

Neuroimaging studies of memory: theory and recent PET results

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Introduction

Until recently, most of our knowledge about the areas of the human brain involved in memory processes came from studies of patients with brain injuries. Beginning with the seminal work of Scoville and Milner (1957), an enormous literature has been produced on memory deficits that result from selective brain lesions (see Volumes 3 and 8 of the *Handbook of Neuropsychology* for several extensive reviews). The results of lesion studies enable researchers to make inferences about normal memory.

Over the past decade, several neuroimaging techniques have been developed that allow us to study the functional anatomy of the normal human brain. These techniques indirectly measure neuronal activity in awake, healthy humans and thus can provide new insights into neuroanatomical correlates of mental functions. Results from neuroimaging studies yield evidence complementary to that gained from lesion studies and can help to provide a broader experimental basis for the study of human memory.

This chapter focuses on one neuroimaging technique, positron emission tomography (PET). Other techniques, such as functional magnetic resonance imaging (fMRI) and single photon emission computed tomography (SPECT) are also being developed and applied to the study of memory. As these techniques share a number of common features, many comments we make about PET are also applicable to other techniques.

The chapter is organized into three main sections: (1) we describe how PET, as a technique, can be employed to study memory; (2) we describe a current model of memory that proposes the existence of multiple forms of memory and memory processes; this framework has had a direct impact on the way neuroimaging researchers have approached the study of memory; (3) we review a number of PET studies of memory and discuss how these studies complement what is already known from other methodologies.

PET as a neuroimaging tool

Performance of any behavioral or cognitive task is subserved by neuronal activity distributed over wide areas of the brain. Changes in this neuronal activity are accompanied by changes in blood flow (Raichle, 1987). PET can measure these changes accurately (Cherry, Woods, Hoffman et al., 1993; Fox, Mintun, Raichle et al., 1986; Mintun, Fox and Raichle, 1989; Raichle, 1987) and thus can be used to identify brain areas that are differentially active during performance of different tasks (Posner, Petersen, Fox et al., 1988). With respect to the domain of memory, this means that brain areas related to specific memory processes can be studied using PET by having subjects engage in memory tasks within the PET scanner. Several technical and methodological features impose constraints on what PET can and cannot do in the study of memory.

How PET measures blood flow

PET measures regional cerebral blood flow (rCBF) by monitoring the accumulation of a radiolabeled isotope in the brain (usually H_2^{15}O). Typically, the radioactive water is injected as a bolus into an arm vein; after which the measurement of rCBF takes about 1 min to complete. This measurement constitutes what is referred to as a 'PET scan'. All neuronal changes in a given brain region are accumulated over the temporal interval of a scan. If brain areas become active or inactive during the scanning period, the resultant PET image will appear as a weighted average. Thus, PET scans have a limited temporal resolution.

PET scans also have finite spatial resolution. Single regions of blood flow change can be localized to within a few millimeters of their sources (see Fox et al., 1986; Fox, Miezin, Raichle et al., 1987). Loci of simultaneously imaged blood flow changes, however, can be resolved as independent sources only if they are separated by a distance that is greater than the reconstructed resolution of the PET image (typically 10–20 mm; see Raichle, 1987 for explanation). Changes occurring on a smaller spatial scale are blurred together.

Averaging PET data

PET data can be meaningfully gathered and analyzed for a single subject (Silbersweig, Stern, Frith et al., 1993). However, because the signal-to-noise properties of individual PET scans are poor, and because interest usually centers on localization of function that represents a typical subject, various averaging routines are commonly used. PET data from individual subjects are merged into a standardized stereotactic space and summed together (Fox, Mintun, Reiman et al., 1988; Friston, Frith, Liddle et al., 1991b). More advanced averaging procedures are being developed to transform PET data into standardized space by using detailed anatomical information from magnetic resonance imaging (MRI) scans.

Between-subject variability

Steinmetz and Seitz (1991) have suggested that individual differences may limit the ability to detect some functional activations when averaging procedures are used. It is possible that averaging across subjects may miss activations that exist in individual subjects or subsets of subjects, either because of anatomical variability that exists across subjects (Raichle, Mintun, Shertz et al., 1991) or because of the multiple strategies that different subjects may adopt for performing a given task (e.g. Raife, Fiez, Raichle et al., 1992). Methods of across-subject standardization have been (Fox, Perlmutter and Raichle, 1985; Fox et al., 1988; Friston et al., 1991b) and are continuing to be developed to deal with anatomical variability. Procedures for signal averaging within subjects are also being employed (Silbersweig et al., 1993).

Nonetheless, robust and reliable activations have been shown to exist across individual subjects (Fox and Pardo, 1991) and groups of subjects (Buckner, Petersen, Ojemann et al., 1994a). Averaging across subjects has proven to be a powerful method for increasing signal-to-noise properties (Mintun et al., 1989), and it has provided the wealth of PET data that have been collected. In the PET memory studies reviewed here, in which averaging procedure were used, the data represent activations shared by a number of subjects.

Experimental design of PET studies

A single PET scan (or group of averaged PET scans) can be thought of as a minute-long snapshot of the brain at work. Such a single snapshot, however, is difficult to interpret because it represents an unknown combination of structural and functional determinants of blood flow (e.g. gray and white matter, differences in capillary density). Fortunately, multiple (6–10) PET scans can be acquired for a single subject during a scanning session. Radioactive water has a short half-life (123 s) and is only present in the blood stream after injection for about 10 min. After the ra-

diolabeled water from one injection has decayed, it is possible to begin another injection with very low exposure of the subjects to the harmful effects of ionizing radiation (Herscovitch, Markham and Raichle, 1983; Raichle, Martin, Herscovitch et al., 1983). In order to gain information about 'functional neuroanatomy', PET studies take advantage of the ability to do multiple scans and attempt to identify changes in rCBF by comparing different task-induced brain states (Fig. 1). As it is difficult to determine an absolute resting blood flow level against which the task-induced changes can be compared, it is necessary to specify at least two tasks experimentally.

We refer to the two tasks that constitute the basic unit of this design in a PET study as 'comparison' tasks. In any given comparison, one of the comparison tasks is designated the 'target' (experimental) task, and the other the 'reference' (control) task. These designations specify the direction of the subtraction of images: the image of the reference task is always subtracted from the image of the target task. Otherwise the designations are arbitrary, and reversible. A task can assume either role in the subtraction. In practice, the target task is usually designed to contain processing demands that are thought to go beyond the processing demands of the reference task.

For example, to identify the brain regions acutely active during visual stimulation, a subject might un-

dergo a PET scan while looking at a flashing checkerboard – the target task. A second PET scan might be acquired while the subject looks at a blank screen – the reference task. The subtraction of the image of the reference task (blank screen) from the image of the target task (flashing checkerboard) reveals the regions in which blood flow differed between the tasks, and thereby 'localizes' the differences in the neuronal processing requirements of the two tasks.

A major challenge in PET studies of memory is in cognitive task design (Fig. 1). Many reported experiments are difficult to interpret simply because the differences between target and reference tasks, and therefore differences in blood-flow images, are underconstrained. The objective is to design two tasks that differ from one another in only a single processing component. As the processing components of tasks are usually not known, one can only approximate this objective. Because it is necessary to always interpret activation differences between two or more PET scans, the challenge of task design consists of the proper selection and implementation of both comparison tasks. The selection of reference tasks is just as important as the selection of target tasks.

1. Activation (blood flow) patterns from single tasks are difficult to interpret, as are differences between widely different tasks. An ideal design would include

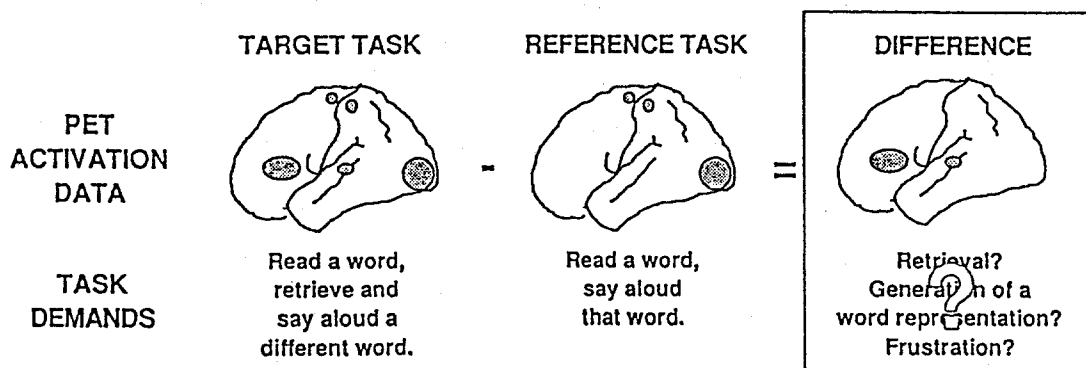


Fig. 1. A diagram showing the logic of PET activation studies. PET activation studies are able to identify brain areas that change in activity between a target (experimental) task and a reference (control) task by observing the difference in PET activation between the two comparison tasks. The difference in activation reflects brain regions that are contributing to the task demands that differ between the target and reference tasks. It is therefore extremely important to analyze the task demands of both the target and reference tasks in order to understand the differences in activation patterns.

at least two comparison tasks which differ from one another by a single processing component.

Task analysis is critical in understanding the differences observed in activation studies. Seemingly unimportant variables, such as stimulus rate, the amount of practice before the beginning of a task, and the format of the presentation of stimuli, may turn out to have large effects on the observed activations, as demonstrated in several studies (e.g. Wise, Hadar, Howard et al., 1991b; Howard, Patterson, Wise et al., 1992; Buckner et al., 1994a; Raichle, Fiez, Videen et al., 1994). All relevant variables must be considered carefully when designing experiments.

II. Task analysis is critical to the understanding of the meaning of PET activations. Variables that are initially thought to be unimportant may turn out to affect greatly the activation patterns observed.

In practice, the use of multiple target and reference tasks can help to avoid misinterpretations caused by not fully understanding the demands of any single task or task pair. If basic cognitive processes exist that are supported by localizable brain areas, similar activations will emerge across experiments. However, one must always keep in mind when looking across experiments that small changes in task designs may produce reliable changes in the cognitive processes required and hence activation patterns. Multiple scan tasks can also be used to produce more complex experimental designs that compare several target tasks to the same reference task. Within such a design, activation differences amongst the multiple comparisons can only be attributed to the demands of the target tasks, because the reference task is held constant. Factorial experimental designs are also possible and can be used to increase interpretive power.

Blood flow change: increases and decreases

Differences in blood flow between a target experimental task and a reference control task fall into two categories: (a) increases in rCBF and (b) decreases in rCBF. The label of the direction of change, increase

or decrease, depends solely on the designations of the two tasks as target and reference. From the point of view of an experimenter, both kinds of changes are equally revealing, and equally important.

Increases in rCBF are thought to indicate brain areas that are 'more involved' in the performance of the target task than the reference task (activations). But it is important to keep in mind that brain areas that show increased activation are not necessarily the only areas that are being used to complete the target task. Brain areas that are used in both the target and reference tasks contribute to both tasks but will cancel each other in a comparison image. It is exactly this ability to subtract out activations that allows PET experiments to isolate brain areas relating to specific sets of processes.

The interpretation of decreases in rCBF is similar. Decreases in rCBF (deactivations) reflect brain areas that are more active in the reference task as compared to the target task. That is, although reference tasks are usually designed to contain fewer processing demands than target tasks, in practice they often contain processing demands that are not included in the target tasks. When this occurs, some brain areas may be less active in the target task than in the reference task (e.g. see Fig. 5 in Raichle et al., 1994). Under such circumstances, subtracting the reference task from the target task reveals an area of relative decrease in activation in the target task.

It is also possible that apparent increases and decreases in comparison PET images result when the overall neuronal activity in a brain area is suppressed. If net activity in a brain area is reduced because of the task demands related to the target task, a decrease in activation will be observed when comparing the target task to the reference task. Increases in activation might be observed if regional neuronal activity is suppressed in the reference task.

III. Any cognitive task can serve the role of either the target task or the reference task. Any reliable difference between the two tasks, whether designated as an 'increase' or a 'decrease', is potentially significant.

PET data analysis

Procedures of PET data analysis usually attempt to answer the same question: what brain regions change in rCBF (activation) between comparison tasks (e.g. target versus reference)? (several other analysis strategies have been described; Horwitz, Grady, Haxby et al., 1992; Friston, Frith, Liddle et al., 1993; Roland, in press). Problems arise because it is not always clear which changes represent biological signal versus noise. Any single PET image of the brain can be divided into thousands of small volumes because of the large volume imaged. A number of statistical procedures have been developed to deal with the problem of separating signal from noise (Fox and Mintun, 1989; Friston, Frith, Liddle et al., 1991a; Worsley, Evans, Marrett et al., 1992).

The statistical procedures should be viewed as a provisional means for identifying meaningful activations. The strongest test of what represents a salient finding lies in the reproducibility and generalization of the results. Findings that are replicated across different experiments or subject groups provide a higher level of certainty than those that are seen just once.

PET measures acute changes in neuronal activity

A final consideration in applying PET to the study of memory is that not all aspects of memory function are necessarily a result of acute increases in net neuronal activity. Physical changes that are believed to underlie lasting forms of memory such as synaptic reorganization and synaptic facilitation may be mediated by mechanisms that occur over extended periods of time (Gall and Lauterborn, 1991). The metabolic demands of such processes and their effects on blood flow are not known. In this respect, some aspects of memory processes may not be revealed by PET activation scans that are acquired over short periods of time. Although it is difficult to specify these processes with certainty, it is not reasonable to assume that all processes produce the same level of PET activation.

For these reasons, it is often difficult to interpret negative findings produced by PET. In practice, there are two types of negative findings. In some instances,

no difference in activation may be observed between a target task and a reference task in an area of brain which has been observed to show an activation change in a different task comparison. Such an observation shows that the brain area in question can modulate blood flow and produce a signal detectable by PET. For that brain area, the absence of activation in a given comparison then can be interpreted as suggesting that net activity remained constant between the target and reference tasks. In other instances, activation is not observed within brain areas that have never shown activity in PET studies. In these cases, the negative finding is more difficult to interpret because there has been no demonstration that PET can detect physiological changes in that structure.

IV. Negative findings, that is absences of observed activations, in PET studies should be interpreted cautiously.

Summary

PET is a neuroimaging technique that can indirectly measure changes in neuronal activity in normal human subjects. By doing so, PET is able to detect relative changes in the brain areas that are differentially involved in the performance of two comparison tasks. The technique has several limitations. These have to do with temporal and spatial resolution, and the difficulty of designing task paradigms that can isolate specific task components or cognitive processes. Negative results with PET are difficult to interpret. Despite these difficulties, PET studies can provide reliable and meaningful data. When carefully designed comparison tasks are used, the PET technique provides a useful complement to other techniques and helps to elucidate neuroanatomical correlates of memory.

Multiple forms of memory and multiple processes

The most notable progress in the study of memory that has occurred over the past several years is the acceptance that 'memory' is not a single function. This conceptual revolution has been fueled by observations of

systematic dissociations in task performances and biological dissociations that cannot be readily accommodated within the unitary-memory framework. Memory at present is understood as multiple systems that differ with respect to their behavioral and cognitive domains as well as their rules of operation. Different forms of memory depend on separate, but not necessarily non-overlapping, sets of brain structures and mechanisms (Warrington, 1981; Tulving, 1983, 1985; Schacter and Moscovitch, 1984; Squire, 1987, 1992; Weiskrantz, 1987, 1990; Tulving and Schacter, 1990; Schacter and Tulving, 1994).

This focus on multiple forms of memory has been of great benefit to PET researchers by providing a framework to guide their efforts. The following sections describing PET studies of memory are ordered according to different forms of memory: procedural, semantic, episodic, and working memory. This division is based on distinctions made at the cognitive level. Procedural memory refers to the learning of motor and cognitive skills; semantic memory refers to the acquisition and use of general information about the world; episodic memory refers to the recollection of specific events; and working memory refers to the short-term maintenance of information. More detailed descriptions of the characteristics of the memory processes relating to each group are included at the beginning of each section. This fourfold grouping allows for a more elaborate classification than other divisions based on (a) the type of tests administered during a memory task (e.g. explicit versus implicit; Schacter, 1987), (b) whether memory tasks primarily address data driven or conceptually driven processes (Roediger and Blaxton, 1987), or (c) whether performance on tasks is impaired after brain damage causing amnesia (e.g. declarative versus non-declarative; Squire, 1987). As research on both the cognitive and neurobiological fronts progress, classification schemes employed are likely to be modified.

V. 'Memory' is not a unitary function. The brain has multiple systems to allow experience to modify how it processes information. These systems may rely on separate brain structures.

Memory tasks are not pure

We organize the sections of this review into four different forms of memory for the sake of exposition only. There is no one-to-one correspondence between tasks and forms of memory. All tasks engage multiple forms of memory, either by virtue of task requirements or subject-determined strategies.

A further important point to be noted is that almost all cognitive tasks are, in a certain sense, 'memory tasks'. They either require that subjects rely on previously acquired information or they cause 'incidental' storage of information in memory systems, or both. For example, obeying experimental instructions in carrying out a 'language' task, or an 'attention' task, depends on retrieval of previously stored information, and is likely to affect the pattern of cerebral blood flow. This means that PET studies ostensibly done for other purposes may reveal the operation of memory. This also means that findings from 'non-memory' studies may be misinterpreted, because memory processes involved in them are overlooked. We will illustrate these points throughout our discussions of PET memory studies.

VI. Memory is pervasive; different kinds of memory processes are present in many cognitive tasks, even when they are not experimentally specified.

Memory processes occur over time

Every single act of memory can be analyzed into stages that extend over time. The situation is more fully described in the General Abstract Processing System (GAPS) model of episodic remembering (Tulving, 1983), but GAPS also holds for other forms of memory.

According to GAPS, an act of memory begins with encoding processes and ends with the use, or retrieval, of the encoded information. Encoding refers to processes related to perceiving and organizing information presented to the senses from the external world as well as information generated by other cognitive systems 'internally'. Encoding processes create representations (engrams, or memory traces) of the information in

memory. Storage refers to the maintenance of the representations over time. Retrieval processes bring a present 'cue' into interaction with the stored information to produce a cognitive or behavioral 'expression' of the information. Within a given memory system, encoding, storage, and retrieval relate to each other in a hierarchical manner. Retrieval depends on storage, and storage depends on encoding, although encoding does not necessarily lead to long-term storage, and storage itself does not guarantee retrieval.

Across different memory systems and events, the hierarchical relations need not hold. Thus, for instance, retrieval of semantic information may co-occur with encoding of the retrieved information into episodic memory as a unique event (Tulving, 1972). Similar relations between retrieval and encoding hold across different acts of memory even within a single system: retrieval of one act of memory may result in simultaneous encoding of relevant information about another act.

It is quite possible that multiple brain pathways underlie these temporally separate stages of memory processing within and between systems. PET studies of memory must pay careful attention to the memory processes that are being addressed. Brain areas required during one set of processes (e.g. storage) need not be active while temporally distinct sets of processes are being engaged (e.g. retrieval).

VII. Memory processes take place over an extended period of time that includes encoding, storage, and retrieval. These temporally distinguishable sets of processes may be subserved by different brain structures and mechanisms.

The existence of multiple forms of memory and distinct sets of processes for each form of memory provides for an interesting interaction that directly affects PET studies of memory. Retrieval during a memory task directed at isolating one memory system may be sufficient to store information in another system. For example, if a subject is asked to name the last five Presidents, the task event may be encoded in episodic memory, even if it is not recalled at a later time. In this example, then, the act of (semantic memory)

retrieving is also an act of (episodic memory) encoding and storage. The dual function of such a cognitive act has direct consequences for PET studies of memory. In practice, it is difficult for an individual memory task to isolate one form of memory, or one set of memory processes. This fact provides a major challenge to researchers when applying imaging technologies to the study of memory. Each memory task must be analyzed carefully to determine what types of memory processes are being elicited incidentally, as well as intentionally.

VIII. Different forms of retrieval and encoding may occur simultaneously. The act of retrieving information from one memory system may cause information to be encoded and stored in another memory system.

PET studies of memory

The following sections provide a selective review of published PET memory studies. Neuroimaging methodology is continually improving as experience with these techniques grows and an increased partnership between neuroscience, neuropsychology, and cognitive science develops. Studies are described whose designs provide the most interpretable findings. Some studies are described in more than one section of the chapter, because their results have implications for different forms of memory.

PET studies of procedural memory

Procedural memory has to do with the acquisition, retention, and performance of skills and procedures. Procedural memory may be broadly thought of as the modification of patterns of behavior, both motor and cognitive, so that the execution of the behavior changes with practice. Procedural memory does not represent a unitary type of memory, but is a heterogeneous group of processes by which experience with tasks modifies the execution of the tasks.

Two characteristics of procedural memory are relevant to a discussion of PET studies. First, procedural memory is measured by observing systematic changes in quantified aspects of performance other than the

propositional or declarative 'contents' of the task. Typical measures are time-based: reaction time, response latency, time to criterion, and other related indices of skilled performance (e.g. accuracy). For PET studies, tasks should be selected so that the overall amount of motoric (and cognitive) activity remains constant during learning. Otherwise, it is difficult to assess the extent to which changes in activation are attributable to changes in the level of skill or execution. For example, if motor activity increases during learning then it is difficult to determine whether increases in PET activation reflect brain areas being used more because of the advanced learning state or simply because of the increased motor activity. Second, performance changes occur relatively gradually (but not necessarily linearly) with increased practice with a task (Fitts, 1964). This means that procedural learning may take place during a PET scan as well as between PET scans, depending on the design of the study.

Several laboratories have used PET to study procedural memory tasks. An extensive review of these studies has been presented by Thach (in press). Most of these studies have addressed the acquisition of motor skills rather than cognitive skills. In general, the design of these studies has called for subjects to perform a task before and after practice. PET scans are acquired during the initial execution of the task and during later phases of execution.

Studies of motor learning

An early blood-flow study that directly addressed procedural learning was done by Seitz, Roland, Bohm et al. (1990). Their task required subjects to touch their right-hand finger tips with their thumb in a set order of sixteen positions which was continuously repeated. PET scans were obtained after minimal practice with the task (initial learning), after 50 min of practice (advanced learning), and after another 50 min of practice (skilled performance). Task comparisons involved the task at different stages of practice. Because the rate of finger movements increased by more than 75% from the initial to the final scan, it is not clear to what extent the observed increases in activation reflect im-

proved skills versus changes in rate of responding. A number of brain areas showed deactivations as practice proceeded. These included areas in right prefrontal cortex in a location the authors describe as the 'Broca homologue area in the right hemisphere' and in right somatosensory cortex. No change was observed in cerebellar cortex but, because the motor output increased dramatically between initial practice and skilled performance, the authors suggest that 'this finding is in accordance with a higher afferent input (climbing fibers) to the cerebellar cortex during the initial phase of learning' (Seitz et al., 1990, p. 60).

Other studies of motor learning have used continuous paced finger movements. Friston, Frith, Passingham et al. (1992) had subjects perform a target task in which subjects touched their right-hand thumb to each of their fingers sequentially. This finger touching task was carried out repetitively across three scans that were separated by 'rest control' tasks that served as the reference scans. It was assumed that processes related to procedural memory were utilized across the three task scans, although actual task performance was not assessed. The main finding related to sequential task performance was that areas in right lateral and medial cerebellar cortex showed a decrease in activation across the sequential PET tasks, compared to the rest conditions. The decreases in activation, however, were partially accounted for by an increase in activation in the rest reference condition.

In another study of paced finger movements, Jenkins, Brooks, Nixon et al. (1994) scanned subjects while they performed a finger sequencing task similar to that of Seitz et al. (1990) with two main differences. First, the subjects were not informed of the finger sequence. Rather, the subjects were required to identify and learn the sequence using an auditory cue as feedback. Second, movements were paced at one movement per 3 s, thus holding constant overall movement levels. Two reference tasks were used. In one, subjects performed a sequence of finger movements that they had learned before the PET session. In the second reference task, subjects simply rested. All movements were made with the right hand. The main findings in this study were that areas in cerebellum, lateral premotor cortex, and parietal cortex bilaterally became acti-

vated more in the motor learning condition than in the motor control task as compared to the rest reference task. In addition, prefrontal cortex was activated only in the motor learning task.

At least two studies have focused on the acquisition of visuo-motor skills using a pursuit motor task. The pursuit motor task requires subjects to hold a stylus on a small target on a revolving disk. Subjects exhibit procedural learning by improving their ability to precisely track the target with the stylus. Performance is measured by recording the percentage of the time that the subjects keep the stylus in contact with the target. Because the speed of rotation is held constant across consecutive trials during learning, this task allows better control over the amount of gross motor activity, making it suitable for PET studies. Grafton, Mazziotta, Presty et al. (1992) reported PET activation during the performance of the pursuit task (right-hand) as compared to a reference task in which subjects followed the revolving target with their eyes only. Their results showed that many brain areas, including those in bilateral motor cortex, SMA, visual cortex, putamen and the cerebellum, were activated more in the pursuit task than in the reference task. More important, three areas showed increased activation as the task was practiced during and between four sequential PET scans: left primary motor cortex, left SMA, and the left thalamus near the pulvinar nucleus. No deactivations were observed, nor were any practice-related changes detected in cerebellar cortex.

In another report, the same group (Grafton, Tyszka and Colletti, 1993) studied the pursuit motor task but extended the scanning procedure over two sessions that included six PET scans in which the pursuit motor task was performed. Performance level stabilized by the fourth PET scan. Activations in six brain areas, including bilateral motor cortex, SMA, and right anterior cerebellum, increased in magnitude across practice. Unlike the previous study (Grafton et al., 1992), no significant longitudinal increase in activation in the left thalamus was reported.

Studies of cognitive skill learning

A study by Raichle et al. (1994) explored the effects

of practice on a target task in which subjects were asked to produce verbs that were meaningfully related to visually presented nouns (verb-generate task). For example, a subject would see the noun 'plane' and respond with the verb 'fly'. In the corresponding reference task, subjects would see comparable nouns and simply repeat (read) them aloud. This pair of tasks has been extensively studied by the Washington University PET group (Petersen, Fox, Posner et al., 1988, 1989), and the functional anatomy associated with the task in typical subjects has been well characterized (Raichle et al., 1994).

In the Raichle et al. (1994) study, subjects were given extended practice on the verb-generate task. PET scans were obtained during three repetitions of the verb-generate task. During a 'naive' scanning condition, subjects were exposed to the task for the first time. After practicing the verb-generate task across eight blocks using the same list of nouns, the subjects were scanned while performing the task in a 'practiced' state. A final 'novel' verb-generate task scan was done while the subjects viewed a new set of nouns. Thus, the novel condition differed from the naive condition with respect to amount of practice related to the general task demands, and from the practiced condition with respect to item-specific practice. Figure 2 shows that performance during this task changed with practice in two ways: response times became quicker and response selection became stereotyped. The decreased reaction times reflected item specific effects, because reaction times returned to their initial longer levels during the novel task.

Comparison of the PET data obtained during the various forms of the verb-generate task to the noun-repetition reference task revealed an interesting pattern of functional change. Activations in anterior cingulate, left prefrontal cortex, left temporal cortex, and the right-lateral cerebellum, initially present during naive performance, disappeared during practiced performance. These areas were again active in the novel condition. A further, important, observation was that these activations were accompanied by reciprocal changes in Sylvian-insular cortex. In the reference condition of reading nouns aloud, bilateral activations in Sylvian-insular cortices have been observed before

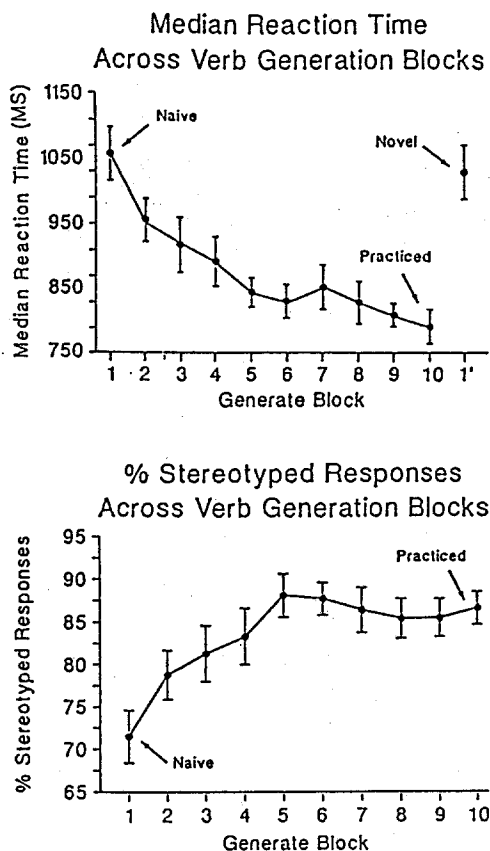


Fig. 2. Two different measures of performance are shown for subjects practicing the verb-generate task of Raichle et al. (1994) in which subjects view nouns and verbally produce meaningfully related verbs. The top figure shows the median reaction times for verb production across ten blocks (labeled 1–10) as the task is practiced with the same set of nouns. Median reaction time is also shown for the novel condition (11) in which the subjects produce verbs to a new set of nouns. The bottom figure shows the percent of stereotyped responses (the same verb is produced repeatedly across practice blocks). As practice progresses, verbal response production becomes stereotyped and requires less time to complete.

(Petersen et al., 1988, 1989) along with activation of primary and supplementary motor cortices. In the naive condition of the verb-generate task, the Sylvian-insular cortices were not active (Fiez and Petersen, 1993). After practice, the Sylvian-insular cortices became active, as if the subjects were now performing a task comparable to the noun-repetition task. Introduction of a new list of words in the novel condition reversed these changes. The authors suggest their data reveal two alternative pathways that can be used to do

the verb-generate task. The first pathway, used in the naive condition, involves several areas including left prefrontal cortex. After practice, when the task was performed in an overlearned state, a Sylvian-insular pathway was involved. The insight from this study is that procedural memory does not simply lead to reductions or increases in the brain areas being used. Rather, procedural learning can lead to the brain using different pathways to complete the same task.

The verb-generate task also illustrates the point that a given experimental task can have components related to several different forms of memory. The verb-generate task is an example of a semantic retrieval task as subjects must retrieve the lexical identity of words and their meanings to complete the task. Likewise, the task is also an episodic encoding task. Both the semantic memory processing demands of this task and the episodic memory demands are discussed in later sections.

Summary

Taken collectively, there are many differences across the several procedural memory tasks that have been reported thus far. In this respect, the use of PET to study procedural memory is still in its beginnings, and the relevant variables that isolate processes will have to be characterized more precisely. Nonetheless, several insights have emerged from the existing PET data. Cerebellar cortex and prefrontal cortex tend to be active during the initial performance of tasks, when the tasks are performed laboriously and are being learned. As tasks become practiced, cerebellar cortex becomes less active but is not always eliminated. For those tasks that produced prefrontal cortex activation, the activation was only present during initial learning and disappeared during over-learned task performance. These observations, taken together with those of Raichle et al. (1994) and Thach (in press), suggest that pathways involving regions in prefrontal cortex and the cerebellum tend to be activated during the initial acquisition of a procedural skill. After the acquisition of the skill, cerebellar cortex is activated to a lesser degree and prefrontal cortex may no longer be differentially involved.

PET studies of semantic memory

Semantic memory refers to the processes by which pieces of information, facts about the world, and general knowledge are acquired and retrieved. Unlike episodic memory, discussed in the next section, semantic memory does not contain information about the context or time associated with the information being remembered. The knowledge of who the name 'Gandhi' represents would be an example of semantic memory; the recollection of the context in which this fact was learned is an example of episodic memory. Some semantic retrieval tasks, such as reading, are highly overlearned and executed with little effort. The use of semantic memory outside of the laboratory takes numerous forms. Our abilities to name objects, know what they are used for, and what to say when we speak are all examples of semantic memory. Similarly, experiments studying semantic memory have taken many forms. Subjects have been asked to name pictures, identify words, order numbers, and speak. A note of caution: In the domain of language, researchers often use the term 'semantic' to refer to processes having to do with the access to the meanings of words or pictures. Our use of the term 'semantic' in the context of memory refers to the generic knowledge of the world, its encoding, storage, and retrieval. It includes but extends beyond purely linguistic knowledge.

It is not an easy matter to separate semantic memory encoding and storage from episodic memory encoding and storage in PET studies. The difficulty resides in the fact that there is no simple way to present information without associating it with an event specific context. In the Episodic Memory section, some experiments are discussed that probably also produce semantic memory encoding. These experiments are included within the later section because processes surrounding episodic encoding could be more directly addressed.

Similarly, tasks that primarily require semantic memory retrieval differ from tasks which rely on episodic memory retrieval because they do not require that semantic retrieval be directed at any specific setting or source. Although access to related episodic information may sometimes augment semantic-

memory performance, in most semantic retrieval tasks episodic information plays a limited role, because it is not of great benefit. For example, if asked to do a semantic retrieval task in which the goal is to read the word 'pencil', one does not benefit from trying to remember where a pencil was seen last (episodic retrieval). Few cognitive tasks, and especially language tasks, exist that do not require some form of semantic retrieval. This is not surprising considering previously acquired information about linguistic units is carried into almost any situation.

PET studies of semantic memory have mainly focused on language tasks. These studies have been reviewed elsewhere in the context of language processing (Demonet, Wise and Frackowiak, 1993; Petersen and Fiez, 1993). In the present review, the focus is on what these studies tell us about semantic memory. As most of these studies were not designed as studies of memory, our interpretations of them may vary from those offered by the authors of the studies.

PET studies of semantic retrieval can be classified in terms of the extent to which the stimulus cues constrain the retrieval event. In some tasks, the experimentally supplied stimulus cue is readily associated with the to-be-retrieved target item. The cue 'drives' the retrieval of the target item in a highly directed, automated manner. Reading a single word is an example of this form of semantic memory retrieval. We label these 'stimulus driven semantic retrieval' tasks. In other tasks, the retrieval cue provides a context, but does not directly specify the target information. More elaboration of the presented information is needed for retrieval of the relevant information in these tasks. We label these 'elaborate semantic retrieval' tasks. The distinction we are making is based on similar distinctions made in the context of verbal output by Raichle et al. (1994) and Frith, Friston, Liddle et al. (1991) and in the context of memory tasks by Roediger and his collaborators (Roediger and Blaxton, 1987; Roediger, Weldon and Challis, 1989).

Studies of stimulus driven semantic retrieval

Petersen et al. (1988, 1989) and Petersen, Fox, Snyder et al. (1990) performed several exploratory studies of

single word processing that included semantic memory retrieval of words. During one PET scan, subjects passively viewed visually presented nouns, one word per s (150 ms stimulus duration). Viewing a visual word, even during passive presentation, is believed to automatically engage low-levels of lexical processing of the word's form (Posner, Sandson, Dhawan et al., 1989). In the Petersen et al. (1988, 1989) study, passive noun viewing, as compared to viewing a fixation point alone (fixation), produced activations bilaterally in striate and extrastriate cortex with more prominent activations on the left. As viewing a fixation point alone contained much less visual stimulation than passive word viewing, it was impossible to tell whether the word-related activations were attributable to the nouns or simply to the increased amount of visual stimulation.

Another study was conducted in an attempt to identify those features of words (e.g. simple visual features, letters, orthographic regularity) that were responsible for the additional activations of the visual cortex (Petersen et al., 1990). The experiment included five tasks. Two of the tasks (fixation and passive noun viewing) were the same as in the earlier

study (Petersen et al., 1988, 1989). Again, activations observed in the passive noun viewing task, when compared to the fixation task, were in bilateral extrastriate cortex. In the three other tasks, visual word-like stimuli were presented: (1) false-fonts, which were sets of letter-like configurations that contained the visual features of English words and letters; (2) consonant letter-strings, which were strings of real letters that did not follow the spelling rules of English (e.g. 'hdjlx'); and (3) pseudowords, which were letter strings that followed the spelling-to-sound regularities of English but were not real lexical units (e.g. 'floop').

By comparing the brain response to each of these word-like stimuli and real English words, Petersen et al. (1990) were able to identify a left-lateralized medial extrastriate brain area that was most activated by real words and pseudowords (Fig. 3). Both of these stimuli obey the general rules of English spelling, a regularity that is learned during childhood. This left-lateralized medial extrastriate region is thus one brain area that can be assigned a role in semantic memory.

Activation in this medial extrastriate region does not seem to be produced in an all-or-none manner. Petersen, Corbetta, Miezen et al. (1993b) observed

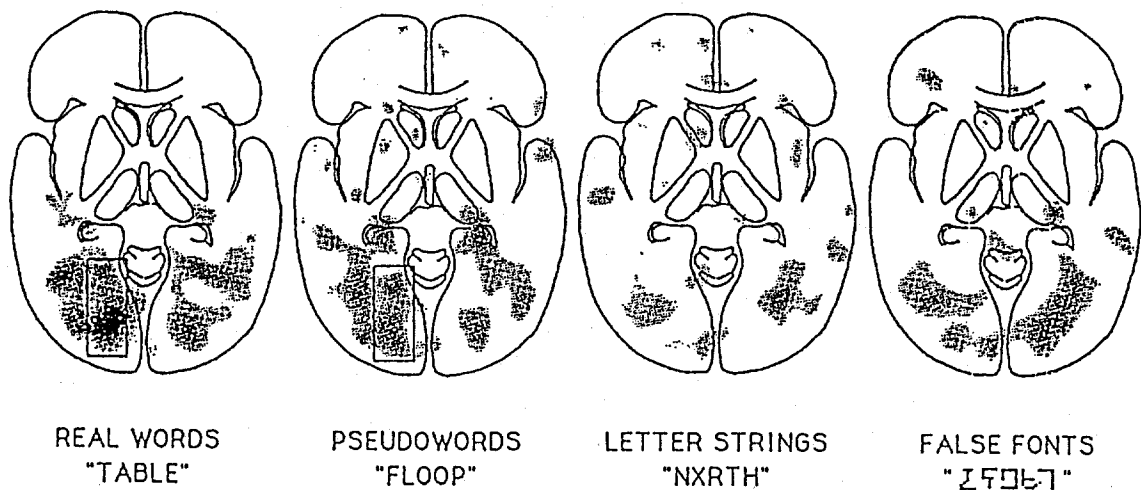


Fig. 3. PET data are shown in horizontal section for four of the target experimental tasks of the Petersen et al. (1990) study. In each of the target tasks subjects viewed one of the four stimuli types labeled under the sections. Activations were identified by comparing the four target tasks to a fixation reference task. As is shown, real words and pseudowords, which are both stimuli forms that obey the spelling-to-sound regularities of English and thus rely on semantic memory, activated a left medial extrastriate area (rectangles). Letter strings and false fonts, which share visual characteristics in common with the other stimuli but do not obey the rules of English, only minimally activated this region.

increased activation in this region between passive word presentation and another, more demanding task (having subjects decide if the words belong in the category 'dangerous animals'). Similarly, Raichle et al. (1994) found different levels of activation in this region across the three different semantic retrieval tasks that varied the amount of practice with the verb-generate task (see Procedural Memory section). Findings such as these suggest that the level of activation in medial extrastriate cortical regions, associated with passive viewing of words and pseudowords, varies across word-related semantic retrieval tasks according to their specific task demands.

Howard et al. (1992) studied a semantic retrieval task similar to that of Petersen et al. (1990). In their study, subjects viewed word stimuli. Words appeared on the screen for 1 s each, at a rate of 40 words per min, and subjects read the words aloud. In the reference task, false-font strings were presented and the subjects kept repeating the word 'crime'. The comparison yielded activations in left posterior middle temporal cortex near angular gyrus. A small, but non-significant, activation was observed in the left-medial extrastriate region reported by Petersen et al. (1990) in their semantic memory retrieval task.

Frith et al. (1991) also studied a semantic retrieval task in which stimulus cues elicited well-practiced responses. Before the PET scan, subjects were given practice in orally producing opposites of presented cue words (e.g. hear 'hot', say 'cold'). The target task consisted of the practiced performance of this task. Compared to a reference task in which subjects read words aloud, the PET data yielded no significant differences in activation between the opposite-generate task and the word reading task, suggesting that the two tasks share a similar functional anatomy.

Studies of elaborate semantic retrieval

Petersen et al. (1988, 1989) examined a more elaborate semantic retrieval task in their original language study. For this task, subjects were instructed to say aloud verbs that were meaningfully related to the visually presented nouns (verb-generate). Words were presented once every second. Activations were ob-

served in left-lateral prefrontal cortex, right-lateral cerebellum, and anterior cingulate. The reference task was noun reading. In a later study (Raichle et al., 1994), these findings were reproduced in a nearly identical study that presented words every 1.5 s. In this later study, left temporal cortex was also activated. The activations in the verb-generate task suggest that left prefrontal cortex, in conjunction with several other brain areas, are used during more elaborate forms of semantic retrieval.

Other studies have also demonstrated left prefrontal cortex activation in many tasks that require elaborate semantic retrieval of words (Fig. 4). Frith et al. (1991) had subjects generate words that began with 'S' while hearing the repetitive aural cue 'next'. Subjects similarly completed an 'F' word-generate task. Compared to a reference task in which subjects repeated aurally presented words, the 'F' and 'S' word-generate tasks showed activation in left-lateral prefrontal cortex near Brodmann's area 46 extending back into area 44. In addition, activation in anterior cingulate cortex was observed. Goldman-Rakic (1994) has suggested, based on cytoarchitectonic mapping done in her own laboratory, that the Frith et al. (1991) prefrontal activation might localize to area 45 and/or area 44 and not in area 46. Squire et al. (1992) and Buckner et al. (1994a) had subjects say aloud words that began with visually presented word-stems ('GRE') across three independent PET experiments. Compared to a reference fixation control task, the stem-cued word-generation tasks activated left prefrontal cortex at or near area 45 and anterior cingulate as well as motor and premotor cortices, and visual areas.

All of the studies activating left prefrontal cortex described thus far have required subjects to make a verbal response. To date, at least three additional studies have shown left prefrontal cortex activations in similar semantic memory retrieval tasks that did not require verbal output. Wise, Chollet, Hadar et al. (1991a) had subjects listen to nouns and think of a list of verbs without saying them aloud. Compared to a reference task in which the subjects rested, activation was present in what the authors describe as 'left Broca's area' falling at or near Brodmann's areas 44 or 45. Kapur, Craik, Tulving et al. (1994) had subjects

- ◇ Petersen et al., 1988
- Frith et al., 1991
- ▽ Wise et al., 1991
- Raichle et al., 1994
- ◊ Kapur et al., 1994
- ▶ Buckner et al., 1994 "Case-Same"
- ▼ Buckner et al., 1994 "Case-Change"
- ▲ Buckner et al., 1994 "Auditory"

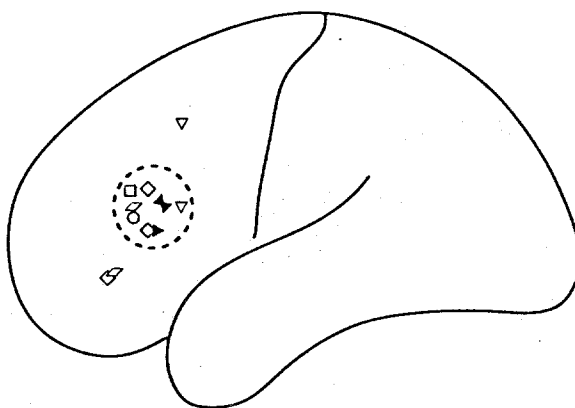


Fig. 4. Symbols are projected onto a lateral view of the left-hemisphere that mark the locations of activations present in elaborate semantic memory retrieval tasks (see text) studied across eight independent experiments. The filled triangles represent three studies that were nearly identical but used different groups of subjects. These filled triangles show an estimate of between subject-group variability. A grouping of responses falls within the dashed circle at or near Brodmann's areas 44 or 45. Other responses extend well outside of this region and are likely to represent sets of functionally distinct activations.

view nouns and decide, by pressing a key, if the nouns represented living or non-living objects. As compared to a reference task in which the subjects decided if nouns contained the letter 'a', activations were observed across left lateral prefrontal cortex near Brodmann's areas 45, 46, 47 and in left area 10. In a similar task, that acquired data on only a small number of subjects, Petersen et al. (1988, 1989) had subjects view nouns and decide if they represented dangerous animals, a task that requires the retrieval of what the words mean. The dangerous animals task produced activation in left prefrontal cortex as compared to a passive noun viewing task.

Although activations were consistently present in left prefrontal cortex across these experiments, the anatomical locations varied somewhat. This raises an interesting question: is the variability in anatomical localization due to the fact that different groups of subjects were used across the studies, or do these differences in anatomical localization reflect distinct functional areas? By replicating very similar tasks across three different groups of subjects, Buckner et al. (1994a) were able to show the range of between-group variability for the stem-cued word-generation task (the filled triangles in Fig. 4). The variance across subject groups was substantially less than the variance observed across experiments. Even when divided by

gender, between group variability was minimal in the stem-cued word-generation task (Buckner Petersen and Raichle, 1994b). Therefore, the differences observed across experiments cannot be entirely attributed to between group variability suggesting that multiple, functionally distinct, areas of left prefrontal cortex are differentially activated across the different tasks. However, a subset of the left prefrontal activations that were observed across the elaborate semantic retrieval tasks formed a closely localized cluster of responses at-or-near Brodmann's areas 44 and 45 (dashed oval in Fig. 4). This region might reflect a common area involved in all of these experiments.

The emphasis on left prefrontal activations should not be taken to mean that elaborate semantic memory retrieval in the domain of language is accomplished by left prefrontal cortical regions alone. Anterior cingulate has also been activated in many of these studies, as have areas in temporal cortex (for a review see Petersen and Fiez, 1993). The complex sets of processes necessary for the performance of semantic retrieval tasks are accomplished by distributed networks of brain areas. We are simply pointing out a set of left prefrontal regions that are reliably activated across a substantial number of elaborate semantic retrieval tasks.

Elaborate semantic retrieval tasks can become stimulus driven

Raichle et al. (1994) explored the conditions under which a task that required elaborate semantic retrieval involved a pathway that activated left prefrontal cortex. This study was discussed in the preceding section on Procedural Memory.

Relevant to semantic memory, Raichle and colleagues showed that the verb-generate task could, after practice, come to be completed without the activation of left prefrontal cortex. As the transition from the pathway involving prefrontal cortex occurred as the task became automatized, the findings further support the notion that the prefrontal cortex is used most during more effortful semantic retrieval. In the practiced state, responses were produced in a quick, stereotyped manner and left prefrontal cortex was not activated. The stereotyped performance resembled that observed during word reading, a highly automated stimulus driven task, that does not require the prefrontal pathway for semantic retrieval to occur. In this regard, semantic retrieval may initially involve a pathway that uses prefrontal cortex and then, as the retrieval event is over-learned and becomes more stimulus driven, alternate pathways may come into play to complete the retrieval event. This may be conceptualized as an interaction of semantic retrieval and procedural memory: brain anatomy underlying semantic retrieval changes as a function of procedural learning.

Summary

Many semantic retrieval tasks using language paradigms have been studied with PET. Heuristically, the retrieval tasks can be divided into those that involve a pathway that activates left prefrontal cortex, and those that do not. At a cognitive level, tasks that activate prefrontal cortex during semantic retrieval tend to demand more elaboration to retrieve the target information. The specific locations of the left prefrontal activations have varied across different tasks. The variability in prefrontal activation sites has been greater across the different tasks than variability observed across different groups of subjects performing

the same task, suggesting that the variation reflects the activation of multiple distinct areas within left prefrontal cortex. A group of closely localized activations appeared at or near Brodmann's areas 44 and 45 across several experiments and may represent a common functional region.

Semantic retrieval tasks in which the cues more directly trigger the response (e.g. single word reading) do not appear to require left prefrontal cortex. One brain area, in left medial extrastriate cortex, has been observed to be involved in early word-form processing (Petersen et al., 1990). Activation in this region appears to be modulated across tasks, suggesting that its participation can be recruited to a higher or lower degree depending on specific task demands. Another study has suggested that a brain area near angular gyrus, in the left posterior middle temporal cortex, can be activated by a different word processing task (Howard et al., 1992).

PET studies of episodic memory

Episodic memory has to do with an individual's recollections of personal events and happenings from the past. It is the form of memory that William James, in his classic *Principles of Psychology*, named 'true memory', and the form that lay people usually associate with 'memory' and 'remembering'. Events and happenings comprise information of two separate kinds: the 'setting' of the event and the 'happenings' in that setting (Tulving, 1983). The 'setting' of the event matches what others have called the 'source' of acquired factual information (Schacter, Harbluk and McLachlan, 1984), and the 'happening' of an event is equivalent to the factual 'contents' of the event such as those in the laboratory that consist in the presentation of some to-be-remembered information (Tulving, 1983).

Episodic recollection of an event consists of the retrieval of information about a particular happening in a particular context, together with the personal perspective of the rememberer associated with an event. It typically includes reference to both kinds of event information – setting and happening, or source and fact – as well as the rememberer's personal participa-

tion in the event. In everyday life, episodic memory is used less frequently than other forms of memory. Episodic memory is only required when it becomes important to remember a specific event, or specific past happenings. Eyewitness testimony, recollection of a day's events, and trying to remember where one put one's keys or glasses are all examples of 'tasks' that depend on episodic memory. In the laboratory, typical episodic memory tasks require subjects to recall or recognize previously studied items. In other episodic tasks, subjects have been asked to remember the temporal order of presented pictures, what words were included on a recently presented list, and to decide which of two people said a phrase.

Several characteristics of episodic memory that have been determined at the cognitive level are relevant to PET studies. First, not all of the information that is perceived forms episodic memories. Craik and Lockhart (1972) observed that encoding was not an all-or-none process and that some forms of encoding better facilitated episodic remembering. For example, a string of printed letters can be encoded at many levels: the visual form may be encoded and understood to represent a word, the phonological sounds the letters represent may be encoded, and the word's meaning may be understood. Episodic memories on verbal tasks are best formed after elaborative encoding of words' meanings. Furthermore, episodic encoding does not require the intention to remember. Information presented within the context of a task that requires processing of word meaning is sufficient to produce remembering, whether or not the subject is instructed to remember. In this regard, in many PET tasks episodic encoding occurs even when eliciting such encoding is not the experimenter's intent.

Second, most conventional episodic memory retrieval tasks also rely on semantic memory retrieval. It is difficult to implement a task in which a specific event is remembered without retrieval of semantic information about the factual contents of the event. For example, recollecting that a word was presented on an earlier study list (episodic retrieval) often involves activating the meaning of the word (semantic retrieval). To isolate processes selectively related to episodic memory retrieval, PET studies use compara-

ble semantic retrieval tasks that do not involve episodic memory as reference tasks.

Studies of episodic memory encoding

Several PET studies of episodic memory encoding have been done to date. They include some studies that were explicitly designed to examine episodic encoding and some designed for other purposes which, nonetheless, had subjects perform tasks known to produce episodic encoding.

A study that directly looked at episodic encoding was reported by Kapur et al. (1994). Subjects were scanned while they viewed nouns presented one at a time at a rate of 40 words per min. They made binary yes/no decisions about each noun. In the 'deep encoding' target task, the decision was whether the noun represented a living thing. In the 'shallow encoding' reference task, subjects had to decide whether the noun contained the letter 'a'. As expected on the basis of previous findings (Craik and Tulving, 1975), encoding occurred more effectively during the deep than the shallow task. Subsequent testing of episodic retrieval yielded 75% correct recognition for the deeply encoded nouns and 57% correct recognition for the shallowly encoded nouns (d' values of 1.30 and 0.81, respectively). The corresponding PET data showed that in comparison with the shallow encoding task, the deep encoding task was associated with activation along left inferior prefrontal cortex near Brodmann's areas 45, 46, 47 and in left prefrontal area 10.

Another study that examined episodic encoding was done by Shallice, Fletcher, Frith et al. (1994). Subjects were scanned while they studied paired associates (e.g. 'poet' – 'Browning') and simultaneously engaged in a distractor task. In one task condition the distractor task was 'easy', in the other it was 'difficult'. The distractor tasks were included in the design to produce differential interference with episodic encoding processes, verified by subsequent cued-recall performance. In the reference tasks, subjects listened passively to the repeated presentation of a single pair of words while performing the appropriate distractor task. The PET findings showed that encoding under the difficult distractor task condition was

associated with activations in bilateral superior temporal cortex, anterior cingulate, and medial frontal cortex near areas 9 and 10. Encoding under the easy distractor task condition produced activations in left superior temporal cortex, anterior cingulate, retrosplenial cortex, and left prefrontal cortex near area 46. Based on these findings, the authors suggest that the left prefrontal cortex and retrosplenial cortex are associated with episodic encoding. However, the other areas activated during the difficult distractor task might also be involved in episodic encoding, because this task produced a subsequent recall performance of 68%.

Several PET studies discussed earlier as elaborate semantic retrieval tasks are also episodic (and possibly semantic) encoding tasks. This is indirectly evidenced by the similarity between the 'episodic encoding' task of Kapur et al. (1994) in which subjects decided if nouns represented living objects and the 'semantic retrieval' task of Petersen et al. (1988, 1989) who had subjects decide if nouns represented dangerous animals. Similarly, the verb-generate tasks (Petersen et al., 1988, 1989; Wise et al., 1991a; Raichle et al., 1994) which required subjects to retrieve and produce verbs meaningfully related to presented nouns are all known to be effective episodic encoding tasks. The verb-generate tasks, as well as most of the other elaborate semantic retrieval tasks discussed in the previous section, activated areas in left prefrontal cortex.

To directly demonstrate that tasks such as the verb-generate task are indeed episodic encoding tasks, Tulving, Kapur, Craik et al. (1994a) conducted a purely cognitive experiment with the materials that Petersen et al. (1988, 1989) had used in their PET studies. Subjects were given the verb-generate and noun reading tasks, in the absence of any reference to memory requirements, and were then tested on a surprise recognition test five days later. Episodic retrieval (recognition) of words encountered during the verb-generate task was substantially higher than for those words encountered during the noun reading task. When this cognitive finding is combined with Petersen et al.'s (1988, 1989) PET findings, and further combined with the results the Kapur et al.'s (1994) study, two conclusions follow: (1) tasks such as verb-generation and 'living/non-living' judgments include

both semantic retrieval processes and episodic encoding processes, and (2) they involve activity in the left prefrontal regions.

Studies of episodic memory retrieval

A number of PET studies have directly addressed episodic memory retrieval (Fig. 6). Squire et al. (1992) reported an early experiment which was later included, with two other similar experiments, in a long report by Buckner et al. (1994a). In all three experiments subjects were presented with study word lists 3–5 min before PET scans. During the PET scans, subjects were presented with stem-cues in uppercase letters and asked to recall study words that began with the stem-cues (stem-cued recall). For example, given 'GAR' a subject might retrieve the word 'garnish' that had been seen in the study list. Across the three experiments, the format of the study words was varied: in the Case-Same experiment, study words were presented visually in uppercase letters ('GARNISH'); in the Case-Change experiment, study words were presented visually in lower-case letters ('garnish'); and in the Auditory experiment, subjects heard study words (hear 'Garnish').

Compared to a reference condition in which subjects viewed stem-cues and completed them with the first word that came to mind (a form of semantic retrieval), stem-cued recall produced a robust activation in right prefrontal cortex at or near area 10 (Fig. 5). This activation was reliable across all three experiments, and was accompanied by smaller right dorsal prefrontal activations (at or near areas 8 or 9) and a left lateralized prefrontal activation. In the Case-Same experiment, an activation was also observed in the region of the right parahippocampal gyrus. To further explore the functional anatomy of the stem-cued recall task, Buckner et al. (1994a) compared the stem-cued recall task to a lower-level fixation reference task that presumably did not subtract away semantic retrieval. In this comparison, activations in the stem-cued recall task included left prefrontal cortex and anterior cingulate, as well as anterior right prefrontal cortex, thus suggesting that the task required both areas associated with elaborate semantic retrieval and additional areas

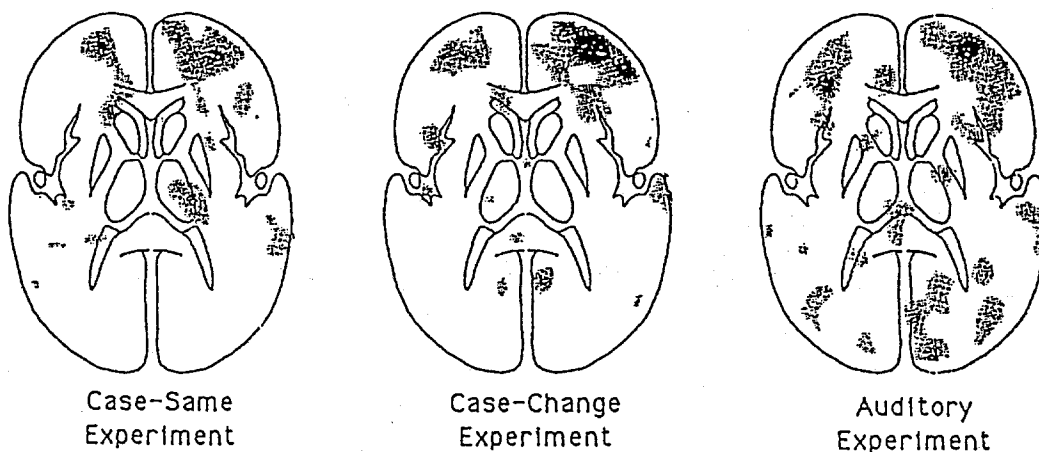


Fig. 5. PET data are shown in horizontal section for three independent episodic memory retrieval experiments reported by Buckner et al. (1994a). Across all three studies, subjects viewed word-stem retrieval cues and recalled words from a previously presented study list. The three experiments differed in regard to the relationship between the presentation format of the study words and test stem cues (see text). Prominent anterior right prefrontal activations were observed across all three studies.

specific to the episodic retrieval demands. Buckner and colleagues suggested that these results might indicate that a pathway involving left prefrontal cortex is used during speech production involving semantic memory retrieval. This pathway may also be involved in explicit (episodic) memory retrieval but additionally involves the participation of right prefrontal cortex to aid in the processes related to episodic memory retrieval. This finding is consistent with the observation that many episodic retrieval tasks typically include semantic retrieval.

Haxby, Horwitz, Maisog et al. (1993) also noted right prefrontal cortex activation in a pictorial episodic memory retrieval task. Subjects studied 32 faces, presented on three study trials, 16 min before a PET scan. During the PET scan, subjects were given a forced choice recognition test of the faces. Compared to a purely perceptual face matching reference task, which did not contain an episodic retrieval demand, activation was observed in right prefrontal cortex along a strip going from Brodmann's areas 45 and 46 to area 10. Activations were also observed in lateral occipital cortex, left pulvinar, and left lateral cerebellum.

Blood flow changes attributable to episodic retrieval were examined in a PET study by Tulving, Kapur, Markowitsch et al. (1994b). Subjects were scanned while they heard sentence-like verbal materi-

als. During some scans, the sentences were all 'new', in that subjects had never heard them before. In others, the sentences were all 'old' in that the subjects had heard them in a non-scanned study session 24 h previously. The subtraction of the new sentence reference image from the old sentence target image yielded a diffuse activation in right prefrontal cortex that began anteriorly near area 10 and extended through areas 46, 9, and into area 6. Activations were also observed in anterior cingulate cortex, and in portions of parietal cortex. These activations were interpreted as marking the components of a complex network of widely distributed cortical regions that are involved in retrieval of episodic information. Deactivations (higher blood flow in the new sentence condition than the old sentence condition) were observed bilaterally in the temporal lobes. These were interpreted as indicating brain regions involved in auditory priming, analogous to similar suggestions made by Squire et al. (1992) and Buckner et al. (1994a) about extrastriate regions and visual priming.

Shallice et al. (1994) have produced another instance of association between episodic retrieval and right prefrontal cortical activation. Before PET scanning, subjects studied 15 paired associates consisting of the same kinds of category – exemplar pairs (e.g. 'poet' – 'Browning') that they had used in their encod-

ing study, reviewed earlier. After a distraction period, the subjects were scanned while they listened to the names of studied categories and verbally recalled the studied exemplars. Compared to reference tasks, in which the subjects either generated an exemplar to a set of novel categories or simply repeated words, activations were observed across right prefrontal cortical areas 10, 46, and 47.

Given the prevalence of right prefrontal activation associated with episodic retrieval, the question arises as to the exact nature of the contribution that regions in right prefrontal cortex make to episodic retrieval tasks. The studies have varied the type of memory task used (recall versus recognition), the length of the retention interval (3 min to 24 h), type of information (words, sentences, faces), and several other characteristics of the tasks. Retrieval of episodic information comprises a number of features such as attention, task demands related to planning and 'search', feelings of familiarity, remembering earlier occurrences, and recollection of the setting or source (specific context) of the retrieved information. Any or all of these component processes of retrieval may be partially or totally subserved by the multiple areas in right prefrontal cortex that have been activated by the PET studies. At present, little empirical evidence exists for drawing more specific conclusions. Future studies will need to be conducted to tease apart these various components.

Summary

PET studies have examined both episodic encoding and episodic retrieval tasks. The PET studies of episodic encoding (which frequently also include semantic encoding and retrieval components) have produced a remarkably consistent pattern of left prefrontal cortex activation. As the relevant tasks all involved verbal materials, it is not yet known whether the consistency will generalize to non-verbal episodic encoding tasks.

The PET studies of episodic retrieval have also produced a remarkably consistent pattern of activations, but in right prefrontal cortex (Fig. 6). However, the right-prefrontal cortex activations did not localize to the same regions across experiments, suggesting task-specific variability. There is a clustering of activations in anterior right prefrontal cortex that appears across experiments; this region is not homologous to the left prefrontal regions activated by the encoding tasks. Participation of right prefrontal cortex is unexpected, considering that some of the retrieval tasks were clearly within the domain of language.

Tulving et al. (1994a) first drew attention to the regularity that left prefrontal cortical regions are differentially more involved in semantic retrieval and episodic encoding than are right prefrontal regions,

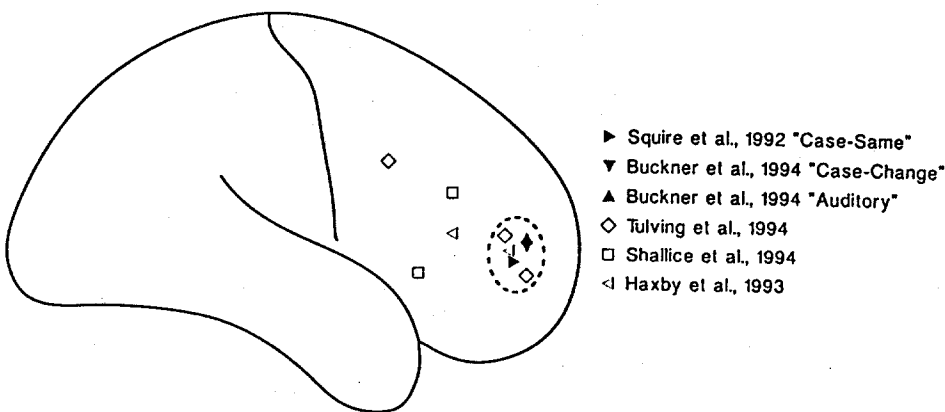


Fig. 6. Symbols are projected onto a lateral view of the right hemisphere that mark the locations of activations present in episodic memory retrieval tasks studied across six independent experiments. The filled triangles represent three similar studies that used different groups of subjects. These filled triangles show an estimate of between subject-group variability. The right prefrontal activations extend over a wide area of cortex with a clustering of activations (dashed oval) falling at or near area 10 in anterior prefrontal cortex.

whereas right prefrontal cortical regions appear to be more involved in episodic retrieval than are left prefrontal regions. This observation of hemispheric encoding/retrieval asymmetry (HERA) is consistent with the suggestion by Buckner et al. (1994a) that right prefrontal cortex is selectively recruited to aid in processes related to explicit (episodic) retrieval. The current experiments leave unspecified the role that these regions play in episodic memory processes, especially that of right prefrontal cortex. Nonetheless, the findings provide a robust dissociation between episodic retrieval and other forms of memory retrieval.

PET studies of working memory

Working memory refers to the processes by which information is represented, manipulated, and utilized internally. As such, working memory involves many processes that share in common the reliance on internal representations that persist over time (as opposed to stimulus-driven representations). Unlike the forms of memory discussed in the previous sections (procedural, semantic, episodic, and priming), working memory does not necessarily involve long-term neural reorganization. Working memory changes persist briefly, lasting on the order of seconds, and are therefore likely to rely more on temporally enhanced neural activity rather than structural changes. Goldman-Rakic (1994) described working memory as 'a distinct operation required for cognition, namely the ability to update and/or bring information to mind from long-term memory and/or to integrate incoming information for the purpose of making an informed decision, judgment, or response' (p. 114). Thus, working memory interacts with the other forms of memories discussed.

A detailed model of the subprocesses involved in working memory has been described by Baddeley (1986, 1992). He has proposed that working memory can be divided into a set of executive processes that control the operations of two slave-systems: a visual-spatial scratchpad and a phonological loop. The visual-spatial scratchpad is a mental buffer that maintains information of object forms and positions of objects, whereas, the phonological loop holds verbal informa-

tion online. Baddeley's model is based principally on observations at the cognitive level and neuropsychological cases. Many of the PET experiments done on working memory have been guided by the Baddeley model.

With regard to PET, it is important to keep in mind several theoretical points that are relevant to working memory. First, the visual-spatial scratchpad and phonological loop of the Baddeley model represent, heuristically, two prominent groupings of working memory processes rather than unitary entities. It is unlikely that a single PET task can demand the complete and exclusive use of the 'phonological loop' or the 'visual-spatial scratchpad'. Already, cognitive (Baddeley, 1986) and physio-logical (Wilson, Ó Scalaidhe and Goldman-Rakic, 1993) studies have begun to subdivide the visual-spatial scratchpad. Second, much of the data that support the existence of specific working memory stores are based on findings that some tasks cannot be performed concurrently. The assumption is then made that the two tasks rely on a common resource, or group of resources. However, this does not necessarily mean they share the same structures at the neuroanatomical level. Research (Raichle, 1994a) has suggested that some brain pathways compete with each another. If this is true, then another explanation for task interference is that two tasks that use two separate pathways can interfere with each other because their separate pathways inhibit one another. Finally, working memory relies heavily on semantic and episodic retrieval. The information that is realized in working memory is often a product of both stimuli in the environment and information that is recalled. As will be seen in the description of the working memory tasks that follows, almost all of the tasks required subjects to manipulate semantic information.

Studies of verbal working memory

Several PET studies have attempted to isolate different forms of verbal working memory. Subjects in a study by Petrides, Alivisatos, Meyer et al. (1993b) were asked to repeatedly say aloud the numbers one through ten in a random order, being careful not to repeat any numbers until all ten numbers had been

used (self-ordered). In a second task, subjects were asked to listen to a set of numbers that included all, except one, of the digits from one to ten. The subjects were asked to determine which digit had been omitted and say it aloud at the end of the sequence (externally ordered). Both of Petrides' tasks required that the subjects maintain within working memory the sequence of digits. In their reference control task, the subjects said aloud digits sequentially going from one to ten. In the self-ordered task, as compared to the reference task, activations were observed in bilateral mid-dorsolateral frontal cortex (areas 9 and 46), anterior cingulate, premotor cortex, and posterior parietal cortex. The externally ordered task activated similar frontal areas and additionally activated right frontopolar cortex (area 10) and more extensive areas in parietal cortex. Directly comparing the self-ordered task to the externally ordered task revealed more activation in brain areas related to speech production in the self-ordered task (area 44, cerebellum) and more activation in brain areas related to speech reception in the externally ordered task (lateral temporal cortex). Frontopolar cortex was activated more in the externally ordered task than in the self-ordered task, however, the activation was just below their threshold for significance in the direct comparison.

Following the Baddeley model of working memory, Paulesu, Frith and Frackowiak (1993a) scanned subjects performing a verbal memory task designed to isolate the phonological loop. Subjects were required to remember six consonants that were presented visually 1 per s, followed by a probe consonant presented 2 s later. The subjects' task was to indicate if the probe consonant was present in the earlier sequence by moving a joy-stick. A reference task was used that was identical to the phonological working memory task except that Korean letters, which are not phonologically codable, were presented instead of letter consonants. Activations were observed bilaterally in prefrontal cortex near area 44, superior temporal gyri, supramarginal gyri near area 40, and insular cortex. Motor and premotor regions, including SMA were also activated. Of these activations, only the activation in area 40 was present when the phonological working memory task was compared to an additional

task in which subjects made rhyme judgments, a task believed not to rely on the phonological loop. From this the authors suggested that Brodmann's area 40 is selectively recruited for processes related to the phonological loop.

In a study by Raife et al. (1992), subjects were presented a set of five words just prior to a PET scan. During the scan they were asked to silently remember the items. Three experimental conditions were defined in terms of the kinds of words used: (a) categorically related nouns, (b) unrelated nouns, or (c) pronounceable non-words. There were two reference tasks: (a) subjects subvocally went through the digits 1–5 repeatedly, or (b) subjects silently watched a fixation point. All three verbal working memory tasks produced activations in SMA and right prefrontal cortex. In addition, a post-hoc analysis revealed that subjects who performed well (they could recite all of the items back to the experimenter after the scans) as compared with those who did not, activated left premotor cortex. The poorer performers activated occipito-temporal cortex. Raife and colleagues suggested that these findings might reflect different strategies used by subjects: the good performers used a phonological strategy, whereas the poor performers used a visual strategy (see also Raichle, 1993).

Prefrontal cortex and verbal working memory

Most studies of verbal working memory tasks have reported, among other things, prominent activations in left prefrontal cortex. Similar findings have been observed in PET studies of cognitive tasks adopted to study other processes that have encompassed components of working memory. Thus, Raichle (1994b) has noted the working memory demands inherent in the verb-generate task, and Goldman-Rakic (1994) has pointed out the working memory demands of the tasks used by Frith et al. (1991). In most of these studies, whether primarily designed to examine working memory or qualifying for inclusion on secondary grounds, activations in left prefrontal brain regions near areas 44, 45, or 46 have been observed.

The general finding that regions within left prefrontal cortex are reliably activated across several verbal

working memory tasks suggests that these brain regions play an important role in verbal working memory. However, it does not suggest a monogamous relationship between working memory and the frontal lobes. On the one hand, extant evidence from PET studies, even if still patchy, suggests that other brain regions are involved in working memory tasks. Thus, there is every reason to believe that working memory operations are subserved by widely distributed neuronal networks. On the other hand, there is a great deal of evidence for the involvement of the prefrontal cortices in many other cognitive functions other than those that are exclusively captured by working memory tasks (Luria and Tsvetkova, 1964; Milner, 1982; Stuss and Benson, 1986; Shallice and Burgess, 1991; Grafman, Sirigu, Spector et al., 1993).

As mentioned, Raife et al. (1992) did not report any prominent prefrontal activations in areas 44, 45, or 46. A possible reason for this exception to what appears to be a general rule concerns the nature of the tasks used. The task used by Raife et al. (1992) required minimal manipulation of information in working memory. The subjects needed simply to hold a set of verbal items in memory without reorganizing them. Other working memory tasks have tended to be more demanding, requiring active mental operations on the information in addition to rehearsal. It is possible that prefrontal cortex is less intensively engaged under conditions in which only maintenance rehearsal of verbal information is required, and more intensively engaged in situations calling for more elaborate processing of verbal material.

Studies of visual-spatial working memory

Several PET studies of visual-spatial working memory have been reported. In a study by Petrides, Alivisatos, Evans et al. (1993a) subjects were scanned while they were engaged in a 'self-ordered' pointing task. In this task, a constant set of eight abstract designs were presented on successive cards. The positions of items changed from card to card. The subject's task was to point to a new, that is a previously not selected, design on each card. Thus to complete the task, the subjects had to maintain within working

memory the set of designs that they had selected previously and monitor their responses accordingly. In the reference task, subjects pointed to the same design across successive cards. The relevant subtraction showed activations observed in left prefrontal cortex area 9, bilateral lateral prefrontal area 46, anterior cingulate, and bilateral posterior parietal cortex. The area 46 activations were much more robust in the right hemisphere.

Jonides, Smith, Koeppe et al. (1993) conducted a well controlled spatial working memory task modeled after primate studies. In their target task, subjects were presented with sets of dots surrounding a central fixation point for a brief period (200 ms). Following a 3-s delay during which the screen was blank, a probe circle appeared and the subjects' task was to determine if one of the dots had appeared within the location of the probe circle. Thus the task required the subjects to maintain a representation of the location of the dots during the delay interval. This spatial memory task was compared to a reference task in which the dots appeared immediately before the probe circle and stayed on when the probe circle appeared. Statistically significant activations were observed only in the right hemisphere in lateral prefrontal area 47, premotor cortex, parietal cortex area 40, and occipital cortex area 19. Interestingly, this spatial working memory task played minimally on semantic retrieval as the objects being manipulated had little meaning and did not activate left prefrontal cortex.

As a complement to their analysis of the brain areas that underlie the phonological loop, Paulesu, Frith, Bench et al. (1993b) examined the functional anatomy of Baddeley's visual-spatial 'sketchpad'. In the target task of this study, subjects had to hold in mind (non-verbalizable) Korean letters. The reference task was the verbal working memory task used in the other study (Paulesu et al., 1993a). Activations were observed posteriorly near the cuneus in areas 19 or 39, bilateral occipito-temporal cortex near area 19 and 37, and right areas 19 or 40. Frontal cortex activations were also observed in prefrontal cortex area 47 and anterior cingulate. Despite differences in the tasks, these findings closely parallel some of the findings of Jonides et al. (1993).

Summary

Several working memory tasks that required both verbal and spatial demands have been studied with PET. The collective results suggest the existence of a distributed set of brain areas that are engaged by these tasks. These areas include regions in prefrontal cortex and anterior cingulate, which have been reliably activated in both verbal and spatial working memory tasks. The verbal working memory tasks have frequently activated left or bilateral prefrontal brain areas that fall at or near areas 44, 45 or 46, whereas the spatial working memory tasks have included bilateral activations with more prominent right-lateralized activations. One study of spatial working memory (Jonides et al., 1993) produced activations only in the right hemisphere. In addition, the spatial working memory tasks have tended to activate parietal cortex brain areas. These findings are consistent with models of working memory function that have been advocated based on animal models (Fuster, 1989; Goldman-Rakic, 1987, 1991).

PET data and lesion studies

A natural question regarding PET findings in memory studies concerns their relation to findings from lesion studies. A discussion of the complete issue would require a chapter of its own. However, a couple of general points are worth making.

Some researchers intuitively expect that the PET data and lesion data should be correlated in a straightforward fashion. Both techniques attempt to identify brain regions that are utilized during different forms of information processing, and therefore both techniques should be comparable at some level. Thus, it is easy to assume that if a brain region is activated in a PET study of a particular task then damage to that region should produce an impairment in the performance of that task. Likewise, it is often assumed that if damage to a certain brain region impairs performance on a task then a PET study of that task should reveal activation in that brain region. However, the relation between PET and lesion data need not be that simple. In what follows, we describe some considerations that should

be taken into account when comparing PET and lesion studies.

When a brain area is activated with PET, all that can be said is that differences between the information processing demands occurring during the target and reference tasks are correlated with activation in that brain region. An analysis of the comparison tasks does not necessarily specify the exact processing demands that were accomplished by the activated brain region. Patients with lesions to that brain region are likely to demonstrate deficits on a particular task only if that task includes the processing demands that elicited the activation. In addition, it is possible that many cognitive tasks used to assay a deficit can be completed with several strategies (and possibly, brain pathways). Under these circumstances, preserved functions may reflect the fact that the cognitive task does not depend critically on the brain region that is lost, even though the healthy subject will use that brain region to accomplish the task as measured by PET.

In practice, it is also difficult to find patients that have lesions restricted to selective brain areas. PET activations often occur in small regions of cortex and thus suggest that processing demands are accomplished by highly localized brain areas. Therefore, lesion studies that classify lesions based on large areas of brain (e.g. right frontal lesions) may have a heterogeneous grouping of patients with many different functional lesions. For example, Roskies (1994) is skeptical about the suggestion that left prefrontal cortex is used for semantic retrieval and episodic encoding, and right prefrontal cortex plays a role in episodic retrieval. Her argument originates from the fact that 'there is little evidence from studies of patients with unilateral frontal damage for an asymmetry in encoding and retrieval, or for problems in recognition' (p. 1991). However, there are no lesion studies of memory function that have looked at a significant number of patients with lesions to either of the main regions activated by the PET studies. Patients with lesions to the left prefrontal cortex area activated by the PET studies often exhibit aphasic symptoms and are typically excluded from studies of memory (e.g. Jetter, Poser, Freeman et al., 1986). Right prefrontal lesions often do not extend into frontopolar cortex, and cur-

rent studies have not included more than a few patients who have damage to this area (e.g. Janowsky, Shimamura, Krtichevsky et al., 1989).

Conversely, the main conclusion that can be drawn from the observation that a lesion in a certain brain area is correlated with impaired performance on certain tasks is that the area plays some kind of role in carrying out the tasks. The role is often difficult to ascertain. For example, damage to the medial temporal lobe impairs performance on a variety of memory tasks. However, it is unclear what the contribution of the medial temporal lobe is to memory function. The medial temporal lobe may play a critical role in encoding, storage, and retrieval or any combination of these. In order to show a relationship between impairments produced by medial temporal lobe lesions and PET activation it would be necessary to scan subjects during a target experimental task that demanded a greater participation of the medial temporal lobe as compared to a reference task. This assumes that the role of the medial temporal lobe is specified and that the medial temporal lobe modulates net neuronal activity, and hence blood flow, in a straightforward manner when it participates in memory function. Current theories of medial temporal lobe memory function propose overall activity patterns that are more complex than those typically observed in cortex (Buzsaki, 1989; Rolls and O'Mara, 1993).

These cautions about expecting a particular relation between PET and lesion studies are not meant to suggest that there should not be any relation. The two techniques offer complementary views of what areas of the brain underlie memory function. Whenever they yield converging evidence, the findings can be regarded as most robust and meaningful. However, many aspects of what a particular PET activation represents and how to interpret a specific lesion finding are underconstrained. In this respect, PET data and lesion data can help to constrain each other (see Fiez et al., 1992 for an example).

Perhaps the most important point is that neuroimaging techniques can provide a kind of evidence that lesion data cannot. For instance, neuroimaging can be, and has been, used to experimentally separate encoding processes from retrieval processes. Changes in

blood flow can be measured for encoding processes independently of subsequent retrieval, and for retrieval processes separately from previous encoding. In a brain-damaged patient encoding and retrieval are difficult to isolate. When such a patient shows impairment on a memory task, it is not known to what extent the impairment is attributable to encoding processes, retrieval processes, or both.

Conclusions

The use of neuroimaging techniques, including PET, to study memory is in its early stages. The number of reported PET studies of memory is still small. Nonetheless, those studies done to date have produced some useful insights and stimulated future questions. Some of the studies have yielded data that are in good agreement with existing ideas of brain function. Others have yielded unexpected findings about the involvement of brain regions in memory. Both kinds of findings, and many more to come, should help to further our understanding of memory.

As more PET data are collected, commonalities across groups of studies will emerge and suggest models of neuroanatomical pathways that underlie memory processes. As of today, two initial models of this kind have been described. One is the model described by Raichle et al. (1994); see also Raichle (1994). It proposes that the retrieval and generation of words can be accomplished by at least two different functional pathways whose activation depends on the degree to which the target task is automated through procedural learning. Another is the HERA (Hemispheric Encoding/Retrieval Asymmetry) model described by Tulving et al. (1994a). The HERA model describes a consistent pattern of greater right prefrontal activation during episodic retrieval tasks and greater left prefrontal activation during episodic encoding tasks. This finding has been observed in a number of PET studies conducted by several different laboratories.

These models are early attempts to describe meaningful patterns that exist across multiple PET studies, and relate these patterns to existing models that have been developed within cognitive and neuropsychol-

ogy. Data may yet be produced that invalidates or further constrains the domains of these models. Completely novel models will also emerge as more data are collected and analyzed. For now, the consistency of the data that has been collected thus far and described by these two existing models shows that neuroimaging can provide fresh insights into the study of memory.

At the most global level, the PET studies have demonstrated how multiple forms of memory processes might interact. Verbal working memory tasks, elaborative semantic retrieval tasks, and episodic encoding tasks have all activated similar left prefrontal regions. One possibility for this regularity is that the PET tasks which have been studied to date have not yet teased apart these various memory processes. Alternatively, this regularity may suggest that, at the functional anatomical level, these processes interact. The brain areas activated in left prefrontal cortex might be part of the neural substrate that maintains representations on-line (working memory) while the representations are manipulated and used to guide further events such as semantic retrieval. At the same time, these representations may themselves be involved in the storage of episodic memories. This simple framework can be used to explain the depth of processing effect at a functional anatomical level (Craik and Lockhart, 1972; Craik and Tulving, 1975). Processing that requires verbal elaboration (deep processing) appears to activate left prefrontal cortex (e.g. Kapur et al., 1994; Raichle et al., 1994), whereas, well automatized language tasks (shallow tasks) do not (Petersen et al., 1988, 1989; Frith et al., 1991). Shallow encoding tasks may not form episodic memories well because they do not require representation of the information in prefrontal cortex.

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