Amnesia, memory and brain systems

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SUMMARY

Bilateral damage to either the medial temporal lobe or the diencephalic midline causes an amnesic syndrome, i.e. a global impairment in the ability to acquire new memories regardless of sensory modality, and a loss of some memories, especially recent ones, from the period before amnesia began. The memory deficit can occur against a background of intact intellectual and perceptual functions. Two themes have been prominent in recent work. First, the amnesic syndrome is narrower than once believed in the sense that a number of learning and memory abilities are preserved (e.g. skill and habit learning, simple forms of conditioning and the phenomenon of priming). Second, the brain system damaged in amnesia has only a temporary role in memory. As time passes after learning, memory is reorganized and consolidated within neocortex, such that eventually medial temporal lobe and diencephalic structures are not needed for storage or retrieval.

1. INTRODUCTION

Memory is a broad topic rooted in both biology and psychology. In the most biological sense, questions about memory are questions about synaptic plasticity, i.e. cellular and molecular questions about how individual neurons can exhibit history-dependent behaviour in the short term and long term, and about how they can behave differently as a function of their recent input. Yet, many important questions about memory are systems questions and functional questions that address a more global, neuropsychological level of analysis. Is memory one thing or many things? What brain systems are involved in memory, and what jobs do they do?

This chapter considers three themes that have been important in recent neuropsychological work on memory. The first theme is the simple idea that memory is to some extent a separable function of the brain that is dissociable from other cognitive functions. Thus, memory functions can sometimes be severely impaired in the absence of other intellectual deficits. The second theme focuses on the successful development in the monkey of an animal model of human memory impairment and the identification of the brain structures in the medial temporal lobe that are important for memory. The third theme concerns the idea that the role of the medial temporal lobe system is important for only one kind of memory. It is essential for conscious recollections of recently occurring facts and events (declarative memory), but not for a large collection of non-declarative memory abilities (e.g. skills and habits, simple classical conditioning and the phenomenon of priming).

2. HUMAN AMNESIA AS AN ISOLATED CONDITION

Bilateral damage to the medial temporal lobe or diencephalic midline can cause memory impairment without affecting other cognitive functions. For example, amnesic patients with medial temporal lobe damage can obtain average or above-average IQ scores on conventional intelligence tests (e.g. the Wechsler Adult Intelligence Scale-Revised) and yet be severely impaired on conventional memory tests (e.g. the Wechsler Memory Scale-Revised) (figure 1). *A priori* one might have supposed that the structures of the brain are so interconnected and interdependent that removal of any single structure should produce a broad band of impairment spread across many functions. However, one of the important lessons of modern neuroscience is that the brain is highly differentiated and specialized. And one of the clear findings from empirical work is that brain lesions can produce highly specific cognitive deficits exquisitely related to the structures and connections that are damaged.

Even allowing for the fact that localized lesions can produce selective deficits, some additional explanation is needed to explain how a lesion of the medial temporal lobe can selectively impair memory. The problem is that the concept of an isolated defect in memory can appear to conflict with the widely held view that perception, information processing and memory are closely connected. For example, long-term memory is thought to be stored in the same cortical areas where the information to be remembered is processed and analysed (Mishkin 1982; Squire 1987; Damasio 1989; Horel 1994; Ungerleider

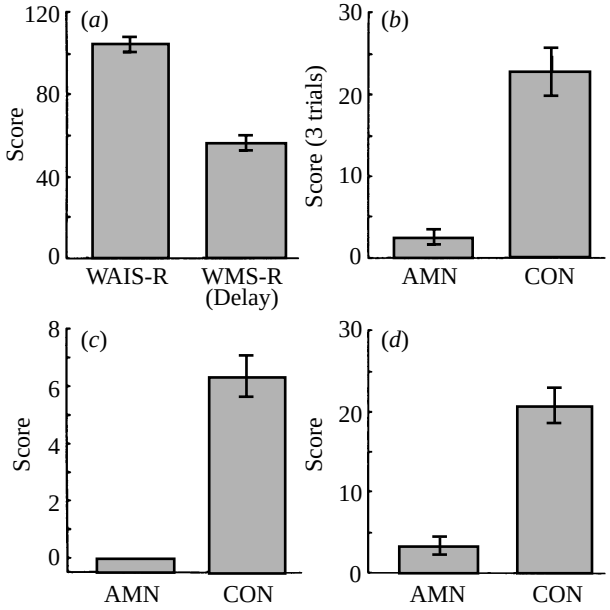

Figure 1. (*a*) Performance of patients with amnesia ($n = 14$) on a standard intelligence test (Full Scale WAIS-R [Wechsler Adult Intelligence Scale-Revised]) and on a standard memory test (WMS-R) [Wechsler Memory Scale-Revised] Delay Index). In the normal population, both tests yield average scores of 100, with a standard deviation of 15. These amnesic patients include seven with alcoholic Korsakoff's syndrome, six with confirmed or suspected damage to the hippocampal formation, and one with a bilateral medial thalamic infarction. Also shown is performance of the same 14 patients with amnesia (AMN) and eight control subjects (CON) on three tests of new learning ability. (*b*) Paired-associate learning measures the ability to learn unrelated word pairs by reporting the second word in a pair when cued with the first word (10 pairs, 3 trials, maximum score = 30). (*c*) Story recall measures 10–15 min delayed retention of a short prose passage consisting of 21 meaning segments (maximum score = 21). (*d*) Diagram recall measures the ability to reconstruct a complex line drawing (Rey Osterreith figure) from memory 10–15 min after copying it (maximum score = 36). Error bars show s.e.m. (From Squire *et al.* 1990.)

1995). Accordingly, if memory is affected, one should also expect some related defect in information processing. As it turns out, the concept of an isolated memory defect can be understood without contradicting this larger principle that memory functions are closely tied to processing and analysis functions.

Consider that the medial temporal lobe is, in fact, thought to accomplish certain kinds of processing and analysis, with memory as the product (Alvarez & Squire 1994; McClelland *et al.* 1995; Teyler & Discenna 1986; Milner 1989). The medial temporal lobe is needed at the time of learning to establish functional connections with widespread areas of neocortex, based on synaptic changes within the medial temporal lobe that occur at the time of learning. Perception and short-term memory are thought to depend on coordinated and distributed activity within neocortex. As documented below, medial temporal lobe lesions spare short-term (immediate) memory, presumably because short-term memory can be supported by neocortex. Thus, the medial temporal lobe is involved in processing and analysing. Its role begins at the time of learning, when it receives highly processed input from neocortical association areas, and it is needed at the time of learning to interact with neocortex. However, its essential role in behaviour is not manifest with the lesion technique unless or until short-term memory can no longer support recollection, e.g. when so much time has passed after learning that performance based on prior experience must draw on long-term, recollective memory. In summary, the medial temporal lobe, like other brain structures, is involved in processing and analysing, but damage to this structure results in a memory deficit because the normal contribution of the structure is not essential until some time has passed after learning.

Studies that assess memory-impaired patients using tests that make severe demands on perceptual operations and short-term memory have consistently found that the patients are entirely intact. For example, amnesic patients exhibited entirely intact digit-span memory, even when the estimate of digit-span ability approached a resolution of one decimal point (Baddeley & Warrington 1970; Cave & Squire 1992). Specifically, both control subjects and amnesic patients with radiologically confirmed damage to the hippocampal formation were able to repeat back an average of 6.8 digits. Similarly, amnesic patients with medial temporal lobe lesions were fully intact at identifying words flashed briefly on a computer screen, and they exhibited normal performance across a wide range of accuracies (Hamann *et al.* 1995). That is, as the experimental conditions were varied such that control subjects improved from nearly 0% correct (with a 33 ms exposure time) to about 90% correct (with a 116 ms exposure time), amnesic patients matched the control subjects at each performance level.

If the medial temporal lobe is to be understood as having memory functions, it should be possible to distinguish its contribution to cognition from the contributions made by other areas of cortex. Lesion studies identify three key features of medial temporal lobe function. First, as suggested above, medial temporal lobe lesions spare short-term memory while impairing long-term memory. The deficit can be described as profound forgetfulness, and the deficit emerges most clearly after some time has elapsed beyond the moment of learning. This dissociation between perception and short-term memory, on the one hand, and long-term memory, on the other hand, is now well established in humans, monkeys (Alvarez *et al.* 1994; Overman *et al.* 1991), and rats (Kesner & Novak 1982; Vnek *et al.* 1995). In contrast, lesions of neocortex impair performance at very short delays, and also impair performance at longer delays (Squire 1987; Goldman-Rakic 1987; Fuster 1995).

The second key feature of medial temporal lobe function is that the medial temporal lobe is involved in memory for a limited period of time after learning. As time passes, memory is gradually reorganized (or consolidated), and information storage in neocortex becomes independent of the medial temporal lobe system. The key finding is that when a medial temporal

lobe lesion is sufficiently delayed after learning, memory is not affected. Five prospective studies now support this conclusion, i.e. recently acquired information is impaired while more remotely acquired information is spared. This finding of temporally graded retrograde amnesia has been obtained using several different species and tasks: object discrimination learning in monkeys (Zola-Morgan & Squire 1990), context-specific fear conditioning in rats (Kim & Fanselow 1992), acquired food preference in rats (Winocur 1990), maze learning in mice (Cho *et al.* 1993), and trace conditioning of the eyeblink reflex in rabbits (Kim *et al.* 1995). In contrast, there is no evidence for temporally graded retrograde amnesia following a neocortical lesion.

Recent theoretical accounts of memory consolidation propose that medial temporal lobe structures direct consolidation in neocortex by gradually binding together the multiple, geographically separate cortical regions that together store memory for a whole event. Further, recent experimental studies show that gradual changes in cortical connectivity can occur as the result of behavioural experience, and they give some hints about how consolidation in neocortex might occur: gradual morphological changes, driven by continuing input, modify the strength of connections between cortical areas (Darian-Smith & Gilbert 1994; Black *et al*. 1990; for review, see Squire & Alvarez 1995).

A third defining feature of medial temporal lobe function is that damage to this region produces a memory impairment that is global and multimodal, i.e. memory is impaired regardless of the kind of material that is presented (for example, objects, words or designs) and the sensory modality in which information is presented (Murray & Mishkin 1984; Suzuki *et al.* 1993). In contrast, the memory problems associated with neocortical lesions are domain-specific, i.e. they are specific to the kind of material that is ordinarily processed and analysed by the damaged area (e.g. faces or words).

In summary, medial temporal lobe lesions produce memory impairment, which occurs against a background of normal cognitive function. The brain has to some extent separated its capacity for intellectual functions and perceptual functions from its capacity to lay down in memory the records that ordinarily result from engaging in intellectual and perceptual work. Inevitably, this conclusion has been easier to reach with humans than with non-human animals. The possibility of speaking with amnesic patients about their condition and the availability of many testing instruments that can be administered quickly greatly facilitate the assessment of human cognitive functions. As a result, the idea that medial temporal lobe lesions selectively impair memory now rests securely on quantitative neuropsychological data. It should also be said that one eventually arrives at the same conclusion simply by spending time with a well-circumscribed amnesic patient and his or her family. The patient and the family describe the problem as a selective memory impairment, and the visitor readily recognizes it as such after observing the patient repeatedly in various natural settings.

By contrast, the analysis of cognitive impairment in non-human animals is difficult to the point that a few investigators still debate whether a medial temporal lobe lesion in monkeys or a hippocampal lesion in rats really impairs memory, or whether the lesion instead impairs perception, motivation or some other factor that can affect performance on tests intended to assess memory (Horel 1994; Ringo 1991; Vanderwolf & Cain 1994). One cannot interview the experimental subject, and the available tests are necessarily indirect assessments of performance that sometimes require weeks or months to administer. Nevertheless, a considerable body of useful work has been done with non-human animals (some of it cited in the previous paragraphs; also see Squire (1992)). The important finding is that lesions in experimental animals, when placed in the same brain regions that are damaged in human amnesia, produce effects similar to what is observed in humans. The net result of all this work was the achievement of an animal model of human amnesia and eventually, with the application of the animal model, the identification of the specific brain structures and connections important for memory.

During the past two decades, research in monkeys and humans has identified a system of anatomically related structures in the medial temporal lobe that is important for memory (for reviews, see Mishkin 1982; Murray 1992; Squire & Zola-Morgan 1991; Zola-Morgan & Squire 1993). This system is schematically illustrated in figure 2, and it is comprised of what we here term the hippocampal region (i.e. the cell fields of the hippocampus proper, the dentate gyrus and the subicular complex) and the cortical areas adjacent to the hippocampal region (i.e. the entorhinal, perirhinal and parahippocampal cortices). All of these cortical areas are anatomically related to the hippocampal region (Van Hoesen 1982; Van Hoesen & Pandya 1975*a*,*b*; Insausti *et al*. 1987; Suzuki & Amaral 1994*a*,*b*). In particular, the perirhinal cortex and the parahippocampal cortex provide nearly two-thirds of the cortical input to the entorhinal cortex (Insausti *et al*. 1987; Suzuki & Amaral 1994*a*). The entorhinal cortex, in turn, provides the major source of cortical projections to the hippocampus and dentate gyrus (Van Hoesen 1982; Suzuki & Amaral 1994*b*). The hippocampal region and the entorhinal cortex, together, make up the hippocampal formation.

3. SEVERITY OF MEMORY IMPAIRMENT DEPENDS ON THE LOCUS AND EXTENT OF DAMAGE WITHIN THE MEDIAL TEMPORAL LOBE MEMORY SYSTEM

Work with monkeys and humans has led to the idea that the severity of memory impairment increases as more components of the medial temporal lobe memory system are damaged. This idea has been supported by a large number of individual studies in monkeys where performance on memory tasks by groups of monkeys with varying damage to the medial temporal lobe has been compared. Initially, these efforts began with large bilateral lesions of the medial temporal lobe that approximated the damage sustained

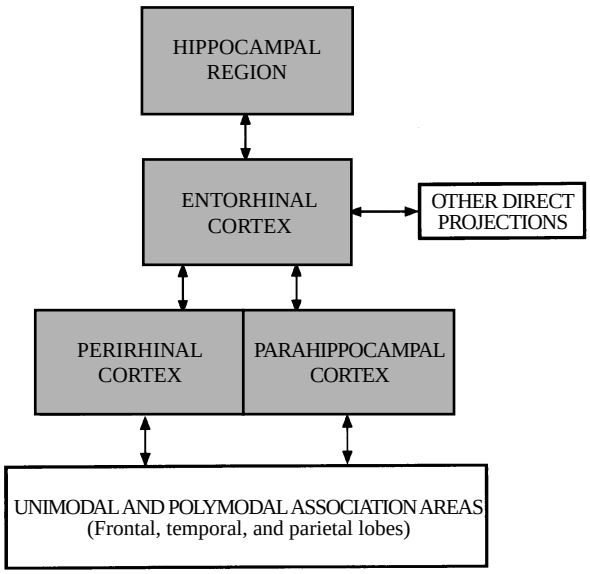

Figure 2. A schematic view of the medial temporal lobe memory system. The perirhinal and parahippocampal cortices receive projections from unimodal and polymodal areas in the frontal, temporal, and parietal lobes. In turn, the perirhinal and parahippocampal cortices account for nearly two-thirds of the cortical input to the entorhinal cortex, the primary source of cortical input to the hippocampal region (i.e. the cell fields of the hippocampus proper, the dentate gyrus, and the subicular complex). The hippocampal region together with the entorhional cortex make up the hippocampal formation. The entorhinal cortex also receives other direct inputs from orbital frontal cortex, cingulate cortex, insular cortex and superior temporal gyrus. All these projections are reciprocal. (From Zola-Morgan *et al*. 1994)

Table 1. *Characteristics of human amnesia that have been produced in monkeys with large bilateral lesions of the medial temporal lobe*

1. Immediate memory is spared
2. Memory for events prior to the onset of amnesia can be affected in a temporally-graded fashion (retrograde amnesia).
3. Memory impairment is not limited to one sensory modality
4. Memory is impaired on a variety of tasks including ones identical to those failed by amnesic patients
5. Memory impairment is exacerbated by increasing the retention delay or the amount of material to be learned
6. Memory impairment is exacerbated by distraction
7. Memory impairment can be enduring
8. Skill-based memory is spared

From Squire & Zola-Morgan (1991).

by the well-studied amnesic patient H.M. (Scoville & Milner 1957). This lesion involved the hippocampal formation, the amygdala, and the surrounding perirhinal and parahippocampal cortices. This lesion, and others in the same region that removed less tissue, reproduced many important features of the memory impairment in patient H.M. and other amnesic patients (table 1; Squire & Zola-Morgan 1991). Note that the first three entries in the table refer to the three key features of medial temporal lobe dysfunction outlined above.

We recently took advantage of accumulated data from more than ten years of testing monkeys to examine the relationship between severity of memory impairment and extent of damage in the medial temporal lobe. We examined behavioural data from 30 monkeys (Zola-Morgan *et al*. 1994). The memory performance in three sets of monkeys with differing extents of damage to the medial temporal lobe memory system was compared to the memory performance in a set of ten normal monkeys. All of the monkeys had completed testing on our standard memory battery (Zola-Morgan *et al*. 1994), and all monkeys had been tested on the tasks in the same order. Findings from a correlational analysis and a factor analysis indicated that four measures derived from the test battery were sensitive to medial temporal lobe damage, presumably because they were good measures of the kind of memory that is dependent on the medial temporal lobe (see below for a discussion of declarative memory). The four measures were: (i) the number of trials to obtain learning criterion on the trial-unique delayed non-matching to sample task the first time it was administered; (ii) the per cent correct score averaged across the 15 s, 60 s and 10 min delay intervals from the delayed non-matching to sample task; (iii) the per cent correct score averaged across all three test days for all four object pairs of the delayed retention of object discriminations task; (iv) the per cent correct score averaged across the 15 s, 60 s and 10 min delay intervals when the delayed non-matching to sample task was administered a second time. The four measures from each of the 30 monkeys were converted to z scores, so that different performance measures could be averaged together.

The main finding was that the severity of memory impairment depended on the locus and extent of damage within the medial temporal lobe memory system (figure 3). Damage limited to the hippocampal region, i.e. the cell fields of the hippocampus proper, the dentate gyrus and the subicular complex (set H), caused significant memory impairment. More severe memory impairment occurred following H damage that included the adjacent entorhinal and parahippocampal cortex (set H^+). The severity of impairment was greater still following H damage that also included all the adjacent cortical regions, i.e. the perirhinal, entorhinal and parahippocampal cortices (set H^{++}).

The finding that monkeys with damage to the hippocampal region together with adjacent cortical regions (sets H^+ and H^{++}) exhibited more severe impairment than monkeys with damage limited to the hippocampal region (set H) emphasizes the importance for memory function of the adjacent cortical regions. Indeed, the damage to these cortical regions probably contributes substantially to the severe memory impairment produced by medial temporal lobe lesions in monkeys and humans (Squire & Zola-Morgan 1991; Zola-Morgan *et al*. 1993). Straightforward evidence for the possible importance of the cortical regions has come

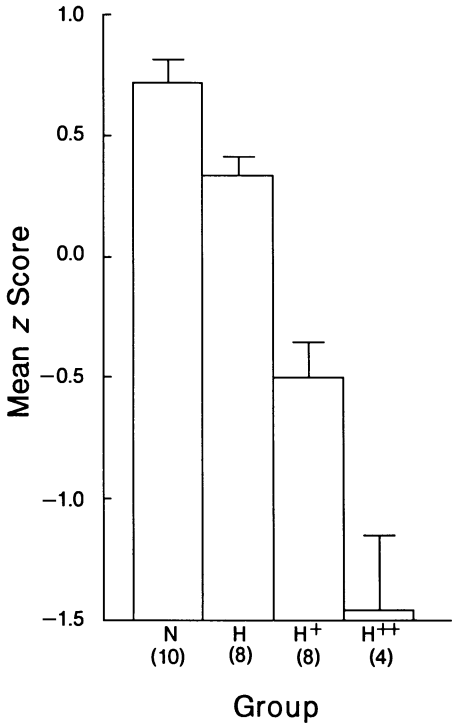

Figure 3. Mean z scores based on the data from four measures of memory for ten normal monkeys (set N), eight monkeys with damage limited to the hippocampal region (H: the dentate gyrus, the cell fields of the hippocampus proper and the subicular complex), eight monkeys with damage that also included the adjacent entorhinal and parahippocampal cortices (set H^+), and four monkeys in which the H^+ lesion was extended forward to include the anterior entorhinal cortex and the perirhinal cortex (set H^{++}). Conversion of the data from the four behavioural measures into z scores permitted tasks that used different performance measures (e.g. trials to criterion, per cent correct) to be compared with each other. As more components of the medial temporal lobe were included in the lesion, the severity of memory impairment increased. Error bars indicate standard errors of the mean. (From Zola-Morgan *et al.* 1994.)

from studies in which direct circumscribed damage has been made to the perirhinal, entorhinal or parahippocampal cortices, either separately or in combination (Moss *et al.* 1981; Zola-Morgan *et al.* 1989; Gaffan & Murray 1992; Meunier *et al.* 1993; Suzuki *et al.* 1993; Leonard *et al.* 1995). For example, monkeys with combined lesions of the perirhinal and parahippocampal cortices (the PRPH lesion) exhibited severely impaired performance on both a visual (Zola-Morgan *et al.* 1989; Suzuki *et al.* 1993) and tactual (Suzuki *et al.* 1993) version of the delayed non-matching to sample task. Moreover, the monkeys with PRPH lesions continued to exhibit impaired performance when retested on the visual version of the delayed non-matching to sample task approximately two years after surgery (Suzuki *et al.* 1993).

More limited lesions of the cortical regions also produce memory impairment. The clearest findings involve lesions limited to the perirhinal cortex. Several studies have now found that monkeys with bilateral lesions limited to the perirhinal cortex exhibit impaired memory (Horel *et al.* 1987; Meunier *et al.* 1993; Ramus *et al.* 1994). Moreover, damage to perirhinal cortex can produce more substantial impairment on the visual delayed non-matching to sample task than damage to any other single component of the medial temporal lobe memory system (Meunier *et al.* 1993; Leonard *et al.* 1995). In addition, the memory impairment following perirhinal lesions is long-lasting (Ramus *et al.* 1994).

It is important to note that the findings from the study described earlier of the relationship between severity of memory impairment and extent of damage in the medial temporal lobe cannot be attributed to a principle like mass action (Lashley 1929). That is, the severity of memory impairment exhibited by the monkeys with H^{++} lesions was not simply due to the fact that they had more damage overall than the monkeys with H^+ lesions. When the H^+ lesion was extended forward to include the amygdala (the H^+A lesion), the memory impairment associated with the H^+ lesion was not increased. Thus, it is not just the extent of damage in the medial temporal lobe that is critical but which specific structures are damaged (Zola-Morgan *et al.* 1994).

Recent information about the anatomical organization of the medial temporal lobe system is consistent with the possibility that structures within the medial temporal lobe make qualitatively different contributions to memory function. In particular, anatomical connections from different parts of neocortex enter the medial temporal lobe memory system at different points. For example, visual association cortex, i.e. area TE, projects more strongly to perirhinal cortex than to parahippocampal cortex, while parietal cortex projects to parahippocampal cortex but not to perirhinal cortex (Suzuki *et al.* 1993; Suzuki & Amaral 1994). Accordingly, one might suppose that damage to perirhinal cortex could produce different effects on memory than damage to parahippocampal cortex.

4. MEMORY, THE HIPPOCAMPAL FORMATION AND THE HIPPOCAMPAL REGION

It is useful to note that the findings of impairment in monkeys in set H supports the view that the hippocampal region itself is critical for memory function. Set H consisted of monkeys from two different studies, i.e. four monkeys with ischaemic damage limited to the hippocampal region (Zola-Morgan *et al.* 1992), and four monkeys with stereotaxic radiofrequency lesions limited to the hippocampal region (Alvarez *et al.* 1995). Both groups exhibited significant and long-lasting memory impairment when evaluated in their respective studies using our standard battery of memory tasks (figure 4). These findings are consistent with two recent preliminary reports of impaired memory in monkeys with lesions of the hippocampal region made by ibotenic acid (Beason-Held *et al.* 1993; Murray & Gaffan 1993).

The finding of impaired memory following bilateral damage limited to the hippocampal region in monkeys is consistent with findings from human amnesia. Since

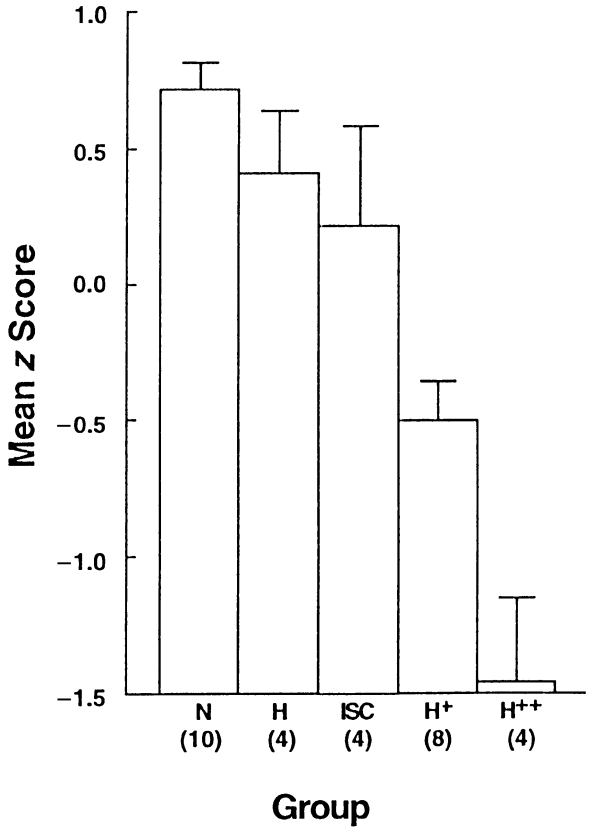

Figure 4. As for figure 3, but with the two groups that comprised set H shown separately. The monkeys in group H sustained neurosurgical lesions limited to the hippocampal region. The monkeys in the ISC group sustained ischaemic lesions limited to the hippocampal region. The H and the ISC groups performed similarly, and both performed better overall than the other operated groups.

the report of amnesic patient R.B. (Zola-Morgan *et al.* 1986), who developed memory impairment following an ischaemic episode that destroyed the entire CA1 field of the hippocampus, four additional case studies of amnesia associated with damage limited to the hippocampal region (or the hippocampal region together with the entorhinal cortex) have become available (Victor & Agamanolis 1990; Rempel-Clower *et al.* 1996).

Three of the patients were involved in our research programme at the Veterans Affairs Medical Center in San Diego, and our laboratory had the opportunity to carry out extensive postmortem analyses of the brains of these three patients (figure 5). All three patients sustained significant memory impairment (table 2). Detailed descriptions of the neuropsychological findings with regard to anterograde and retrograde memory impairment together with detailed descriptions of the neuropathological findings for each patient are described elsewhere (Rempel-Clower *et al.* 1996). Patient G.D., like patient R.B. (Zola-Morgan *et al.* 1986), had damage restricted primarily to the CA1 region of the hippocampus. Patients L.M., W.H., and an amnesic patient reported by Victor & Agamanolis (1990), all had more extensive lesions than R.B and G.D., involving all the cell fields of the hippocampus and the dentate gyrus (L.M. also had some cell loss in the entorhinal cortex; W.H. also had entorhinal damage as well as cell loss in the subicular complex).

The finding of impaired memory following bilateral damage limited to the hippocampal region has also been reported for rats (for reviews, see Jarrard 1993; Jaffard & Meunier 1993). Accordingly, the finding from rats, monkeys and humans are in good correspondence (Squire 1992). Damage limited to the hippocampal region in all three species can produce significant and long-lasting memory impairment. Moreover, the work in monkeys (specifically, the finding that the severity of memory impairment increases as more components of the medial temporal lobe memory system are damaged) is fully consistent with findings from human amnesia (figures 3 and 5). The moderately severe memory impairment in the patients just described who had damage limited to the hippocampal formation can be contrasted with the more severe memory impairment observed in patient H.M. Patient H.M. sustained bilateral resection of the medial temporal lobe, including the hippocampal region and adjacent cortical regions (Corkin 1984; Scoville & Milner 1957; Corkin *et al.* 1994).

Although the neuropathological findings from well-studied individual patients support the idea that the hippocampus itself is an important and essential component of the medial temporal lobe memory system, there is one possible concern. Is it possible that, in addition to the pathological changes detected within the hippocampus itself, some additional (covert) pathology occurred outside the hippocampus that did not progress to cell death and that would therefore not have been detected in a postmortem histopathological examination? This is a concern because if covert damage did occur in structures important for memory, then the undetected neuronal damage and not the hippocampal damage that was detected might account for the memory impairment.

This possibility can be addressed by evaluating the behavioural performance of monkeys who sustained a period of global ischaemia. The ischaemia produced identifiable bilateral damage to the CA1 field of the hippocampus and to the hilar region of the dentate gyrus (Zola-Morgan *et al.* 1992). One then compares the memory performance of the ischaemic animals to the performance of normal monkeys and monkeys with different surgical lesions (specifically, the H, H^+ and H^{++} lesions described in figure 3). In this way, one uses the data from the lesion groups as a behavioural assay for evaluating the ischaemic animals. The result, illustrated in figure 4, is that the ischaemic animals had a mild memory impairment, similar in severity to the impairment of the H group. Their deficit was significantly less severe than the impairment exhibited by the H^+ and H^{++} groups. Accordingly, it seems unlikely that ischaemia produced significant, widespread neuropathology in areas related to memory function beyond what was detected within the CA1 and hilar regions. That is, it appears that the ischaemic monkeys, and by extension patients R.B. and G.D., did not have substantial covert neuropathology

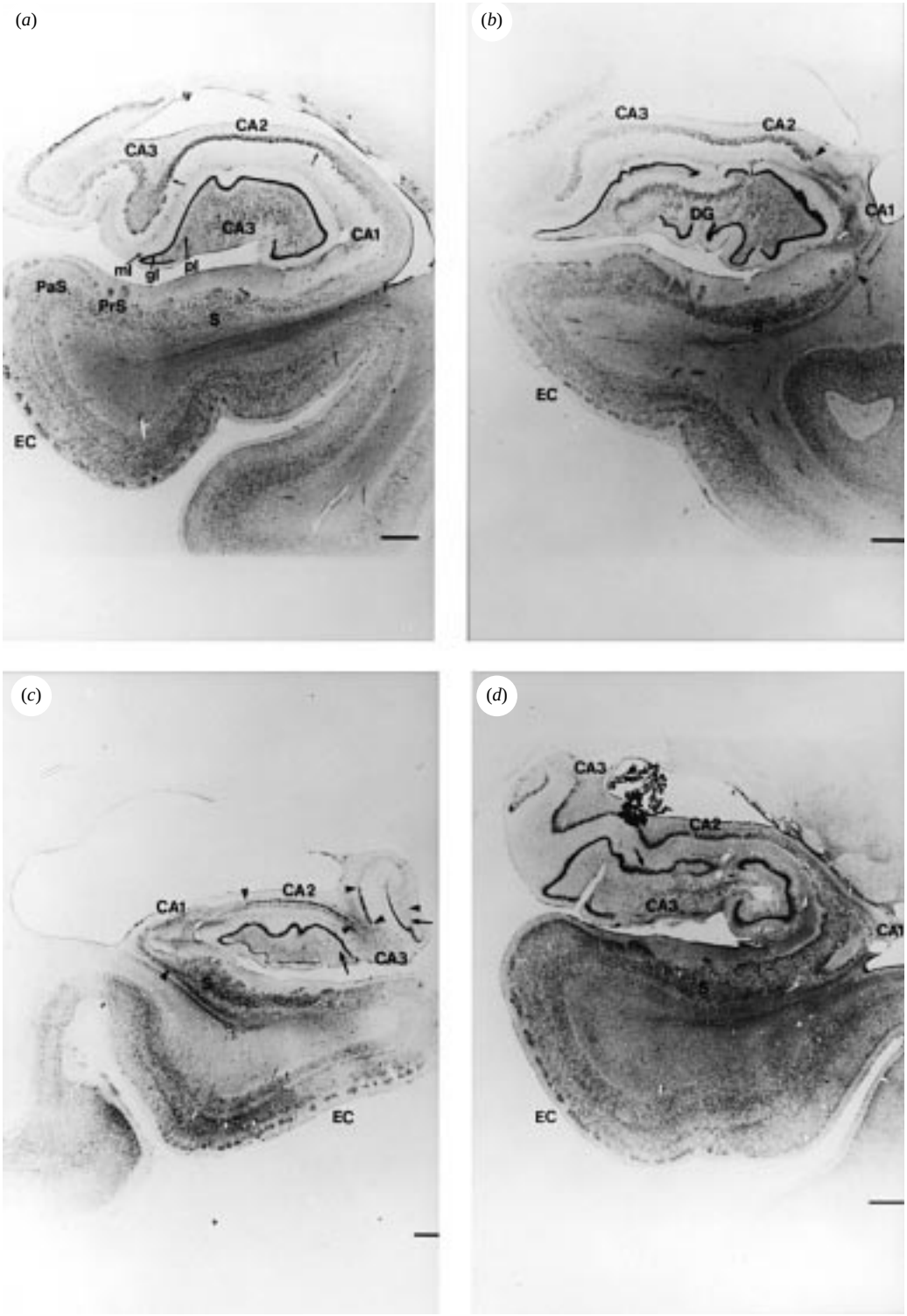

Figure 5. (*a*) Coronal section through a normal right hippocampal region stained with thionin. The hippocampus proper can be divided into three distinct fields, designated CA1, CA2 and CA3 (the CA3/CA2, CA2/CA1 and CA1/subiculum borders are indicated by arrows). The CA1 region begins where the pyramidal cell layer begins to broaden at the border of the CA2 field and extends to the subiculum (S). The CA1 field and the subiculum overlap at their border, which runs oblique to the cell fields. (*b*) Coronal section through the right hippocampal region of patient G.D. The lesion includes most of the cells in the CA1 region (marked by arrowheads). (*c*) Coronal section through patient L.M.'s left hippocampal region. Note the extensive loss of CA3 pyramidal cells and the nearly complete loss of CA1 pyramidal cells (arrowheads indicate the borders of the CA fields). There is also extensive loss of polymorphic cells in the hilus of the dentate gyrus (arrows). (*d*) Coronal section through W.H.'s left hippocampal region. Extensive pyramidal cell loss is evident in cell fields CA1 and CA3. Less substantial cell loss occurred in field CA2. The dentate gyrus appears very abnormal, with dispersion of the granule cells (arrow) and complete loss of polymorphic cells. Patchy cell loss is evident in the subiculum and there was patchy cell loss in the entorhinal cortex as well. Abbreviations: CA1, CA2, CA3, cell fields of the hippocampus; ml, molecular layer; gl, granular layer; pl, polymorphic layer; DG, dentate gyrus; S, subiculum; PrS, presubiculum; PaS, parasubiculum; EC, entorhinal cortex.

Table 2. *Summary of neuropsychological and neuropathological findings from four patients with bilateral damage to the hippocampal formation*

patient	anterograde amnesia	retrograde amnesia	damage to the hippocampal formation
R.B.	moderate	minimal	CA1 field
G.D.	moderate	minimal (?)	CA1 field
L.M.	extensive	extensive	CA1, CA2, CA3 fields dentate gyrus entorhinal cortex
W.H.	severe	extensive	CA1, CA2, CA3 fields dentate gyrus, subiculum entorhinal cortex

The question mark for GD indicates that some uncertainty remains about the interpretation of his performance on remote memory tests.

beyond the hippocampus that contributed to their memory impairment (also see Squire & Zola 1996).

A different conclusion about the possible significance of covert pathological change was reached in an earlier study of two groups of monkeys: three with surgical lesions of the hippocampal formation and three with lesions due to posterior cerebral artery occlusion that appeared to have less neuronal damage than the surgical group but a more severe memory impairment (Bachevalier & Mishkin 1989). However, the monkeys in the two groups did not have equivalent preoperative experience with the test used to assess memory, so it is unclear how to compare their memory performance.

In summary, the available data support the idea that the hippocampus itself is important for memory and that, in addition, the adjacent entorhinal, perirhinal and parahippocampal cortices play an essential role. The organization of the afferent input into the medial temporal lobe system is entirely consistent with the possibility that different parts of the system make qualitatively different contributions to memory (Suzuki & Amaral 1994*a*,*b*).

5. MULTIPLE FORMS OF MEMORY

An important finding of neuropsychological studies of memory is that medial temporal lobe damage affects only one kind of memory. This finding, and others, led to the idea that memory is not a single entity but is composed of several separate systems. The kind of memory impaired in amnesia has been termed declarative or explicit memory. Non-declarative (or implicit) memory is unaffected. (The term 'procedural' has also been used to describe some kinds of non-declarative memory, particularly skill learning.) Declarative memory is typically assessed by tests of recall, recognition or cued recall. It refers to the capacity for conscious recollections about facts and events. It is specialized for rapid, even one-trial learning and for forming conjunctions between arbitrarily different stimuli as in paired-associate learning.

It should be emphasized that the concept of declarative memory does not derive its meaning solely from a determination of what amnesic patients can and cannot learn. That is, the concept of declarative memory is not locked into a circularity around the performance of amnesic patients. Studies with human and non-human animals have begun to develop a property list that describes the characteristics of declarative memory independently of data from amnesia. One important idea is that declarative memory is specialized to detect variance, i.e. to detect what is different or unique about the events of a particular time and place. Non-declarative memory is specialized for detecting invariance, i.e. for extracting from moment to moment what is common to the stimulus environment (Sherry & Schacter 1987; Knowlton *et al*. 1994; Squire 1992). An additional proposal is that declarative memory is flexible and available to multiple response systems, whereas non-declarative memory is inflexible and limited to the response systems that participated in the original learning (Cohen 1984; Cohen & Eichenbaum 1993; Squire 1994; Reber *et al*. 1996).

Whereas declarative memory is a brain-systems construct, tied to the brain structures and connections damaged in amnesia, non-declarative memory refers to a heterogeneous collection of several kinds of memory that in turn depend on distinct brain systems. Thus, classical conditioning of skeletal musculature depends on the cerebellum (Thompson & Krupa 1994), conditioning of emotional responses depends on the amygdala (LeDoux 1987; Davis 1992), and habit learning (win-stay, lose-shift responding) depends on the neostriatum (Salmon & Butters 1995; Packard *et al*. 1989). Perceptual priming probably depends on changes in early-stage cortical areas involved in processing the stimuli that are primed (Squire *et al*. 1992).

Non-declarative memory thus refers to a variety of ways in which experience can lead to altered dispositions, preferences and judgements without affording any conscious memory content. Performance changes as the result of experience and in this sense deserves the term memory, but performance changes without an accompanying sense that memory is being consulted. The organism simply behaves differently than it did previously. In many cases, performance changes gradually, as when one learns gradually about the causal strucure of the world and acquires procedures for interacting with the world (in the case of conditioning, or skill learning, or win–stay, lose–shift habit learning). Sometimes performance can change rapidly (in the case of priming, or fear conditioning, or conditioned taste aversion). In the latter cases, the possibility of rapid change may be built into evolutionarily important systems that are specialized to process or associate particular kinds of information.

In summary, memory is not a unitary faculty, but is composed of multiple, separate systems. The medial temporal lobe memory system, which has been the primary focus of this paper, supports declarative memory. Amnesic patients with damage to this system have an impairment of declarative memory, but they are intact at a wide variety of tasks that assess priming (Schacter *et al*. 1993), skills and habits (Knowlton *et al*. 1994; Reber & Squire 1994), and they are able to acquire knowledge about categories when given a

series of examples, as in artificial grammar learning or prototype learning (Knowlton *et al*. 1992; Knowlton & Squire 1994*a*,*b*, 1996; Squire & Knowlton 1995).

6. CONCLUSION

The cognitive and neuroanatomical work described here should be viewed as a first step in analysing how the brain has organized its memory functions, which can open the door to more detailed neurobiological analysis. With respect to declarative memory, it should soon be possible to study representations directly in neocortex with the technique of single-cell recording, to observe directly the development of neural plasticity, and to determine how the medial temporal lobe interacts with neocortex during learning, consolidation and retrieval. In this regard, the paradigms developed by Miyashita and his colleagues appear to hold particular promise (Sakai & Miyashita 1991; Higuchi & Miyashita 1995). With respect to non-declarative memory, it is now possible to identify particular brain systems that are essential for particular kinds of memory. The next step will be to determine whether these systems are essential for the acquisition, storage or expression of memory, and to identify exactly where the synaptic changes occur that support each kind of memory.

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