

# Effective Auditory–Verbal Encoding Activates the Left Prefrontal and the Medial Temporal Lobes: A Generalization to Illiterate Subjects

Karl Magnus Petersson,\* Alexandra Reis,† Alexandre Castro-Caldas,† and Martin Ingvar\*

\*Cognitive Neurophysiology R2-01, Department of Clinical Neuroscience, Karolinska Institute, Karolinska Hospital, 171 76 Stockholm, Sweden; and †Language Laboratory, Centro de Estudos Egas Moniz, Hospital Santa Maria, 1600 Lisbon, Portugal

Received November 3, 1998

**Recent event-related fMRI studies indicate that the prefrontal (PFC) and the medial temporal lobe (MTL) regions are more active during effective encoding than during ineffective encoding. The within-subject design and the use of well-educated young college students in these studies makes it important to replicate these results in other study populations. In this PET study, we used an auditory word-pair association cued-recall paradigm and investigated a group of healthy upper middle-aged/older illiterate women. We observed a positive correlation between cued-recall success and the regional cerebral blood flow of the left inferior PFC (BA 47) and the MTLs. Specifically, we used the cued-recall success as a covariate in a general linear model and the results confirmed that the left inferior PFC and the MTL are more active during effective encoding than during ineffective encoding. These effects were observed during encoding of both semantically and phonologically related word pairs, indicating that these effects are robust in the studied population, that is, reproducible within group. These results generalize the results of Brewer *et al.* (1998, *Science* 281, 1185–1187) and Wagner *et al.* (1998, *Science* 281, 1188–1191) to an upper middle aged/older illiterate population. In addition, the present study indicates that effective relational encoding correlates positively with the activity of the anterior medial temporal lobe regions.** © 1999

Academic Press

**Key Words:** memory; encoding; hippocampus; medial temporal lobe; cued recall; PET; functional neuroimaging.

## INTRODUCTION

Functional neuroimaging studies of memory processes have consistently indicated that encoding and retrieval of long-term memory information activate a distributed network of interacting brain regions. Two systems that have been the focus of memory research are the medial temporal lobe (MTL) memory system (Squire *et al.*, 1993; Squire and Zola-Morgan, 1991) and

the prefrontal cortex (PFC) (Buckner, 1996; Cabeza and Nyberg, 1997a; Fletcher *et al.*, 1997; Nyberg *et al.*, 1996a; Shimamura, 1995; Tulving *et al.*, 1994a).

The relation between MTL activations in functional imaging studies and different memory processes is complex and not well understood (Fletcher *et al.*, 1997; Tulving and Markowitsch, 1997). However, lesion data (Scoville and Milner, 1957; Zola-Morgan *et al.*, 1986) and functional neuroimaging data indicate that the MTL memory system plays an essential role in long-term declarative memory, for example, in episodic encoding (Gabrieli *et al.*, 1997; Stern *et al.*, 1996; Tulving *et al.*, 1994b) and retrieval from long-term memory (Buckner *et al.*, 1995; Petersson *et al.*, 1997; Schacter *et al.*, 1996; Squire *et al.*, 1992b). In addition, lesion (Shimamura, 1995; Wheeler *et al.*, 1995) and functional neuroimaging data (Dolan and Fletcher, 1997; Fletcher *et al.*, 1998a,b; Wagner *et al.*, 1998a) indicate that the prefrontal regions are important for encoding and retrieval of information. Lesions of the MTL system affect memory encoding and consolidation (Squire, 1992) while lesions to the PFC seem to affect the use of encoding and retrieval strategies (Fletcher *et al.*, 1997; Incisa della Rocchetta and Milner, 1993; Petrides, 1989; Stuss *et al.*, 1994). In addition, the prefrontal and MTL activity may be sensitive to the material being encoded, the task instructions, and the encoding strategy used (Kelley *et al.*, 1998). There are also some indications that the prefrontal activations are sensitive to material-specific processing during retrieval (Wagner *et al.*, 1998b), consistent with neuropsychological demonstrations that left and right frontal lesions differentially impact verbal and nonverbal episodic memory (Milner *et al.*, 1991).

The results of two recent event-related fMRI studies indicate that effective encoding (i.e., encoding of stimuli later recognized) activated the PFC and the MTL more than ineffective encoding (i.e., encoding of stimuli not later recognized), using either visuospatial (Brewer *et al.*, 1998) or verbal material (Wagner *et al.*, 1998c). Both studies used a group of well-educated young

(18–35 years) college students of both sexes (A. D. Wagner and J. Brewer, personal communication). Similar results, using young subjects (mean age 25) in a blocked fMRI study, also indicate that effective encoding is related to increased MTL activation (Fernandez *et al.*, 1998). The within-subject design in these studies makes it important to replicate these results in other study populations.

In the present PET study, we studied a population of upper middle-aged/older illiterate women during encoding of word pairs for later cued recall. We used the cued-recall scores obtained after each encoding PET scan as a measure of effective encoding and entered the cued-recall scores as a covariate in a general linear model to study the relation between effective encoding and regional cerebral blood flow (rCBF) during the encoding scans. Previous results, in a different study population using the same paradigm as described below, indicate that the MTL regions are bilaterally engaged (Petersson *et al.*, 1998a). Based on previous data, including the event-related fMRI results using verbal material (Wagner *et al.*, 1998c), and the regions of the PFC described in recent reviews of the functional organization of memory (Buckner, 1996; Fletcher *et al.*, 1997), we hypothesized that the activity of the left inferior frontal (BA 44/45/47) and the MTL regions would correlate positively with cued-recall success.

This study is part of an ongoing project focusing on the modulatory influence of educational level/literacy on the functional organization of the adult human brain (see, e.g., Castro-Caldas *et al.*, 1998; Petersson *et al.*, 1998a,b,c; Reis and Castro-Caldas, 1997).

## MATERIALS AND METHODS

### Subjects

In this study, subjects are classified as illiterate when they, for social reasons, had never entered school and had no knowledge of reading or writing (see further Castro-Caldas *et al.*, 1998; Reis and Castro-Caldas, 1997). This definition of illiteracy should be distinguished from functional illiteracy which is not considered in this study. Functionally illiterate subjects were not included since their previous exposure to and acquisition of phonemic/graphemic associations implies experience and the existence of a visuographic representation system based on phonology. In the course of the selection process, all subjects underwent a letter recognition task in which single letters or very common acronyms were shown (e.g., common trademarks, television channels). Illiterate subjects were included if they were unable to recognize any of the letters or acronyms containing information. The ability to write their own name was not an exclusion criterion.

Seven right-handed healthy female subjects ( $63 \pm 5$  years (mean  $\pm$  SD), range 55–71) from the same socio-

cultural background in a village of southern Portugal were selected. Previous diseases potentially involving the brain were ruled out by clinical assessment and previous clinical information provided by the local doctor, as well as by morphological investigations. Diagnostic MRI scans were classified as normal (except in one case, indicating changes in the white matter and slight central atrophy; however, this subject's memory performance was above average). In order to rule out dementia or other cognitive dysfunction, the subjects were submitted to a screening test. The test battery included simple tasks like object naming, object identification, phrase comprehension, repetition of words and phrases, verbal fluency, limb and oral praxis, general knowledge, and episodic memory tasks (Garcia and Guerreiro, 1983). The subjects were fully functional in their daily lives and maintained regular work efficiently. For social reasons (see further Castro-Caldas *et al.*, 1998; Reis and Castro-Caldas, 1997) none of the subjects had entered school. During the selection process the subjects practiced and were tested on the same experimental tasks that were used during the PET scanning. The word lists (three phonological lists, three semantic lists) used in the selection process were composed of 10 word pairs that were later randomly included in the experimental lists. The selection of subjects was performed approximately 2–3 months before the PET experiment. The study was approved by the local Ethics and Radiation Safety Committees at the Karolinska Hospital.

In order to make behavioral comparisons (and as part of another PET study), we selected eight right-handed healthy literate female subjects (mean  $58 \pm 6$  years, range 52–68) with sociocultural background similar to that of the illiterate subjects and from the same Portuguese village as the illiterate group (Petersson *et al.*, 1998a). The literate subjects were selected by the same procedures as described above. In particular, previous diseases potentially involving the brain or cognitive dysfunction were ruled out by clinical assessment, diagnostic MRI scans (all classified as normal), and screening tests. The subjects were fully functional in their daily lives and maintained regular work efficiently. All subjects had 4 years of schooling, had regular reading and writing habits, and performed normally on reading comprehension and writing tests. The behavioral data for both groups were acquired under identical conditions (see further below). Informed consent was given by all subjects participating in the study.

### The Lists of Word Pairs

Two types of 14 word-pair lists were constructed. The first type (semantic) consisted of semantically associated word pairs (e.g., *bilhete-comboio*, ticket-train). Super-sub-ordinate word pairs were not included. The

second type (phonological) consisted of phonologically associated word pairs and care was taken to not include (obvious) semantically associated word pairs. The phonological relation between words was created by changing the initial phoneme (e.g., *selo-pelo*, stamp-hair). Seven different lists of each type were constructed (1 list of each type served as extra list in case any of the PET scans failed). The words used were common concrete nouns selected from the Portuguese language frequency tables (Nascimento *et al.*, 1987), carefully selected to be relevant for the sociocultural context of the southern Portuguese village. The word lengths (one- to three-syllable words) in the semantic and phonological lists were counterbalanced. The length of the first word was matched to the length of second word in each word pair, also preserving the CV structure. The lists of word pairs and the list of cue words were recorded for auditory presentation during encoding and cued recall. The word pairs were recorded with an interpair interval of 1300 ms and with 500 ms between the words in a pair in the encoding lists. The cue words were recorded with an interstimulus interval of 8 s in the retrieval lists. The lists were auditorily presented and the subject was instructed to memorize the word pairs during encoding. During retrieval the subjects were cued with the first word of a word pair and were instructed to recall the second or, if not remembered, to say "passo." Different lists were used for each new encoding scan as well as for each new retrieval scan, balanced across subjects.

### The Experimental Paradigm

The subjects were scanned with their eyes closed in encoding (SE, encoding of a semantic list; PE, encoding of a phonological list), retrieval (SR, retrieval of a semantic list; PR, retrieval of a phonological list), and rest (RS). The five different tasks were repeated three times for each subject, presented in a randomized order in blocks of five. All aspects of the experimental paradigm were practiced on a training list in the PET camera until the subjects reached full understanding and performance was satisfying. The training list was composed of 12 word pairs (6 semantic and 6 phonological; each word pair was randomly chosen from a list; the lists were randomly chosen without replacement from the 14 lists available). Words were auditorily presented by earphones and the subjects adjusted the sound level to their own preference. During RS the subjects were scanned with eyes closed and ambient noise. Well before the RS scans started the subjects were instructed to relax and to not think or do anything so the subjects would be in a relaxed state during scanning. During the encoding task (eyes closed) the subjects were instructed to learn the list of word pairs for later recall. In the encoding task the list of word pairs was encoded once and PET scanning was done

during encoding (SE and PE). After the encoding scan there was a short pause (15 s), followed by cued recall of the same list, when no scanning was done. The recall performance was recorded to ensure that encoding had occurred and was used as a covariate of interest as an indicator of effective encoding during the encoding scan (cf. *Data Analysis*). The retrieval task started with encoding of an auditorily presented list of word pairs. After encoding there was a short pause (15 s), and then retrieval of the same list started. During retrieval the subjects were cued with the first word of a word pair. This was repeated twice with approximately 20–30 s between the encoding–retrieval cycles and performance was recorded after both the first and the second retrieval. PET data were acquired during the second retrieval. The encoding was done twice in order to increase performance and reduce possible reencoding of the material (Pettersson *et al.*, 1997; Tulving and Markowitsch, 1997). See Fig. 1 for a schematic representation of the paradigm.

### PET Scanning

Repeated measurements of rCBF (15 scans/subject, 3 scans/state) were made with an Ecat Exact HR PET scanner in 3D-sampling mode (Wienhard *et al.*, 1994) and bolus injections of [<sup>15</sup>O]butanol (Berridge *et al.*, 1990) producing 60-s tracer uptake images. Scatter corrections were made and a 2D-transmission scan was used for attenuation correction. To ensure that the levels of radioactivity in the subjects had returned to background before starting a new scan, there was at least 10 min between successive scans.

### Data Analysis

The PET images were realigned, spatially normalized, and transformed into an approximate Talairach–Tournoux stereotactic space (Talairach and Tournoux, 1988), isotropic Gaussian filtered (14-mm FWHM), proportionally scaled to account for global confounders, and analyzed with statistical parametric mapping (SPM96; Friston *et al.*, 1995). The general linear model was used to model rCBF data and relevant contrasts corresponding to null hypotheses were used to generate statistic images SPM[Z] (cf. Frackowiak *et al.*, 1997). Each encoding scan was followed by cued recall of the same list just encoded. In the correlation analysis, the cued-recall performance was used as an indicator of effective encoding during the encoding scan. The cued-recall performance was included as a covariate in the general linear model. Subject (block) effects were also modeled. This analysis was performed for the two different encoding tasks SE and PE separately. The coordinates of local maxima refer to the approximate Talairach–Tournoux space as defined by the SPM96 template (for further details on the SPM96 software see

the SPM Web site <http://www.fil.ion.ucl.ac.uk/spm/>). Given the regional specific hypothesis related to the inferior PFC and the MTL regions, local activation maxima with  $Z > 2.33$  (or omnibus significance  $P < 0.01$ ) were considered significant.

## RESULTS AND DISCUSSION

### Behavioral Results

It is of interest to note that illiterate subjects often perform less well compared to matched literate subjects on cognitive tasks (Ardila *et al.*, 1989; Garcia and Guerreiro, 1983; Rosselli *et al.*, 1990), including several memory tasks (Ardila *et al.*, 1989). (For a review of the influence of educational level and culture on neuropsychological testing see Castro-Caldas *et al.*, 1997.) This can be understood since formal education not only brings about reading and writing skills but in general also more effective cognitive strategies for problem solving and information processing. Illiterate subjects often develop more idiosyncratic strategies for solving problems compared to the literate group (cf. Castro-Caldas *et al.*, 1997). Therefore, when comparing the learning abilities of literate and illiterate subjects, relative measures of learning capacity are often relevant. Since both groups encoded and retrieved some of the word-pair lists twice (Fig. 1) we used the increase in cued-recall performance from the first to the second retrieval occasion as an index of the learning capacity. The average increase in cued-recall performance in the illiterate group (semantic lists,  $2.4 \pm 0.7$ ; phonological lists,  $2.2 \pm 0.8$ ) was comparable to that in the matched literate group (semantic lists,  $1.6 \pm 0.8$ ; phonological lists,  $2.3 \pm 0.8$ ). This and the screening for cognitive dysfunction indicate that there was no general learning deficit in the group of illiterate subjects in this study.

The behavioral performance was recorded during cued recall after each encoding scan and before and during each retrieval scan (Table 1; Fig. 1). Consistent with previous results on illiterate and literate subjects

**TABLE 1**

Mean Cued-Recall Performances in the Illiterate Subjects during the Different Retrieval Periods (See Fig. 1 for a Schematic Overview of the Experimental Paradigm)

List type	Cued recall after encoding scans	Cued recall before retrieval scans	Cued recall during retrieval scanning
Semantic	$6.4 \pm 1.1$	$6.8 \pm 1.2$	$9.2 \pm 1.3$
Phonological	$2.3 \pm 0.9$	$3.0 \pm 1.7$	$5.1 \pm 2.1$
<i>P</i> value	0.02	0.01	0.01

*Note.* The *P* values relate to the outcome of testing the mean differences between list types (Wilcoxon paired *t* test).

(Reis and Castro-Caldas, 1997), the cued-recall scores were significantly better on semantically related compared to phonologically related word pairs. This performance difference indicates that the processing of the semantic lists increases learning compared to the phonological lists (Table 1). Assuming that the encoding of the semantic lists involves more elaborate (or deep) processing than encoding of the phonological lists, this effect is similar to the levels of processing effect (Baddeley, 1997; Craik and Jennings, 1992; Craik and Lockhart, 1972).

Previous findings indicate that the illiterate population processes phonological information differently from literate subjects (Morais, 1993; Morais *et al.*, 1979). For example, illiterate subjects have greater difficulties with certain tasks involving phonological processing, including pseudoword repetition (Castro-Caldas *et al.*, 1998), verbal fluency with a phonological criterion (Reis and Castro-Caldas, 1997), and digit span (Castro-Caldas *et al.*, 1997). In order to investigate this issue further, we compared the illiterate group to the matched literate group on the difference in cued-recall performance between semantic and phonological lists; that is, we compared the mean cued-recall score differences [SE – PE] between the literate and the illiterate group.

### Encoding scans

Scan - Encoding	Cued Recall Performance data
-----------------	------------------------------

### Retrieval scans

Encoding (1)	Cued Recall Performance data	Encoding (2)	Scan - Cued Recall Performance data
--------------	------------------------------	--------------	-------------------------------------

**FIG. 1.** Retrieval data were acquired after encoding scans and before and during retrieval scans.

The average cued-recall score difference [SE – PE] was significantly greater in the illiterate compared to the literate group (Table 2). This indicates that the illiterate subjects do not utilize the phonological association between the words of the phonological lists as effectively as the literate subjects, replicating previous findings (Reis and Castro-Caldas, 1997). This may be an encoding effect, a retrieval effect, or both. The present data are consistent with the previous results indicating that illiterate subjects process phonological information differently from literate subjects (Castro-Caldas *et al.*, 1997, 1998; Morais, 1993; Morais *et al.*, 1979; Reis and Castro-Caldas, 1997).

### PET Results

It has been hypothesized that activation of the left middle-inferior prefrontal region leads to effective encoding (Fletcher *et al.*, 1997, 1998) and that the MTL memory system is especially important for episodic encoding (Squire, 1992; Squire and Zola-Morgan, 1991). To test if effective encoding correlates with rCBF in the left inferior PFC and the MTL regions, we used the individual cued-recall scores acquired after the encoding scans as covariates in the general linear model. We tested this separately for the SE and the PE covariates (Table 3; Fig. 2).

There was a significant positive correlation in the left inferior frontal gyrus (BA 47) in both SE ( $[x, y, z] = [-52, 38, -12]$ ,  $Z = 3.52$ ) and PE ( $[x, y, z] = [-52, 42, -12]$ ,  $Z = 3.10$ ). In addition there were significant positive correlations in the right MTL (hippocampus/parahippocampal gyrus, BA 28/34/35) in both SE ( $[x, y, z] = [30, -12, -20]$ ,  $Z = 3.61$ ) and PE ( $[x, y, z] = [30, -12, -22]$ ,  $Z = 3.36$ ), as well as in the left MTL (hippocampus/parahippocampal gyrus, BA 28/36) in SE ( $[x, y, z] = [-26, -10, -14]$ ,  $Z = 2.55$ ). In PE, there was also a positive correlation in the left MTL (hippocampus/parahippocampal gyrus, BA 28/36) ( $[x, y, z] = [-26, -12, -14]$ ,  $Z = 2.27$ ) even though it did not reach the chosen significance level.

These results indicate that the left inferior PFC and

**TABLE 2**

Comparing the Mean Differences in Semantic and Phonological Cued-Recall Performances between the Literate and the Illiterate Group; That Is,  $[SE - PE]_{\text{literate}} - [SE - PE]_{\text{illiterate}}$

Group	SE – PE after encoding scans	SE – PE before retrieval scans	SE – PE during retrieval scanning
Illiterate	4.1 ± 1.3	3.8 ± 1.6	4.0 ± 2.1
Literate	1.7 ± 1.7	2.2 ± 1.7	1.4 ± 1.2
<i>P</i> value	0.01	0.08	0.01

*Note.* The *P* values relate to the outcome of testing the mean differences with Mann–Whitney *U* test.

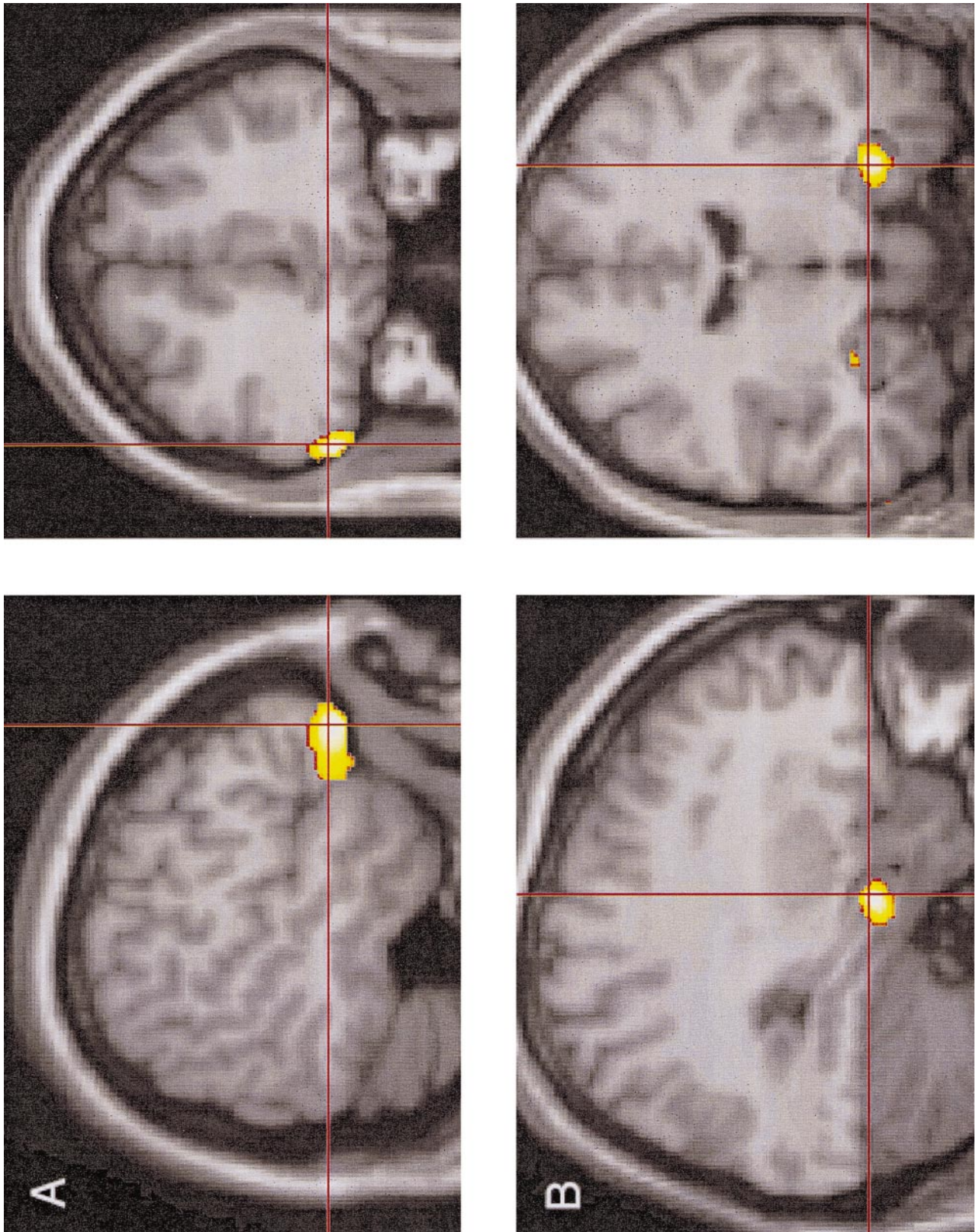
**TABLE 3**

Local Maxima of Positive Correlation between Cued-Recall Performance and Activation in the Left Inferior Prefrontal and the Medial Temporal Lobe Regions during Encoding of Semantic (SE) and Phonological (PE) Lists

Region	Brodman area	$[x, y, z]$			<i>Z</i> score
SE					
Inferior frontal gyrus	47 sin	–52	38	–12	3.52
Hippocampus/parahippocampal gyrus	28/36 dx	30	–12	–20	3.61
Hippocampus/parahippocampal gyrus	28/34/35 sin	–26	–10	–14	2.55
PE					
Inferior frontal gyrus	47 sin	–52	42	–12	3.10
Hippocampus/parahippocampal gyrus	28/36 dx	30	–12	–22	3.36
Hippocampus/parahippocampal gyrus	28/34 sin	–26	–12	–14	2.27

the MTLs are important for processes subserving effective encoding. These results are consistent with recent event-related FMRI studies indicating that effective encoding activates prefrontal and MTL regions more than ineffective encoding (Brewer *et al.*, 1998; Wagner *et al.*, 1998c). Both these studies used well-educated college students. Similar results, using young subjects (mean age 25), in a metabolic FDG-PET study (Alkire *et al.*, 1998) and a blocked FMRI study (Fernandez *et al.*, 1998) also indicate that effective encoding is related to increased MTL activation. Since long-term memory processes are thought to be general purpose mechanisms, it is important that these results are replicated in other study populations. We specifically tested if effective encoding of lists of auditorily presented word pairs (measured as cued-recall success) correlated positively with the activity of the left inferior PFC and the MTL regions in a population of healthy upper middle-aged/older illiterate women. We found positive correlations in these regions in two independent sets of scans (given the study population), that is, for SE and PE scans separately. This indicates that these results are robust in our study population.

Recent FMRI data indicate that the PFC and MTL activity may be sensitive to the material being encoded or retrieved from long-term memory (Kelley *et al.*, 1998; Wagner *et al.*, 1998b). It is also possible that the PFC and MTL activity is modulated by the encoding strategy used by the subjects. Wagner *et al.* (1998) used verbal material and found that the left inferior PFC and the left MTL were specifically involved in effective episodic encoding, while Brewer *et al.* (1998) used visuospatial material and found that the right inferior frontal PFC and the bilateral MTL were involved in effective encoding, that is, when the subjects were later



**FIG. 2.** Activity in the left inferior prefrontal and the medial temporal lobes during encoding of semantic lists that correlated positively with cued-recall success scores acquired after each encoding scan. The SPM[Z] is thresholded at  $Z = 2.33$ .

able to retrieve the study material. In this study of illiterate subjects, both the right and the left MTL were related to effective episodic encoding of verbal material. This may indicate that the illiterate subjects did not use a pure language-based encoding strategy. In particular, since the words used were common concrete nouns easy to visualize, the subjects may have used visuospatial imagery as an encoding strategy in addition to language-based processing. Based on the findings of material-specific lateralization of prefrontal activation (Kelley *et al.*, 1998; Wagner *et al.*, 1998b), we also investigated our data in the right PFC. We found a positive correlation in the right frontopolar region (BA 10) in both SE ( $[x, y, z] = [18, 44, -8]$ ,  $Z = 3.01$ ) and PE ( $[x, y, z] = [18, 46, -6]$ ,  $Z = 2.60$ ).

An alternative interpretation of these findings relates to the possibility that language processing in illiterate subjects may under some circumstances recruit bilateral brain areas to a greater extent than in literate subjects. There are some data consistent with such an explanation (Cameron *et al.*, 1971; Castro-Caldas *et al.*, 1998; Lecours *et al.*, 1987a,b; Wechsler, 1976). However, this issue is complex and there are other data indicating that this may not always be the case (Damásio *et al.*, 1976a,b). In addition, previous results in the group of literate subjects with the same sociocultural background indicate that the MTL regions are bilaterally engaged by this paradigm in encoding compared to retrieval (Pettersson *et al.*, 1998a). Whatever the case may be, to confirm the bilateral MTL processing in encoding, we investigated the activation pattern of the MTL regions using contrasts between conditions in a general linear model. Since there were no significant differences in the MTL regions between SE and PE or SR and PR, or in the interaction contrast  $[SE - SR - PE + PR]$  and its reverse, we pooled the data into an encoding state E and a retrieval state R. Consistent with the results above, there were significant bilateral MTL activations in E - R (Table 4). We also analyzed the contrast SE - SR and PE - PR separately. The results indicate significant bilateral MTL activations in both SE - SR and PE - PR (Table 4). However, it should be noted that in encoding versus rest comparison, only the left MTL activation was significant in the illiterate group ( $[x, y, z] = [-34, -14, -22]$ ,  $Z = 2.74$ ). The same pattern was observed in the literate group, that is, the right MTL activation was statistically weaker than the left in encoding versus rest (Pettersson *et al.*, 1998a). In addition, the left inferior frontal and left MTL were activated in the literate group during encoding (E) compared to rest (Pettersson *et al.*, 1998a). These results were replicated in the illiterate group (data not shown).

Most functional neuroimaging studies use relatively young, usually well-educated subjects for pursuing different questions concerning the functional organiza-

TABLE 4

Local Maxima Comparing Encoding with Retrieval in the Left Inferior Prefrontal and the Medial Temporal Lobe Regions

Region	Brodmann area	$[x, y, z]$			Z score
SE - SR					
Inferior frontal gyrus	47 sin	-44	30	-10	3.50
Hippocampus/parahippocampal gyrus	28/34 dx	22	-10	-14	3.75
Parahippocampal gyrus	28/34 sin	30	-12	-20	3.44
Hippocampus/parahippocampal gyrus	28/34/35 sin	-26	-10	-16	3.34
PE - PR					
Inferior/middle frontal gyrus	47 sin	-34	38	-14	1.94
Hippocampus/parahippocampal gyrus	28/34/35 dx	18	-14	-12	3.97
Hippocampus/parahippocampal gyrus	28/34 sin	-32	-14	-14	3.43
E - R					
Inferior frontal gyrus	47 sin	-36	36	-12	2.81
Hippocampus/parahippocampal gyrus	28/34/35 dx	22	-12	-14	5.14
Hippocampus/parahippocampal gyrus	28/34 sin	-30	-12	-16	4.50

tion of the brain. Recently it has been pointed out that results obtained in such study populations need replication in other populations (Bäckman *et al.*, 1997). This is important since most functional neuroimaging studies use within-subject designs or fixed effects models (Holmes and Friston, 1998; Woods, 1996). For example, it is known that older subjects perform less well on some memory tests than younger adults (Craik and Jennings, 1987, 1992), and several PET studies of memory using older subjects have reported results, including changes in the PFC and MTL regions (Bäckman *et al.*, 1997; Cabeza *et al.*, 1997b; Grady *et al.*, 1995; Schacter *et al.*, 1996), that have been interpreted as indicating that age-related memory deficits may be attributed to both impaired encoding and retrieval (Nyberg *et al.*, 1996a) and that these may reflect both less efficient processing and functional compensation (Cabeza *et al.*, 1997b). In a recent electrophysiological study (Mark and Rugg, 1998) it was concluded that the processes supporting episodic memory retrieval, including those dependent on the PFC, are relatively unaffected by advancing age. One possible way of interpreting these data is that the suggested age-related rCBF changes observed with PET indicate an age-related encoding failure. In this PET study of upper middle-aged/older illiterate women, effective episodic encoding correlated with the activity in the PFC and the MTL regions similar to the observations in young study populations (Alkire *et al.*, 1998; Brewer *et al.*, 1998; Fernandez *et al.*, 1998; Wagner *et al.*, 1998c). In our previous PET study of the literate group (Pettersson

*et al.*, 1998a) we found no obvious differences in the activation pattern during either encoding or retrieval compared to the activation patterns described in younger populations (Buckner, 1996; Cabeza and Nyberg, 1997a; Fletcher *et al.*, 1997). However, the subjects of the PET studies investigating age-related effects referred to above were on average 5–10 years older than our subjects. This may indicate that the age-related changes observed in some of the PET studies of older subjects may develop at 60–70 years of age.

Earlier PET results indicate that the left middle-inferior PFC (Kapur *et al.*, 1994a,b) subserves semantic processing related to the levels of processing effect. In this context, if encoding of the semantic lists involves more elaborate processing than the phonological lists, then this may be reflected in a greater activity in the left PFC when SE and PE are compared directly. This was indeed the case and a left posterior-inferior frontal region (BA 47) similar to the previous left-inferior PFC was more activated in SE compared to PE. However, the effect was statistically weak and the local maximum was located more posterior ( $[x, y, z] = [-44, 16, -12]$ ,  $Z = 1.94$ ), even if the left inferior PFC regions overlapped when a lower threshold was used ( $Z = 1.64$ , or omnibus  $P = 0.05$ ). More interesting, perhaps, was the fact that correlation between the left-inferior PFC activity and the cued-recall success was greater in PE compared to SE ( $[x, y, z] = [-52, 44, -12]$ ,  $Z = 2.62$ ). This was also the case in the MTL regions ( $[x, y, z] = [30, -12, -22]$ ,  $Z = 2.75$ ;  $[x, y, z] = [-26, -12, -14]$ ,  $Z = 1.77$ ).

Finally, PET studies of episodic encoding have typically observed both anterior and posterior MTL activations. In contrast, fMRI studies have observed almost exclusively posterior MTL activations (Lepage *et al.*, 1998; Schacter and Wagner, 1999). One possible explanation of this observation is the fact that fMRI is relatively more insensitive in the anterior-inferior compared to the posterior-superior MTL, while this is not the case with PET. An interesting alternative hypothesis (Schacter and Wagner, 1999) observes that several of the PET studies detecting anterior MTL activations used experimental paradigms in which relations across multiple stimuli were processed and in which there was an explicit goal of associating two or more stimuli. This has been called relational, configural, or conjunctural learning (e.g., Cohen and Eichenbaum, 1993; Eichenbaum, 1994; Rudy and Sutherland, 1994; Squire, 1992). In contrast, few fMRI studies have examined relational encoding, one exception being the study of Roberts *et al.* (1997), which observes anterior MTL activations. All previous studies investigating effective encoding (Alkire *et al.*, 1998; Brewer *et al.*, 1998; Fernandez *et al.*, 1998; Wagner *et al.*, 1998c) required item encoding with no explicit relational demand and

these studies observed posterior MTL activation associated with subsequent memory. In this PET study we used an encoding task that demands interitem relational or associative processing and observed a significant correlation between anterior MTL activity bilaterally and the subsequent memory performance. The results are consistent with the hypothesis of Schacter and Wagner (1999) suggesting that relational encoding is related to the anterior MTL.

## CONCLUSION

In this PET study we investigated a group of healthy upper middle-aged/older illiterate women. The results presented are consistent with several recent functional neuroimaging studies indicating that the prefrontal and medial temporal regions are more active during effective than in ineffective encoding. Using an auditory word-pair association cued-recall paradigm, we observed positive correlations between cued-recall success and the activity in the left inferior prefrontal and the medial temporal regions during encoding. These correlations were observed during encoding of both semantically and phonologically related word pairs. This indicates that these effects are robust in the studied population, that is, reproducible within group in two independent sets of scans. The results of the present study also indicate that effective relational or conjunctural encoding correlates positively with the activity of the anterior medial temporal lobe regions.

## ACKNOWLEDGMENTS

This study is part of the EU Biomed 1 program (BMHI CT94-1261) and was financed in part by grants from the Swedish Medical Research Council (8276), the Karolinska Institute, the Knut and Alice Wallenberg Foundation, the Family Ekman Foundations, the Swedish Bank Tercentenary Fund, and Project STRIDE (No. 352/92-JNICT). The authors thank the volunteers for their participation and appreciate the help of the Portuguese Embassy in Stockholm. We thank Gustav von Heijne, Ellenor Andersson, Peter Söderholm, Walter Pulka, and the Karolinska pharmacy for unique technical assistance. We also thank Anthony D. Wagner for valuable comments on an early version of this work.

## REFERENCES

- Alkire, M. T., Haier, R. J., Fallon, J. H., and Cahill, L. 1998. Hippocampal, but not amygdala, activity at encoding correlates with long-term, free recall of nonemotional information. *Proc. Natl. Acad. Sci. USA* **95**:14506–14510.
- Ardila, A., Rosselli, M., and Rosas, P. 1989. Neuropsychological assessment in illiterates: Visuospatial and memory abilities. *Brain Cognit.* **11**:147–166.
- Bäckman, L., Almkvist, O., Andersson, J., Nordberg, A., Winblad, B., Reineck, R., and Långström, B. 1997. Brain activation in young and older adults during implicit and explicit retrieval. *J. Cognit. Neurosci.* **9**:378–391.
- Baddeley, A. 1997. *Human Memory: Theory and Practice*, rev. ed. Earlbaum, Hove, UK.



- Berridge, M. S., Cassidy, E. H., and Terris, A. H. 1990. A routine, automated synthesis of oxygen-15-labeled butanol for positron tomography. *J. Nucl. Med.* **31**:1727-1731.
- Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H., and Gabrieli, J. D. E. 1998. Making memories: Brain activity that predicts how well visual experience will be remembered. *Science* **281**:1185-1187.
- Buckner, R. L. 1996. Beyond HERA: Contributions of specific prefrontal brain areas to long-term memory retrieval. *Psychonom. Bull. Rev.* **3**:149-158.
- Buckner, R. L., Petersen, S. E., Ojemann, J. G., Miezin, F. M., Squire, L. R., and Raichle, M. E. 1995. Functional anatomical studies of explicit and implicit memory retrieval tasks. *J. Neurosci.* **15**:12-29.
- Cabeza, R., and Nyberg, L. 1997a. Imaging cognition: An empirical review of PET studies with normal subjects. *J. Cognit. Neurosci.* **9**:1-26.
- Cabeza, R., Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., Jennings, J. M., Houle, S., and Craik, F. I. 1997b. Age-related differences in neural activity during memory encoding and retrieval: A positron emission tomography study. *J. Neurosci.* **17**:391-400.
- Cameron, R. F., Currier, R. D., and Haerer, A. F. 1971. Aphasia and literacy. *Br. J. Disord. Commun.* **6**:161-163.
- Castro-Caldas, A., Petersson, K. M., Reis, A., Stone-Elander, S., and Ingvar, M. 1998. The illiterate brain. Learning in childhood influences the functional organization of the adult brain. *Brain* **121**:1053-1063.
- Castro-Caldas, A., Reis, A., and Guerreiro, M. 1997. Neuropsychological aspects of illiteracy. *Neuropsychol. Rehab.* **7**:327-338.
- Cohen, N. J., and Eichenbaum, H. 1993. *Memory, Amnesia, and the Hippocampal System*. MIT Press, Cambridge, MA.
- Craik, F. I. M., and Jennings, J. M. 1992. Human memory. In *Handbook of Aging and Cognition* (F. I. M. Craik and T. A. Salthouse, Eds.), Erlbaum, Hillsdale, NJ.
- Craik, F. I. M., and Lockhart, R. S. 1972. Levels of processing: A framework for memory research. *J. Verb. Learn. Verb. Behav.* **11**:671-684.
- Craik, F. I. M., and McDowd, J. M. 1987. Age differences in recall and recognition. *J. Exp. Psychol.* **13**:474-479.
- Damásio, A. R., Castro-Caldas, A., Grosso, J. T., and Ferro, J. M. 1976a. Brain specialization for language does not depend on literacy. *Arch. Neurol.* **33**:300-301.
- Damásio, A. R., Castro-Caldas, A., Grosso, J. T., and Ferro, J. M. 1976b. Letter to the Editor. *Arch. Neurol.* **33**:662.
- Dolan, R. J., and Fletcher, P. C. 1997. Dissociating prefrontal and hippocampal function in episodic memory encoding. *Nature* **388**:582-585.
- Eichenbaum, H. 1994. The hippocampal system and declarative memory in humans and animals: Experimental analysis and historical origins. In *Memory Systems 1994* (D. L. Schacter and E. Tulving, Eds.), pp. 147-202. MIT Press, Cambridge, MA.
- Fernandez, G., Weyerts, H., Schrader-Bölsche, M., Tendolkar, I., Smid, H. G. O. M., Tempelmann, C., Hinrichs, H., Scheich, H., Elger, C. E., Mangun, G. R., and Heinze, H.-J. 1998. Successful verbal encoding into episodic memory engages the posterior hippocampus: A parametrically analyzed functional magnetic resonance imaging study. *J. Neurosci.* **18**:1841-1847.
- Fletcher, P. C., Frith, C. D., and Rugg, M. D. 1997. The functional neuroanatomy of episodic memory. *Trends Neurosci.* **20**:213-218.
- Fletcher, P. C., Shallice, T., and Doland, R. J. 1998a. The functional roles of prefrontal cortex in episodic memory. I. Encoding. *Brain* **121**:1239-1248.
- Fletcher, P. C., Shallice, T., Frith, C. D., Frackowiak, R. S. J., and Doland, R. J. 1998b. The functional roles of prefrontal cortex in episodic memory. II. Retrieval. *Brain* **121**:1249-1256.
- Frackowiak, R. S. J., Friston, K. J., Frith, C. D., Dolan, R. J., and Mazziotta, J. C., Eds. 1997. *Human Brain Function*. Academic Press, San Diego.
- Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J.-P., and Frackowiak, R. S. J. 1995. Statistical parametric maps in functional imaging: A general linear approach. *Hum. Brain Mapp.* **2**:189-210.
- Gabrieli, J. D. E., Brewer, J. B., Desmond, J. E., and Glover, G. H. 1997. Separate neural bases of two fundamental memory processes in the human medial temporal lobe. *Science* **276**:264-266.
- Garcia, G., and Guerreiro, M. 1983. Pseudo-dementia from illiteracy. 6th European Meeting of the International Neuropsychological Society, Lisbon.
- Grady, C. L., McIntosh, A. R., Horwitz, B., Maisog, J. M., Ungerleider, L. G., Mentis, M. J., Pietrini, P., Schapiro, M. B., and Haxby, J. V. 1995. Age-related reductions in human recognition memory due to impaired encoding. *Science* **269**:218-221.
- Holmes, A. P., and Friston, K. J. 1998. Generalisability, random effects and population inference. *NeuroImage* **7**:S754.
- Incisa della Rocchetta, I., and Milner, B. 1993. Strategic search and retrieval inhibition: The role of the frontal lobes. *Neuropsychologia* **31**:503-524.
- Kapur, S., Craik, F. I. M., Tulving, E., Wilson, A. A., Houle, S., and Brown, G. M. 1994a. Neuroanatomical correlates of encoding in episodic memory: Levels of processing effect. *Proc. Natl. Acad. Sci. USA* **91**:2008-2011.
- Kapur, S., Rose, R., Liddle, P. F., Zipursky, R. B., Brown, G. M., Stuss, D., Houle, S., and Tulving, E. 1994b. The role of the left prefrontal cortex in verbal processing: Semantic processing or willed action? *NeuroReport* **5**:2193-2196.
- Kelley, W. M., Miezin, F. M., McDermott, K. B., Buckner, R. L., Raichle, M. E., Cohen, N. J., Ollinger, J. M., Akbudak, E., Conturo, T. E., Snyder, A. Z., and Peterson, S. E. 1998. Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. *Neuron* **20**:927-936.
- Lecours, A. R., Mehler, J., Parente, M. A., Aguiar, L. R., Silva, A. B., Caetano, M., Camarotti, H., Castro, M. J., Dehaut, F., Dumais, C., Gauthier, L., Gurd, J., Leitão, O., Maciel, J., Machado, S., Melaragno, R., Oliveira, L. M., Paciornik, J., Sanvito, W., Silva, E. S., Silifrandi, M., and Torné, C. H. 1987a. Illiteracy and brain damage. 2. Manifestations of unilateral neglect in testing "auditory comprehension" with iconographic materials. *Brain Cognit.* **6**:243-265.
- Lecours, A. R., Mehler, J., Parente, M. A., Beltrami, M. C., Silva, A. B., Tolipan, L. C., Cary, L., Castro, M. J., Carrono, V., Chagastelles, L., Dehaut, F., Delgado, R., Evangelista, A., Fajgenbaum, S., Fontoura, C., Karmann, D. F., Gurd, J., Torné, C. H., Jakubovicz, R., Kac, R., Lefevre, B., Lima, B., Maciel, J., Mansur, L., Martinez, R., Nobrega, M. C., Osorio, Z., Paciornik, J., Papaterra, F., Penedo, M. A. J., Saboya, B., Scheuer, C., Silva, A. B., Spinardi, M., and Teixeira, M. 1987b. Illiteracy and brain damage. 3. A contribution to the study of speech and language disorders in illiterates with unilateral brain damage (initial testing). *Neuropsychologia* **26**:575-589.
- Lepage, M., Habib, R., and Tulving, E. 1998. Hippocampal PET activations of memory encoding and retrieval: The HIPER model. *Hippocampus* **8**:313-322.
- Mark, R. E., and Rugg, M. D. 1998. Age effects on brain activity associated with episodic memory retrieval. An electrophysiological study. *Brain* **121**:861-873.
- Milner, B., Corsi, P., and Leonard, G. 1991. Frontal-lobe contribution to recency judgements. *Neuropsychologia* **29**:610-618.
- Morais, J. 1993. Phonemic awareness, language and literacy. In *Reading Disabilities: Diagnosis and Component Processes* (R. M.

- Joshi and C. K. Leong, Eds.), pp. 175–184. Kluwer Academic, Dordrecht.
- Morais, J., Cary, L., Alegria, J., and Bertelson, P. 1979. Does awareness of speech as a sequence of phones arise spontaneously? *Cognition* **7**:323–331.
- Nascimento, M. F., Rivenc, P., and Cruz, M. L. 1987. Portugues fundamental, metodos e documentos. Instituto Nacional de Investigação Científica, Centro de Linguística da Universidade de Lisboa, Lisbon.
- Nyberg, L., Cabeza, R., and Tulving, E. 1996a. PET studies of encoding and retrieval: The HERA model. *Psychonom. Bull. Rev.* **3**:135–148.
- Petersson, K. M., Elfgrén, C., and Ingvar, M. 1997. A dynamic role of the medial temporal lobe during retrieval of declarative memory in man. *NeuroImage* **6**:1–11.
- Petersson, K. M., Reis, A., Castro-Caldas, A., and Ingvar, M. 1998a. Activation of the medial temporal lobe during encoding of word-pairs in older middle-aged women. *NeuroImage* **7**:S844.
- Petersson, K. M., Reis, A., Askelöf, S., Castro-Caldas, A., and Ingvar, M. 1998b. Differences in verbal repetition in literate and illiterate subjects: A network analysis. *NeuroImage* **7**:S218.
- Petersson, K. M., Reis, A., Askelöf, S., Castro-Caldas, A., and Ingvar, M. 1998c. Differences in inter-hemispheric interactions between literate and illiterate subjects during verbal repetition. *NeuroImage* **7**:S217.
- Petrides, M. 1989. Frontal lobes and memory. In *Handbook of Neuropsychology* (F. Boller and J. Grafman, Eds.), pp. 75–90. Elsevier, Amsterdam.
- Reis, A., and Castro-Caldas, A. 1997. Illiteracy: A bias for cognitive development. *J. Int. Neuropsychol. Soc.* **3**:444–450.
- Rombouts, S., Machielsen, W., Witter, M., Barkhof, F., Lindeboom, J., and Scheltens, P. 1997. Visual association encoding activates the medial temporal lobe: A functional magnetic resonance imaging study. *Hippocampus* **7**:594–601.
- Rosselli, M., Ardila, A., and Rosas, P. 1990. Neuropsychological assessment in illiterates. II. Language and praxic abilities. *Brain Cognit.* **12**:281–296.
- Rudy, J. W., and Sutherland, R. J. 1994. The memory-coherence problem, configural association, and the hippocampal system. In *Memory Systems 1994* (D. L. Schacter and E. Tulving, Eds.), pp. 119–146. MIT Press, Cambridge, MA.
- Schacter, D. L., Savage, C. R., Alpert, N. M., Rauch, S. L., and Albert, M. S. 1996. The role of the hippocampus and frontal cortex in age-related memory changes: A PET study. *NeuroReport* **7**:1165–1169.
- Schacter, D. L., and Wagner, A. D. 1999. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus*, **9**:7–24.
- Scoville, W. B., and Milner, B. 1957. *J. Neurol. Neurosurg. Psychiat.* **20**:11–21.
- Shimamura, A. P. 1995. Memory and frontal lobe function. In *The Cognitive Neurosciences* (M. S. Gazzaniga, Ed.), pp. 803–813. MIT Press, Cambridge, MA.
- Squire, L. R. 1992. Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.* **99**:195–231.
- Squire, L. R., Knowlton, B., and Musen, G. 1993. The structure and organization of memory. *Annu. Rev. Psychol.* **44**:453–495.
- Squire, L. R., Ojemann, J. G., Miezin, F. M., Petersen, S. E., Videen, T. O., and Raichle, M. E. 1992. Activation of the hippocampus in normal humans: A functional anatomical study of memory. *Proc. Natl. Acad. Sci. USA* **89**:1837–1841.
- Squire, L. R., and Zola-Morgan, S. 1991. The medial temporal lobe memory system. *Science* **253**:1380–1386.
- Stern, C. E., Corkin, S., Gonzalez, R. G., Guimaraes, A. R., Baker, J. R., Jennings, P. J., Carr, C. A., Sugiura, R. M., Vedantham, V., and Rosen, B. R. 1996. The hippocampal formation participates in novel picture encoding: Evidence from functional magnetic resonance imaging. *Proc. Natl. Acad. Sci. USA* **93**:8660–8665.
- Stuss, D. T., Alexandre, M. P., Palumbo, C. L., Buckle, L., Sayer, L., and Pogue, J. 1994. Organizational strategies of patients with unilateral or bilateral frontal lobe injury in word list learning tasks. *Neuropsychology* **8**:355–373.
- Talairach, J., and Tournoux, P., Eds. 1988. *Co-planar Stereotaxic Atlas of the Human Brain*. Thieme, Stuttgart.
- Tulving, E., Kapur, S., Craik, F. I. M., Moscovitch, M., and Houle, S. 1994a. Hemispheric encoding/retrieval asymmetry in episodic memory: Positron emission tomography findings. *Proc. Natl. Acad. Sci. USA* **91**:2016–2020.
- Tulving, E., Markowitsch, H., Kapur, S., Habib, R., and Houle, S. 1994b. Novelty encoding networks in the human brain: Positron emission tomography data. *NeuroReport* **5**:2525–2528.
- Tulving, E., and Markowitsch, H. J. 1997. Memory beyond the hippocampus. *Curr. Opin. Neurobiol.* **7**:209–216.
- Wagner, A. D., Desmond, J. E., Glover, G. H., and Gabrieli, J. D. 1998a. Prefrontal cortex and recognition memory: Functional-MRI evidence for context-dependent retrieval processes. *Brain* **121**:1985–2002.
- Wagner, A. D., Poldrack, R. A., Eldridge, L. L., Desmond, J. E., Glover, G. H., and Gabrieli, J. D. E. 1998b. Material-specific lateralization of prefrontal activation during episodic encoding and retrieval. *NeuroReport* **9**:3711–3717.
- Wagner, A. D., Schacter, D. L., Rotte, M., Koutsmal, W., Maril, A., Dale, A. M., Rosen, B. R., and Buckner, R. L. 1998c. Building memories: Remembering and forgetting verbal experiences as predicted by brain activity. *Science* **281**:1188–1191.
- Wechsler, A. F. 1976. Crossed aphasia in an illiterate dextral. *Brain Lang.* **3**:164–172.
- Wheeler, M. A., Stuss, D. T., and Tulving, E. 1995. Frontal lobe damage produces episodic memory impairment. *J. Int. Neuropsychol. Soc.* **1**:525–536.
- Wienhard, K., Dahlbom, M., Eriksson, L., Michel, C., Bruckbauer, T., Pietrzyk, U., and Heiss, W.-D. 1994. The ECAT EXACT HR: Performance of a new high resolution positron scanner. *J. Comput. Assist. Tomogr.* **18**:110–118.
- Woods, R. P. 1996. Modeling for intergroup comparisons of imaging data. *NeuroImage* **4**:S84–S94.
- Zola-Morgan, S., Squire, L. R., and Amaral, D. G. 1986. Human amnesia and the medial temporal region: Enduring memory impairment following a bilateral lesion to field CA1 of the hippocampus. *J. Neurosci.* **6**:2950–2967.