The relationships between the anterograde amnesic syndromes associated with diencephalic and temporal lobe pathology is examined in the light of recent findings. It is proposed that a common feature of anterograde amnesia is damage to part of an "extended hippocampal system" comprising the hippocampus, the fornix, the mamillary bodies, and the anterior thalamic nuclei. Damage to this system results in deficits in the recall of episodic information, the core symptom of anterograde amnesia. In contrast, lesions in this system need not disrupt tests of recognition memory when they primarily tax familiarity judgements. It is assumed that familiarity judgements depend on other regions (e.g. the rhinal cortex in the case of temporal lobe amnesia) and that the extended hippocampal system is principally involved in those aspects of recognition that are retrieval-based rather than familiarity-based. These proposals arise from new evidence on the performance of delayed nonmatching-to-sample by animals, from a meta-analysis of the performance of amnesic subjects on a test of recognition memory, and from new research into the pattern of connections between the medial temporal lobe and the medial diencephalon in primates.

INTRODUCTION

The review by Mayes and Downes (this issue) identified several important gaps in our understanding of anterograde amnesia and pointed to future areas of profitable research. One gap concerns the anatomical basis of anterograde amnesia. Although dysfunctions in different brain regions can result in anterograde amnesia, the contribution of individual structures and their inter-relationships still remains a matter of uncertainty and debate. The failure to
resolve this central issue is partly due to lack of amnesic subjects with specific patterns of pathology, but it may also be due to the complexity of the relationships between those regions contributing to amnesia.

Pathology in various brain regions, most typically in the medial diencephalon of the medial temporal lobe, can result in anterograde amnesia. This finding has been viewed in two quite different ways. One interpretation is that the amnesias associated with these different regions result from damage to the same functional system. This view is supported by the many direct anatomical connections between the regions in question, and the similarities between the respective mnemonic deficits. An alternative view is that a number of largely independent dysfunctions can lead to the memory losses characteristic of amnesia. This view emphasises those dissociations that have been reported between different amnesic states (Parkin & Leng, 1990; Parkin & Leng, 1993). It also predicts that connections, such as those through the fornix, which relay information between the medial temporal lobe and the diencephalon need not be crucial for normal memory (Squire & Zola-Morgan, 1991). Clearly these two views must be resolved before the anatomy of anterograde amnesia can be fully understood. The resolution of this issue will also benefit a longstanding practical problem associated with studies of amnesia, namely how best to allocate amnesic subjects into meaningful groups.

The most obvious grouping of amnesic subjects is between those who have principally suffered temporal lobe damage and those who have principally suffered diencephalic damage. This division can readily be applied to some of the more common causes of amnesia (e.g. Korsakoff’s disease, herpes encephalitis, vascular accidents, tumours). Furthermore, reports that damage to the fornix, which links the hippocampal formation with the diencephalon, does not result in amnesia indicates that this grouping represents a qualitative division (Bengoechea et al., 1954; Woolsey & Nelson, 1975). Other support has come from evidence that, unlike diencephalic amnesics, temporal lobe amnesics display faster than normal rates of forgetting (Huppert & Piercy, 1979; Squire, 1981). This difference has, however, proved difficult to sustain (Freed, Corkin, & Cohen, 1987). Likewise, the view that fornix damage does not cause amnesia has been strongly challenged (Gaffan & Gaffan, 1991), and there is now growing evidence that fornix transection can lead to pronounced impairments in episodic memory (Gaffan, Gaffan, & Hodges, 1991). Perhaps the strongest evidence for a qualitative difference between diencephalic and temporal lobe amnesia would come from a reliable double association, but as yet none has been forthcoming.

The likely limitation of any simple distinction based on diencephalic pathology versus temporal lobe pathology is indicated by the fact that these two brain regions have extensive anatomical interconnections. Further evidence has come from PET studies showing that quite different pathologies can result in abnormal levels of activity in common diencephalic and temporal regions (Fazio
et al., 1992). Such findings highlight the difficulty in separating subjects based on a simple division between temporal lobe and diencephalic pathology.

In this review we wish to propose a different neuropathological grouping of anterograde amnesias. This grouping starts with the assumption that a common feature of all diencephalic and temporal lobe amnesias is the involvement of at least part of the “extended hippocampal system” (i.e. the hippocampus, fornix, mammillary bodies, anterior thalamus, and, possibly, the cingulum bundle), and that damage to different parts of this system produces very similar impairments (Delay & Brion, 1969). It should be added that the term “hippocampus” refers to the hippocampal fields CA1–4, the dentate gyrus, and the subicular complex. The rhinal cortices (perirhinal and entorhinal) are treated separately. Amnesics can then be initially divided into (a), those with memory dysfunctions due almost solely to selective lesions in parts of the extended hippocampal system, and (b), those with additional pathology in certain subcortical and cortical sites that can extend the nature of the memory loss so that it involves other aspects of memory. Within this latter group there are likely to be further divisions based on the locus of the pathology, in particular, the extent of frontal lobe and temporal lobe involvement. The frontal lobe dysfunctions are assumed to result from direct cortical damage, or from pathology in the thalamic nucleus medialis dorsalis, or from a combination of both (e.g. Korsakoff’s disease). The temporal lobe dysfunctions are assumed to arise from pathology that involves regions such as the rhinal cortex, the parahippocampal gyrus, the temporal pole, and amygdala. The starting point of this proposal, that all amnesias involve dysfunctions in the extended hippocampal system, helps to explain why it has proved so difficult to demonstrate a reliable double dissociation between different amnesic conditions.

Three strands of evidence point to these proposed distinctions: (1) The effects of selective limbic lesions in animals on the acquisition and performance of delayed nonmatching-to-sample tasks; (2) A comparison between the ability of amnesic subjects to perform tests of recall and tests of recognition; (3) The results of tracing studies that have mapped the pattern of anatomical connections between the temporal lobe and the medial diencephalon.

1. ANIMAL STUDIES

The lack of patients with confirmed, selective pathology has led to numerous studies examining the effects of selective lesions in animals. The favoured approach has been to compare the performance of animals on tests of delayed nonmatching-to-sample (DNMS). In these tests, which tax recognition memory, the animal is first shown a distinctive stimulus (the sample). After the delay of between a few seconds to a few minutes, during which the animal is left in the apparatus, the animal is required to select between two stimuli, the now familiar sample and a novel alternative. Selection of the novel item (i.e. nonmatching)
leads to a reward. Typically the stimuli are distinctive, three-dimensional "junk" objects and are "trial-unique" (that is, a given object does not reappear within a series of sessions). The choice of this task arises from the fact that a deficit in recognition memory is regarded as a prominent, core feature of amnesia (Haist, Shimamura, & Squire, 1992; Parkin & Leng, 1993; Squire & Shimamura, 1986). Furthermore, when amnesic patients have been given memory tests closely modelled on the DNMS design they perform poorly (Aggleton, Nicol, Huston, & Fairbairn, 1988; Squire, Zola-Morgan, & Chen, 1988).

Before considering the results of individual experiments it must be pointed out that the surgical method used when making the lesion may be of enormous importance. The favoured technique for research using monkeys has often been aspiration, even for subcortical sites. This is because the target region can be confirmed at the time of surgery, an extremely important factor when studying small-sized groups. On the other hand, stereotaxy has the advantage that it helps to minimise damage to regions outside the target area and it facilitates the use of neurotoxins, so aiding the selectivity of lesions. The importance of distinguishing between these different surgical techniques is highlighted by the fact that the direct surgical approach most often used to aspirate the amygdala or the hippocampus in monkeys results in additional temporal damage (Gaffan & Lim, 1991). This additional damage includes the rhinal cortex, an area of particular importance. Indeed, lesions just restricted to the rhinal cortices can themselves produce very severe DNMS deficits (Meunier, Bachevalier, Mishkin, & Murray, 1993; Murray, 1992; Squire & Zola-Morgan, 1991).

DNMS tasks using trial-unique or session-unique stimuli have been devised for rats as well as monkeys, and the effects of various selective lesions appear to be broadly consistent across the different species. Damage to the perirhinal cortex in monkeys severely impairs DNMS performance (Fig. 1; Meunier et al., 1993; Murray, 1992; Squire & Zola-Morgan, 1991), and there is similar, preliminary evidence from studies of lesions centred in the perirhinal area of rats (Mumby & Pinel, 1994; Otto & Eichenbaum, 1992). Entorhinal damage may also contribute to the rhinal DNMS deficit (Meunier et al., 1993). In contrast to these effects, lesions of the hippocampus have much milder effects (Fig. 1; Mishkin, 1978; Murray, 1992), but it must be remembered that these surgeries also involve caudal parts of the rhinal cortex. Indeed, in those studies where hippocampal lesions result in minimal rhinal damage standard DNMS performance may be largely unaffected (Aggleton, Hunt, & Rawlins, 1986b; Alvarez, Zola-Morgan, & Squire, 1995; O’Boyle, Murray, & Mishkin, 1993; but see Beason-Held, Rosene, & Moss, 1993). As a consequence it appears that selective hippocampal damage is not sufficient to disrupt DNMS performance when it is tested in the standard manner. Consistent with this is the finding that fornix lesions often have little, if any, effect on DNMS performance in monkeys (Gaffan, Gaffan, & Harrison, 1984; Bachevalier, Saunders, & Mishkin, 1985a; Zola-Morgan, Squire,
and can spare DNMS performance in rats (Aggleton, Hunt, & Shaw, 1990; Rothblat & Kromer, 1991; Shaw & Aggleton, 1993). Fornix damage can, however, exacerbate the effects of other lesions that disrupt DNMS performance (Bachevalier, Parkinson, & Mishkin, 1985b), and so this tract does
appear to convey information that can aid performance of the task. Although this may reflect the involvement of hippocampal connections, it might alternatively reflect the involvement of entorhinal–thalamic projections (Meunier et al., 1993), some of which are carried in the fornix (see Section 3).

It now appears that the hippocampal involvement in DNMS performance is very minor compared to that of the adjacent rhinal cortices, a view borne out by single unit recording studies in monkeys and rats (Brown, Wilson, & Riches, 1987; Zhu, Brown, & Aggleton, 1995a) and recent c-fos experiments (Zhu, Brown, McCabe, & Aggleton, 1995b). Although confirmation of this conclusion will have to await the result of more studies into the effects of cytotoxic lesions in the primate perirhinal cortex as well as the hippocampus, it will be seen that this conclusion is largely consistent with what is presently known about the effects of selective damage to the diencephalic targets of the hippocampus.

There has been less research into the effects of diencephalic lesions on DNMS performance in animals. The few studies show that mammillary body lesions do not disrupt DNMS tasks performed by monkeys or rats (Aggleton et al., 1990; Aggleton & Mishkin, 1985; Zola-Morgan et al., 1989a). In contrast, thalamic lesions in the region of nucleus medialis dorsalis (MD) impair both the acquisition and performance of DNMS tasks (Aggleton & Mishkin, 1983b; Hunt & Aggleton, 1991; Zola-Morgan & Squire, 1985b). More anterior thalamic lesions made by aspiration can also disrupt DNMS performance (Aggleton & Mishkin, 1983b), and exacerbate the effects of lesions in the region of medialis dorsalis (Aggleton & Mishkin, 1983a,b). The approach used to reach the anterior thalamus in these studies did, however, result in much fibre damage, and there is a need to re-examine these findings using more discrete lesion techniques. This view is reinforced by recent research showing that selective neurotoxic lesions of the anterior thalamus in rats do not disrupt the spontaneous recognition of novel objects (Aggleton, Neave, Nagle, & Hunt, 1995a).

Taken together, DNMS studies indicate that the hippocampus and its direct diencephalic targets (the mammillary bodies and the anterior thalamus) have only a minor role in recognition memory when it is assessed in this manner. If the DNMS task is truly a benchmark test for anterograde amnesia (Zola-Morgan & Squire, 1985a) then one would have to conclude that pathology in these regions is relatively unimportant for the appearance of anterograde amnesia. In fact it is known that the same set of structures (i.e. the “extended hippocampal system”) is vital for other aspects of memory, and this finding might help resolve the anomaly of how hippocampal pathology can seem so central to amnesia but barely affect DNMS performance.

It has long been known that damage to the rat hippocampus can produce striking impairments on a variety of spatial memory tasks (O’Keefe & Nadel, 1978), including delayed forced alternation in a T-maze (Aggleton et al., 1986b). The sensitivity of this task to hippocampal dysfunction allows it to be used as a behavioural assay with which to test the contribution of diencephalic regions to
mnemonic tasks dependent on the hippocampus. Such studies show that normal performance depends on the mammillary bodies as well as the hippocampus, fornix, and anterior thalamic nuclei (Aggleton et al., 1995a; Aggleton & Sahgal, 1993), the magnitude of the lesion deficit being greatest after hippocampectomy and least after mammillary body damage. Similar results are found for an automated test of spatial working memory, delayed nonmatching-to-position in an operant chamber (Aggleton et al., 1992; Aggleton & Sahgal, 1993). These findings point to an extended hippocampal system which may not be necessary for recognition memory but which is critical for normal spatial memory in the rat. A comparable series of spatial experiments has yet to be conducted with monkeys, although it has been shown that fornix lesions impair T-maze forced alternation in rhesus monkeys (Murray et al., 1989), and that hippocampal, fornix, and mammillary body lesions can all markedly disrupt place discrimination reversals (Jones & Mishkin, 1972; Mahut, 1972; Holmes, Butters, Jacobson, & Stein, 1983).

These findings suggest that certain diencephalic targets of the hippocampus are very closely involved in the normal functioning of the hippocampus. As a consequence the distinctions based on temporal lobe versus diencephalic amnesia are likely to be misleading if these syndromes are, in part, a result of damage to these closely integrated structures. The difficulty in dissociating between diencephalic and temporal lobe syndromes might be further heightened if it were to be shown that the reciprocal projections back to the temporal lobe from the diencephalon constitute part of this functional system. Preliminary findings indicate that the cingulum bundle, which conveys projections from the anterior thalamic nuclei to the temporal region, may conduct information that is important for allocentric spatial memory in the rat (Aggleton et al., 1995b). This result is consistent with the notion of a partially reciprocal temporal lobe—diencephalic system.

Although these studies have focused on spatial memory there is growing evidence that this same functional system is involved in other, closely related aspects of memory (Gaffan, 1992b, 1994b; Rawlins et al., 1993). An example of this concerns evidence that lesions of the fornix will disrupt the acquisition of concurrent discriminations when the stimuli to be discriminated are complex scenes that often contain common elements (Gaffan, 1992b). This finding has recently been explored in more detail and it appears that the critical feature is whether the task requires the spatial array of the elements in the stimuli to be discriminated (Gaffan, 1994b). These results have been taken to indicate that the fornix, and hence the hippocampus, is important for the scene-specific memory of objects (Gaffan, 1992a, 1994a,b). There is also recent evidence that the mammillary bodies are involved in this same process (Gaffan, Parker, & Gutmikov, 1995). As a consequence the hippocampal system is thought to aid the normal recall of episodic information as it permits the subject to distinguish or recreate the unique scene associated with the to-be-remembered item (Tulving,
1983; Gaffan, 1992a, 1994b), a process that will reduce interference from other similar events (Gaffan, 1994b). From this it can be predicted that anterior thalamic lesions will also disrupt similar concurrent discriminations, although this has yet to be tested. It can be seen that these recent findings are consistent with the notion that damage to the extended hippocampal system will disrupt the normal recall of episodic memory, the hallmark of anterograde amnesia.

If it is accepted that the extended hippocampal system mainly contributes to recall rather than recognition, then the severe DNMS deficits associated with lesions in either the medial temporal lobe or the medial diencephalon (Aggleton & Mishkin, 1983a; Mishkin, 1978; Murray, 1992; Squire & Zola-Morgan, 1991) must involve other structures. In the case of the medial temporal lobe this appears to be the perirhinal cortex (Meunier et al., 1993; Murray, 1992; Squire & Zola-Morgan, 1991) the entorhinal cortex (Meunier et al., 1993), and perhaps the parahippocampal cortex (Squire & Zola-Morgan, 1991, Zola-Morgan, Squire, Amaral, & Suzuki, 1989; but see Ramus, Zola-Morgan, & Squire, 1994). Although the perirhinal region has extensive connections with the hippocampus, its contribution to recognition memory seems to be largely independent of that structure. This conclusion comes from the difference in the severity of the DNMS deficit following rhinal and hippocampal lesions (see Fig. 1) and is reinforced by recent evidence of a double dissociation between the contributions of the perirhinal cortex and the hippocampus to memory (Gaffan, 1994a). In that study it was found that perirhinal lesions produced a much greater disruption of a delayed matching-to-sample task than fornix transection. In contrast, the fornix lesions impaired a spatial task while perirhinal lesions had little or no effect (Gaffan, 1994a).

The origin of the diencephalic DNMS deficit is less certain. Evidence from animal lesion studies indicates that the thalamic nucleus medialis dorsalis (MD) contributes to the deficit (Aggleton & Mishkin, 1983b; Hunt & Aggleton, 1991; Zola-Morgan & Squire, 1985b). This accords with the fact that MD receives direct inputs from the perirhinal cortex, via the inferior thalamic peduncle (Aggleton, Desimone, & Mishkin, 1992; Murray, 1992). It is, however, the case that the magnitude of the MD lesion deficit is insufficient to account for the full extent of the diencephalic DNMS impairment (Aggleton & Mishkin, 1983a,b). This may be because the published studies have failed to destroy all of MD, but it seems more likely that damage to other fibre tracts in the region of the medial thalamus is required in order to produce the full recognition deficit. The latter proposal is consistent with the location of the pathology in thalamic amnesia (Cramon, von Hubel, & Schuri, 1985; Graff-Radford, Tranel, Van Hoesen, & Brandt, 1990; Markowitsch, 1988) and the apparent lack of amnesics with lesions confined to MD (Markowitsch, 1982; Kritechevsky, Graf-Radford, & Damasio, 1987). One possibility is that damage to the mamillothalamic tract not only brings about a recall deficit but also accentuates the recognition impairment associated with MD damage. The mamillothalamic tract effect on recognition memory might be due to the disruption of fornical projections to the
mammillary bodies and anterior thalamus, which on their own are often not vital for DNMS performance, but when combined with other damage may potentiate lesion effects. Evidence for this comes from the effect of fornix transection when combined with lesions of the amygdala and temporal stem (Bachevalier et al., 1985b), and from the mild deficit associated with fornix transection on a delayed matching-to-sample task that used complex, naturalistic scenes as stimulus material (Gaffan, 1994a). It should be added that although these fornical effects imply a contribution from the hippocampus, they could prove to result from entorhinal disconnections (Meunier et al., 1993) (see Section 3). It is also possible that damage close to the mammillothalamic tract might involve other important fibre tracts. For example, lesions in this region may increase the disruption of fibres connected with the prefrontal cortex (Bachevalier & Mishkin, 1986; Schacter, 1987), and this might further add to the thalamic recognition deficit. The resolution of these issues will require a systematic analysis of highly selective diencephalic lesions.

2. RECALL AND RECOGNITION IN AMNESIA

One of the most striking conclusions from this brief review of animal studies is that there is a mismatch between those areas often thought to be responsible for anterograde amnesia and those that disrupt DNMS performance. To account for this it is suggested that damage to the hippocampus or its diencephalic targets impairs the recall of episodic information (i.e. produces amnesia) but need not severely affect recognition (i.e. spares DNMS performance). In contrast, those pathologies that affect both the extended hippocampal system and other cortical regions may severely disrupt recall and recognition. Because this latter group of subjects is far commoner than those with selective damage, the large majority of amnesic subjects will perform poorly when tested on analogues of DNMS tasks.

Up to now recognition has been considered as if it were a single process. In fact, there is a strong consensus that recognition involves two processes (Gardiner & Parkin, 1990; Horton, Pavlick, & Moulin-Julian, 1993; Jacoby & Dallas, 1981; Mandler, 1980). One of these permits a recognition judgement to be made on the basis of stimulus familiarity (stimulus fluency). The other involves the retrieval of episodic or contextual information associated with the item to be recognised. These processes are seen as additive and separate (Mandler, 1980). Following from the previous discussion concerning the contribution of the extended hippocampal system to episodic memory, it is assumed that damage to this system spares familiarity-based recognition but can disrupt retrieval-based components. As a consequence, hippocampal system damage will be expected to disrupt only certain tests of recognition, i.e. those in which explicit retrieval of information about the target item is used to aid recognition. Related to this it is assumed that the standard DNMS task, as given to monkeys or rats, is essentially a test of familiarity judgements and so is little affected by extended hippocampal system damage. This assumption concerning
the DNMS task will, however, require independent support as there is the danger of lapsing into a circular argument.

A clear prediction from the current proposals is that a few amnesics will show disproportionately mild recognition deficits in the face of substantial recall deficits, and that these cases will be those with more selective damage to the hippocampus or its subcortical outputs. There is, however, a major obstacle in testing this prediction. This concerns the relative rarity of amnesic subjects with discrete damage to the hippocampal system. In order to minimise this problem we decided to compare performance on a standard test of recognition that has been administered to many amnesic subjects (Aggleton & Shaw, 1996). We therefore conducted a literature survey of all amnesics who had taken the Recognition Memory Test or RMT (Warrington, 1984). This test is divided into two parts, one a test of word recognition, the other a test of face recognition. In each part the subject is shown a series of 50 sample stimuli (words or faces) and then tested in a forced-choice manner, i.e. each sample is paired with a novel stimulus. The subject must indicate which word or face they previously saw. From this it can be seen that the RMT procedure closely resembles delayed matching-to-sample with a list of 50 items.

The survey produced 33 studies which gave the RMT scores of a total of 112 people described as suffering from anterograde amnesia. These were then placed in 11 groups according to their aetiology and pathology. The groups were: alcoholic Korsakoff (n = 39), Post-encephalitic (n = 19), Anterior Communicating Artery Aneurysm (n = 9), Splenial tumours (n = 7), Bilateral Thalamic infarcts or tumours (n = 8), Left Thalamic infarcts, (n = 4), Fornix (n = 2), Hippocampus (n = 3), Other Temporal Lobe (n = 3), Mammillary Body region (n = 2), and those amnesics who did not fit into any of the preceding groups (Others n = 16). Mean performance levels are shown in Fig. 2.

Comparisons using age-matched, normative data provided by Warrington (1984) revealed that only three amnesic groups failed to show a clear impairment (P > .05, one-tailed tests) on both the Words and the Faces subtests. These were the Hippocampus, Fornix, and Mammillary Body subjects. This lack of impairment for both RMT subtests persisted even when these three groups were combined (n = 7) (Aggleton & Shaw, 1996). These same three groups also performed significantly better than the Post-encephalitic amnesics on the RMT subtests. These findings indicate that damage focused in the hippocampal system can largely spare recognition, as measured by the RMT. Additional support has come from a series of five patients with bilateral fornix damage, reported after the completion of this review (McMackin, Cockburn, Anslow, & Gaffan, 1995). All five cases were described as showing moderate or severe losses of memory, yet of the ten RMT scores (five words and five faces), only one was more than 1.65 standard deviations (P < .05) below the normative scores for that age group (Warrington, 1984). This apparent lack of effect of hippocampal system damage clearly echoes the findings from animal studies using the DNMS task.
Although the evidence of an unusually mild recognition deficit in those cases with selective hippocampal system damage is consistent with the main proposal outlined in this review, there are other possible explanations for this pattern of results. One possibility is that the criteria for inclusion in these three groups (Hippocampus, Fornix, Mammillary Body) may have led to a bias towards those subjects with only partial damage to the critical region. This is because those subjects with complete or near-complete damage to these structures are the same subjects most likely to have pathology that extended into other, adjacent regions, and so cause them to be placed in different groups. It is therefore possible that the subjects in these three groups only suffered partial damage to the relevant...
structures and so only suffered a mild amnesia. Given that recognition tasks are typically much easier than tests of recall, this might then explain the apparent lack of an RMT deficit.

This alternative explanation rests on the assumption that the subjects in the Hippocampus, Fornix, and Mammillary Body groups displayed only a mild amnesia. In order to test this possibility we examined that subset of amnesics who had been tested on both subtests of the RMT and on the Wechsler Memory Scale Revised or WMSr (Wechsler, 1987). The WMSr was selected because the Delayed Recall and the General Memory indices that are derived from the test are regarded as valid measures of the severity of amnesia (Butters et al., 1988). This produced a group of five amnesics with Hippocampal System damage and 27 Other Amnesics. As expected, the mean RMT scores of the two groups differed for both the Words [Hippocampal System = 41.4, Other Amnesics = 34.7, t(30) = 2.14, \( P < .05 \)] and the Faces [Hippocampal System = 42.2, Other Amnesics = 34.9, t(30) = 2.40, \( P < .05 \)] subtests. In contrast, the mean scores of the two groups of amnesics for the Delayed Recall (Hippocampal System = 60.4, Other Amnesics = 56.9) and the General Memory (Hippocampal System = 76.4, Other Amnesics = 68.4) indices did not differ (both \( P > .2 \)). The somewhat lower performance of the Other Amnesics on the General Memory Index is principally due to the alcoholic Korsakoff subjects (n = 14) who comprised the majority of the Other Amnesics and who are known to score particularly poorly on this measure (Butters et al., 1988).

A final comparison examined whether the Hippocampal System subjects showed an unusually large discrepancy between their RMT and WMSr scores. An analysis of variance was used to compared the combined scores for the two RMT tests (Words plus Faces) with the Delayed Recall Index from the WMSr (Fig. 3). The group by test interaction, indicative of a disproportionate difference between the two groups, was found to be close to significance \([F(1,30) = 3.65, \ P = .066] \). Among the Other Amnesics, however, there was one subject who may have suffered damage to the extended hippocampal system but not to other regions that might disrupt memory. This amnesic was diagnosed as having a hypothalamic tumour (Parkin & Hunkin, 1993), which is likely to have directly invaded the mammillary bodies. The precise locus of this tumour was not, however, described. In view of the uncertain status of this subject he was removed from the previous analysis. This resulted in a significant interaction between RMT scores and Delayed Recall Index for the two groups of amnesics \([F(1,29) = 5.47, \ P = .026] \). It should be added that this hypothalamic tumour case could not be included in the Mammillary Body group as the extent of his pathology had not been directly assessed. In contrast, all of the subjects in the three Hippocampal System groups (Hippocampus, Fornix, Mammillary Body) had received at least MRI confirmation of the location of their pathology. In the case of two of the Hippocampus subjects, post-mortem reports (Rempel-Clower, Zola-Morgan, & Squire, 1994) were able to verify that both patients had suffered
complete, bilateral lesions of the CA1 field of the hippocampus. In one of these cases there was additional damage in CA3, and minor pathology outside the hippocampal region in both cases. From the pathology in these two cases and that in a third amnesic patient, RB, who had also been carefully studied (Zola-Morgan, Squire, & Amaral, 1986), it would appear that damage in the hippocampal region is sufficient to produce anterograde amnesia.

It can be seen that these analyses are consistent with the conclusion that subjects with selective hippocampal system damage can have an amnesia of standard severity but show relative sparing of recognition memory. The results from the RMT test are, however, preliminary and should at this stage be treated with caution. This is because the pattern of recognition test results might be task-dependent. As has been indicated, the extent to which a particular recognition task taxes familiarity-based judgements may prove to be of critical importance. With this in mind it is relevant to note that the Faces subtest of the RMT (the
Words subtest was not examined) is not susceptible to extreme switches in context between the sample phase and the test phase (Parkinson & Aggletton, 1994). This is consistent with the view that this test, as standardly applied, makes little demand on retrieval-based processes. In addition, there is evidence that changes to the type of stimuli or to the way they are tested (forced-choice versus yes/no) might affect the outcome of recognition tests given to amnesics (Hanley, Davies, Downes, & Mayes, 1994; Parkin, Yeoman, & Bindschaedler, 1994). Further complications arise from the fact that some tests of recognition are prone to ceiling effects. This particular problem was considered in a recent study of an amnesic subject with selective mammillary body damage (Holdstock, Shaw, & Aggletton, 1995). By carefully manipulating task difficulty it was possible to show that this factor could not account for the sparing of forced-choice recognition over those delays tested. Thus, in spite of these issues, it is clear that the RMT results support the proposal that hippocampal system damage is sufficient to induce the severe recall deficit in amnesia and that the main recognition deficit principally arises from dysfunctions in other regions.

3. ANATOMICAL CONSIDERATIONS

The third strand of evidence concerns research into the anatomical connections between the medial temporal lobe and the medial diencephalon in the primate brain. This information principally comes from axonal transport studies in monkeys (rhesus macaque and cynomolgus macaque) as it has not been possible to study the equivalent connections in the human brain in the same detail. In light of the current proposals a number of key anatomical questions emerge.

A central question concerns the extent of the perirhinal cortex projections to the medial diencephalon. This could help to identify that part of the diencephalic amnesic syndrome thought not to depend on the hippocampal system, and also clarify the relationship between the DNMS deficits found in monkeys following certain diencephalic and temporal lobe lesions. It will also be important to discover the route of these rhinal–thalamic connections and the extent to which they rely on the fornix or on other pathways. This is of interest because transection of the fornix appears to disrupt the recall of episodic events but may often have only a small effect on recognition. According to the current proposal this is because the fornix largely carries information from the hippocampus and so does not contribute to familiarity judgements. It is, however, likely that the current proposals would have to be modified if it were found that perirhinal efferents contribute substantially to the fornix or if there were significant hippocampal projections to the mammillary bodies and anterior thalamic nuclei that do not pass through the fornix.
(i) Hippocampal (Subicular) Projections to the Thalamus and Mammillary Bodies

The hippocampal projections to the anterior thalamic nuclei (nuclei AV/AM/AD) and the mammillary bodies (MB), which originate in the subiculum, all appear to travel through the fornix. Thus if retrograde tracers are placed in the MB or in the anterior thalamic nuclei and the fornix is cut, no labelled cells are found in the subiculum (Saunders, Aggleton, & Mishkin, 1996). Similarly, if the fornix is cut and anterograde tracers are placed in the subiculum no label is found in the mammillary bodies or the anterior thalamic nuclei (Aggleton et al., 1986a). The other major target for hippocampal–thalamic projections is the lateral dorsal nucleus (LD), but this receives both a fornical and a non-fornical component (Aggleton et al., 1986a). Like the projections to the anterior thalamic nuclei, cells in the deep layers of the subiculum contribute to the fornix projection to LD (Saunders et al., 1996). But in addition to this subicular contribution there is a substantial component that arises in the pre- and parasubiculum that does not pass through the fornix (Saunders et al., 1996). This projection appears to course laterally to the temporal stem before passing caudally towards the pulvinar. It then arches around and over the pulvinar before coursing rostrally to reach LD (Aggleton et al., 1986a). It can be seen, therefore, that the fornix carries all of the hippocampal projections to the mammillary bodies and to the anterior thalamic nuclei AM, AV, and AD, but that there is a sizeable alternative projection to LD. As yet, projections from the hippocampus to the medial dorsal nucleus of the thalamus (MD) have not been demonstrated.

(ii) Entorhinal Cortical Projections to the Thalamus

The entorhinal cortex (area 28) is, for the most part, positioned rostral and medial to the hippocampus with the most caudal part, 28M, medially adjacent to the pes hippocampi (Saunders & Rosene, 1988). Area 28 has usually been considered a transitional cortex between the lateral neocortex of the temporal lobe and the archicortex of the hippocampus. It is from the cells of layers 2 and 3 that the perforant path originates and thus provides the major access for cortical information into the hippocampus. Historically its role was considered little more than a relay of cortical information into and out of the hippocampus and is often regarded as part of, or an extension of, the hippocampus. Recent anatomical studies (Aggleton et al., 1986a; Rosene & Saunders, 1987; Russchen, Amaral, & Price, 1987; Suzuki, 1996; Saunders et al., 1996) have demonstrated that this region has a much wider array of subcortical projections than previously thought, and as a consequence its mnemonic contributions may be more diverse than initially proposed.

All divisions of the entorhinal cortex project to the medial thalamic region. Results from injections of both retrograde and anterograde tracers have demonstrated projections to both the anterior thalamic nuclei and the medial
dorsal nucleus, as well as the mammillary bodies. The routes of these projections have been determined by cutting the fornix or the central amygdalofugal pathway prior to the injection of tracers in the thalamus or temporal lobe (Aggleton et al., 1986a; Saunders et al., 1996). These manipulations have demonstrated the variability of these routes.

Injections of amino acids in the entorhinal cortex result in light label in AV/AM (Aggleton et al., 1986a) and this is consistent with the finding of retrogradely labelled cells in area 28 after AV injections (Saunders et al., 1996). The number of these entorhinal cells is, however, considerably less than that seen in the subiculum. Transection of the fornix resulted in a reduction of these labelled cells but did not eliminate all of them, suggesting a very light nonfornical component to the AV/AM projection. Indeed anterograde tracing experiments appear to confirm a very light nonfornical projection via the temporal stem/temporo-pulvinar bundle that passes LD to reach AV/AM. As for the projection to MD, it also appears to arise from all parts of area 28, but it only has one route, that via the inferior thalamic peduncle. Fibres could be traced through and around the amygdala, after which they join the interior thalamic peduncle to enter the rostral thalamus and pass around the mammillothalamic tract before reaching the magnocellular part of MD.

In contrast to the relatively light projections to AV/AM and MD, there is a much denser projection from the entorhinal cortex to the lateral dorsal nucleus. For the most part the source of this projection is located in the medial bank of the rhinal sulcus (28S). This LD projection, like that from the pre- and parasubiculum, does not course through the fornix. These nonfornical LD projections, in some part, appear to follow the same route as the pre- and parasubiculum projections to LD. They might also contribute to the inferior thalamic peduncle and then course caudally to LD.

Thus the entorhinal cortex has connections to rostral (anterior thalamic nuclei) and caudal (MD and LD) parts of the medial thalamus with fibres coursing not only through the fornix but via other routes. Some of these nonfornical projections pass in close proximity to the mammillothalamic tract. In addition to these thalamic projections there is a light projection from all sections of area 28 to the MB. In comparison to the subicular projection to the MB, which arises from an enormous number of cells, the entorhinal projection to the MB arises from a very limited population of cells. This small projection courses through the fornix.

(iii) Perirhinal Cortex Projections to the Thalamus and Mammillary Bodies

The perirhinal cortex is closely associated with the entorhinal cortex and like the entorhinal cortex provides a relay of cortical information into the hippocampus. This region lateral to the rhinal sulcus is composed of areas 35 and 36. Area 35
comprises the lateral bank of the rhinal sulcus and area 36 extends laterally as a transition area between the rhinal cortex and the temporal neocortex. Tract tracing studies, both anterograde and retrograde, have shown no evidence of a projection from the perirhinal cortex to the anterior nuclei of the thalamus. In contrast there appears to be a reasonably dense projection to magnocellular MD (Aggleton et al., 1986a; Russchen et al., 1987). Transection of the VAF path resulted in an absence of retrogradely labelled cells in the perirhinal cortex after injections into MD, thus the route to MD is similar to that from the entorhinal cortex and the amygdala. In contrast to the entorhinal cortex, there was no evidence of a projection from perirhinal cortex to LD.

(iv) Origin of the Fornical Fibres in the Temporal Lobe

A direct way of determining those fields of the temporal lobe that contribute efferent fibres to the fornix is to place HRP gel into a cut section of the fibre tract (Saunders et al., 1996). Retrogradely labelled cells, indicating the origin of the fornix, are found throughout the hippocampus and in the superficial layers of the entorhinal and perirhinal cortex. Once again, this shows that the fornix does carry some non-hippocampal efferents, i.e. those from the entorhinal and perirhinal cortices. Although this technique cannot ascertain where these projections are targeted, it has been shown that the entorhinal cortex has a relatively small number of fornical projections to the MB and AV/AM. The perirhinal cortex does not, however, project via the fornix to medial thalamic regions and these labelled cells may reflect target regions outside the diencephalon.

In conclusion, there are relatively few nonhippocampal and nonfornical projections to AV/AM and LD from the medial temporal lobe. The most robust thalamic projections from outside of the hippocampus are from the entorhinal cortex and perirhinal cortex to LD and MD, respectively. In addition, there is a substantial nonfornical projection from the pre- and parasubiculum to LD. This appears to leave the projections from the rhinal cortex to MD to account for most of the recognition deficit found in diencephalic amnesia, but disconnection studies using monkeys have called this into question by showing that a lesion thought to cut this pathway produces only mild DNMS impairments (Bachevalier et al., 1985a). This study also showed that fornix lesions could exacerbate this mild DNMS deficit, a result that may reflect the transection of the relatively few entorhinal efferents that use the fornix with a loss of the retrieval components of recognition. The relative lack of effect associated with any individual disconnection suggests that the diencephalic recognition deficit stems from a combination of these effects, as well as a disruption of frontal connections (Bachevalier & Mishkin, 1986). Finally, in the light of the current proposal it would be interesting to know whether LD, which is sometimes regarded as part of
the anterior thalamic nuclei, contributes to either recognition or recall processes, and whether damage to this region can accentuate other memory deficits.

GENERAL CONCLUSIONS

Evidence from a variety of sources appears consistent with a revised grouping of amnesias. In this formulation, damage to at least one part of the ‘extended hippocampal system’ (hippocampus, fornix, mammillary bodies, anterior thalamic nuclei) is regarded as a common feature of all anterograde amnesias, and is principally responsible for the characteristic recall deficit. For this reason different amnesic conditions will share many features and be difficult to dissociate. Frequently overlaid on this hippocampal system deficit will be additional temporal lobe, frontal lobe, or diencephalic damage. This extra damage leads to other impairments that include a more pronounced recognition deficit. The extent to which this additional damage may also exacerbate the basic recall deficit, or the extent to which the recognition deficit is exacerbated by hippocampal system damage, remains to be determined and these are now issues of high priority. It has, for example, been suggested that the relative sparing of recognition memory after hippocampal system damage reflects the ability of animals or amnesic subjects to make accurate judgements based on familiarity. It is, however, also predicted that hippocampal system damage will disrupt the retrieval-based component of recognition memory and this will require examination.

It is assumed that anterograde amnesia usually results from a combination of different deficits that reflect dysfunctions in more than one functional system. It is hoped, however, that this reformulation of the disorder with its emphasis on the extended hippocampal system will make it easier to interpret the findings from neuropathological studies and to assemble appropriate groups in order to look for meaningful dissociations between different amnesic states. One intriguing issue concerns those amnesias associated with aneurysms of the anterior communicating artery. They are of particular interest as it has been claimed that this disorder does not involve those regions responsible for temporal lobe or diencephalic amnesia (Parkin & Leng, 1993), and they may therefore prove to be an exception to the proposal that all anterograde amnesias involve the extended hippocampal system. In view of the fact that the pathology associated with these aneurysms can involve parts of the fornix, may disturb the cingulum bundle as well as the cingulate cortex, and can on occasions extend into the anterior thalamus (Hanley et al., 1994) it seems more parsimonious to assume that they are another example of an amnesia principally due to disruption of the extended hippocampal system. This can only be confirmed by very careful post-mortem analyses of such cases.

Finally, one important class of evidence that may prove to have a considerable bearing on the details outlined in this proposal comes from studies
of functional imaging (Fazio et al., 1992). These studies have helped to show the extent to which discrete diencephalic and discrete temporal lobe lesions can disrupt processing in other brain regions. Initial evidence indicates that in amnesia there may be hypoactivity in areas quite distal to the actual site of pathology and such information is likely to have a significant influence on the future analysis of amnesia.

REFERENCES


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