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NEUROANATOMY OF MEMORY

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INTRODUCTION

Three important developments have occurred in the area of memory during the past decade. The first was the recognition that there is more than one kind of memory (Cohen 1984; Schacter 1987; Squire 1982; Tulving 1985). Declarative memory (or, explicit memory) affords the capacity for conscious recollections about facts and events. This is the kind of memory that is usually referred to when the terms "memory" or "remembering" are used in ordinary language. Declarative memory can be contrasted with nondeclarative (or implicit) memory, a heterogeneous collection of nonconscious abilities that includes the learning of skills and habits, priming, and some forms of classical conditioning. In these cases, experience cumulates in behavioral change, but without affording access to any memory content. The distinction between declarative and nondeclarative memory is fundamental, because it has turned out that different kinds of memory are supported by different brain systems.

The second important development was the establishment of an animal model of human amnesia in the monkey (Mahut & Moss 1984; Mishkin 1982; Squire & Zola-Morgan 1983). In the 1950s, Scoville & Milner (1957) described the severe amnesia that followed bilateral surgical removal of the medial temporal lobe (patient H.M.). This important case demonstrated that memory is a distinct cerebral function, dissociable from other perceptual and cognitive abilities. Subsequently, surgical lesions of the medial temporal lobe in monkeys, which approximated the damage sustained by patient H.M., were shown to reproduce many features of human memory impairment. In particular, both monkeys and humans were

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impaired on tasks of declarative memory, but fully intact at skill and habit learning and other tasks of nondeclarative memory. This achievement set the stage for identifying which structures and connections within the medial temporal lobe are important for declarative memory.

The third development was the emergence of new technologies for studying anatomy and function in living subjects. Magnetic resonance imaging (MRI) is beginning to provide detailed information about the anatomy of damage in patients with memory impairment (spatial resolution <1.0 mm). Studies using positron emission tomography (PET) provide images of regional blood flow or local glucose metabolism in the brains of normal subjects as they perform specific tasks of learning and memory.

This review summarizes recent findings concerning the anatomy of memory. We focus on the brain regions where damage can cause impairment of declarative memory: the medial temporal lobe, the diencephalon, and the basal forebrain (for other reviews, see Damasio 1984; Markowitsch 1988; Markowitsch & Pritzel 1985; Squire 1987).

THE MEDIAL TEMPORAL LOBE

During the last several years, work with monkeys and new information from patients have identified the structures in the medial temporal lobe that are important for declarative memory. These structures are the hippocampus (including the dentate gyrus and subicular complex) and adjacent cortical areas that are anatomically related to the hippocampus, especially the entorhinal, perirhinal, and parahippocampal cortices (Squire & Zola-Morgan 1991). The work with monkeys has depended on several tasks known to be sensitive to human amnesia (Squire et al 1988), including retention of simple object discriminations and the simultaneous learning of multiple pairs of objects (eight-pair concurrent discrimination learning). The most widely used memory task has been trial-unique delayed nonmatching to sample (Mishkin & Delacour 1975). In this test of recognition memory, the monkey first sees a sample object. Then after a delay, the original object and a novel object are presented together, and the monkey must displace the novel object to obtain a food reward. New pairs of objects are used on each trial. A recent report questioned the usefulness of the delayed nonmatching task for studying memory in monkeys (Ringo 1991). Percent correct data were transformed to a discriminability measure (using the d′ measure from signal detection theory) to reanalyze the data from several laboratories. Performance appeared to be just as impaired at short retention intervals as at long retention intervals. If true, this finding would raise the possibility that the impairment caused by medial temporal lobe lesions in monkeys is in perception, attention, or some other cognitive

function, rather than memory. However, the studies that were surveyed by Ringo (1991) had been designed primarily to assess the severity of impairment, not to compare short and long retention intervals. Studies with delayed nonmatching to sample that have used appropriate designs (Alvarez-Royo et al 1992; Overman et al 1990; Zola-Morgan & Squire 1985b, Figure 5) show clearly that medial temporal lobe lesions impair performance at long delays, but not at short delays. This is true whether the data are analyzed by using percent correct or the d′ measure. This finding is consistent with the facts of human amnesia and supports the validity of the delayed nonmatching task for studying recognition memory in monkeys.

The current era of studies in the monkey began with a large medial temporal lobe removal to approximate the damage in amnesic patient H.M. (Mishkin 1978). This lesion has been termed the H^+A^+ lesion (Squire & Zola-Morgan 1988), where H refers to the hippocampus (including the dentate gyrus and the subicular complex); A, the amygdala; and $^+$, the cortical regions adjacent to the hippocampus and the amygdala that are necessarily damaged when either of these structures is removed by using a direct surgical approach (i.e. the perirhinal, entorhinal, and parahippocampal cortices). The H^+A^+ lesion produces severe memory impairment (Mahut et al 1981; Mishkin 1978; Zola-Morgan & Squire 1985a).

Memory is also impaired following a lesion that involves only the posterior portion of the medial temporal lobe (the H^+ lesion), although the impairment is not as severe as with the H^+A^+ lesion (Mishkin 1978; Zola-Morgan et al 1989a). The H^+ lesion involves the hippocampus proper, the dentate gyrus, the subicular complex, the posterior portion of the entorhinal cortex, and the parahippocampal cortex. Recent studies indicate that the more severe memory impairment associated with H^+A^+ lesions, as compared with H^+ lesions, results from cortical damage, not from amygdala damage. An important clue came from a study in which the amygdala was damaged separately (the A lesion), and the cortex adjacent to the amygdala was spared (Zola-Morgan et al 1989b). Monkeys with A lesions performed as well as normal monkeys on four different memory tasks, including delayed nonmatching to sample. In addition, extending the H^+ lesion forward to include the amygdala (the H^+A lesion) did not exacerbate the memory impairment associated with H^+ lesions on any of these tasks. Similar findings have been reported in several studies in the rodent (Squire 1992a, Table 3).

These findings focused attention on the cortex adjacent to the amygdala, i.e. the perirhinal and entorhinal cortices (see also Murray 1992). Neuroanatomical evidence had shown that the perirhinal and the caudally adjacent parahippocampal cortices provide nearly two thirds of the cortical

input to the entorhinal cortex (Insausti et al 1987a). Because entorhinal cortex is, in turn, the major source of projections to the hippocampus and dentate gyrus, there was reason to suppose that damage to the perirhinal cortex might affect memory. Moreover, in a behavioral study of monkeys with removals of anteroventral temporal cortex, the most affected animal had a lesion involving perirhinal cortex (Horel et al 1987). When the H^+ lesion was extended forward to include the perirhinal cortex (the H^{++} lesion), memory impairment was greater than after H^+ or H^+A lesions (Zola-Morgan et al 1993). The impairment following H^{++} lesions remained stable for more than one year after surgery. Finally, monkeys with lesions of the perirhinal and parahippocampal cortices, which included damage to projections to the entorhinal cortex from other cortical areas (the PRPH lesion), exhibited long-lasting memory impairment in both the visual and tactual modalities (Suzuki et al 1993; Zola-Morgan et al 1989c).

These findings point to the importance for normal memory function of the hippocampus and adjacent cortical regions, including the perirhinal, parahippocampal, the entorhinal cortices. The perirhinal, entorhinal, and parahippocampal cortices are not simply routes by which information from the neocortex can reach the hippocampus. The fact that the memory deficit is more severe when these cortical regions are damaged (e.g. H^{++} lesion versus H^+A or H^+ lesion) indicates that these regions must also be important for memory function. The implication is that information from neocortex need not reach the hippocampus itself for some memory storage to occur.

The Involvement of the Hippocampus in Memory

Although the hippocampal region has been linked to memory function since patient H.M. was first described (Scoville & Milner 1957), the hippocampus itself has only recently been identified as a critical structure. Neuropathological findings from a patient with permanent circumscribed memory impairment following global ischemia (patient R.B.) revealed a bilateral lesion involving the entire CA_1 field of the hippocampus (Zola-Morgan et al 1986; for a related case, see Victor & Agamanolis 1990). This result suggested that damage to the hippocampus itself is sufficient to produce a clinically significant and long-lasting memory impairment. Additional information has come from high-resolution MRI studies of patients with circumscribed memory impairment, which revealed that the hippocampal formation was reduced in size (Press et al 1989; Squire et al 1990). Finally, studies of regional cerebral blood flow using PET have been carried out with normal subjects while they performed tasks of reading, word completion from three-letter stems, and recall from a

recently presented word list using three-letter stems as cues (Squire et al 1992). The largest area of activation in the memory recall task was in the posterior medial temporal lobe in the region of the hippocampus and the parahippocampal gyrus. No activation was detected in the amygdala.

In the monkey, two approaches have been used to assess the role of the hippocampus itself. First, stereotaxic neurosurgery was combined with MRI to improve the accuracy of circumscribed surgical lesions (Alvarez-Royo et al 1991). Monkeys prepared using this technique (the H lesion) were as impaired as monkeys with H^+ lesions on the delayed nonmatching to sample task when delays reached ten minutes (Clower et al 1991). Overall, however, as measured by performance at the shorter delay intervals of the delayed nonmatching to sample task, as well as by performance on two other tasks (retention of object discriminations and eight-pair concurrent discrimination learning), the monkeys with H lesions were less impaired than monkeys with H^+ lesions. This finding is consistent with the idea that the cortex adjacent to the hippocampus makes a contribution to memory, in addition to the contribution made by the hippocampus itself.

The second approach was to establish an animal model of global ischemia in the monkey (Zola-Morgan et al 1992). This procedure consistently produced a highly selective pattern of damage: bilateral loss of CA_1 and CA_2 pyramidal cells of the hippocampus, together with substantial bilateral loss of somatostatin-staining cells in the hilar region of the dentate gyrus (the ISC lesion). Cell loss was greater in the caudal portion of the hippocampus than in the rostral portion. Except for patchy loss of cerebellar Purkinje cells, significant damage was not detected outside the hippocampus. On the delayed nonmatching to sample task, monkeys with ISC lesions were about as impaired as monkeys with H^+ lesions. However, like the H group, the ISC group performed significantly better than the H^+ monkeys on other tasks. Thus, the overall level of memory impairment following ISC lesions was similar to the level associated with H lesions and less than the level associated with H^+ lesions.

These findings from monkeys make several points. They support the long-standing view that the hippocampus is important for memory. Indeed, even incomplete damage to the hippocampus is sufficient to impair memory. Although the original findings from patient R.B. made this same point, it had been difficult to exclude entirely the possibility that some additional neural damage might have occurred in R.B. that was not detected in histological examination. However, because ISC monkeys obtained better memory scores overall than H^+ monkeys, it seems reasonable to think that the ISC animals (and, by extension, patient R.B.) did not have widespread neuropathological damage affecting memory beyond what was detected histologically. Finally, the finding that even partial damage to the

hippocampus produced a significant and enduring memory impairment in monkeys contrasts sharply with the absence of impairment following virtually complete lesions of the amygdala. Experiments with rats and monkeys suggest that the amygdala is important for other kinds of memory, including the development of conditioned fear and other forms of affective memory in which the valence of a neutral stimulus is strongly altered by experience (Davis 1986; Gallagher et al 1990; Kesner 1992; LeDoux 1987; McGaugh 1989).

THE DIENCEPHALON

Damage to the midline diencephalic region was first linked to amnesia in humans nearly a century ago (Gudden 1896). Although it is now accepted that medial diencephalic damage is sufficient to cause severe amnesia, the specific structures and connections that must be damaged to cause memory impairment have not yet been identified. The two structures most frequently implicated have been the mammillary nuclei (MN) and the mediodorsal thalamic nucleus (MD) (Markowitsch 1988; Victor et al 1989). The idea that damage to the MN impairs memory originated in the finding that the MN are consistently damaged in alcoholic Korsakoff's syndrome. However, the MN are not the only site of damage. In two thorough studies of postmortem material, in which significant memory impairment was well documented during life (Mair et al 1979; Mayes et al 1988), four patients exhibited marked neuronal loss in the medial MN together with a band of gliosis in the medial thalamus located along the wall of the third ventricle adjacent to the medial magnocellular portion of MD. Neuropathological findings from Korsakoff's syndrome have led to the view that damage to MD itself is critical, either alone (Victor et al 1989) or in combination with MN (Butters 1984).

During the past several years, new data have become available concerning memory loss and medial thalamic damage. One study used computed tomography (CT) to identify the common damage in seven patients with memory impairment following medial thalamic infarctions (von Cramon et al 1985). This analysis identified as the important sites the mammillothalamic tract and the ventral portion of the internal medullary lamina, which forms the ventrolateral boundary of MD. A second radiographic study of two amnesic patients with bilateral thalamic infarctions suggested that the lesions responsible for memory impairment damaged the mammillothalamic tract and the inferior thalamic peduncle at the level of the anterior nucleus (Graff-Radford et al 1990; for an additional single case, see Malamut et al 1992). Both studies concluded that disconnection of both the anterior nucleus and MD from other structures is required to

produce severe memory impairment. At the same time, it remains unclear how much memory impairment would occur following damage limited to either nucleus alone or to other medial thalamic nuclei, such as the intralaminar nuclei. Thus, MD has been identified as damaged in several single-case studies of thalamic infarction (cf. Guberman & Stuss 1981; Winocur et al 1984), but additional damage was also present, as would be expected given that the thalamic arteries supply more than one thalamic nucleus.

The idea that amnesia results when several diencephalic nuclei are damaged conjointly is consistent with the radiographic findings from patient N.A. (Squire et al 1989a). This individual developed amnesia, especially for verbal material, following a penetrating stab wound to the brain, and CT scans had initially indicated a lesion in the region of the left mediodorsal nucleus. Subsequently, MRI studies revealed more extensive damage in the left thalamus. In addition, the injury likely damaged the mammillothalamic tract, and the MN appeared to be damaged bilaterally. The thalamic damage involved the internal medullary lamina, the ventral portion of MD, the intralaminar nuclei, and the ventral lateral and ventral anterior nuclei. Mori et al (1986) described a patient with a very similar left thalamic lesion caused by infarction.

In the monkey, circumscribed bilateral MN lesions produced a measurable memory impairment (Aggleton & Mishkin 1985; Zola-Morgan et al 1989a), but one that was mild compared with the impairment associated with lesions of the hippocampal formation or related cortex. More severe memory impairment also occurred following lesions that included the anterior thalamic nucleus, MD, and midline nuclei (Aggleton & Mishkin 1983a). This impairment was greater than when the lesion involved either the anterior or posterior half of the larger lesion (Aggleton & Mishkin 1983b).

Additional information comes from the recent development of an animal model of alcoholic Korsakoff's syndrome in the rat (Mair et al 1988). Rats that were recovered from approximately two weeks of pyrithiamine-induced thiamine deficiency exhibited diencephalic lesions similar to the lesions that occur in Korsakoff's syndrome: bilaterally symmetric lesions in the MN and in the medial thalamus in the area of the internal medullary lamina (Mair et al 1988). Additional studies of this animal model of Korsakoff's syndrome used radio frequency lesions to damage separately the internal medullary lamina, the MN, or the midline nuclei. Rats with radio frequency lesions of the internal medullary lamina were impaired on a spatial alternation task to the same extent as rats with thiamine deficiency. Rats with MN lesions or midline nuclei damage performed normally (Mair & Lacourse 1992; Mair et al 1992).

The recent studies with experimental animals are consistent with the findings from human amnesia in showing the importance of damage within the medial thalamus for producing memory loss, especially damage in the internal medullary lamina. Lesions in the internal medullary lamina would be expected to disconnect or damage several thalamic nuclei, including intralaminar nuclei and MD. Evidence from rats and monkeys suggests that the MD may be an important structure (Aggleton & Mishkin 1983b; Mair et al 1991; Zola-Morgan & Squire 1985b). The separate contributions of MD, the anterior nucleus, and the intralaminar nuclei remain to be explored systematically with well-circumscribed lesions.

THE BASAL FOREBRAIN

Some patients with ruptured aneurysms of the anterior communicating artery exhibit persisting memory impairment, together with personality change. The critical damage reportedly involves the basal forebrain (Alexander & Freedman 1984; Damasio et al 1985a,b; Phillips et al 1987). The basal forebrain is the primary source of cholinergic innervation of cortex. It includes the medial septal nucleus and the diagonal band of Broca, which project to the hippocampal formation mainly through the fornix, and the nucleus basalis, which projects widely to frontal, parietal, and temporal cortices (Mesulam et al 1983). The idea that basal forebrain damage, and damage to cholinergic neurons in particular, can impair memory gained additional support from reports that patients with Alzheimer's disease, who exhibit memory impairment as a prominent early symptom, show decreased activity of choline acetyltransferase (ChAT) in the cortex and hippocampus and markedly reduced cell numbers in the basal forebrain (Coyle et al 1983).

Recent work has raised questions about the relationship between cholinergic dysfunction and memory impairment. For example, some behavioral effects of damage to nucleus basalis in rats are not related to cholinergic dysfunction. Thus, lesions of the nucleus basalis produced by quisqualic acid injections produced less severe behavioral impairment and sometimes no impairment, compared with lesions produced by ibotenic acid, despite the fact that quisqualic acid results in larger decreases in cortical levels of ChAT than did ibotenic acid (Dunnett et al 1987). In macaque monkeys, combined ibotenate lesions of the nucleus basalis, the medial septal nucleus, and the diagonal band, but not separate lesions of these areas, produced significant memory impairment (Aigner et al 1991). However, the performance of the impaired group recovered fully by about six months after surgery. These findings suggest that extensive damage to the basal forebrain, not just nucleus basalis lesions, is necessary for even

transient memory impairment to be observed. Squirrel monkeys with basal forebrain lesions exhibited long-lasting behavioral deficits (Irle & Markowitsch 1987). However, the work in rodents just described raises the possibility that cholinergic dysfunction is not responsible for these impairments.

Lesions of the basal forebrain can impair memory, but a range of other behavioral deficits has also been described (for reviews, see Dekker et al 1991; Fibiger 1991; Kesner 1988; Olton & Wenk 1987). In rats, for example, deficits in attention have been reported to be the principal cognitive effect of nucleus basalis lesions (Robbins et al 1989). Although early work suggested that similar cognitive effects occurred following damage to any of the components of the basal forebrain (Hepler et al 1985), it is now clear that medial septal lesions and nucleus basalis lesions produce strikingly different effects. In an important study, Olton et al (1988) compared the performance of rats with ibotenic acid lesions of the medial septal area or nucleus basalis with the performance of rats with surgical lesions of the fornix or frontal cortex. Rats with damage to the medial septum or the fornix exhibited similar deficits on a memory task that required accurate timing of the duration of a tone. Neither group was impaired on a second, divided-attention task in which animals had to time the duration of a tone through a period when an interfering tone was also present. In contrast, damage to either the nucleus basalis or frontal cortex impaired performance on the divided-attention task, but had no effect on the memory task. These results indicate that the components of the basal forebrain are involved in different cognitive functions. Only medial septal damage produced a clear memory impairment, possibly by direct disruptive effects on the hippocampal formation (Buzsaki & Gage 1989; Mizumori et al 1989). Indeed, the strong anatomical connections between the basal forebrain and the medial temporal lobe suggest that the effects of basal forebrain damage in monkeys and humans, including patients with Alzheimer's disease, result from disruption of information processing within the hippocampus and other medial temporal lobe structures (Damasio et al 1985b; Squire 1987). Interestingly, in the case of Alzheimer's disease, neuropathological studies have found prominent pathology in the entorhinal cortex and the subiculum of the hippocampal formation (Hyman et al 1984), as well as in the perforant pathway, the principal source of cortical input to the hippocampus (Hyman et al 1986). These abnormalities effectively disconnect the hippocampus from widespread areas of neocortex and could be sufficient in themselves to account for the memory impairment associated with this disease.

In summary, work with rats, monkeys, and humans indicates that unitary formulations of basal forebrain function are not appropriate. The

nucleus basalis appears to be more important in attentional functions than in memory functions. The medial septal area, as well as the diagonal band, can influence memory functions, perhaps by virtue of the strong anatomical connections, including cholinergic connections, to the hippocampal formation.

FROM BRAIN STRUCTURES TO BRAIN SYSTEMS

The identification of critical brain structures in the medial temporal lobe and the midline diencephalon provides only a first step to understanding the neuroanatomy of memory. The connections among these regions, and between these regions and putative sites of long-term memory storage in neocortex, must also be identified. For perceptual processing in neocortex to persist as long-term memory, information from neocortex must reach medial temporal lobe structures (Mishkin 1982; Squire & Zola-Morgan 1991). Projections from neocortex arrive initially in the parahippocampal cortex (area TF/TH) and perirhinal cortex. Further processing then occurs at the next stage, the entorhinal cortex, and in the several stages of the hippocampal formation (dentate gyrus, CA_3, and CA_1). This connectivity provides the hippocampus and related structures with access to ongoing cortical activity at widespread sites throughout the neocortex. Information can then be returned to neocortex via the subiculum and entorhinal cortex.

Information processed in the medial temporal lobe is also routed to critical areas for memory in the diencephalon. Thus, the mammillary nuclei receive a major input from the subiculum of the hippocampal formation through the fornix, and the mammillary nuclei originate a major projection to the anterior nucleus through the mammillothalamic tract. The hippocampal formation also sends direct projections to the anterior nucleus. The mediodorsal nucleus of the thalamus, in addition to its well-described projections from the amygdala, receives a fairly prominent projection from perirhinal cortex. Somewhat weaker projections to the mediodorsal nucleus also originate in the subiculum and in area TF of parahippocampal cortex (Amaral 1987). In addition, the basal forebrain has widespread projections to medial temporal lobe and can potentially modulate its function (Insausti et al 1987b).

One important target of diencephalic and medial temporal lobe structures is the frontal lobe, especially ventromedial frontal cortex. The anterior nucleus and the mediodorsal nucleus project to both ventromedial and dorsolateral frontal cortex. In addition, both the entorhinal cortex and the subiculum send significant projections to ventromedial cortex, especially its medial orbital surface (Insausti et al 1987a; Carmichael & Price 1991). One possibility is that the ventromedial frontal cortex, together

with the medial temporal lobe and medial thalamus, constitutes a component of the neural system essential for the formation of long-term memory (Bachevalier & Mishkin 1986). Another possibility is that the medial temporal lobe and medial thalamus work conjointly to establish long-term memory and that the projections to the frontal lobe provide a route by which recollections can be translated into action. The frontal lobes are important in guiding behavior at the time of both information encoding and information retrieval, especially when information must be organized and retained for temporary use in short-term (or working) memory (Fuster 1989; Goldman-Rakic 1987).

Recently, Irle & Markowitsch (1990) reported that squirrel monkeys with conjoint bilateral lesions of five different structures (the hippocampus, the amygdala, the anterior thalamic region, the mediodorsal thalamic nucleus, and the septum) performed better on the delayed nonmatching to sample task than monkeys with lesions limited to one or two of these structures (the hippocampus, the hippocampus plus amygdala, or the anterior and mediodorsal thalamic regions). If true, this finding would be unique and important, because of the implication that massive damage to the declarative memory system is somehow less disruptive than damage to specific structures within the system. However, the data presented are not compelling. First, the study involved only two monkeys in each of the single and double-lesion groups. Second, monkeys in the multiple (fivefold) lesion group were significantly impaired on the delayed nonmatching task. Third, a close reading of the paper indicates that, contrary to the proposal in the paper (p. 86), the comparison between the monkeys in the fivefold lesion group ($n = 4$) and the three groups of monkeys with single or double lesions ($n = 6$; Table 4, p. 89) did not approach statistical significance.

BRAIN SYSTEMS AND MEMORY

Medial temporal lobe structures and the medial thalamus are components of a memory system that is essential for the formation of long-term declarative memory. Memory depends on this system for only a limited period of time after learning. This conclusion rests partly on the finding that remote memory is often fully intact in amnesic patients (Squire et al 1989b) and on the finding of temporally graded retrograde amnesia in prospective studies of monkeys (Zola-Morgan & Squire 1990) and rats (Kim & Fanselow 1992; Winocur 1990) with lesions. Thus, medial temporal lobe and medial thalamic structures are not the repository for permanent memory. This system is required at the time of learning and during a lengthy period thereafter, while a slow-developing, more permanent memory is established elsewhere, presumably in neocortex (Squire 1992a).

Short-term memory is independent of these brain structures and is fully intact in amnesia, whether it is assessed in the conventional manner by verbal tests of digit span or by tests of nonverbal short-term memory, including spatial short-term memory (Cave & Squire 1992). Skills and habits, priming, and some forms of conditioning are also independent of the medial temporal lobe and the medial thalamus. Whereas declarative memory depends on an interaction between the neocortex and these structures, many skills and habits depend on the neocortex and the neostriatum (Packard et al 1989; Wang et al 1990). Perceptual priming likely depends on posterior cortical areas, such as extrastriate cortex in the case of visual priming (Squire et al 1992). Classical conditioning of skeletal musculature depends on essential pathways in the cerebellum (Thompson 1986). Declarative and nondeclarative memory can seem rather similar to each other. For example, an animal can select an object on the delayed nonmatching to sample test or can select the same object when it is presented in a task of habit learning [e.g. the 24-hour concurrent discrimination task (Malamut et al 1984)]. However, these are different kinds of learning, the resulting knowledge has different characteristics, and different brain systems are involved (Squire 1992b).

The question naturally arises as to whether damage to the medial temporal lobe or to the medial thalamus produces similar or different kinds of memory impairment. Although the two regions probably make distinct contributions to normal memory, it is also possible that the two regions belong to a larger functional system and that their separate contributions would be difficult to detect with behavioral measures. Although possible differences have been proposed between diencephalic and medial temporal lobe amnesia (Parkin 1984), there is currently little evidence to support such a difference. For example, whereas one early suggestion concerned differences in the rate of forgetting in long-term memory, McKee & Squire (1992) recently demonstrated that amnesic patients with confirmed medial temporal lobe lesions or diencephalic lesions have virtually identical forgetting rates for information within long-term memory.

Another suggestion, influenced by work with rodents, has been that the hippocampus is involved especially in computing and storing information about allocentric space (O'Keefe & Nadel 1978). In our view, however, spatial memory is better understood as a good example of the broader category of (declarative) memory abilities, which includes memory for spatial locations, but also includes memory for word lists, faces, odors, and tactual impressions (Squire & Cave 1991). For amnesic patients with confirmed damage to the hippocampal formation or diencephalon, spatial memory impairment was proportional to the severity of impairment on

other measures of declarative memory (Cave & Squire 1991); for additional discussion, see *Hippocampus* 1991, 1: 221–92.

One sense in which one should expect to find functional specialization within the medial temporal lobe system follows from the fact that anatomical connections from different parts of neocortex enter the system at different points. For example, parietal cortex projects to parahippocampal cortex, but not to perirhinal cortex, and inferotemporal cortex projects more strongly to perirhinal cortex than to parahippocampal cortex (Suzuki et al 1991). These anatomical facts provide a way to understand why anterior medial temporal lobe lesions, which damage perirhinal cortex, and posterior medial temporal lobe lesions, which damage parahippocampal cortex, might differentially affect spatial memory (Parkinson et al 1988).

CONCLUSIONS

Cumulative and systematic research with monkeys and rats and related research with humans has identified structures and connections important for declarative memory in the medial temporal lobe and the midline diencephalon. The important structures within the medial temporal lobe are the hippocampus, and adjacent, anatomically related entorhinal, perirhinal, and parahippocampal cortices. The amygdala is not a part of this system. The important structures in the diencephalon appear to be the anterior thalamic nucleus, the mediodorsal nucleus, and connections to and from the medial thalamus within the internal medullary lamina. With respect to the basal forebrain, the nucleus basalis appears to be involved more in attentional functions than in memory functions. Other components of the basal forebrain can influence memory functions by virtue of their anatomical projections to the hippocampal formation.

The declarative memory system is fast, has limited capacity, and has a crucial function beginning at the time of learning in establishing long-term memories. This function involves binding together the multiple areas in neocortex that together subserve perception and short-term memory of whole events. Gradually, the neocortex comes to support long-term memory storage independently of the medial temporal lobe and diencephalon.

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CONTENTS