

Hemispheric Specialization in Human Dorsal Frontal Cortex and Medial Temporal Lobe for Verbal and Nonverbal Memory Encoding

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Summary

The involvement of dorsal frontal and medial temporal regions during the encoding of words, namable line-drawn objects, and unfamiliar faces was examined using functional magnetic resonance imaging (fMRI). Robust dorsal frontal activations were observed in each instance, but lateralization was strongly dependent on the materials being encoded. Encoding of words produced left-lateralized dorsal frontal activation, whereas encoding of unfamiliar faces produced homologous right-lateralized activation. Encoding of namable objects, which are amenable to both verbal and nonverbal encoding, yielded bilateral dorsal frontal activation. A similar pattern of results was observed in the medial temporal lobe. These results indicate that regions in both hemispheres underlie human long-term memory encoding, and these regions can be engaged differentially according to the nature of the material being encoded.

Introduction

Human neuropsychological and functional neuroimaging studies have highlighted the importance of both frontal cortex and medial temporal lobe structures in long-term memory processes (Scoville and Milner, 1957; Janowsky et al., 1989; Squire et al., 1992; Cohen and Eichenbaum, 1993; Tulving et al., 1994; Shimamura, 1995; Buckner et al., 1995). However, the specific roles of these regions in mnemonic processes is still a matter of considerable debate (Swick and Knight, 1996; Rugg et al., 1996; Schacter et al., 1996; Gabrieli et al., 1997; Buckner et al., 1998a, 1998b).

Neuropsychological findings have suggested material-specific lateralization of brain involvement in memory processes, with greater left medial temporal lobe

involvement for verbal materials and greater right medial temporal lobe involvement for nonverbal materials (Milner, 1971, 1972, 1982).

By contrast, material-specific laterality effects have only rarely been observed in imaging studies of memory processes (e.g., Martin et al., 1997). Instead, neuroimaging findings have suggested brain lateralization according to the temporal stage of memory processing. One of the most consistent findings from functional imaging studies has been greater left frontal lobe involvement across a wide range of tasks that promote long-term memory encoding and greater right frontal lobe involvement during memory retrieval tasks (Tulving et al., 1994; Nyberg et al., 1996; Buckner and Koutstaal, 1998). The present study focuses on encoding and attempts to address the apparent inconsistency between neuropsychological and functional imaging findings. The effects of several different encoding conditions on activations in frontal cortex and the medial temporal lobe are examined.

Results

Experiment 1

In Experiment 1, three encoding conditions were examined in which materials differed along two dimensions: (1) how easily a verbal label could be applied to each item, and (2) how much nonverbal, pictorial detail was represented in each item. In all conditions, subjects were instructed to remember the items for a later memory test (i.e., intentional encoding). During the three separate encoding conditions, subjects were shown visual words, namable line-drawn objects, or unfamiliar faces (Figure 1A). The word-encoding task was expected to depend upon verbal processing. The namable object-encoding task was expected to depend upon both verbal and nonverbal processing. The face-encoding task was expected to depend upon nonverbal processing, as unfamiliar faces are visually complex, and no preexisting verbal label is available (Meadows, 1974).

Behavioral Results

Accurate performance on a subsequent yes/no recognition memory test was used as an indication that successful encoding occurred. Recognition accuracy (expressed as percent correct), averaged across subjects, was 74% for the words (70% hits, 22% false alarms), 83% for the objects (81% hits, 15% false alarms), and 74% for the faces (68% hits, 20% false alarms). An analysis of variance (ANOVA) revealed a significant main effect of material type ($F[2,8] = 5.91, p < 0.05$) and no significant main effect of order ($F[1,4] = 4.09, p > 0.1$). The interaction was not significant ($F < 1$). Post-hoc statistical tests revealed significant differences in performance across the recognition tasks. The percentage of correctly classified objects was significantly greater than the percentage of correctly classified words ($F[1,4] = 8.42, p < 0.05$) and the percentage of correctly classified faces ($F[1,4] = 9.28, p < 0.05$). There was no significant difference between word recognition and face recognition ($F < 1$).

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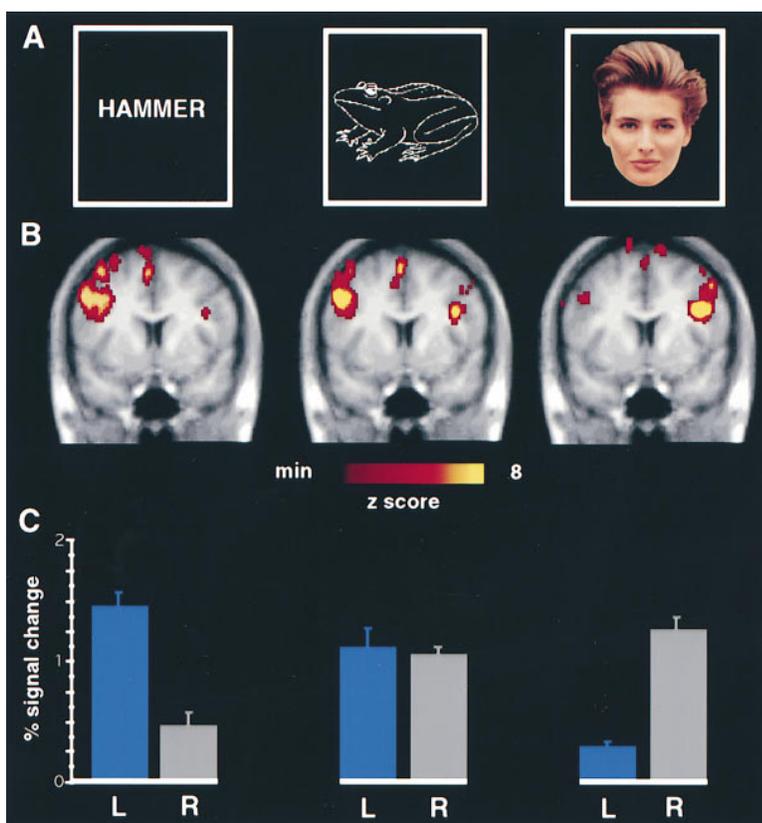


Figure 1. Dorsal Frontal Responses in Experiment 1 during Word, Object, and Face Encoding Averaged across Subjects

(A) Examples of stimuli for the word-, object-, and face-encoding tasks.

(B) Coronal sections show significant dorsal frontal activations averaged across all five subjects in Experiment 1. Images are in the Talairach and Tournoux (1988) atlas space. Colored pixels exceeded the statistical threshold and are superimposed on corresponding anatomy images. The left side of the images corresponds to the left side of the brain. Sections from left to right correspond to word, object, and face encoding in comparison to fixation. Peak activations were observed in left dorsal frontal cortex ($-47, 9, 34$) for word encoding, left ($-47, 7, 36$) and right ($37, 3, 26$) dorsal frontal cortex for object encoding, and right dorsal frontal cortex ($37, 3, 26$) for face encoding.

(C) Percent signal change in left (L) and right (R) dorsal frontal cortex across all subjects. Graphs from left to right correspond to word, object, and face encoding in comparison to fixation. Bars indicate standard error of the mean (SEM). An analysis of variance revealed a hemispheric asymmetry for two encoding conditions, with significantly greater signal intensity in left than right dorsal frontal cortex for word encoding and significantly greater right than left for face encoding. Object encoding produced strong bilateral activations of magnitudes similar to word encoding in the left hemisphere and face encoding in the right hemisphere.

fMRI Results

Figure 1B shows significant dorsal frontal activations for each encoding condition averaged across the five subjects in Experiment 1. In the word-encoding task, significant activation was observed in left dorsal frontal cortex at or near Brodmann area 6 or 44. The object-encoding task produced significant bilateral activation in homologous dorsal frontal regions. The face-encoding task produced significant activation in right dorsal frontal cortex.

To explore more directly the behavior of these regions, signal intensity for both left and right dorsal frontal cortex was compared across each encoding condition. An ANOVA examining effects of hemisphere (right/left), encoding task (word/object/face), and the hemisphere-by-task interaction term revealed a significant main effect of encoding condition ($F[2,8] = 8.97, p < 0.01$) and a significant interaction between hemisphere and condition ($F[2,8] = 38.97, p < 0.0005$).

Post-hoc statistical tests revealed that the word- and face-encoding tasks produced different patterns of activation across the hemispheres (Figure 1C). Word encoding produced greater left than right dorsal frontal activation ($F[1,4] = 38.85, p < 0.0005$), whereas face encoding produced greater right than left dorsal frontal activation ($F[1,4] = 39.01, p < 0.0005$). There was no significant magnitude difference across hemispheres for object encoding ($F < 1$). There were also significant effects of encoding condition within hemisphere. Both word encoding and object encoding produced greater left dorsal frontal activation than did face encoding (words $F[1,4] =$

$54.48, p < 0.0005$; objects $F[1,4] = 27.29, p < 0.001$). Face encoding and object encoding produced greater right dorsal frontal activation than did word encoding (faces $F[1,4] = 25.98, p < 0.005$; objects $F[1,4] = 13.76, p < 0.001$). Thus, the pattern of results that was qualitatively observed in the statistical z-maps was statistically present in an analysis of the hemisphere-by-task interaction and direct comparisons across encoding conditions.

Activation maps created from individual statistical images revealed the same pattern of activation in each of the five subjects (Figure 2A). Moreover, in each subject, the signal intensity for left dorsal frontal cortex was greater than right dorsal frontal cortex during word encoding, while the signal intensity for right dorsal frontal cortex was greater than left dorsal frontal cortex during face encoding (Figure 2B). Thus, clear differential activation of dorsal frontal regions occurred during encoding tasks that used different stimuli.

A similar, but not identical, pattern of activation was observed in the medial temporal lobe within or near the hippocampal formation (Figure 3A). Right medial temporal regions, like right dorsal frontal regions, were activated preferentially by the object- and face-encoding tasks. However, all three encoding tasks produced significant activation in left medial temporal regions.

Signal intensities for left and right medial temporal regions were compared across each encoding condition. An ANOVA examining effects of hemisphere (right/left), encoding task (word/object/face), and the hemisphere-by-task interaction term revealed a significant

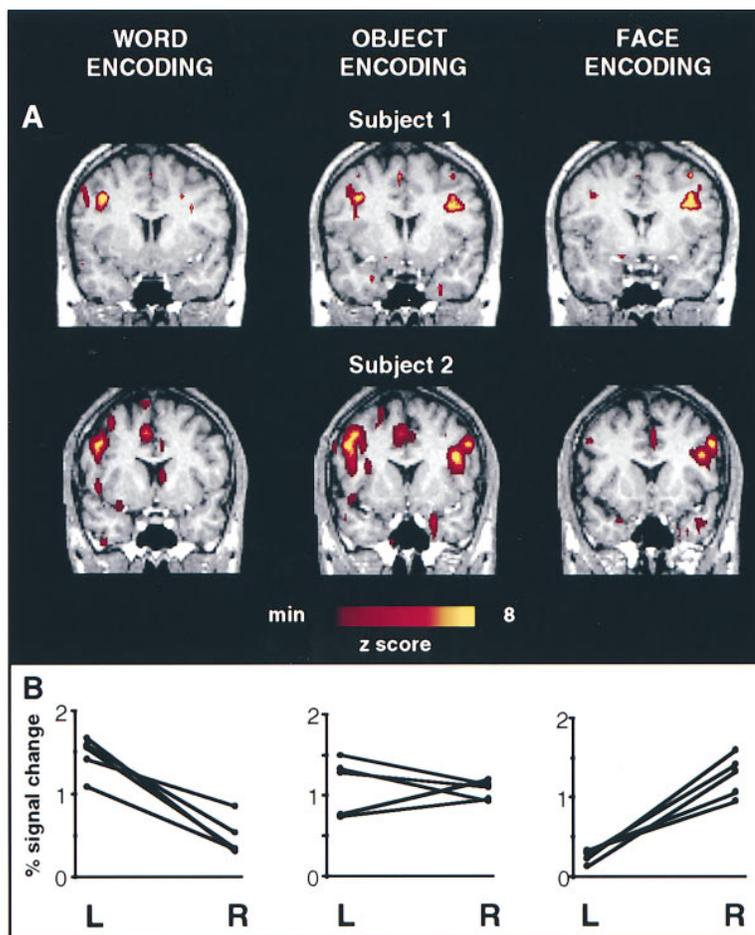


Figure 2. Dorsal Frontal Responses in Experiment 1 for Individual Subjects during Each Encoding Task

(A) Coronal sections from two individual subjects show dorsal frontal regions significantly activated in each encoding task relative to fixation. Images are in the Talairach and Tournoux (1988) atlas space. Colored pixels exceeded the statistical threshold and are superimposed on corresponding anatomy images. The left side of each image corresponds to the left side of the brain. In each subject, word encoding yielded a significant left-lateralized dorsal frontal activation, object encoding produced significant bilateral activation, and face encoding produced a significant right-lateralized activation. These effects were readily apparent in each of the five subjects examined.

(B) Percent signal change in left (L) and right (R) dorsal frontal cortex for all five subjects individually. Graphs from left to right correspond to word, object, and face encoding in comparison to fixation. Each line corresponds to left and right signal intensities from one subject. All five subjects showed greater left than right activation during word encoding and greater right than left activation during face encoding.

main effect of task ($F[2,8] = 18.04, p < 0.005$) and a significant interaction between hemisphere and task ($F[2,8] = 69.98, p < 0.0001$).

Post-hoc comparisons revealed that the word- and face-encoding tasks produced different patterns of activation across the hemispheres (Figure 3B). Word encoding produced greater left than right medial temporal activation ($F[1,4] = 38.85, p < 0.0001$), whereas face encoding produced greater right than left medial temporal activation ($F[1,4] = 39.01, p < 0.0001$). There was no significant magnitude difference across hemispheres for object encoding ($F[1,4] = 3.19, p > 0.1$). There were also significant effects of encoding conditions within hemisphere. In the left medial temporal region, object encoding produced greater activation than did face encoding ($F[1,4] = 9.59, p < 0.05$). However, the difference between word encoding and face encoding was not significant. This was the only statistical exception to the pattern of activation observed in dorsal frontal cortex. In the right medial temporal region, face encoding produced greater activation than both word encoding ($F[1,4] = 246.48, p < 0.0001$) and object encoding ($F[1,4] = 22.42, p < 0.005$). The difference between object encoding and word encoding was also significant ($F[1,4] = 120.21, p < 0.0001$).

Figure 4 and Table 1 summarize significant activations in other brain regions that were observed during each encoding condition. Many of these activations were located bilaterally in primary and extrastriate visual cortex.

Qualitatively, the object- and face-encoding tasks appeared to produce greater activity than the word-encoding task in these regions. The word-encoding task appeared to produce stronger left than right fusiform activation. All three tasks produced activation in posterior parietal cortex. Additional activations were noted in left inferior frontal cortex and supplementary motor area (SMA) for the word- and object-encoding tasks. The face-encoding task produced weak activations in right inferior frontal cortex and SMA that did not reach statistical significance.

Experiment 2

To replicate and extend the observations in Experiment 1, five additional subjects were examined during a second experiment. To confirm the findings from Experiment 1, subjects were scanned during identical intentional encoding conditions. To ensure that the frontal and medial temporal lobe activations observed in Experiment 1 were not caused simply by the presentation of the materials, subjects were also scanned during three passive viewing conditions. In the passive viewing conditions, subjects were asked to view words, objects, and faces without further task demands.

Behavioral Results

As expected, subjects showed greater recognition for items from the intentional encoding conditions than for items from the passive viewing conditions ($F[1,4] =$

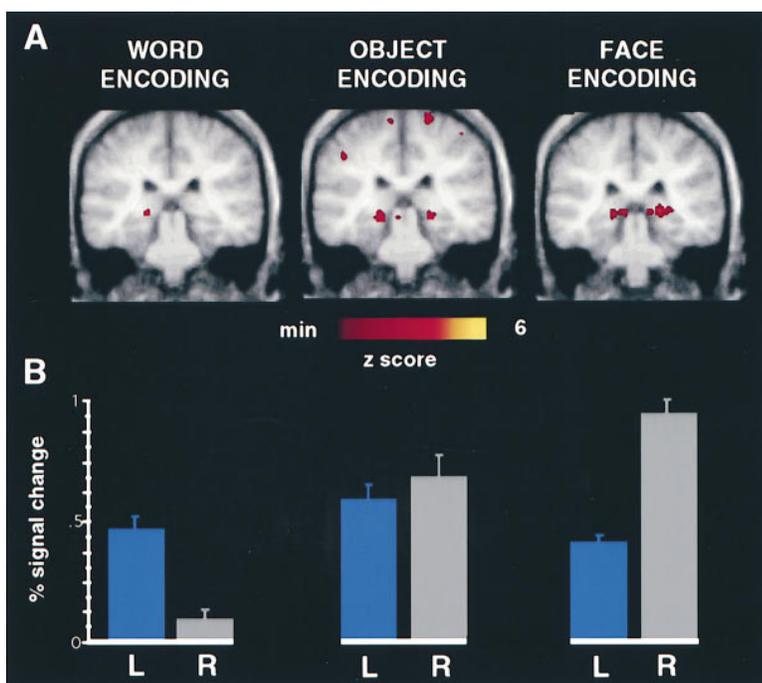


Figure 3. Medial Tempalobe Responses in Experiment 1 during Word, Object, and Face Encoding Averaged across Subjects

(A) Coronal sections show significant medial temporal lobe activations averaged across all five subjects in Experiment 1. Images are in the Talairach and Tournoux (1988) atlas space. Colored pixels exceeded the statistical threshold and are superimposed on corresponding anatomy images. The left side of the images corresponds to the left side of the brain. Sections from left to right correspond to word, object, and face encoding in comparison to fixation. Peak activations were observed in the left medial temporal lobe for word encoding ($-17, -35, -2$), object encoding ($-17, -35, -8$), and face encoding ($-17, -33, -2$) and in the right medial temporal lobe for object encoding ($19, -33, -7$) and face encoding ($19, -35, 0$).

(B) Percent signal change in the left (L) and right (R) medial temporal lobe across all subjects. Graphs from left to right correspond to word, object, and face encoding in comparison to fixation. Bars indicate standard error of the mean (SEM). Hemispheric asymmetries were noted for two of the encoding conditions, with significantly greater signal intensity in the left than right medial temporal region for word encoding and significantly greater right than left for face encoding. Object encoding produced strong bilateral activations of comparable magnitudes.

301.77, $p < 0.0001$). Recognition accuracy (expressed as percent correct), averaged across the five subjects, was 86% for the words (80% hits, 8% false alarms), 91% for the objects (87% hits, 5% false alarms), and 79% for the faces (71% hits, 13% false alarms) from the intentional encoding conditions and only 60% (48% hits, 28% false alarms), 63% (48% hits, 22% false alarms), and 57% (46% hits, 32% false alarms) from the passive viewing conditions, respectively. Performance in all passive viewing conditions was better than chance (paired t tests, $df = 4$, $p < 0.05$ for words, $p < 0.05$ for objects, and $p = 0.055$ for faces). While the instructions clearly produced an effect on memory performance, the above chance performance ($>50\%$) during the passive viewing conditions indicated that some incidental encoding occurred.

fMRI Results

Figure 5 shows signal intensities in dorsal frontal and medial temporal lobe regions for encoding and passive viewing conditions averaged across the five control subjects. An ANOVA examining effects of stimulus material (word/object/face), instruction (intentional encoding/passive viewing), and hemisphere (left/right) was performed on both regions. Several results are notable.

The pattern of activations observed in dorsal frontal cortex and medial temporal lobe structures during the intentional encoding conditions replicated the results described in Experiment 1. For both regions, the ANOVA revealed significantly greater left than right activation for the word-encoding task (dorsal frontal $F[1,4] = 154.78$, $p < 0.0001$; medial temporal $F[1,4] = 66.30$, $p < 0.0001$), significant bilateral activations of comparable magnitude for the object-encoding task (dorsal frontal $F[1,4] = 4.94$, $p > 0.05$; medial temporal $F < 1$), and

significantly greater right than left activation for the face-encoding task (dorsal frontal $F[1,4] = 83.54$, $p < 0.0001$; medial temporal $F[1,4] = 83.99$, $p < 0.0001$). The effects of encoding conditions within hemisphere also replicated the results observed in Experiment 1. In the left hemisphere, word encoding produced greater activation than did face encoding in dorsal frontal cortex ($F[1,4] = 133.75$, $p < 0.0001$), but there was no significant difference between word and face encoding in the medial temporal region ($F = 3.04$, $p > 0.1$). Object encoding produced greater activation than face encoding in left dorsal frontal cortex ($F[1,4] = 72.44$, $p < 0.0001$) and greater activation than both word encoding ($F[1,4] = 41.45$, $p < 0.0005$) and face encoding ($F[1,4] = 66.91$, $p < 0.0001$) in the left medial temporal region. In the right hemisphere, object and face encoding produced greater activation than did word encoding in both regions (all $p < 0.0001$).

The passive viewing tasks produced much weaker activations that were not consistent with this activation pattern. With one exception (passive word viewing produced greater left than right dorsal frontal activation, $F[1,4] = 18.01$, $p < 0.005$), there were no significant effects for any of the post-hoc comparisons performed on the passive viewing conditions.

When intentional encoding and passive viewing conditions were compared directly, several significant differences were noted. There was an overall main effect of encoding instruction (intentional encoding versus passive viewing) for both regions (dorsal frontal $F[1,4] = 166.42$, $p < 0.0005$; medial temporal $F[1,4] = 66.75$, $p < 0.002$). Further post-hoc analyses revealed significant differences in both dorsal frontal cortex and the medial temporal region between intentional word encoding and

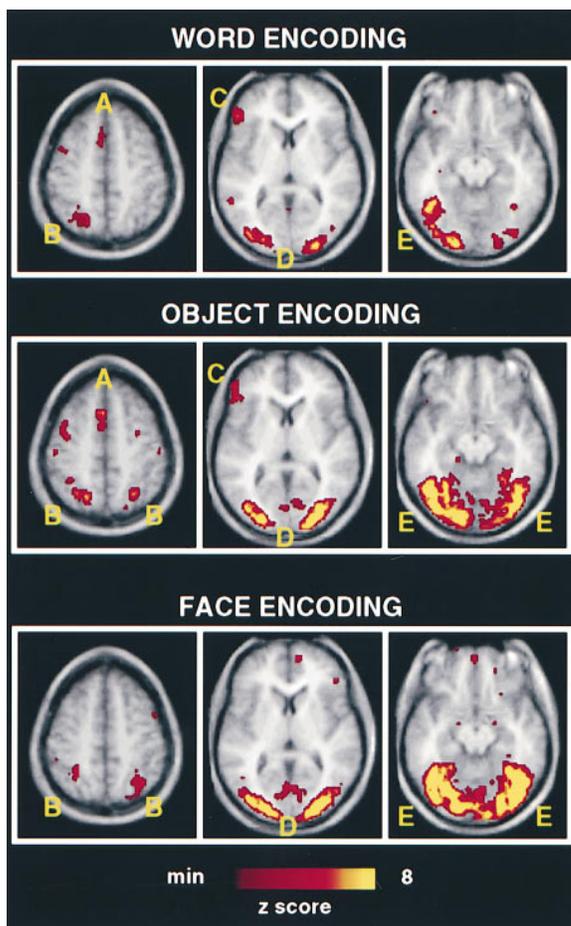


Figure 4. Whole-Brain Responses in Experiment 1 during Word, Object, and Face Encoding Averaged across All Subjects

Whole-brain statistical activation maps are shown for the three encoding conditions in comparison to fixation. Images are axial sections in the Talairach and Tournoux (1988) atlas space. Sections from left to right correspond to $z = 48$, $z = 6$, and $z = -12$. Colored pixels exceeded the statistical threshold and are superimposed on corresponding anatomy images. The left side of the images correspond to the left side of the brain. In both the word- and object-encoding conditions, clear activation was observed in SMA (A), left posterior parietal cortex (B), left inferior frontal cortex (C), posterior visual cortex (D), and left fusiform gyrus (E). The object-encoding condition produced additional activations in right posterior parietal cortex (B) and right fusiform gyrus (E). In the face-encoding condition, clear activation was observed in left and right posterior parietal cortex (B), posterior visual cortex (D), and left and right fusiform gyrus (E).

passive word viewing in the left hemisphere (left dorsal frontal $F[1,4] = 105.32$, $p < 0.0001$; left medial temporal region $F[1,4] = 52.32$, $p < 0.0001$), intentional face encoding and passive face viewing in the right hemisphere (right dorsal frontal $F[1,4] = 70.54$, $p < 0.0001$; right medial temporal region $F[1,4] = 96.21$, $p < 0.0001$), and intentional object encoding and passive object viewing in both hemispheres (left dorsal frontal $F[1,4] = 69.79$, $p < 0.0001$; right dorsal frontal $F[1,4] = 110.93$, $p < 0.0001$; left medial temporal region $F[1,4] = 78.53$, $p < 0.0001$; right medial temporal region $F[1,4] = 71.96$, $p < 0.0001$).

Discussion

Encoding tasks that placed varying demands on verbal and nonverbal processing were used to assess responses in frontal and medial temporal lobe regions. Hemispheric specialization was observed for both regions. We consider each region separately.

Dorsal Frontal Cortex

Dorsal frontal cortex showed left-lateralized activation during word encoding, bilateral activation during object encoding, and right-lateralized activation during face encoding. The greater activation of left dorsal frontal cortex for the encoding of words is consistent with results from several neuroimaging studies that report left dorsal frontal activations during tasks that promote encoding of verbal materials (Kapur et al., 1994; Demb et al., 1995; Kapur et al., 1996; Dolan et al., 1997; Buckner and Koutstaal, 1998). By contrast, the greater activation of right dorsal frontal cortex during the encoding of unfamiliar faces presumably reflects processes more directly related to the encoding of nonverbal information. Consistent with this view, Klingberg and Roland (1998) also report activation of right dorsal frontal cortex during tasks that encourage encoding of nonverbal information. The encoding of namable objects produced dorsal frontal activation in both hemispheres. Interestingly, memory performance was greatest for the namable objects and may reflect encoding enhancement for materials that have access to dual codes (Paivio and Csapo, 1973) and, as revealed by our data, access to bilateral frontal processing.

While studies that have examined verbal encoding tasks consistently report left-lateralized frontal activations, three previous imaging studies have examined encoding of faces but have variously reported left, right, and bilateral frontal activations (Grady et al., 1995; Haxby et al., 1995, 1996; Courtney et al., 1997). In one experiment, Grady, Haxby, and colleagues compared a face-encoding task to a face-matching task. In this study, subjects were instructed to memorize faces that were presented in a complex stimulus array (e.g., one face and two nonsense patterns). During the control task, subjects viewed an array of three faces and were asked to decide whether the first face matched the second face or the third face. Under these circumstances, several left frontal regions, distinct from the frontal regions described here, were activated (Grady et al., 1995; Haxby et al., 1996).

In a prior study of face working memory, which was also likely to encourage long-term memory encoding, Haxby and colleagues examined the effects of delay interval on frontal responses (Haxby et al., 1995). At short delay intervals (1 s), a right-lateralized frontal response was observed; at longer delays (>6 s), the response shifted to a left frontal region. In a subsequent face working memory study, Courtney and colleagues observed across-subject variance with right, left, and sometimes bilateral frontal activation in different subjects (Courtney et al., 1997).

Several factors make it difficult to reconcile these findings with the current data. First, most of the frontal

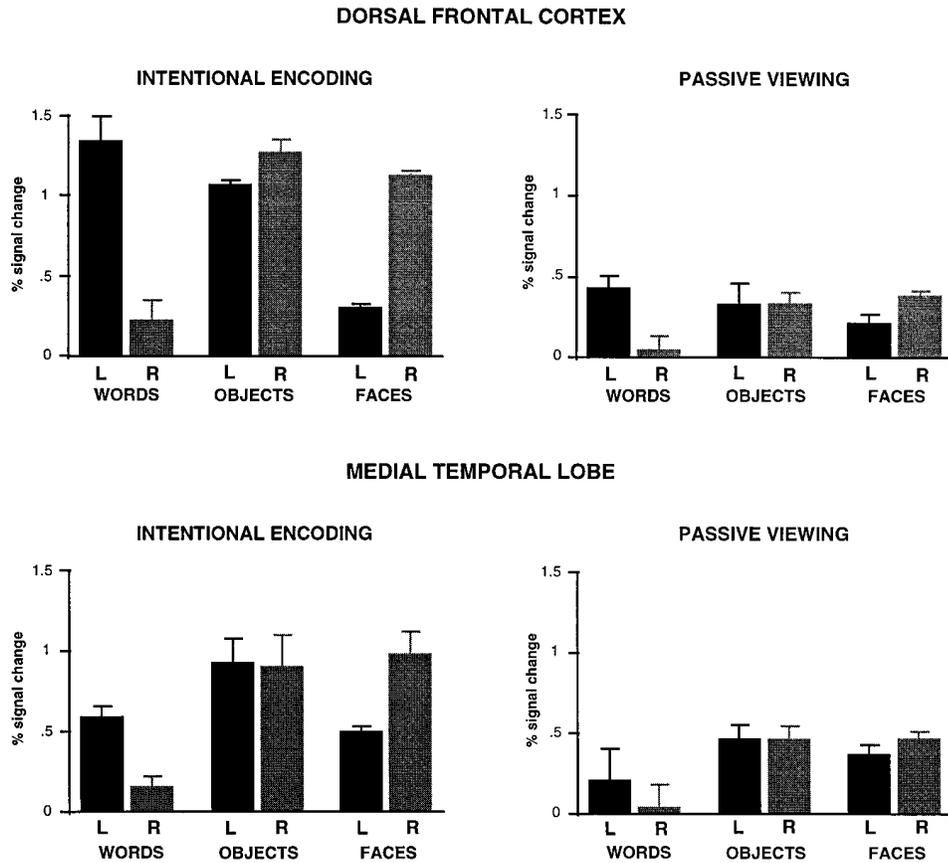


Figure 5. Percent Signal Change in Left (L) and Right (R) Dorsal Frontal Cortex and the Left and Right Medial Temporal Region across Intentional Encoding and Passive Viewing Conditions in Experiment 2

Bars indicate standard error of the mean (SEM). For both regions, the pattern of dorsal frontal and medial temporal activation observed during the three intentional encoding conditions replicated the results described in Experiment 1. In addition, clear effects of task instruction (intentional encoding versus passive viewing) were observed in both regions, with greater left activation during intentional encoding than passive viewing of words, greater right activation during intentional encoding than passive viewing of faces, and greater bilateral activation during intentional encoding than passive viewing of objects.

responses reported in these studies were inferior to the frontal responses observed here and may represent frontal regions that are distinct from the dorsal frontal regions described in the present study. Dorsal frontal activations of the kind reported here and elsewhere (Kapoor et al., 1996; Dolan and Fletcher, 1997; Buckner and Koutstaal, 1998) were not observed in either hemisphere in two of the earlier studies of face encoding and face working memory. In the face working memory study that did report dorsal frontal activations (Courtney et al., 1997), the relative contribution (regression coefficient) of the right dorsal frontal region was greatest for face encoding, whereas the relative contribution of the left dorsal frontal region was greatest across the delay interval (when no face was present).

Second, the encoding tasks employed across these three studies differed from the current one along several dimensions. For example, in the face-encoding study by Grady, Haxby, and colleagues, subjects viewed 32 faces during each encoding scan and were allowed 4 s to encode each face. In the present study, subjects were presented with twice the number of faces during each

face-encoding scan and were allowed only 2 s to encode each face. We suspect that such differences might affect the choice of encoding strategies adopted to successfully encode faces. For example, allowing 4 s to process each face may permit the use of verbal-based encoding strategies. At shorter presentation rates, adoption of verbal-based encoding strategies may become less effective. This might also explain the shift from right to left frontal activity that Haxby and colleagues observed in their working memory study as delay interval increased. In fact, Haxby and colleagues attribute this shift in lateralization to a change in encoding strategy. They suggest that right prefrontal activity reflects reliance on a nonverbal, icon-like representation of a face when delay intervals are brief, whereas left prefrontal activity potentially reflects verbal rehearsal of descriptions or facial features that can be used more effectively when delay intervals are long. Thus, lateralization of frontal activity may be sensitive to both the kind of material being operated on and the encoding strategies encouraged by the task.

Although we obtained robust dorsal frontal activations

Table 1. Identification of BOLD Signal Increases during Encoding Tasks versus Fixation

Brain region	Word Encoding				Object Encoding				Face Encoding			
	x	y	z	Z score	x	y	z	Z score	x	y	z	Z score
Fusiform gyrus												
Left BA 37	-43	-61	-12	5.95	-41	-56	-17	9.48	-37	-61	-18	10.80
	-35	-55	-17	5.61								
Right BA 37	35	-50	-18	2.38	41	-50	-16	8.09	43	-65	-16	11.68
Left BA 18	-41	-76	-12	3.43	-21	-87	-15	8.66	-27	-73	-12	9.78
	-33	-85	-17	2.98	-40	-76	-12	7.43	-39	-77	-12	8.08
Right BA 18					42	-74	-13	7.47	37	-77	-15	10.71
									24	-82	-12	6.72
Lateral occipital cortex												
Left BA 18	-33	-85	-2	7.43	-37	-81	8	9.19	-23	-89	8	9.80
					-30	-87	9	6.01	-36	-82	4	6.43
Right BA 18	23	-93	0	6.85	25	-90	8	7.18	23	-91	8	8.62
	34	-85	0	3.94	35	-83	0	7.00	35	-83	2	6.78
Right BA 19					27	-81	19	5.58	29	-81	28	6.99
Medial occipital cortex												
BA17					-2	-77	0	4.83	-2	-85	-8	5.10
									3	-87	-12	3.46
Left BA 17/18	-17	-93	-7	6.38	-19	-93	0	5.33	-13	-92	-4	8.44
Right BA 17/18					16	-96	3	6.78	11	-98	-6	6.78
Inferior frontal cortex												
Left BA 44/45	-49	29	6	3.93	-48	26	6	2.74				
Posterior parietal cortex												
Left BA 7/40	-27	-67	54	2.58	-20	-65	46	4.10	-34	-51	54	2.56
Right BA 7/40					27	-63	47	2.91	29	-61	53	4.22
Supplementary motor area												
BA 6	-5	5	54	2.45	-4	3	49	2.47				
BA 6/32					-4	14	47	3.58				

Activations determined to be significant ($p < 0.001$) are listed for each encoding condition along with the best estimate of their location. BA, approximate Brodmann area location. Coordinates are from the Talairach and Tournoux (1988) atlas. Locations of activations are defined based on the functional responses superimposed on averaged anatomical MRI images and are referenced to the Talairach atlas.

under intentional encoding conditions but not under passive viewing conditions that produced some incidental encoding, it is not likely that the intentional/incidental variable dictates whether activation will be observed in dorsal frontal cortex. Several studies have reported robust, left dorsal frontal activations during tasks that encourage incidental encoding of verbal materials (Kapur et al., 1994; Demb et al., 1995; Buckner and Koutstaal, 1998). Such tasks do not require explicit memorization but are nonetheless excellent verbal encoding tasks because of the strong demands they place on effortful verbal processing. The passive viewing tasks used in the present study did not require effortful processing and thus produced weak incidental encoding. Our claim then is that tasks that require effortful processing activate regions in dorsal frontal cortex; different types of effortful processing, which tend to be invoked differentially by different stimulus types, activate regions in different hemispheres of dorsal frontal cortex.

Collectively, these results suggest that there exist multiple frontal regions that allow different kinds of information to be encoded. The hemispheric asymmetry in dorsal frontal cortex for verbal and nonverbal encoding, particularly the strong right bias for face encoding, is inconsistent with the encoding aspect of the Hemispheric Encoding/Retrieval (HERA) model. Originally, the HERA model was based on imaging findings that

examined encoding of verbal materials (Tulving et al., 1994). The HERA model, in its current form, suggests that left frontal regions may be preferentially involved in memory encoding, irrespective of the type of information to be processed (Nyberg et al., 1996).

Medial Temporal Lobe

Similar hemispheric asymmetries were noted in medial temporal lobe structures within or near the hippocampal formation. The greater left than right involvement during word encoding and the greater right than left involvement during face encoding are consistent with the laterality effects reported by Martin and colleagues (1997) for verbal and visual aspects of word and object encoding, and with neuropsychological work showing asymmetries in verbal versus nonverbal memory deficits following left versus right medial temporal lobe damage (Milner, 1971, 1972, 1982). However, in both the present study and the study by Martin and colleagues, left medial temporal lobe structures were activated by all material types (both verbal and nonverbal). In fact, namable objects produced stronger activation of left medial temporal lobe structures than words and faces in the present study and words and nonsense objects in the Martin et al. (1997) study. This suggests that the preferred material for left medial temporal lobe structures may be material that combines both verbal and visual attributes. This

also contrasts with the strong left bias observed in dorsal frontal cortex for verbal materials. Right medial temporal lobe structures responded poorly to pure verbal materials and instead showed preference for visual materials. Thus, regions in the right medial temporal lobe appear to be specialized for the processing of visual rather than verbal attributes. Regions in the left medial temporal lobe, at least for these studies, do not appear to be as specialized for any particular material type.

Other studies have reported unilateral activations in medial temporal regions. For example, previous studies of face encoding (Grady et al., 1995; Haxby et al., 1996) report right, but not left, medial temporal activation. By contrast, Dolan and Fletcher (1997) report left, but not right, medial temporal activation related to the encoding of verbal materials. However, several functional imaging studies have failed to detect medial temporal lobe involvement in experiments designed to produce encoding of verbal materials (Kapur et al., 1994; Fletcher et al., 1995; Buckner and Goutstaal, 1998). Moreover, while some imaging studies have reported bilateral medial temporal lobe involvement during encoding of novel visual stimuli, such as complex scenes (Stern et al., 1996; Tulving et al., 1996; Gabrieli et al., 1997), these studies did not report the laterality effects (right > left) observed here and elsewhere (Grady et al., 1995; Haxby et al., 1996) for faces.

The pattern of activation shown here suggests that medial temporal lobe regions can be modulated by both material type and task instruction. Therefore, a more systematic exploration of the relation between medial temporal lobe activity and both the nature of the materials to be remembered and the encoding strategies employed may help to clarify what have thus far been inconsistent findings in the literature.

Conclusions

We have demonstrated, with a simple design and reliable data, that the nature of the materials to be memorized (words versus objects versus faces) and the manner in which the materials are to be processed (intentional encoding versus passive viewing) are critical in determining the relative hemispheric contributions of the dorsal frontal region and, to a similar extent, the medial temporal lobe. The results lend themselves to a straightforward verbal/nonverbal processing distinction. These results are also consistent with multiple code views of encoding that have not been demonstrated previously with imaging. Presumably, these effects are mediated by the choice of encoding strategies encouraged by the materials and task and the specific encoding operations that ensue. For example, the absence of a preexisting verbal label for unfamiliar faces likely promotes the use of nonverbal encoding for the face stimuli, whereas having dual codes available for the namable objects permits the use of both verbal and nonverbal encoding for the object stimuli (Paivio and Csapo, 1973). What we have shown here is that such factors can exert control over the brain regions activated during memory encoding in normal subjects.

Experimental Procedures

Subjects

Ten subjects (six male, four female) between the ages of 18 and 23 were recruited from the local Washington University community. All

subjects were strongly right-handed as measured by the Edinburgh handedness inventory (Raczkowski et al., 1974), without any significant abnormal neurological history, and were normal or corrected-to-normal in visual acuity. Subjects were paid \$25 for each hour of their participation and gave informed consent in accordance with guidelines set by the Human Studies Committee of Washington University.

Functional Imaging

Imaging was performed on a Siemens 1.5 Tesla Vision System (Erlangen, Germany). Visual stimuli were generated using an Apple Power Macintosh computer and the program PsyScope (Cohen et al., 1993). Stimuli were projected to subjects with a Sharp LCD projector (model XGE850) onto a screen positioned at the head end of the bore. Subjects viewed the screen through a mirror. A fiber-optic, light-sensitive key press interfaced with the PsyScope Button Box (Carnegie Mellon University, Pittsburgh, PA) was used to record subjects' behavioral performance. A thermoplastic face mask was used to minimize head movement.

Structural images were acquired using a sagittal MP-RAGE three-dimensional T1-weighted sequence (repetition time [TR] = 9.7 ms, echo time [TE] = 4 ms, flip angle α = 12°, inversion time [TI] = 300 ms, voxel size 1.25 × 1 × 1 mm). Functional images were collected in runs using an asymmetric spin-echo echo-planar sequence sensitive to blood oxygenation level-dependent (BOLD) contrast (T2*) (TR = 2500 ms, T2* evolution time = 50 ms, α = 90°). During each functional run, 102 sets of 16 contiguous, 8-mm-thick axial images were acquired parallel to the anterior-posterior commissure plane (3.75 × 3.75 mm in-plane resolution), allowing complete brain coverage at a high signal-to-noise ratio (Conturo et al., 1996, Soc. Neurosci., abstract). Motion artifact was examined and corrected automatically within each functional run and across runs using a rigid-body rotation and translation correction (Friston et al., 1994; Snyder, 1996).

Behavioral Tasks

Two separate studies were conducted. In Experiment 1, five subjects (three male, two female) were scanned while performing three encoding tasks: visual word encoding, line-drawn object encoding, and face encoding. A recognition memory test was administered after the third encoding task. This sequence was then repeated so that each subject performed six memory-encoding tasks and two recognition tests. Visual words (3–10 letters in length) were presented during the word-encoding tasks (Geneva font; letters subtended ~0.5° of visual angle). Namable line-drawn objects (Snodgrass and Vanderwart, 1980) were presented during the object-encoding scans (this set contained objects with naming agreement > 60%, mean = 91%). Unfamiliar faces were presented during the face-encoding scans (Cohen et al., submitted). When presented on the screen, the objects and faces subtended ~6° of visual angle vertically and ~6° horizontally. Each functional run lasted 255 s and was comprised of seven blocks; four of these were "task" blocks and three were "fixation" blocks. The task and fixation blocks alternated. Each task block lasted 40 s; each fixation block lasted 25 s. Sixteen items were presented during each task block (2000 ms stimulus duration, 500 ms interstimulus interval). Task instructions were to pay careful attention to each item for a later memory test. During the fixation blocks, a cross-hair was present and instructions were to fixate. Within an individual run, only one type of item (words, objects, or faces) was presented during the four task blocks. Task order (word encoding, object encoding, and face encoding) was varied across subjects.

In Experiment 2, five additional subjects (three male, two female) performed both intentional encoding and passive viewing tasks. Two subjects performed intentional encoding tasks during the first three runs and passive viewing tasks during the remaining three runs. The three intentional encoding tasks (words, objects, and faces) were identical to the encoding tasks described above. Following the encoding runs, subjects were given a recognition memory test. After the memory test was completed, the subjects were informed that the memory portion of the experiment had ended. During the remaining three runs, subjects passively viewed words, objects, and faces. Procedurally, this phase was identical to the intentional encoding phase; the two phases differed only in the

instructions given to the subjects. For the passive viewing conditions, subjects were instructed to examine each item but were told that they would not be required to remember them. Contrary to these instructions, a "surprise" recognition memory test was administered following the three passive viewing runs. For the remaining three subjects, the task order was reversed; subjects performed the three passive viewing tasks first and the three intentional encoding tasks second.

Data Analysis

Unpaired *t* tests between task and fixation blocks were used to compute images of *z*-statistics for each encoding condition. Individual subject *z*-images were then transformed into standardized atlas space based on the Talairach and Tournoux atlas (1988) and averaged across subjects to create a mean *z*-image for each encoding condition (corrected for multiple comparisons; Ollinger, 1997, *Int. Soc. Magn. Reson. Med. Fifth Sci. Meet.*). This correction rejects single-voxel regions and ensures that $p < 0.001$, where *p* is the probability of a single erroneous activation in the image volume. An automated peak-search algorithm (Mintun et al., 1989) identified the location of peak activations based on *z*-value and cluster size.

To compare signal intensities across the encoding conditions in an unbiased manner, regions of interest were defined as follows. For each subject, a difference image comparing the task blocks from all three encoding conditions to the fixation blocks was created (word encoding + object encoding + face encoding versus fixation). In this manner, each encoding condition contributed equally to each subject's difference image. In Experiment 2, a combined difference image comparing task blocks from all six conditions (three intentional encoding and three passive viewing) to fixation was created for each subject. An overall group image was also created for each experiment by averaging the five individual difference images.

The maximum difference peaks were identified within the left and right frontal cortex and the left and right medial temporal lobe in each subject's combined difference image (with the constraint that the activation was within 10 mm of the overall group focus obtained from each experiment). Spherical regions (3 mm radius) were defined around each of these peak activations, and mean percent signal change for each separate task comparison (e.g., word encoding versus fixation) was then computed for the right and left frontal and medial temporal lobe regions in each subject and used for ANOVAs.

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