Memory beyond the hippocampus

Endel Tulving* and Hans J Markowitsch†

Improved neuroanatomical knowledge, technical and methodological innovations (such as PET), and more refined conceptualizations of memory have inspired a reappraisal of theoretical beliefs regarding the role of the hippocampus in memory. In the past few years, it has become apparent that the influence of the medial temporal lobe regions extends beyond memory and that memory processes (such as encoding, consolidation and retrieval) involve not only the hippocampus and the medial temporal and diencephalic regions, but also widely distributed neocortical and perhaps even cerebellar regions.

Addresses
*Rotman Research Institute of Baycrest Centre, 3560 Bathurst Street, North York, Ontario, Canada M6A 2E1; e-mail: tulving@psych.toronto.edu
†Physiological Psychology, University of Bielefeld, PO Box 10 01 31, D-33501 Bielefeld, Germany; e-mail: marko@post.uni-bielefeld.de

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Abbreviations

DNMS	delayed nonmatching-to-sample (task)
HERA	hemispheric encoding/retrieval asymmetry
MTL	medial temporal lobe
PET	positron emission tomography

Introduction

The hippocampus continues to fascinate, challenge, beguile, and frustrate those who seek to understand its 'role' in memory. We here review recent advances that have been made in the search for answers to questions about the relation of the hippocampus and other medial temporal lobe (MTL) structures to memory processes. Some of these advances represent the cumulative fruits of past efforts, others have their source in innovations (such as more refined surgical procedures in the work with experimental animals and the use of functional neuroimaging techniques in the work with healthy humans and neurological patients), whereas still others reflect the increasingly more careful thought that is being bestowed on the problem. In our review, we focus on ablation work with monkeys and on PET studies of healthy human adults, and we consider the lessons learned from studies in other genres. Because of the title of the journal in which this review appears, we also offer our opinions on accomplishments, problems, and promises.

Among the questions asked about the hippocampus is the perennial 'What is the role of the hippocampus in memory?' and its many variants and versions. In its simple form, of course, it is not answerable, because it is predicated on false premises: it singles out as special only one of many structures that are known to be involved in memory, it assumes a specific role (or a few limited roles) for this structure, and it also implies that the hippocampus does not have any non-memory roles. If these premises are untrue, as we believe they are, the question itself, and answers proposed to it, can be viewed as more of a hindrance than an aid to the understanding of the relation between the hippocampus and memory.

Because of the enormous complexity of the MTL region and an equal complexity of memory processes, more useful at the present time is research that is directly directed at the untangling of the neuroanatomical and behavioral Gordian knot. This is the kind of research that systematically analyzes the anatomical and behavioral wholes of interest into their natural constituent parts, and then attempts to understand how the parts function and interact together to create memory.

Functional neuroanatomy of the medial temporal lobes

The MTL system, which comprises the hippocampus and surrounding structures, has attracted researchers on the basis of its morphological appearance, which include a regular neuronal layering and distinctive activation patterns (i.e. theta rhythm and long-term potentiation [1•]), and its position within the mammalian brain, which makes it a link between neocortical areas on the one side and other limbic regions on the other [2••,3]. The conventional classification of the MTL structures distinguishes between the 'hippocampus proper', consisting of Ammon's horn, the dentate gyrus, and the subiculum [4], and the 'perihippocampal region', consisting of the entorhinal cortex (area 28), perirhinal cortex (areas 35 and 36), and parahippocampal gyrus (areas TH and TF).

Mass action in the medial temporal lobe?

From the initial attention paid to the hippocampus proper as the 'locus' of memory [5], the focus of interest has gradually shifted to include the areas 'beyond' the hippocampus, that is, other MTL structures [6,7], and, from there, to the surrounding allocortical structures. The relevant evidence has been derived from lesion studies of non-human primates [8–10,11••]. In the course of this move 'beyond', the basic pre-theoretical orientation to the issues of the MTL and memory has also changed.

Until recently, a popular approach has consisted in the treatment of the whole medial-temporal region as the critical system of memory, in which the extent of 'memory impairment' varied directly with the amount of tissue excised. An example is a study in which memory impairment in lesioned monkeys was assessed

by the delayed nonmatching-to-sample (DNMS) task [12]. Performance on this task was only slightly impaired following bilateral ablation of the hippocampus and amygdala; the impairment was increased following the addition of a bilateral entorhinal lesion and was further increased when bilateral perirhinal and parahippocampal lesions were added to the other two. The inference can be drawn from these findings that the MTL region functions as an integral system in which all components contribute positively to behavioral performance and that operates according to a kind of a Lashleyan 'principle of mass action'. An analogous account in humans has also been proposed [13].

The integral MTL system is usually associated with a similarly integral view of the kind of memory, called 'declarative' or 'explicit', that the system serves. Declarative memory can be assessed by an extensive variety of tasks, such as DNMS and place learning in the Morris water maze.

Anatomico-functional diversity

The alternative orientation—in our view, a potentially more productive one—is exemplified in the work by Leonard *et al.* [9] and Meunier *et al.* [14]. Both teams of researchers found, surprisingly, that lesioning of the entorhinal cortex—known to occupy a pivotal position as the bottleneck for incoming and outgoing fibers from widespread association areas of the neocortex [6]—had only minor and transitory deleterious effects on memory performance.

Even more jarring, by traditional standards, are the more recent findings of Meunier *et al.* [15•], who have reported that the additional removal of the hippocampal formation and parahippocampal gyrus, following an earlier combined entorhinal and perirhinal lesion, led to an enhanced performance on the DNMS task. Findings of the same kind of lesion-induced facilitation of memory performance had been reported earlier by Irle and Markowitsch (see [16,17]), who worked primarily with cats. Meunier *et al.* [15•] have interpreted their findings in terms of interactions among multiple functional subdivisions within the MTL.

Related to this view, Henke and Wieser [18•] have reported a case in which bilateral MTL damage did not produce an amnesic syndrome, a finding that led the authors to suggest "that a probably misunderstood too rigid 'hippocampal memory hypothesis' must be revised." Furthermore, there may be important interactions for memory processing between the hippocampal formation and surrounding allocortical [10,11••] and neocortical [19–23] structures. Among the newer findings are those that point to a more important role of the rhinal cortex than of the hippocampal formation for information storage [11••,24].

This alternative interactionist orientation is based on the assumption of functional diversity within and beyond MTL regions: many different brain regions are involved in the learning and performance of any given task, each contributing to the many subprocesses of the aggregate in its own unique manner. If so, an important research objective becomes that of mapping particular neuroanatomical regions, and their combinations, to particular aspects of behavioral tasks, and their combinations [25]. In line with the view of an interactionist functional diversity are findings concerning the involvement of components of the hippocampal system in spatial functions, in human [26•,27], as well as non-human [28,29] subjects.

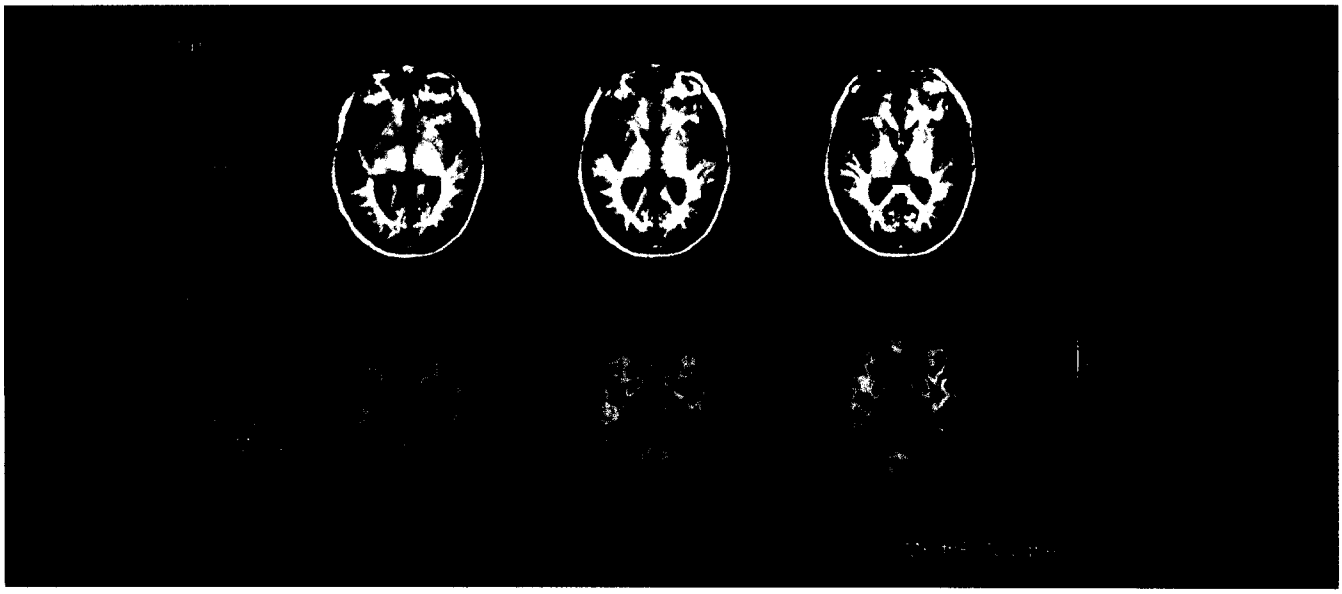
Growing evidence that plasticity of the brain leads to reorganization of function in response to hippocampal and other MTL lesions [30•] can also be accommodated more readily within the interactionist orientation. Such plasticity seems to be especially prevalent in cases of patients suffering from epilepsy [18•,31••,32,33]. It raises questions as to the appropriateness of concepts, such as 'fixed loci' and 'centers of memory' [34], and points to a more promising alternative of searching for interactive networks in which nodal structures, such as those in the MTLs, make specific contributions to the workings of the whole.

Medial temporal lobes and clinical memory disorders

Patients showing memory deficits after heart attack (or more generally after hypoxia) have frequently been used as models to study mnemonic consequences of MTL pathology. Now a recent report questions the validity of this approach [35]. Not only does it look as if the brain damage in these patients may go considerably beyond MTLs to other cerebral structures, it may also be the case that the only way to detect this damage requires dynamic brain imaging. Figure 1 illustrates the situation. In addition to the involvement of the hippocampal formation, the figure shows dysfunctioning of structures surrounding this complex, as well as one of medial diencephalic regions (that is, regions that are frequently considered as separate from the MTL memory system).

Other issues to which researchers are becoming sensitive concern individual differences among clinical patients and as yet little understood processes occurring over time that seem to be related to the variability of memory disorders. Ontogenetic developments [36] and protracted pathological processes, such as in epilepsy and other brain diseases [2••,37–40,41•,42–46], or merely increasing age [47–53] add to the inter-individual variability of results. (Such inter-individual variability has also been reported in the animal literature: Zola-Morgan *et al.* [54] had a monkey with widespread MTL damage who nevertheless obtained such anomalously high scores throughout testing that its data were not included in the statistical analyses.)

Figure 1



Extent of brain damage after heart attack. **(a)** MRI (magnetic resonance imaging) and **(b)** Flurodeoxyglucose (FDG)-PET scans of horizontal sections through the brain of a patient after suffering a heart attack. Note the widespread reduction in cerebral metabolism in the temporal lobes and the diencephalic region (b). This patient's brain demonstrates that heart attacks may not only result in hippocampal damage, but may also induce widespread tissue affections beyond the hippocampal area. CMRGl, cerebral metabolic rate of glucose. Adapted from [35].

Finally, even environmental stress and other psychogenic variables have been shown to influence hippocampal tissue [55•,56•,57,58,59•]. And while the general dissociation between processing of verbal material by the left and non-verbal material by the right hemisphere still appears to be valid [60,61], this differentiation seems to be less strict for women [62].

Hippocampus and novelty

The concept of novelty has a long tradition in neuroscience. Recent investigations have lent new life to the concept in the frame of hippocampal information processing [63,64,65•,66–68]. Grossberg and Merrill [64] have suggested that the hippocampal system combines novelty-based modulation of recognition learning and reinforcement learning with a steering of adaptively timed attention and inhibition of orienting responses. In one PET study of neuroanatomical correlates of novelty versus familiarity [68], it was proposed that novelty assessment represents an early stage of long-term memory encoding, and that probability of encoding information into long-term storage varies directly with its novelty. Studies using normal and brain-damaged subjects, and methods such as PET, functional magnetic resonance imaging (fMRI) and event-related potentials, all indicate that especially the right and possibly the more posterior hippocampal and parahippocampal regions might be engaged in responding to novel happenings [65•,66,67]. They furthermore stress the idea of the interaction of the hippocampal structures with sensory-related neocortical regions.

Future work may clarify the extent to which the concept of novelty is relevant to the understanding of other puzzling findings, such as the one reported by Schneider *et al.* [69]: solvable anagrams increased and unsolvable decreased hippocampal activation in a PET study. Novelty detection or assessment, of course, involves many subprocesses, and it may interact with processes such as attention [70] and emotion [19,71••,72], thus representing yet another aspect of 'beyond'.

Memory processes beyond the hippocampus

While the hippocampal structures are involved in functions beyond memory as such, the reverse is true as well: memory processes involve structures beyond the hippocampal system [22,73,74]. Indeed, it is becoming more and more widely accepted that no single brain structure can be 'critical' in and of itself, and that the contributions of any given brain region to memory depend on its interconnections and interactions with other regions. Thus, involvement of non-hippocampal structures have been reported in studies emphasizing the role of the hippocampal formation in memory encoding and retrieval. In the report of Rempel–Clower *et al.* [13], some additional damage in memory-related areas distant from the hippocampal ones (mammillary bodies, medial septal nuclei) was mentioned. These may contribute to the severity of the observed impairments, as suggested by comparisons of these cases with others whose primary damage was in such loci [75,76].

The idea that memory processes are subserved by widely distributed functional circuits encompassing a number of cortical, and even cerebellar, regions has been strongly supported by evidence from functional neuroimaging studies [77•,78–85]. Although, like any other technique, neuroimaging has its limitations [80], it also has certain advantages over other methods. One such is that it allows one to examine the neuroanatomical correlates of encoding separately from those of retrieval, and vice versa [78,86]. Such a separation is seldom achieved in lesion-based analyses of memory. Another advantage is that functional neuroimaging allows one to readily distinguish between the processes of episodic and semantic memory, especially with respect to retrieval [78,80].

In PET studies of laboratory analogues of episodic memory, subjects observe the presentation of items such as words or faces and are later tested for their memory for these events. Changes in the regional cerebral blood flow (rCBF), correlated with changes in neuronal activity, may be measured during encoding, during retrieval, or both. PET studies of memory consistently reveal the involvement of multiple cortical and subcortical regions in encoding and retrieval, the exact locations of observed changes in cerebral blood flow depending on the details of the tasks and procedures used. Thus, for instance, many PET studies have now shown differential involvement of left prefrontal cortical regions in encoding, and right prefrontal cortical regions in retrieval of episodic information, a pattern referred to as HERA (hemispheric encoding/retrieval asymmetry) [78,87–89]. Interestingly, since the appearance of the HERA model, a number of articles have described clinical cases that point to a role of right hemispheric neocortical structures in the retrieval of autobiographic (episodic) information from the distant past [19,57,58,90,91,92•]. An attendant development is the renewed emphasis on fiber systems, such as the fornix, in memory processes [25,92•,93].

PET and the hippocampus

Early failures to observe hippocampal activations in functional neuroimaging studies led to the widely spread impression that PET was not a suitable technique for studying the contribution of the hippocampal formation to memory processes in man [79,94]. More recently, however, the picture has become brighter. Blood flow changes in the hippocampal formation and adjacent cortical regions in the MTLs have been reported in a number of studies from different laboratories [49,63,83,87,95••,96,97•,98]. It has even been shown that retrieval performance of individual subjects may be correlated with changes in blood flow, in both hippocampal regions [99] and in the amygdaloid complex [71••]. However, as yet, no meaningful pattern of MTL activations and their connections to activations of other brain regions in relation to memory processes has emerged.

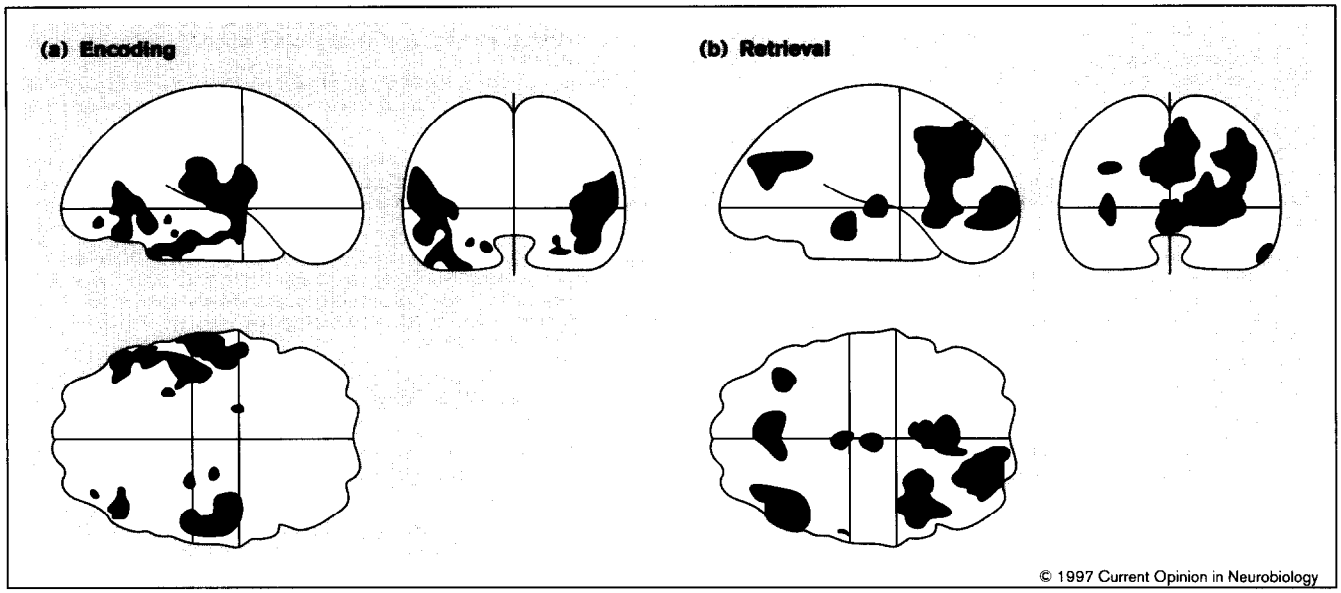
Encoding and retrieval

When one thinks of patterns of memory-related blood flow changes, one of the obvious distinctions to consider is that between encoding and retrieval. The common assumption has been that the hippocampus and other MTL structures play a more important role in encoding and consolidation than in retrieval [6,100]. The idea that retrieval of information relies on brain regions different from those involved in encoding and consolidation has been around for some time. The thought that the differences extend beyond the hippocampus [22,57], and the ability to identify these regions through neuroimaging, however, are of more recent origin. PET studies have indeed revealed the involvement of MTL regions in encoding, but they have also done so for retrieval. Because retrieval frequently entails encoding, the encoding/consolidation hypothesis could be saved by assuming that the retrieval-related MTL activations in fact reflect the encoding components of retrieval. However, at present, this is pure conjecture.

Figure 2 provides an illustration of the kind of evidence that has become available through the PET technique. It shows differences in the changes in blood flow between encoding (initial learning) and retrieval (subsequent test). The data were pooled from four different experiments ([99,101,102]; S Köhler, M Moscovitch, G Winocur, S Houle, AR McIntosh, personal communication) that differed in several ways, including the nature of items to be remembered, but that were identical in other ways, in that their design included a direct comparison between encoding and retrieval, with all other conditions, including perceptual displays and behavioral responses, held constant. In such a meta-analysis, the material-specific influences are minimized and the resulting brain maps can be assumed to more directly reflect neuroanatomical correlates of general encoding and retrieval processes. Because of the large total sample of subjects (N = 48), the data are robust. Brain regions common to both encoding and retrieval are not seen in Figure 2, because they are 'subtracted out' in this analysis. Such common regions undoubtedly exist. What is novel and interesting is the extent of the differences in the functional neuroanatomy of encoding and retrieval processes.

Figure 2 shows several extensive cortical regions that were differentially active in encoding and in retrieval. Encoding engages temporal lobes bilaterally, left fusiform gyrus and perirhinal cortex in the MTL, plus, putatively, right parahippocampal gyrus, and entorhinal cortex bilaterally. Retrieval engages right frontal regions, anterior cingulate cortex, thalamus, brainstem, and midline parietal activations—cuneus and precuneus. Finally, Figure 2 leaves the general impression that encoding processes engage the two hemispheres more-or-less symmetrically, whereas retrieval processes are correlated with changes in blood flow predominantly in the right hemisphere, together with

Figure 2



Brain regions are differentially active during encoding and retrieval, as indicated by differences in regional cerebral blood flow in a direct within-subjects comparison. **(a)** Brain regions more active during encoding than retrieval, including bilateral temporal lobes, left fusiform gyrus extending to the perirhinal cortex, right parahippocampal gyrus, and bilateral entorhinal cortex. **(b)** Brain regions more active during retrieval than during encoding, including right frontal lobe, anterior cingulate cortex, thalamus, brainstem, and cuneus/precuneus. The statistical parametric mapping (SPM) was conducted with software from the Wellcome Department of Cognitive Neurology (London, UK). The SPM displays shown here include sagittal views from the right, coronal views from the back, and transverse views from the top of the brain. The data were pooled from four different PET studies involving a total of 48 healthy subjects ([99,101,102]; S Köhler, M Moscovitch, G Winocur, S Houle, AR McIntosh, personal communication)

medial cortical regions. This latter pattern may represent a natural extension of the HERA model.

The increasing complexity of the brain correlates of memory, as revealed by functional neuroimaging, is illustrated by a PET study [103] designed to identify brain regions involved in general versus specific processes of encoding and retrieval of word-events, comprised of information about items, their location, and the time of their appearance. The data showed that some regions were involved regardless of the type of information processed, whereas others were involved in the processing of some kinds of information but not others. In the present context, perhaps the most interesting observation was the highly specific activation of the left hippocampus/parahippocampal associated with encoding of item (word) information, rather than with encoding generally or with encoding of location or time.

It is from these kinds of bits and pieces of information, if reliable, that the brain maps of memory within and beyond hippocampus and MTL regions will have to be assembled.

Conclusions

Recent findings from lesion work with non-human primates and functional neuroimaging studies with healthy human subjects have led to a de-emphasis of the role of the hippocampus in learning and memory, and have pointed to regions beyond the hippocampus, in the MTL as well as the neocortex, as equally important components of memory circuits in the brain. The emerging orientation towards the MTL regions in memory is based on the assumptions of their anatomical and functional diversity, a dynamic interaction among specific structures, and a synergistic relation between MTL and other, widely distributed cerebral regions. Neuroimaging studies have revealed, first, a frontal hemispheric asymmetry between encoding and retrieval processes in episodic memory, second, sizeable differences in the neuroanatomical correlates of encoding and retrieval in other brain regions, and third, activations of MTL regions associated with both encoding and retrieval processes. The current general picture of the neuroanatomy of memory is one of a spirited re-evaluation of previously held theoretical positions and a vigorous pursuit of the implications of new and unexpected discoveries.

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