the HIGH condition, but had no such effect on response times in Experiment 1 or on accuracy in either experiment. Performance is shown in Fig. 3.

3.2. fMRI results: working-memory load

The contrast HIGH > LOW (delay) reveals activation associated with working-memory load in both experiments (see Table 1 and Fig. 4). As expected, given the similarity of the no-organization conditions across the two experiments, the contrast maps proved quite similar. For both experiments, activation was observed in nearly identical locations in right DLPFC (BA 9), in supplementary motor area (BA 6), and on the left side extending from posterior VLPFC (BA 44) up through posterior DLPFC (BA 9) to premotor cortex (BA 6). Additional activations were observed bilaterally in inferior frontal gyrus (BA 47) in Experiment 2; activation in this region could also be observed at a weaker threshold of $p < .005$ in Experiment 1. In addition to the frontal cortex activations, load-related activations were also observed in both experiments bilaterally in superior parietal cortex. Each superior parietal activation cluster also extended into parts of inferior parietal cortex and precuneus.

3.3. fMRI results: organization

In each experiment, the contrast ORG > HIGH (delay) revealed regions of activation associated with maintenance of

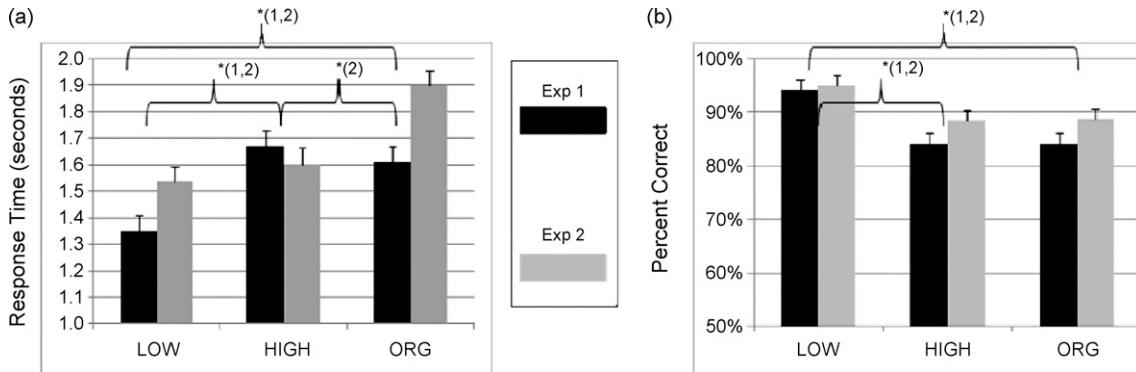


Fig. 3. Behavioral performance in each experiment, including response time (a) and accuracy (b). Performance on the low-load working-memory condition was significantly faster and more accurate than either of the other two conditions, in both experiments. Performance on the HIGH and ORG conditions was similar, except that response times were greater for ORG trials in Experiment 2.

Table 1

Activation clusters for the contrast HIGH > LOW (delay period), for both experiments, thresholded at $p < 0.001$ (uncorrected) with an extent threshold of 5 voxels

Region	x, y, z (mm)	Z	k	p (cluster)
Experiment 1				
L. PPC (BA 7, BA 40, precuneus)	-27, -63, 39	5.96	891	<0.001
R. PPC (BA 7, BA 40, precuneus)	30, -69, 48	5.06	891	<0.001
L. posterior latPFC (BA 9, 44)	-39, 15, 30	4.89	585	<0.001
L. premotor cortex (BA 6)	-42, -3, 33	4.55	585	<0.001
SMA (BA 6)	0, 0, 63	4.67	186	<0.001
R. DLPFC (BA 9)	42, 36, 36	4.18	39	<0.001
Cuneus/BA 17/BA 18	9, -84, 12	3.93	31	<0.001
Culmen/lingual gyrus	-9, -69, -12	4.37	66	<0.001
Experiment 2				
L. PPC (BA 7, BA 40, precuneus)	-27, -72, 36	5.18	394	<0.001
R. PPC (BA 7, BA 40, precunes)	33, -69, 48	4.94	244	<0.001
L. premotor cortex (BA 6)	-51, -6, 54	5.27	317	<0.001
L. posterior latPFC (BA 9, 44)	-51, 9, 30	4.56	317	<0.001
SMA (BA 6, 8)	-6, 6, 60	5.19	266	<0.001
R. SMA (BA 6)	30, -3, 72	4.39	52	<0.001
R. DLPFC (BA 9)	39, 36, 33	4.09	66	<0.001
L. insula	-33, 18, 0	4.17	75	<0.001
L. inferior frontal gyrus (BA 47)	-48, 9, 6	3.81	25	<0.001
R. inferior frontal gyrus (BA 47)	42, 15, 3	4.62	138	<0.001
L. fusiform gyrus	-42, -57, 24	4.06	39	<0.001

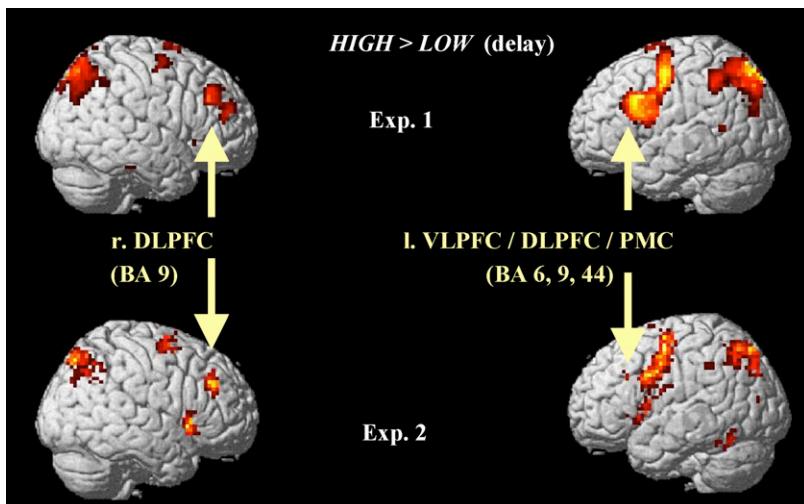


Fig. 4. Activation images from the contrast HIGH > LOW (delay) from Experiment 1 (top) and from Experiment 2 (bottom). Images are thresholded at $p < .001$ (uncorrected, with an extent threshold of 5 voxels).

Table 2

Activation clusters for the contrast ORG > HIGH (delay period), for both experiments, thresholded at $p < .001$ (uncorrected) with an extent threshold of 5 voxels

Region	<i>x, y, z</i> (mm)	<i>T</i>	<i>Z</i>	<i>k</i>	<i>p</i> (cluster)
Experiment 1					
L. SPL (7)	-21, 66, 60	4.54	3.5	54	0.004
R. SPL (7)	21, -69, 57	4.06	3.25	6	0.27
L. postcentral gyrus	-39, -33, 57	6.26	4.26	21	0.05
L. MTG/MOG (39, 19)	-45, -78, 9	6.42	4.31	14	0.10
R. MTG (21)	66, -33, -12	5.18	3.81	10	0.16
L. MOG	-30, -81, 12	4.98	3.72	27	0.03
R. STG	39, 12, -21	3.91	3.16	7	0.03
Experiment 2					
L. SPL (7)	-6, -78, 51	5.88	4.11	94	<0.001
R. SPL (7)	18, -78, 48	5.46	3.93	43	<0.001
L. IPL (40)	-39, -48, 39	5.56	3.97	145	<0.001
R. IPL (40)	42, -54, 48	4.38	3.42	10	<0.001
L. SMA/PMC (6, 8)	-24, 6, 57	6.79	4.44	226	<0.001
R. SMA/PMC/DLPFC (6, 8, 9)	39, 30, 39	5.09	3.76	86	<0.001

organized content (see Table 2 and Fig. 5). While this contrast revealed several clusters of activation for each experiment, the only regions that were activated across both experiments were left and right SPL (BA 7; right SPL cluster was only marginally significant in Experiment 1). In Experiment 2, inferior parietal cortex (BA 40) was also activated bilaterally as were parts of right DLPFC (BA 9), bilateral premotor cortex (PMC; BA 8) and supplementary motor area (SMA; BA 6). None of these regions were activated in Experiment 1 at $p < .001$; however, right posterior DLPFC/PMC was activated in Experiment 1 at the weaker threshold of $p < .005$. In Experiment 1, activation

was also observed in posterior middle temporal gyrus, on both the left and right sides; activation in this region was absent in Experiment 2 even at $p < .005$.

Because in Experiment 2 the number of letters in the ORG condition matched the number in the LOW condition (unlike Experiment 1, where ORG and HIGH conditions had the same number of letters), the ORG > LOW (*delay*) contrast was also examined for Experiment 2 as a further probe of organization-related activity (see Table 3 and Fig. 6). Activations present for this contrast include those present for ORG > HIGH (*delay*), and several additional locations as well. In particular, both left

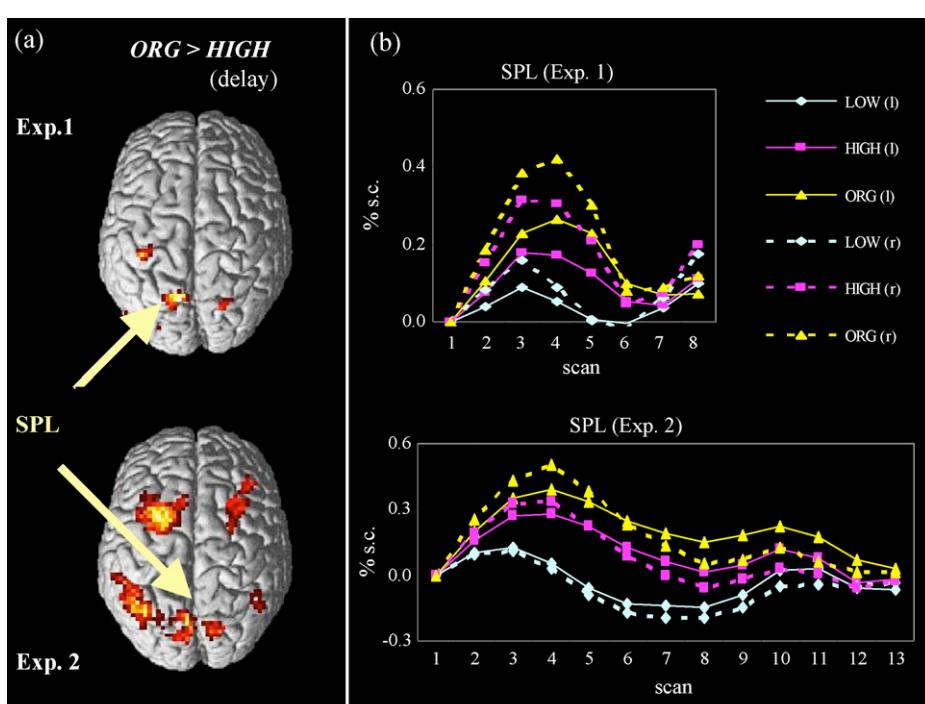
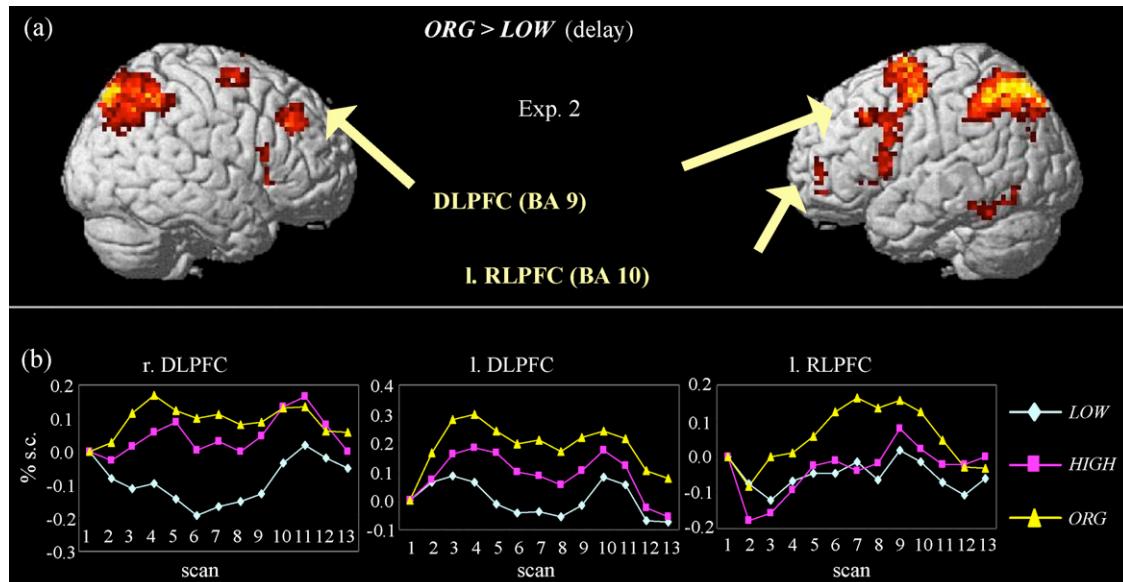


Fig. 5. (a) Activation maps from the contrast ORG > HIGH (*delay*), associated with maintenance of organized content, from Experiment 1 (top) and from Experiment 2 (bottom). Images are thresholded at $p < .001$ (uncorrected), with an extent threshold of 5 voxels. (b) BOLD timecourses from the left and right superior parietal activation clusters from each experiment.

Table 3

Activation clusters for the contrast ORG > LOW (delay period), for Experiment 2, thresholded at $p < 0.001$ (uncorrected) with an extent threshold of 5 voxels

Region	<i>x, y, z</i> (mm)	T	Z	k	<i>p</i> (cluster)
Experiment 2					
L. PPC (BA 7, BA 40, precuneus)	-36, -48, 45	9.8	5.3	1430	<0.001
R. PPC (BA 7, BA 40, precuneus)	36, -51, 48	8.3	4.9	1430	<0.001
Medial frontal (BA 6)	-3, 6, 60	7.8	4.8	562	<0.0001
L. middle frontal (BA 6)	-30, -9, 54	7.1	3.6	562	<0.0001
L. VLPFC (BA 44)	-57, 15, 15	5.6	3.9	562	<0.0001
L. insula	-30, 21, 0	4.6	3.5	11	<0.001
R. middle frontal (BA 6)	30, -6, 63	6.1	4.2	48	<0.001
R. VLPFC (BA 44)	54, 15, 18	5.1	3.8	126	<0.001
L. RLPFC (BA 10)	-30, 51, 0	5.8	4.1	19	<0.001
R. DLFPC (BA 9)	45, 36, 36	5.7	4.0	81	<0.001
L. middle occipital gyrus	-48, -66, -9	5.7	4.0	23	<0.001

Fig. 6. (a) Activation map for the contrast *ORG > LOW*, for Experiment 2, thresholded at $p < .001$ (uncorrected) with an extent threshold of 5 voxels. (b) BOLD activation timecourses from activation clusters in right DLPFC (top), left DLPFC (middle), and left RLPFC (bottom).

and right DLPFC (BA 9) were engaged for this contrast. An additional activation cluster in left rostralateral PFC (RLPFC, BA 10) was observed here.

Organization effects associated with the cue period were examined with the contrast *ORG > HIGH* (*cue*) (see Table 4 and Fig. 7). Of primary interest, similar activation clusters appeared in right DLPFC (BA 9) in both studies. Left DLPFC was activated as well in Experiment 1 (marginally significant), but left-side frontal activations were limited to PMC/SMA in Experiment 2. As in the delay-period analysis, activation was observed in bilateral SPL (BA 7).

4. fMRI results: functional connectivity

Task-related increases in functional connectivity between SPL and PFC were observed in both experiments. In Experiment 2, both the *HIGH-LOW* and *ORG-HIGH* contrasts revealed several prefrontal regions with increased connectivity to SPL (Fig. 8, bottom). However, increases related to load were located more ventrally, within ventral DLPFC and VLPFC, whereas

increases related to organization were located more dorsally, in DLPFC and also in RLPFC. In Experiment 1, no significant differences in functional connectivity with SPL were found between experimental conditions. However, examination of the whole-brain activation maps associated with the *HIGH* and *ORG* conditions, at an increased threshold of $p < .0001$ (uncorrected), reveals bilateral DLPFC for *ORG* but no regions of increased connectivity for *HIGH* (Fig. 8, top).

4. Discussion

4.1. Parietal cortex and organization in WM

These experiments show that superior parietal cortex (SPL, BA 7) is especially active during both the cue and delay periods of working-memory tasks that involve maintenance of content in an organized or structured manner. This finding suggests that bilateral SPL is involved in both the creation and maintenance of organizational structure in working memory. Since SPL is frequently linked to representation of spatial information, the

Table 4

Activation clusters for the contrast ORG > HIGH (cue), for both experiments, thresholded at $p < .001$ (uncorrected) with an extent threshold of 5 voxels

Region	x, y, z (mm)	T	Z	k	p (cluster)
Experiment 1					
R. DLPFC (BA 9, 46)	45, 15, 33	7.87	4.19	52	0.002
L. DLPFC (BA 9)	-45, 12, 27	4.40	3.43	8	0.18
R. SPL (BA 7)	21, -66, 51	4.58	4.08	31	0.014
L. SPL (BA 7)	-21, -66, 57	6.15	4.21	50	0.003
L. SPL (BA 7), precuneus	-24, -75, 39	6.51	4.35	78	<0.001
R. SPL (BA 7), precuneus	6, -63, 36	5.80	4.08	24	0.027
R. fusiform gyrus, declive	36, -60, -21	5.98	4.15	95	<0.001
L. inferotemporal gyrus	-48, -63, -6	4.19	3.63	18	0.05
L. MOG (BA 19)	-30, -81, 12	4.62	3.54	8	0.18
L. fusiform gyrus (BA 37)	-36, -57, -18	4.40	3.43	7	0.21
Experiment 2					
R. DLPFC (BA 9, 46)	51, 30, 36	5.17	3.80	7	<0.001
L. PMC (BA 8)	-36, 27, 51	4.85	3.58	10	<0.001
L. SMA (BA 6)	-27, 12, 60	4.97	3.71	39	<0.001
PPC/R. MOG (BA 7, 40, 19)	0, -75, 36	11.92	5.73	1441	<0.001
L. MOG (BA 19, 37)	-45, -69, 3	9.10	5.13	183	<0.001
Posterior cingulate	-12, -69, 12	5.16	3.80	11	<0.001
L. lingual gyrus	-9, -87, -15	4.93	3.69	11	<0.001
L. STG (BA 39)	-42, -60, 18	4.70	3.29	11	<0.001

present data support our hypothesis that parietal representations of spatial concepts are employed to impose organization on sets of items held in working memory.

However, alternative explanations of parietal activity in our task must be considered. The suggestion by Marshuetz et al. (2000) that magnitude representations in parietal cortex support working memory for item sequences could be relevant to our findings. Indeed, magnitude representations might be sufficient to support grouping, as employed in Experiment 1; under a magnitude encoding, each group could be associated with a different magnitude, much as items in a sequence. However, the relational organization in Experiment 2 does not lend itself eas-

ily to a magnitude encoding. The possibility for an item A to have specific relations to items B and C, without any specific relation between items B and C – a key characteristic of the polytree structure employed in Experiment 2 – is not consistent with a simple number line or magnitude representation, since items on a number line always have a specific relation to every other item on that line.

Parietal activity in working memory has been linked to phonological storage, a likely process in both of our experiments given the use of alphanumeric stimuli. The simplest prediction here is that phonological storage should increase with working-memory load; both SPL and IPL exhibit this pattern. It is possible

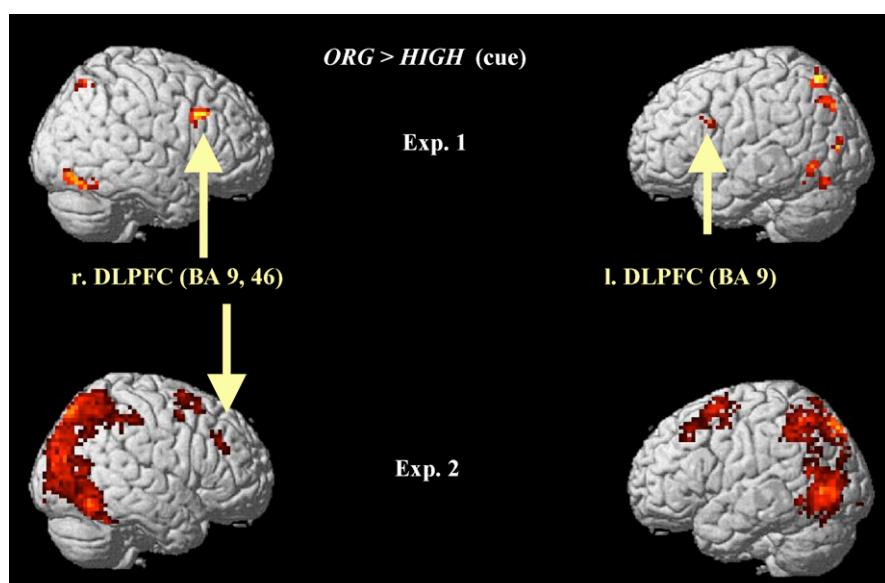


Fig. 7. Activation images from the contrast ORG > HIGH (cue), thresholded at $p < 0.001$ (uncorrected) with an extent threshold of 5 voxels, for Experiment 1 (top) and Experiment 2 (bottom). These images reveal areas of activation that are associated with organization during the cue period of the trial. Notably, activation in right posterior DLPFC is observed across both studies.

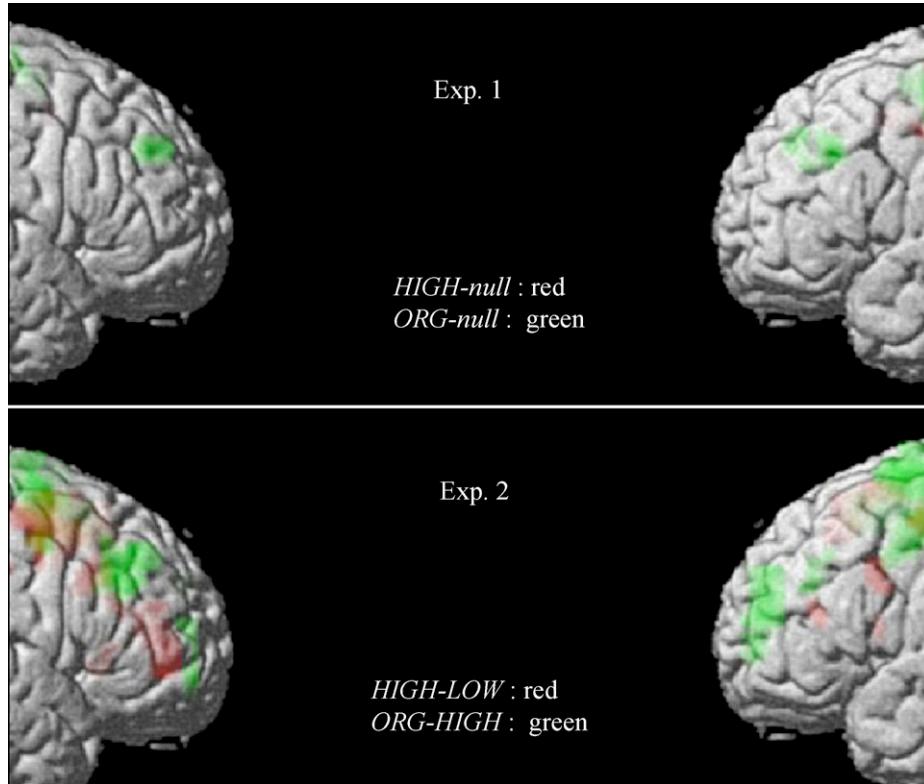


Fig. 8. Frontal regions showing increased correlation with a bilateral SPL seed, in Experiment 1 (top) and Experiment 2 (bottom). The beta-series correlation method was utilized. SPL seed regions were obtained separately for each study from the ORG-HIGH contrast. For Experiment 1, effects of condition (HIGH and ORG) are shown at the threshold $p < .0001$ (uncorrected, 5 voxel extent). Note that the contrast between these conditions did not actually reveal significant differences, even at $p < .005$. For Experiment 2, contrast between conditions is shown at the standard threshold ($p < .001$ uncorrected, 5 voxel extent).

at organization of items, independently of load, also tends to increase the requirement for phonological rehearsal (e.g. verbalization of groups or relationships). If this is the case, then our hypothesis regarding the involvement of spatial representations PPC cannot be easily distinguished from the hypothesis that PPC phonological representations play a primary role. While IPL is often active in tasks that involve working memory for phonological information (including the current experiments), most specific tests of phonological storage point to a primary role for IPL, and not SPL (Baldo & Dronkers, 2006; Becker, MacAndrew, et al., 1999; Jonides et al., 1998; Kirschen, Davison, et al., 2006; Paulesu, Frith, et al., 1993; Wager & Smith, 2003). Thus, the pattern of activity observed in IPL in our studies may well reflect phonological storage, but this is unlikely to be the case for SPL. However, specific involvement of SPL phonological storage cannot be completely ruled out on the basis of the current results alone.

One potential confound for Experiment 2 is the possibility that the presence of visuospatial stimuli (arrows) in the organization condition that is not present in the other conditions directly leads to increased parietal activity. Visuospatial representations SPL might be engaged simply by maintenance of the arrow stimuli, and not by maintenance of the more abstract relational link between the letters and numbers. However, this is unlikely for two reasons. First, subjects were instructed to maintain the organized items in a form that would allow for quick retrieval, and the timing of the task, with a relatively unhurried cue period

but a short response period, reinforced this instruction. Any attempt to maintain the cue stimulus in a predominantly visuospatial manner, without consideration of the items and their relationships, should have been subject to a large cost at retrieval time, since the retrieval cues did not match the original stimuli in terms of item locations or arrow directions. Indeed, in post-experiment introspective reports on strategy use, no subject reported that they simply tried to maintain the full visual stimulus, although a variety of strategies were described. A second, and perhaps more compelling, argument against the possibility that simple memory for visuospatial objects produced the results of Experiment 2 is that a similar pattern of SPL activation was observed in Experiment 1, where this potential confound was not present.

Although not designed to test the specific hypothesis described here, other studies have provided evidence that PPC is involved in working-memory organization, in particular for serial order memory (e.g. Bor, Duncan, et al., 2006; Marshuetz et al., 2000). In fact, a recent review of neuroimaging studies indicated that, among cortical Brodmann Areas, BA 7 is the most specialized for maintenance of order information (Wager & Smith, 2003). Thus, a primary contribution of the current study is the finding that this involvement of BA 7 in working memory is not limited to serial order memory, but also includes memory for other kinds of organization such as grouping and relational structure. That parietal involvement should be general to a wide variety of organizational schemes is a key prediction

of our model, since the representation of spatial information is taken by the model to be a highly flexible substrate onto which many different organizational structures can be mapped.

4.2. Lateral PFC and organization

Current findings strongly support the first main prediction of our working-memory model. However, the evidence relating to the other main model prediction – that DLPFC, like PPC, would be particularly engaged during working-memory maintenance by organization demand – was mixed. The results from Experiment 2, including increased right DLPFC activation during the delay period for ORG relative to HIGH, increased activation in left and right DLPFC for ORG relative to LOW, and the increases in dorsal DLPFC and RLPFC functional connectivity with SPL associated with organization demand, lend support to our hypothesis. It does appear that DLPFC, and possibly also RLPFC, supports maintenance of relationally organized content. However, evidence for organization-related delay-period activation in DLPFC in Experiment 1 was weak. There was no significant organization-related DLPFC activation for the delay-period regressor, and no significant difference in functional connectivity between conditions. There was, however, bilateral DLPFC activation for organization associated with the cue regressor, and at least the appearance of enhanced functional connectivity between SPL and DLPFC (though this was not statistically significant). The overall DLPFC result is consistent with two primary interpretations: either DLPFC is engaged by organization, the weak result in one of two tests notwithstanding, or DLPFC is specifically engaged by relational organization, but not by grouping.

Clear evidence of organization-related DLPFC increases associated with the cue period, rather than with the delay period, was found in both studies. This suggests that (right) DLPFC may be particularly involved in the setup or creation of an organized information set, but possibly less involved in the maintenance of organization over time. In our model of working-memory maintenance, DLPFC serves to link parietal spatial representations with posterior item representation areas. Although the model predicts sustained activity within DLPFC, as part of a reverberatory circuit, throughout the period of maintenance, it also predicts that activity within this region should be greatest during the initial establishment of that circuit. Thus, the presence of organization-related increases in DLPFC during the cue period, even if not during the delay period, is broadly consistent with the model that has been proposed.

4.3. Working-memory load

According to the process-specificity theory, the role of VLPFC in working memory is to support basic maintenance of information. Note that a VLPFC role in supporting maintenance does not imply that VLPFC is the locus of storage. In our connectionist model, nodes in a VLPFC sub-network perform this function via reverberatory interaction with posterior item representations. Maintenance of more items yields more interaction and thus more activity in the VLPFC sub-network,

so the straightforward prediction is that VLPFC activity should be especially sensitive to the number of items, captured in both studies by the HIGH > LOW contrast. The model does not predict that VLPFC should be further engaged by organization, since it places no additional demands on VLPFC during organization trials. However, the possibility that VLPFC exhibited organization-related activation due to its interaction with DLPFC could not be entirely discounted.

Results of the present study, particularly the observation of delay-period activity for HIGH > LOW (but not ORG > HIGH) across both experiments in left posterior VLPFC (BA 44), tend to support a role for VLPFC in maintenance but not organization. That the load effect is most evident in left BA 44 is expected, given that this VLPFC region in particular has in the past been strongly associated with maintenance of verbal and item information (Smith & Jonides, 1999). It should be noted that our manipulation of load is not process-pure, in the sense that mechanisms other than storage may be engaged in the transition from low load to high load (see next section).

With regard to VLPFC, neither our predictions nor our results here are particularly novel; however, the nature of VLPFC involvement in working memory is far from settled. It has recently been argued that (visual) working-memory storage is mediated entirely by posterior regions, and not by any part of PFC (Postle, Druzgal, et al., 2003). Current results are consistent with the idea that working-memory storage involves more than just PFC; it is highly likely that the inferior parietal activations observed in the current study are also related to storage of the alphanumeric items. However, the current findings do suggest that PFC also has a role to play.

4.4. Load, organization, and chunking

In addition to the expected activation of left VLPFC with increased WM load, load-related bilateral DLPFC and PPC activation was observed in both studies as well. These activations were not a priori predictions of our model, but were not unexpected in light of other studies of working-memory load. It has been previously suggested that DLPFC engagement during high-memory-load tasks reflects chunking of information, and that this is closely related to other conceptions of WM manipulation (Rypma, 2005). Chunking, a process that aids memory performance in high-load situations (Gobet, Lane, et al., 2001), may be similar to organization as has been described here—and especially similar to the grouping process in Experiment 1. Once chunks have been created, the process of maintaining chunked information should be just another example of the maintenance of organized information. To the extent that this is the case, our model would clearly predict DLPFC and SPL activation associated with chunking demand. Previous studies have indicated that chunking engages lateral PFC; specifically, this region was more activated in response to stimulus sets that afforded a natural grouping, relative to those that did not (Bor et al., 2004). Chunking thus serves as a highly plausible explanation for the DLPFC activations observed for the HIGH > LOW contrasts in the current experiments, as well as for the relative lack of activation observed for ORG > HIGH, especially in Experiment 1.

Despite the similarity between chunking and organization, there are some potentially important differences as well: chunking involves information reduction and it is implicit to a given task, whereas organization, as we have described it, involves an increase in information load and is an explicit part of the task. Engagement of chunking would predict some loss of item information, while engagement of organization processes would not. In a chunking condition in which structure over a set of items was encouraged as an aid to memory but not required for responding were contrasted with an organization condition in which structure was an essential part of the response, we would predict any similarities but also some differences. SPL, which appears to support maintenance of structure, should be most engaged by organization trials since it is those trials in which maintenance of organization is most essential to the task. However, it should be engaged to some extent by chunking trials as well, relative to those trials on which chunking does not occur. DLPFC, primarily supporting the creation of structure rather than its maintenance, should be engaged during the cue period for both chunking and organization trials. These predictions have yet to be tested; thus, the possibility that the presence of chunking-related activity in the high-working-memory-load condition might be masking organization-related activity, especially in DLPFC, cannot be discounted. Additional studies that address this complication directly will be needed to fully elucidate the role of DLPFC in working-memory organization.

An alternative explanation for the similar activation patterns observed for our manipulations of load and organization is that the activations observed for the organization condition relative to the high-load condition merely reflect added load (e.g. addition of the information that defines the organizing scheme). Based on the data, this possibility cannot be entirely discounted; however, there are several reasons why we expect that this is not the case. In Experiment 1, where the high-load and organization conditions involved the same number of items, there was an increase in information with the addition of the grouping indicator. However, grouping of items (chunking) should tend to reduce demands on working memory. In Experiment 2, though information-theoretic calculation suggests (though cannot prove) that the information stored for the high-load condition is actually greater than that stored for the organization condition, because the number of possible items (30 different alphanumeric characters) is greater than the number of possible arrows (2).

If participants explicitly maintained transitive relationships in Experiment 2 then this could indeed result in higher load for the organization condition. However, this is unlikely for several reasons. First, transitive relationships were only tested on a fraction of organization trials. Second, in piloting several versions of this task, we found that the cost of maintaining an additional relation (beyond three) far outweighed any benefit obtained from avoiding transitive inference at the time of the probe. Finally, participants' reports in response to a general question about strategy use did not suggest that they had tried to maintain the transitive relationships.

In addition to these task-related explanations, there is another reason to believe that organization-related SPL activation was

not simply an effect of load. Although SPL is frequently activated in contrasts between high and low working-memory load, as in the present study, the totality of the evidence suggests that it is not involved in simple object or verbal storage. In one study, which used letter arrays similar to those used here, a four-item load condition was contrasted with a one-item load condition; this contrast revealed activation in VLPFC, but not in SPL (Bunge, Ochsner, et al., 2001). Furthermore, in a meta-analysis of working-memory studies, it was shown that SPL is only infrequently activated by increases in verbal or object load (Wager & Smith, 2003). It is thus unlikely that SPL activation in the present study, or in others, reflects simple verbal or object load effects. SPL is frequently activated by spatial working-memory load (Wager & Smith, 2003). But given the assumption behind our model, that SPL encodes spatial relationships, this is entirely to be expected. Organization processes in our model do involve an increased load placed on spatial representations, and so may, from the standpoint of SPL activation, be indistinguishable from increases in spatial working-memory load.

Additional studies should help to further clarify the relationship between organization, load, and chunking. One planned follow-up will utilize a factorial design in which simple load (number of letters) and organization demand are varied independently. In addition, organization trials will be separated into those that involve transitive inference and those that do not. It is expected that the results of this follow-up study will confirm and extend those presented here.

In addition to the activations that were related to our hypotheses, several additional regions were activated by the manipulation of load or organization demands. Notably, premotor cortex (BA 6, 8) was activated bilaterally for high versus low working-memory load, and also in Experiment 2 for organization. Activity in this region often reflects motor preparation (Passingham, 1988), and it is possible that increased attention to response preparation was evident in the more difficult trials, or alternatively that the motor system was engaged to assist with maintenance (e.g. via simulated or actual finger-counting). Also of note was the bilateral activation in posterior temporal cortex and middle occipital gyrus linked to organization demand. It is possible that subjects' visualization of organized structure contributed to activation in this region.

5. Summary

Our model of working memory suggests specific functions of SPL, DLPFC, and VLPFC, in the short-term maintenance of organized content. Specifically, spatial representations in SPL serve as the substrate onto which organizational structure is mapped, DLFPC maps maintained items onto that relational structure, and VLPFC maintains and provides access to posterior item representations. This yields several predictions: (1) SPL should be engaged by organization demand in working memory, (2) DLPFC should also be engaged by organization demand, (3) SPL and DLPFC should functionally connected, especially when organization is required, and (4) VLPFC should be engaged by working-memory load. Of these predictions, the

first and fourth were confirmed in two separate experiments; evidence favors though fails to reliably confirm the second and third predictions as well. SPL (BA 7) was active in both experiments when it was necessary to maintain items in an organized manner. VLPFC, particularly left BA 44, demonstrated increased activation in the context of increased working-memory load, but was not additionally sensitive to organization demands. DLPFC (BA 9) was engaged in response to the cue for organization trials, relative to high working-memory load trials, in both experiments; however, DLPFC engagement by organization during the delay period was clearly evident in only one of the two experiments. Similarly, increased functional connectivity between DLPFC and SPL during organization trials was clearly evident in only one of the two experiments (though is suggested by the pattern of results in the other). The weakness of the evidence for organization-related DLPFC activation during the delay period may be attributable to the presence of chunking-related activity during high-memory-load conditions. Additional experiments that specifically address the similarities and differences between organization and chunking will be needed to fully clarify these results.

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