# PET studies of encoding and retrieval:
# The HERA model

LARS NYBERG, ROBERTO CABEZA, and ENDEL TULVING
*Rotman Research Institute of Baycrest Centre, University of Toronto*
*North York, Ontario, Canada*

We review positron emission tomography (PET) studies whose results converge on the hemispheric encoding/retrieval asymmetry (HERA) model of the involvement of prefrontal cortical regions in the processes of human memory. The model holds that the left prefrontal cortex is differentially more involved in retrieval of information from semantic memory, and in simultaneously encoding novel aspects of the retrieved information into episodic memory, than is the right prefrontal cortex. The right prefrontal cortex, on the other hand, is differentially more involved in episodic memory retrieval than is the left prefrontal cortex. This general pattern holds for different kinds of information (e.g., verbal materials, pictures, faces) and a variety of conditions of encoding and retrieval.

The use of functional neuroimaging techniques such as positron emission tomography (PET) and magnetic resonance imaging (fMRI) has added a new dimension to the study of cognition. Not only do these techniques help to localize cognitive processes in the human brain, they can also contribute to theory development. In this paper, we illustrate the latter function of PET by reviewing studies of memory that led to the hemispheric encoding/retrieval asymmetry (HERA) model (Tulving, S. Kapur, Craik, Moscovitch, & Houle, 1994).

The traditional study of the neuroanatomy of cognitive functions has been based on lesion analyses. These studies have produced a wealth of knowledge about brain function, and have helped to identify many vital brain structures underlying cognitive processes. Studies with aphasic patients, for example, have pinpointed two main regions of the network subserving language (Mesulam, 1990)—Broca's area in the left frontal operculum and Wernicke's area in the left temporo-parietal junction (for reviews, see Benson, 1988; Geschwind, 1972). In the domain of learning and memory, studies with amnesic patients have pointed to structures with a key role in memory, such as the diencephalon, the medial temporal lobes, the temporal poles, and the frontal lobes (for reviews, see Butters & Stuss, 1989; Markowitsch, 1995; Markowitsch & Pritzel, 1985; Schacter, 1987; Squire & Zola-Morgan, 1991).

Although useful, the lesion approach has its limitations. First, it is well known that the brain has the capacity of reorganization following damage. For this reason, studying the damaged brain need not always illuminate the workings of a healthy brain. Second, accidental and disease-induced lesions in the human brain are usually extensive, making precise localization of functions difficult. They frequently produce deficits in different neurocognitive processes that may depend on structures that are functionally independent but happen to lie near each other (Wise et al., 1991). Third, regions distant from the lesion site can malfunction, because they are affected by the degeneration process, or because of lack of input. Finally, a complex behavior subserved by a distributed network across many brain regions may be disrupted by a lesion in only one of these regions, especially if it represents an informational bottleneck close to the input or output points of the network (Markowitsch, 1995; Steinmetz & Seitz, 1991).

In recent years, the problem of identifying the neuroanatomical basis of cognitive functions has been simplified dramatically with the introduction of functional neuroimaging techniques. These techniques can compensate the limitations of the lesion approach, by allowing in vivo localization of cognitive functions in the intact brain, thus avoiding the problems of reorganization, degeneration, and interruption of information flow. Moreover, whereas the lesion approach can reveal only those structures that are essential for a certain behavior, functional neuroimaging methods can potentially identify the whole network of brain regions involved by the behavior, including both essential and nonessential structures. For these reasons, lesion and neuroimaging approaches can supplement each other (Steinmetz & Seitz, 1991).

Positron emission tomography is the most mature functional neuroimaging technique available (Posner & Raichle, 1994; Raichle, 1994a). Since the seminal studies by Petersen and colleagues (Petersen, Fox, Posner, Mintun, & Raichle, 1988; Petersen, Fox, Snyder, & Raichle, 1990), PET has been intensively employed to investigate the neural correlates of various cognitive functions (for reviews, see Frackowiak, 1994; Frackowiak & Friston, 1994; Raichle, 1994b), including language (for reviews,

see Démonet, Wise, & Frackowiak, 1993; Petersen & Fiez, 1993), perception (e.g., Köhler, S. Kapur, Moscovitch, Winocur & Houle, 1995; Kosslyn et al., 1994; Sergent, Ohta, & Macdonald, 1992), attention (for a review, see Petersen, Corbetta, Miezin, & Shulman, 1994), and memory (for a review, see Buckner & Tulving, 1995). Memory has become the most intensively investigated cognitive function, with studies concerning working memory (e.g., Jonides et al., 1993; Paulesu, Frith, & Frackowiak, 1993; Petrides, Alivisatos, Evans, & Meyer, 1993; Petrides, Alivisatos, Meyer, & Evans, 1993), episodic memory (e.g., Andreasen, O'Leary, et al., 1995a, 1995b; Buckner, Petersen, et al., 1995; Cabeza, S. Kapur et al., in press; Fletcher et al., 1995; Grasby et al., 1993; S. Kapur et al., 1995; Nyberg et al., 1995; Schacter et al., 1995; Squire et al., 1992; Tulving, S. Kapur, Markovitsch, et al., 1994), semantic memory (e.g., Démonet et al., 1992; Frith, Friston, Liddle, & Frackowiak, 1991a; S. Kapur, Rose, et al., 1994; Petersen et al., 1988; Wise et al., 1991), priming (Bäckman et al., 1995; Buckner, Petersen, et al., 1995; Schacter, Alpert, Savage, Rauch, & Albert, 1996; Squire et al., 1992), and procedural memory (e.g., Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Molchan, Sunderland, McIntosh, Herscovitch, & Schreurs, 1994; Seitz & Roland, 1992).

An important feature of functional neuroimaging is that it makes possible the separation between different component processes of cognitive functions. Thus, a question can be raised as to the "locus" of impairment in the memory functioning of special populations (amnesics, older adults): is it at encoding, or at retrieval? It is difficult to distinguish these processes with the use of traditional neuropsychological methods, but PET does allow us to study encoding independently of retrieval, and retrieval independently of encoding. This capability of PET, to provide independent assessment of encoding- and retrieval-related activity, has already yielded important information.

For an example, it is well known that older adults perform less well on certain memory tests than younger adults (Craik & Jennings, 1992). Is the difference attributable to neural changes affecting encoding, retrieval, or both? Grady et al. (1995) compared brain activations in young and older subjects during the study and subsequent recognition of photographed faces. The patterns of brain activation of young and elderly subjects differed during the study phase, in that young but not old subjects showed prominent activation of the left prefrontal and medial temporal cortices during encoding. Differences in retrieval-related activity were also observed, but these did not involve medial-temporal regions (cf. Cabeza, Tulving, et al., 1995; Schacter, Savage, Alpert, Rauch, & Albert, in press). These results suggest that age-related memory deficits are attributable to both inadequate encoding of the to-be-remembered information and impaired retrieval processes, but that the functional neuroanatomy underlying these deficits is different at encoding and retrieval.

PET data are also capable of suggesting ideas that have not been conceived on the basis of cognitive or neuropsychological evidence. One of these is the hypothesis that there are separate "novelty" and "familiarity" circuits in the brain (Tulving & Kroll, 1995; Tulving, Markowitsch, Craik, Habib, & Houle, 1996; Tulving, Markowitsch, S. Kapur, Habib, & Houle, 1994). Another is the main focus of the present paper—namely, the idea proposed 2 years ago on the basis of the results of a number of studies from different laboratories, and given the name of *hemispheric encoding/retrieval asymmetry* (HERA) model, of prefrontal involvement in episodic-memory encoding and retrieval (Tulving, S. Kapur, Craik, et al., 1994).

In this article, we describe the HERA model, review the initial data together with more recent relevant evidence, and discuss the findings and their implications. The introduction of the HERA model will also serve as an illustration to the readers of the *Psychonomic Bulletin & Review* of how PET can be used to study cognitive functions such as memory. More detailed discussions of the PET method, its strengths and limitations, are available elsewhere (Buckner & Tulving, 1995; Posner & Raichle, 1994; Raichle, 1994a; Roland, Kawashima, Gulyas, & O'Sullivan, 1995).

## THE PET METHOD IN THE STUDY OF COGNITION

PET can measure different physiological brain processes, including oxygen consumption, glucose metabolism, interaction with drugs, and blood flow. Most cognitive PET studies have focused on cerebral blood flow, because this measure provides the most reliable index of moment-to-moment brain function (Raichle, 1994a). PET measures cerebral blood flow by detecting the distribution of a tracer (radioactive isotope) in the brain. The tracer is typically introduced into the vascular system of the brain by injecting it with a small amount of water into a vein in the arm. The tracer of choice for cognitive studies is oxygen 15. The tracer emits positrons which collide with electrons nearby, originating photons, which are registered by several rings of detectors surrounding the subject's head. The pattern of photon counts reflects the distribution of the tracer in the brain, the distribution of cerebral blood flow, and hence, the pattern of brain activity (for a review, see Posner & Raichle, 1994).

Because only small amounts of the tracer are necessary for reliable measurements, and because the tracer decays rapidly (the half-life of oxygen 15 is only 2 min), the exposure of subjects to radiation poses no significant risk. The fast decay and small amount of the tracer allow several consecutive scans in the same subject (i.e., within-subject designs). A standard cognitive PET experiment consists of 6–10 scans per subject, made 10–15 min apart. During each scan (or *injection*), the measurement of blood flow begins a few seconds after the injection, when the tracer reaches the brain. The cognitive task (e.g., reading

of words, recognition of pictures) usually commences 30–60 sec before the injection. This procedure ensures that the subject is immersed in the task when the actual blood flow measurement begins. Each scan lasts 40–70 sec.

The regional differences in blood flow yielded by the scan represent time-integrated measures of the neuronal activity during this period of time. All variations of brain activity during the scan *window* overlap on the same image, just as all light variations overlap on the same picture while the shutter in a photographic camera is open. Thus, PET can identify the total brain activity associated with a particular protracted task (e.g., reading of words), but not the activity associated with a particular trial within a task (e.g., reading a particular word). In this sense, PET can be said to have a limited temporal resolution. Combining PET with other techniques with a better temporal resolution, such as recording of event-related potentials, is one way to address this limitation. Another limitation is that it can be difficult to differentiate between essential and nonessential structures on the basis of PET data. As noted above, for this reason it may be fruitful to combine a PET approach and a lesion approach to the study of cognition.

Although regional cerebral blood flow (rCBF) data can be obtained and interpreted for single subjects, the signal-to-noise ratio in the blood flow data is usually increased by multiple scans per subject per condition, and by pooling the data for a number of subjects (Fox, Mintum, Reiman, & Raichle, 1988). Typically, 6–18 subjects are tested in a study, enough to obtain reliable data (Andreasen, Arndt, et al., 1995). Before the images of different subjects can be averaged together, individual differences in brain shape are controlled by warping each image to a common brain space. This process can be based on brain landmarks inferred from the PET images (Friston, Frith, Liddle, & Frackowiak, 1991), or on magnetic resonance images (MRIs) of the subjects (Worsley, Evans, Marrett, & Neelin, 1992). Both methods give comparable results (Arndt et al., 1995).

The PET image from a single scan cannot be interpreted, so PET data are reported in the form of comparisons between two or more scans. The most widely used method of comparison, referred to as the *subtraction method*, is based on *change-distribution analysis* (Fox, 1991; Fox et al., 1988). This method consists of comparing a *target* (critical, experimental, test) condition (or task) to a *reference* (baseline, control, neutral) condition (or task), and evaluating differences in activity between conditions on a pixel-by-pixel basis with the $t$ statistic (Friston et al., 1995). Because the subtraction method reveals differences in cerebral blood flow between two tasks, any description of data requires the specification of both tasks. To make an assertion about the rCBF pattern associated with a single task is as meaningless as a statement that children are smaller and smarter.

An important objective of PET *activation* studies, not always easy to achieve, is to select tasks for comparison that differ from one another only in terms of the process of interest (Buckner & Tulving, 1995; Petersen et al., 1988;

Roland, 1982; Roland et al., 1995). If the selection of tasks is successful, the *target − reference* subtraction image (the image yielded by subtracting blood flow measurements made in the reference condition from the target condition) indicates the brain regions that are differentially involved in the process or processes of interest.

Like arithmetic subtraction, comparisons of activity associated with one PET image with that associated with another can yield positive, negative, or no differences in a given brain region. A brain region that shows a higher level of blood flow during the target task than during the reference task is said to show *differential activation*, or simply *activation*. A brain region that shows a lower level of blood flow during the reference task than during the target task (i.e., a negative result of the *target − reference* subtraction) is said to show *deactivation*. Some writers prefer to report their results in terms of *activations* only. This is easy to do, because an A–B activation is identical with the B–A deactivation.

Brain regions that do not show up in a given subtraction are not differentially active, as defined by the particular statistical threshold. However, this does not necessarily mean that they do not influence task performance in different ways in the two tasks. It is quite possible for interregional covariance patterns to differ between two tasks, in the absence of any difference in absolute mean level of activity. The use of covariance-based approaches allows for the detection of such effects (McIntosh & Gonzalez-Lima, 1994; see also Friston, Frith, Liddle, & Frackowiak, 1993).

A further alternative to pairwise image subtraction in analyzing PET data is offered by the parametric approach, which involves systematic variation of an independent variable across scans. The analysis identifies brain areas in which blood flow is highly correlated with the variable. For example, Price et al. (1992), who manipulated auditory word presentation rate across five scans (10, 30, 50, 70, or 90 words per minute), found that blood flow in primary auditory areas increased linearly with the rate. Because of their obvious advantages, such as those of being more sensitive and of offering a more dynamic picture of brain activity, parametric and covariance-based methods are likely to become more widely used in the future. Up to now, the large majority of cognitive PET studies, including all those mentioned in connection with HERA in the present paper, have employed the subtraction method.

PET results—activations and deactivations—are presented in two ways: (1) graphically, as activation maps of the brain, and (2) numerically, in terms of the neuroanatomical locations of the *peaks* of active areas. The locations of these peaks are indicated by their three-dimensional $(x, y, z)$ coordinates in reference to a stereotaxic brain atlas. The industry standard right now is the Talairach and Tournoux atlas (1988). The use of this common metric for localization allows ready comparison of PET results across experiments and across laboratories, independently of writers' predilections in the matter of neuroanatomical nomenclature. It also allows

large-scale meta-analyses of PET data (e.g., Markowitsch & Tulving, 1994a, 1994b) that is an indispensable precondition for the ultimate goal of mapping the human brain/mind.

## THE HERA MODEL

The HERA model represents a theoretical hypothesis about an observed empirical regularity concerning the doubly asymmetrical involvement of prefrontal regions in memory tasks. It was suggested by the findings of the initial PET studies at Toronto (S. Kapur, Craik, et al., 1994; Moscovitch et al., 1995; Tulving, S. Kapur, Markowitsch, et al., 1994), was buttressed by the findings of related studies that had been done in other laboratories (see Tulving, S. Kapur, Craik, et al., 1994 ), and is now further supported by more recent studies. The model can be summarized as follows. The left prefrontal cortex is differentially more involved in retrieval of information from semantic memory, and in simultaneously encoding novel aspects of the retrieved information into episodic memory, than is the right prefrontal cortex. The right prefrontal cortex, on the other hand, is differentially more involved in episodic memory retrieval than is the left prefrontal cortex.

The HERA model accounts for the asymmetric pattern of PET activation in the prefrontal cortex by means of two distinctions made in cognitive psychology of memory: (1) semantic versus episodic memory (Tulving, 1972, 1983), and (2) encoding versus retrieval processes (e.g., Tulving & Pearlstone, 1966). Semantic memory is concerned with people's general knowledge of the world (Lockhart, Craik, & Jacoby, 1976), whereas episodic memory is concerned with conscious recollection of personally experienced events (Tulving, 1993). *Encoding* refers to the processes by which information is incorporated into memory, and *retrieval* refers to the processes involved in actualizing (ecphorizing) the information stored in memory.

Left prefrontal involvement in episodic-memory encoding was initially observed in a study by S. Kapur, Craik, et al. (1994). In that study, rCBF was measured with $^{15}$O-labeled water while subjects, healthy male university students, engaged either in a *shallow* or a *deeper* encoding of single nouns according to the standard levels-of-processing paradigm (Craik & Tulving, 1975). During some scans, the subjects made shallow orthographic judgments concerning the presence or absence of the letter *a* in the presented word. During others, they made deeper semantic living/nonliving judgments about the presented nouns. Other conditions were held constant between the two types of encoding. A long string of experiments has shown that the differences in encoding operations lead to substantial differences in the performance in a subsequent explicit memory test (Lockhart & Craik, 1990). In the S. Kapur, Craik, et al. (1994) study, too, subsequent yes/no recognition, measured after the PET scans were completed, showed an advantage for seman-

tically encoded words over orthographically encoded words: The corresponding mean hit minus false positive rates were 0.50 and 0.32.

The PET data showed that when the blood flow associated with shallow encoding was subtracted from that associated with the deeper encoding (*deep − shallow* subtraction), an extensive region in the left prefrontal cortex was differentially activated. These results revealed an association between blood flow data and encoding processes. Relative to shallower encoding, deeper processing at encoding (1) was accompanied by a prominent left prefrontal activation, and (2) resulted in higher recognition of the studied material. This prefrontal activation was asymmetric: There was no hint of any differences between the encoding conditions in right prefrontal regions. Thus, the data suggested that the left prefrontal cortex plays a special role, or is related to brain structures that play a special role, in encoding of episodic memory information.

Two other PET studies done at about the same time were designed to examine rCBF differences associated with episodic-memory retrieval, or more specifically, recognition. In one (Tulving, S. Kapur, Markowitsch, et al., 1994), healthy young male volunteers' brains were scanned while they recognized sentence-like constructions (e.g., "a servant in name only—BRIDESMAID"). In some scans the sentences were novel, in the sense that the subjects had never heard them before; in others they were familiar, in that the subjects had listened to their presentation the day before. All other conditions were held constant between the two types of scan. In the other recognition study (Moscovitch, S. Kapur, Köhler, & Houle, 1995), volunteers' brains were scanned while they performed a perceptual matching task or forced-choice recognition tasks with displays of line drawings of three objects (Snodgrass & Vanderwart, 1980). In the recognition tasks, some displays were identical with displays that the subjects had studied. Others displays were altered with respect to the spatial position of the objects or the identity of one of the three objects.

The critical subtractions in both experiments showed higher activation associated with the target task than with the baseline task in a number of cortical regions. Recognition of familiar sentences in the Tulving, S. Kapur, Markowitsch, et al. (1994) study involved a prominent strip of increased activation in the right dorsolateral prefrontal cortex that extended from Brodmann area 10 through areas 46 and 9 to area 6. There was also increased activation in the left frontal area, but most of it was situated along the cingulate sulcus, near the medial prefrontal cortex. In the Moscovitch et al. (1995) study, subtracting activity associated with the matching task from the retrieval tasks yielded, in addition to posterior activations, differential activation of the right prefrontal cortex. However, left frontal regions were not differentially activated during retrieval. Thus, asymmetric activation of the frontal lobes was also observed in the two retrieval studies, but the pattern was opposite to that seen in the S. Kapur,

Craik, et al. (1994) encoding study: during retrieval (recognition), right prefrontal regions were more active than left prefrontal regions.

## SEMANTIC RETRIEVAL AND EPISODIC ENCODING

The asymmetric pattern of prefrontal activation in these three studies prompted a review of the available literature in search of comparable findings regarding the involvement of the frontal lobes in encoding and retrieval. An initial problem was the fact that no other PET studies had yet been conducted to study episodic encoding processes. It was possible to think, however, that several PET studies that had been conducted to study other cognitive functions, including speech and language, would qualify as memory encoding studies even though no memory tests had been given or mentioned in those studies.

The well-known and widely used *verb-generation* task, introduced by Petersen et al. (1988), illustrates this reasoning. In this task, subjects see or hear different nouns, presented at a rate of, say, 1.5 sec per item, and they have to respond by producing meaningfully related verbs (e.g., hear "ladder," say "CLIMB"; or see "cup," say "DRINK"). During the scan, subjects generate a whole series of verbs to the presented nouns. In the corresponding reference task (noun-repetition), subjects see or hear nouns and have to repeat back the same word (e.g., hear "PAPER," say "paper"). From the perspective of PET, the verb-generation task and the noun-repetition task perform two functions concurrently: retrieval of information from semantic memory and encoding of information into episodic memory. For the subject to be able to respond with an appropriate verb to a presented stimulus noun he/she must retrieve relevant information from semantic memory. But information about this event is also encoded into episodic memory: The subject, with a certain probability, can subsequently remember that he/she heard "car" and said "DRIVE." Whether or not subjects have been instructed to memorize the material under these conditions is immaterial. It is the nature of encoding processes, or encoding operations, rather than the subject's intention to learn, that determines the retrievability of stored information (Craik & Lockhart, 1972; Hyde & Jenkins, 1969). We surmised, therefore, that the verb-generation task is a more effective encoding task than the noun-repetition task. Subjects would be expected to remember a larger proportion of nouns following the verb-generation task than following the noun-repetition task. If so, the left-frontal activation in verb-generation tasks that had been reported (Petersen et al., 1988; Wise et al., 1991) could be hypothesized to reflect not only semantic retrieval processes but also episodic-memory encoding processes.

To verify the conjecture regarding the verb-generation task, the Washington University noun–verb pairs were used in a standard levels-of-processing task (Craik & Tulving, 1975). Subjects, 82 undergraduates, participated in two sessions. In the first session, they were exposed to four lists of 20 printed nouns each. In two of the lists, their instructions were to write appropriate verbs as responses to the nouns (deeper encoding task). In the other two lists, the instructions were to copy (repeat) the nouns (shallower encoding task). Speed of completion was emphasized, and no mention was made of any later test. The conditions were counterbalanced over subjects and lists. The second session was held 5 days later. The subjects were given an unexpected yes/no recognition test consisting of the 80 original nouns plus 80 new nouns, randomly mixed. They had to decide whether or not they had seen a given noun in any of the lists presented five days before. The experiment yielded the expected outcome: Recognition of nouns, measured in terms of hit minus false-positive rates, was .39 following the generation of verbs to the nouns and .15 following repeating the nouns. Thus it looked as if verb generation was a more effective or deeper incidental episodic encoding task. Insofar as the Washington University PET studies had shown the verb-generation task to be associated with higher activation of the left prefrontal cortex than that observed in the noun-repetition task, the combined pattern of data corresponded nicely to that found in the initial PET study of encoding (S. Kapur, Craik, et al., 1994): Deeper encoding is associated with higher left than right frontal neuronal activity, and it also enhances subsequent episodic-memory retrieval.

## EPISODIC ENCODING AND LEFT PREFRONTAL ACTIVATION

The finding that the verb-generation task, nominally a task that involves retrieval of semantic-memory information, is a more efficient episodic encoding task than noun repetition implies that PET studies may reveal rCBF associated with episodic encoding, even when they are not explicitly designed to do so. The idea is that any two tasks that differ in their episodic-memory consequences act like verb-generation and noun repetition, or like deeper and shallower encoding tasks. For example, a comparison between visually presented noun repetition and a baseline task in which subjects merely observe cross hairs on the screen would be expected to produce a blood flow pattern similar to that produced by the comparison between verb generation and noun repetition, because noun repetition will produce more episodic encoding (and more semantic retrieval) than will watching the cross hairs. Facts show that it does (Petersen et al., 1990). Armed with these kinds of insights, and at least partly supported by empirical facts, we searched the existing PET literature, identified a number of studies that fitted the prescription of "incidental encoding studies," and reported them (Tulving, S. Kapur, Craik, et al., 1994). These results are summarized in Table 1 together with the listing of findings from more recent episodic encoding studies, both "incidental" and "intentional." (For the purposes of the present discussion, we ignore posterior cortical, cerebellar, and subcortical PET activations reported in these studies.)

In the 18 listed studies, comprising a total of 21 comparisons, rCBF was measured while subjects were en-

**Table 1**
**Prefrontal PET Activations Associated With Incidental and**
**Intentional Episodic Memory Encoding**

| Study | Target Task | Reference Task | Prefrontal Cortex | |
|---|---|---|---|---|
| | | | Left | Right |
| *Incidental* | | | | |
| Petersen et al. (1988) | verb generation | noun repetition | + | − |
| Petersen et al. (1990) | word reading | fixation | + | − |
| Raichle et al. (1994) | | | | |
|    Trial 1 | verb generation | noun repetition | + | − |
|    Trial 9 | verb generation | noun repetition | − | − |
| Wise et al. (1991) | verb generation | rest | + | − |
| Frith et al. (1991a) | word generation | rest/count/lexical decision | + | − |
| Frith et al. (1991b) | word generation | word repetition | + | − |
| Fletcher et al. (1995) | instance generation | category repetition | − | − |
| Buckner, Petersen, et al. (1995) | word-stem completion | fixation | + | − |
| Bäckman et al. (1995) | word-stem completion | word-stem viewing | − | − |
| S. Kapur, Craik, et al. (1994) | semantic decision | orthographic decision | + | − |
| Démonet et al. (1992) | semantic decision | phonetic decision | + | − |
| Demb et al. (1995)† | semantic task | easy nonsemantic task | + | − |
| Demb et al. (1995)† | semantic task | difficult nonsemantic task | + | − |
| *Intentional* | | | | |
| Shallice et al. (1994)* | category-instance learning | number hearing | + | − |
| Fletcher et al. (1995)* | category-instance learning | number hearing | + | − |
| S. Kapur et al. (1996) | noun-pair learning | noun-pair reading | + | − |
| Haxby et al. (1996)* | face learning | face matching | + | − |
| Grady et al. (1995)* | face learning | face matching | + | − |
| Owen et al. (in press) | object-location learning | object-location Rn | + | − |
| Owen et al. (in press) | location learning | location Rn | + | − |

Note—Statistically significant evidence of prefrontal involvement is indicated by +, absence of similar evidence by −. *Studies listed consecutively with asterisks have overlapping data. †fMRI studies.

gaged in target activities that bring about episodic encoding of information, whether incidentally or intentionally, and reference activities that bring about no or less episodic encoding. For each study, the target and reference tasks are indicated. A few studies, asterisked in Table 1, report identical or overlapping data, but most of the comparisons are independent. The question of interest is whether the level of blood-flow in the prefrontal cortex in these studies was higher in the target than in the reference task, that is, whether the *target − reference* subtraction yielded a significant activation in the prefrontal cortex: left, right, both, or neither. A plus sign in the appropriate column indicates the presence of such an activation; a minus sign signifies its absence.

Table 1 shows that frontal encoding activations in the listed studies, when they were observed at all, were exclusively restricted to the left hemisphere. This pattern held for both incidental and intentional encoding. Because these studies, with a single exception (the related articles by Haxby et al., in press, and Grady et al., 1995), used verbal materials, it is not entirely clear whether the pattern would hold for other kinds of materials, but the fact that Grady and Haxby, and their colleagues, obtained left-frontal encoding activation with faces suggests that the pattern may turn out to be more general.

We briefly note some details of a few of the studies listed in Table 1. The target task in several incidental encoding studies involved word generation. Frith et al.

(1991a; Frith, Friston, Liddle, & Frackowiak, 1991b) used a verbal fluency task, Raichle et al. (1994) and Wise et al. (1991) used verb generation, the Fletcher et al. (1995) study involved generation of instances from category names (e.g., "US president"–"CLINTON"), and Buckner, Petersen, et al. (1995) and Bäckman et al. (1995) used a (nonprimed) stem-completion task. It is reasonable to assume that all these different generation tasks involved more semantic memory retrieval, and hence led to deeper episodic encoding, than did their respective baseline task. Petersen et al. (1988) compared noun reading with the reference task of looking at cross hairs on the screen. Noun reading, or noun "repetition," is a shallow encoding task in comparison with more elaborate semantic tasks such as generation. However, as we argued earlier, word reading should produce more episodic encoding than should observing a cross-hair fixation point.

The Demb et al. (1995) study was done with functional magnetic resonance imaging (fMRI) rather than PET. Although the technique is somewhat different, fMRI also provides information about local changes in blood flow, and the logic of data analysis is similar to that of the subtraction method. Demb et al. used a semantic target task (abstract/concrete judgments) and two nonsemantic reference tasks, an easy one, and a difficult one. Both *target − reference* comparisons yielded similar left prefrontal activations, thus suggesting that this activation is largely independent of task difficulty.

All studies involving an intentional encoding condition found increased left prefrontal activation. S. Kapur et al. (1996) compared a condition in which subjects tried to learn meaningful paired associates (e.g., *penguin–tuxedo*) to one in which they simply silently read similar word pairs. It was found that the left prefrontal cortex was more involved in the former task. In another study of paired associate learning (Fletcher et al., 1995; Shallice et al., 1994), subjects tried to learn the instances of category–instance pairs (e.g., *poet–Browning*). This task was performed simultaneously with an easy distractor task (assumed not to impair episodic encoding) or a difficult distractor task (assumed to impair episodic encoding). When the condition involving episodic encoding plus easy distraction was compared with the reference condition (listening to numbers), left prefrontal activation was observed. In contrast, when encoding plus difficult distraction was compared with the reference condition, no left prefrontal activation was observed. This result helps to constrain the interpretation of the left-frontal activation to that of episodic encoding.

Three entries in Table 1 show missing prefrontal encoding activation. We believe that other such "exceptions" will be found as more studies accumulate. From the point of view of HERA, the critical issue is the claim that encoding is more associated with left frontal activity. The data strongly suggest that the claim is valid. It is difficult to explain why some studies do not show the expected results, but we will nevertheless offer some tentative explanations for the exceptions listed in Table 1. If nothing else, the discussion of the exceptions help to illustrate the necessity of considering both the target and the reference tasks when one is interpreting PET data.

As noted above, the target task in the Fletcher et al. (1995) study involved generation of instances from category names, and the reference task required subjects to repeat the category name. It is possible to speculate that subjects covertly generated instances also in the repetition task, thereby canceling out the left prefrontal involvement in the subtraction. A similar explanation may be used to account for the absence of left prefrontal activation in the Bäckman et al. (1995) study in which word-stem completion was compared with word-stem viewing; the latter task may engender spontaneous, covert stem completion. The third apparent exception to the general left-frontal encoding pattern, the verb-generation study by Raichle et al. (1994), allows a somewhat more informed conjecture. The important design feature of that study concerned the manipulation of the stage of practice at which PET measures were obtained. When the subjects were performing the verb-generation task for the first time, the subtraction of the noun-repetition reference condition from verb generation yielded the now standard outcome: a region of activation in the left prefrontal cortex, without similar activation in the right frontal lobe. However, this pattern held only for naive subjects. After an additional eight practice trials in generating verbs to the same set of nouns, the left prefrontal activation disappeared. This disappearance was at least partly attribut-

able to the increased familiarity of the materials rather than to increased familiarity with the procedural aspects of the task: When the "practiced" subjects had to generate verbs to a novel set of nouns, the left prefrontal activation reappeared.

The disappearance of the left prefrontal activation after practice with the same items implies that not every act of semantic-memory retrieval is encoded into episodic memory, only novel events are. Events such as seeing a noun and generating a related verb to it tend to be novel and are therefore encoded for long-term storage. When the same nouns have appeared repeatedly, in the same situation and context, and have elicited the same verb repeatedly, the noun–verb events cease to be novel, and cease to be encoded into episodic memory. According to this reasoning, the left-frontal encoding operations, exemplified by the studies in Table 1, are performed on the incoming information to the extent that it is situationally novel. To what extent novelty assessment relies on frontal mechanisms is not yet clear (Knight, 1984, in press). There is some evidence that the brain's decisions about the novelty of stimuli may be subserved by regions outside the frontal lobes (Tulving, Markowitsch, et al., 1994; Tulving et al., 1996; Wilson & Rolls, 1993). There is also behavioral evidence that the novelty of presented items, when the frontal encoding operations are held constant, affects the items' memorability: subsequent recognition of novel words is higher than that of familiar words (Kinsbourne & George, 1974; Tulving & Kroll, 1995). Alternatively, following repeated trials of verb generation based on the same nouns (Raichle et al., 1994), the amount of semantic retrieval processes involved may not be significantly different from simple word repetition, and hence the degree of left frontal involvement is the same.

In summary, the pattern of data in Table 1 suggests that both incidental and intentional episodic encoding is associated with increased neuronal activity in left rather than right prefrontal regions. The generalization is secure for verbal materials, but so far only promising for nonverbal information. In general, however, Table 1 provides good empirical support for the asymmetrical frontal localization of encoding. We now look at the evidence for asymmetry of retrieval.

## EPISODIC RETRIEVAL AND RIGHT PREFRONTAL ACTIVATION

Table 2 summarizes the now available evidence that speaks to the issue of the association between right-frontal activation and episodic retrieval. In the 25 listed studies, comprising a total of 32 comparisons, rCBF was measured with PET while subjects were engaged in target tasks in which previously encoded verbal or nonverbal information was retrieved by recall or recognition, and in comparable reference tasks. The outcomes of the comparisons are indicated by larger and smaller pluses, indicating larger or smaller activations, and minuses, indicating absences of significant activations. A few stud-

ies listed in Table 2 report identical or overlapping data, but most of the comparisons are independent.

The retrieval studies used a variety of to-be-remembered materials. The verbal target tasks included cued recall with word-stem cues (Bäckman et al., 1995; Buckner, Petersen, et al., 1995; Schacter et al., 1996; Squire et al., 1992), category-cued recall (Fletcher et al., 1995; Shallice et al., 1994), word-pair recall (Buckner, Raichle, et al., 1995; Cabeza et al., 1995), and word recognition (Andreasen, O'Leary, et al., 1995b; Cabeza et al., 1995; S. Kapur et al., 1995; Nyberg et al., 1995). The nonverbal target tasks involved recognition of faces (Grady et al., 1995; Haxby et al., 1993, 1996; N. Kapur et al., 1995), complex colored pictures of scenes (Tulving, Markowitsch, et al., 1994; Tulving et al., 1996, colored visual patterns (Roland et al., 1995), identities or locations of line drawings of objects (Moscovitch et al., 1995), and odors (Jones-Gottman, Zatorre, Evans, & Meyer, 1993).

The corresponding reference tasks generally involved exposure to the same kinds of stimulus materials.

The whole pattern of data in Table 2 suggests that a large majority of retrieval studies has yielded results showing asymmetrical activation of prefrontal regions. The asymmetry takes either of two forms—(1) activation on the right, no activation on the left, or (2) greater activation on the right than on the left—but, insofar as all blood flow data from image subtractions are relative, the two forms tell the same story: The right prefrontal cortex is more involved in episodic retrieval than is the left prefrontal cortex.

As was the case with the encoding studies, there are exceptions to the general right-frontal retrieval pattern. One of these, a study of face recognition by N. Kapur et al. (1995), showed no prefrontal activation. We have no ready explanation for the discrepancy between this study and others shown in Table 2 (Andreasen, O'Leary,

Table 2
Prefrontal PET Activations Associated With Verbal and Nonverbal Episodic Memory Retrieval

| Study | Target Task | Reference Task | Prefrontal Cortex Left | Right |
|---|---|---|---|---|
| *Verbal* | | | | |
| Squire et al. (1992)* | word-stem cued recall | word-stem completion | − | + |
| Buckner, Petersen, et al. (1995)* | | | | |
| Different case | word-stem cued recall | word-stem completion | − | + |
| Auditory | word-stem cued recall | word-stem completion | − | + |
| Buckner, Raichle, et al. (1995) | cued recall | word repetition | + | + |
| Shallice et al. (1994)* | cued recall | instance generation | − | + |
| Fletcher et al. (1995)* | cued recall | instance generation | − | + |
| Schacter et al. (1996) | word-stem cued recall | word-stem completion | + | + |
| Bäckman et al. (1995) | word-stem cued recall | word-stem completion | + | + |
| Cabeza et al. (1995) | cued recall | word-pair reading | − | + |
| Petrides et al. (1995) | cued recall | word repetition | − | + |
| Petrides et al. (1995) | free recall | word repetition | + | + |
| Tulving, S. Kapur, Craik, et al. (1994) | studied sentence Rn | nonstudied sentence Rn | + | + |
| S. Kapur et al. (1995) | word Rn | semantic decision | + | + - |
| Andreasen, O'Leary, et al. (1995b) | word Rn | word reading | + | + |
| Nyberg et al. (1995) | studied (concep.) word Rn | word reading | − | + |
| Nyberg et al. (1995) | studied (percep.) word Rn | word reading | − | + |
| Nyberg et al. (1995) | nonstudied word Rn | word reading | − | + |
| Cabeza et al. (1995) | word-pair Rn | word-pair reading | − | + |
| *Nonverbal* | | | | |
| Haxby et al. (1993)* | face Rn | face matching | − | + |
| Haxby et al. (1996)* | face Rn | face matching | − | + |
| Grady et al. (1995)* | face Rn | face matching | − | + |
| N. Kapur et al. (1995) | face Rn | face gender decision | − | − |
| Andreasen et al. (1995a) | face Rn | face gender decision | − | + |
| Tulving, Markowitsch, et al. (1994)* | studied picture Rn | nonstudied picture Rn | + | + |
| Tulving et al. (1996)* | studied picture Rn | nonstudied picture Rn | + | + |
| Roland et al. (1995) | visual pattern Rn | visual pattern learning | − | + |
| Moscovitch et al. (1995) | object identity Rn | object matching | − | + |
| Moscovitch et al. (1995) | object position Rn | object matching | − | + |
| Schacter et al. (1995) | abstract object Rn | object perception | − | − |
| Owen et al. (in press) | object-location Rn | object-location learning | − | + |
| Owen et al. (in press) | location Rn | location learning | − | + |
| Jones-Gottman et al. (1993) | odor Rn | no-odor inhalation | − | + |

Note—Statistically significant evidence of prefrontal involvement is indicated by +, absence of similar evidence by −. A smaller plus sign indicates prefrontal cortex with smaller or weaker activation, according to the authors.    *Studies listed consecutively with asterisks have overlapping data.    Rn, recognition; concep., conceptual processing at study; percep., perceptual processing at study.

et al., 1995a; Haxby et al., 1996; Grady et al., 1995) that did yield asymmetric right-frontal activation associated with recognition of previously studied faces. In two other studies (Bäckman et al., 1995; Schacter et al., 1996), in which stem-cued recall was used as the target task and (nonprimed) stem completion as the reference task, prefrontal activations were found bilaterally. Again, the reason for the discrepancy between this outcome and the outcomes of the studies by Squire et al. (1992) and Buckner, Petersen, et al. (1995), in which the same comparison tasks were used, and in which the right-frontal asymmetry was observed, are not clear and must await clarification by future studies. Petrides, Alivasatos, and Evans (1995) found bilateral prefrontal activation in a comparison of free recall and word repetition, and right prefrontal activation only in a comparison of paired-associate cued recall and word repetition. The subjects were highly practiced on the paired-associate task, so this task may have involved less semantic retrieval than the free-recall task did (cf. Demb et al., 1995; Raichle et al., 1994).

More generally, there are at least three possible reasons for the observation of left-frontal activation in comparisons that are classified as "retrieval" by the experimenter. First, left-frontal activation would be expected to be present in comparisons in which the target task involves encoding to the extent that the reference task does not. Second, because encoding processes are not complete following a single presentation trial, and continue over trials, one would expect to see activation on the left during recall and recognition tests that signifies additional encoding. Andreasen, O'Leary, et al. (1995b) observed more left-frontal activation when they tested their subjects' recognition of relatively *underlearned* (single-trial presentation) in comparison with recognition of *overlearned* materials, and indeed they interpreted this finding by assuming that underlearned materials are more

likely to undergo further encoding than are well-learned materials. In the Raichle et al. (1994) study, as we have discussed, the prominent left-frontal activation essentially vanished over some 15 min of practice on the task with the same items, further supporting the argument. Third, in tasks such as stem-cued recall, retrieval of episodic information may be mediated by retrieval of semantic information ("What words would complete this stem?"), and such semantic retrieval would engage left-frontal regions. Finally, activations in PET studies are determined not only by the comparison tasks used, but also by the power and sensitivity of the design and variability among the subjects. Therefore, the absence of left-frontal activation in nominal retrieval studies is important primarily because it serves to underline the retrieval asymmetry in the frontal lobes. Such absences do not mean, and must not be interpreted as suggesting, that the left-frontal regions are not involved in episodic retrieval (Buckner & Tulving, 1995).

In summary, the pattern of data in Table 2 suggests that episodic retrieval is associated with higher neuronal activity in right rather than left prefrontal regions. The pattern seems to hold rather generally for different kinds of materials (words, sentences, faces, drawings of objects, odors); for different tests, such as recall and recognition; and for material tested after short (30-sec) and longer (24-h, 7-day) retention intervals. Thus, the studies summarized in Table 2 provide good empirical support for an asymmetrical frontal localization of episodic retrieval.

Figure 1 presents a graphic overview of most of the data that we have considered in this paper. The peak activations of the studies that reported the Talairach and Tournoux (1988) stereotactic coordinates are projected onto the left and right lateral surface of a schematic brain. Coordinates were not available for a few studies, and some others provided more than a single peak. Neuronal activ-
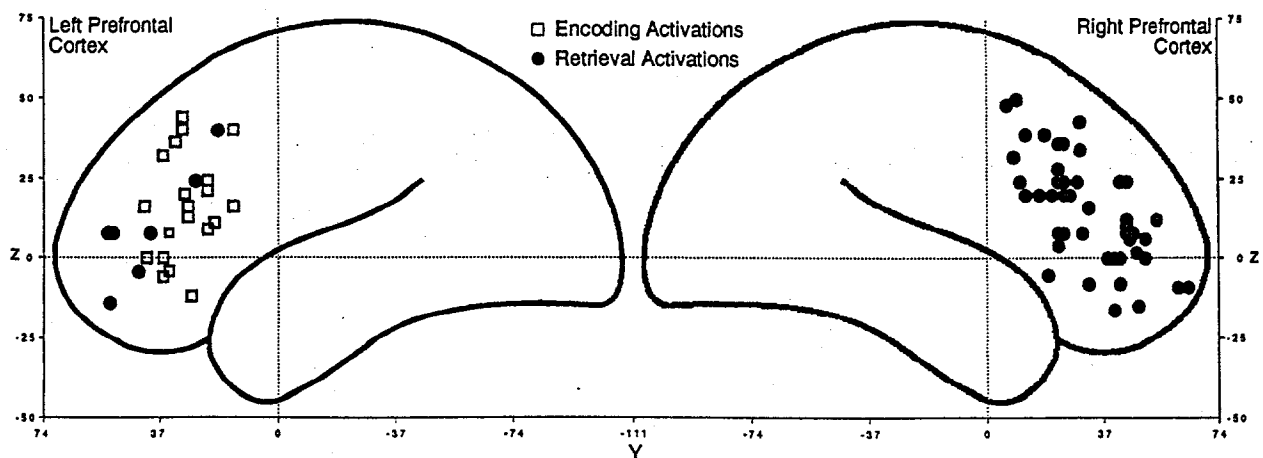


Figure 1. Significant encoding and retrieval activation peaks from subtractions shown in Tables 1 and 2. In the case of subtractions producing more than one significant peak, all the peaks were included to reflect the extent of the activation. The peaks are projected onto the left and right lateral surfaces according to the *y* (posterior/anterior) and *z* (inferior/superior) coordinates of the brain atlas of Talairach and Tournoux (1988).

ity related to encoding is indicated by empty squares, and activity related to retrieval is indicated by filled circles. These data illustrate (1) the general frontal hemispheric asymmetry as specified in HERA, and (2) the variability of loci from different studies within the hemispheres.

It is important to notice that a hemispheric encoding/retrieval asymmetry may also exist outside the frontal lobes. Examination of the studies that included an intentional encoding condition, in which the relevant subtraction should have canceled out activations specifically related to language processing, shows that activation was found in the left temporal lobe in all the studies and that activation was found in the right temporal lobe in only one (Fletcher et al., 1995). In addition, in all the studies, increased activation was found in the anterior cingulate cortex. In one of these studies (Grady et al., 1995), the activation was located along the midline, whereas in the others the activation was left-sided. With respect to retrieval, increased activation in the parietal lobes has been found in several studies. In some cases, the activation has been bilateral (see, e.g., Schacter et al., 1995; Tulving, S. Kapur, Markowitsch, et al., 1994). In other cases, unilateral activation has been observed, and in these cases it has predominantly been located in the right hemisphere (Grady et al., 1995; N. Kapur et al., 1995; S. Kapur et al., 1995; Moscovitch et al., 1995).

Moreover, recent data from our laboratory (Cabeza et al., in press; S. Kapur et al., 1996) confirm the findings of asymmetry beyond the frontal regions. The data are provided by a direct within-subjects comparison of an intentional encoding condition with a retrieval condition. During encoding, subjects studied related word pairs; during retrieval they performed a yes/no recognition test on presented word pairs. The results of this comparison are presented in Figure 2: encoding was associated with increased activation in several regions in the left hemisphere, including the prefrontal cortex. Re-

trieval, on the other hand, was associated with right-sided activation in frontal as well as temporal-parietal regions. Thus, the results of this comparison support the idea of an encoding/retrieval asymmetry that extends beyond the frontal regions.

## RELATED OBSERVATIONS

In addition to the data in relation to HERA that were derived from formal memory studies and that were summarized in Tables 1 and 2, other observations from less formal "memory experiments" have lent credibility to the model. We will mention some of them briefly.

Kosslyn et al. (1994) reported a PET study of perceptual identification of visually presented objects, and, among other locations, observed prefrontal activation. They interpreted these in terms of the "top-down perceptual processing" component subsystem of object identification. In the context of the present discussion, the left prefrontal activation can be seen as indicating episodic memory encoding. The right-frontal activation can be attributed to the retrieval processes, because the presented objects were repeated during the scan (S. Kosslyn, personal communication, October 7, 1993) and were presumably recognized as such by the subjects.

Tamas, Shibasaki, Horikoshi, and Ohye (1993) did a PET study to examine metabolic activation of the brain associated with speech. Their target task was "speech-from-memory": subjects were asked to talk aloud about the previous day's experiences; their reference task was resting. The *speech — rest* subtraction yielded, among other active loci, a unilateral activation of the right frontal lobe (frontal operculum).

A third example is provided by a study of the role of the right hemisphere in the interpretation of figurative aspects of language (Bottini et al., 1994). A comparison of a condition in which subjects decided whether sen-
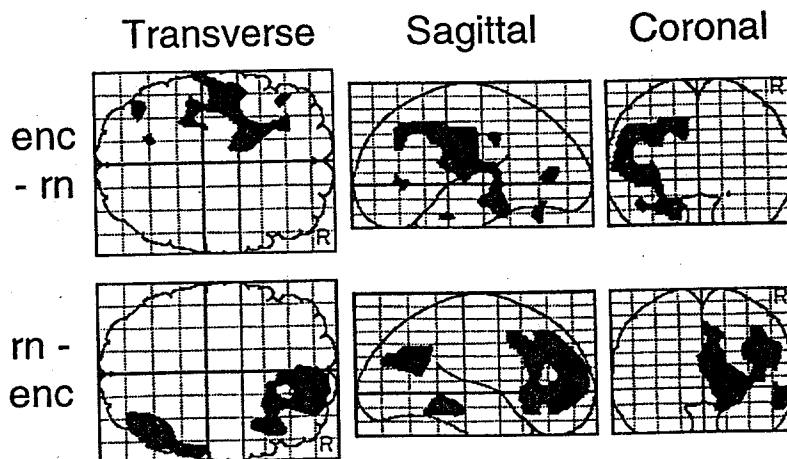


Figure 2. Results of a direct within-subject comparison between encoding and retrieval processes. The three brain projections at the top (transverse, sagittal, and coronal) correspond to the subtraction *encoding minus recognition*. The three brain projections at the bottom (transverse, sagittal, and coronal) correspond to the subtraction *recognition minus encoding*.

tences were plausible metaphors with a reference condition in which subjects decided whether sentences were plausible at the literal level of analysis showed increased right prefrontal activation associated with the metaphor task. As a possible interpretation of this finding, the authors suggested that the interpretation of metaphors may sometimes involve personal experiences—that is, retrieval of information from episodic memory.

In a study evaluating whether measuring blood flow with PET could be used for assessment of language dominance, Pardo and Fox (1993) subtracted activation associated with word reading from that associated with the verb generation task and compared activity in right and left anterior frontal cortex. In keeping with HERA, they found higher left-sided than right-sided activity in 9 out of 10 patients.

A final example is provided by a case study of a patient suffering from transient global amnesia (Baron et al., 1994). Consistent with findings of right frontal involvement in episodic memory retrieval, PET scanning in the acute phase of the episode showed right frontal cortex hypometabolism. The patient was PET scanned again after recovering from the amnesia, and no evidence of hypometabolism was found at this time.

## CONCLUSIONS

The studies we have reviewed here provide good support for the HERA model. Episodic encoding processes engage the left-frontal regions more than the right-frontal regions, whereas episodic retrieval processes engage the right-frontal regions more than left-frontal regions. Admittedly, HERA provides only a gross description of the relation between two sets of concepts, one concerning physiological processes described neuroanatomically (differences in rCBF in left and right prefrontal cortex), the other having to do with psychological processes described behaviorally (the distinction between encoding and retrieval processes of episodic and semantic memory). Clearly such a picture, painted with a broad brush, is only a beginning.

In this paper we have overlooked many important aspects and possible extensions of HERA. We have completely disregarded the typically numerous PET activations in other regions of the brain that have been reported by all reviewed PET studies. We have not discussed the well-known fact that the prefrontal regions are large and that they comprise a variety of more specific cytoarchitectonic, hodological, and neurochemical regions (Stuss & Benson, 1986), and we have neglected the fact that the studies whose data support HERA have displayed considerable variability in more precise localization of memory functions within the frontal regions. A promising beginning in trying to define selective involvement in memory retrieval of specific prefrontal regions has recently been made by Buckner (1996). We have treated both encoding and retrieval as kinds of unitary processes, although it is rather clear that both consist of several

more specific subprocesses. We have not brought into our discussion some of the latest, "hottest" data suggesting a specific psychological role of the right prefrontal regions in episodic retrieval, one that can be described in terms of concepts such as "retrieval attempt," and "retrieval mode" (S. Kapur et al., 1995; Nyberg et al., 1995; Schacter et al., 1996). We have not discussed the relationship of the PET findings of a strong involvement of the frontal lobes in episodic memory to results from lesion studies. Although frontal lesions impair episodic memory performance on recall as well as recognition tests (Wheeler, Stuss, & Tulving, 1995), patients with frontal lesions are not amnesic. We have not addressed possible reasons for the asymmetric involvement of the frontal lobes in episodic encoding and retrieval. The fact that the asymmetry has been shown for a variety of different materials indicates that it is not simply a question of verbal versus nonverbal processing (Owen, Milner, Petrides, & Evans, in press)—at least not in a simple sense. Preliminary observations from our laboratory indicate that right frontal regions may inhibit activity in left frontal cortex during retrieval (Nyberg et al., in press), whereas the opposite may hold true during encoding. If true, these observations would suggest that encoding and retrieval operate in an antagonistic manner. All these, and many other issues, undoubtedly will be the subjects of thorough examination and discussion in the years to come. We have little doubt that future research will reveal a much richer and more complex picture than HERA in its present form suggests.

### REFERENCES

ANDREASEN, N. C., ARNDT, S., CIZADLO, T., O'LEARY, D. S., WATKINS, G. L., BOLES PONTO, L. L., & HICHWA, R. D. (1995). Sample size and statistical power in [$^{15}O$] $H_2O$ studies of human cognition. Manuscript submitted for publication.

ANDREASEN, N. C., O'LEARY, D. S., ARNDT, S., CIZADLO, T., HURTIG, R., REZAI, K., WATKINS, G. L., BOLES PONTO, L. L., & HICHWA, R. D. (1995a). Neural substrates of face recognition. Manuscript submitted for publication.

ANDREASEN, N. C., O'LEARY, D. S., ARNDT, S., CIZADLO, T., HURTIG, R., REZAI, K., WATKINS, G. L., BOLES PONTO, L. L., & HICHWA, R. D. (1995b). Short-term and long-term verbal memory: A positron emission tomography study. Proceedings of the National Academy of Science, 92, 5111-5115.

ARNDT, S., CIZADLO, T., ANDREASEN, N. C., ZEIEN, G., HARRIS, G., O'LEARY, D. S., WATKINS, G. L., BOLES PONTO, L. L., & HICHWA, R. D. (1995). A comparison of approaches to the statistical analysis of [$^{15}O$]$H_2O$ PET cognitive activation studies. Journal of Psychiatry, 7, 155-168.

BÄCKMAN, L., ALMKVIST, O., ANDERSSON, J., NORDBERG, A., WINDBLAD, B., REINECK, R., & LÅNGSTRÖM, B. (1995). Brain activation in young and older adults during implicit and explicit retrieval. Manuscript submitted for publication.

BARON, J. C., PETIT-TABOUÉ, M. C., LE DOZE, F., DESGRANGES, B., RAVENEL, N., & MARCHAL, G. (1994). Right frontal cortex hypometabolism in transient global amnesia: A PET study. Brain, 117, 545-552.

BENSON, D. F. (1988). Classical syndromes of aphasia. In F. Foller & J. Grafman (Eds.), Handbook of neuropsychology (Vol. 1, pp. 267-280). Amsterdam: Elsevier.

BOTTINI, G., CORCORAN, R., STERZI, R., PAULESU, E., SCHENONE, P., SCARPA, P., FRACKOWIAK, R. S. J., & FRITH, C. D. (1994). The role of

the right hemisphere in the interpretation of figurative aspects of language: A positron emission tomography activation study. *Brain*, 117, 1241-1253.

BUCKNER, R. (1996). Beyond HERA: Contributions of specific prefrontal brain areas to long-term memory retrieval. *Psychonomic Bulletin & Review*, 3, 149-158.

BUCKNER, R. L., PETERSEN, S. E., OJEMANN, J. G., MIEZIN, F. M., SQUIRE, L. R., & RAICHLE, M. E. (1995). Functional anatomical studies of explicit and implicit memory retrieval tasks. *Journal of Neuroscience*, 15, 12-29.

BUCKNER, R. L., RAICHLE, M. E., MIEZIN, F. M., & PETERSEN, S. E. (1995). PET studies of the recall of pictures and words from memory. *Society for Neuroscience Abstracts*, 21, 1441.

BUCKNER, R. L., & TULVING, E. (1995). Neuroimaging studies of memory: Theory and recent PET results. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology* (Vol. 10, pp. 439-466). Amsterdam: Elsevier.

BUTTERS, N., & STUSS, D. T. (1989). Diencephalic amnesia. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology* (Vol. 3, pp. 107-148). Amsterdam: Elsevier.

CABEZA, R., KAPUR, S., CRAIK, F. I. M., MCINTOSH, A. R., HOULE, S., & TULVING, E. (in press). Functional neuroanatomy of recall and recognition: A PET study of episodic memory. *Journal of Cognitive Neuroscience*.

CABEZA, R., TULVING, E., KAPUR, S., MCINTOSH, A. R., JENNINGS, J. M., NYBERG, L., HOULE, S., CRAIK, F. I. M. (1995). *Age-related decreases and increases in brain activity during encoding, recall, and recognition*. Manuscript in preparation.

CRAIK, F. I. M., & JENNINGS, J. M. (1992). Human memory. In F. I. M. Craik & T. A. Salthouse (Eds.), *Handbook of aging and cognition* (pp. 51-110). Hillsdale, NJ: Erlbaum.

CRAIK, F. I. M., & LOCKHART, R. S. (1972). Levels of processing: A framework for memory research. *Journal of Verbal Learning & Verbal Behavior*, 11, 671-684.

CRAIK, F. I. M., & TULVING, E. (1975). Depth of processing and the retention of words in episodic memory. *Journal of Experimental Psychology: General*, 104, 268-294.

DEMB, J. B., DESMOND, J. E., WAGNER, A. D., VAIDYA, C. J., GLOVER, G. H., & GABRIELI, J. D. E. (1995). Semantic encoding and retrieval in the left inferior prefrontal cortex: A functional MRI study of task difficulty and process specificity. *Journal of Neuroscience*, 15, 5870-5878.

DÉMONET, J.-F., CHOLLET, F., RAMSAY, S., CARDEBAT, D., NESPOULOUS, J.-L., WISE, R., RASCOL, A., & FRACKOWIAK, R. S. J. (1992). The anatomy of phonological and semantic processing in normal subjects. *Brain*, 115, 1753-1768.

DÉMONET, J.-F., WISE, R., & FRACKOWIAK, R. S. J. (1993). Language functions explored in normal subjects by positron emission tomography: A critical review. *Human Brain Mapping*, 1, 30-47.

FLETCHER, P. C., FRITH, C. D., GRASBY, P. M., SHALLICE, T., FRACKOWIAK, R. S. J., & DOLAN, R. J. (1995). Brain systems for encoding and retrieval of auditory-verbal memory: An in vivo study in humans. *Brain*, 118, 401-416.

FOX, P. T. (1991). Physiological ROI definition by image subtraction. *Journal of Cerebral Blood Flow & Metabolism*, 11, A79-A82.

FOX, P. T., MINTUN, M. A., REIMAN, E. M., & RAICHLE, M. E. (1988). Enhanced detection of focal brain responses using intersubject averaging and change-distributed analysis of subtracted PET images. *Journal of Cerebral Blood Flow & Metabolism*, 8, 642-653.

FRACKOWIAK, R. S. J. (1994). Functional mapping of verbal memory and language. *Trends in Neurosciences*, 17, 109-115.

FRACKOWIAK, R. S. J., & FRISTON, K. J. (1994). Functional neuroanatomy of the human brain: Positron emission tomography—a new neuroanatomical technique. *Journal of Anatomy*, 184, 211-225.

FRISTON, K. J., FRITH, C. D., LIDDLE, P. F., & FRACKOWIAK, R. S. J. (1991). Comparing functional (PET) images: The assessment of significant change. *Journal of Cerebral Blood Flow & Metabolism*, 11, 690-699.

FRISTON, K. J., FRITH, C. D., LIDDLE, P. F., & FRACKOWIAK, R. S. J. (1993). Functional connectivity: The principal-component analysis of large (PET) data sets. *Journal of Cerebral Blood Flow & Metabolism*, 13, 5-14.

FRISTON, K. J., HOLMES, A. P., WORSLEY, K. J., POLINE, J.-P., FRITH, C. D., & FRACKOWIAK, R. S. J. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, 2, 189-210.

FRITH, C. D., FRISTON, K. J., LIDDLE, P. F., & FRACKOWIAK, R. S. J. (1991a). A PET study of word finding. *Neuropsychologia*, 29, 1137-1148.

FRITH, C. D., FRISTON, K. J., LIDDLE, P. F., & FRACKOWIAK, R. S. J. (1991b). Willed action and the prefrontal cortex in man: A study with PET. *Proceedings of the Royal Society of London: Series B*, 244, 241-246.

GESCHWIND, N. (1972). Language and the brain. *Scientific American*, 226, 76-83.

GRADY, C. L., MCINTOSH, A. R., HORWITZ, B., MAISOG, J. M., UNGERLEIDER, L. G., MENTIS, M. J., PIETRINI, P., SCHAPIRO, M. B., & HAXBY, J. V. (1995, July 14). Age-related reductions in human recognition memory due to impaired encoding. *Science*, 269, 218-221.

GRASBY, P. M., FRITH, C. D., FRISTON, K. J., BENCH, C., FRACKOWIAK, R. S. J., & DOLAN, R. J. (1993). Functional mapping of brain areas implicated in auditory-verbal memory function. *Brain*, 116, 1-20.

GRASBY, P. M., FRITH, C. D., FRISTON, K. J., SIMPSON, J., FLETCHER, P. C., FRACKOWIAK, R. S. J., & DOLAN, R. J. (1994). A graded task approach to the functional mapping of brain areas implicated in auditory-verbal memory. *Brain*, 117, 1271-1282.

HAXBY, J. V., HORWITZ, B., MAISOG, J. M., UNGERLEIDER, L. G., MISHKIN, M., SCHAPIRO, M. B., RAPOPORT, S. I., & GRADY, C. L. (1993). Frontal and temporal participation in long-term recognition memory for faces: A PET-rCBF activation study. *Journal of Cerebral Blood Flow & Metabolism*, 13(Suppl. 1), 499.

HAXBY, J. V., UNGERLEIDER, L. G., HORWITZ, B., MAISOG, J. M., RAPOPORT, S. L., & GRADY, C. L. (1996). Face encoding and recognition in the human brain. *Proceedings of the National Academy of Science*, 93, 922-927.

HYDE, T. S., & JENKINS, J. J. (1969). Differential effects of incidental tasks on the organization of recall of a list of highly associated words. *Journal of Experimental Psychology*, 83, 472-481.

JENKINS, I. H., BROOKS, D. J., NIXON, P. D., FRACKOWIAK, R. S. J., & PASSINGHAM, R. E. (1994). Motor sequence learning: A study with positron emission tomography. *Journal of Neuroscience*, 14, 3775-3790.

JONES-GOTTMAN, M., ZATORRE, R. J., EVANS, A. C., & MEYER, E. (1993). Functional activation of right hippocampus during an olfactory recognition memory. *Society for Neuroscience Abstracts*, 19, 1002.

JONIDES, J., SMITH, E. E., KOEPPE, R. A., AWH, E., MINOSHIMA, S., & MINTUN, M. A. (1993). Spatial working memory in humans as revealed by PET. *Nature*, 363, 623-625.

KAPUR, N., FRISTON, K. J., YOUNG, A., FRITH, C. D., & FRACKOWIAK, R. S. J. (1995). Activation of human hippocampal formation during memory for faces: A PET study. *Cortex*, 31, 99-108.

KAPUR, S., CRAIK, F. I. M., JONES, C., BROWN, G. M., HOULE, S., & TULVING, E. (1995). Functional role of the prefrontal cortex in memory retrieval: A PET study. *Neuroreport*, 6, 1880-1884.

KAPUR, S., CRAIK, F. I. M., TULVING, E., WILSON, A. A., HOULE, S., & BROWN, G. M. (1994). Neuroanatomical correlates of encoding in episodic memory: Levels of processing effect. *Proceedings of the National Academy of Science*, 91, 2008-2011.

KAPUR, S., ROSE, R., LIDDLE, P. F., ZIPURSKY, R. B., BROWN, G. M., STUSS, D., HOULE, S., & TULVING, E. (1994). The role of left prefrontal cortex in verbal processing: Semantic processing or willed action? *Neuroreport*, 5, 2193-2196.

KAPUR, S., TULVING, E., CABEZA, R., MCINTOSH, A. R., HOULE, S., & CRAIK, F. I. M. (1996). *The neural correlates of intentional learning of verbal materials: A PET study in humans*. Manuscript in preparation.

KINSBOURNE, M., & GEORGE, J. (1974). The mechanism of the word-frequency effect on recognition memory. *Journal of Verbal Learning & Verbal Behavior*, 13, 63-69.

KNIGHT, R. T. (1984). Decreased response to novel stimuli after prefrontal lesions in man. *Electroencephalography & Clinical Neurophysiology*, 59, 9-20.

KNIGHT, R. T. (in press). Distributed cortical network for visual stimulus detection. *Journal of Cognitive Neuroscience*.

KÖHLER, S., KAPUR, S., MOSCOVITCH, M., WINOCUR, G., & HOULE, S.

(1995). Dissociation of pathways for object and spatial vision in the intact human brain. *Neuroreport*, **6**, 1865-1868.

KOSSLYN, S. M., NATHANIEL, M. A., THOMPSON, W. L., CHABRIS, C. F., RAUCH, S. L., & ANDERSON, A. K. (1994). Identifying objects seen from different viewpoints: A PET investigation. *Brain*, **117**, 1055-1071.

LOCKHART, R. S., & CRAIK, F. I. M. (1990). Levels of processing: A retrospective commentary on a framework for memory research. *Canadian Journal of Psychology*, **44**, 87-112.

LOCKHART, R. S., CRAIK, F. I. M., & JACOBY, L. L. (1976). Depth of processing, recognition and recall. In J. Brown (Ed.), *Recall and recognition* (pp. 75-102). New York: Wiley.

MARKOWITSCH, H. J. (1995). Anatomical basis of memory disorders. In M. S. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 765-779). Cambridge, MA: MIT Press.

MARKOWITSCH, H. J., & PRITZEL, M. (1985). The neuropathology of amnesia. *Progress in Neurobiology*, **25**, 189-287.

MARKOWITSCH, H. J., & TULVING, E. (1994a). Cognitive processes and cerebral cortical fundi: Findings from positron-emission tomography studies. *Proceedings of the National Academy of Science*, **91**, 10507-10511.

MARKOWITSCH, H. J., & TULVING, E. (1994b). Cognitive processing in cerebral cortical sulci. *Neuroreport*, **6**, 413-418.

MCINTOSH, A. R., & GONZALEZ-LIMA, F. (1994). Structural equation modeling and its application to network analysis in functional brain imaging. *Human Brain Mapping*, **2**, 2-22.

MESULAM, M.-M. (1990). Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Annals of Neurology*, **28**, 597-613.

MOLCHAN, S. E., SUNDERLAND, T., MCINTOSH, A. R., HERSCOVITCH, P., & SCHREURS, B. G. (1994). A functional anatomical study of associative learning in humans. *Proceedings of the National Academy of Science*, **91**, 8122-8126.

MOSCOVITCH, M., KAPUR, S., KÖHLER, S., & HOULE, S. (1995). Distinct neural correlates of visual long-term memory for spatial location and object identity: A positron emission tomography (PET) study in humans. *Proceedings of the National Academy of Science*, **92**, 3721-3725.

NYBERG, L., MCINTOSH, A. R., CABEZA, R., NILSSON, L.-G., HOULE, S., HABIB, R., & TULVING, E. (in press). Network analysis of PET rCBF data: Ensemble inhibition during episodic memory retrieval. *Journal of Neuroscience*.

NYBERG, L., TULVING, E., HABIB, R., NILSSON, L.-G., KAPUR, S., HOULE, S., CABEZA, R., & MCINTOSH, A. R. (1995). Functional brain maps of retrieval mode and recovery of episodic information *Neuroreport*, **7**, 249-252.

OWEN, A. M., MILNER, B., PETRIDES, M., & EVANS, A. C. (in press). A specific role for the right parahippocampal gyrus in the retrieval of object-location: A positron emission tomography study. *Journal of Cognitive Neuroscience*.

PARDO, J. V., & FOX, P. T. (1993). Preoperative assessment of the cerebral hemispheric dominance for language with CBF PET. *Human Brain Mapping*, **1**, 57-68.

PAULESU, E., FRITH, C. D., & FRACKOWIAK, R. S. J. (1993). The neural correlates of the verbal component of working memory. *Nature*, **362**, 342-345.

PETERSEN, S. E., CORBETTA, M., MIEZIN, F. M., & SHULMAN, G. L. (1994). PET studies of parietal involvement in spatial attention: Comparison of different task types. *Canadian Journal of Experimental Psychology*, **48**, 319-338.

PETERSEN, S. E., & FIEZ, J. A. (1993). The processing of single words studied with positron emission tomography. *Annual Review of Neuroscience*, **16**, 509-530.

PETERSEN, S. E., FOX, P. T., POSNER, M. I., MINTUN, M. [A.], & RAICHLE, M. E. (1988). Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature*, **331**, 585-589.

PETERSEN, S. E., FOX, P. T., SNYDER, A. Z., & RAICHLE, M. E. (1990, August 31). Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. *Science*, **249**, 1041-1044.

PETRIDES, M., ALIVASATOS, B., & EVANS, A. C. (1995). Functional ac-

tivation of the human ventrolateral frontal cortex during mnemonic retrieval of verbal information. *Proceedings of the National Academy of Science*, **92**, 5803-5807.

PETRIDES, M., ALIVASATOS, B., EVANS, A. C., & MEYER, E. (1993). Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proceedings of the National Academy of Science*, **90**, 873-877.

PETRIDES, M., ALIVISATOS, B., MEYER, E., & EVANS, A. C. (1993). Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proceedings of the National Academy of Science*, **90**, 878-882.

POSNER, M. I., & RAICHLE, M. E. (1994). *Images of mind*. New York: Scientific American Books.

PRICE, C., WISE, R., RANSAY, S., FRISTON, K. [J.], HOWARD, D., PATTERSON, K., & FRACKOWIAK, R. [S. J.] (1992). Regional response differences within the human auditory cortex when listening to words. *Neuroscience Letters*, **146**, 179-182.

RAICHLE, M. E. (1994a). Images of the mind: Studies with modern imaging techniques. *Annual Review of Psychology*, **45**, 333-356.

RAICHLE, M. E. (1994b, April). Visualizing the mind. *Scientific American*, pp. 58-64.

RAICHLE, M. E., FIEZ, J. A., VIDEEN, T. O., MacLEOD, A.-M. K., PARDO, J. V., FOX, P. T., & PETERSEN, S. E. (1994). Practice-related changes in human brain functional anatomy during nonmotor learning. *Cerebral Cortex*, **4**, 8-26.

ROLAND, P. E. (1982). Cortical regulation of selective attention in man: A regional cerebral blood flow study. *Journal of Neurophysiology*, **48**, 1059-1078.

ROLAND, P. E., KAWASHIMA, R., GULYAS, B., & O'SULLIVAN, B. (1995). Positron emission tomography in cognitive neuroscience: Methodological constraints, strategies, and examples from learning and memory. In M. S. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 781-788). Cambridge, MA: MIT Press.

SCHACTER, D. L. (1987). Memory, amnesia, and frontal lobe dysfunction. *Psychobiology*, **15**, 21-36.

SCHACTER, D. L., ALPERT, N. M., SAVAGE, C. R., RAUCH, S. L., & ALBERT, M. S. (1996). Conscious recollection and the human hippocampal formation: Evidence from positron emission tomography. *Proceedings of the National Academy of Science*, **93**, 321-325.

SCHACTER, D. L., REIMAN, E., UECKER, A., POLSTER, M. R., YUNG, L. S., & COOPER, L. A. (1995). Brain regions associated with retrieval of structurally coherent visual information. *Nature*, **368**, 633-635.

SCHACTER, D. L., SAVAGE, C. R., ALPERT, N. M., RAUCH, S. L., & ALBERT, M. (in press). The role of the hippocampus and frontal cortex in age-related memory loss. *Neuroreport*.

SEITZ, R., & ROLAND, P. (1992). Learning of sequential finger movements in man: A combined kinematic and positron emission tomography (PET) study. *European Journal of Neuroscience*, **4**, 154-165.

SERGENT, J., OHTA, S., & MacDONALD, B. (1992). Functional neuroanatomy of face and object processing. *Brain*, **115**, 15-36.

SHALLICE, T., FLETCHER, P., FRITH, C. D., GRASBY, P., FRACKOWIAK, R. S. J., & DOLAN, R. J. (1994). Brain regions associated with acquisition and retrieval of verbal episodic memory. *Nature*, **368**, 633-635.

SNODGRASS, J. G., & VANDERWART, M. A. (1980). A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology: Human Learning & Memory*, **6**, 174-215.

SQUIRE, L. R., OJEMANN, J. G., MIEZIN, F. M., PETERSEN, S. E., VIDEEN, T. O., & RAICHLE, M. E. (1992). Activation of the hippocampus in normal humans: A functional anatomical study of memory. *Proceedings of the National Academy of Science*, **89**, 1837-1841.

SQUIRE, L. R., & ZOLA-MORGAN, S. (1991, September 20). The medial temporal lobe memory system. *Science*, **253**, 1380-1386.

STEINMETZ, H., & SEITZ, R. J. (1991). Functional anatomy of language processing: Neuroimaging and the problem of individual variability. *Neuropsychologia*, **29**, 1149-1161.

STUSS, D. T., & BENSON, D. F. (1986). *The frontal lobes*. New York: Raven Press.

TALAIRACH, J., & TOURNOUX, P. (1988). *Co-planar steorotaxic atlas of the human brain*. New York: Thieme Medical Publishers.

TAMAS, L. B., SHIBASAKI, T., HORIKOSHI, S., & OHYE, C. (1993). General activation of cerebral metabolism with speech: A PET study. *International Journal of Psychophysiology*, 14, 199-208.

TULVING, E. (1972). Episodic and semantic memory. In E. Tulving & W. Donaldson (Eds.), *Organization of memory* (pp. 381-403). New York: Academic Press.

TULVING, E. (1983). *Elements of episodic memory.* New York: Oxford University Press.

TULVING, E. (1993). What is episodic memory? *Current Perspectives in Psychological Science*, 2, 67-70.

TULVING, E., KAPUR, S., CRAIK, F. I. M., MOSCOVITCH, M., & HOULE, S. (1994). Hemispheric encoding/retrieval asymmetry in episodic memory: Positron emission tomography findings. *Proceedings of the National Academy of Science*, 91, 2016-2020.

TULVING, E., KAPUR, S., MARKOWITSCH, H. J., CRAIK, F. I. M., HABIB, R., & HOULE, S. (1994). Neuroanatomical correlates of retrieval in episodic memory: Auditory sentence recognition. *Proceedings of the National Academy of Science*, 91, 2012-2015.

TULVING, E., & KROLL, N. (1995). Novelty assessment in the brain and long-term memory encoding. *Psychonomic Bulletin & Review*, 2, 387-390.

TULVING, E., MARKOWITSCH, H. J., CRAIK, F. I. M., HABIB, R., &

HOULE, S. (1996). Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cerebral Cortex*, 6, 71-79.

TULVING, E., MARKOWITSCH, H. J., KAPUR, S., HABIB, R., & HOULE, S. (1994). Novelty encoding networks in the human brain: Positron emission tomography data. *Neuroreport*, 5, 2525-2528.

TULVING, E., & PEARLSTONE, Z. (1966). Availability versus accessibility of information in memory for words. *Journal of Verbal Learning & Verbal Behavior*, 5, 381-391.

WHEELER, M. A., STUSS, D. T., & TULVING, E. (1995). Frontal lobe damage produces episodic memory impairment. *Journal of the International Neuropsychological Society*, 1, 525-536.

WILSON, F. A., & ROLLS, E. T. (1993). The effects of stimulus novelty and familiarity on neuronal activity in the amygdala of monkeys performing recognition memory tasks. *Experimental Brain Research*, 93, 367-382.

WISE, R., CHOLLET, F., HADAR, U., FRISTON, K. [J.], HOFFNER, E., & FRACKOWIAK, R. [S. J.] (1991). Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain*, 114, 1803-1817.

WORSLEY, K. J., EVANS, A. C., MARRETT, S., & NEELIN, P. (1992). A three-dimensional statistical analysis for CBF activation studies in human brain. *Journal of Cerebral Blood Flow & Metabolism*, 12, 900-918.