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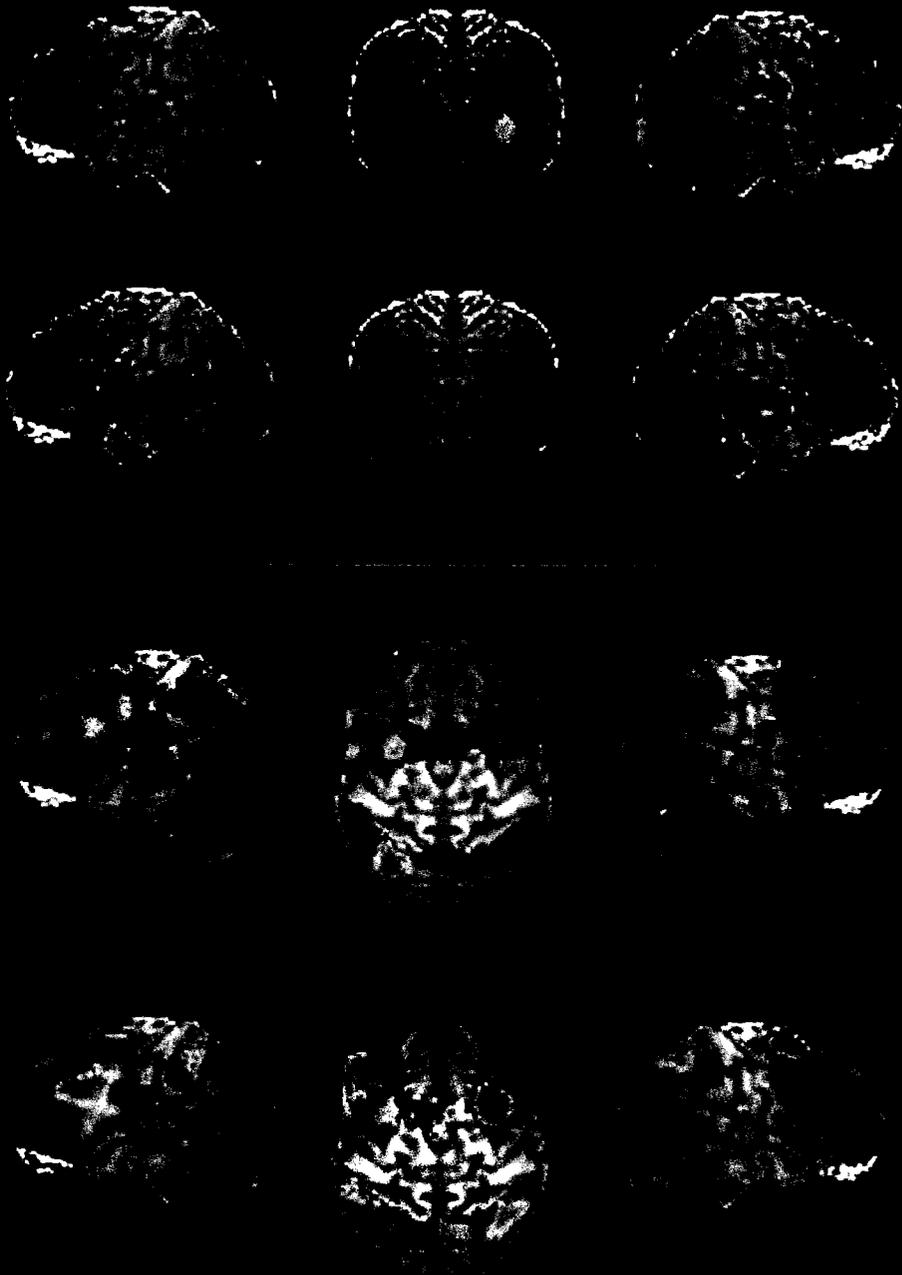
NeuroImage

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Cover Photo. Rows 1 and 2 show left lateral, posterior, and right lateral views of PET activation reflecting brain regions tied to visual-verbal (row 1) and auditory-verbal (row 2) encoding processes. Rows 3 and 4 show left lateral, superior, and right lateral views of PET activation reflecting brain regions mediating working memory processes for visually (row 3) and aurally (row 4) presented verbal material. See the article by Schumacher *et al.* in this issue.

PET Evidence for an Amodal Verbal Working Memory System

ERIC H. SCHUMACHER,^{*1} ERICK LAUBER,^{*2} EDWARD AWH,^{*} JOHN JONIDES,^{*} EDWARD E. SMITH,^{*}
AND ROBERT A. KOEPPE[†]

^{*}Department of Psychology and [†]Division of Nuclear Medicine, University of Michigan, Ann Arbor, Michigan 48109

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Current models of verbal working memory assume that modality-specific representations are translated into phonological representations before entering the working memory system. We report an experiment that tests this assumption. Positron emission tomography measures were taken while subjects performed a verbal working memory task. Stimuli were presented either visually or aurally, and a visual or auditory search task, respectively, was used as a control. Results revealed an almost complete overlap between the active memory areas regardless of input modality. These areas included dorsolateral frontal, Broca's area, SMA, and premotor cortex in the left hemisphere; bilateral superior and posterior parietal cortices and anterior cingulate; and right cerebellum. These results correspond well with previous research and suggest that verbal working memory is modality independent and is mediated by a circuit involving frontal, parietal, and cerebellar mechanisms. © 1996 Academic Press, Inc.

INTRODUCTION

Current models of working memory postulate two processing components for verbal material: a phonological store and a phonological rehearsal mechanism (Baddeley, 1992). These mechanisms are assumed to process amodal mental representations (i.e., representations that are independent of input modality). Before storage and rehearsal ensue, modality-specific representations of verbal material are presumably translated into amodal phonological codes.

Researchers have begun to use neuroimaging techniques to investigate the neural correlates of the verbal working memory system. The results from these studies converge on a model that involves left inferior frontal gyrus (typically described as Broca's area) and other speech-related areas for rehearsal, and superior and posterior parietal cortices for storage.

Petrides *et al.* (1993) found significant bilateral activation in mid-dorsolateral frontal, premotor, and posterior parietal cortices when activation related to a task in which subjects repeated the numbers from 1 to 10 in order was subtracted from activation related to a task in which subjects randomly generated aloud the numbers from 1 to 10, without repetition. The latter task required subjects to hold in working memory the digits that they already said while new digits were generated. The former task did not require much use of working memory. The active areas are therefore presumably involved in the storage and maintenance of verbal material.

Paulesu *et al.* (1993) reported evidence that frontal areas mediate the rehearsal of verbal material, whereas parietal areas mediate the storage of such material. Their experiment required subjects either to remember a set of English letters (memory task) or to make rhyming judgments about English letters (rhyming task). When the control task, in which subjects made nonverbal decisions about unfamiliar Korean letters, was subtracted from the memory task, significant activation remained in bilateral SMA, Broca's area, and left posterior parietal cortex, among other areas. The posterior parietal activation was associated with the memory but not the rhyming task. This suggests that posterior parietal cortex mediates working memory storage. By contrast, Paulesu *et al.* (1993) found that activation in Broca's area was associated with both the memory and the rhyming tasks, which suggests that this area mediates working memory rehearsal.

Awh *et al.* (1996) showed directly that Broca's area is part of the circuit for phonological rehearsal and that bilateral superior and posterior parietal cortices mediate working memory storage. Their experiment included one experimental and two control tasks. The experimental task was a continuous-performance, two-back task. Subjects saw a sequence of letters, one at a time, and responded positively if the current letter was identical to the one seen two previously in the sequence and negatively otherwise. This task requires subjects to hold at least two letters in working memory at all times and to keep track of the temporal order of the

¹To whom correspondence and reprint requests should be addressed. E-mail: eschu@umich.edu.

²Present address: Department of Psychology, University of Georgia.

letters so that working memory can be correctly updated. One control task was a one-letter search task. Subjects again saw a sequence of letters one at a time, but now responded positively if a prespecified target letter appeared and negatively otherwise. The second control task was a rehearsal task. Again, a sequence of letters was presented one at a time, but now subjects silently repeated each letter as it appeared. The subtraction of activation in the search condition from that in the two-back condition revealed significant activation in Broca's area and left posterior parietal cortex, as well as bilateral activation in premotor cortex, SMA, the superior parietal lobule, and cerebellum. Because the two-back task required both working memory storage and rehearsal and the search task required neither, these activations were identified with storage and rehearsal processes. Of these areas, only the parietal and SMA regions remained active when the rehearsal condition was subtracted from the two-back condition. This suggests that the remaining regions (*viz.*, Broca's area, premotor cortex, and cerebellum) are largely involved in rehearsal, but not storage.

Other researchers have found similar results using similar continuous-performance tasks. Cohen *et al.* (1994) found bilateral frontal activation using functional magnetic resonance imaging (fMRI) when subjects performed a two-back task. (This experiment measured only the frontal cortex, and therefore there was no opportunity to find activation in the parietal cortex.) Smith *et al.* (in press) used a similar three-back task. When a search condition was subtracted from the three-back condition, Broca's area and left posterior parietal, left dorsolateral frontal, and bilateral superior parietal cortices remained active.

The studies described above provide strong support for a frontal-parietal verbal working memory circuit. However, all of these studies used visual stimuli. This leaves open the possibility that the circuitry identified for verbal working memory in these experiments is specific to the visual modality. Indeed, there is some evidence for a very different pattern of brain activation in a verbal working memory task when information is acquired by ear rather than by eye (Grasby *et al.*, 1993). In the latter work, one experimental task (subspan task) required subjects to remember and immediately recall five words presented aurally. When a rest condition, which was performed on a different set of subjects, was subtracted from the experimental condition, significant activation remained in left anterior cingulate, right parahippocampal gyrus, right cerebellum, bilateral superior temporal cortex, and thalamus. There was no significant activation in Broca's area or superior parietal or posterior parietal cortices. Perhaps the assumption that verbal working memory is modality independent is unwarranted. There may be a verbal working memory system specific to auditory material,

which is different from the verbal working memory system invoked when information is presented visually.

Further evidence consistent with modality-specific verbal working memory systems comes from studies of brain-damaged patients. For example, patient K.F. has a smaller working memory capacity for verbal material presented aurally than for verbal material presented visually, shows a phonological similarity effect for verbal material presented aurally but not for visually presented verbal material, and shows a diminished recency effect only for aurally presented verbal material (Warrington and Shallice, 1972). Other patients show similar deficits (for a review, see McCarthy and Warrington, 1990; Shallice and Vallar, 1990). These patients typically have damage to their inferior parietal cortex, suggesting that this region may be involved in auditory-verbal but not visual-verbal working memory.³

Indirect evidence for modality-specific working memory systems comes from studies of nonhuman primates. Although these studies do not involve verbal processing, they clearly indicate that primate memory is organized by modality. Colombo *et al.* (1990) used delayed matching-to-sample (DMS) tasks to show that cells in the primate superior temporal cortex specifically mediate the retention of auditory material. Using similar procedures, Miyashita and Chang (1988) discovered cells in the anterior-ventral temporal cortex that mediate the retention of visual information, and Koch and Fuster (1989) discovered cells in the superior parietal cortex (area 5a) that mediate the retention of haptic information.

The evidence reviewed above motivates the present experiment. On the one hand, there is a good deal of neuroimaging evidence for a frontal-parietal circuit for verbal working memory in humans when information is presented visually; on the other hand, there is some evidence of a different circuit involving superior temporal and inferior parietal cortex when information is presented aurally. Is the assumption of an amodal verbal working memory system valid or do modality-specific verbal working memory systems exist in humans? To address this question, we used a three-back verbal working memory task in which items were presented visually in one condition and aurally in another. The two experimental conditions require two comparable control conditions. In both, subjects engaged in a three-letter search task, with the target letters presented visually in one condition and aurally in the other. If verbal working memory is the same for

³ This is not the interpretation offered by Warrington and Shallice (1972). They proposed one verbal working memory system. Patients with damage to it do not show as large of a deficit for visually presented verbal material as for aurally presented verbal material because they rely on a generalized visual storage buffer to compensate for the damaged system.

visual and auditory inputs, then subtraction of the visual search from the visual three-back condition should yield a pattern of activation identical to that obtained from subtracting the auditory search from the auditory three-back condition. Furthermore, examining the particular patterns of activation that result from both subtractions should provide information about the working memory circuit implicated by both modalities.

MATERIALS AND METHODS

Subjects

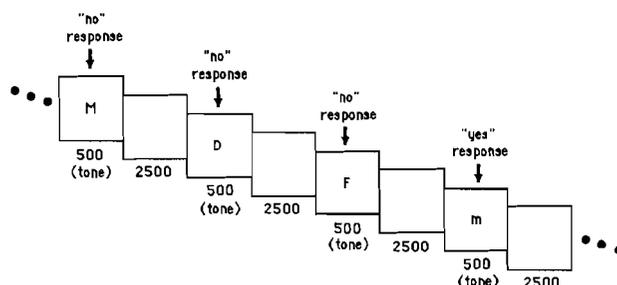
Eight right-handed subjects (four males and four females) were paid \$110 each for participating in the experiment. All subjects gave informed consent prior to testing according to guidelines in place at the University of Michigan.

Design and Materials

The experiment consisted of two sessions. In the first session, subjects practiced the tasks; in the second session, positron emission tomography (PET) scans were conducted. Two tasks were used: a verbal working memory task and a search task. In both tasks, letters were presented one at a time with a 2500-ms interstimulus interval. Eighteen letters were used: all the consonants except L, W, and Y. Subjects made their responses on a two-button computer mouse held in their right hand. The experiment was run on a Macintosh IIfx with a Sony SRS-38 speaker positioned to the left of the monitor and was programmed using PsyScope software (Cohen *et al.*, 1993). At the beginning of each session, the monitor was positioned 18 in. from the subject and the speaker volume was set at a comfortable level.

The memory task (illustrated in Fig. 1) was a three-back task (adapted from Gevins and Cutillo, 1993). Letters appeared one at a time. If the currently presented letter was identical to the letter presented three previously in the sequence, subjects pressed the right mouse button; if not, subjects pressed the left mouse button. Each block consisted of 45 letters; 15 letters were three-back targets, 3 letters were one-back *distractors* (i.e., a match between the current letter and the letter one back in the series), and 3 letters were two-back distractors (i.e., a match between the current letter and the letter two back in the series). All other letters were determined randomly. The memory task required continuous maintenance of verbal working memory. On a trial-by-trial basis, subjects had to: remember the last 3 letters as well as their temporal order; compare the current letter with the one that occurred three back; and update their memory set by dropping the oldest letter and adding the newest one.

Visual 3-Back Task



Auditory 3-Back Task

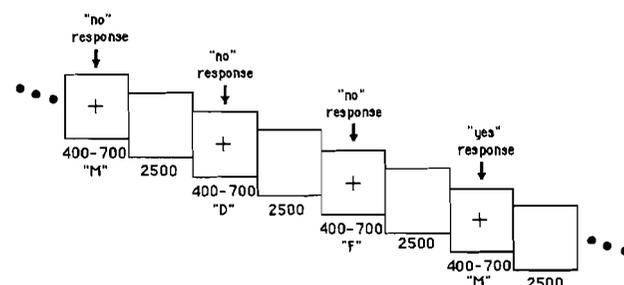


FIG. 1. Example of the three-back task for both modalities of presentation. Each square represents a successive screen on the monitor. The correct subject response is shown above each square. The duration of each screen (in ms) and the sound presented (tone or letter) appear below.

The control task was a 3-letter search task. The search set remained constant for each subject throughout the experiment. Subjects pressed the right mouse button if the letter presented was in their search set and the left button otherwise. Each block consisted of 48 letters. The subject's search set was presented as the first 3 letters of each block. Of the remaining 45 letters, 15 were from the subject's search set (5 of each letter) and the others were randomly determined. The working memory load for this task was relatively low, but its perceptual and response requirements were identical to those of the memory task.

The modality in which the letters were presented was also varied. On half the trial blocks of each task, the letters were presented visually, whereas on the other half they were presented aurally. When presentation was visual, the letters appeared centered on the display monitor for 500 ms, black against a white background. The case, upper or lower, varied randomly by trial to prevent a visual-matching strategy. Forty-eight-point Geneva font was used throughout. A complex tone sounded during the 500 ms that the letter was visible. When the letters were presented aurally, their presentation duration ranged from 400 to 700 ms. The voice, male or female, varied randomly by trial to prevent an auditory-matching strategy. A fixation cross (presented in 48-point Geneva font) appeared when the letter began, centered on the monitor for 500 ms. The

tone and the fixation cross were presented to control for perceptual encoding in the two modalities.

Experimental Procedure

Each subject participated in a practice session on the day before the PET scan. In this session, subjects completed two successive blocks of both tasks in both modalities.

In the PET session, subjects completed a total of eight blocks while being scanned, two for each task in each modality. Task and modality order were counter-balanced across subjects. The three-back and search task blocks were interleaved, but all blocks presented in one modality occurred before blocks of the other modality. Subjects completed four more practice blocks while in the scanner but before being scanned, one block for each task in each modality. These practice blocks were presented in the order that was used during the PET scan.

After the PET session, subjects answered a detailed questionnaire about their strategies for performing each task in each modality.

Imaging Procedure

A Siemens ECAT EXACT-47 PET scanner was used. It produced 47 contiguous slices that were 3.375 mm (center-to-center) apart. The reconstructed in-plane resolution was 10 mm FWHM. Subjects were positioned in the scanner and their head position was recorded. Head position was verified before each scan. Each subject had an intravenous catheter inserted into his or her right arm.

The experimenter administered an intravenous bolus of 50 mCi $H_2^{15}O$ at the beginning of each scan as the subject began the block. PET scanning began after the count rate increased above the background level (after approximately five letters) and continued for 60 s. Each presentation (letter plus interstimulus interval) took approximately 3000 ms; therefore, the scan consisted of about 20 letter presentations. Twelve minutes separated each scan to allow the background radiation to decay to a 1% level.

PET Data Analysis

Regional cerebral blood flow (rCBF) changes between two different conditions were assessed by subtraction analysis of PET image sets (Friston *et al.*, 1991; Worsley *et al.*, 1992). First, intrasubject registration by an automated algorithm corrected motion between scans within a subject's PET session (Minoshima *et al.*, 1993a). PET image sets for each subject were then transformed to a standard bicommissural stereotactic system (Talairach and Tournoux, 1988). The transformation procedure consisted of three steps: (a) detection of the mid-sagittal plane of the brain (Minoshima *et al.*,

1992), (b) detection of the bicommissural (AC-PC) line of the mid-sagittal plane (Minoshima *et al.*, 1993b), and (c) linear scaling followed by nonlinear warping of the brain to remove anatomic differences among subjects (Minoshima *et al.*, 1994). Next, a subtraction image set was created for each subject between the averaged images of the two tasks within each modality (i.e., auditory memory minus auditory control and visual memory minus visual control). The subtraction image sets were then averaged across subjects, producing a group average subtraction image set consisting of mean and standard deviation of CBF changes for each brain pixel. Pixel standard deviations were averaged within the brain (pooled variance), and *t* statistical values were calculated for each pixel using the pooled variance estimate and corrected for multiple nonindependent comparisons (Friston *et al.*, 1991; Worsley *et al.*, 1992). Significant CBF changes were localized using stereotactic coordinates and displayed on a standard nonlinearly warped MRI for visual interpretation.

RESULTS AND DISCUSSION

Behavioral Results

We found no difference between subjects' mean accuracy on memory blocks in the two modalities (93% in each). However, subjects were significantly faster to respond to letters on visual three-back blocks (1076 ms) than on auditory three-back blocks (1254 ms), $t(7) = 2.99$, $P < .02$. Perhaps it takes longer to encode verbal material presented aurally than material presented visually, at least in part because the auditory presentation is itself spread out in time. All subjects reported that, in both memory conditions, they tried to repeat the letters to themselves, adding the new letter and deleting the old one. No subject reported using different strategies for the same task in the two modalities.⁴

PET Results

Modality effects on working memory: Memory minus control subtractions. The memory and control tasks differ mainly in the load placed on working memory. Therefore, subtracting the activation in the control task from the activation in the memory task should reveal brain areas that mediate verbal working memory. For each modality, Table 1 shows the significant areas of activation and deactivation that remain after this subtraction. The areas of activation are shown superimposed on an MRI in Fig. 2.

⁴ Behavioral data for the control task blocks were lost due to a technical error, but informal observation suggests that subjects were extremely accurate. Additionally, subjects were 97% accurate in a similar control task in the experiment conducted by Smith *et al.* (in press).

TABLE 1

Significant Activation and Deactivation Foci in the Memory Minus Control Subtractions, Separated by Input Modality

Stereotaxic coordinates				z score	Brain area
x	y	z			
Visual					
Left hemisphere					
26	1	54	5.4	SMA (Area 6)	
8	-67	43	4.5	Superior parietal (Area 7)	
28	-60	40	6.3	Posterior parietal (Area 40)	
46	-4	34	4.8	Premotor (Area 6)	
48	17	22	4.8	Broca's area (Area 45)	
44	44	18	4.5	Dorsolateral frontal (Area 46)	
51	10	9	4.0**	Broca's area (Area 44)	
10	50	32	-4.7	Anterior frontal (Area 9)	
53	-6	-20	-4.6	Mid-temporal (Area 21)	
Right hemisphere					
-30	5	47	4.2***	SMA (Area 6)	
-12	-67	47	3.4***	Superior parietal (Area 7)	
-39	-46	36	3.5***	Posterior parietal (Area 40)	
-28	-58	-25	5.3	Cerebellum	
-30	5	-34	-4.5	Anterior temporal (Area 38)	
Midline					
-1	14	40	4.5	Anterior cingulate (Area 32)	
1	55	14	-6.0	Anterior frontal (Area 10)	
-1	46	-16	-7.1	Inferior frontal (Area 11)	
Auditory					
Left hemisphere					
24	1	45	5.1	SMA (Area 6)	
26	-62	45	4.2*	Superior parietal (Area 7)	
39	-42	38	5.8	Posterior parietal (Area 40)	
42	10	29	5.7	Broca's area (Area 44)	
46	26	25	6.2	Dorsolateral frontal (Area 46)	
57	5	16	4.8	Premotor/Broca's area (Area 6/44)	
48	19	7	4.7	Broca's area (Area 44/45)	
10	53	29	-6.0	Anterior frontal (Area 9)	
48	-1	-22	-5.5	Mid-temporal (Area 21)	
28	8	-32	-4.7	Anterior temporal (Area 38)	
Right hemisphere					
-28	5	52	7.7	SMA (Area 6)	
-15	-62	45	4.5	Superior parietal (Area 7)	
-39	-51	40	5.6	Posterior parietal (Area 40)	
-17	-60	-22	5.4	Cerebellum	
-15	53	32	-5.5	Anterior frontal (Area 9)	
-30	5	-29	-4.7	Medial temporal (Area 28)	
Midline					
8	8	45	5.0	Anterior cingulate (Area 32)	
6	-69	-25	4.7	Cerebellum	
-6	35	52	-5.4	Superior frontal (Area 8)	
3	-46	25	-4.8	Posterior cingulate (Area 23)	
1	-55	16	-4.6	Posterior cingulate (Area 23)	
1	53	16	-7.7	Anterior frontal (Area 9/10)	
-1	32	-14	-7.7	Inferior frontal (Area 11)	

Note. Brodmann areas are shown in parentheses. Deactivations are shown in italic.

* Not significant but homologous to a significant region.

** Not significant in visual subtraction but significant in auditory subtraction.

Focusing on activations in the left hemisphere, the significant areas in the two modalities are in good correspondence. The same areas are active in both modalities. The locations of the activation peaks (shown in Table 1) differ somewhat by modality, but the active regions and their extent are similar (see Fig. 2). In fact, the only difference is that the auditory modality produced two significant local maxima within Broca's area, whereas the visual modality produced only one. Furthermore, the areas active in both the left and the right hemispheres in both modalities correspond well with the significant areas of activation found in previous investigations of verbal working memory (Awh *et al.*, 1996; Cohen *et al.*, 1994; Paulesu *et al.*, 1993; Petrides *et al.*, 1993; Smith *et al.*, in press).

The two subtractions, however, are not identical. One noticeable difference between them is that the auditory subtraction produced more right hemisphere activation (especially in right SMA) than the visual subtraction. Despite this difference, areas active in one subtraction are active in the other. As shown in Table 1, in the auditory subtraction, the z score for the activation peak in right SMA is 7.7; in the visual subtraction, the z score for the activation peak in the same area is 4.2. Thus, the activation difference is a quantitative rather than qualitative one.⁵ Additional analyses that directly compare the two memory minus control subtractions will be discussed later.

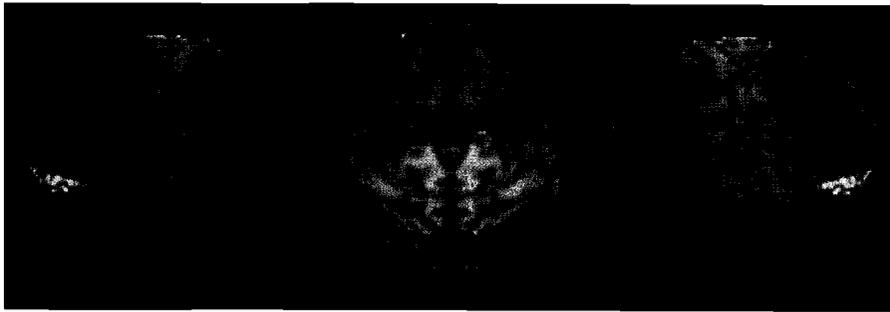
Table 1 also includes the significant deactivations. Although the functional role of these deactivations remains unclear, the pattern of deactivations is similar for both subtractions. All areas significantly deactive in the visual subtraction are significantly deactive in the auditory subtraction, except right Brodmann area (BA) 38. The auditory subtraction produced five deactive areas that were not found in the visual subtractions: right BA 28, left BA 38, midline BA 8, and two sites in midline BA 23.

Referring to the activations, one way to gauge the correspondence between the patterns in the two memory minus control subtractions shown in Fig. 2 is to subtract the activation that remains after one modality subtraction from the activation that remains after the other subtraction (e.g., (auditory memory - auditory control) - (visual memory - visual control)). Table 2 shows the significant foci for each modality that remain after these *double subtractions*.⁶ These areas of activation are shown superimposed on an MRI in Fig. 3.

⁵ The right hemisphere activation was due almost entirely to the four female subjects (see Lauber *et al.*, 1994, for more details on gender differences in this and other working memory studies).

⁶ Only one of each double, memory minus memory, and control minus control subtraction was performed. Visual activation was subtracted from auditory activation. Positive activation is assumed to reflect auditory processing, and negative activation is assumed to reflect visual processing.

Visual Memory - Control



Auditory Memory - Control



Left Lateral

Superior

Right Lateral

FIG. 2. PET images of activation in the memory minus control subtractions. Activations in the visual modality are at the top of the figure; activations in the auditory modality are at the bottom of the figure. Activation with a z score of 1.65 or greater is shown. Significant areas of activation are shown in yellow and red.

Notice that right SMA is not active in the auditory double subtraction ($z < 3.5$), further suggesting that the difference between the two modalities in the activation level of this area is quantitative and not qualitative. In fact, the only area that is significantly active is Broca's area in the auditory double subtraction. This is also a quantitative rather than qualitative difference: Broca's area is active in both memory minus control subtractions, but the inferior portion of the region is more active in the auditory than the visual modality (see Table 1).

Modality effects on encoding: Memory minus memory and control minus control subtractions. The similarities in the two memory minus control subtractions and the lack of significant effects in the double subtractions support the hypothesis that verbal working memory is

amodal. Relying on a negative result (the double subtractions), however, is not fully convincing. It may be that different working memory systems exist for visual and auditory inputs, but that noise in our data, poor experimental control, or both kept us from finding evidence for these systems.

We can deflect this criticism by showing that our experiment is sufficiently sensitive to find modality-specific processing, namely, processing that is tied to encoding. This sensitivity is revealed by examining the activation pattern that remains after the subtraction of one memory condition from the other, and after the subtraction of one control condition from the other. Both of these subtractions show evidence of modality-specific encoding processes (i.e., occipital activations for visual presentations and temporal activations for audi-

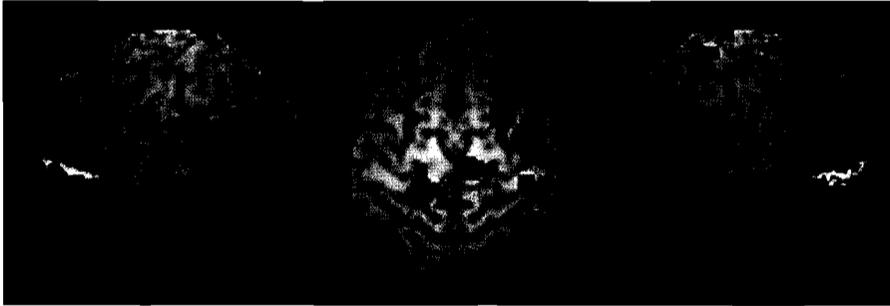
FIG. 3. PET images of activation in the double subtractions. Activations in the visual modality are at the top of the figure; activations in the auditory modality are at the bottom of the figure. Activation with a z score of 1.65 or greater is shown. The significant area of activation is shown in yellow.

FIG. 4. PET images of activation in the memory-minus-memory subtractions. Activations in the visual modality are in the top of the figure, activations in the auditory modality are in the bottom of the figure. Activation with a z -score of 1.65 or greater is shown. Significant areas of activation are shown in yellow.

(Vis Mem-Con) - (Aud Mem-Con)



(Aud Mem-Con) - (Vis Mem-Con)



3 Left Lateral Superior Right Lateral

Visual Memory - Auditory Memory



Auditory Memory - Visual Memory



4 Left Lateral Posterior Right Lateral

TABLE 2

Significant Activation Foci in the Double Subtractions				
Stereotaxic coordinates				
x	y	z	z score	Brain area
Visual–auditory				
(no significant foci)				
Auditory–visual				
51	26	2	4.5	Left hemisphere Broca's area (Area 45)

Note. Broadmann areas are shown in parentheses.

tory presentations). Table 3 shows the significant foci that remain after these subtractions. Part A of the table shows the memory minus memory subtractions, and part B shows the control minus control subtractions. The areas of activation for the memory minus memory subtractions are shown superimposed on an MRI in Fig. 4. Note that none of the regions active in the memory minus control subtractions (Table 1 and Fig. 2) are active in the memory minus memory or control minus control subtractions. This indicates a difference between working memory areas, on the one hand, and encoding areas, on the other.

In the visual minus auditory memory subtraction, only one area is significantly active: BA 18 near the lingual gyrus in the right occipital cortex. Paulesu *et al.* (1993) found activation in the left lingual gyrus in the experiment discussed previously and speculated that this area was involved in the processing of visual letters. Petersen *et al.* (1988) found bilateral activation in this area when a condition that presented only a fixation cross was subtracted from a condition that presented words. Perhaps BA 18 is involved in translating visual representations into phonological ones.

The auditory minus visual memory subtraction revealed several sites of significant activation. These sites include: left BA 22, bilateral BA 21, and left BA 47. Zatorre *et al.* (1992) argue that these temporal regions (i.e., BA 21 and BA 22) are involved in the processing of complex auditory symbols. Perhaps BA 21 and BA 22 mediate the translation of auditory representations into phonological ones. The other significant area (BA 47) is nearly the same region that was active in the auditory double subtraction (although the activation peak has shifted inferiorly).

In the control subtractions, the only significantly active area is left BA 21 in the auditory minus visual subtraction, but all areas (except left BA 22) that were significantly active in the memory subtractions show some activation in the control subtractions, although not strictly significant.

Modality effects on the verbal working memory circuit: Voxels of interest analysis. As a test of the reliability of the hypothesized frontal–parietal verbal working memory circuit, we identified the coordinates of *active*, *deactive*, and *background* regions from the memory minus control subtraction in Smith *et al.* (in press) and used them to create voxels of interest (VOIs) that were then applied to the present data. Recall that Smith *et al.* (in press) also used a visual three-back task to test for verbal working memory. The active VOIs were generated from the coordinates of the peak voxel from each of the 10 regions with the highest level of activation reported by Smith *et al.* (in press). The deactive VOIs were generated from the coordinates of the peak voxel from each of the 10 regions with the highest level of deactivation in the Smith *et al.* (in press) data. The background regions within the brain were generated from the coordinates of the peak voxel

TABLE 3

Significant Activation Foci in the Memory Minus Memory and Control Minus Control Subtractions, Separated by Input Modality

Stereotaxic coordinates				
x	y	z	z score	Brain area
(A) Memory minus memory				
Visual–auditory				
26	–89	0	3.1*	Left hemisphere Occipital (Area 18)
–26	–85	0	4.9	Right hemisphere Occipital (Area 18)
Auditory–visual				
48	–33	4	4.5	Left hemisphere Superior temporal (Area 22)
53	30	–2	4.5	Inferior dorsolateral frontal (Area 47)
51	–17	–2	4.4	Mid-temporal (Area 21)
–64	–13	–2	4.6	Right hemisphere Mid-temporal (Area 21)
(B) Control minus control				
Visual–auditory				
28	–91	0	2.6**	Left hemisphere Occipital (Area 18)
–28	–87	–11	3.2**	Right hemisphere Occipital (Area 18)
Auditory–visual				
28	28	0	3.3**	Left hemisphere Inferior dorsolateral frontal (Area 47)
53	–17	–2	4.4	Mid-temporal (Area 21)
–66	–28	–4	2.9**	Right hemisphere Mid-temporal (Area 21)

Note. Broadmann areas are shown in parentheses.

* Not significant but homologous to a significant region.

** Not significant in control subtraction but significant in memory subtraction.

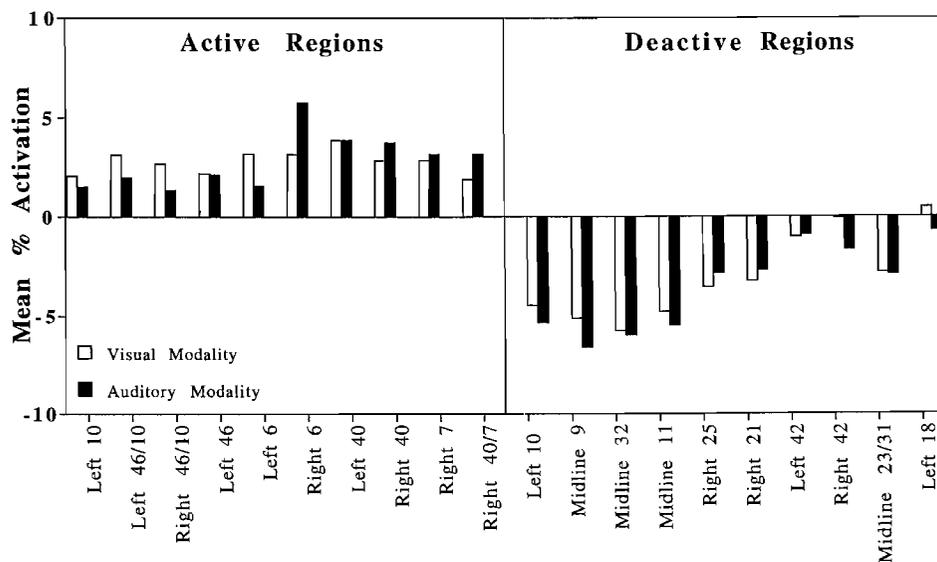


FIG. 5. Activation in the memory minus control subtraction for VOIs based on Smith *et al.* (in press). VOIs based on active regions are on the left-hand side of the figure, and VOIs based on deactive regions are on the right. Results for the visual modality (white bars) are distinguished from results for the auditory modality (black bars).

from 14 regions with a z score between ± 0.5 in the Smith *et al.* (in press) data. In all cases, VOIs were defined by centering a sphere of 2 cm diameter on the coordinates of these peak voxels of interest. We then calculated the mean activation in each spherical VOI for both modalities in the memory minus control subtractions of the current experiment. Figure 5 shows the mean activation levels in the active and deactive VOIs for the two modalities. Figure 6 shows the mean activation levels in the background VOIs for the two modalities.

An analysis of variance test was performed on these data, with modality (auditory and visual) and VOI type (active, deactive, and background) as factors. Modality was not significant, $F(1, 62) = 0.243$. VOI type was significant, $F(2, 62) = 58.51, P < .001$. Planned comparisons revealed that, compared to background regions, active regions were significantly more active, $t(46) = 5.67, P < .001$, and deactive regions were significantly less active, $t(46) = -6.05, P < .001$. The mean activation difference between the memory and the control activations was 2.81, -3.26 , and 0.21% for active, deactive, and background regions, respectively. Thus, in the present experiment, task-related areas (i.e., active and deactive regions) as revealed by Smith *et al.* (in press) are active or deactive to similar degrees in both modalities. This suggests that the present data are orderly in their indication of areas involved in the verbal working memory circuit. Additionally, areas previously found to be unrelated to verbal working memory (i.e., the background regions) show a random pattern of activation here.

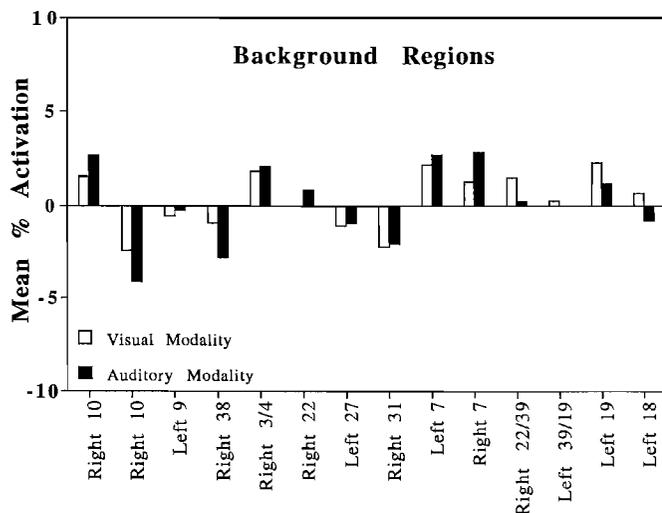


FIG. 6. Activation in the memory minus control subtractions in background VOIs based on Smith *et al.* (in press). Results for the visual modality (white bars) are distinguished from results for the auditory modality (black bars).

CONCLUSIONS

These data indicate that verbal working memory is amodal and involves a frontal–parietal neural circuit. The memory minus control subtractions for the two input modalities show similar activation patterns in areas hypothesized to be involved in verbal working memory (i.e., Broca’s area, right cerebellum, bilateral SMA, and superior and posterior parietal cortices) (see Table 1 and Fig. 2). Further analyses showed that all brain regions previously found to be involved in verbal

working memory are also involved in this experiment (see Fig. 5). Additionally, the overlap between the activation patterns in both memory minus control subtractions is almost complete. Only one area remains significantly active in either double subtraction (see Table 2 and Fig. 3). The finding that visual areas are active in the visual minus auditory memory subtraction and that auditory areas are active in the auditory minus visual memory subtraction (Table 3a and Fig. 4) buttresses our claim that the double subtraction results are valid and not due to a lack of sensitivity. Taken together, these findings provide strong support for a verbal working memory system that is indifferent to the modality of input.

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REFERENCES

- Awh, E., Jonides, J., Smith, E. E., Schumacher, E. H., Koeppe, R. A., and Katz, S. 1996. Dissociation of storage and rehearsal in verbal working memory. *Psychol. Sci.* **7**(1):25–31.
- Baddeley, A. D. 1992. Working memory. *Science* **255**:556–559.
- Cohen, J. D., MacWhinney, B., Flatt, M. R., and Provost, J. 1993. PsyScope: A new graphic interactive environment for designing psychology experiments. *Behav. Res. Methods Instrum. Comput.* **25**:257–271.
- Cohen, J. D., Froman, S. D., Braver, T. S., Casey, B. J., Servan-Schreiber, D., and Noll, D. C. 1994. Activation of the prefrontal cortex in a nonspatial working memory task with functional MRI. *Human Brain Mapping* **1**:293–304.
- Colombo, M., D'Amato, M. R., Rodman, H. R., and Gross, C. G. 1990. Auditory association cortex lesions impair auditory short-term memory in monkeys. *Science* **247**:336–338.
- Friston, K. J., Frith, C. D., Liddle, P. F., and Frackowiak, R. S. J. 1991. Comparing functional (PET) images: The assessment of significant change. *J. Cereb. Blood Flow Metab.* **11**:690–699.
- Gevins, A. S., and Cutillo, B. C. 1993. Neuroelectric evidence for distributed processing in human working memory. *Electroencephalogr. Clin. Neurophysiol.* **87**:128–143.
- Grasby, P. M., Frith, C. D., Friston, K. J., Bench, C., Frackowiak, R. S. J., and Dolan, R. J. 1993. Functional mapping of brain areas implicated in auditory-verbal memory function. *Brain* **116**:1–20.
- Koch, K. W., and Fuster, J. M. 1989. Unit activity in monkey parietal cortex related to haptic perception and temporary memory. *Exp. Brain Res.* **76**(2):292–306.
- Lauber, E., Jonides, J., Koeppe, R., Awh, E., Schumacher, E., Smith, E., and Minoshima, S. 1994. Differences in processing spatial information by women and men as revealed by PET. *Proc. 24th Meeting Soc. Neurosci.* **20**(2):1291. [Abstract]
- McCarthy, R. A., and Warrington, E. K. 1990. *Cognitive Neuropsychology: A Clinical Introduction*. Academic Press, San Diego.
- Minoshima, S., Berger, K. L., Lee, K. S., and Mintun, M. A. 1992. An automated method for rotational correction and centering of three-dimensional functional brain images. *J. Nucl. Med.* **33**:1579–1585.
- Minoshima, S., Koeppe, R. A., Fessler, J. A., Mintun, M. A., Berger, K. L., Taylor, S. F., and Kuhl, D. E. 1993a. Integrated and automated data analysis method for neuronal activation studies using O-15 water PET. In *Quantification of Brain Function—Tracer Kinetics and Image Analysis in Brain PET* (K. Uemura, N. A. Lassen, T. Jones, and I. Kanno, Eds.), pp. 409–418. International Congress Series 1030, Tokyo: Excerpta Medica.
- Minoshima, S., Koeppe, R. A., Mintun, M. A., Berger, K. L., Taylor, S. F., Frey, K. A., and Kuhl, D. E. 1993b. Automated detection of the intercommissural line for stereotactic localization of functional brain images. *J. Nucl. Med.* **34**:322–329.
- Minoshima, S., Koeppe, R. A., Frey, K. A., and Kuhl, D. E. 1994. Anatomical standardization: Linear scaling and nonlinear warping of functional brain images. *J. Nucl. Med.* **35**:1528–1537.
- Miyashita, Y., and Chang, H. S. 1988. Neuronal correlate of pictorial short-term memory in the primate temporal cortex. *Nature* **331**:68–70.
- Paulesu, E., Frith, C. D., and Frackowiak, R. S. J. 1993. The neural correlates of the verbal component of working memory. *Nature* **362**:342–344.
- Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M., and Raichle, M. E. 1988. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* **331**:585–589.
- Petrides, M., Alivisatos, B., Meyer, E., and Evans, A. C. 1993. Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proc. Natl. Acad. Sci. USA* **90**:878–882.
- Shallice, T., and Vallar, G. 1990. The impairment of auditory-verbal short-term storage. In *Neuropsychological Impairments of Short-Term Memory* (G. Vallar and T. Shallice, Eds.), pp. 11–53. Cambridge Univ. Press, Cambridge, UK.
- Smith, E. E., Jonides, J., and Koeppe, R. A. in press. Dissociating verbal and spatial working memory using PET. *Cerebral Cortex*.
- Talairach, J., and Tournoux, P. 1988. *Co-planar Stereotaxic Atlas of the Human Brain*. Thieme, Stuttgart, New York.
- Warrington, E. K., and Shallice, T. 1972. Neuropsychological evidence of visual storage in short-term memory tasks. *Quart. J. Exp. Psych.* **24**:30–40.
- Worsley, K. J., Evans, A. C., Marrett, S., and Neelin, P. 1992. A three-dimensional statistical analysis for rCBF activation studies in human brain. *J. Cereb. Blood Flow Metab.* **12**:900–918.
- Zatorre, R. J., Evans, A. C., Meyer, E., and Gjedde, A. 1992. Lateralization of phonetic and pitch discrimination in speech processing. *Science* **256**:846–848.