

Dissociating Verbal and Spatial Working Memory Using PET

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Three experiments used positron emission tomography (PET) to study the neural basis of human working memory. These studies ask whether different neural circuits underlie verbal and spatial memory. In Experiment 1, subjects had to retain for 3 sec. either the names of four letters (verbal memory) or the positions of three dots (spatial memory). The PET results manifested a clear cut double dissociation, as the verbal task activated primarily left-hemisphere regions whereas the spatial task activated only right-hemisphere regions. In Experiment 2, the identical sequence of letters was presented in all conditions, and what varied was whether subjects had to remember the names of the letters (verbal memory) or their positions in the display (spatial memory). In the verbal task, activation was concentrated more in the left than the right hemisphere; in the spatial task, there was substantial activation in both hemispheres, though in key regions, there was more activation in the right than the left hemisphere. Experiment 3 studied only verbal memory, and showed that a continuous memory task activated the same regions as the discrete verbal task used in Experiment 1. Taken together, these results indicate that verbal and spatial working memory are implemented by different neural structures.

Working memory is typically defined as a storage system that holds a limited amount of information for a brief time, where that information is in a rapidly accessible state and can be changed from moment to moment. In humans, such a system is critical for a variety of tasks such as mental arithmetic and comprehending spatial directions. In the former, a current total might have to be kept in mind and updated with each incoming digit; in the latter, a spatial route would need to be stored as it is constructed from the incoming information. Working memory is crucial for intelligent functioning in humans and in nonhuman animals. Without it, an organism would have great difficulty in dealing with problems that require one to record features of a constantly changing environment, and to keep these features "on line" as they are used to guide behavior.

Many researchers have proposed that working memory may be implemented in the brain by heightened neural activity in specific regions, consistent with data on its brief duration and its quick turnover of information (see Hebb, 1949, for an early statement of this position). In recent years, the neural basis of working memory in nonhuman primates has been studied extensively (e.g., Goldman-Rakic, 1987; Gnadt and Andersen, 1988; Wilson et al., 1993). This research supports the idea that working memory is mediated by heightened neural activity, notably in prefrontal and parietal regions. Furthermore, there appear to be different kinds of working-memory buffers, as indicated by the fact that neurons in different regions of the prefrontal cortex are active when monkeys have to store spatial information than when they have to store object information (Wilson et al., 1993). The dissociation of spatial and object working memory has also been documented in humans using positron emission tomography (Smith et al., 1995).

Although these results indicate important parallels between humans and nonhuman primates, there is reason to

believe that humans possess another working memory buffer that is unique to our species. This is a verbal buffer that stores speech-like material, such as phonological and articulatory information. The verbal buffer and its relation to the spatial buffer are the predominant concerns of the present article.

There are two domains of data that point to the existence of a separate verbal buffer. One is the existence of neurological patients with left-hemisphere, largely posterior damage, who are more impaired in their short-term retention of verbal material than nonverbal material (see Shallice, 1988, for a review). The second source of relevant evidence comes from strictly behavioral studies of normal subjects. If subjects' primary task putatively involves verbal working memory, and they are required to concurrently perform a secondary task, their performance on the primary task will be more disrupted if the secondary task requires the short-term storage of verbal rather than visual information; if the primary task involves visual working memory, then performance on the primary task is more disrupted when the secondary task requires visual storage (e.g., Logie et al., 1990).

These results suggest that separate mechanisms are involved in the short-term storage of verbal and visual information, but say little about what brain circuits mediate these mechanisms. Studies of neurological patients with deficits in working memory are not sufficiently telling because the lesions that cause the deficits are often large, covering a number of functionally distinct areas. Neuroimaging studies, however, have begun to uncover something about the nature of working-memory circuits in normal human brains. Here, we present the results of three studies using positron emission tomography (PET) that inform us about the neural bases of verbal and spatial working memory. Each study focuses on two issues: (1) Is the neural basis of verbal working memory distinct from that of spatial working memory? (2) What brain circuits mediate verbal and spatial working memory?

Experiment 1: Verbal versus Spatial Working Memory

In our initial study we built on results of an earlier study from our laboratory that documented the brain activation involved in spatial working memory (Jonides et al., 1993). We devised a verbal task comparable to the one used to study the spatial buffer so that we could compare the activation patterns for spatial and verbal working memory.

Materials and Methods

Tasks

The *spatial memory* task from our prior research is presented schematically in Figure 1 (top row). On each trial, subjects began by fixating a cross in the center of a screen for 500 msec. The cross was followed by three target dots that were randomly arrayed on the circumference of an imaginary circle and that remained in view for only 200 msec. Next the fixation cross appeared alone for a retention interval of 3000 msec. The retention interval was followed by a location probe, available for 1500 msec, that consisted of a single outline circle that either encircled the location of one of the previous

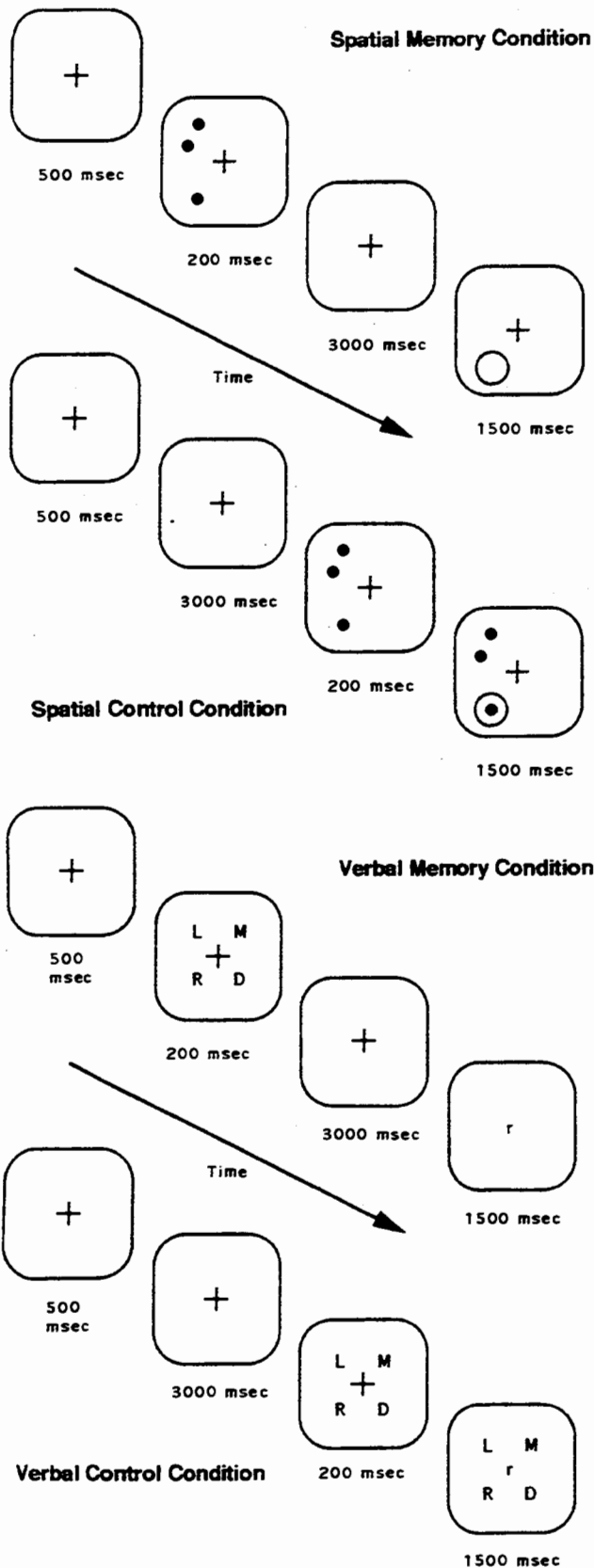


Figure 1. Schematic drawings of the events on each trial of the spatial memory and spatial control conditions (top) and verbal memory and verbal control conditions (bottom), experiment 1.

dots or not. The subjects' task was to press a response button once or twice to indicate whether or not the probe encircled the location of a target dot. Successful performance on this spatial memory task requires numerous processes in addition to remembering spatial information, for example, attending to the inputs and selecting and executing a response—but our goal was to focus on the memory component. In order to remove the effects of these nonmemory processes from the activation patterns of the PET images, a control condition was devised that included these processes but not memory. [This follows the subtraction methodology developed by Posner et al. (1988).] This spatial control task is schematized in Figure 1 (second row). Again, each trial began with a fixation cross, but in this condition the cross remained in view for 3500 msec (the duration of the fixation plus retention intervals in the spatial memory task). The three dots were then presented for 200 msec, followed immediately by a probe display in which the three dots and probe circle were presented simultaneously. As in the memory condition, subjects had to indicate whether or not the probe encircled a dot, but in this case their response was based on the presentation of probe and dots simultaneously so that no memory of dot location was needed. Thus, this spatial control task includes very similar trial events to the spatial memory task but no memory requirement. In both tasks, the probe matched one of the targets half the time.

The *verbal memory* task was a variant of a widely used item-recognition task developed by Sternberg (1966), and it was designed to be similar in structure to the spatial memory task. It is schematized in Figure 1 (third row). Each trial consisted of four events: (1) a fixation cross presented for 500 msec; (2) four targets, each one an uppercase letter, exposed for 200 msec; (3) a return to just the fixation cross for a retention interval of 3000 msec; and (4) a probe, available for 1500 msec, that consisted of a single lowercase letter. The subject's task was to indicate whether or not the probe had the same name as any of the targets. Because the targets and probe were in different cases, subjects were induced to represent the targets in a verbal code (phonological or articulatory). In the *verbal control* task (Fig. 1, fourth row), the sequence of trial events consisted of (1) a fixation cross, (2) continuation of the fixation cross for another 3000 msec, (3) four uppercase target letters presented for 200 msec, and (4) a lowercase probe letter along with the four uppercase target letters. Again, the subject's task was to indicate whether or not the probe was identical in name to any of the targets, but in this case the decision could be made without any stored information. In both tasks, the probe matched one of the targets half the time.

PET Procedure

Subjects were first familiarized with the PET apparatus. Then each subject had an intravenous catheter inserted into his or her right arm for administration of the radioactive tracer. Subjects were positioned in the scanner with a band across the forehead attached to a head holder to constrain head movement. For the spatial tasks, two separate groups of subjects were tested: one group of eight subjects had two scans each of the memory condition and control condition; the other group of 10 subjects had three scans each of the memory and control conditions. For the verbal tasks, another group of 11 subjects were tested; they had three scans each of the memory and control conditions.

In both the spatial and verbal tasks, each scan consisted of 20 trials in sequence. In both tasks, the sequence began just prior to the injection of the radionuclide, at which time a bolus injection of 66 mCi of ^{15}O -labeled water was given. PET acquisition (using a Siemens CTI-931/08-12) began 5 sec after the count rate was observed to increase above the background level, and continued for 60 sec thereafter, during which time the sequence of items continued to be presented. The trials continued until after the PET scan was completed. Scans were performed at intervals of 14 min, allowing time for the ^{15}O to decay.

The PET images for each subject were first transformed to a stereotactic coordinate system (Minoshima et al., 1992, 1993), and then linearly scaled to the dimensions of a standard atlas brain (Talairach and Tournoux, 1988). After normalizing pixel values for global flow-rate differences among scans (Fox et al., 1985), the data were averaged across the subjects performing each task, thereby obtaining means and variances for all four conditions of interest. For both the spatial and verbal tasks, difference images were created by subtracting activation in the control task from that in the memory task. These

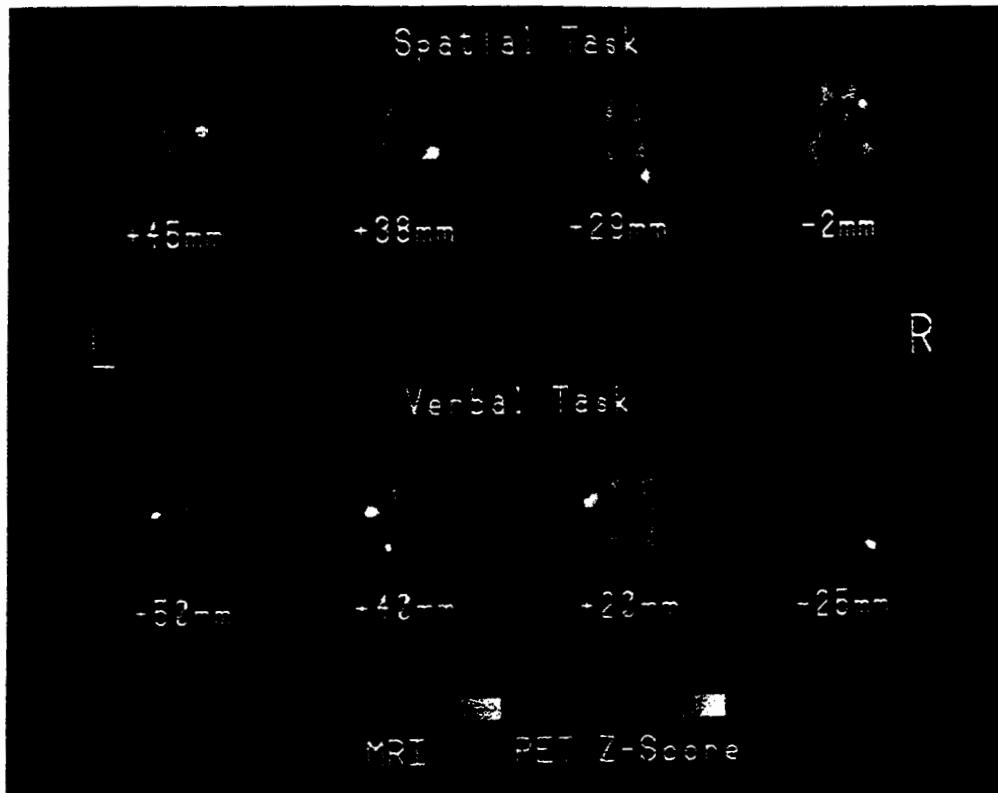


Figure 2. PET images of the statistically significant activation sites in the spatial memory task (*top*), and the verbal memory task (*bottom*). Each image is superimposed on an MRI image of a composite brain for the purpose of illustrating the anatomical localization of the activation foci. In the spatial memory task (*top*), the *middle two images* include activation foci that are cut off due to the fact that the remaining activation fell outside the field of view of the camera; similarly, in the verbal memory task (*bottom*), activation foci at the top of the brain were cut off due to limitations of the camera. Note that in the spatial memory task all four significant foci of activation are in the right hemisphere, whereas in the verbal memory task most of the significant foci of activation are in the left hemisphere. Stereotaxic coordinates of the significant foci of activation are given in Table 1 (Experiment 1).

difference images were then analyzed by performing post hoc *t* tests on a voxel-by-voxel basis and correcting the outcomes for multiple comparisons (Friston et al., 1991; Worsley et al., 1992).

Results and Discussion

The analysis results in a map of cerebral areas that showed significant increases in regional cerebral blood flow. Figure 2 (*top*) presents four brain images showing the significant areas of activation in the spatial task; the bottom row of the figure presents the images for the significant areas in the verbal task. The number below each image gives its z-coordinate (an indication of how inferior or superior the relevant brain region is). These areas of activation have been superimposed on a composite magnetic resonance image so as to provide some anatomical localization. The coordinates defining each area of activation are given in Table 1 (under Experiment 1).

Starting with the results for the spatial tasks (Fig. 2, *top*), note that all four significant regions of activation are in the right hemisphere. The most inferior of these regions (the rightmost image) is in ventrolateral frontal cortex; this region is somewhat inferior and posterior to that implicated in single-cell studies of working memory (e.g., Wilson et al., 1993), and is centered in area 47 ("area" is used as shorthand here for "Brodmann area"). Moving up the brain, the next two sites of reliable activation are in area 19 in occipital cortex and area 40 in parietal cortex (Fig. 2, *top*, middle two images). Finding activation in these two regions is consistent with prior research on human visuospatial processing and memory. Area 19 has been found to be active when subjects are explicitly instructed to maintain visual images of simple forms (e.g., Kosslyn et al., 1993), and likely our subjects had to maintain visual images of the dot locations. Area 40 is known for its involvement in spatial processing and memory, as lesions in this region frequently lead to impairments in spatial judgments and memory for spatial information (e.g., Warrington and Rabin, 1970; Egly et al., 1994). The final region of activation in the spatial task is area 6 in premotor cortex (Fig. 2,

top, leftmost image). It fits less well with prior work on spatial processing. Note that activation of this region cannot be attributed to the response requirements of the task. For one thing, subjects always made their responses with their right hand, which would have led to activation in left-hemisphere motor regions, not right-hemisphere ones; for another, any activation due to response processes should have been subtracted out, since the control task involved these processes as well.

In sum, the two posterior areas, 19 and 40, fit with prior work on visual-spatial processing, and may be part of a network for encoding and storing spatial information. The other two areas, 6 and 47, have not figured in prior findings on spatial processing; later, we will suggest that they may play a role in rehearsing visual-spatial information.

Turning now to the results for the verbal task (Fig. 2, *bottom*), note that most of the significant areas of activation are in the left hemisphere. These regions include area 40 in parietal cortex (see the second image from the left), and three regions in frontal cortex, corresponding to area 44 (Broca's area), the inferior aspect of area 6 (the premotor area), and the superior aspect of area 6 (the supplementary motor area, or SMA). [In Fig. 2 (*bottom*), Broca's area is evident in the second image from the right, whereas the premotor area and SMA are visible in the leftmost image.] Activation in these regions is consistent with prior research. The left-hemisphere parietal region is known to be involved in verbal working memory (e.g., Petrides et al., 1993b). Indeed, area 40 is the most frequent site of damage in patients who have impaired verbal working memory (McCarthy and Warrington, 1990; Vallar and Shallice, 1990). The three left-hemisphere frontal regions likely play a role in implicit speech, consistent with the role they play in explicit speech (Petersen et al., 1988). Given these facts, the left-hemisphere regions activated in the item-recognition task comprise a plausible network for storing and rehearsing information in verbal working memory.

Table 1
Stereotaxic coordinates, Z scores, and brain areas for the significant activation foci: experiments 1-3

Brain area	Coordinates			Z score
	x	Y	z	
Experiment 1				
Verbal memory				
Left Hemisphere				
SMA (area 6)	1	5	52	4.4
Post parietal (areas 40/7)	24	-55	43	5.3
Premotor (area 6)	48	-6	40	5.8
Broca's (area 44)	44	12	22	5.0
Broca's (area 44)	55	3	20	5.7
Thalamus	17	-4	9	4.3
Insular cortex	28	14	4	5.3
Right hemisphere				
Cerebellum	-33	-60	-25	5.4
Midline				
Ant. cingulate (area 32)	-6	19	38	4.6
Spatial memory				
Right hemisphere				
Premotor (area 6)	-24	1	50	6.3
Post. parietal (area 40)	-37	-40	40	6.3
Occipital (area 19)	-28	-69	34	5.3
Inf. frontal (area 47)	-33	19	-2	5.4
Experiment 2				
Verbal memory				
Left hemisphere				
Post. and sup. parietal (areas 40/7)	37	-49	40	5.4
Prefrontal (area 9/46)	39	32	29	5.5
Broca's and prefrontal (areas 44/45/46/10)	37	44	20	6.7
Prefrontal (areas 10/46)	37	55	2	4.8
Right hemisphere				
Sup. parietal (area 7)	-10	-64	47	4.3
Prefrontal (areas 46/9/10)	-35	41	25	4.3
Spatial memory				
Left hemisphere				
SMA (area 6)	12	-1	58	4.7
Sup. parietal (area 7)	19	-67	50	5.0
Post. parietal (area 40)	44	-46	43	5.5
Post. and sup. parietal (areas 40/7)	26	-53	40	4.8
Prefrontal (areas 46/10)	33	44	20	4.7
Right hemisphere				
Sup. parietal (area 7)	-12	-64	50	4.6
SMA/premotor (area 6)	-30	3	47	6.9
Post. parietal (area 40)	-42	-49	40	7.4
Prefrontal (areas 46/9)	-35	28	29	5.5
Experiment 3				
Verbal memory				
Left hemisphere				
SMA	6	3	54	5.2
SMA/premotor (area 6)	28	1	52	6.0
Sup. parietal (area 7)	17	-60	45	5.7
Post. parietal (area 40)	33	-46	38	5.4
Broca's (area 44)	42	17	22	4.4
Cerebellum	30	-49	-45	5.7
Cerebellum	26	-67	-50	5.1
Cerebellum	28	-62	-52	5.2
Right hemisphere				
SMA/premotor (area 6)	-24	3	52	5.5
Sup. parietal (area 7)	-26	-55	50	4.6
Sup. parietal (area 7)	-12	-64	47	5.3
Cerebellar vermis	-1	-64	-25	4.8
Cerebellum	-24	-62	-45	4.6
Midline				
Ant. cingulate (area 32)	3	12	40	5.0

There were other regions activated in the verbal task as well. Two of these have surfaced in other PET studies of cognition: a right-hemisphere cerebellar site and a midline structure, the anterior cingulate. The cerebellar site has been argued to mediate aspects of the planning and execution of speech (Paulesu et al., 1993), so it, too, may play a role in

inner speech or rehearsal. The anterior cingulate has been found active in other studies of cognitive tasks (e.g., Pardo et al., 1990), and has typically been interpreted as reflecting attentional processes. The remaining two areas of activation in the verbal task were the left-hemisphere thalamus and insular cortex (these are not shown in Fig. 2). We have no ready explanation for their involvement in the verbal task, nor did they surface again in subsequent experiments reported here.¹

Consider now the difference in activation patterns between the spatial and verbal tasks. At a gross level of analysis, the results manifest a striking double dissociation between the two tasks, with the spatial task leading to activation only in right-hemisphere regions, and the verbal task leading to activation primarily in left-hemisphere regions. This double dissociation implies that different neural systems mediate spatial and verbal working memory.

At a more fine-grained level of analysis, we can contrast the main anatomical areas involved in the two tasks. Both spatial and verbal tasks show activation in posterior parietal and premotor regions. The major differences in anatomical regions between the tasks are that the spatial task resulted in activation in occipital and ventrolateral frontal sites (areas 19 and 47, respectively), whereas the verbal task resulted in activation in Broca's area and SMA (areas 44 and 6, respectively). It is tempting to interpret this pattern of commonalities and differences by the following two hypotheses: (1) The posterior parietal areas are responsible for storage of information, with right-hemisphere areas storing spatial information and left-hemisphere areas storing verbal information. (2) The other activated areas mediate rehearsal processes.

The latter claim seems very plausible for the verbal task. The three left-hemisphere frontal areas—Broca's, premotor, and SMA—presumably mediate implicit speech, which is the major means of rehearsing verbal information. Moreover, other PET studies have shown that conditions requiring rehearsal but not memory lead to activation in these same left-hemisphere frontal regions (Paulesu et al., 1993; Awh et al., 1995a). In the spatial task, frontal areas 6 and 47 may play an analogous role to the frontal areas just described for the verbal task. That is, areas 6 and 47 could be responsible for the active maintenance or rehearsal of visual-spatial information, perhaps by mediating an implicit process that attends to each stored dot position in sequence and recomputes its coordinates (Baddeley, 1986; see also Awh et al., 1995b, for some support for this rehearsal hypothesis). It is possible that area 19 also contributes to visual-spatial rehearsal, given that it has been found active in studies where subjects have to maintain visual images briefly (Kosslyn et al., 1993). The fact that area 19 is primarily a sensory area, however, fits less well with a putative rehearsal function.

Although our interpretation of the results for the verbal task is in line with other PET work (e.g., Paulesu et al., 1993), our interpretation of the spatial task, particularly the notion of spatial rehearsal, is speculative.²

Experiment 2: A Purer Comparison of Verbal and Spatial Working Memory

While experiment 1 offers compelling evidence of differences in circuitry between spatial and verbal working memory, four methodological issues compromise the confidence that one can have in the results of this study.

(1) Different stimuli were used in the spatial and verbal tasks (dots vs letters), and some aspect of this difference (other than the spatial-verbal contrast) may have been responsible for the different activation patterns that we obtained.

(2) Different subjects were used in the spatial and verbal tasks, and some unnoticed difference in the subject samples

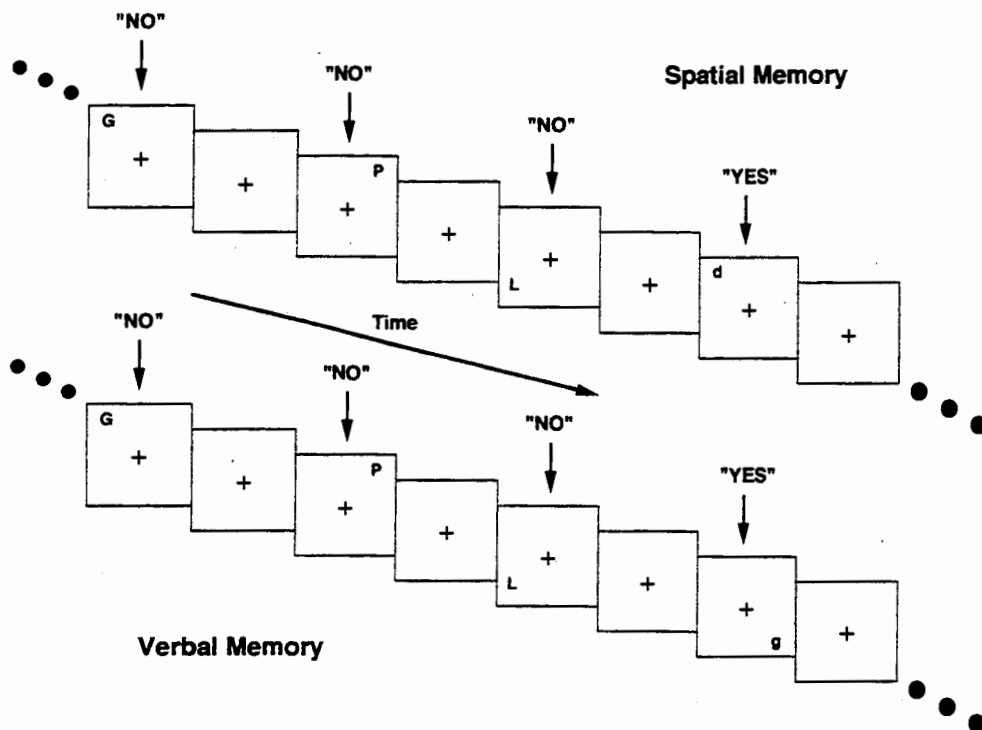


Figure 3. Schematic drawings of the events on each trial of the spatial memory condition (top) and the verbal memory condition (bottom), experiment 2.

may have artifactually contributed to the difference in activation patterns.

(3) In the control conditions of both tasks, the final trial event—probe plus target items—was more visually complex than the final trial event in the memory conditions—probe alone (see Fig. 1). Consequently, the control condition required some perceptual processing that the memory condition did not, and this extra processing violates part of the logic underlying the subtraction method used in PET studies of cognition (see Posner et al., 1988).

(4) Though our interest is in storage processes, the amount of time during the PET scans that was devoted to storage was not that substantial. More precisely, each trial of the verbal task (or the spatial one) plus the intertrial interval required 5.45 sec, of which 2.45 sec were devoted to nonstorage processes (fixation time, target presentation time, probe presentation time, and the intertrial interval). If we define the duty cycle of a process to be the percentage of time that the process must be performed, then the duty cycle of storage was only 55% in our verbal and spatial tasks.

The main purpose of experiment 2 was to address these methodological issues, permitting a purer test of the hypothesis that spatial and verbal working memory are mediated by different neural mechanisms.

Materials and Methods

Tasks

The four methodological problems were mitigated by using a continuous memory task adapted from one developed by Gevins and Cutillo (1993). In all conditions, subjects were presented a continuous stream of single letters, each for 500 msec, with a 2500 msec interval between successive letters; each letter appeared at a randomly chosen location around an imaginary circle centered on the fixation cross. Thus, the position and identity of the letters varied in each stimulus stream. Some blocks of trials corresponded to a verbal memory condition, whereas others corresponded to a spatial memory condition (see Fig. 3 for schematic representations of the two memory conditions).

In the *verbal memory* condition, subjects had to decide whether

or not each letter matched in identity (regardless of position) the one presented three back (not the previous letter, nor the one before that, but the one prior to that). Subjects pressed a button once or twice to indicate positive or negative responses, respectively. In the *spatial memory* condition, subjects had to decide whether or not the position of each letter matched the position of the letter presented three back (regardless of letter identity). In both conditions, one-third of the letters provided matches that required positive response (there were also three matches one-back and three two-back in both tasks so that subjects could not use mere familiarity as the basis of their responses). The two memory conditions therefore differed only with respect to whether the subject's task was to store verbal (letter) or spatial information; the stimuli were the same, addressing the first problem described above. The second problem was also addressed in that the same subjects performed both verbal and spatial tasks.

These *three-back* tasks are very demanding with respect to storage processes. For one thing, the tasks maximize the duty cycle of storage processes: the subject must continuously hold in working memory either three or four letters or positions to perform the task successfully, the three immediately preceding ones plus the new item for comparison. The duty cycle of storage was therefore 100%, which overcame the fourth limitation of the first experiment. In addition, the three-back tasks required constant reshuffling of the contents of working memory. With the arrival of each new item, subjects must not only have inserted it into working memory, but also dropped or inhibited one of the current items of working memory while maintaining the other two.

Separate control conditions were used for the verbal and spatial conditions. Both controls were search tasks, and both involved the same sequence of events as in the memory conditions, thereby eliminating the third problem with experiment 1 (the somewhat non-comparable control conditions). In the present *verbal control* condition, subjects had to decide whether or not each item matched a letter from a fixed set of three letters that was identified at the beginning of the experiment; in the *spatial control* condition, subjects had to decide whether or not each item's position matched one of three locations identified at the beginning of the experiment. Because the three items that had to be kept in memory were constant throughout a block of trials (indeed, they were constant throughout the whole experiment for a subject), the load on working memory was substantially less in these control conditions than in the memory

conditions. In both control conditions, one-third of the trials required positive responses.

Finally, note that the three-back memory task also differs from the item-recognition task in that it requires coding the stored letters with regard to their temporal order (only a match three-back counts, not one one-back or two-back), and constantly changing these temporal codes as new letters are presented. Thus, in contrast to the item-recognition task, the three-back task requires subjects to perform computations on stored material. Many behavioral researchers have taken this kind of computation-plus-storage task as the paradigm case of working memory (e.g., Baddeley, 1986).

PET Procedure

Subjects were first familiarized with the PET apparatus, and then had an intravenous catheter inserted into their right arms. Again, subjects had a band across their foreheads attached to a head holder to restrict movement.

In this experiment, eight subjects were tested. They had received previous training in both memory tasks, and were selected on the basis of being able to perform the tasks well. Each subject had eight scans, two each of the memory and control conditions. Each scan consisted of 42 letters (all consonants) presented in sequence. The sequence began just prior to the injection of the radionuclide, at which time a bolus injection of 50 mCi of ^{15}O -labeled water was given. PET acquisition (using a Siemens ECAT EXACT-47 scanner, 15 cm field of view) began 5 sec after the count rate was observed to increase above the background level and continued for 75 sec thereafter, during which time the sequence of letters continued to be presented. The trials terminated after the PET scan was completed. Scans were performed at intervals of 12 min, allowing time for the ^{15}O to decay. The analysis of the PET data paralleled that in experiment 1.

Results and Discussion

Global Results

Subtraction of the control conditions from their corresponding memory conditions revealed numerous areas of significant activation. The areas of activation for the spatial task are presented in Figure 4 (top), and those for the verbal task are in the bottom row (the coordinates for the areas are given in Table 1, Experiment 2). In the verbal task, activation is clearly concentrated more in the left than the right hemisphere; in the spatial task, there is substantial activation in both hemispheres, though in key regions (see below) there is more activation in the right than the left hemisphere. This differential lateralization is in line with our previous double dissociation between spatial and verbal working memory, and provides further evidence that two different neural systems are involved.

One other global aspect of the activation data is worth noting. The magnitudes of the activations in this experiment, which ranged between 6% and 9%, were substantially greater than those in the preceding study, which ranged between 3% and 6%. One likely cause of the increased activation is the increased duty cycle of storage processes (and perhaps other memory processes), which is a consequence of the continuous nature of the three-back task. Another possible cause of the increased activation is the partial reshuffling of working memory occasioned by each new item, where only one current occupant of the buffer had to be inhibited while the other two had to be kept active. Still another possible cause of the increased activation is that successful performance in the three-back task requires coding the letters in working memory with regard to their temporal order. At least three different factors, then, may have combined to make the three-back task more demanding than the item-recognition task.

Specific Regions

Consider now the specific regions significantly activated in the three-back tasks, starting with the spatial task (Fig. 4, top).

Two of the regions were the same as ones found in the previous study, area 40 of right parietal cortex and right premotor cortex (see the two leftmost images). There were also two additional right-hemisphere regions significant in the present spatial task, area 46 of dorsolateral prefrontal cortex (see Fig. 4, top, rightmost images), and area 7 of posterior parietal cortex (second image from the left). Right-hemisphere area 46 has proved significant in other neuroimaging studies of human, nonverbal, working memory (Petrides et al., 1993a; McCarthy et al., 1994), and area 7 has been found active in another continuous working memory task in our laboratory. (We should note that limitation in the field of view of the PET camera used for experiment 1 prevented us in that experiment from imaging area 7 in all subjects.) Hence, all the right-hemisphere regions found active in the spatial task are compatible with prior results on spatial working memory.

There were also a number of left-hemisphere regions active in the present spatial task that were not active in experiment 1. These include areas 7 and 40 of parietal cortex, area 46 of prefrontal cortex, and SMA. Most of these regions are the left-hemisphere homologs of the right-hemisphere regions that we have already discussed. Furthermore, the magnitude of the activation in these four left-hemisphere homologs is less than that found in the right-hemisphere sites ($t = 3.75$, $p < 0.01$). Given these facts, the left-hemisphere activations under discussion may reflect the functional recruitment of left-hemisphere mechanisms to assist in an unusually demanding version of what is normally a right-hemisphere task. An alternative account of the left-hemisphere activations under discussion is that they are nonfunctional spillovers. That is, given the intense activation in the homologous right-hemisphere regions, and given the multiplicity of connections between right- and left-hemisphere homologous regions, some activation from the right-hemisphere regions may simply overflow to left-hemisphere homologs. (We note that there was some evidence of activation in homologous regions in the spatial task of experiment 1 as well, although this activation did not reach conventional levels of statistical significance.) Further research will be needed to determine whether the left-hemisphere activations of interest primarily reflect functional recruitment, nonfunctional spillover, or the possibility that the three-back spatial task is intrinsically bilateral (in the sense that it requires equal and complimentary contributions from both hemispheres).³

We turn now to the specific regions activated in the verbal task (Fig. 4, bottom). Two of the active regions were left-hemisphere areas that were also active in the item-recognition task of experiment 1: area 40 of parietal cortex (leftmost image) and area 44, or Broca's area (second image from the right). There was an additional left-hemisphere region significant in the present task, area 46 of prefrontal cortex (second image from the left), which has been found to be activated in other verbal working-memory tasks (Petrides et al., 1993b; Cohen et al., 1994). Thus, all active left-hemisphere areas are compatible with prior results on verbal working memory.⁴

There were also a number of right-hemisphere regions active in the present verbal task that were not active in experiment 1: these include areas 7 and 40 of parietal cortex and areas 46 and 9 of prefrontal cortex. Notably, two of these regions are the right-hemisphere homologs of the left-hemisphere areas that we have already discussed. Furthermore, the magnitude of the activation in these four right-hemisphere regions is less than that found in the left-hemisphere sites ($t = 2.09$, $p < 0.05$). These results parallel those found in the spatial task, and, again, suggest the possibility of functional recruitment or nonfunctional spillover.

In addition, we note that some areas that were significantly active in the spatial and verbal tasks of experiment 1 were

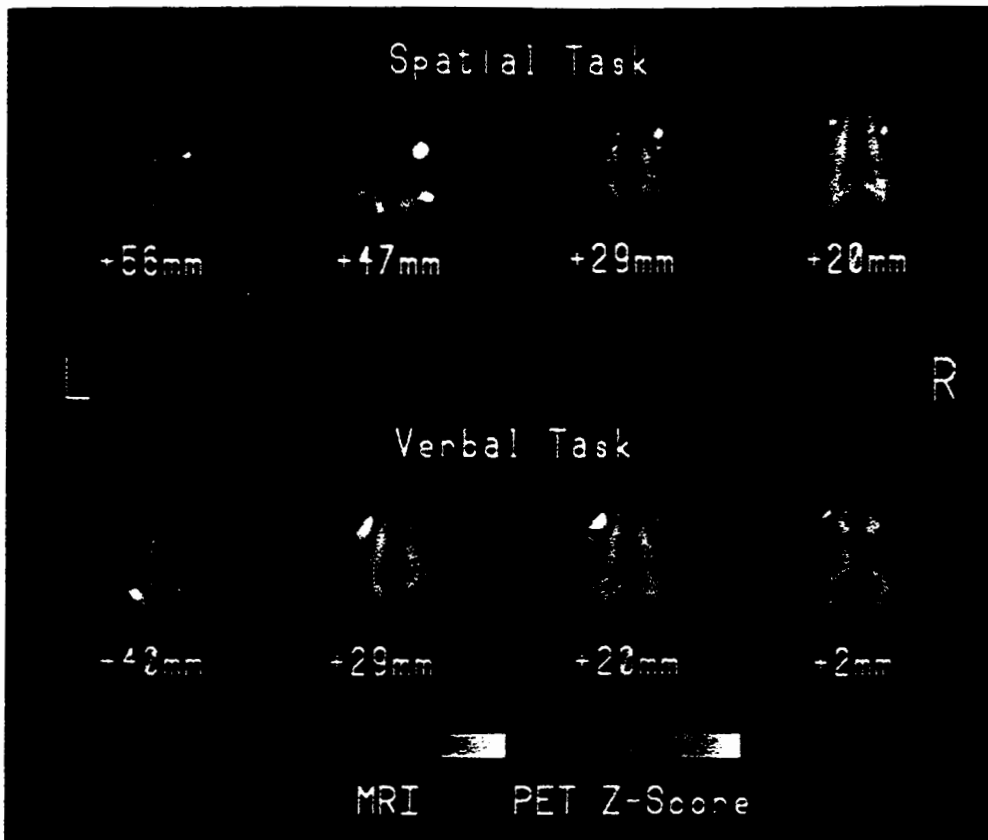


Figure 4. PET images of statistically significant activation sites in the spatial memory condition (*top*) and the verbal memory condition (*bottom*). Each image is superimposed on an MRI image of a composite brain. Note that in the verbal memory task the activation is greater in the left than the right hemisphere, whereas in the spatial memory task the activation is greater in the right hemisphere in key regions (see text). Stereotaxic coordinates of all significant foci of activation are given in Table 1 (Experiment 2).

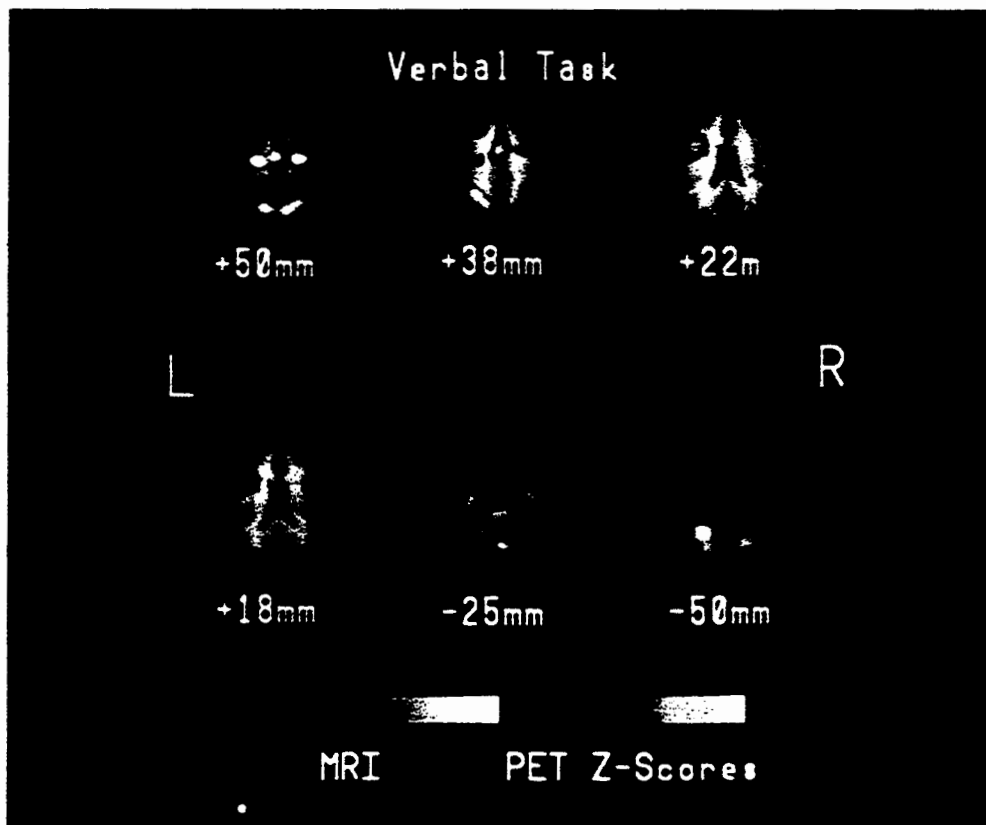


Figure 5. PET images of statistically significant activation sites in the verbal memory condition. Each image is superimposed on an MRI image of a composite brain. Note the substantial activation in the left-hemisphere areas that supposedly underlie rehearsal—Broca's area, premotor area, and SMA. Stereotaxic coordinates are given in Table 1 (Experiment 3).

not active in the present tasks. With regard to the spatial task, two such areas are right-hemisphere regions, area 19 of occipital cortex and area 47 of ventrolateral frontal cortex. We suspect that the main reason why these two regions did not show significant activation in the present study is that they mediate processes that, to some extent, were required by the control condition as well as the memory condition, and, hence, were subtracted out of the difference image. Recall that our spatial control task required subjects to search for any one of three prespecified locations. Although this search task had less of a working memory load than the spatial memory task, subjects still reported trying to keep active the target locations in the control task, which suggests they were actively rehearsing the locations. If the control task involved visual-spatial rehearsal, and if such rehearsal is mediated by right-hemisphere area 47, and perhaps area 19 as well, then such areas are unlikely to be active after subtracting the control from the memory condition.

With regard to the verbal task, there were two left-hemisphere regions significantly active in the item-recognition task of experiment 1 but not the present verbal task, the premotor area and SMA. These areas may have failed to be significantly active in the present study for a reason similar to that for the spatial case. The left-hemisphere premotor area and SMA presumably mediate verbal rehearsal processes, and such processes were apparently used in the verbal control condition (search for any one of three letters). Consequently, when the verbal control was subtracted from the verbal memory condition, enough of the rehearsal processing may have been removed to make the premotor area and SMA activations insignificant. The other two areas significant only in experiment 1 are the anterior cingulate and a right-hemisphere cerebellar site. To the extent the cerebellar site contributed to rehearsal, we would again expect its activity to be artifactually lowered.

Let us summarize. At a global level, this study, like the preceding one, shows dissociations between spatial and verbal working memory. Moreover, what seems to drive the double dissociation is lateralization of function, with the spatial task leading to more right-hemisphere activation (in critical regions) and the verbal task leading to more left-hemisphere activation. This lateralization holds up even when we consider specific regions, such as areas 40 or 46.

When the level of analysis moves to specific regions, it is helpful to divide the results into three cases, corresponding to whether (1) the active regions were the same as those found in experiment 1 (common regions), (2) the active regions were new ones (new regions), or (3) the regions active in experiment 1 were not active in the present study (missing regions). The common regions in the spatial task include two right-hemisphere areas, area 40 and the premotor area 6, whereas those in the verbal task include two left-hemisphere areas, areas 40 and 44. These common regions are very robust, as we have found right-hemisphere areas 40 and 6 significant in still another spatial task (Smith et al., 1995), and we and others have found left-hemisphere areas 40 and 44 active in numerous other verbal tasks (e.g., Paulesu et al., 1993; Petrides et al., 1993b; Awh et al., 1995a). With regard to new regions, the most striking finding was that many of the new regions in the spatial task were the left-hemisphere homologs of right-hemisphere regions that were highly active, whereas some of the new regions in the verbal task were the right-hemisphere homologs of the left-hemisphere regions that were highly active. In short, the additional areas tend to be homologs of areas that typically mediate the task, which suggests that the homologs may be recruited to assist in the processing or they may reflect excessive activation that spills over to the opposite hemisphere. The finding that some regions active in experiment 1 are missing from the signifi-

cant regions of the present study seems to be due mainly to our use of control conditions in the present study that led to some rehearsal processing. Consequently, the structures mediating these processes were to some extent subtracted out of the difference images.

Finally, some comment should be made about the relation of our spatial results to those obtained with nonhuman primates in comparable tasks. As noted earlier, area 46 is the closest analog to the area that appears to mediate spatial working memory in nonhuman primates (e.g., Goldman-Rakic, 1987). Although right-hemisphere area 46 was not significantly active in the spatial task of experiment 1, it was in the present spatial task. Moreover, two recent experiments have found evidence for the activation of area 46 in spatial working memory tasks (McCarthy et al., 1994; Smith et al., 1995). The bulk of the evidence thus suggests that area 46 is involved in spatial memory in humans, just as it is in nonhuman primates.

Experiment 3: A Further Test of Verbal Working Memory

We have suggested that the regions active in experiment 1 but not experiment 2 (1) may mediate rehearsal processes, and (2) may have been substantially involved in the control conditions of experiment 2. These two assumptions can be partly tested by considering the results of an experiment that we initially performed for a different reason (Awh et al., 1995a). The experiment deals only with verbal working memory. It includes a verbal memory condition similar to the one in the previous study, but a control condition that is less likely to invoke rehearsal processes. We would expect that a comparison of the memory and control conditions in this experiment should reveal all, or most, of the areas found active in the verbal task of experiment 1.

Materials and Methods

Tasks

The verbal memory task was very similar to the verbal task in the previous study, except that it required a two-back rather than a three-back decision. That is, now subjects had to decide whether or not each letter matched in identity the one presented two-back, indicating their decision by pressing a button once or twice. A continuous stream of 42 consonants was presented, with each letter occurring for 500 msec with a 2500 msec interval between letters. Subjects made their two-back memory decision about each letter. Again, one-third of the letters required positive responses (and there were occasional matches positioned one-back and three-back).

Importantly, the verbal control condition was a simplified version of the search control that we used in the previous experiment. Subjects saw the same continuous stream of letters as in the memory condition, and for each letter indicated whether or not it matched a single prespecified target. Now there was only one prespecified target rather than three: hence, the load on working memory and rehearsal should have been minimal. When this search control is subtracted from the memory condition, we should find active all, or most, of the areas that were active in our initial item-recognition task of experiment 1.

PET Procedure

The procedure was very similar to the one used in the previous study. However, now there were three conditions (one of which is not relevant to our present concerns) rather than four, and three scans were conducted of each of the memory and control conditions. Other aspects of the methodology—bolus injection, scanner, timing of the PET images, etc.—were the same as in experiment 2. Our analysis of the PET data paralleled that in the previous studies.

Results and Discussion

Subtracting the control from the memory condition resulted in a number of significant areas of activation. They are presented in Figure 5 (with coordinates of the areas given in Table 1, Experiment 3). Most of the active areas are in the

left-hemisphere, though there are a few significant right-hemisphere areas as well.

The critical results concern the specific regions activated. First, and most importantly, the main areas that were significant in our initial item-recognition task are again significant here. These common regions include four left-hemisphere areas—area 40 (see Fig. 5, top, second image from the left), and the trio of Broca's, premotor, and SMA that we have attributed to rehearsal (the latter two areas are evident in the leftmost region of the top row). The remaining two common regions are the anterior cingulate (middle image of the top row) and a right-hemisphere cerebellar site (rightmost image in the bottom row). The only areas significant in experiment 1 but not here are the left-hemisphere thalamus and insular cortex, for neither of which did we have a ready interpretation. All in all, the data in Figure 5 support the contention that verbal working-memory tasks result in activation in parietal areas that mediate storage and frontal areas that implement rehearsal. Apparently, the failure to find the complete rehearsal circuit in our three-back task of the previous study was, indeed, due to the use of an overly demanding search control.

There are also a number of areas in Figure 5 that were not active in the item-recognition task of experiment 1. One of these is left-hemisphere area 7. Any activity in this region in experiment 1 would have been cut off by the limitation in the field of view of the PET camera. Three other regions active in the present study but not in experiment 1 are in the right hemisphere, and include area 40, the premotor area, and SMA. These areas are homologs of left-hemisphere areas that we have already considered, and may reflect recruitment or spillover.⁵

Conclusions

Our findings provide support for the claim that the neural basis of verbal working memory is distinct from that of spatial working memory. Furthermore, the results lead to hypotheses about the circuits involved in these two memory buffers. In the course of providing evidence about these issues, several points of general interest have emerged, and five of these are briefly summarized here.

Laterality

The most striking difference between spatial and verbal working memory is that spatial memory involves predominantly right-hemisphere regions, whereas verbal memory involves mainly left-hemisphere regions. This laterality difference was demonstrated in both experiments 1 and 2, which used quite different tasks. It fits with other research contrasting visual-spatial and verbal processing in humans (see Kolb and Whishaw, 1990).

Possibility of Functional Recruitment

The most notable departures from laterality occurred in experiments 2 and 3. With regard to experiment 2, in the spatial task there was activity in left-hemisphere regions that were homologs to the main right-hemisphere regions involved, whereas in the verbal task there was activity in right-hemisphere regions homologous to the main left-hemisphere regions involved. These results raise the possibility that the homologous regions were recruited to aid in executing an unusually demanding working-memory task (an alternative is that the homologous activity is a nonfunctional spillover). Some comparable results were obtained in experiment 3, which also used a demanding task. (There was even a hint of an involvement of homologous areas in experiment 1.)

Dissociation from Other Buffers

The results of experiments 1 and 2 indicate that the verbal buffer is distinct from the spatial buffer, but is it also distinct

from other buffers? Another working memory buffer that has been studied with both humans and nonhuman primates is an object buffer that briefly stores visual information about the identity of objects. PET studies with humans show that object working memory tasks lead to activation primarily in the left hemisphere (Smith and Jonides, 1994). This is like our verbal task. However, when the objects are difficult to describe (thereby eliminating or reducing verbal processes), the activations in an object task are confined to posterior regions of the left hemisphere, including area 40 and a site in inferotemporal cortex (Smith et al., 1995). These results are unlike what we found in our verbal task, and they suggest that there is a double dissociation between verbal and object working memories. Thus, we are left with the hypothesis that verbal, object, and spatial working memories are all distinct mechanisms.

Storage versus Rehearsal

We have suggested at various points that each working memory buffer includes two distinct neural circuits, with one implementing a storage function and the other a rehearsal function. This suggestion seems particularly plausible for the verbal buffer, where the storage circuit presumably involves left-hemisphere posterior parietal regions (area 40 in particular), whereas the rehearsal circuit involves, at a minimum, the left-hemisphere frontal regions corresponding to Broca's area, premotor area, and SMA. [There is more direct evidence for this distinction in Awh et al. (1995a) and Paulesu et al. (1993).]

Task Difficulty

The switch from item-recognition (the verbal task in experiment 1) to a continuous task (the verbal tasks in experiments 2 and 3) was accompanied by an increase in the level of activation in areas common to the two kinds of tasks, and an increase in the number of areas significantly active (the latter being mainly homologs, as discussed in Possibility of Functional Recruitment, above). We attribute these increases to the increased difficulty of the "n-back" tasks compared to the task of experiment 1, specifically the increase in duty cycle of storage (and other memory processes), the constant reshuffling of the contents of working memory, and the need to temporally code the contents of working memory. It remains a task for further research to sort out the neural consequences of each of these sources of complexity.

Notes

1. Inspection of the actual images suggests that the anterior cingulate was also activated in the spatial task, but at a level that just failed to reach significance in our stringent statistical analysis. Specifically, in the spatial task, two distinct voxels in the anterior cingulate had Z scores of 4.0 and 3.9, which just missed our statistical cutoff.

2. Regarding the spatial task, there is one region notable by its absence—right-hemisphere area 46 in prefrontal cortex. This area is the closest analog to the prefrontal region that has been shown to be critically involved in spatial memory in nonhuman primates (e.g., Goldman-Rakic, 1987). The next study will show involvement of this area in a spatial memory task, and we defer until then discussion of differences between human and monkey data.

3. We are indebted to P. Reuter-Lorenz for bringing our attention to the distinction between recruitment and spillover.

4. There is, however, one respect in which our results do differ from prior findings: two of our active regions are substantially anterior to where others have localized them. The region that we are calling "area 46" is about a centimeter anterior to where Petrides et al. (1993) localized it, while the region that we are referring to as "Broca's area" is over a centimeter anterior to where Paulesu et al. (1993) localized it. The discrepancy involving Broca's area is particularly bothersome, given that the present placement of Broca's area is substantially anterior to where even we localized it in experiment

1. If we look for activity in regions closer to the usual localizations of Broca's area, we, in fact, find some active voxels but their level of activity fail to reach significance. The discrepancy between the present results about Broca's area and previous findings could reflect the fact that our subtractions (memory minus control) underestimated the amount of rehearsal in the memory conditions—see the ensuing discussion in the text.

5. Some comment should be made about the behavioral data in this study and in the preceding two. Across all three experiments, behavioral accuracy was quite high, typically averaging 90% or better, and ranging from a low of 84% in the spatial memory condition of experiment 1 to a high of 100% in the spatial control of experiment 1 and the verbal control of experiment 3. This high level of accuracy is important, as it indicates that subjects were, indeed, executing the processes that we were trying to describe at a neuroanatomical level. Another observation is that behavioral accuracy was *always* lower in a memory condition than in its corresponding control, which supports the assumption that the memory conditions always required at least some additional process, namely, storage and/or rehearsal.

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