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Frontal cortex, laterality, and memory: encoding *versus* retrieval

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Abstract. The cerebral hemispheres differ in their capabilities and response to verbal *versus* nonverbal visual material. *A priori*, it might thus be expected that the right hemisphere would be best activated during a mnemonic task with fMRI when using nonverbalizable images, and the left hemisphere with verbal material. However, previous psychological tests had shown a high degree of similarity in measures of memory for these disparate items. It was thus hypothesized that extensive commonality in the areas activated would prevail when this previously tested material was employed with fMRI. Six subjects underwent fMRI with four types of trials in blocks: fixating; passively viewing 12 words and 12 nonverbalizable images; endeavoring to remember (encoding) another set of 12 words and images; endeavoring to recognize (retrieve) previously viewed words or images. Passive viewing produced small islands of activation in left *versus* right frontal cortex for words and images, respectively. Endeavoring to remember enlarged the areas of activation and produced some bilaterality. Retrieval greatly augmented activation as well as bilaterality, and some 20% of the activated frontal volume was shared by words and images. Thus, on the one hand, the distribution of activation upon retrieval differed substantially for words versus images, but on the other, as predicted, there was considerable commonality. Predominant laterality of activation in some areas shifted between encoding and retrieval (HERA), importantly involving different regions for words versus images. Of course, processes other than memory per se are undoubtedly involved in these distributions of fMRI activation in frontal cortex, yet the nature of the to-be-remembered items is clearly a major factor, in accord with the asymmetric lateralization in their basic representation.

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INTRODUCTION

The two cerebral hemispheres display distinct differences in capability. Such relative isolation of function may well arise because, due to the large size of the human brain, local processing is significantly faster than interhemispheric communication across relatively large distances (Ringo et al. 1994). This, however, declares nothing as to why, for instance, in the great majority of the population, language is predominantly dependent upon the left hemisphere, and various visuospatial analyses proceed most efficiently in the right hemisphere. This arrangement was dramatized in patients undergoing therapeutic transection of the forebrain commissures, and produced a large body of literature endeavoring to specify and understand these questions of laterality (e.g., Benson and Zaidel 1985, Bryden 1982, Davidson and Hugdahl 1995, Harnad et al. 1977, Hellige 1993, Leporé et al. 1986, Trevarthen 1990). A new level of interest has now been added by the advent of neuroimaging, demonstrating a remarkable, puzzling, and unanticipated participation of both hemispheres in a wide variety of perceptual and cognitive processes. Among the more unusual manifestations of this shifting laterality is the fact that when written or spoken verbal material is to be remembered, the activation, as expected, commonly involves the left frontal cortex (Broca's area, etc.); but when it comes to recalling or recognizing that "encoded" information, it is the right prefrontal cortex that is often a primary focus of the engendered activity. This situation has been codified as Hemispheric Encoding/Retrieval Asymmetry (HERA) by Tulving and his colleagues (Lepage et al. 2000, Nyberg et al. 1995, Tulving et al. 1994). The HERA principle is put forward as a description, not as an explanation.

There has been an intense examination of this question, endeavoring to delineate what the conditions are that do or do not produce the HERA outcome in frontal cortex. The arguments, and data (e.g., Buckner 2000, Cabeza and Nyberg 2000, Fletcher and Henson 2001, Johnson et al. 2003, Kirchoff 2000), focus around three factors: whether the laterality is dependent upon the type of material, e.g., verbal versus pictorial; whether it is related to different features of the task, e.g., maintaining the memory, monitoring performance; or whether there is a consistent parcellation of the activity into different frontal areas (D'Esposito and Postle 2002). The variety of tasks employed, despite the often convoluted interpretations, makes resolution of these questions difficult. In addition, there is an inevitable anatomical uncertainty in detail, given a) the two-fold variation in size (volume or cross section, individually commensurate) of neural structures comprising the mature human visual system (Andrews et al. 1997); b) the considerable variance in anatomically defined location of Brodman areas 9 and 46 (Rajkowska and Goldman-Rakic 1995) and Broca's area (Brodman 44 and 45, Amunts et al. 1999); and c) the morphing of the individual anatomies into a common representation for analysis, as in the procedure of Talairach and Tournoux (1988).

Essentially without exception, when verbal material is visually encoded, the left frontal cortex is activated, and this is also true for spoken input (Fletcher et al. 1995). The "unexpected" component of the HERA paradigm, frontal cortical activation greater on the right than on the left upon retrieval of verbal material, is also widely observed (Allan et al. 2000, Brewer et al. 1998, Buckner 1996, Fletcher et al. 1998, Henson et al. 1999, Heun et al. 1999, Iidaka et al. 2000, Johnson et al. 2003, MacLeod et al. 1998, Nyberg et al. 2000, Rugg et al. 1996, Rypma et al. 1999, Stern et al. 2000, Wagner et al. 1998b). It bears emphasis, of course, that several regions other than frontal cortex show activation specifically associated with retrieval, and in differing circumstances different prefrontal areas are involved (Barde and Thompson-Schill 2001, D'Esposito and Postle 2002, Fletcher and Dolan 1999, Fletcher et al. 1998, Haxby et al. 2000, Henson et al. 2000, Lepage et al. 2000, Owen et al. 1999). In addition, these and other studies note a significant degree of bilateral prefrontal participation during retrieval of verbal material. In some instances the attempt at retrieval has been sufficient to promote the right prefrontal activation even though the item to-be-remembered actually was novel (Buckner and Koutstaal 1998, Johnson et al. 2003, Kapur et al. 1995, Wagner et al. 1998a), i.e., attempted retrieval is sufficient; although others have found that while the right anterior prefrontal cortex is activated by successful retrieval, it shows nothing when all the presented items are novel (Rugg et al. 1998).

Verbal material has been used for the great majority of studies. For the few that used nonverbal material the interpretation is confused by ready naming of the "pictures" employed (or even such "nonverbal" material as different letter fonts). In a few instances, however, truly nonverbal memory has been tested. Golby et al. (2001), testing encoding of abstract patterns, found activation of the right prefrontal cortex, as opposed to the left for encoding words. Kelley et al. (1998) found a comparable effect for encoding of faces *versus* words. Wagner et al. (1998b) are alone in having tested nonverbalizable images (textures) *versus* words in both the encoding and retrieval modes. Contrary to expectation from the HERA paradigm, they reported that left frontal cortex was more active than the right for both encoding and retrieval of words, and *vice versa* for the textures. However, the analysis proceeded solely from difference scores, i.e., for words the left frontal cortex was more active than the right, etc.; but no measure of right frontal cortex during encoding of words was given. Thus any bilaterality was ignored for either material or process. The experiments are also complicated by use of 1.5-s presentations of the stimuli, promoting the intrusion of ocular scanning into the encoding phase.

The full picture as to the lateralization of activation during retrieval of words versus truly noverbalizable images thus remains ill-defined. The present study has been undertaken to provide a more complete resolution of this issue of laterality of retrieval for these two "modalities," whose encoding clearly meets expectations of addressing left *versus* right frontal areas, respectively. The opportunity to pursue this problem has been significantly enhanced by a prior, thorough study of the mnemonic features of a set of words and nonverbalizable images. These experiments (Doty and Savakis 1997) were designed to test whether the putative hemispheric differences, left for words, right for images, would be reflected in some characteristic of memory for these two types of material. The colored, abstract images (e.g., Fig. 1) and four-letter words were presented in a continuous recognition task of 240 trials, in which on half the trials the items were novel ("new") and were encountered again ("old") after 1-31 intervening items. Sub-

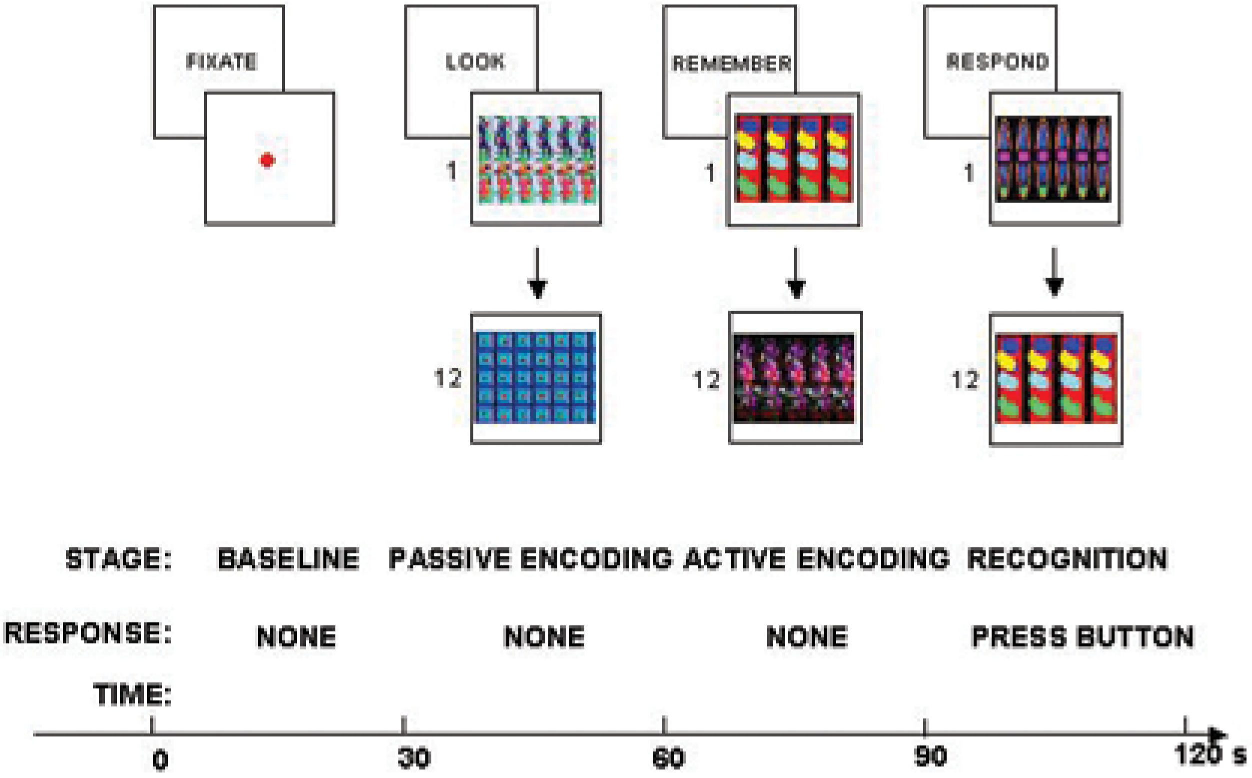

Fig. 1 Schematic representation of blocks in the continuous recognition task. There were four 30-s blocks. Each began with a written instruction appearing on the projection screen for 2.3 s. During block 1(FIXATE), the participant fixated a small red dot throughout the 30 s. For block 2 (LOOK), the fixation spot appeared for 500 ms before each presentation of 12 images (illustrated) or 12 words, each of which lasted 200 ms and was followed by a blank screen for 1.6 s. The same procedure was followed in block 3 (REMEMBER), during which the participant endeavored to "memorize" the 12 images or 12 words that were presented. At block 4, following the instruction "RESPOND", 12 images or 12 words were presented, half of which had been presented in any preceding block 3 episode, and the participant had to evidence recognition (retrieval) by pressing one or the other button of a computer mouse depending on whether the item had or had not been seen before. Three such repetitions were presented seriatim for images and then for words, or *vice versa*.

jects distinguished "new" from "old" items. The images were more difficult to remember, i.e., reaction times were longer and retention less accurate; but when the results were normalized, both accuracy and reaction time as a function of number of intervening items were highly similar for the words *versus* images. Thus, despite the presumed difference in the laterality of their processing, the multiple similarities in pattern of mnemonic performance suggests considerable overlap or commonality in the underlying circuitry. In employing herein the identical materials and procedure with fMRI, two questions can be answered: what is the pattern of activation for encoding and retrieval for words *versus* images; and can a commonality be discerned in the loci activated by mnemonic processing of these distinctly different types of material?

METHOD

Subjects

Six (4 male and 2 female, average age 31.8 years) right handed, native English speaking volunteer graduate students and staff members participated in this study. All procedures and the consent form for participation were approved by the Research Subjects Review Board of the University of Rochester. Each participant had normal or corrected to normal vision, normal color vision, and no history of neurological problems.

Procedure

After reading and signing the consent form, and responding to a handedness questionnaire (Oldfield 1971), the participant was given a practice session outside the scanning facility. Practice was identical to the task to be performed in the scanner, using entirely comparable, but different, material from that to be used in the experiment *per se*. The participant was instructed to respond as fast and as accurately as possible in the retrieval block. While in the scanner, padding and tape were used to constrain head position, and the participant was reminded to remain as immobile as possible.

Stimuli

Two sets of 108 words and of 108 nonverbalizable, abstract, colored images were used (Fig. 1). All the words were monosyllabic four-letter words with a median use frequency of 19 (Francis and Kucera 1982). Homonyms (prey/pray) or synonyms (chef/cook), or rarities (adyt) were excluded. Randomly selected words were projected in white on a black background. Sets of images were randomly selected from a collection of several hundred (Doty and Savakis 1997). These images lacked features that would make them readily available to verbal description and, essentially, could not be rehearsed. All the stimuli were projected from a PC computer onto a white screen standing at the participant's feet while lying inside the MRI scanner. Participants viewed the stimuli *via* a mirror system mounted on the head coil. The stimuli subtended a visual angle of roughly 5 by 3°.

Task

A continuous recognition task, used previously with the identical items (Doty and Savakis 1997) was modified into a block design. Each set of data for this continuous recognition task consisted of four blocks lasting 30 s each (Fig. 1) as follows: block 1) fixation of a continually present small red dot at center of the screen; block 2) passive viewing: observing a series of 12 words or 12 images; block 3) remembering: viewing of a similar series of 12 words or images, as in the previous stage, but with instructions to remember them; block 4) retrieval: endeavoring to recognize which of a series of 12 words or 12 images had been seen previously in block 3 and which had not. Only items of block 3, and an equal number of novel items, were repeated, but of course items from block 2 inevitably increased the mnemonic load. By pressing one of the two mouse buttons the participant indicated whether a presented word or image was "new", or had been seen previously, "old". The response finger associated with a particular response (i.e., index or middle finger) and the hand used for responding (i.e., left or right hand) were counterbalanced across the participants. Thus, S indicating the data set of the four blocks as above, I for images, W for words, and numerals the number of the data set, the entire experimental sequence consisted of: S-I-1, S-I-2, S-I-3, S-W-1, S-W-2, S-W-3, commencing with images or words being alternated across participants.

Each block of the task began with a written prompt (Fig. 1) that lasted for 2.3 s: FIXATE for the baseline block 1; READ (silently) for words or LOOK for images in passive viewing block 2; REMEMBER for the deliberate encoding block 3; and RESPOND in retrieval block 4, respectively. In the three blocks that included stimulus presentations the trial began with the presentation of a fixation point for 500 ms, followed by the stimulus presentation for 200 ms, and then a blank screen for 1,600 ms. Hence, a trial lasted 2,300 ms. This relatively fast rate of stimulus presentation was intended to discourage rehearsal of the verbal material. Each block consisted of the instruction prompt and 12 stimuli, yielding 30 s per block. In order to make the blocked recognition task more similar to the continuous recognition task (i.e., more demanding, Fig. 2), the repeated stimuli (i.e., "old") in the retrieval block for the second and third repetitions included block 3 stimuli from any preceding repetition.

Statistical evaluation of performance

Accuracy scores and reaction times for correct responses were submitted to a 2 × 3 repeated measures ANOVA with task (words, images) and data set (repetition 1, repetition 2, repetition 3) as within subject factors. All *post-hoc* analyses were carried out using the Tukey honestly significant difference test.

Scanning

All MR imaging was performed using a 1.5 T MR imaging scanner (Signa Horizon Echo-Speed, version 5.8 software, GE Medical Systems, Milwaukee, Wisconsin) with a standard quadrature head coil. T1 weighted images of 8 slices with an orientation parallel to the AC-PC line were scanned first. The FOV was 24 cm, slice thickness 7 mm, with a gap of 2.5 mm between the slices. These anatomical images were used for image co-registration in the Talairach and Tournoux (1988) transformation. The MR sequence used for functional studies was a single-shot spiral sequence (TR/TE/FA = 2000/50/80; matrix size = 128 × 128) (Glover and Lee 1995). Slice locations of the functional scans were exactly the same as those for the T1-weighted anatomical images. The 8 slices covered approximately 54 mm of cerebrum above the AC-PC line, and 19 mm of cere-

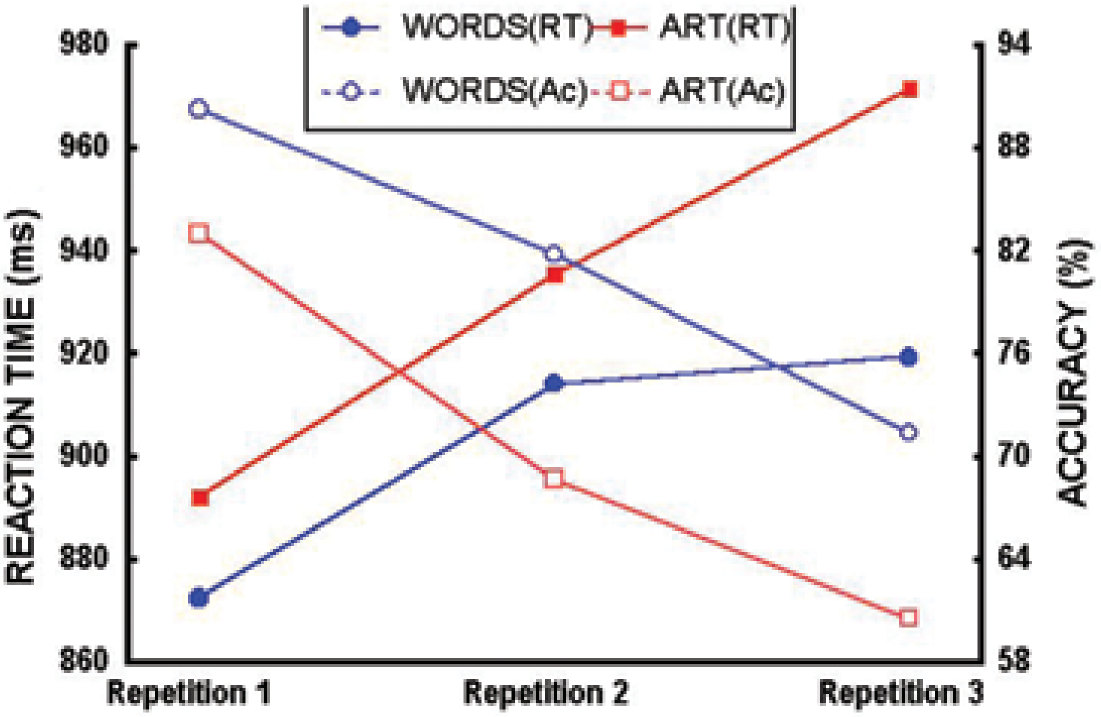

Fig. 2 Reaction times and accuracy for recognition in the three repetitions each of images and words, block 4, retrieval. The "blocks" in the Figure refer to the first, second and third time that block 4 was repeated. Note a) that performance is consistently worse for images than for words, and that b) there is a progressive diminution in accuracy and increase in reaction time as the "inventory" of to-be-remembered items accumulates. This provides evidence that the participants were endeavoring to perform the task as instructed.

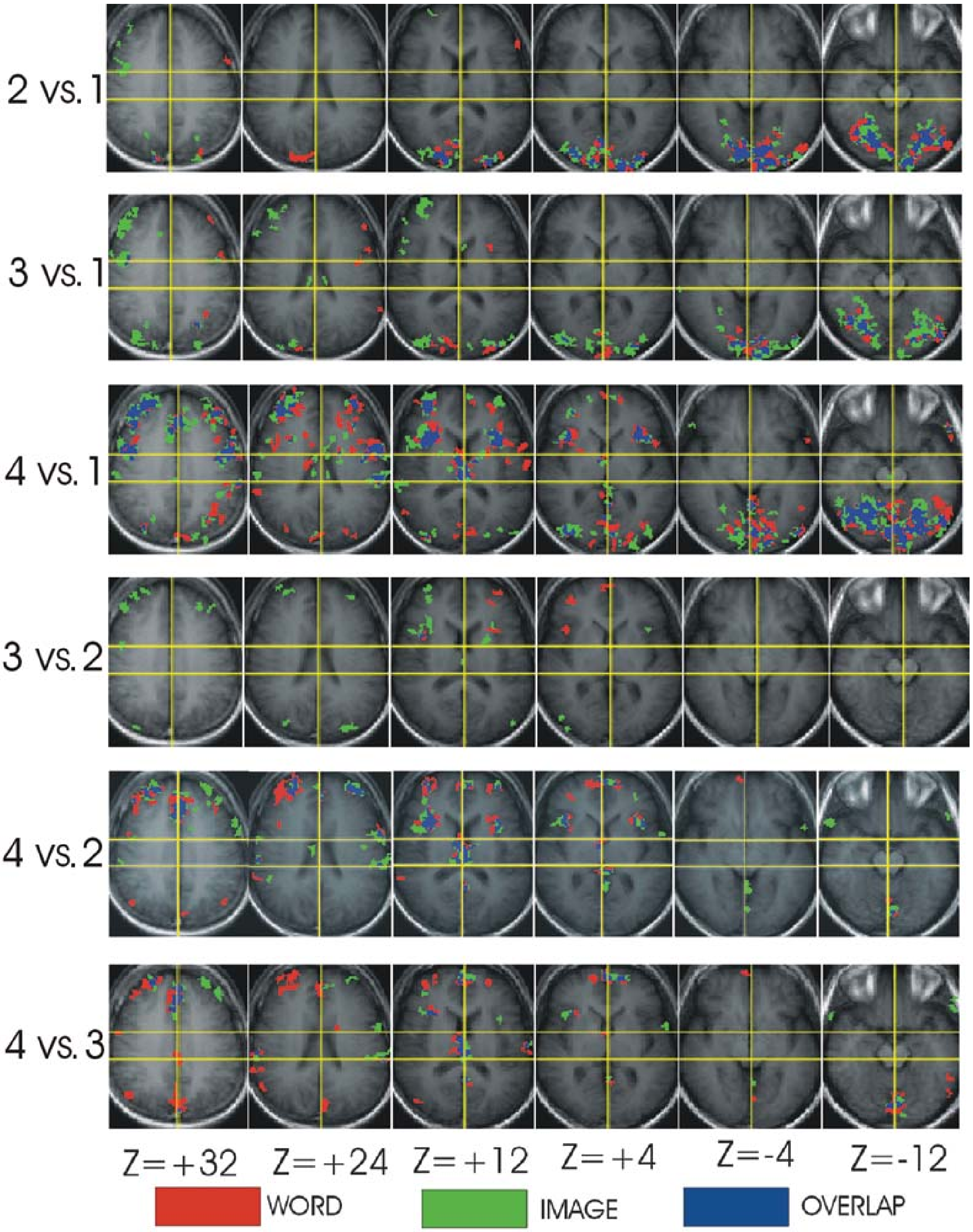

Fig. 3 Activation patterns at six contiguous levels (of the eight scanned; uper and lower gave no data of interest) in Talairach/Tournoux coordinates (Z values), comparing the various blocks with each other. 1 – fixation, 2 – passive viewing, 3 – instructed to remember, 4 – recognizing novel from previously presented items. The horizontal lines indicate the levels of the anterior and posterior commissures. Left side of figure is right side of brain. Note increased frontal activity for remember *versus* passive viewing (2 *versus* 1, 3 *versus* 1 and 3 *versus* 2). The recognition block (4 *versus* 1) calls forth a high level of activation, increasing somewhat even in the occipital ("visual") areas. The pattern comparing recognition with passive viewing (4 *versus* 2) is quite similar to that for recognition *versus* "encoding" (4 *versus* 3) save that the latter shows slightly less differentiation. Absence of occipital activity in the lower three comparisons indicates the high degree of similarity for the visual processing in the three instances.

brum below it. Initiation of scanning for each block was triggered by a computer generated pulse and was synchronized with stimulus presentation. It took 2 s to acquire an image (scan) of the 8 slices. Since each of the four blocks within a repetition lasted 30 s, 15 scans were acquired per block; and since the full procedure (repetition) was performed three times, a total of 45 samples was accumulated for each experimental condition in a single, continuous 6-min imaging scan.

Image processing

Data were analyzed using software based on codes originally developed at Yale University written in MATLAB (The MathWorks, Natick, Mass., USA). All slices were aligned to the anatomical scans. Scans were examined for the possibility of head motion by using a center-of-mass measurement, in which the center of gravity for image intensity above a pre-set threshold for every BOLD image acquisition was calculated and compared. Images in a time series were discarded and omitted from further processing if there was any deviation of the measured center of gravity exceeding 1/3 pixel in the image plane, or 3% in brain pixel count, when compared with the image acquired at the beginning of a time series. There was no motion detected for data in this study determined with the above criterion. The image intensities, however, were corrected for linear temporal drifting in the scanner before activated pixels in each image slice were calculated. Each brain (anatomical image and activation map) was spatially normalized into a standard Talairach-Tournoux form with x, y, and z coordinates. A composite anatomical image for each slice was obtained by averaging these transformed anatomical images for the six participants.

Initially, hemodynamic lag in response of the brain was taken into consideration with a 6-s (three scans) delay between epochs of stimulus presentation and scans considered as "activated". A split t-test was then used to create statistical maps of the t statistic for each voxel for each block across three repetitions. The areas reported as being "activated" consisted of voxels appearing in all measurements that resulted in a corrected overall value $P<0.01$. Further adjustment for avoiding type I error was achieved by using cluster-size threshold (Forman et al. 1995). Only activation patterns of cluster size 8 or greater of contiguous voxels were further analyzed, thus yielding $P<0.00001$ per voxel as the overall measure of validity. These statistical t-test maps were used in contrasting one block with another, e.g., fixation *versus* passive viewing. For qualitative analysis, a composite activation image (Fig. 3), calculated from the median of the t-value from the six participants, was made for each slice and overlaid onto the corresponding composite anatomical images.

Bilateral regions of interest (ROI) were chosen on the basis of observed activation levels in the individual subjects. These ROI were defined as volumes from the Talairach and Tournoux (1988) system; each ROI encompassing well-established gyral and sulcal patterns and Brodmann areas (BA - Tables I and II). The frontal ROIs unilaterally occupied a volume delineated as 950 voxels for the medial frontal, BA9/10; premotor, BA6, 250 voxels; superior frontal BA9/10, 775 voxels; middle frontal, BA9/46, 1100 voxels; inferior frontal, BA44/45/46/47, 875 voxels.

RESULTS

Performance

At block 4 (retrieval) over the three repetitions of trials, for both words and for images, reaction times increased, (Fig. 2) nonsignificantly, from 873 to 919 ms for words, 892 to 972 ms for images. Analysis for accuracy revealed a main effect of task ($F_{1,5}$=6.71, P=0.05), where accuracy was higher for the words (M = 81%) than for images (M = 71%). There was also a significant main effect for block ($F_{2,10}$=4.55, P=0.04). *Post-hoc* analyses indicated that the mean accuracy scores in the third block were significantly lower than for the first: accuracy decreased, from 90 to 71% for words ($F_{1,5}$=14.16, P=0.01), and 83 to 60% for images ($F_{1,5}$=18.39, P=0.008). There was no statistically significant interaction between task and block (P>0.10), indicating that the retention functions were similar for both tasks (Fig. 2). In other words, the progressive decrease in accuracies and increase in RTs for both tasks across the three blocks indicates similar proactive interference effects during retrieval for both tasks.

fMRI results

Encoding

For block 2, passive viewing (Fig. 3, 2 vs. 1), activation was confined almost entirely to occipital "visual" areas (striate, circumstriate, lingual and fusiform areas), although small islands of frontal activation were present, left hemisphere for words, right for images. When the participants were specifically instructed to remember, block 3 (Table I, Fig. 3, 3 vs. 1), there was a similar widespread activation of occipital areas, and a considerable increase in participation of frontal cortex. In the latter case (Table III, Fig. 3, 3 vs. 1) a clear asymmetry was evident in that left hemisphere activation predominated for words, right for images; yet there were also frontal areas in the right hemisphere minimally activated by either words or images (Tables I and III).

Comparison of "remember" *versus* "passive viewing" (block 3 *versus* block 2; Fig. 3, 3 vs. 2, Table III) shows the difference between "active" and "passive" encoding to lie almost exclusively with activation of frontal cortex for the former, the occipital activation being common to the two situations. In total voxel count (Table III) this comparison shows frontal activation bilater-

Table I

Coordinates for center of activation of ROIs in Talairach/Tournoux space during encoding

Region	Brodman Areas	H	Word			Image		
			Talairach Coordinates					
			x	y	z	x	y	z
Medial Frontal Gyrus	9/10	L						
		R						
Superior Frontal Gyrus	9/10	L						
		R				19	44	22
Middle Frontal Gyrus	9/46	L	-37	42	20			
		R				39	41	20
Inferior Frontal Gyrus	44/45	L	-53	19	18			
		R				50	22	18
Premotor Area	6	L	-49	3	27	-48	2	30
		R	44	2	29	45	3	31
Cingulate Gyrus	32	L						
		R				10	21	25
Anterior Insula	45/47	L	-34	9	6			
		R						
Supramarginal Gyrus	40/39	L	-52	-48	30			
		R						
Angular Gyrus	39	L						
		R						
Lateral Occipital Region	19	L	-33	-77	17	-33	-80	18
		R	29	-78	18	30	-80	20
Lateral Occipital Region	18	L	-27	-88	7	-28	-89	5
		R	23	-87	8	27	-86	8
Striate Cortex	17	L	-8	-83	1	-8	-87	0
		R	8	-85	3	8	-86	1
Cuneus	18/19	L				-4	-92	19
		R	4	-85	20			
Lingual Gyrus	18/19	L	-10	-67	-2	-10	-68	-1
		R	8	-66	-1	12	-63	-2
Fusiform Gyrus	18/19/37	L	-35	-67	-16	-32	-69	-16
		R	26	-65	-16	27	-64	-16

(H) hemisphere, (L) left, (R) right

ally equivalent for words, whereas a strong preponderance of right hemisphere participation is present for images.

Retrieval

Testing for recognition, block 4, compared with simple fixation (Tables II and III, Fig. 3, 4 vs. 1), produced a dramatic increase in activation throughout the frontal cortex bilaterally. To a large degree this intensity of activation was also reflected in the fact that much of the frontal pattern included regions that were activated by either words or images, whereas such overlap had been sparse at block 3, encoding. There was also activation of nonoverlapping areas for words and for images bilaterally in the parietal area (Fig. 3, 4 vs. 1).

For words there were two loci, superior frontal and middle frontal (BA9,10 and 46) where activation was

Table II

Coordinates for center of activation of ROIs in Talairach/Tournoux space during retrieval

Region	Brodman Areas	H	Word			Image		
			Talairach Coordinates					
			x	y	z	x	y	z
Medial Frontal Gyrus	9/10	L	-6	55	14	-6	53	11
		R	4	55	10	7	55	12
Superior Frontal Gyrus	9/10	L	-22	40	22	-19	49	24
		R	20	49	25	19	53	25
Middle Frontal Gyrus	9/46	L	-37	39	25	-36	41	23
		R	35	46	22	36	44	23
Inferior Frontal Gyrus	44/45	L	-53	18	22	-51	20	22
		R	45	17	21	49	20	15
Premotor Area	6	L	-49	3	27	-49	3	28
		R	47	4	29	46	3	30
Cingulate Gyrus	32	L	-9	16	21	-8	14	25
		R	10	21	22	8	21	24
Anterior Insula	45/47	L	-34	15	8	-33	17	8
		R	33	16	9	35	16	10
Supramarginal Gyrus	40/39	L	-48	-47	29	-49	-44	29
		R	49	-42	30			
Angular Gyrus	39	L	-40	-73	26	-40	-70	28
		R						
Lateral Occipital Region	19	L	-28	-85	5	-27	-88	3
		R	28	-89	8	26	-84	13
Lateral Occipital Region	18	L	-27	-77	23	-30	-80	24
		R	27	-83	23	31	-77	21
Striate Cortex	17	L	-8	-83	2	-8	-86	0
		R	8	-83	6	8	-84	0
Cuneus	18/19	L	-3	-88	22	-4	-84	25
		R	6	-85	26	5	-85	23
Lingual Gyrus	18/19	L	-12	-65	-1	-5	-65	-2
		R	5	-66	-3	4	-65	-2
Fusiform Gyrus	18/19/37	L	-30	-72	-16	-31	-66	-16
		R	31	-63	-16	28	-64	-16

(H) hemisphere, (L) left, (R) right

Table III

Number of activated voxels in frontal cortex

ROI	Total voxels	Side	Remember (encoding) vs. passive viewing			Remember (encoding) vs. fixation			Recognize (retrieval) vs. fixation		
			Image	Word	Either	Image	Word	Either	Image	Word	Either
Medial frontal	950	R		14 (1%)		9 (1%)			68 (7%)	58 (6%)	27 (3%)
BA9/10	950	L		8 (1%)					102 (11%)	58 (6%)	26 (3%)
Superior frontal	775	R	41 (5%)			19 (2%)			133 (17%)	97 (13%)	45 (6%)
BA9/10	775	L	15 (2%)	8 (1%)					45 (6%)	40 (5%)	
Middle frontal	1,100	R	94 (9%)	26 (2%)		213 (20%)	8 (1%)		328 (30%)	225 (20%)	171 (16%)
BA9/46	1,100	L	24 (2%)	28 (3%)			19 (2%)		140 (13%)	169 (15%)	52 (5%)
Inferior frontal	875	R				15 (2%)			90 (10%)	53 (6%)	13 (1%)
BA44/45/46/47	875	L					10 (1%)		55 (6%)	90 (10%)	14 (2%)
Premotor	250	R	21 (8%)			66 (26%)	12 (5%)	11(4%)	78 (31%)	56 (22%)	45 (18%)
BA6	250	L	8 (3%)			11 (4%)	32 (13%)		169 (68%)	152 (61%)	140 (56%)
Sum	3,950	R	156 (4%)	40 (1%)		322 (8%)	20 (0%)	11(0%)	697 (18%)	489 (12%)	301 (8%)
Sum	3,950	L	47 (1%)	44 (1%)		11 (0%)	61 (2%)		511 (13%)	509 (13%)	232 (7%)

Empty frames signify that no significantly activated voxels were present. Percent, in parentheses, is that of the total voxels activated of the total available in the relevant ROI.

now greater on the right (Table III); and for images the medial frontal and premotor regions (BA6, 9 and 10) the left frontal activity exceeded that on the right. In other words, there was in these instances a reversal (HERA) of the lateralization found for encoding, block 3. Save for the much greater activation associated with images, the overall frontal activity (Table III, Sums) was roughly the same bilaterally for retrieval of words or images.

Activity in the occipital cortex during retrieval was augmented compared to that present during passive viewing or endeavoring to remember (blocks 2 , 3 and 4, Fig. 3). It is not surprising that words and images activated many of the same occipital regions, nor that words and images activate occipital areas in either hemisphere. The complex pattern of occipital activation across the various conditions, however, provides no obvious clues as to its significance.

It can be seen (Fig. 3, 4 vs. 2, 4 vs. 3) that the activation revealed in Fig. 3, 4 vs. 1 is quite uniformly different from that seen with either passive viewing or encoding (2 vs. 1, 3 vs. 1), save that the activity in occipital areas is common to all three conditions (passive viewing, encoding, or retrieval), The HERA pattern is particularly clear in Fig. 3, Z +32 and +24, 4 vs. 3, that is otherwise not so obvious in 4 vs. 1.

DISCUSSION

Distribution of activity in frontal cortex

Figure 3 and Table III provide qualitative and quantitative overviews of the experiment. There are many features of note, varying considerably in their magnitude.

Merely looking at the words or images without endeavoring to remember them (Fig. 3, 2 vs. 1) produces activity primarily in the posterior visual areas with minimal involvement of frontal cortex. However, such frontal activation that does occur (Fig. 3) is fully consistent with expectation, left hemisphere for words, right for images (e.g., Golby et al. 2001, Kelley et al. 1998, Wagner et al. 1998b); and the minimal action belies the fact that if tested, subjects can subsequently remember a fair number of such passively viewed items (Kelley et al. 1998, Rugg et al. 1997). When the subjects specifically strive to remember the material, there is a substantial increase in frontal activation, as others have also found (Kelley et al. 1998, Rugg et al. 1997), being particularly clear for images (Fig. 3, 3 vs. 1, 3 vs. 2); and now there is also bilateral activation as well, when compared to passive viewing (Fig. 3). Right hemispheric activation predominates for images in the latter case (Table III).

The more interesting situation comes with retrieval (recognition). From Fig. 3 and Table III it can be seen that retrieval is characterized in frontal cortex by a strong increase in activation, as well as an increase in bilaterality and overlapping activation. It is immediately apparent that the HERA principle (Tulving et al. 1994 – see Introduction), reversal of lateralization between encoding and retrieval, is present in some areas for words and in others for images. Accepting that encoding is more prevalent in left frontal areas for words and right for images, Table III shows the opposite upon retrieval for superior and middle frontal areas (BA 9, 10 and 46) for words, and medial frontal and premotor (BA 9, 10, 6) for images; although given the generally low level of activation at encoding, the effect is more in contrasting the left *versus* right activation at retrieval. Thus, in some respects the data confirm and continue the puzzle of this reversal in degree of hemispheric activation between encoding and retrieval (HERA), and definitively extend it to include the case with nonverbalizable images; yet it also complicates the situation significantly, in that the HERA effect differs in location for words *versus* images. This difference in location, reflecting a reversal in laterality in the two instances (words *versus* images), may suggest that some fundamental mnemonic principle is in play, distinctly distinguishing the processes of encoding from those of retrieval.

Other noteworthy findings are (Table III): the overall increase in activation, the bilaterality (in sum, slightly greater for right (images?) than for left (words?) in Table III), and the major increase in loci that are activated both by words and by images. These results are generally compatible with, and appreciably extend, those of Wagner et al. (1998b).

However, although the experiments were conducted in the context of memory, these results with retrieval remain ambiguous in relation to memory *per se*. Several other processes are at work, e.g., attention, effort at retrieval (Donaldson et al 2001, Wagner et al. 1998a), the decision, and the monitoring of the response (see, e.g., Fletcher and Henson 2001); and these different features may involve differing loci within the frontal lobe (D'Esposito and Postle 2002, Fletcher and Dolan 1999, Haxby et al. 2000, Henson et al. 2000, Lepage et al. 2000, Owen et al. 1999). It seems likely that much of this increase in frontal activation (Table III) associated with retrieval involves the effort and decision, etc., attendant to the mnemonic process; but the actual production of the response, finger movement, makes no distinguishable appearance in the data.

As noted in the Introduction, much effort has been devoted to endeavors to parcellate these various mnemonically associated features within anatomical loci in the frontal lobe, a task severely complicated by anatomical variation and the compilation of data from several individuals. The present data make one important contribution to this argument, the distribution of activation is significantly dependent upon the nature of the to-be-remembered stimuli (Table III), whatever the other factors contributing to the pattern.

Slight activity can be noted in parietal cortex, on the left, and differing in location for words *versus* images (Table II, Fig. 3). The left parietal area has previously been reported for retrieval of words (Henson et al. 1999, Konishi et al. 2000), and has been associated with choice of response, regardless of which hand is used to make it (Schluter et al. 2001). The present data are compatible with such observations, save that the difference in activated parietal locale for words *versus* images is perhaps puzzling. Absence of significant activity in hippocampus or medial temporal lobe areas should also be remarked, although it remains uncertain as to why hippocampal activation is obtained in some cases but not in others. A recent review found that it appeared in less than half of some 50 cases (Lepage et al. 1998).

Finally, it bears emphasis that the stringent criteria for acceptance of data, combined with the small number of subjects involved, assures a robust statistical validity for the results obtained, and thereby suggests there broad applicability. It remains uncertain as to what degree the high acceptance threshold accounts for the sparseness of the activation (percent of total voxels, Table III) observed in most of the regions of interest, or whether there actually may be closely restricted foci of activity. Again, however, this question founders on the blurred anatomy consequent to the compilation of data from different individuals.

Commonality in locus of activation by words and images

The data are in full accord with the supposition, prompted by the prior behavioral results (Doty and Savakis 1997), that mnemonic processes for words and images must at some point share common mechanisms despite their predilection to activate different hemispheres. The data suggest that this commonality is associated almost exclusively with retrieval (Table III), and involves all the observed frontal areas to some degree. The overlap (Table III) constitutes roughly 20% of the activated frontal volume in each hemisphere, although only 7-8% of the observed space available. This overlap and bilaterality are also concordant with the ready accessibility of this same material of words and images when "cross-hemispheric" retrieval is required (Kavcic and Doty 2002).

Images are slightly more difficult to remember than words in this paradigm (Fig. 2), and there is a corresponding, but minimal, disparity in favor of greater activated volume for images (Table III). Incrementing frontal activity in relation to more challenging mnemonic tasks has also been noted by Grady et al. (1996) and Rypma et al. (1999).

CONCLUSIONS

First, these observations further confirm the proclivity of verbal material to favor left hemispheric processing and visual material the right. Such distinction is complete in frontal areas with passive viewing herein of 4-letter words or nonverbalizable, abstract images. An effort to remember (encode) these words or images produces more widespread activation, and to some degree it becomes bilateral. The further requirement to retrieve (recognize) these items yields not only a great increase in activation and bilaterality, but also evidences considerable overlap, wherein either words or images activate the same loci. While the frontal patterns of activation cannot be ascribed wholly to mnemonic processes *per se*, the sharing or commonality in anatomical locus during retrieval of these otherwise disparate materials is concordant with data showing remarkable similarity in measures of behavioral performance in remembering them. The results thus show, on the one hand, that verbal and nonverbal material unequivocally yield different spatial distributions of activity among frontal areas and, on the other hand, that upon retrieval the words and the images also share a considerable amount of the activated cortical volume.

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