Maintenance versus manipulation in verbal working memory revisited: an fMRI study

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Abstract

Working memory (WM) is the ability to keep a limited amount of information "on line" for immediate use during short intervals. Verbal WM has been hypothesized to consist of neuroanatomically segregated components, i.e., maintenance (storage, rehearsal, and matching) and manipulation (reordering or updating), corresponding to ventrolateral and dorsolateral prefrontal cortex. Previous imaging studies of maintenance vs manipulation processes in WM have produced inconsistent results, which may have been due to methodological issues such as low statistical power and the use of insertion (subtraction) designs. In the present functional magnetic resonance imaging study we used parametric versions of both a prototypical maintenance task (Sternberg) and a prototypical manipulation task (*n*-letter back task) in 21 healthy subjects. Increased signal correlated with load common for both tasks was found in bilateral dorsolateral and anterior prefrontal, left ventrolateral prefrontal, and bilateral parietal regions. Workload × task interactions were found in bilateral dorsolateral prefrontal cortex for manipulation vs maintenance, but also for responding vs encoding (storage) in the maintenance task. Therefore, our data support a functional rather than a neuroanatomical distinction between maintenance and manipulation, given our finding that these tasks differentially activate virtually identical systems.
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Keywords: Verbal working memory; Parametric; Maintenance; Manipulation; fMRI

Introduction

Working memory (WM) is characterized as the ability to keep a limited amount of information "on line" for immediate use during short intervals (Baddeley, 1996). Despite extensive research, controversy still exists with regard to the precise anatomical specification of its components (reviewed by Fletcher and Henson, 2001). An important distinction made within the literature is between type of material (stimulus location vs stimulus form) and type of processes (manipulation vs maintenance). *Maintenance* has been defined as tranferring, maintaining (including rehearsal), and matching of information in WM (Fletcher and Henson, 2001), whereas *manipulation* refers to the additional reorganization or updating of each memory set.

It has been proposed that both subdivisions (location vs form, and manipulation vs maintenance) may correspond to distinct roles for dorsolateral prefrontal cortex (DLPFC, medial and superior frontal gyrus) and ventrolateral PFC (VLPFC, inferior frontal gyrus), in WM (Levi and Goldman-Rakic, 2000; Petrides, 1996). The former subdivision has been challenged in recent publications (Owen et al., 1998; Nystrom et al., 2000; Postle et al., 2000) where no support for a neuroanatomical specialization for stimulus type was found. The subdivision of process (manipulation vs maintenance) has strong affiliations to the neuropsychological model proposed by Baddeley (1996), who distinguished between a coordinating "central executive" and subsidiary "slave systems" (phonological loop and visuospatial scratch-pad).

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Neuroimaging studies of WM maintenance have commonly used delayed match to sample (DMTS) tasks such as the Sternberg task, in which subjects are shown a set of stimuli (letters or objects), which disappears after 5–10 s (encoding phase). This is followed by one (or several) single stimuli; the subject's task is to judge whether the single stimulus was contained in the initial set (responding phase). To isolate maintenance processes, this task can be contrasted against a baseline condition during which the subject is shown the set and the single stimulus simultaneously. The letter version of this task has been shown to give rise to significant activations in left parietal, inferior frontal, and motor areas (Awh et al., 1996; Paulesu et al., 1993) where the left inferior parietal regions may serve as a phonological store, and the VLPFC as a subvocal rehearsal system (Baddeley, 1996).

A prototypical WM maintenance and manipulation task, on the other hand, is the *n*-back task, in which the subject is presented with a series of individual stimuli and has to respond when a stimulus is identical to a stimulus *n* positions earlier (usually two or three). The letter version of this task is associated with left (or bilateral) activations in parietal cortex, VLPFC, and DLPFC in addition to motor areas, whereas spatial or object versions tend to activate right-sided regions (Owen et al., 1998; Smith et al., 1996). The extent to which these regions are specific for maintenance and/or manipulation in WM is not clear from these data, as multiple (sensory, cognitive, and motor) functions are required to perform these tasks.

A potential drawback in many previous WM imaging studies is their use of subtraction designs, where the specificity of active vs baseline differences for the (cognitive) function under study is often questionable (Friston et al., 1996; Sidtis et al., 1999). This was demonstrated by D'Esposito et al. (1998), who reported that some of the lateral PFC regions identified by subtracting a nonmnemonic baseline from the active condition during a two-back task were also activated when comparing this nonmnemonic task to a low-level baseline. To improve specificity, several researchers have used parametric versions of these WM tasks (Braver et al., 1997; Jansma et al., 2000; Nystrom et al., 2000; Rypma et al., 1999), enabling identification of regions in which activity increases with task load. Both Braver et al. (1997) and Jansma et al. (2000) were able to show that activity in DLPFC and parietal cortex increased linearly with task load during performance of the letter and spatial version of the *n*-back, respectively. This approach, however, does not allow identification of subprocesses within WM. For example, in the Rypma et al. (1999) study it was found that during performance of the Sternberg task, six-letter strings compared to three-letter strings (against a one-letter string baseline) produced additional activations in L DLPFC. The authors explained this as due to strategic encoding differences, although from their data could not be assessed whether these activation differences arose during encoding/rehearsal, responding, or both.

Recently, a new method to separate component processes has been provided by the enhanced temporal resolution of event-related functional magnetic resonance imaging (fMRI) (Cohen et al., 1997; D'Esposito et al., 1999; Rypma and D'Esposito, 1999). In the study by Rypma and D'Esposito, activations in DLPFC during a DMTS task were load-dependent during encoding, but not responding, whereas VLPFC activations did not show an effect of memory load. It was therefore concluded that DLPFC may be specifically involved in encoding during a WM task, as was also proposed in their earlier article (Rypma et al., 1999). These authors did not, however, report encoding × responding comparisons, although their data indicate that DLPFC was activated primarily during responding. This would suggest the involvement of executive processes during responding, for example, due to searching WM contents and response selection. In the Cohen et al. (1997) study, where a parametric *n*-back task was used, the only region showing an interaction between maintenance (storage) and manipulation (set updating) was Broca's area, explained in terms of subvocal rehearsal of verbal material rather than updating. The latter finding is difficult to reconcile with a specific role for DLPFC in manipulation of WM material, although the reasons for this failure to identify manipulation-specific regions are unclear. A common problem in event-related designs, however, is their relative lack of power compared to otherwise identical blocked designs.

An alternative means to compare maintenance and manipulation is to utilize two tasks in the same group of subjects, so that commonly activated areas as well as task by region interactions can be identified. Until now, most investigators have used "difficult" and "easy" variants of the same task, with and without manipulation (e.g., alphabetization) of stored material. A potential methodological problem is therefore that task type is confounded with task difficulty unless both maintenance load and manipulation load are varied. In several studies, evidence for a neuroanatomical manipulation/maintenance distinction was found, although the areas associated with manipulation were not uniform (L parietal cortex (Collette et al., 1999), L DLPFC (Postle et al., 1999; Stern et al., 2000), and R DLPFC (Tsukiura et al., 2001; Wagner et al., 2001), respectively). Possible explanations include differences in task paradigms, and a lack of sensitivity due to a small number of subjects.

In the present study, we adopted a different approach. In order to specifically assess both common and differential activations, we employed parametric versions of the two prototypical WM tasks described earlier. In our version of the Sternberg task, maintenance load (defined as the number of items which have to be kept "on line") was varied by using string lengths of two to seven letters, whereas the *n*-letter back task contained four steps (baseline and one to three back). We also included a relatively large ($n = 21$) sample of subjects to increase sensitivity. We hypothesized that increasing task load in both tasks would be associated with increasing activation in the lateral prefrontal–parietal

network described earlier. We also expected that increased manipulation load (as in the *n*-back), but not maintenance load, would lead to increased dorsolateral prefrontal activation. However, because maintenance load increases primarily during the Sternberg (two to seven items in our version, compared to one to three for the *n*-back), we also expected task by region interactions in left parietal cortex, in view of its putative role in phonological storage. We performed an additional analysis in which encoding/rehearsal and responding during the Sternberg were modeled as different conditions. This allowed us to investigate task load-related activations during encoding vs responding. Whereas we expected that VLPFC and left parietal cortex would be activated during both encoding/rehearsal, and responding, we wanted to explore whether DLPFC would be activated in a load-dependent manner during encoding (Rypma et al., 1999; Rypma and D'Esposito, 1999) or due to additional executive demands during responding.

Materials and methods

Subjects

Subjects were recruited through local advertisements at the faculty of Psychology of the University of Amsterdam. Twenty-two subjects (15 female, 7 male; ages 22.7 ± 3.6 years) participated in the study. All gave informed consent after the rationale of the study had been explained.

Task paradigms

Prior to scanning, all subjects practiced both tasks outside the scanner, using a personal computer.

n-letter back

The four-step parametric version of the *n*-letter back task employed in this study was similar to the Braver et al. (1997) paradigm. Subjects saw single letters projected on a screen and were requested to press a right hand response key when (i) the letter "x" appeared (baseline), (ii) the projected letter was the same as the last shown letter (one-back), (iii) the projected letter was the same as the letter preceding the last shown letter (two-back), (iv) the projected letter was the same as the letter preceding the last two shown letters (three-back). Each condition was presented four times, in pseudo-randomized order. Each block consisted of 20 stimuli (six targets, stimulus duration 1 s, stimulus onset asynchrony (SOA) 3 s) and was preceded by a condition-specific instruction (6 s).

Sternberg

We used a six-step parametric version of the letter Sternberg task. In each condition, subjects were instructed to memorize a letter string of varying length (2–7 letters) during 10 s (8-s presentation of each letter string followed

by a 2-s pause) after which 15 single letters (stimulus duration 1 s, SOA 2.5 s) were projected on a screen. Subjects were requested to press one of two right-hand keys to indicate if the letter had been in the string (Y/N). Each block was introduced by the text "New string will follow" [nieuwe reeks volgt] during 5 s; each condition was repeated three times, giving 18 blocks, in randomized order.

Technical details

Functional magnetic resonance imaging was performed at the Department of Radiology of the outpatient clinic of the Vrije Universiteit Academic Hospital, using a 1.5-T Vision whole-body system (Siemens, Erlangen, Germany) equipped with a head volume coil. Axial multislice T_2^*-weighted images were obtained with a gradient-echo planar sequence (TE = 60 ms, TR = 3.48 s, 64 × 64 matrix, 32 slices, 3 × 3-mm in-plane resolution, slice thickness 3 mm with a 1-mm interslice gap), covering the entire brain. Each session consisted of two functional MRI subsessions during which 306 (*n*-back) and 280 (Sternberg) volumes were acquired, with the two tasks in counterbalanced order across subjects. Between the subsessions, a T_1-weighted anatomical MR scan (magnetization-prepared rapid acquisition gradient echo (MPRAGE); inversion recovery-prepared; inversion time, 300 ms; flip angle, 8 degrees; matrix size 256 × 256; FOV 220 × 220 mm; 0.78 × 0.78 × 2-mm voxel size) was acquired.

Statistical analysis

Psychometric data (error rates and reaction times) were analyzed using a standard statistical package. Performance scores for each condition were defined as (number of items − number of errors)/(number of items) × 100%. Imaging data were analyzed with SPM99 (Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk). After discarding the first two scans of each time series to allow for magnetic saturation effects, images were realigned and spatially normalized into anatomical standard space (Talairach and Tournoux, 1988) using each subject's coregistered structural T_1 image, and resliced to 3 × 3 × 3-mm isotropic voxels. The data were smoothed spatially with an 8-mm isotropic Gaussian kernel. Subsequently, data were bandpass-filtered and analyzed in the context of the general linear model, using boxcar regressors convolved with the canonical hemodynamic response to model responses during each condition. Linear contrasts for task load (−3,−2,−1,1,2,3 for the Sternberg task and −2,−1,1,2 for the *n*-back task) were computed for each subject. The resulting contrast images were fed into a second level or random effects analysis to assess group effects for task load for both tasks, as well as load × task type interactions (masked with the appropriate task load contrasts). In addition, we performed a conjunction analysis to assess common activations for both tasks. In a separate analysis, encoding/
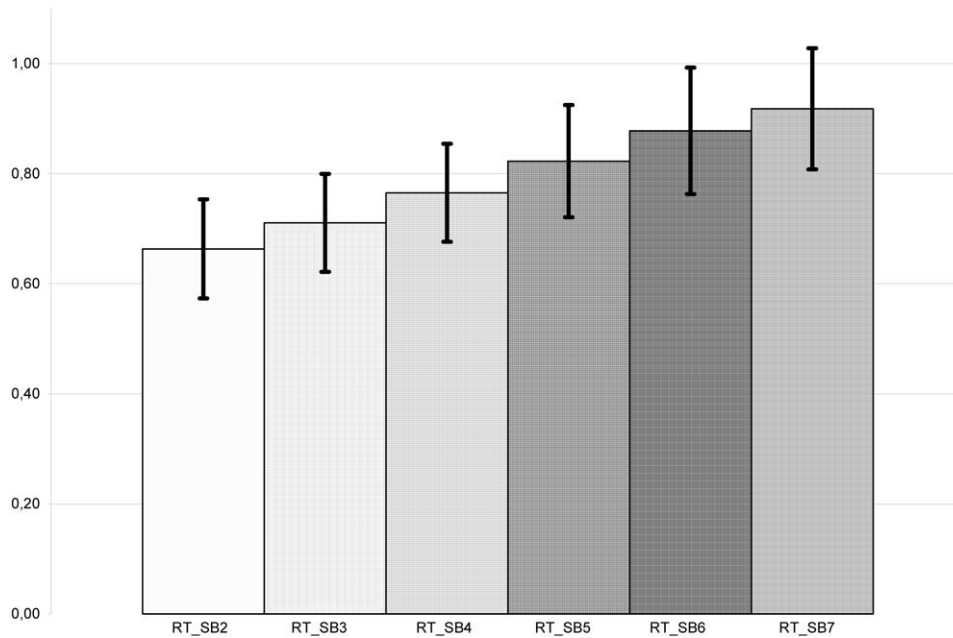
Fig. 1. Reaction times (mean ± SD) during performance of the Sternberg task.

rehearsal and responding during performance of the Sternberg were modeled as different conditions. For these, similar contrasts for task load were computed to assess common areas for encoding and responding, as well as encoding × responding interactions. We also computed individual orthogonalized contrasts for encoding and responding to perform a second-level conjunction analysis to identify common areas. Main effects for task load, as well as the results of the conjunction analyses, are reported at $P < 0.05$ corrected for multiple comparisons. Interaction effects are reported at $P < 0.001$ uncorrected and masked (inclusively) at $P < 0.001$ uncorrected.

Results

One scanning session (4.7%) was aborted due to intervening panic. Analysis of psychometric data (ANOVA) of the remaining 21 subjects showed for both tasks load-related increases in reaction times (n-back: $F(3,18) = 14.1$, $P < 0.001$; Sternberg: $F(5,16) = 18.1$, $P < 0.001$) and decreases in performance scores (n-back: $F(3,18) = 4.7$, $P = 0.017$; Sternberg: $F(5,16) = 30.0$, $P < 0.001$). Reaction times for the n-back ranged from 0.57 s (X) to 0.86 s (three-back) (Fig. 1), and for the Sternberg from 0.66 s (string length two) to 0.92 s (string length seven) (Fig. 2). Mean performance for both tasks was high (for the n-back, $97.7 \pm 1.7\%$; for the Sternberg, $94.7 \pm 2.2\%$).

Results of analysis of imaging data are reported in Tables 1–4. Areas showing a linear increase in activity with increasing task load during performance of the Sternberg were bilateral DLPFC, left VLPFC, left parietal cortex,

supplementary motor cortex, and cerebellum (Table 1, left; Fig. 3). For the n-back, we found bilateral DLPFC and VLPFC, left anterior PFC, bilateral parietal cortex, L inferior temporal cortex, SMA, and cerebellum (Table 1, right; Fig. 4).

Common areas for both tasks are listed in Table 2 (left). These included bilateral anterior PFC, bilateral DLPFC, left VLPFC, bilateral parietal cortex, L inferior temporal cortex, SMA, and cerebellum. Load × task type interactions were found mainly in favor of the n-back, in bilateral DLPFC, R VLPFC, bilateral parietal cortex, SMA, and cerebellum. For the Sternberg > n-back comparison, only bilateral occipital cortex was found (Table 2, right).

In a separate analysis, encoding and responding within the Sternberg were modeled as different conditions. Task load-related activity during encoding was found in L VLPFC, L posterior DLPFC, R parietal cortex, and SMA (Table 3, left). During responding, we found bilateral DLPFC, L VLPFC, bilateral parietal cortex, SMA, and cerebellum (Table 3, right; Fig. 5). Common areas for load-related activity during encoding and responding were found
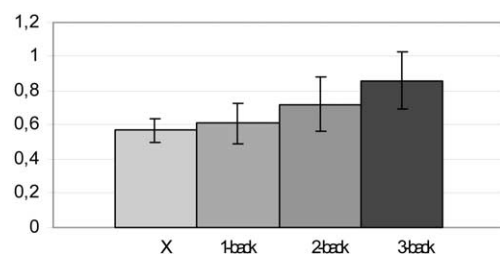

Fig. 2. Reaction times (mean ± SD) during performance of the n-letter back task.

Table 1
Areas showing significant ($P < 0.05$ corrected) linear task load-related increase in activity during performance of the Sternberg and *n*-back task

Region	Sternberg			*n*-back		
	Talairach coordinates	Z score	BA area	Talairach coordinates	Z score	BA area
L prefrontal						
Anterior				−36 48 21	5.5	10
Dorsolateral	−51 12 36	5.7	9	−48 24 30	7.0	9
	−48 24 27	5.4	9	−45 36 27	6.7	9
Ventrolateral	−51 12 3	5.3	44	−51 12 9	7.1	44
R prefrontal						
Anterior						
Dorsolateral	54 12 36	4.9	9	54 15 36	6.5	9
	45 33 33	5.1	9	45 36 36	6.8	9
Ventrolateral				54 12 18	6.5	44
L parietal	−45 −42 54	4.8	40	−45 −39 51	>8	40
L inferior temporal				−45 −54 −15	5.2	37
SMA	6 18 60	5.5	6	9 12 63	7.8	6
Cerebellum	21 −57 −42	4.7		39 −57 −42	6.6	

Note. BA, Brodmann area; SMA, supplementary motor area.

to be bilateral DLPFC, L VLPFC, bilateral parietal cortex, motor cortex, and cerebellum (Table 4, left). Encoding × responding interactions were found only for responding > encoding, in bilateral DLPFC, L parietal cortex, and motor cortex (Table 4, right).

In addition, we investigated the possibility that the task × load interaction effects were due to parametrization differences (three memory conditions in the *n*-back vs six in

the Sternberg). To this end, we compared the difference between two adjacent steps in the *n*-back (two-back vs one-back) and two steps at a maximal distance in the Sternberg (string length seven vs two). This comparison, however, again showed significant interaction effects in bilateral parietal cortex and R VLPFC in favor of the *n*-back task; when we lowered the threshold to $P < 0.005$ we also found L DLPFC and L anterior PFC.

Table 2
Areas jointly activated ($P < 0.05$ corrected) during performance of the Sternberg and *n*-back task and areas showing task × workload interactions
(masked with main effect for task load, both at $P < 0.001$ uncorrected)

Region	Sternberg and *n*-back				*n*-back > Sternberg		Sternberg > *n*-back	
	Talairach coordinates	Minimum T-score	Z score	BA area	Talairach coordinates	Z score	Talairach coordinates	Z score
L prefrontal								
Anterior	−42 39 30	4.7	6.2	9				
Dorsolateral	−42 12 33	6.7	>8	9				
	−51 12 36	7.1	>8	9	−51 9 36	3.2		
	−45 36 27	5.0	6.5	9				
Ventrolateral	−51 12 3	6.5	7.8	44				
R prefrontal								
Anterior	30 48 15	3.7	5.2	46/10				
	33 51 30	4.0	5.5	9				
Dorsolateral	42 42 30	6.0	7.5	46	36 42 42	3.4		
	45 33 33	6.1	7.5	9				
	48 18 33	4.9	6.5	9/44				
Ventrolateral					54 9 18	4.4		
L parietal	−45 −42 54	5.8	7.2	40	−45 −39 51	4.5		
R parietal	36 −48 51	5.3	6.8	40	36 −45 51	5.2		
L inf temporal	−42 −51 −12	5.2	6.7	37				
L occipital				19			−18 −63 30	4.0
R occipital				19			15 −63 30	3.9
SMA	6 18 60	6.8	>8	6	21 6 63	5.9		
Cerebellum	21 −57 −42	5.4	6.9					
	36 −54 −42	4.5	6.0		39 −57 −42	3.2		
	−24 −54 −39	4.4	5.9					

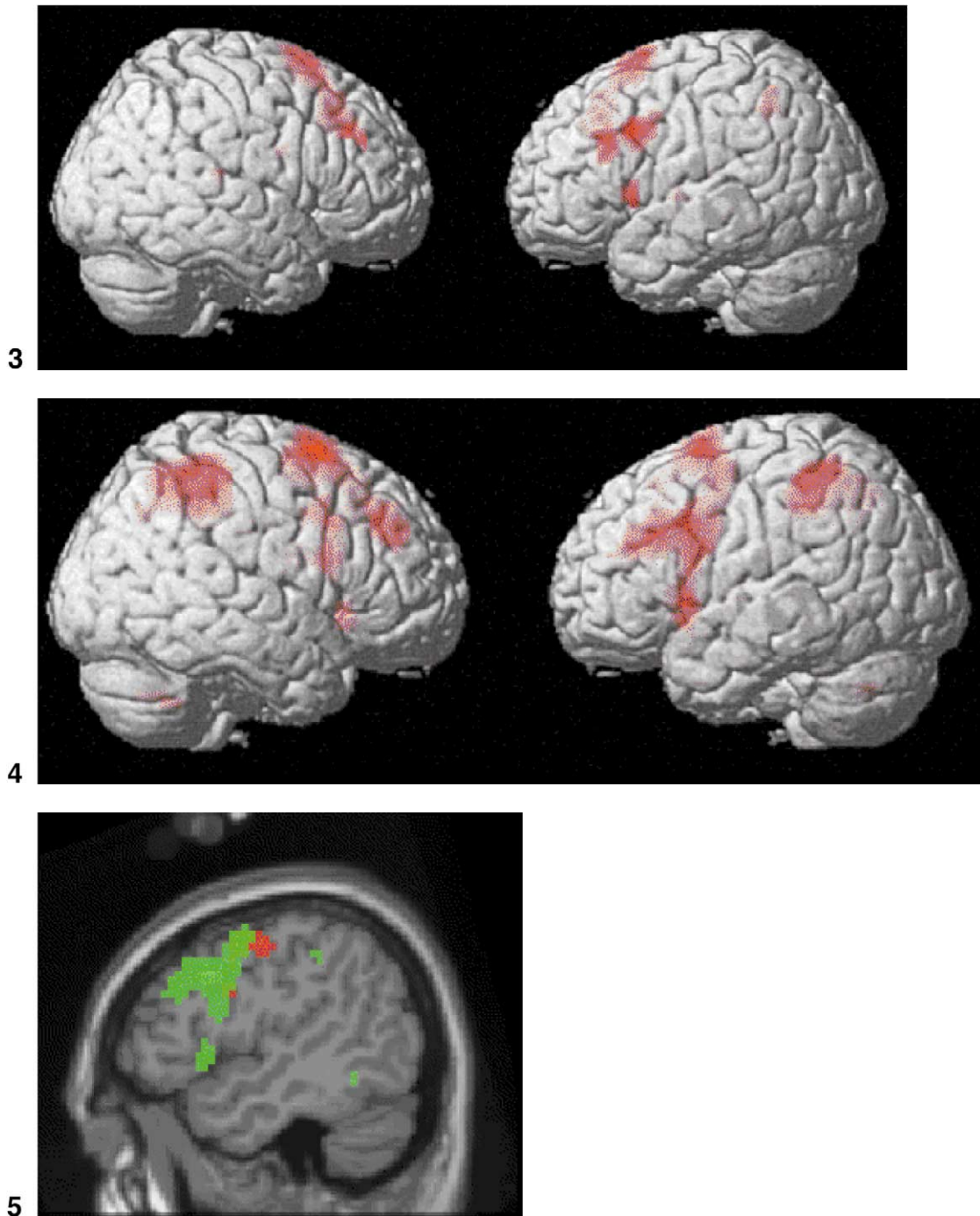*Note.* BA, Brodmann area; SMA, supplementary motor area.

Fig. 3. Areas showing activation linearly associated with task load during performance of the Sternberg task ($P < 0.05$ corrected for multiple comparisons).

Fig. 4. Areas showing activation linearly associated with task load during performance of the *n*-letter back task ($P < 0.05$ corrected for multiple comparisons).

Fig. 5. Areas showing activation linearly associated with task load during encoding (red) and responding (green) in the Sternberg task ($P < 0.05$ corrected for multiple comparisons).

Discussion

In the present study, we found that performance of two parametric working memory tasks, one maintenance task and one manipulation task, resulted in highly similar patterns of task load-related activation in bilateral dorsolateral prefrontal cortex, left ventrolateral PFC, and left parietal cortex, as well as cerebellum and SMA. Our results with regard to the *n*-back task are in agreement with those reported in earlier parametric *n*-back studies (Braver et al., 1997; Jansma et al., 2000). Similarly, activation of DLPFC has also been previously reported for the Sternberg task at

Table 3
Areas activated ($P < 0.05$ corrected) during encoding and responding of the Sternberg task

Region	Encoding		Responding	
	Talairach coordinates	Z score	Talairach coordinates	Z score
L prefrontal				
Dorsolateral	−48 6 27	4.8	−45 3 36	6.2
			−45 12 33	6.5
Ventrolateral	−51 15 0	5.0	−51 15 0	6.5
R prefrontal				
Dorsolateral			45 33 33	5.4
			48 18 36	4.8
Ventrolateral				
L parietal			−51 −36 42	5.0
R parietal	36 −45 57	5.0	42 −51 54	4.7
L inferior temporal			−42 −51 −12	5.3
SMA	27 0 57	4.9	24 15 60	5.0
			−6 9 63	6.4
Cerebellum			18 −63 −39	4.8

Note. SMA, supplementary motor area.

higher task loads (Rypma et al., 1999; Rypma and D'Esposito, 1999). In these latter two studies, it was concluded that the DLPFC was primarily involved during encoding, either due to changes in encoding strategy at higher task loads, or due to cognitive operations usually associated with complex tasks, such as monitoring the contents of WM, or updating and coordinating multiple memory buffers. Rypma et al. (1999) suggested that "manipulation" during encoding may be necessary when memory load exceeds maintenance capacity, resulting in a shift to alternative mnemonic strategies such as relying on the temporal order in which the to-be-memorized stimuli were presented (if at all possible), or forming associations between items in the memory set. However, neither the string lengths used in the Rypma et al. studies (three and six) nor those used in

ours (two to seven) exceed normal working memory span. It has been argued recently by Cowan (2001) that WM span is likely to be four rather than seven, but this refers primarily to maintenance in the absence of rehearsal. When rehearsal is not blocked, WM span for letter or number strings is increased, consistent with Baddeley's observation (1996) that the phonological loop operates in real time and subjects are able to remember as many words or letters as they can rehearse in about 2 s (Cowan, 2001). In addition, several findings from the present study argue against the hypothesis that manipulation processes occur during encoding. First, the alternative mnemonic strategies suggested by Rypma et al. are characteristic for long-term memory function, not WM. This would predict additional involvement of the medial temporal lobe during encoding of large memory sets in the Sternberg, but no such findings were reported in their study (the MTL has, however, been implicated previously in WM tasks, particularly those using complex stimuli (Postle et al., 2000, Stern et al., 2001)). In the present study, we did find evidence of bilateral anterior parahippocampal gyrus activation during encoding (at $P < 0.0005$ uncorrected), but this was *negatively* correlated with task load. Second, the finding in our study as well as in others (Jou, 2001) that reaction times during performance of the Sternberg increased in a near-perfect linear way does not suggest a major change in strategy at higher task loads. Third, and most important, if manipulation occurs primarily during encoding, one would expect encoding/responding interactions at higher task loads in DLPFC in favor of the encoding phase, which is exactly the opposite of what we found. In the present study, load-associated activity in left posterior DLPFC and L VLPFC occurred during both encoding and responding, but significant interaction effects were found in bilateral middle DLPFC for responding > encoding. Therefore, we are led to conclude that responding may in itself involve DLPFC, particularly at higher task loads. This does not imply that "manipulation" processes necessarily occur

Table 4
Areas jointly activated ($P < 0.05$ corrected) during encoding and responding of the Sternberg task and areas showing encoding × responding interactions ($P < 0.001$ uncorrected)

Region	Encoding and responding			Responding > encoding	
	Talairach coordinates	Minimum T score	Z score	Talairach coordinates	Z score
L prefrontal					
Dorsolateral	−48 6 27	5.6	7.1		
	−39 27 33	4.0	5.5	−48 24 42	3.5
Ventrolateral	−51 15 0	6.0	7.4		
R prefrontal					
Dorsolateral	42 42 30	3.8	5.3		
	54 12 39	4.3	5.8	48 21 33	3.1
L parietal	−45 −45 57	4.4	5.9	−60 −36 39	3.5
	−42 −36 39	4.4	5.9		
R parietal	42 −39 45	4.9	6.5		
SMA	−9 9 63	5.3	6.8	−6 −6 60	3.3
Cerebellum	24 −63 −36	4.8	6.4		

Note. SMA, supplementary motor area.

during responding. It should be noted that "maintenance" is arguably not identical to the function of the phonological loop, or "slave system" (i.e., storage and rehearsal) in Baddeley's model, since it also includes searching of WM contents and matching.

Although in the model of Petrides et al. it has been assumed that VLPFC is primarily responsible for retrieval of information and organization of responses (Stern et al., 2000), this may entail considerable executive demands at higher task loads. Therefore, we suggest that the most parsimonious explanation of our data is that handling large memory sets during responding activates DLPFC even in a maintenance task. This conclusion is in agreement with results by Rowe et al. (2000), who found that DLPFC activity during performance of a spatial WM task was specifically associated with response selection. In a similar vein, Braver and Bongiolatti, in a recent study (2002), demonstrated that maintenance during a delayed response task was associated with DLPFC activity, regardless of the presence of a semantic classification subtask.

In the present study, task × load interactions were mainly found in favor of the *n*-back task, in bilateral DLPFC, bilateral parietal cortex, R VLPFC, SMA, and cerebellum. In the Sternberg > *n*-back comparison, only bilateral occipital activity was observed, presumably reflecting processing of visually more complex stimuli in the Sternberg. We failed, on the other hand, to identify interactions in L parietal cortex in favor of the Sternberg, a finding at variance with our expectation of a "double dissociation" in which varying maintenance load (as in the Sternberg) would be associated with L parietal activity. The latter finding needs, however, to be interpreted with caution, as it can be argued that maintenance load increases in the *n*-back as well. However, even when we contrasted two adjacent steps in the *n*-back task (one- and two-back) to two steps at maximal distance in the Sternberg (string length seven and two), we found interaction effects in bilateral parietal cortex in favor of the *n*-back. Moreover, L parietal cortex activity was not associated with encoding load, a finding which is difficult to reconcile with its hypothesized function as a phonological store. Therefore, alternative explanations such as participation in executive functioning (Cohen et al., 1997; Collette et al., 1999) or increased attentional demands (Honey et al., 2000) during performance of the *n*-back need to be considered.

Our finding of clear task × load interactions in favor of the *n*-back task, on the other hand, confirms our hypothesis of increased DLPFC activity during performance of a manipulation task. However, our data also strongly suggest that both tasks essentially activate the same distributed system, because all areas (with the exception of R VLPFC) found in the interaction were also identified in our conjunction analysis, implicating a process-specific functional hierarchy rather than a neuroanatomical segregation. It can be argued that the right-sided region, found in the interaction, is in agreement with the hypothesis of a neuroanatomical disso-

ciation (it was also activated in association with task load in the Sternberg, but only when the threshold was lowered to $P < 0.005$ uncorrected). However, this argument supports only a lateralization difference (bilateral vs left-sided), not a within-PFC segregation between maintenance and manipulation.

Our task × load interaction results are in agreement with some, but not all, earlier studies contrasting manipulation/maintenance tasks. In the Collette et al. (1999) study, interaction effects were found only in L parietal cortex. However, as PFC activations were not reliably demonstrated during their WM task, their design may not have been sensitive enough to detect changes in this region. In the Stern et al. (2000) study, interaction effects were found in L medial DLPFC for the "difficult" subtask relative to the "easy" one, interpreted by the authors as support for a neuroanatomical distinction between maintenance and manipulation. In this L DLPFC region, however, significant activation was also found in the easy condition relative to baseline. In the same vein, D'Esposito et al. (1999) reported that both maintenance and manipulation tasks activated ventral and dorsolateral PFC. However, the fact that manipulation activated L DLPFC to a greater extent was considered evidence for a processing model of functional specialization within PFC by these authors. In the study by Postle et al. (1999), DLPFC activation during a manipulation task was found in all of their subjects, but only in a minority (two of five) during a maintenance task. Tsukiura et al. (2001) concluded that R DLPFC was specifically involved in manipulation, whereas L DLPFC was associated with maintenance. In the Wagner et al. (2001) study, during a simple word rehearsal task, L VLPFC was activated, whereas R DLPFC was additionally active during a semantic classification task. These latter results, however, are not at odds with those of the present study, because their subjects were not requested to make responses during the scanning session. Taken together, these data do not unequivocally support a neuroanatomical manipulation/maintenance segregation within lateral PFC, although the results of Stern et al. (2000) and D'Esposito et al. (1999) appear to be compatible with the hypothesis of a functional dissociation, as suggested by our data.

Considering that in our study both tasks activated identical regions, but to a different extent, we explored the possibility that this resulted from a difference in parametrization between the two tasks employed in this study. The *n*-back has a relatively low-level baseline (X) and only three memory conditions, whereas our version of the Sternberg has six. Therefore, it was conceivable that the workload × task interactions in favor of the *n*-back were aspecific, resulting from a steeper increase in task difficulty, rather than a maintenance/manipulation difference. Although we cannot completely rule out this possibility, it seems unlikely in view of our finding that the difference between two adjacent steps in the *n*-back

compared to two steps at a maximal distance in the Sternberg still showed larger activations for the *n*-back, not only in bilateral parietal cortex, but also in R VLPFC and (at a slightly lower threshold) L middle and anterior PFC. Finally, it should be stressed that the bilateral DLPFC and parietal regions found both in the conjunction and in the interaction of *n*-back and Sternberg were similarly involved in conjunction and interaction of encoding and responding within the Sternberg. Therefore, these data are compatible with the notion of a hierarchical functional organization, in which both tasks (maintenance and manipulation), or components within one task (encoding and responding), differentially activate identical systems within DLPFC and parietal cortex. A similar model has been proposed by Haxby et al. (2000) with regard to component processes of visual working memory: "distinctions between functions . . . are a matter of degree of participation . . . . , not a discrete parcellation of different functions to different modules" (Miller, 2000).

The present study has two limitations due to our choice of a blocked design: although this increases experimental power, it lacks the temporal resolution available when an event-related design is employed. We also did not select correct responses post hoc, which, however, we felt was justified because the overall error rate was very low.

In summary, we compared two parametric working memory letter tasks, one varying maintenance load, and one varying (primarily) manipulation load, and found that in both tasks, load was associated with activity particularly in bilateral DLPFC, left VLPFC, and bilateral parietal cortex. Workload × task interactions were found in bilateral DLPFC for manipulation vs maintenance, but also for responding vs encoding in the maintenance task. Therefore, we conclude that our data support a functional rather than a neuroanatomical distinction between maintenance and manipulation, given our finding that these tasks differentially activate virtually identical systems.

Acknowledgments

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