

Hierarchical organization of cognitive memory

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SUMMARY

This paper addresses the question of the organization of memory processes within the medial temporal lobe. Evidence obtained in patients with late-onset amnesia resulting from medial temporal pathology has given rise to two opposing interpretations of the effects of such damage on long-term cognitive memory. One view is that cognitive memory, including memory for both facts and events, is served in a unitary manner by the hippocampus and its surrounding cortices; the other is that the basic function affected in amnesia is event memory, the memory for factual material often showing substantial preservation. Recent findings in patients with amnesia resulting from relatively selective hippocampal damage sustained early in life suggest a possible reconciliation of the two views. The new findings suggest that the hippocampus may be especially important for event as opposed to fact memory, with the surrounding cortical areas contributing to both. Evidence from neuroanatomical and neurobehavioural studies in monkeys is presented in support of this proposal.

1. INTRODUCTION

Long-term cognitive memory, often referred to as declarative (Squire 1982) or propositional (Tulving 1993) memory, is critically dependent on the part of the medial temporal lobe that comprises the 'hippocampal system', a set of heavily interconnected structures consisting of the hippocampus and the underlying entorhinal, perirhinal and parahippocampal cortices. According to one functional view, the medial temporal hippocampal system contributes in a unitary fashion to cognitive memory ability, which includes both memory for specific events (episodic memory) and memory for factual information (semantic memory). This single-system, unitary-process view is based on results that suggest that the episodic and semantic memory impairments of amnesic patients with medial temporal-lobe damage vary together in a graded manner depending on the extent of damage to the hippocampal system as a whole (Rempel-Clower *et al.* 1996; Squire & Zola 1996). The importance of this cerebral region for both components of cognitive memory is exemplified by the well-studied amnesic patient H.M., who at the age of nearly 30 years underwent bilateral removal of the medial temporal lobe for relief of drug-resistant epilepsy (Scoville & Milner 1957). Extensive neuropsychological evaluation has shown that H.M. exhibits equally profound impairments for both facts (Gabrieli *et al.* 1988) and events (Scoville & Milner 1957; Milner *et al.* 1968); and a recent magnetic

resonance imaging study confirmed that his cerebral excision included bilateral removal of the rostral half of the hippocampus, together with the entorhinal and part of the perirhinal cortices (Corkin *et al.* 1997).

According to an alternative functional view, the core defect in anterograde amnesia is the loss of episodic memory, in that the semantic memory of some amnesic patients appears to be relatively preserved (Kinsbourne & Wood 1975, 1982; Schacter & Tulving 1982; Wood *et al.* 1982). A particularly clear instance of such sparing was found in patient K.C., who also became densely amnesic at age 30, in his case after extensive brain injury, including bilateral medial temporal damage, sustained in a motorcycle accident. K.C. is unable to remember events for more than a few seconds; however, when tested for learning under conditions in which associative interference was held to a minimum, he was able to acquire a high level of factual information involving vocabulary items and to retain this new information for more than a year (Tulving *et al.* 1991; Hayman *et al.* 1993). The question of what brain damage might be responsible for such a dissociation of effects within cognitive memory has not yet been specifically addressed.

In this paper, evidence is presented that may help reconcile the two contending views described above. The evidence is based in part on behavioural and magnetic resonance imaging (MRI) data that were gathered recently in patients who became amnesic as a result of pathology incurred very early in life (Vargha-Khadem *et al.* 1997). These new findings,

considered together with extant data on the neuroanatomy of the medial temporal hippocampal system as well as on the behavioural profiles of patients with adult-onset amnesia and of animals with selective medial temporal lesions, suggest the possibility that cognitive memory and its neural substrates are both organized hierarchically. Specifically, it is proposed as a working hypothesis that the cortices subjacent to the hippocampus are necessary for both episodic and semantic memory, whereas episodic memory (but not semantic) is critically dependent, in addition, on the stimulus processing provided by the hippocampus itself.

2. NEUROANATOMY OF THE HIPPOCAMPAL SYSTEM

To provide a framework for a discussion of the functional organization of the hippocampal system, this paper begins by briefly summarizing the anatomical organization of this region of the temporal lobe. It has long been known that the modality-specific cortical sensory processing areas in the monkey project in a stepwise and increasingly convergent manner onto the 'highest-order' association areas, including the prefrontal cortex, the cingulate cortex, the cortex in the dorsal bank of the superior temporal sulcus, and the hippocampus (Jones & Powell 1970). More recently, neuroanatomical studies focused on the hippocampus have begun to chart the precise pathways through which cortical sensory inputs activate this particular structure. A schematic diagram of these connections is shown in figure 1.

The diagram illustrates several important principles of organization. First, the hippocampal system receives a strong convergence of both modality-specific and polymodal input, rendering each component of the system a higher-order polymodal association area (Jones & Powell 1970; Van Hoesen & Pandya 1975*a,b*; Van Hoesen *et al.* 1975). Second, sensory information from widespread areas of the neocortical mantle enters the medial temporal lobe primarily via projections to the perirhinal and parahippocampal cortices. These areas provide the major cortical input to the entorhinal cortex; the entorhinal cortex, in turn, provides the major input to the hippocampus. The entorhinal cortex and hippocampus together constitute the 'hippocampal formation'. Third, the perirhinal and parahippocampal cortices serve not only as the major port of entry into the hippocampal formation but also as its major cortical output, via dense, reciprocal projections. Thus the perirhinal and parahippocampal cortices constitute the major communication links between widespread areas of sensory cortex on the one hand and the hippocampal formation on the other.

Although all of the cortical areas in the medial temporal lobe receive convergent projections from multiple sensory modalities, these areas can be differentiated by their distinctive sources of input. These inputs can be broadly characterized as arising from cortical areas in the various modalities important for analysing stimulus quality (ventral processing streams), from cortical areas important for analysing stimulus location (dorsal processing streams), or from

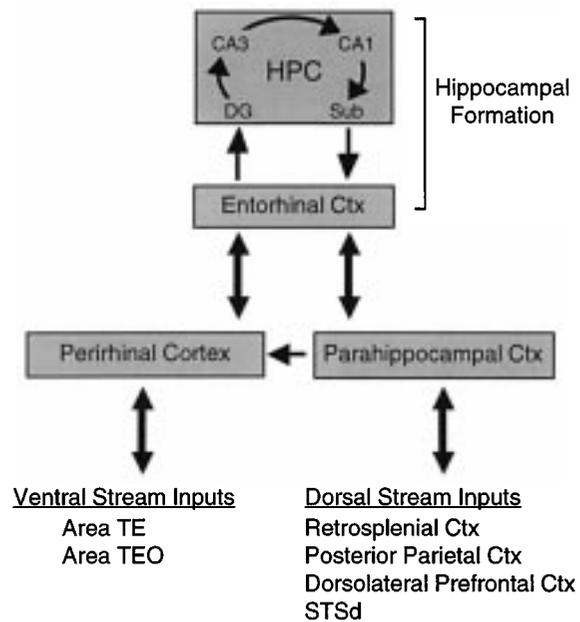


Figure 1. Schematic diagram of the connections of the medial temporal hippocampal system (filled boxes), depicting its hierarchical organization. The areas listed under ventral and dorsal streams are those providing the strongest inputs to the perirhinal and parahippocampal cortices, respectively. Abbreviations: CA1 and CA3, pyramidal-cell subfields of the hippocampus; Ctx, cortex; DG, dentate gyrus; HPC, hippocampus; STSd, dorsal bank of the superior temporal sulcus; Sub, subicular complex, including the subiculum, presubiculum and parasubiculum; TE and TEO, cortical subdivisions of Bonin & Bailey (1947)

both. Thus, the perirhinal cortex is distinguished by its prominent projections from ventral processing streams, receiving nearly two-thirds of its cortical inputs from the adjacent ventral-stream visual areas, TE and TEO (Suzuki & Amaral 1994*a*). Compared with the perirhinal cortex, the parahippocampal cortex receives a far greater proportion of its inputs from dorsal-stream areas, including the posterior parietal cortex, the retrosplenial cortex, the dorsolateral prefrontal cortex and the dorsal bank of the superior temporal sulcus (Martin-Elkins & Horel 1992; Suzuki & Amaral 1994*a*). Thus, whereas both the perirhinal and parahippocampal cortices receive projections from multiple sensory modalities, each is characterized by prominent ventral- and dorsal-stream inputs, respectively.

As already indicated, the entorhinal cortex receives most of its projections from the adjacent perirhinal and parahippocampal cortices, which provide approximately two-thirds of all entorhinal cortical inputs (Insausti *et al.* 1987). Consequently, within the hippocampal system, the entorhinal cortex serves as a second tier of convergence, a characterization that is also supported by an analysis of the laminar sources and terminations of the interconnections of this region. Specifically, both the perirhinal and parahippocampal cortices project to entorhinal cortex in a feedforward-like manner, whereas the latter reciprocates these projections in a feedback-like manner (Suzuki &

Amaral 1994*b*). Finally, the entorhinal cortex provides the strongest direct cortical projections to the hippocampus, via dense outputs terminating on the granule cells of the dentate gyrus.

The hierarchical pattern of medial temporal connections described above provides important clues to the mnemonic contributions of these areas. First, the differential patterns of cortical inputs to the perirhinal and parahippocampal cortices suggest that these two areas may be contributing to different aspects of memory. Whereas the parahippocampal cortex may participate primarily in memory for spatial location, the perirhinal cortex may serve mainly for memory of stimulus quality. Second, the further convergence of inputs from these two areas onto the entorhinal cortex, and subsequently onto the hippocampus, suggests that these latter areas may be specialized for forms of memory requiring the additional integration of sensory information that only they afford.

3. FINDINGS IN PATIENTS WITH EARLY HIPPOCAMPAL DAMAGE

Although extremely valuable insights into the organization of memory have been gained from the study of amnesic patients, especially the distinction between cognitive memory and non-cognitive memory (e.g. procedural learning, classical conditioning, priming), it has not yet been possible to evaluate the effects of subtotal medial temporal damage in relation to the episodic–semantic memory distinction outlined in the introduction. Most cases of human amnesia are not informative in this regard because their medial temporal pathology was either not selective or not well documented. Notable exceptions to this generalization are three recent reports of amnesic patients in which postmortem histological analyses revealed medial temporal pathology limited largely to the hippocampus in each case (Zola-Morgan *et al.* 1986; Victor & Agamanolis 1990; Rempel-Clower *et al.* 1996). Importantly, these studies demonstrated for the first time that even such limited damage produces a clinically significant amnesia. Unfortunately, however, none of the above patients had been evaluated for possible differences in the degree to which their amnesia affected the episodic compared with the semantic components of cognitive memory.

A unique opportunity to assess the role of the hippocampus in memory has recently been provided by the discovery of three patients with amnesia due to hippocampal pathology sustained, in two of the cases, very early in life (a detailed description of the behavioural and MRI findings in all three cases is presented by Vargha-Khadem *et al.* (1997)). Briefly, each of the three patients developed pronounced memory impairment as a result of an anoxic–ischaemic episode associated in one case with difficult delivery at birth (Beth, now aged 14), in another with either premature birth or convulsions suffered at age 4 (Jon, now 19), and in the third with an accidental, toxic dose of theophylline, an anti-asthmatic, at age 9 (Kate, now 22). Memory impairments in Beth and Jon were not noted until they were about 5–6 years

old, but in Kate they were evident immediately after her accidental drug dose.

Beth, Jon, and Kate were first examined neuropsychologically at the ages of 13, 16, and 19, respectively, at which time all three patients were found to have memory quotients on the Wechsler Memory Scale that fell about 20 points below the level predicted by their verbal IQs. Of the three, Jon has the highest verbal IQ (109), well within the average range, whereas Beth and Kate scored in the low-average range (82 and 86, respectively; Beth's relatively low IQ may be at least partly explained by the findings from MRI described below). Consistent with findings in patients with adult-onset amnesia, Beth, Jon, and Kate performed nearly at floor levels on all the delayed-recall tests of the Wechsler Memory Scale, as well as on other standard tests of delayed recall, while scoring well within normal limits on various standard tests of immediate memory.

Although the delayed-recall tasks on which the three patients were impaired do not explicitly measure episodic memory function, the symptom that initially brought each one of them to our attention was a pronounced memory loss for everyday events, the hallmark of an impairment in episodic memory. As reported by their parents, none of the three patients is well oriented in either place or time, can provide a reliable account of the day's activities, or can reliably remember messages, stories, visitors, appointments, etc. Indeed, their everyday-memory losses (which were confirmed with the Rivermead behavioural memory test (Wilson *et al.* 1985), a quantitative measure of event memory in a laboratory setting), are so severe that none of the patients can be left on his or her own for any extended period, much less hold a job or lead an independent life.

Yet, surprisingly, despite their disabling loss of episodic memory, all three patients have developed normal language and social competence, including conversational and interpersonal skills, and all were educated in mainstream schools. They have learned to read and write and have acquired new factual information at levels consistent with their verbal IQs rather than with predictions that might well have been made on the basis of their pronounced amnesic syndrome. The IQ levels themselves, as reflected, for example, in all three patients' fully normal scores on the Vocabulary, Information, and Comprehension subtests of the Wechsler Intelligence Scales, are a striking indication of their preserved ability to acquire factual knowledge in the face of early-onset amnesia. In sum, their social, linguistic, literacy, and intellectual attainments all seem to point to a disproportionate sparing of semantic compared with episodic memory.

The neuropathology in the three patients was assessed with quantitative magnetic resonance techniques (Jackson *et al.* 1993; Gadian *et al.* 1996; Van Paesschen *et al.* 1997), as well as through visual inspection of the scans. The quantitative measurements revealed that the hippocampi, which could be seen to be atrophic in each case, are reduced bilaterally to about 50% (43, 50, and 61% for Beth, Jon, and Kate, respectively) of the mean volume in normal subjects. Further, even the preserved hippocampal tissue is highly

abnormal in each (as reflected by bilaterally elevated hippocampal T2 water values obtained with the T2-relaxometry method). Outside the hippocampus, the only detectable pathology in Jon and Kate was some diffuse abnormality in the right temporal lobe (as indicated by marginally abnormal ratios of the signal intensity for *N*-acetylaspartate to the sum of the signal intensities for choline-containing compounds and creatine + phosphocreatine, measured with magnetic resonance spectroscopy). This type of abnormality was not found in either temporal lobe in Beth, but visual inspection of her scans revealed increased T2-weighted signal intensity in the periventricular and peritrigonal white matter accompanied by a marked loss of this white matter, together with thinning of the corpus callosum. These extrahippocampal abnormalities in Beth could help account for her relatively low IQ.

Although the magnetic resonance findings suggest that the only abnormality all three patients have in common is bilateral pathology of the hippocampal formation, the possibility cannot be excluded that, in each case, some undetected pathology actually extends beyond the hippocampus into the underlying cortices. Indeed, some results to be described below raise questions about the integrity of the parahippocampal cortex in particular. Nevertheless, the evidence in all three patients suggesting relative sparing of semantic compared with episodic memory, and relative preservation of the medial temporal cortex as compared with the hippocampus, leads to the proposal that the cortex subjacent to the hippocampus may be sufficient to support their relatively spared semantic memory.

4. COMPARISON WITH STUDIES OF MEMORY IN MONKEYS

Additional results that are compatible with the foregoing proposal were obtained on a series of computerized recognition memory tasks that were administered to both the amnesic patients and 11 normal controls. The tasks included one-trial recognition for lists of words, non-words, familiar faces and unfamiliar faces; these tasks were similar in principle to measures of one-trial stimulus recognition widely used in studies on monkeys. Other tasks in the series assessed one-trial associative recognition for lists of paired items involving each of the materials described above, as well as multitrial associative recognition for lists of non-word pairs, face pairs, voice-face pairs, and object-place pairs. These tasks, too, have parallels with those used in monkeys (stimulus-stimulus association: Spiegler & Mishkin 1979; Murray & Mishkin 1985; Murray *et al.* 1993; and object-place association: Parkinson *et al.* 1988; Angeli *et al.* 1993). The great majority of the recognition tasks yielded results in the amnesic patients that are strikingly similar to those that have been obtained in monkeys with hippocampal lesions. For tasks requiring one-trial stimulus recognition, on which monkeys with hippocampal lesions exhibit little (Zola-Morgan *et al.* 1992, 1994) or no impairment (Murray & Mishkin 1996), the patients likewise were not significantly

impaired. Again like monkeys with hippocampal lesions, the patients were not significantly impaired on recognition tasks involving either one-trial (Spiegler & Mishkin 1981) or multitrial (Murray & Mishkin 1985; Murray *et al.* 1993) stimulus-stimulus associations. In sharp contrast to these results are those from numerous studies in monkeys, which demonstrate that lesions of the cortex underlying the hippocampus, particularly lesions that include the perirhinal and entorhinal cortices, produce severe and long-lasting deficits in both item and associative recognition (Spiegler & Mishkin 1979; Murray & Mishkin 1986; Zola-Morgan *et al.* 1989, 1993; Meunier *et al.* 1993; Murray *et al.* 1993; Suzuki *et al.* 1993; Goulet & Murray 1995). The contrasting effects of the hippocampal and perirhinal-entorhinal lesions in monkeys strongly imply that the computerized tasks given to the patients would have revealed clear-cut deficits had the patients sustained a substantial amount of damage to the perirhinal-entorhinal complex.

Before considering the further implications of the recognition memory data, it is first necessary to consider a potential exception to the similarity of results obtained in the amnesic patients and in monkeys with hippocampal lesions. The one computerized task on which the patients showed a severe deficit, all three scoring far below all the control subjects, was the one requiring memory for object-place associations. Initially, this result too appeared to parallel an earlier finding in hippocampotomized monkeys, because such monkeys had exhibited severe impairment on an analogous task (Parkinson *et al.* 1988; Angeli *et al.* 1993). However, preliminary evidence from an ongoing study on the effects of separate lesions of the hippocampus and parahippocampal cortex (Malkova & Mishkin 1997) suggests that the object-location memory deficit in the monkeys studied earlier arose from damage to parahippocampal tissue, which had been removed in association with the hippocampotomy, rather than from removal of the hippocampus itself. If this preliminary interpretation is upheld, further investigations will be needed to resolve the discrepancy between the impairment in object-location memory in the amnesic patients and the lack of such an impairment in monkeys with selective hippocampal lesions. One possible resolution might be that the greater memory load in the human test compared with the one given to the animals (a list length of 20 object-place pairs compared with a list length of two such pairs) requires the spatial memory capacity of the hippocampus, which could well exceed that of the parahippocampal cortex. Alternatively, the impairment in the patients could reflect undisclosed damage to the parahippocampal cortex, consonant with the preliminary neurobehavioural evidence in monkeys as well as with the connective evidence described in the section on neuroanatomy.

5. A HIERARCHY OF NEUROCOGNITIVE MEMORY PROCESSES

As already indicated, the patients' performance on the other, non-spatial, recognition tests corroborates

the suggestion from the magnetic resonance findings that their perirhinal–entorhinal cortices, at least, are substantially spared. Further, in conjunction with their amnesic profile, the recognition data are consistent with the proposal that such partial preservation of their medial temporal cortices may be sufficient to support their semantic memory. It is important to point out that this proposal does not imply that the recognition tests measure semantic memory specifically; but neither do they measure only episodic memory. The distinction between these two types of mnemonic store refers to differences in their long-term contents, not to differences in the way those two types of contents were first acquired. Whenever a new item, association, or fact is being encoded for storage, that sensory information necessarily arrives in the form of an evolving event or episode rich in temporal, spatial, and other situational contexts, overlain with whatever mental and emotional experiences the subject brings to the event. How much of this abundant contextual information is retained in the long term largely determines to which category of cognitive memory the stored information should be assigned: to context-rich episodic memory or to context-free semantic memory.

The recognition memory tests may therefore more appropriately be viewed as measures of the basic sensory memory ability that is essential for the entry of information into both types of long-term store. Considered in this way, the neurobehavioural evidence in the patients suggests that, in the presence of a severely compromised hippocampus, the basic sensory memory functions served by the subjacent cortex are largely sufficient for entry of sensory information into context-free semantic memory but not into context-rich episodic memory, which must therefore require the additional information processing that is normally provided by the hippocampal circuit at the top of the hierarchy (see figure 1). The proposal is consistent with the anatomical evidence, which indicates progressively greater convergence, and presumably association, of sensory inputs as one ascends the hierarchy within the hippocampal system.

The proposal is also consistent with the notion that ontogenetic development of the semantic memory ability that underpins social, linguistic, and intellectual competence precedes development of, and may even also underpin, the ability to store and recollect earlier episodes (Tulving 1995). It is of interest in this connection that the amnesia in the two patients who had sustained hippocampal pathology very early in life did not become evident until they were 5–6 years old, long after they had acquired the social skills, speech and language, and factual knowledge that are normal for that age.

6. IMPLICATIONS FOR RESEARCH

Despite its plausibility, the above proposal can only be considered a working hypothesis. The evidence for a behavioural dissociation in the amnesic patients with early hippocampal injury is largely based on the striking contrast between their episodic memory failures and semantic memory achievements in

everyday life, that is, in situations that are difficult to compare directly. Additional evidence must therefore be gathered under controlled learning and retention conditions to determine whether the differences in their episodic and semantic memory are indeed greater than can be accommodated by a single-system, unitary-process view (Hamann & Squire 1995).

The applicability of the episodic–semantic memory distinction to the effects of brain injury in general, and of medial temporal damage in particular, has been much debated in the literature on late-onset amnesia, but thus far without a clear resolution (Glisky *et al.* 1986; McKoon *et al.* 1986; Shimamura & Squire 1989; Wood *et al.* 1989; Horner 1990; Ostergaard & Squire 1990; Tulving *et al.* 1991; Hayman *et al.* 1993; Hamann & Squire 1995). One possible explanation for the conflicting reports is that most of the previously studied patients had relatively unspecified or unselective pathology. According to the proposal being advanced here, a dissociation between the two components of cognitive memory can be expected only in cases where the hippocampus has been damaged selectively, the underlying cortices having remained largely intact. The correlative prediction is that extensive damage to the underlying cortices, which serve as the essential links between the sensory processing streams and the hippocampus, should produce severe impairment in both components of cognitive memory, whether or not the hippocampus itself is directly affected. The advent of quantitative magnetic resonance techniques, which are likely to be gradually refined and extended, will enable increasingly accurate assessment of the neuropathology in patients with amnesia and, consequently, examination of the predicted difference in outcome after the two types of damage.

Improved neuropathological assessment, together with the discovery that anoxic–ischaemic episodes early (Vargha-Khadem *et al.* 1997) as well as later (Zola-Morgan *et al.* 1986; Victor & Agamanolis 1990; Rempel-Clower *et al.* 1996) in life can lead to relatively selective hippocampal pathology, affords an opportunity to clarify the role of not only the lesion variable but also the variable of age at injury. The relative sparing of semantic memory in the patients studied here, two of whom incurred their hippocampal injury at a time when plasticity and compensatory potential are still at their peak, could well turn out to be greater than the sparing observed in patients who have sustained comparable damage in adulthood. Conversely, in other cognitive (e.g. intellectual) domains, the early onset of their amnesia may have disadvantaged them relative to those with late-onset amnesia, on the supposition that these other domains depend on cognitive memory ability far more for their initial development than for their later maintenance.

The possibility that cognitive memory is organized hierarchically also has implications for the search for an animal model of human amnesia. The amnesic symptoms in humans that are due to impairment in context-free semantic memory may be modelled in animals, at least in part, by the severe deficits in context-free associative memory that are produced by

lesions of entorhinal, perirhinal, and parahippocampal cortices. However, an animal model must be considered incomplete unless those human amnesic symptoms that are due to an impairment in context-rich episodic memory are also reproduced. According to the present analysis, such symptoms are likely to be recognized in animals only if they are seen in the absence of a basic associative memory impairment, that is, only if they consist of deficits limited to context-rich associative memory due to selective hippocampal lesions.

The authors of the original report on the patients with early medial temporal pathology (Varga-Khadem *et al.* 1997) included K. E. Watkins, A. Connelly and W. Van Paesschen; we are indebted to all of them for their critical contributions to that study, on which this chapter leans so heavily. In addition, we thank A. Incisa della Rochetta, who helped design the computerized tests and collect the data on some of the control subjects.

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