

CHAPTER TWENTY

Brain/mind correlates of human memory

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The neurocognitive approach to the study of memory has received a good deal of support from brain imaging methods such as positron emission tomography (PET). PET has been used not only to localize memory processes, but also to arbitrate theoretical disputes. On the localization side, PET studies have pointed to the existence of extensive cortical and subcortical memory circuits that are specific to encoding and retrieval processes. With respect to disputes, PET studies have helped to distinguish between episodic and semantic memory. The HERA model holds that episodic memory encoding processes, together with semantic memory retrieval processes, differentially engage the left hemisphere, whereas episodic memory retrieval processes differentially engage the right hemisphere, including the right prefrontal cortex. The function of the frontal lobes includes the establishment, maintenance, and switching the episodic retrieval mode and other kinds of neurocognitive sets.

Les méthodes d'imagerie cérébrale, telle la tomographie par émission de positrons (TEP), ont fourni un bon appui à l'analyse neurocognitive des phénomènes mnémotechniques. La TEP a été exploitée non seulement afin de localiser les processus de mémorisation, mais également dans le but de trancher certaines querelles théoriques. En rapport avec les questions de localisation, les études exploitant la TEP ont montré l'existence de larges circuits, aussi bien corticaux que sous-corticaux, qui sont spécifiques aux processus d'encodage et de recouvrement. En ce qui a trait aux querelles, elles ont facilité la distinction entre mémoire épisodique et mémoire sémantique. Le modèle AHER (Asymétrie hémisphérique pour l'encodage et le recouvrement) postule que les processus d'encodage responsables de la mémoire épisodique, de même que les processus de recouvrement en mémoire sémantique, font intervenir l'hémisphère gauche de manière différentielle; par contre, les processus de recouvrement en mémoire épisodique feraient intervenir de manière différentielle l'hémisphère droit, y compris le cortex préfrontal droit. La fonction des lobes frontaux inclut la mise en place, le maintien et le renversement du mode de recouvrement épisodique et d'autres types d'attitudes neurocognitives.

INTRODUCTION

In this chapter I discuss findings from recent positron emission tomography (PET) studies of memory that have contributed to our understanding of memory.

Psychologists have generally shied away from, or at least largely ignored, the connection between brain activity and mental processes in memory, for what have been good reasons. Edwin "Garry" Boring, one of the great historians of psychology, wrote on this topic almost 50 years ago:

Where or how does the brain store its memories? That is a great mystery . . . The physiology of memory has been so baffling a problem that most psychologists in facing it have gone positivistic, being content with hypothesized intervening variables or with empty correlations. (Boring, 1950, p. 670)

He went on to elaborate on the reasons for such a state of affairs:

In general it seems safe to say that progress in this field is held back, not by lack of interest, ability or industry, but by the absence of some one of the other essentials for scientific progress. Knowledge of the nature of the nerve impulse waited upon the discovery of electric currents and galvanometers of several kinds. Knowledge in psychoacoustics seemed to get nowhere until electronics developed. *The truth about how the brain functions may eventually yield to a technique that comes from some new field remote from either physiology or psychology.* (Boring, 1950, p. 688, emphasis added)

We now have witnessed the birth and development of several new techniques that have helped to change the situation: EEG and ERP (event-related potentials), MEG (magnetoencephalography), fMRI (functional magnetic resonance imaging), and PET (positron emission tomography). These mutually complementary techniques are being increasingly used by multidisciplinary research teams in which psychologists play an important role (Hari, 1994; Näätänen & Alho, 1995; Picton, 1995; Posner & Raichle, 1994; Raichle, 1994). Although the application of these techniques to the study of memory is still in its very early stages, they have already opened new vistas and yielded valuable information (Buckner & Tulving, 1995; Cabeza & Nyberg, 1997; Fletcher, Dolan, & Frith, 1995a; Fletcher et al., 1995b; Nyberg, Cabeza, & Tulving, 1996a). These initial successes leave no doubt that the potential of the imaging techniques is tremendous. Other newer techniques, such as near-infrared optical imaging (Gratton et al., 1995), and analyses of power spectra in EEG recordings (Klimesch, Schimke, & Schwaiger, 1994), may turn out to be equally or even more exciting. It is safe to predict that all these techniques, and others as yet unknown, will revolutionize the study of the brain/mind very much in the same way in which the telescope changed the study of the heavens and the microscope reformed the investigation of the invisible structure of the world around us.

My purpose here is to illustrate the progress in the understanding of memory that neuroimaging techniques have made possible. I draw my examples from work done with PET, because I am most familiar with it, and have been personally involved in some of it.

The chapter consists of seven sections. The first section concerns memory. The major point I make here is that memory can be and has been studied from several different perspectives. I will distinguish between two approaches to memory: cognitive and neurocognitive. The pursuit of problems of memory guided by the neurocognitive approach has led to ideas about different forms of memory, organized into multiple systems and subsystems. In this chapter I am concerned primarily with episodic memory.

In the second section I summarize how PET is used in cognitive studies of memory, what it can do and what it cannot do. Although the PET method is very useful, like any other technique it has shortcomings, and these have to be kept in mind when using it. I will also make the point that there are two rather independent functions that PET studies serve. The first one is widely known: PET allows us to identify brain regions that are differentially involved in memory; it can be used to *localize* memory processes in the brain. The second is less apparent but equally important: PET helps to *arbitrate* theoretical disputes.

In the third section I illustrate the localization function of PET by presenting some recent findings pertaining to the hippocampus and its adjacent allocortical areas in the medial temporal lobes. The medial temporal lobe (MTL) regions have been widely regarded as an important brain structure of memory; some even think of it as the "seat" of memory in the brain. The hippocampus has been difficult to capture in PET studies, but some data are available, and I will mention them.

In the fourth section I provide another example of how PET localizes processes. There are large regions of the brain that are more involved in processes of episodic-memory encoding than retrieval, and other large areas are more involved in the processes of episodic-memory retrieval than encoding.

In the fifth section, I summarize and discuss PET data that have been classified under the label of HERA: hemispheric encoding/retrieval asymmetry. Left frontal brain regions are more involved in encoding, whereas right frontal regions are more involved in retrieval. This finding illustrates both the localization function and the arbitration function, because it clearly separates semantic and episodic retrieval neuroanatomically.

In the sixth section I review data suggesting that the right-frontal brain activity, which is strongly associated with episodic-memory retrieval, actually signifies a mental retrieval *set* rather than actual retrieval success. The brain sites that are involved in successful retrieval, or ecphory, seem to be situated in more posterior cortical areas.

I conclude with a brief summary of what we have learned from these initial PET studies.

MEMORY

The scientific study of human memory began a little more than a hundred years ago (Ebbinghaus, 1885). The progress we have made since then has been truly remarkable, especially that in the last couple of decades. There has been a literal explosion of new methods, new approaches, new questions, and new ideas, and the pace of activity and discovery is clearly accelerating. Here it is useful to distinguish between two different approaches to the study of memory. I refer to them as cognitive and neurocognitive. Cognitive is historically older and somewhat narrower in its scope than neurocognitive, which encompasses the cognitive approach, but also goes considerably beyond it.

We can draw a thumbnail sketch of the cognitive approach as follows: It is oriented towards psychological issues of memory. It usually works "bottom-up" from phenomena of memory to their more general theoretical explanations. Much of the empirical evidence is derived from controlled experiments with normal human subjects. The explanations of experimental findings rely heavily on concepts such as information processing and cognitive processes. The ultimate objective of the research is thought of as the construction of comprehensive theories and models of memory. Researchers in the cognitive tradition tend not to take much interest in studies of animals or brain-damaged patients, and they seldom try to relate their findings to brain processes, perhaps for the reasons of the kind that Boring speculated about.

The neurocognitive approach adopts the basic cognitive orientation but its domain extends beyond the purely psychological. It takes its inspiration not only from cognitive (experimental) psychology, but also from developmental psychology, neuropsychology, psychopharmacology, biopsychology, evolutionary biology, and brain sciences. It seeks evidence relevant to the understanding of memory from a variety of sources, including work with animals and brain-damaged patients. Its objective is to understand not only memory processes but also the relation between such processes and brain structures and mechanisms that support them. It frequently works "top-down", beginning with broad ideas about the organization and functioning of memory and evaluating those ideas in light of evidence from a wide range of sources, which recently have come to include neuroimaging.

These two working definitions are summarized in Table 20.1 that lists some of the characteristic features of the two approaches in point form.

The top-down neurocognitive orientation is aimed at elucidation of the nature of memory as an important part of the brain/mind. It is concerned with questions such as, What is memory? How many different kinds of memory are there? How did they evolve? For what purpose? How is memory related to (i.e. similar to and different from) other categories of brain/mind, such as perception, thought, and language? How are different kinds of memory related to one another? How are memory systems similar and different in different species? How does memory change with ontogenetic development?

TABLE 20.1
Two approaches to the study of memory

<i>Cognitive</i>	<i>Cognitive neuroscience</i>
Psychological	Biological
Bottom-up	Top-down
Epistemological	Ontological
Models; causes	Organization; classification
Explanatory	Descriptive
Predictions	No predictions
Human adults	"Higher" animals
Memory tasks	Memory systems
Mentalistic	Reductionistic
Cognitive processes	Brain/mind correlations
Behavior	Brain lesions; neuroimaging

Most of the traditional psychological research on memory, guided by the cognitive approach, does not throw much light on these kinds of questions. It can be conducted, and largely has been conducted since Ebbinghaus (1885), without raising such questions. Because it has been quite successful in its endeavours, the absence of the neurocognitive concerns from the cognitive agenda has not diminished it.

Although the top-down biological approach is concerned with issues such as the organization of memory as an extensive neurocognitive system, whereas the bottom-up approach is concerned with psychological explanation of memory phenomena, the two approaches are not alternatives. They must not be thought of as seeking rival formulations of memory. They *complement* each other. The students of memory interested in biological organization and those who are interested in psychological explanation are like two teams of engineers digging a tunnel under a mountain, starting at opposite sides with the objective of meeting, end-to-end, in the middle. We need to be aware of their separate starting points and different routes. The failure to do so will create unnecessary conflict and futile debates.

A central issue in memory research today concerns the basic nature of the organization of memory. The traditional assumption for a long time was that of a unitary memory. More recently, under the general direction of the neurocognitive approach, this assumption is gradually being replaced by the assumption of multiple memory systems (Foster & Jelicic, in press; Schacter & Tulving, 1994a). According to one current formulation, it is possible to distinguish among five major human memory systems (Schacter & Tulving, 1994b): procedural, PRS (perceptual representation system), primary (or working), semantic, and episodic. In this chapter I am concerned with episodic memory, especially in relation to semantic memory (Tulving, 1991, 1993).

Episodic memory makes possible the "autonoetic" recollection of personally *experienced events as experienced* (Perner & Ruffman, 1995; Wheeler, Stuss, & Tulving, 1997), including "miniature events" such as the presentation of words or other discrete items in the memory laboratory. The appearance of such an item in a particular experiment list is a to-be-remembered event (Tulving, 1983).

Semantic memory, on the other hand, is a brain system that makes possible acquisition, retention, and use of generic knowledge of the world. Whereas the episodic system is concerned with autonoetic recollection of personal experiences, the semantic system is concerned with "noetic" knowledge acquired and used in the course of life's happenings. The cognitive operations involved in encoding of information are very similar for episodic and semantic memory, but retrieval of information from one of the two systems can occur independently of the retrieval from the other system (Tulving, 1995).

PET

Let us now turn to PET, positron emission tomography. PET works by measuring cerebral blood flow by detecting the distribution of a radioactive isotope, usually ^{15}O , that has been injected with a small amount of water into the general blood flow of the subject. Sophisticated computer algorithms are used to localize the changes in this distribution to specific sites in the three-dimensional brain. Because mental activity that occurs during any cognitive task is tightly correlated with neuronal activity in the brain, and because neuronal activity is correlated with changes in the cerebral blood flow, changes in the blood flow that PET detects reflect the brain correlates of mental activity.

A subject in a typical "activation" PET study usually participates in one scanning session that includes 6 to 10 single scans, spaced about 10 minutes apart. Each scan lasts about 2 minutes during which the subject is engaged in a particular directed mental activity. The cognitive activity begins at the start of the 2-minute period, shortly after the subject receives the injection, the tracer reaches the brain in about 8 seconds, and then the actual scanning begins, lasting between 40 and 60 seconds.

The pattern of the blood flow (functional brain map) is usually derived from the data pooled over a number of scans of a particular kind (involving a fixed mental task) from a sample of subjects. The brain map yielded by such a procedure represents the *average* not only of the subjects but also of all of the mental activity in which the subjects engaged during the 40–60sec duration of the scan. This means that the typical brain map yielded by PET is like a composite photograph: It contains the *cumulated* traces of the total activity of a number of brains over the duration of relevant single scans. Like any single observation made by an experimenter, such a map is not interpretable: It is not possible to attribute any of its details to any aspects of the mental task.

This is why the logic of the most widely used PET procedure is based on a comparison of scans (Buckner & Tulving, 1995; Petersen, Fox, Posner, Mintun, & Raichle, 1988). The simplest comparison involves the subtraction of one brain map obtained during one scan, from a map obtained during another scan. The *difference* between the two brain maps reflects the *difference* between the mental activities in which the subjects engaged during the two scans.

This, then, is what PET can do: Provide data on a rough *correlation* of differences between two mental activities and differences between two brain maps reflecting localized neuronal activity. These data, like all others in science, are informative and potentially useful to the extent that they are reliable. A single finding may at best serve to focus the researcher's interest, and not much more. This is why an important objective of PET studies of memory at the present early stage of the proceedings is the garnering of systematic and reliable data. Eventually these data will guide the construction of meaningful models of the brain/mind relations in memory.

Because of the relatively poor temporal resolution, PET cannot be used to study short-lived processes or to find out what happens to individual items. Thus, if we "pick up" different brain regions in a particular comparison of tasks, we have no way of telling anything about the temporal relations in their activity; we know nothing about the flow of information among the identified regions. For that purpose, EEG and MEG-based techniques are much more suitable.

PET data can be used to *localize processes* to specific brain regions. But it is also important to realize that PET data can equally well help us to *clarify theoretical issues*, quite independently of specific loci of memory processes. An example is the distinction between episodic and semantic memory. Although all students of memory accept and use the distinction at a descriptive level, in the sense of different kinds of information or different tasks, there is as yet no general agreement as to the biological reality of the distinction. Many people still believe that episodic and semantic memory are just two different modes of operation of a large declarative memory system. This attitude is quite unlike that towards, say, vision and audition. Everyone agrees that they represent different brain systems; no one argues that they are just two different ways or modes in which the general "distant sensation" system operates. The reason for the different attitudes is obvious. In the case of two sensory modalities there are clearly visible differences in the anatomy, whereas in the case of memory anatomical differences have, until recently, been mostly a matter of inference.

This is where PET studies can help. As we will see presently, there are prominent differences in the brain maps produced by retrieval of otherwise similar semantic and episodic information. The anatomical differences are particularly striking in the frontal lobes. But the point I want to make here is that the exact localization of these differences does not matter. The hypothesis that episodic and semantic memory represent different brain systems would gain support from any finding of systematic differences in brain activity, regardless

of the brain regions involved. Thus, PET can function as an *arbiter* in theoretical disputes, quite independently of specific localization of any particular process in the brain.

LOCALIZATION: HIPPOCAMPUS AND MTL

The long history of research showing that the hippocampal formation in the medial temporal lobes plays a critical role in memory is well known to most psychologists. Much of the relevant evidence is derived from studies of patients with damage to these structures who show impairment in various kinds of memory processes (Markowitsch & Pritzel, 1985; Milner, 1966; Squire, 1993). So, what is the story of PET and the hippocampus? An early study done by Squire and colleagues at Washington University (Squire et al., 1992) did reveal evidence of the involvement of the right parahippocampal region in explicit recall, but many other studies of memory, done subsequently, failed to detect any hippocampal activity (Andreasen et al., 1995; Buckner et al., 1995; Fletcher et al., 1995b). The impression quickly spread therefore that PET is insensitive or inadequate to "pick up" a small structure such as the hippocampus. Actually this is not quite true.

A number of PET memory studies have now identified the involvement of the hippocampus in memory. The difficulty so far has been in detecting any *general pattern* in the data. Activations of MTL regions have been observed unilaterally in the left hemisphere or in the right hemisphere, as well as bilaterally; they have been observed during encoding as well as during retrieval; they have been found with verbal materials and nonverbal materials (Blaxton, 1996; Cabeza & Nyberg, 1997; Tulving & Markowitsch, 1997).

A different kind of a PET finding of the involvement of the MTL regions in memory processes is one of correlation, across individual subjects, between hippocampal activity, as revealed by ratio-adjusted measures of blood flow, and behavioral memory performance. The graph in Fig. 20.1 illustrates this type of finding. The data come from a joint Swedish-Canadian PET project done in Toronto on recognition of previously studied words (Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996d). The abscissa of the graph in Fig. 20.1 represents the relative amount of blood flow in a region near the left hippocampus in each individual subject's brain. The ordinate represents individual subjects' recognition performance expressed in terms of the hit rate. Thus, each point in the scatterplot represents an individual subject. We see that the higher a subject's blood flow at this hippocampal site, the higher was his or her recognition memory performance. The finding was replicated in two different scans within the study, and replicated, at a slightly different hippocampal site, in another study, done independently of the first one (Nyberg et al., 1996b). Similar individual subjects' correlations have been reported for the amygdala and recall of emotional material by Larry Cahill and colleagues, at the University of California at Irvine

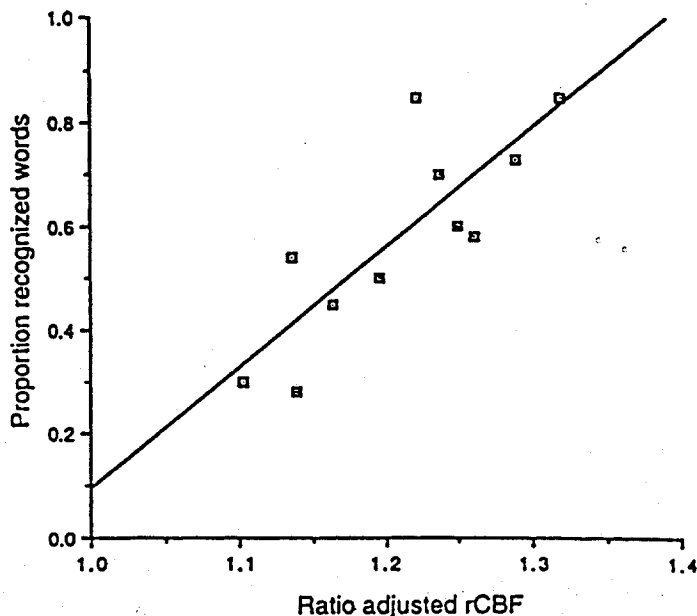


FIG. 20.1 Scatterplot showing a positive relation between episodic memory retrieval (hit rates in recognition) and standardized measures of regional cerebral blood flow at a site in left medial temporal lobe (Talairach & Tournoux, 1988, stereotactic x,y,z coordinates: -24, 2, -16). Each data point represents one of 11 subjects. From Nyberg, McIntosh, Houle, Nilsson, and Tulving (1996), *Nature*, 380, 715-717.

(Cahill et al., 1996), and between response latencies in imagery and activation of occipital regions by Stephen Kosslyn and colleagues at Harvard (Kosslyn, 1996).

In summary of this section, then, we can say that although it has not always been easy to detect "hippocampal" (MTL) activation in PET studies of memory, more recent experiments have produced promising data. Different regions in the medial temporal lobes are involved in various aspects of memory, and some may be directly related to memory performance. Although a clear larger picture is still missing, the PET data have at least in general terms confirmed and elaborated evidence from lesion studies of brain damaged patients (Markowitsch & Pritzel, 1985; Milner, 1966; Squire, 1993).

ARBITRATION: ENCODING AND RETRIEVAL

Let us now proceed to examine encoding and retrieval processes "in the brain". We can think of the psychological issue here as this: Are encoding and retrieval processes basically similar or basically different? It has been traditionally assumed that retrieval is largely a matter of "reactivation" of encoding processes.

Bower and Hilgard attributed the idea to earlier generations of researchers, such as Wolfgang Köhler (1938), and summarized it as follows:

Recall or remembering involves the reactivation of a given memory trace; in effect, it is a revival of the same perceptual processes that corresponded to the original perception. The trace continues to exist as an active process in the nervous system; but is of too low an intensity to enter consciousness. In recall, a cue selects out and amplifies the intensity of a particular trace to raise it over the threshold of consciousness. (Bower & Hilgard, 1981, p. 311)

Many others, on the basis of different kinds of evidence, have adopted a similar position, assuming that retrieval consists essentially of recapitulation of the same patterns of mental or neural activity that occurred when the original event was perceived and comprehended (Craik, 1983; Köhler et al., in press; Nyberg et al., 1996d; Rosler, Heil, & Hennighausen, 1995). Quite independently of actual findings, it makes sense to imagine that particular processes must run their course in order to store some information in memory, and that the same processes must run the same course again when the stored trace is reactivated at retrieval. The question is, how large is the overlap? Are there differences as well as similarities between encoding and retrieval processes?

As long as we are limited to purely behavioral data, the question of similarities or differences is not easy to handle. However, when we pose the question at the level of brain activity, the issue becomes more tractable. All we need to do is to measure, and then compare, regional blood flow while subjects are (1) encoding some material into memory, and (2) retrieving the same, previously encoded material. When we subtract the retrieval map from the encoding map, we will see those brain regions that were more active during encoding than during retrieval; when we subtract the encoding map from the retrieval map, we will see those brain regions that were more active during retrieval than during encoding.

Figure 20.2 shows "encoding regions" and "retrieval regions". These data were provided by a direct comparison of brain maps associated with study and test of experimental materials. The data here were pooled from four different experiments, and are based on a total of 48 subjects. The four experiments were carried out at Toronto (Cabeza et al., 1997; Kapur et al., 1996; Köhler et al., in press; Nyberg et al., 1996b). The experiments differed with respect to a number of details, including the to-be-remembered materials, but they were identical in that all included scanning of both encoding and retrieval. Thus, in every one of the four experiments, subjects were studying the items during some scans, and taking a recognition or recall test during other scans. In composite comparisons, such as this one, therefore, commonalities related to encoding or retrieval are accentuated, whereas specific activations related to specific features of individual studies are likely to be cancelled out.

The "encoding regions" here (on the left of Fig. 20.1) are brain regions in which regional blood flow was higher during encoding than during retrieval.

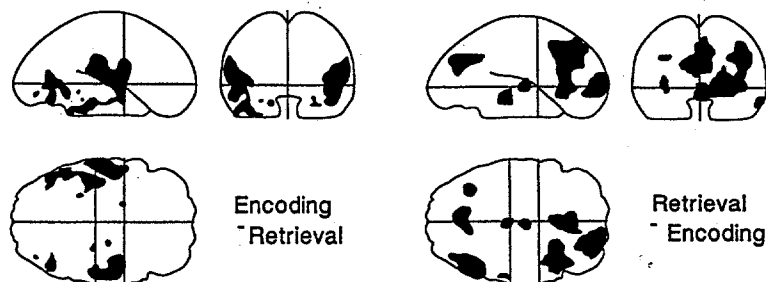


FIG. 20.2 PET results of a direct comparison between encoding and retrieval. Left: brain regions that are more active during encoding than during retrieval (temporal lobes bilaterally, left fusiform gyrus and perirhinal cortex in the medial temporal lobe, right parahippocampal gyrus, and entorhinal cortex bilaterally). Right: brain regions that are more active during retrieval than during encoding (right prefrontal cortex, anterior cingulate cortex, thalamus, brainstem, and midline parietal regions near cuneus and precuneus). Data were pooled from four different PET studies in which a total of 48 young healthy subjects participated. Reprinted from Tulving & Markowitsch, 1997.

They include bilateral temporal lobes, left fusiform gyrus that extends to the perirhinal cortex in the medial temporal lobe, as well as small but statistically highly significant activations in the hippocampal regions bilaterally, namely in the entorhinal cortex, and in the right parahippocampal gyrus. We can think of these regions as representing components of widely distributed neuroanatomical “encoding circuits”.

Encoding, of course, is a highly complex process that consists of many subprocesses, and therefore the knowledge we have gained from this analysis is rather gross. But these data put us greatly ahead in our understanding of memory processes in the brain, when we compare where we are now with where we were, say, only five years ago.

Two points are worth noting. First, given that the brain maps shown in Fig. 20.2 represent the *relative* amounts of activations at encoding and retrieval, areas showing greater activation at encoding (as in the left half of Fig. 20.2) may also be interpreted as showing relatively *less* activation at retrieval. This reduced activation has sometimes been attributed to perceptual priming (Demb et al., 1995; Squire et al., 1992; Tulving et al., 1994b). The idea is that primed items require less processing at retrieval, and this reduced processing is reflected in the attenuation of the activation of the regions that subserve the initial encoding. In light of the massive size and multiplicity of the regions that show such “deactivation” it is somewhat unlikely that they all signify priming. Moreover, the regions showing “deactivations” in the medial temporal regions (Fig. 20.2, also Tulving, Markowitsch, Craik, Habib, & Houle, 1996), cannot be critically involved in priming, because patients with lesions in these regions have been shown to perform indistinguishably from normal subjects in perceptual priming studies.

Second, the absence of activation in most regions of the brain in this subtractive comparison does not mean that these regions were not involved with encoding or retrieval. A direct comparison of the kind made here does not reveal any brain regions that are equally active during both encoding and retrieval, nor does it distinguish between equally active and equally inactive regions. It is quite possible that some of the "blank" regions in Fig. 20.2 were equally active in encoding and retrieval, and therefore cancelled out in the subtraction. Indeed, we know from other analyses that there exist many brain regions that are involved in both encoding and retrieval (e.g. Köhler et al., in press; Nyberg et al., 1996b). The present data simply highlight the differences.

The right half of Fig. 20.2 shows "retrieval regions": brain regions that were more active during retrieval than during encoding in the data pooled from the four experiments (Cabeza et al., 1997; Kapur et al., 1996; Köhler et al., in press; Nyberg et al., 1996b). Retrieval activation was especially prominent in the right frontal lobes; this area will be discussed in more detail later. Other regions that were more active in retrieval than in encoding include the anterior cingulate cortex, and midline parietal activations in cuneus and precuneus. There was also a conspicuous activation in the thalamus. Altogether these regions can be thought of as representing the most prominent components of widely distributed neuroanatomical "retrieval circuits".

The "retrieval regions" shown in Fig. 20.2 agree remarkably well with episodic-memory retrieval regions recently identified by Randy Buckner and his colleagues at Washington University (Buckner, Raichle, Miezin, & Petersen, 1996). The right frontal and medial parietal (precuneus-cuneus) activations seen in the right half of Fig. 20.2 also agree well with observations made by Tim Shallice and Paul Fletcher, and their colleagues, in London, England (Shallice et al., 1994; Fletcher et al., 1995a,b).

These data illustrate what is now well known from many other PET studies of memory, namely, that there are distinctive and easy-to-identify differences in locations that are differentially active in encoding versus those that are differentially active in retrieval. Thus, although encoding and retrieval processes do share common brain processes, their substrates in the brain are also quite different.

The "encoding regions" and "retrieval regions" shown in Fig. 20.2 look massive, but the appearance here, as in all other such pictures of PET activations, is deceptive (Roland, Kawashima, Gulyas, & O'Sullivan, 1995). In either case, the "activated" areas shown comprise less than 2 per cent of the volume of the brain. Their extent in the subtraction analysis is determined not only by the cerebral blood flow changes associated with the encoding and retrieval tasks, but also by the threshold selected for the comparison by the experimenter. Here the threshold is conservative: Only those brain regions where the differences between the compared conditions reached the z -score of 4.5 ($P < .0001$) are shown in Fig. 20.2. The adoption of a lower threshold would, of course, have resulted in the expansion of the boundaries of the encoding and retrieval "circuits".

ARBITRATION: HERA

Let us now turn to the so-called HERA model. HERA stands for hemispheric encoding/retrieval asymmetry. Initial PET studies investigating encoding and retrieval processes in episodic memory, done at Toronto (Kapur et al., 1994; Moscovitch, Kapur, Köhler, & Houle, 1995; Tulving et al., 1994a,b), the Hammersmith Hospital in London (Shallice et al., 1994; Fletcher et al., 1995b) and Washington University (Buckner et al., 1995; Squire et al., 1992) suggested a surprising empirical regularity: Left prefrontal cortex is differentially more involved than right in encoding information into episodic memory, whereas right prefrontal cortex is differentially more involved than left in episodic memory retrieval. Because in many cases episodic encoding (for instance, deep encoding judgments) involve semantic memory retrieval, the HERA model assigns semantic-memory retrieval also to the left frontal lobe. We call HERA a model, because we have used two paired concepts from cognitive psychology, namely encoding and retrieval, and episodic and semantic memory, to make sense of the highly regular asymmetry in neuronal activity.

Let me illustrate HERA with an example from a PET study done at Toronto with university students as subjects (Cabeza et al., 1997; Kapur et al., 1996). Subjects were scanned under two conditions. In one, they saw pairs of words, such as PENGUIN—TUXEDO, and they had to think of a meaningful relation between the words of each pair. They were also told that their memory for these pairs would be tested. Two processes occur in this situation. First, subjects make use of their semantic knowledge (general knowledge of the world) in relating the paired words to each other, that is, they engage in semantic-memory retrieval. Second, the presented information is encoded and stored in episodic memory, that is, subjects later on remember that they saw such and such pairs of words. In the other experimental condition, subjects again saw pairs of words, such as PENGUIN—TUXEDO, and they had to decide whether the pair had appeared in the study list. This is an episodic-memory retrieval (recognition) condition.

The left part of Fig. 20.3 shows the results yielded by the subtraction of the retrieval activations from the encoding activations: extensive regions in the left hemisphere, including prefrontal cortex, were more strongly activated during encoding than during retrieval. The right part of Fig. 20.3 shows an asymmetrical pattern of the other kind: activation on the right but not left. This pattern was yielded by the subtraction of the blood flow pattern associated with the encoding condition from that associated with retrieval (recognition). In addition to the right frontal retrieval activation, there are other posterior regions that were more involved in recognition than in initial study. Although in this particular study the HERA pattern extended well beyond the frontal regions, this is not always the case. For the time being at least we speak of HERA mostly in connection with the frontal regions of the brain.

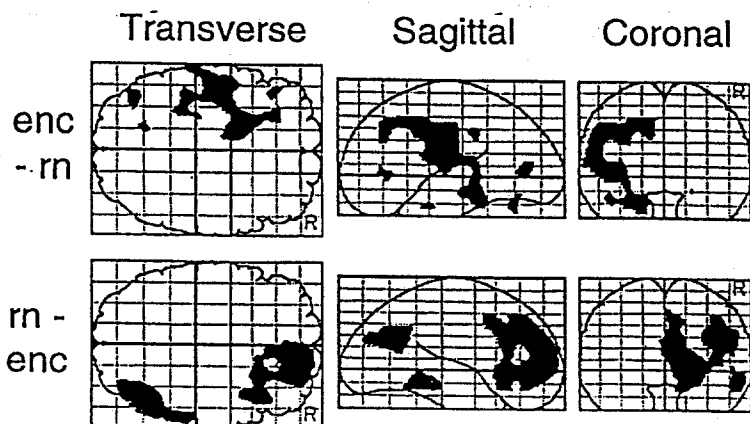


FIG. 20.3 Brain maps illustrating the HERA model. Left hemispheric regions, including the frontal lobe, are more active than right hemispheric regions during intentional study of pairs of words (at the top of the figure), whereas right hemispheric regions, including the frontal lobe, are more active than left hemispheric regions during recognition of the same pairs of words (at the bottom of the figure). Average data for 12 young healthy subjects. From Kapur et al., 1996, and Cabeza et al., in press. Figure reprinted from Nyberg, Cabeza, and Tulving (1996), *Psychonomic Bulletin and Review*, 3, 135–148.

The HERA Model

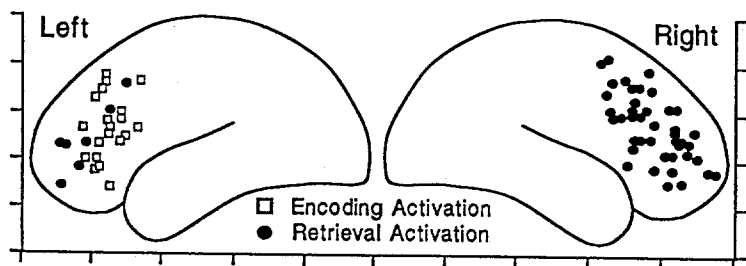


FIG. 20.4 A schematic representation of the HERA model. Data pooled from 25 different PET studies of episodic-memory encoding and retrieval. Each data point represents the outcome of the subtractive analysis of encoding or retrieval against suitable reference conditions. The peaks of activated regions are projected to the left and right lateral surface of the brain. Figure reprinted from Nyberg, Cabeza, and Tulving (1996), *Psychonomic Bulletin and Review*, 3, 135–148.

Although initially unexpected, the HERA pattern in the frontal lobes is now well established and indeed represents one of the most robust facts of the PET-memory literature. Figure 20.4 presents a schematic summary of the results of 25 relevant PET studies from different laboratories whose results were available in May 1996 (Nyberg et al., 1996a). The distribution of the peaks of activations shown in the graph tell the story of the asymmetry. All encoding activations

were located in the left hemisphere, none were on the right, whereas a large majority of retrieval activations were on the right, with a few also appearing on the left. This pattern provides massive support for the HERA model. It holds widely, for different kinds of material (both verbal and nonverbal), for different kinds of encoding and retrieval tasks, and despite a great deal of variability in other experimental conditions. However, as shown in Fig. 20.4, within the general left/right encoding/retrieval regularity there exists considerable variability in localization of function, depending on particular conditions of the studies in the set. This variability invites more detailed analyses of the data, some of which have already been reported (Buckner, 1996; Nyberg et al., 1996b).

The HERA findings illustrate both localization and arbitration functions of PET. Not only do they tell us something about what brain regions are involved in memory processes such as encoding and retrieval, they also help to arbitrate the issue of the biological reality of the distinction between episodic and semantic memory. The fact that semantic retrieval seems to be localized largely to the left, whereas episodic retrieval involves processes subserved by regions in the right hemisphere (Andreasen et al., 1995, 1996; Haxby et al., 1996) points to basic differences in the neuroanatomy of the two memory systems. An especially pleasing feature of the episodic/semantic retrieval asymmetry is that it is consistent with the possibility that the two hemispheres play different roles in subserving *autonoetic* and *noetic consciousness*, which in theory are associated with episodic and semantic memory (Tulving, 1985; Wheeler et al., 1997).

FRONTAL LOBES AND RETRIEVAL SET

What are we to make of the frontal lobes showing up as prominently as they have in many PET studies of episodic memory? It happens that we have available some data that address this question, with respect to the right frontal (episodic retrieval) activity. When people are tested in an explicit memory test, such as recognition, two things happen: (1) They try to think back to a particular study episode, trying to decide whether the test item before them also appeared in that episode (retrieval attempt), and (2) they succeed in doing so in many cases (retrieval success).

The data from two PET studies (Kapur et al., 1995; Nyberg et al., 1995) suggest that the right frontal activation reflects retrieval attempt rather than, or perhaps in addition to, retrieval success (McIntosh, Nyberg, Bookstein, & Tulving, 1997; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1996; see also Schacter, Alpert, Savage, & Rauch, 1996). Two independent variables were manipulated in these studies: (1) presence versus absence of retrieval attempt, and (2) successful versus failed retrieval. There were two relevant findings. First, the PET data confirmed the overall HERA pattern, showing prominent right frontal activation in successful retrieval (recognition of previously studied words as "old"). Second, such prominent right frontal activation was also present when subjects

attempted to recognize test items but failed to do so, because all the test items were "new", not previously seen in the experiment. Thus, the fact that the right frontal lobe shows activation in both cases suggests that this activation does not depend on retrieval success but rather reflects attempts at retrieval, or the episodic "retrieval mode" (Tulving, 1983).

These studies also revealed other regions, in more posterior brain areas, that were more active in successful remembering than in unsuccessful remembering. These regions presumably reflect the processes involved in actual retrieval ("storage sites") of the information that subjects used in successful recognition.

Although the jury is still out on the issue of the involvement of right frontal lobe regions in episodic retrieval, the available data leave little doubt that the maintenance of the episodic retrieval mode is one of the important roles that the right frontal lobe plays, most likely in close interaction with other regions (Nyberg et al., 1996c).

What is this retrieval mode that we think we have spotted in the frontal lobes? A plausible hypothesis is that is simply a particular instance of the important concept of "set". Set, under various names, has been studied in psychological laboratories from the earliest days, beginning with the Würzburg school. A great deal of evidence suggests that set plays an exceedingly important role in all sorts of mental activity. It does so by determining the kind of processing that is to be performed on incoming stimuli and inhibiting the many other kinds of processing that the brain is capable of performing on the same stimuli.

Thus, neuroimaging findings suggest that one of the main functions of the frontal lobes is the establishment, maintenance, and switching of sets. This idea is in good agreement with a great deal of clinical and neuropsychological evidence that is pointing in the same direction, and that has been discussed under the rubrics of sustained and selective attention, executive functions, supervision, monitoring, organizing, temporal sequencing, and so on. Many of these concepts can be thought of as referring to different kinds of set, that is, readiness for specific action coupled with inhibition of other possible actions.

CONCLUSION

Let me sum up under the title "lessons learned". What is it that we now know about memory that we did not know, or did not quite know, before these early PET studies were carried out? We have learned a number of things.

We have learned that PET can be used both to localize cognitive processes and to arbitrate theoretical disputes.

We have learned that PET is capable of "picking up" the hippocampus, but that there is as yet no simple way of describing exactly what the role of the hippocampus is.

We have learned that memory circuits in the brain are much more extensive than previously thought, clearly going beyond the medial temporal regions that

have received a great deal of attention before. They encompass many widely distributed subcortical and cortical regions.

We have learned that memory circuits in the brain, even if extensive, are quite specific, perhaps surprisingly so. Even the separation between encoding circuits and retrieval circuits is quite striking.

We have learned that a curious hemispheric asymmetry exists between encoding and retrieval in episodic memory, as well as between episodic retrieval and semantic retrieval.

Finally, we have reaffirmed the highly specific role of the frontal lobes as the master control center of the cognitive operations of the brain, influencing cognitive processing and mental phenomena through the adoption, maintenance, and switching of sets.

At the start of this chapter, I quoted "Garry" Boring, the historian, and one of my professors when I was a graduate student: "The truth about how the brain functions may eventually yield to a technique that comes from some new field remote from either physiology or psychology." If he came back today, to find out how his prophecy has fared, I am sure he would be as impressed and pleased with what has happened as we all are. He would be even more impressed, I think, to find out how quickly, in just a few years after the introduction of the new technique, our understanding of the brain/mind relations in memory has begun to change. He would call it genuine progress.

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