# The Effect of Divided Attention on Encoding and Retrieval in Episodic Memory Revealed by Positron Emission Tomography

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## Abstract

■ The effects of divided attention (DA) on episodic memory encoding and retrieval were investigated in 12 normal young subjects by positron emission tomography (PET). Cerebral blood flow was measured while subjects were concurrently performing a memory task (encoding and retrieval of visually presented word pairs) and an auditory tone-discrimination task. The PET data were analyzed using multivariate Partial Least Squares (PLS), and the results revealed three sets of neural correlates related to specific task contrasts. Brain activity, relatively greater under conditions of full attention (FA) than DA, was identified in the occipital-temporal, medial, and ventral-frontal areas, whereas areas showing relatively more activity under DA than FA were found in the cerebellum, temporo-parietal, left anterior-cingulate gyrus, and bilateral dorsolateral-prefrontal areas. Regions more active during encoding than during retrieval were located in the hippocampus, temporal and the prefrontal cortex of the left hemisphere, and regions more active during retrieval than during encoding included areas in the medial and right-prefrontal cortex, basal ganglia, thalamus, and cuneus. DA at encoding was associated with specific decreases in rCBF in the left-prefrontal areas, whereas DA at retrieval was associated with decreased rCBF in a relatively small region in the right-prefrontal cortex. These different patterns of activity are related to the behavioral results, which showed a substantial decrease in memory performance when the DA task was performed at encoding, but no change in memory levels when the DA task was performed at retrieval. ■

## INTRODUCTION

Recent advances in functional neuroimaging techniques enable us to measure activity in the human brain while the subject is listening, thinking, paying attention, or remembering. In particular, memory functions in normal subjects have been investigated intensively by using positron emission tomography (PET), and these studies have shed light on the neural correlates of encoding and retrieval processes in episodic memory (for reviews, see Cabeza & Nyberg, 1997; Fletcher, Frith, & Rugg, 1997). In behavioral studies of recall and recognition, it is impossible to disentangle the separate effects of the two processes because differences in performance could be due to differences in encoding or retrieval. Neuroimaging studies provide the unique opportunity to observe encoding and retrieval processes separately. Previous studies of episodic memory using verbal materials indicate that left-prefrontal regions of the brain are predominantly activated during episodic memory encoding; and, conversely, right-prefrontal regions are predominantly activated during episodic retrieval (Fletcher et al., 1995; Shallice et al., 1994; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). In contrast, Kelley et al. (1998) and Wagner et al. (1998) reported that the right-

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prefrontal area is activated during encoding of nonverbal materials.

One of the main purposes of the present study was to examine the effects of divided attention (DA) on encoding and retrieval processes in human episodic memory by using PET. When subjects are engaged in two different tasks at once, they have to divide attention between the tasks and allocate mental resources to each task. Behavioral studies have shown that DA at encoding is associated with a substantial decrement in later memory performance, whereas DA at retrieval results in comparatively slight declines in memory (Anderson, Craik, & Naveh-Benjamin, 1998; Craik, Govoni, Naveh-Benjamin, & Anderson, 1996; Baddeley, Lewis, Eldridge, & Thomson, 1984). This pattern of results was found in cases where secondary task costs were equivalent for encoding and retrieval, so it is not the case that retrieval is simply protected at the expense of the concurrent task. It seems, rather, that whereas encoding is easily disrupted by other ongoing processes, retrieval is more or less obligatory once the retrieval cue is provided or generated (Craik et al., 1996). An important question in this regard is whether there exists one common pool of attentional resources that can be allocated differentially to various mental operations, depending on the relative importance of each operation. Some studies have suggested an affirmative answer to this question. For example, event-related potential studies using the dual-task paradigm have shown that there exists a reciprocity in the availability of resources for the primary task (visual detection) and the secondary task (auditory detection), and the allocation of resources may vary according to the relative difficulty of the tasks (Wickens, Kramer, Vanasse, & Donchin, 1983). Other authors have talked in terms of cortical control functions, rather than in terms of processing resources. For example, Duncan's (1995) notion is that tasks, which show large drops in performance from full attention (FA) to DA conditions, require substantial amounts of controlled processing. By Duncan's view, episodic encoding tasks, which show a large performance drop under DA conditions, should require greater amounts of frontal control than episodic retrieval tasks, which show comparatively small drops under DA conditions.

Several previous studies have used PET in the DA (dual-task) paradigm, but to our knowledge, only two have used episodic memory as one of the tasks (Fletcher, Shallice, & Dolan, 1998; Shallice et al., 1994). These investigators studied verbal learning while performing either an easy or a difficult perceptual-motor task. The experiment thus examined the effects of DA during the encoding phase of a memory task; the effects of DA at retrieval were not studied. The major finding relevant to the present experiment was that—relative to the easy distracting task—performance of the difficult distracting task greatly reduced activation in the left-prefrontal cortex.

In the present study, subjects performed a memory task and a secondary task concurrently; the memory task involved encoding or retrieval of visually presented word pairs and verbal responses, whereas the secondary task involved easy or difficult auditory tone discrimination and manual responses. Based on previous results for verbal-memory tasks, we expected to see left-prefrontal activation associated with FA encoding (Tulving et al., 1994), and that this activation would be reduced in the DA condition (Fletcher et al., 1995; Shallice et al., 1994). Similarly, we expected to find right-prefrontal activation associated with FA retrieval, and given that DA at retrieval has only small effects on memory performance, we speculated that deactivation due to DA might be small.

# RESULTS

## Behavioral Data

Table 1 shows cued recall performance and mean reaction times in the tone-discrimination task in the four experimental conditions. Recall performance was lowered substantially (0.79 to 0.58) when attention was divided at encoding, but recall was affected only minimally (0.78 to 0.75) when attention was divided at retrieval. A two-way analysis of variance conducted on cued recall performance showed a main effect of encoding/retrieval, $F(1,11)=7.31$, $p<.05$, a main effect of attention (FA vs. DA), $F(1,11)=13.46$, $p<.01$, and a significant interaction between attention and encoding/retrieval, $F(1,11)=11.15$, $p<.01$. This is similar to the pattern reported by Craik et al. (1996). The tone-task data show that response times were slower in the two-tone (DA) condition than in the one-tone (FA) condition. A two-way ANOVA on these data revealed a significant main effect for attention only, $F(1,11)=21.22$, $p<.01$.

## PET Data

### *Latent Variables and Task Contrasts*

The Partial Least Squares (PLS) analysis produced three LVs depicting the distribution of brain activity related to particular task contrasts. The design scores for each latent variable (LV) are shown in Figure 1. The first LV (LV1) distinguished FA from DA; the difference between FA and DA design scores was larger during encoding than during retrieval. Therefore, the singular image for LV1 segregates brain activity related to DA from brain activity related to FA, particularly during encoding. The second LV (LV2) distinguished retrieval from encoding; the difference between retrieval and encoding design scores was larger under conditions of FA than DA. Therefore, the singular image for LV2 segregates brain activity related to retrieval from activity related to encoding, particularly under FA conditions. The last LV (LV3) revealed an interaction of the

**Table 1**. Behavioral Performance on the Memory Task and Tone Discrimination Task (Standard Deviation in Parentheses)

| | *Full attention* | *Divided attention* |
|---|---|---|
| *(A) Proportion of words recalled* | | |
| Encoding | 0.79 (0.12) | 0.58 (0.20) |
| Retrieval | 0.78 (0.10) | 0.75 (0.14) |
| *(B) Mean reaction time (msec) on the tone discrimination task* | | |
| Encoding | 389 (118) | 523 (108) |
| Retrieval | 385 (125) | 501 (93) |

memory task (encoding and retrieval) and the secondary task (FA and DA). That is, positive saliencies reflect cortical areas that are particularly related to DA at encoding and/or FA at retrieval, whereas negative saliencies reflect areas related to FA at encoding and/or DA at retrieval. The statistical significance for each LV assessed by the permutation test indicated that all LVs were highly significant (LV1, $p<.0001$; LV2, $p<.0001$; and LV3, $p<.002$). The proportion of the cross-block covariance accounted for was 42% for LV1, 39% for LV2, and 17% for LV3.

### Brain Images

Tables 2–4 show the region name, Brodmann's area (BA), and Talairach coordinates of the local maxima that survived our statistical threshold in each LV (i.e., the ratio of the salience to its standard error was higher than 2.0 and spatial extent was larger than 50 voxels). Figure 2 shows the patterns of brain activity plotted on a standard MRI atlas related to LV1 (top), LV2 (middle), and LV3 (bottom), respectively, that survived an assessment for reliability using the bootstrap technique (i.e., the ratio of the salience to its standard error was higher than 2.0).

Figure 2 (top) and Table 2 show the brain regions associated with LV1. In Figure 2 (top), positive saliencies are depicted in red and yellow and reflect those areas that were relatively more active under conditions of FA, whereas negative saliencies are depicted in blue and reflect those areas that were relatively more active under DA. Table 2A shows that the areas that were relatively more associated with FA were in frontal, anterior-cingulate, and occipital regions. The frontal activations occurred in two different areas, a ventrolateral region (BA 11 and BA 47), and a superior-frontal region (BA 10). In these regions of the left hemisphere, rCBF was greater in FA than in DA during both memory conditions (Figure 3a and b). Areas of the occipital lobe that were relatively more active under FA conditions involve regions in BA 18/19. Table 2B shows the areas that were relatively more active under conditions of DA. The table shows that two large clusters were located symmetrically in temporo-parietal regions, including a large part of primary and association auditory cortex. The cluster in the left temporo-parietal region extended to the left anterior-cingulate gyrus (BA 24/32; $x, y, z = -4, 6, 36$). In the frontal lobes, there were two symmetrical areas of activation extending from BA 9 to BA 46 in the middle-frontal gyrus in both hemispheres. In the left-prefrontal cortex and in the left anterior-cingulate gyrus, rCBF was greater in DA than in FA during both memory conditions (Figure 3c and d). Finally, three clusters were identified in the cerebellum.

In Figure 2 (middle), the brain image distinguishes retrieval (shown in red and yellow) from encoding (shown in blue) as delineated by the design scores for LV2. Table 3A shows that several areas of the frontal cortex were relatively more active during retrieval than during encoding; these areas include the medial-frontal area, the right anterior-cingulate gyrus, and two areas in

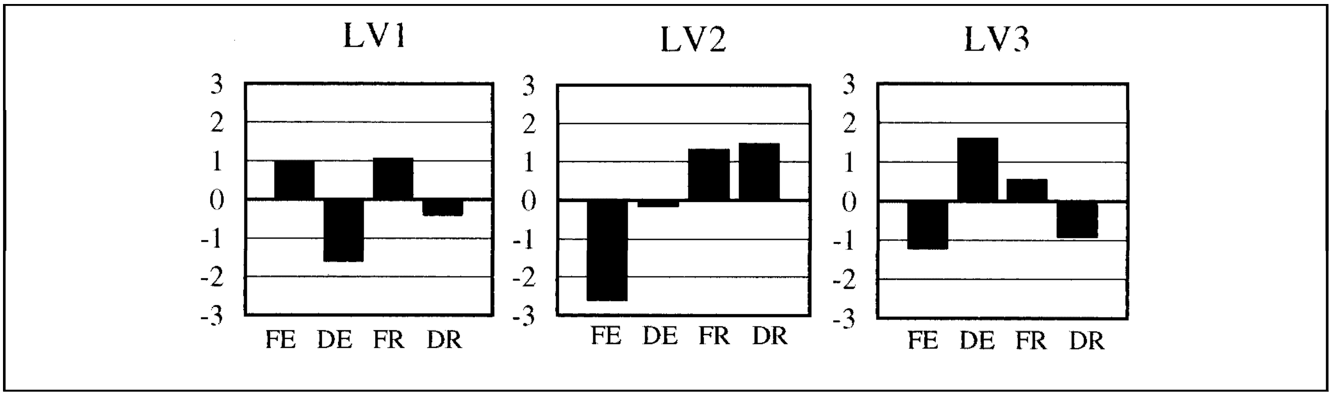

**Figure 1.** Relationships among the experimental conditions in each latent variable (LV) as revealed by PLS analysis. Each bar represents the design score for each condition (FE=FA at encoding, DE=DA at encoding, FR=FA at retrieval, and DR=DA at retrieval) and has positive or negative value. Left: LV1 segregates FA conditions (positive) from DA conditions (negative), at both encoding and retrieval. Middle: LV2 segregates retrieval (positive) from encoding (negative) in both FA and DA. Right: LV3 indicates an interaction of attention (FA vs. DA) and memory (encoding vs. retrieval).

**Table 2**. Brain Region, Brodmann's Area (BA), and Coordinates of Local Maxima for LV1

| *Salience* | *No.* | *Region name* | *L/R* | *BA* | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|
| (A) | | | | | | | |
| Positive (full attention) | | Frontal lobe | | | | | |
| | 1 | Superior-frontal gyrus | L | 10 | – 2 | 56 | 20 |
| | 2 | Ventral-frontal area | L | 11/47 | – 28 | 28 | – 20 |
| | | Inferior-frontal gyrus | L | 47 | – 34 | 14 | – 16 |
| | 3 | Ventral-frontal area | R | 25 | 14 | 6 | – 12 |
| | 4 | Anterior-cingulate gyrus | R | 32/24 | 6 | 40 | 0 |
| | | Occipital lobe | | | | | |
| | 5 | Lingual gyrus | | 18 | 0 | – 78 | 4 |
| | 6 | Middle-occipital gyrus | L | 19 | – 32 | – 90 | 20 |
| (B) | | | | | | | |
| Negative (divided attention) | | Frontal lobe | | | | | |
| | 1 | Middle-frontal gyrus | L | 46/9 | – 32 | 36 | 28 |
| | 2 | Middle-frontal gyrus | R | 46/9 | 28 | 28 | 20 |
| | 3 | Premotor area | R | 6 | 40 | – 4 | 24 |
| | | Parietal/temporal lobe | | | | | |
| | 4 | Inferior-parietal lobule | L | 40 | – 52 | – 26 | 24 |
| | | Superior-temporal gyrus | L | 22 | – 54 | – 38 | 12 |
| | 5 | Inferior-parietal lobule | R | 40 | 52 | – 32 | 28 |
| | | Superior-temporal gyrus | R | 22 | 50 | – 48 | 16 |
| | | Cerebellum | | | | | |
| | 6 | Cerebellum | L | | – 26 | – 56 | – 24 |
| | 7 | Cerebellum: medial | R | | 8 | – 60 | – 28 |
| | 8 | Cerebellum: lateral | R | | 28 | – 46 | – 28 |

Clusters which survived the bootstrap (see Methods) and are larger than 50 voxels are listed. Region name and BA indicate the conventional anatomical name (gyrus, lobule, etc.) and Brodmann's area in which the local maximum (i.e., with the highest salience in the cluster) is shown. When the cluster includes several regions of the brain, two or more maxima are shown in the table.

the right middle-frontal gyrus. In the right-prefrontal cortex and in the right anterior-cingulate gyrus, rCBF was greater during retrieval than during encoding under FA (Figure 3e and f). In addition, retrieval was associated with activity in the insula, subcortical areas (involving the thalamus, putamen, and globus pallidus), two posterior areas (cuneus and posterior cingulate), and one region in the cerebellum. The areas that were relatively more active during encoding than retrieval are shown in Table 3B. They include two left-frontal areas (BA 8/9, 45/46) and three further left-lateralized areas in the hippocampus and temporal lobe. In the left inferior-frontal gyrus, rCBF was greater in FA than in DA during encoding; whereas in the left hippocampus, rCBF during encoding was comparable between FA and DA conditions (Figure 3g and h). Finally, the four occipital regions are shown in Table 3B.

As shown by the design scores (Figure 1), LV3 was characterized by a significant interaction between attention (FA vs. DA) and memory (retrieval vs. encoding). Brain regions with a positive salience (Table 4A; red and yellow areas in Figure 2, bottom) were predominantly related to DA at encoding and/or FA at retrieval. These regions included the right middle-frontal gyrus, the left inferior-temporal gyrus and adjacent hippocampal areas, the right insula, and a number of regions in occipital cortex. Brain regions with a negative salience (Table 4B; blue areas in Figure 2, bottom) were predominantly related to FA at encoding and/or DA at retrieval. These regions included clusters in the left-

**Table 3**. Brain Region, Brodmann's Area (BA), and Coordinates of Local Maxima for LV2

| *Salience* | *No.* | *Region name* | *L/R* | *BA* | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|
| (A) | | | | | | | |
| Positive (retrieval) | | Frontal lobe | | | | | |
| | 1 | Medial frontal | L | 10 | –10 | 48 | 4 |
| | 2 | Middle-frontal gyrus | R | 10 | 22 | 44 | 20 |
| | 3 | Middle-frontal gyrus | R | 10 | 22 | 42 | –8 |
| | 4 | Anterior-cingulate gyrus | R | 32 | 2 | 36 | 20 |
| | | Insula/subcortical | | | | | |
| | 5 | Insula/globus pallidus | L | | –32 | 2 | 4 |
| | 6 | Thalamus | L | | –6 | –16 | 8 |
| | 7 | Insula/putamen | R | | 28 | 6 | –4 |
| | | Other | | | | | |
| | 8 | Posterior cingulate gyrus | | 30/23 | 0 | –48 | 16 |
| | 9 | Cuneus | R | 18 | 2 | –102 | 12 |
| | 10 | Cerebellum | L | | –10 | –78 | –16 |
| (B) | | | | | | | |
| Negative (encoding) | | Frontal lobe | | | | | |
| | 1 | Middle-frontal gyrus | L | 8/9 | –24 | 16 | 40 |
| | | Inferior-frontal gyrus | L | 45/46 | –46 | 26 | 12 |
| | | Temporal lobe | | | | | |
| | 2 | Fusiform gyrus | L | 19 | –44 | –68 | –12 |
| | | Inferior-temporal gyrus | L | 20 | –40 | 8 | –28 |
| | | Hippocampus | L | | –22 | –10 | –16 |
| | 3 | Inferior-temporal gyrus | R | 20 | 32 | –22 | –28 |
| | | Occipital lobe | | | | | |
| | 4 | Middle-occipital gyrus | L | 19 | –32 | –72 | 16 |
| | 5 | Cuneus | R | 17 | 22 | –68 | 12 |
| | 6 | Inferior-occipital gyrus | R | 19 | 30 | –90 | –12 |
| | 7 | Middle-occipital gyrus | R | 19 | 42 | –74 | –4 |

and right-frontal lobes, the anterior-cingulate, subcortical regions, bilateral-temporal regions and the left inferior-parietal lobule, and a single cluster in occipital regions.

### *Correlations Between rCBF and Memory Performance*

We examined correlations between ratio-adjusted blood flow and memory performance in two general brain areas. First, given the results of previous studies showing that semantic processing at encoding is associated with activations in the left-prefrontal cortex, and also with high levels of subsequent memory performance (Kapur et al., 1994), we calculated correlation coefficients between recall and rCBF in frontal regions during encoding. This procedure yielded two significant positive correlations—one in the left inferior-frontal gyrus in the FA at encoding condition ($r=+0.61$; Figure 4, top), and the second in the left inferior-frontal gyrus in the DA at encoding condition ($r=+0.71$; Figure 4, middle). It also seemed possible that greater attention to the secondary task during the DA condition at encoding would be associated with poorer subsequent memory. Accordingly, we calculated correlation coeffi-

**Table 4**. Brain Region, Brodmann's Area (BA), and Coordinates of Local Maxima for LV3

| | | | | | | | | *Effect of DA* | |
|---|---|---|---|---|---|---|---|---|---|
| *Salience* | *No.* | *Region name* | *L/R* | *BA* | *x* | *y* | *z* | *Enc* | *Ret* |
| (A) | | | | | | | | | |
| Positive (DA at encoding and/or FA at retrieval) | | Frontal lobe | | | | | | | |
| | 1 | Middle-frontal gyrus | R | 8 | 36 | 14 | 44 | | dec |
| | | Insula/temporal lobe | | | | | | | |
| | 2 | Inferior-temporal gyrus | L | 20/21 | –40 | –6 | –20 | | dec |
| | 3 | Hippocampus | L | | –26 | –20 | –16 | | dec |
| | 4 | Insula | R | | 44 | 8 | 0 | inc | |
| | 5 | Parahippocampal gyrus | R | 30 | 22 | –34 | 0 | | dec |
| | | Occipital lobe | | | | | | | |
| | 6 | Middle-occipital gyrus | L | 19 | –38 | –66 | –8 | | dec |
| | 7 | Fusiform gyrus | L | 18 | –24 | –102 | –16 | | dec |
| | 8 | Posterior-cingulate gyrus | R | 31 | 18 | –50 | 28 | | dec |
| | 9 | Occipital gyrus | R | 19 | 32 | –88 | 24 | | dec |
| (B) | | | | | | | | | |
| Negative (FA at encoding and/or DA at retrieval) | | Frontal lobe | | | | | | | |
| | 1 | Superior-frontal gyrus | L | 10/9 | –10 | 62 | 24 | dec | |
| | 2 | Inferior-frontal gyrus | L | 46 | –46 | 34 | 8 | dec | |
| | 3 | Inferior-frontal gyrus | L | 44 | –50 | 8 | 28 | dec | inc |
| | 4 | Supplementary motor area | L | 6 | –2 | 16 | 44 | | inc |
| | 5 | Inferior-frontal gyrus | R | 47 | 48 | 18 | –8 | | inc |
| | | Subcortical | | | | | | | |
| | 6 | Caudate nucleus | L | | –12 | 4 | 12 | dec | inc |
| | 7 | Thalamus | L | | –10 | –14 | 0 | | inc |
| | 8 | Thalamus | R | | 10 | –16 | 4 | | inc |
| | | Temporal/parietal lobe | | | | | | | |
| | 9 | Middle-temporal gyrus | L | 21 | –52 | –32 | –4 | dec | |
| | 10 | Inferior-temporal gyrus | L | 37 | –54 | –56 | –12 | dec | |
| | 11 | Inferior-parietal lobule | L | 40 | –36 | –48 | 32 | | inc |
| | 12 | Superior-temporal gyrus | R | 22 | 40 | –34 | 8 | | inc |
| | | Occipital lobe | | | | | | | |
| | 13 | Lingual gyrus | L | 19 | –14 | –60 | 0 | | |

Enc=Encoding; Ret=Retrieval; inc=increase; dec=decrease.

cients between recall and rCBF in the right-temporal regions on the assumption that this area is primarily responsible for auditory analysis. One significant negative correlation was found in the right middle-temporal gyrus in the DA at encoding condition ($r = -0.58$; Figure 4, bottom).

## DISCUSSION

The purpose of the present study was to explore the neural correlates of DA effects on memory encoding and retrieval processes. In line with previous studies (Craik et al., 1996; Baddeley et al., 1984), our study showed that division of attention during the encoding phase of a memory task reduces subsequent performance substantially, but that division of attention during retrieval has only slight effects.

## General Effects of DA

### *Prefrontal Areas*

LV1 segregated spatial patterns of brain activation associated with the FA condition from those associated with the DA condition. Table 2 and Figure 2 (top) show that several areas of frontal cortex were activated preferentially under conditions of FA. These involved a right-ventral area (BA 25), a left-ventral area (BA 11/47), and the uncinate fasciculus, which connects the frontal and temporal lobes. As shown in the rCBF responses to the DA manipulation (Figure 3a), it seems likely that these frontal areas are associated with the encoding of word pairs and presentation of retrieval cues, and that these effective memory operations are greatly reduced under DA conditions. A particularly interesting novel finding, which provides converging evidence for the connection between left prefrontal-cortical activation and subsequent memory performance, is the correlation between rCBF in the left inferior-frontal gyrus (BA 47) and later recall under FA conditions (Figure 4, top). This correlation shows that individuals who perform best on the memory task are also those who show the greatest degree of left-prefrontal activation during the encoding phase. An additional region of activity, greater rCBF in FA than in DA during both memory conditions (Figure 3b), was found in the frontal pole (BA 10). Activation in this area has been reported to be associated with a passive auditory task, when compared to a more demanding judgment task (Zatorre, Evans, & Meyer, 1994), and with easier, as opposed to more difficult, verbal memory-encoding tasks (Grasby et al., 1994).

Two discrete clusters in the middle-frontal gyrus (BA 46/9) of both hemispheres were more activated by DA than by FA conditions. The blood flow response to DA in the left middle-frontal gyrus was substantially similar between encoding and retrieval (Figure 3c). This part of the frontal lobe has been regarded as crucial for a variety of complex functions in human cognition, such as motivation, planning, attention, working memory, and interference (Fuster, 1997). Thus, the prefrontal regions that were preferentially active in the DA conditions of the present study are presumably related to the higher processing demands associated with management of the two concurrent tasks. This interpretation is borne out by the results of at least some neuroimaging studies employing dual-task or DA paradigms. For example, Benedict et al. (1998), Klingberg (1998), Johannsen et al. (1997), Madden et al. (1997), and Corbetta, Miezin, Dobmeyer, Shulman, and Petersen (1991) have all found right or bilateral, dorsolateral-prefrontal activation associated with dual-task processing. However, in a

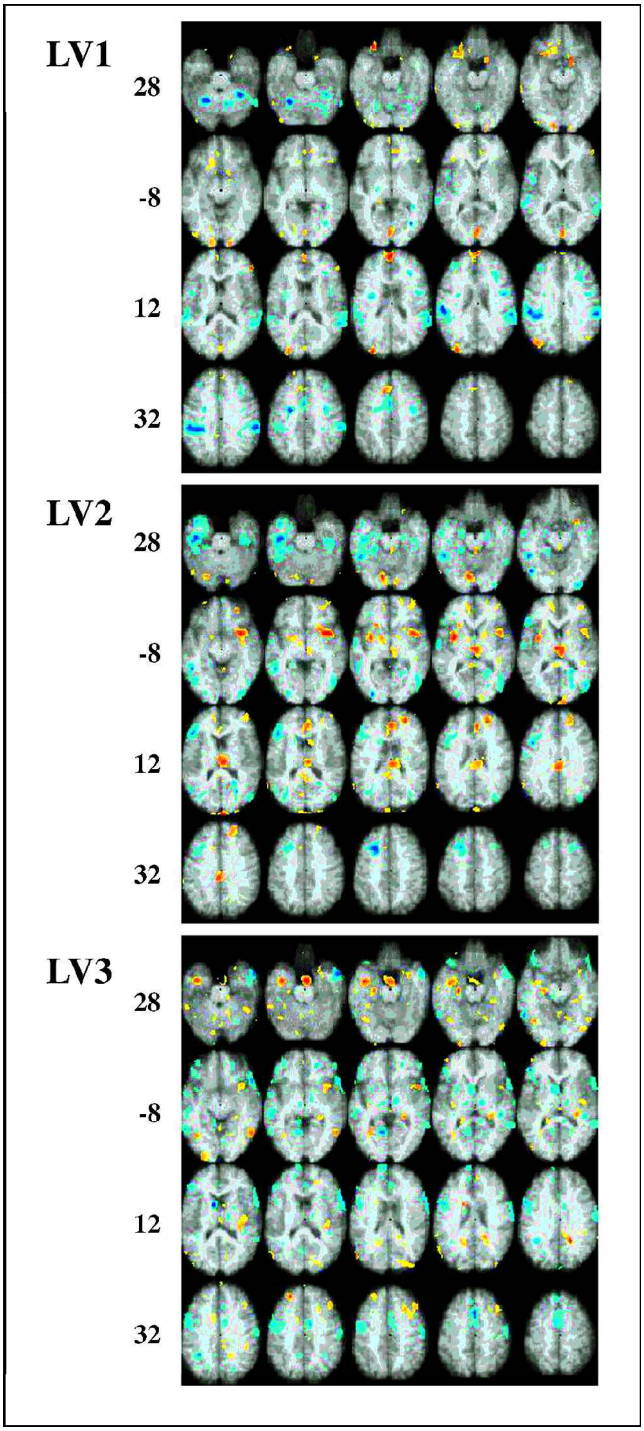

**Figure 2.** Top: Spatial distributions of brain activity related to FA (plotted in yellow and red) and DA (plotted in blue) as delineated by LV1 (see Results, Table 2, and Figure 1) shown on standard MR images (from – 28 to +48 mm relative to AC–PC line in 4-mm increments). Numbers on the left of the figure represent levels of the $z$-axis from the atlas of Talairach and Tournoux (1988) of each image in the first column. The right side of the image represents the right side of the brain. Middle: Brain activity related to retrieval (plotted in yellow and red) and encoding (plotted in blue) as delineated by LV2 (see Results, Table 3, and Figure 1). Bottom: Brain activity related to DA at encoding and/or FA at retrieval (plotted in yellow and red) and FA at encoding and/or DA at retrieval (plotted in blue) as delineated by LV3 (see Results, Table 4, and Figure 1).

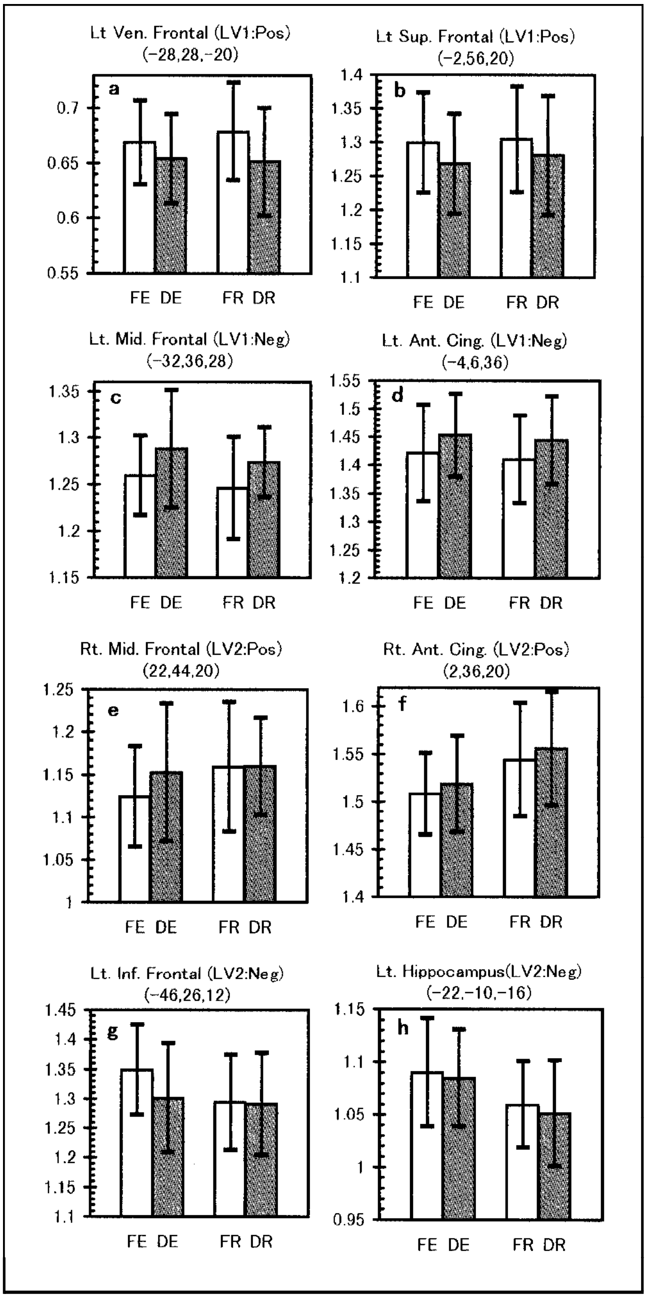

**Figure 3.** Ratio-adjusted rCBF of peak voxels in eight representative brain areas (coordinates in parentheses) that showed the main effect of attention conditions (LV1) and memory conditions (LV2). White and gray columns represent mean value, and vertical bars represent plus and minus one standard deviation in each experimental condition. The eight representative brain areas are (significant ($p<.05$) results of $t$-test at encoding (Enc) or at retrieval (Ret), in FA (FA) or in DA (DA) are indicated in parentheses): (a) left ventral-frontal area (Enc, Ret), (b) left superior-frontal gyrus (Enc, Ret), (c) left middle-frontal gyrus (Enc, Ret), (d) left anterior-cingulate gyrus (Enc, Ret), (e) right middle-frontal gyrus (FA), (f) right anterior-cingulate gyrus (FA, DA), (g) left inferior-frontal gyrus (FA), and (h) left hippocampus (DA). FE=FA at encoding; DE=DA at encoding; FR=FA at retrieval; DR=DA at retrieval; Pos=positive salience; Neg=negative salience. Note: Significant ($p<.05$) results of $t$-test for other peak voxels are indicated in parentheses (for region name, see Tables 2 and 3); Table 2–A; No. 3 (Ret), 4 (Enc), 5 (Ret), and 6 (Ret), Table 2–B; No. 3, (Enc, Ret), 4 (Enc, Ret), 5 (Enc, Ret), 6 (Ret), 7 (Enc, Ret), and 8 (Enc), Table 3–A; No. 1 (FA), 4 (FA, DA), 5 (FA, DA), 6 (FA), 7 (FA), 8 (FA), 9 (FA), and 10 (FA), Table 3–B; No. 3 (FA), 6 (FA), and 7(FA, DA).

paradigm similar to our own, Fletcher et al. (1995) did not find increased activation in dorsolateral-prefrontal areas when a difficult secondary task was compared to an easy secondary task during encoding. They reported a specific increase in rCBF in the left anterior-cingulate gyrus during a difficult secondary task compared to an easy secondary task during encoding. However, they found no increased activation in dorsolateral-prefrontal areas associated with the difficult secondary task, instead, they found decreased activation in the left-prefrontal areas.

Despite some inconsistent results, there is mounting evidence that the bilateral-prefrontal cortex is involved in the control of complex tasks, especially those necessitating the management of several simultaneous streams of information. The description of such tasks may focus on the inhibitory control of sensory inputs and resistance to distraction (Knight, Grabowecky, & Scabini, 1995) or on the concept of working memory (D'Esposito et al., 1995). The common feature among these previous studies, and in the present study, appears to be that dorsolateral-prefrontal activation is found in association with tasks that require active maintenance and manipulation of information regardless of the stimulus type, and with tasks requiring inhibitory control of some channels of information, or active integration of different sensory streams.

### *Cingulate Gyrus and Cerebellum*

In FA conditions, the rostral part of anterior-cingulate gyrus was activated mainly in the right hemisphere. Neuroanatomical studies in monkies have shown that the rostral part of the anterior-cingulate gyrus is strongly connected to the temporal lobe (Vogt & Gabriel, 1993). The bilateral ventral-frontal activity, including uncinate fasciculus, which connects the frontal lobe and temporal lobe, may relate to the cingulate activity through the rich connection between these structures. In DA conditions, the left temporo-parietal region extended to the left anterior-cingulate gyrus. In this voxel, the rCBF response was comparable between the two memory conditions (Figure 3d). Fletcher et al. (1995) and Shallice et al. (1994) also found that this general area was associated with a difficult distractor task (relative to an easy distractor task). Furthermore, similar anterior-cingulate activations have been reported during the control of oculomotor, manual and speech responses (Paus, Petrides, Evans, & Meyer, 1993), and during intentional learning (Kapur et al., 1996). In light of these previous findings, it seems likely that the DA-associated activity in the left anterior-cingulate gyrus in our study is associated with increased attention to the secondary task, and perhaps also with the selection of the appropriate motor response in the two-tone task.

Other motor-related regions associated with the DA conditions were found in the cerebellum. Two clusters

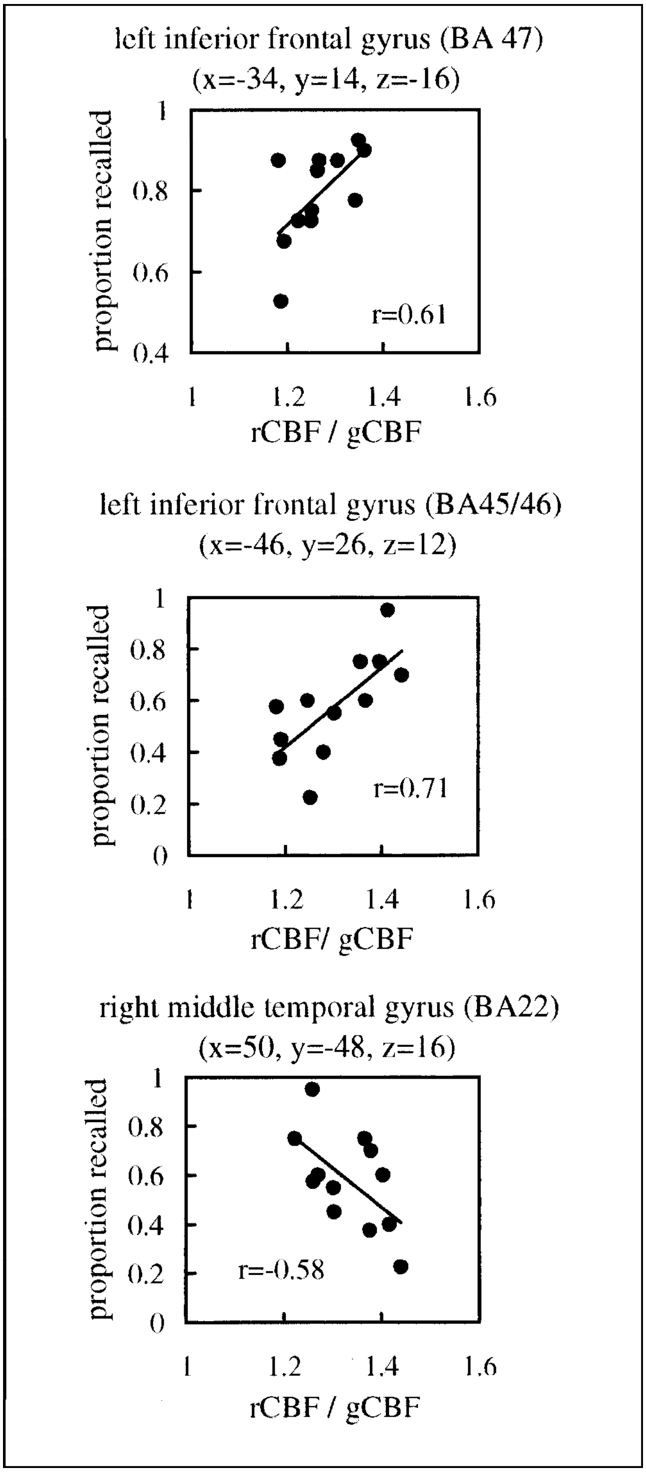

**Figure 4.** Significant correlations between ratio-adjusted rCBF and memory performance. Top: A significant positive correlation ($r = 0.61$, $p < .05$) between rCBF in the left inferior-frontal gyrus (BA 47) and memory performance following FA at encoding. Middle: A significant positive correlation ($r = 0.71$, $p < .01$) between rCBF in the left inferior-frontal gyrus (BA 45/46) and memory performance following DA at encoding. Bottom: A significant negative correlation ($r = -0.58$, $p < .05$) between rCBF in the right middle temporal gyrus (BA 22) and memory performance following DA at encoding.

were located in the lateral and medial part of the right hemisphere. The motor-response demands in our study differed between FA and DA (i.e., one button in FA vs. two buttons in DA), and mean reaction time was significantly longer in DA than in FA. Thus, the right-cerebellar activity most likely reflects the increased demands of the secondary task. An alternative possibility is that the cerebellum is involved in higher cognitive processes (Schmahmann, 1996). Shulman et al. (1997) have suggested that activation in the right cerebellum is related to nonmotor cognitive processes. Also, patients with cerebellar damage are severely impaired in their ability to shift attention between visual and auditory modalities (Courchesne et al., 1994). It is therefore possible that the cerebellar activity observed in DA condition in the present study reflects some mixture of processes relating to both motor control and cognitive processing.

### *Posterior Sensory and Perceptual Areas*

Occipital brain activity increased in visual areas (BA 18/19) in the FA conditions, but it increased in bilateral temporo-parietal areas in the DA conditions. These results are consistent with those of O'Leary et al. (1997), whose procedure also included concurrent visual and auditory tasks. They found more occipital activation when subjects were paying greater attention to visual stimuli, and more auditory cortex activation when subjects were paying greater attention to auditory stimuli. Thus, our results suggest that under FA conditions the subjects were able to pay greater attention to the visually presented words and perhaps make better visual images of the word pairs, and that by contrast, under DA conditions the subjects were paying more attention to the auditory stimuli. In support of the latter suggestion, we did find a significant negative correlation between rCBF in the right superior-temporal gyrus (BA 22) during encoding under DA conditions and later memory performance (Figure 4, bottom). In a more general sense, these results support the idea that attention modulates the increase of rCBF to sensory systems.

Bilateral activity in the inferior-parietal lobule (BA 40), including the supramarginal gyrus, was related to DA. This region is situated at the border of auditory, visual, and somatosensory cortices and is therefore considered to be associated with more than one sensory modality (Pandya & Yeterian, 1990). A difficult auditory task, as compared with an easy auditory task, was found to activate the inferior-parietal lobule bilaterally (Zatorre et al., 1994). These investigations suggest that the greater effort associated with the two-tone discrimination in the DA condition was the reason for the bilateral parietal activity found in the present study.

## Brain Activity Related to Encoding and Retrieval

LV2 indicated that the frontal regions that were more activated during retrieval included two clusters located in the right middle-frontal gyrus (BA 10)—one in the medial-frontal gyrus and one in the anterior-cingulate gyrus. By contrast, frontal regions that were more activated during encoding than retrieval included a large cluster extending from BA 45/46 to BA 8/9 in the left hemisphere. With respect to verbal materials, such as word pairs, the predominance of the right-prefrontal activation during episodic retrieval and the left-prefrontal activation during episodic encoding is in line with many previous neuroimaging studies (Kelley et al., 1998; Cabeza & Nyberg, 1997; Fletcher et al., 1997). One particularly interesting finding from the present study was that rCBF in the left-prefrontal area was reduced by the DA manipulation (Figure 3g), whereas rCBF in the right-prefrontal area was not (Figure 3e). In addition, activation in the left inferior-frontal gyrus was positively correlated with subsequent memory performance (Figure 4, middle). These results strongly suggest that the left-prefrontal area is playing an important role in episodic memory encoding, and that effective memory operations during encoding are disrupted by DA.

The involvement of the hippocampus and adjacent areas during episodic memory encoding is indicated by an activation of the left hippocampus (Table 3B). This hippocampal activation ($x = -22$, $y = -10$, $z = -16$) is close to the region reported by Dolan and Fletcher (1997) ($x = -16$, $y = -14$, $z = -12$) and is located in the anterior part of the structure. This result adds further evidence relevant to the hypotheses that tasks requiring relational processing of stimuli (word pairs in the present study) preferentially activate the anterior hippocampus (Schacter & Wagner, 1999), and that the anterior/posterior axis of the hippocampus may differentially relate to encoding/retrieval processes, respectively (Lepage, Habib, & Tulving, 1998). As seen in Figure 3h, rCBF during encoding in the left hippocampus is minimally affected by the DA manipulation. It seems possible that this structure is automatically involved in processes that register novelty of the presented materials during encoding (Tulving, Markowitsch, Craik, Habib, & Houle, 1996) and is therefore relatively immune from distraction. Bilateral insula and the adjacent subcortical structures, including putamen, globus pallidus, and thalamus, were predominantly associated with retrieval. Several PET studies of episodic retrieval have demonstrated activation in the insula, basal ganglia, and thalamus (Cabeza et al., 1997b; Fletcher et al., 1995; Shallice et al., 1994).

### Brain Activity Related to the Interaction Between Memory and Attention

LV3 was characterized by a significant interaction between memory (encoding/retrieval) and attention (FA/DA). Our interpretation of this interaction was guided by the results of the post hoc $t$ tests (see right-hand column of Table 4). Below, we consider the specific effects of DA during encoding and retrieval separately.

### Specific Effects of DA During Encoding

In the case of encoding, a large number of areas in the left-frontal cortex showed a decrease in activity in DA compared to FA conditions. These areas include the superior- and inferior-frontal gyrus (BA 10/9, 46, and 44 in Table 4B). In light of the many previous studies linking left-prefrontal regions to semantic processing (e.g., Kapur et al., 1994), we interpret these observed decreases as indicating impaired semantic processing under DA conditions. The reduction of left-frontal activation observed in the present study is in line with a similar reduction in the left-frontal activity during DA at encoding conditions reported by Fletcher et al. (1998) and Shallice et al. (1994). Indeed, one site in particular ($x$, $y$, $z = -46$, 34, 8) is remarkably close to the location at which Fletcher et al. (1995) and Shallice et al. (1994) also reported that encoding-related brain activity was disrupted by DA ($x$, $y$, $z = -48$, 34, 8). Furthermore, in a supplementary analysis of our data set using statistical parametric mapping (SPM96), subtraction of DA at encoding from FA at encoding revealed a significant activation in the left inferior-frontal gyrus ($x$, $y$, $z = -36,30,8$; $z$-value $= 5.44$), indicating that DA reduced activity in this area during encoding. This replication attests to the reliability of our finding from the multivariate PLS analysis. Other decreases in activation as a function of DA at encoding were found in the left inferior-temporal gyrus (BA 37), and the left middle-temporal gyrus (BA 21). It seems likely that these reductions in activation in the temporal lobe are associated with some impairment in visual processing of word pairs during encoding. Activity in the caudate nucleus was decreased by DA during encoding but was increased by DA during retrieval; however, the interpretation of this interaction is unclear.

### Specific Effects of DA During Retrieval

Given that the present behavioral results showed that DA at retrieval caused very little reduction in memory performance (Table 1), it might be expected that the areas associated more with retrieval than with encoding would show little change in activation levels as a function of the FA/DA manipulation. This expectation was met in the current analysis: The activity was never reduced by DA during retrieval in all of the right-prefrontal areas that were preferentially active during retrieval (see Table 3A). These results suggest that memory performance is not disrupted by DA during retrieval because DA does not interfere with the retrieval-related processes that are mediated by the right-prefrontal cortex. However, other regions that were not preferentially related to retrieval processes were affected by DA. These include the right middle-frontal gyrus (BA 8), left inferior-temporal area (BA 20/21), and several regions in the occipital cortex (BA 18, 19, 31). Although located in the right-prefrontal cortex, BA 8 is rarely found to be activated during episodic retrieval, but was activated during a sustained attention task (Pardo, Fox, & Raichle, 1991). Decreases in activation due to DA at retrieval were also found in the posterior part of the right-parahippocampal gyrus, extending to the insula cortex. Corbetta et al. (1991) found deactivation due to DA compared to selective attention in the medial-temporal lobe and in the right insula, indicating an involvement of this region in visual attention. An interpretation for the reduced activity due to DA in the left hippocampus is unclear. However, we speculate that this structure relates more to encoding than to retrieval under DA conditions, whereas there is no such relation under FA conditions. This speculation was confirmed by *t* tests that showed greater activity in the left hippocampus during encoding than retrieval in DA conditions ($p<.01$), but no difference in activity between these processes during FA conditions ($p>.10$). Activity in the left inferior-frontal gyrus (BA 44) was decreased by DA at encoding and increased by DA at retrieval. This pattern may reflect the disruption of semantic processes during DA at encoding, combined with the compensatory recruitment of semantic processes during DA at retrieval. Another frontal region in the right inferior-frontal gyrus (BA 47) showed increased activity by DA at retrieval. Speculatively, this may reflect some increase in processing operations necessary to compensate for the difficulty of carrying out retrieval successfully under DA conditions.

### Conclusions

In line with previous studies, the present experiment found that the areas more active during encoding than retrieval were situated predominantly in the left hemisphere—in the frontal lobe, temporal lobe, and hippocampus. There is now general agreement that the encoding of verbal information takes place in the left-prefrontal cortex, both in dorsal regions (e.g., Kelley et al., 1998) and in more ventral regions (e.g., Gabrieli, Poldrack, & Desmond, 1998; Wagner et al., 1998; Kapur et al., 1994). Further, Gabrieli et al. (1998) make the case that areas in the left inferior-prefrontal cortex are concerned with semantic processing, and that activations in this region decrease as the need for semantic processing declines, as with the repeated generation of the same verbs to a repeated series of nouns (Raichle et al., 1994). Our observation that activation in the left inferior-frontal gyrus decreases in DA as opposed to FA conditions at encoding thus supports the findings of Fletcher et al. (1995) and Shallice et al. (1994), and suggests that the reduction in memory performance associated with DA at encoding is attributable to a reduction in the quality or effectiveness of semantic processing under those conditions. In contrast, activity in the left hippocampus seems less vulnerable to distraction, possibly showing that the hippocampus is engaged in relatively automatic processes such as novelty detection.

With regard to retrieval, in line with many previous studies (e.g., Cabeza & Nyberg, 1997; Tulving et al., 1994) we found activations in the right-prefrontal (BA 10) and subcortical areas, including putamen, globus pallidus, and thalamus. However, in striking contrast to the reduction in the left-frontal activations associated with DA at encoding, the right-frontal activations observed at retrieval were unaffected by the shift from FA to DA conditions, and this lack of effect on cortical activity was accompanied by a lack of effect on memory performance. The exact reasons for this interesting conjunction of cortical and behavioral effects are still unclear. Perhaps BA 10 is involved in other working memory and monitoring activities that do not change much between FA and DA conditions (MacLeod, Buckner, Miezin, Petersen, & Raichle, 1998), or perhaps aspects of verbal retrieval occur with relatively little need for control processes when cues are provided, as in the present case (Craik et al., 1996; Baddeley et al., 1984). It certainly seems that verbal retrieval processes must involve some semantic operations and, in this regard, it may be of interest that LV3 shows an area of the left inferior-frontal gyrus (BA 44), whose activity is decreased by DA at encoding but increased by DA at retrieval (see Table 4). Speculatively, this may represent a case of compensatory semantic processing under conditions of DA at retrieval, much as has been noted to occur in the retrieval processing of older adults compared with younger adults (Cabeza et al., 1997a).

## METHODS

### Subjects

Twelve normal healthy volunteers (three males and nine females, 21 to 31 years old, mean=24.4, *SD*=3.0 years) participated in the study after giving informed consent. All subjects spoke English fluently and were right-handed. No subject had a history of psychiatric or neurological diseases. None of the subjects was taking any drug that affected cerebral blood flow. The study was approved by the joint ethics committee of the University of Toronto and the Baycrest Centre for Geriatric Care.

### Experimental Design

Prior to the PET session, the subjects participated in a training session consisting of short versions of the tasks to be performed during the experiment. In the experiment itself, the subjects were instructed to perform the memory task and the secondary task (tone discrimination) concurrently. In the memory task, 160 moderately related word pairs (e.g., dentist–glove) were used as materials. The word pairs were those used by Cabeza et al. (1997b) and were divided into eight lists of 20 pairs and presented on a computer monitor suspended about 70 cm in front of the subject. The presentation rate of the pairs was 5 sec/pair, with a 1-sec interstimulus interval. When scanning was performed during encoding, the 20 word pairs were presented and the subject's task was to read aloud the second word of the pair and silently make a visual image connecting the two words to each other. In these cases, retrieval was performed under FA conditions in the inter-scan interval following the encoding phase. When scanning was performed during retrieval, the word pairs were encoded under FA in the interval before the relevant retrieval scan. During the retrieval phase, the first word of each pair was presented in a random order with respect to the order in which the pairs were presented in the encoding phase, at a rate of 5 sec/pair, but the second word of the pair was replaced with "word?" (e.g., dentist–word?). Subjects were told to recall the original word from visual imagery of the pairs made during encoding phase or say "pass". The duration of the encoding or retrieval phase was 2 min. A simple arithmetic task (counting backward) filled a 1-min interval between encoding and retrieval.

In the tone-discrimination task, two different tones (high = 660 Hz and low = 220 Hz; duration = 500 msec; 1.5 sec between tones) were used. The tones were presented by speakers behind the PET scanner so that they were heard in the subject's midline. The loudness of the tone was set at a comfortable level for each subject. In order to keep the FA and DA conditions as similar as possible, the tone-discrimination task consisted of an easy and a difficult tone task. The easy tone task involved the repeated presentation of the low tone only and conditions involving this task were designated FA. The subject pressed the same key after each tone. The difficult tone task involved a random presentation of the low tone and the high tone and conditions involving this task were designated DA; in this case, the subject pressed the left button in response to the low tone and the right button in response to the high tone. The subjects responded to the tones using their right hand and the reaction time and accuracy of each response were recorded. The easy or difficult tone task was presented either during encoding or retrieval, thus creating a 2×2 experimental design with encoding vs. retrieval, and easy (FA) vs. difficult (DA) tone tasks as factors. The four conditions were therefore: (1) FA at encoding, (2) DA at encoding, (3) FA at retrieval, and (4) DA at retrieval. It should be noted that different memory lists were used for each condition.

The subject performed each of the four experimental conditions twice in each of two cycles. In each cycle, four PET scans were conducted 11 min apart. The order of the experimental conditions in the first cycle was counterbalanced across subjects, and the order of conditions in the second cycle was a mirror image of the first cycle (A1B1C1D1–D2C2B2A2) to avoid order effects. The two cycles were separated by approximately 17 min.

## PET Methods

PET scans were obtained with a GE PC2048-15B scanner, which acquired 15 axial images of the brain. The axial resolution (FWHM) was 6.9 mm and the in-plane resolution was 5 mm. After taking a transmission scan using a rotating pin source, 60-sec emission scans were performed following a bolus injection of 35 mCi of $H_2{}^{15}O$. Integrated tissue radioactivity counts were used as a measure of cerebral blood flow to eliminate the need for arterial blood sampling. A thermoplastic facemask was used to minimize head movement. Each task was started approximately 30 sec before the commencement of the 60-sec emission scan and continued for 2 min. To prepare the data for the statistical analyses, the PET scans from each subject were realigned to the first scan using the AIR software (Woods, Mazziotta, & Cherry, 1993). Following realignment, all images were transformed into a standard space (Talairach and Tournoux, 1988) using SPM95 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, MA, USA). As a final preprocessing step, the images were smoothed using an isotropic Gaussian kernel of 10-mm FWHM and the two scans for each condition were averaged.

For the statistical analysis of the PET data, we employed PLS (McIntosh, Bookstein, Haxby, & Grady, 1996) to identify spatial patterns of brain activity significantly related to the experimental conditions. PLS is a multivariate statistical method that has recently been applied to functional neuroimaging analysis. The data submitted to PLS analysis include a design matrix of experimental (orthonormal Helmert) contrasts and an image matrix of the ratio-adjusted rCBF data. Singular value decomposition is then performed on the cross-covariance of the design matrix and the image matrix, resulting in a series of orthogonal LVs. Each LV has three elements: (1) design saliencies that specify how strongly the effects coded in the design contrasts are represented by the pattern of brain activity for each LV; (2) image saliencies that specify the positive or negative relation of each voxel to the experimental effect; and (3) the singular value, which is the covariance between the design saliencies and image saliencies. The square of the singular value, divided by the sum of the squared cross-covariance between the design matrix and the image matrix, yields the proportion of the sum of the squared cross-block covariance explained by the pair of latent variables; this value can be considered comparable to the $R^2$ value used in regression analyses. To aid in the interpretation of each LV, we show design scores (Figure 1), which are computed by multiplying the design saliences by the original contrast vectors. Spatial distributions of image saliences related to each LV are presented in Figure 2. Mean values and standard deviations of ratio-adjusted rCBF for the four experimental conditions in eight representative peak voxels are shown in Figure 3. Correlation coefficients between ratio-adjusted rCBF and memory performance in the three representative peak voxels are computed and presented in Figure 4.

### *Statistical Assessment of the PET Data*

The significance levels of the PLS analyses were assessed by permutation tests and bootstrap estimations. Permutation tests (McIntosh et al., 1996; Edgington, 1980) were performed to test the statistical significance of each LV. In each of 500 permutation trials, the subjects' images were randomly assigned to experimental conditions, and a new singular value decomposition of the cross-covariance matrix was performed. The statistical significance of the LV is assigned a probability value based on the number of times the singular value for the permuted data exceeded the singular value for the original data. The advantage of the permutation method is that it does not rely on distributional assumptions underlying most parametric statistical methods.

The stability or reliability of the image saliences in each LV was determined using bootstrap estimation (Sampson, Streissguth, Barr, & Bookstein, 1989; Efron and Tibshirani, 1986). Subjects were randomly resampled with replacement and a new PLS was performed. This procedure was performed 100 times and a standard error of each image salience was computed. Peak voxels in which the ratio of the salience to its standard error was higher than 2.0 were considered reliable. The location of reliable image saliences for brain areas, which were larger than 50 voxels, are reported in terms of brain region, gyrus, and BA as defined in the Talairach and Tournoux (1988) atlas (Tables 2–4).

Finally, to facilitate the interpretation of an interaction between memory (encoding/retrieval) and attention (FA/DA), these effects were assessed separately by means of $t$ test calculated subsequent to the PLS analysis. The results for LV1 and LV2 are shown in Figure 3. For LV3, areas in which DA during encoding or retrieval significantly ($t(11)>2.2$, $p<.05$) increased or decreased activation relative to FA conditions are shown in the two right-hand columns of Table 4.

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