

REVIEW

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Functional brain imaging of episodic and semantic memory with positron emission tomography

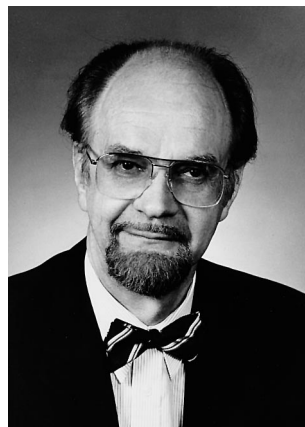
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Abstract Human memory is composed of several independent but interacting systems. These include a system for remembering general knowledge, semantic memory, and a system for recollection of personal events, episodic memory. The results of positron emission tomography

(PET) studies of regional cerebral blood flow indicate that networks of distributed brain regions subservise episodic and semantic memory. Some networks seem to be generally engaged in memory processes whereas the involvement of others is specific to factors such as the type of information to be remembered or the level of retrieval success. The PET findings help to understand memory dysfunction (a) by showing that multiple brain regions are involved in different memory processes and (b) by sharpening the interpretation of the functional role of different brain regions.

Key words Human · Memory · Brain · Positron emission tomography · Network

Abbreviations *PET* Positron emission tomography · *rCBF* Regional cerebral blood flow · *fMRI* Functional magnetic resonance imaging



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Introduction

A central theme in current research on human memory is that of multiple memory systems. One very broad distinction is between a system for maintaining information over limited periods of time, working memory [1], and a variety of long-term memory systems, including episodic and semantic memory [2–4]. Episodic memory makes possible recollection of personally experienced events whereas semantic memory underlies an individual's knowledge of the world. The strength of the evidence for distinguishing between episodic and semantic memory has been questioned (e.g., [5]), and some 10 years ago in response to the criticism it was noted that evidence from functional neuroimaging would be critical in settling the issue whether episodic and semantic memory systems can be differentiated in terms of both cognitive functions and underlying brain structures [6]. Today, as described below, such evidence does exist.

Historically, selective effects of brain lesions on performance of tasks that depend differentially on respective

systems have been used to identify brain regions critical for different forms of memory. A limitation with lesion studies, however, is that they give information only concerning whether the specific damaged region is somehow necessary for task performance. It is becoming increasingly clear that complex cognitive and memory processes rely on the integrity of extended networks of brain regions rather than on the workings of individual regions [7]. While it may be possible to overcome this limitation in animal lesion studies by systematic analyses of highly specific lesions and their combinations, many cognitive and memory processes can be studied only with humans. For example, it is not yet known how to distinguish between episodic and semantic memory in animals. Animals cannot be asked whether they recollect a previous happening, or whether they know the proper response in a given situation. This is why in the literature on animal memory these two systems are frequently collapsed as “declarative” memory [8]. The parsimonious assumption is that many experimental procedures used to assess memory in monkeys, such as the delayed matching-to-sample task, reflect the operations of semantic rather than episodic memory [9].

Another problem with lesion studies is that there is a real possibility of the damaged brain not mediating cognitive performance in the same way as the intact brain. It is known that the brain has the capacity of functional reorganization or compensation [10]. Hence studying a damaged brain need not always illuminate the workings of the healthy brain.

A solution to these problems is offered by the possibility of studying cognitive processes in the intact human brain with modern functional neuroimaging techniques. In this brief review we discuss some recent results from positron emission tomography (PET) studies of episodic and semantic memory. By showing that multiple brain regions are involved differentially in episodic and in semantic memory, the results support the notion of large-scale networks subserving cognition and memory. Before turning to the studies, we briefly outline the way in which the data are acquired and analyzed.

Functional neuroimaging

Several techniques exist for examining potential correlations between cognitive function and underlying neuroanatomy [11–13]. Here we are concerned principally with PET studies of regional cerebral blood flow (rCBF). Neural correlates of cognitive functions are also studied with functional magnetic resonance imaging (fMRI). This technique provides both anatomical and functional information, and it has been suggested that PET and fMRI should be used in parallel, with PET providing a general description of the circuit of brain regions underlying a particular task and fMRI providing details of particular areas within the circuit [14]. To determine the time course of information flow within a circuit it may be necessary to use further techniques such as recordings

of electrical activity from the scalp (for a review see [15]).

Memory functions, as with other cognitive functions, rely on changes in local neuronal activity. Changes in neuronal activity are accompanied by changes in rCBF, and these changes can be measured by PET [16]. Because data from a single PET scan are uninterpretable, data are usually reported in the form of comparisons between scans. In the typical case this involves comparing the rCBF pattern associated with a target task with that associated with a reference task. This comparison reveals brain regions in which the activity is significantly higher or lower during the target task than during the reference task [17–18]. The target and reference tasks are selected to differ only with respect to the process of interest. The basic assumption is that the regions showing differential activity between the two task conditions are important for this process.

The task-comparison approach to the analysis of PET data has been very successful, and it continues to be frequently used. A potential shortcoming of this approach is that it rests on the assumption of linear additivity of biological processes subserving linear additive cognitive processes. This has led to the development of methods which do not rest on this assumption, such as correlating of rCBF with graded cognitive and physiological parameters (see [19]). More recently, different multivariate methods have been applied to PET data [20–22]. Each of these three main data-analytic approaches is represented in the empirical papers reviewed below.

Semantic memory

In conventional studies of semantic memory, subjects’ brains are scanned while they are engaged in thinking about or retrieving particular instances of their knowledge about the world in the broadest sense. For example, in a PET study of brain areas mediating knowledge of common objects, the rCBF patterns correlated with the subjects’ activity of generating words denoting (a) colors or (b) actions associated with black-on-white line drawings of objects were compared with the rCBF pattern associated with naming similar objects [23]. In both comparisons increased activity during the generation tasks was observed in certain common areas, namely left prefrontal cortex and left posterior parietal cortex.

It was further found that the two generation tasks also produced activations in brain regions unique to each. Thus color naming led to increased activity in a region in the ventral temporal lobe bilaterally, but with stronger activation in the left hemisphere, whereas generation of action words activated a more dorsal region in left middle temporal gyrus. The region in the ventral temporal lobe that was selectively activated by thinking of and naming the colors of objects was located near the area involved in color perception. Similarly, the left middle temporal region activated during generation of action words was just anterior to the area involved in perception of motion.

Additional support for the notion that retrieval of object information from semantic memory activates specific regions depending on type of information recovered comes from a study of brain regions involved in naming animals and tools shown to the subject in pictorial form [24]. Naming animals selectively activated the left medial occipital lobe, whereas naming tools involved increased activation in other regions including a left middle temporal region. The location of the latter region was nearly identical to the location of the region that was found to be activated during generation of action words (see [23]), suggesting that this region may be the site for stored knowledge of visual motion associated with using objects (see [24]).

With respect to general regions, i.e., regions whose activation does not seem to depend on the type of information retrieved, several studies have found left prefrontal activation during various kinds of semantic memory retrieval (see [25–26]). These studies used tasks such as generating related verbs to presented nouns [27], generating words beginning with a particular letter [28] or letters [29], and judging whether presented words refer to living or nonliving things [30]. A relevant additional observation from a fMRI study is that the increased left prefrontal activity during semantic retrieval does not reflect the differences in the difficulty of the compared tasks [31]. Rather, it looks as if left prefrontal cortical regions are part of an executive mechanism that contributes to retrieval of semantic information (see [31]).

In summary, retrieval of information from semantic memory is generally correlated with increased neuronal activity in some brain regions, whereas the activity in others seems to depend on the type of information retrieved. Such findings suggest the existence of “general” and “specific” networks underlying semantic memory retrieval. Similar general and specific retrieval networks have been tentatively identified in episodic memory, although their location in the brain is rather different.

Episodic memory

Laboratory studies of episodic memory consist of two phases. In the first (acquisition, or encoding) phase, subjects are presented with discrete items of a particular kind (e.g., words, word pairs, pictures of objects). In the second (retrieval) phase, subjects are tested for the information acquired during the encoding phase. The important difference from semantic-memory retrieval here is that subjects must remember a particular past event (the presentation of an item in the encoding phase) rather than just using their general knowledge of the kind tested in studies of semantic memory.

A recent PET study identified a pattern of brain regions showing increased activity during acquisition and retrieval of three different kinds of episodic information about the appearance of single words [32]: (a) item information, (b) spatial information, and (c) time information. In each encoding phase subjects were shown words

in two separate, successive lists, each word appearing on the left or the right of a computer screen. In the item encoding condition they were instructed to remember what the words were. In the spatial-encoding condition they were instructed to remember the words as well as the location – left or right. In the time-encoding condition they were instructed to remember the words as well as the time of their appearance – first or second list. Three retrieval conditions corresponded one-to-one to the three encoding conditions. In each retrieval phase subjects were shown single words in the center of the screen and, depending on the condition, had to decide (a) whether the word had been shown in the encoding phase, (b) whether the word had appeared on the left or the right of the screen, and (c) whether the word had appeared in the first or the second list.

PET data showed that (a) in all encoding conditions there is increased activation in left prefrontal cortex and in left fusiform gyrus, and that (b) in all retrieval conditions there is increased activity in right prefrontal cortex, anterior cingulate, and midbrain. These brain regions are interpreted as representing components of “general” networks of brain regions subserving episodic encoding and retrieval of different kinds of information (see Fig. 1).

The observation that left prefrontal cortex is generally involved in episodic encoding is consistent with several previous PET studies of episodic encoding of verbal and nonverbal stimuli (see [33–35]). In all of these studies the specific location of the activation has been near Brodmann areas 45 and 46. Kapur and colleagues [36] suggested that increased activity in this region during episodic encoding reflects semantic processing.

Similarly, a general involvement of right prefrontal regions in episodic retrieval is consistent with the results of a number of PET studies (see [25–26, 33–35]). The involvement of right prefrontal brain regions in episodic retrieval has attracted substantial interest. The results of several studies indicate that activation of some right prefrontal regions during episodic retrieval is largely independent of the extent to which successful retrieval occurs and may instead reflect processes related to retrieval attempt or being engaged in a retrieval mode [37–39]. The degree of activation in other right prefrontal regions may be related to the level of retrieval success [40–41]. The observation that activation in some right prefrontal brain regions is unrelated to level of retrieval performance whereas degree of activation in others may be related to level of retrieval success underscores the functional heterogeneity of the prefrontal cortex (see [42]).

Higher levels of episodic retrieval have been associated with higher levels of activity in other brain regions as well. A recent PET study identified a pattern of brain regions that distinguished an episodic retrieval condition involving high levels of retrieval from conditions involving lower levels of retrieval success [41]. In agreement with the many lesion studies that have indicated an association between episodic memory and hippocampus (see [43]) this pattern include bilateral medial-temporal re-

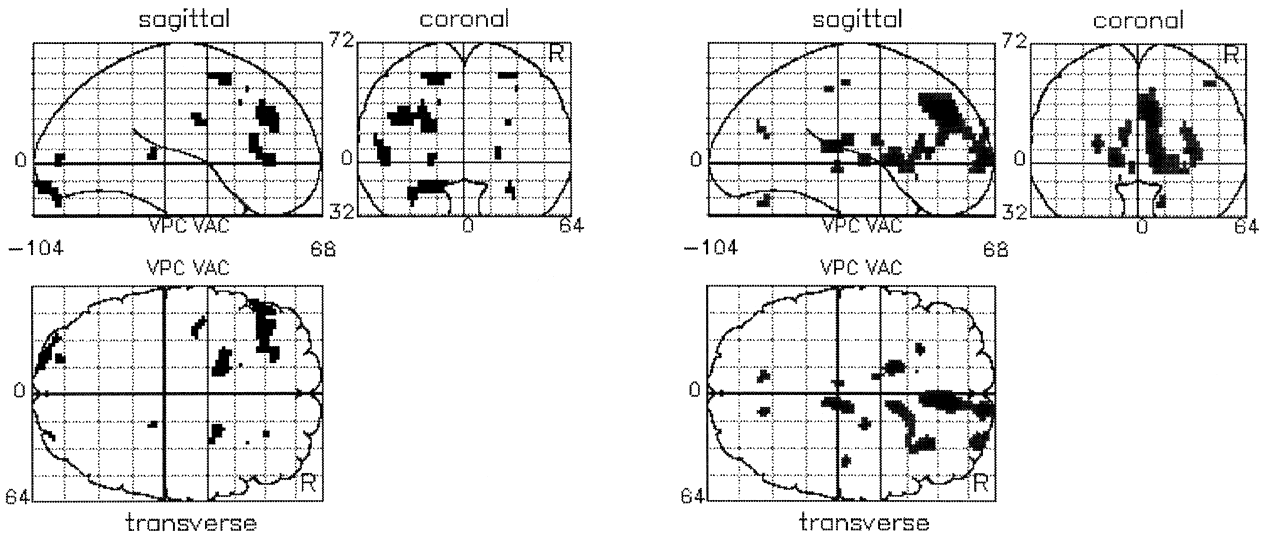


Fig. 1 Brain regions activated during episodic encoding (*left*) and episodic retrieval (*right*). The activations are shown in three different views; from the right (sagittal), from the back (coronal), and from the top (transverse). (From [32])

gions. Other prominent parts of the pattern include left temporal polar and left superior temporal regions.

Taken together the results of PET studies of episodic memory are consistent with the results of PET studies of semantic memory in suggesting that some brain regions are generally involved during retrieval whereas the involvement of others is related to specific factors such as actual recovery of information. Importantly, different components seem to define the networks underlying episodic and semantic retrieval. The difference is especially striking within the frontal lobes, with left prefrontal regions generally activated during semantic memory retrieval and right prefrontal regions during episodic retrieval. Thus, as envisaged more than a decade ago [6], results from functional neuroimaging have provided support for the distinction between these memory systems (see [44]). Regarding anatomical connections between activated regions it has been suggested that during episodic memory retrieval right prefrontal regions connect to right anterior temporal and other posterior structures in the right hemisphere via the ventral branch of the uncinate fascicle [45]. The same structural combination in the left hemisphere has been proposed to be responsible for semantic memory retrieval [46].

Clinical implications

The results of functional neuroimaging studies of episodic and semantic memory indicate that networks of distributed brain regions underlie performance. This view, that memory performance is mediated by distributed networks across many brain regions, has important clinical implications in that it predicts that performance may be interrupted by a lesion in any of the involved regions. Empirical data support this prediction by showing that lesions in an-

atomically distinct regions may impair the same function, although the degree of impairment depends on lesion site [47]. Moreover, by suggesting that some brain regions are generally involved in memory encoding and retrieval (“general networks”) whereas others are specifically involved depending on factors such as the type of information to be remembered and level of retrieval success (“specific networks”), the results sharpen the understanding of the functional role of different brain regions.

Consider, for example, the observation that some right prefrontal brain regions seem to be generally involved in episodic memory retrieval (see [25–26; 33–35; 42]). This observation indicates that these prefrontal regions are not involved in the actual recovery of stored information but rather in general functions such as initiating, maintaining, and organizing retrieval processes. In line with this view, a recent meta-analysis of neuropsychological studies on brain-damaged patients have shown that although these patients are not amnesic, they do have impairments on tests of free recall, cued recall, and recognition [48]. The strong right-sided lateralization observed in PET studies of episodic retrieval could not be predicted from patient studies, but some case studies indicate a critical role of right prefrontal regions in episodic memory retrieval [49–50]. There is also an interesting observation of right frontal cortex hypometabolism in transient global amnesia [51]. In line with the present view, the latter study suggested that transient amnesia is a syndrome with several possible foci of dysfunction.

Furthermore, the demonstration by PET that medial-temporal lobe activity is related to retrieval success implicates this region in the actual recovery of information [41] (see also [39, 52–54]). This supports the hypothesis, based on clinical observations of anterograde and temporally graded retrograde amnesia following medial-temporal lobe lesions [43, 55–56], that the medial-temporal region is involved during recovery of new episodic information. The basis for this involvement, it is assumed, is that the medial-temporal region integrates the various neocortical storage sites which ultimately represents the episode. When these sites have become integrated, the

involvement of medial-temporal regions in episodic retrieval is no longer crucial (for neural network simulations of this process, see [57–58]). Thus, by this view, successful retrieval is not a product of hippocampal function alone, and the PET results provide information about brain regions which may interact with medial-temporal regions during recovery. One example is the left superior temporal gyrus [41], and previous experimental findings indicate that this region is implicated in episodic memory representation (see [46]).

Conclusion

The results of the above PET studies illustrate the main point of this paper: memory processes are subserved by widely distributed networks of brain regions. Neuroimaging studies are playing an important role in identifying network components, and in sharpening the understanding of the functional role of various regions. Interestingly, recent work suggests that the functional role of a region may vary depending on the areas with which it is interacting [59]. A critical task for future research will therefore be to specify task-specific patterns of interactions between network components (see [60] for an example of a network analysis of PET data on word reading and episodic recognition).

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