THE CONTRIBUTION OF THE ANTERIOR THALAMIC NUCLEI TO ANTEROGRADE AMNESIA

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Abstract—This paper first reviews the anatomical, pathological, and neuropsychological evidence implicating the anterior thalamic nuclei in memory processes. It is concluded that there is much indirect evidence indicating that anterior thalamic dysfunction is an important factor in anterograde amnesia. More direct evidence for the involvement of the anterior thalamic nuclei in memory processes emerges from two experiments with rats that examined performance of a spatial test of working memory, delayed nonmatching-to-position. The first study revealed that neurotoxic lesions of the anterior thalamic nuclei and radiofrequency lesions of the fornix both produce equivalent performance deficits. In contrast, lesions of the mamillary bodies were without effect. A second study showed that lesions of the fornix and removal of the hippocampus produced very similar deficits. These data indicate that while the involvement of the anterior thalamic nuclei in certain memory functions depends on inputs from the hippocampus, this involvement need not depend on indirect afferents via the mamillary bodies.

INTRODUCTION

It has been known for almost a century that damage to brain structures in the medial diencephalon can severely disrupt memory. This has led to numerous attempts to define the critical regions and determine their functional roles. Much of the early evidence came from studies of Korsakoff's disease and so focused attention on the mamillary bodies. The discovery in the 1950s that hippocampal damage was also associated with anterograde amnesia seemed to implicate the mamillary bodies further as there is a substantial projection linking these two regions via the fornix. In view of these and related findings, Delac and Brion [17] proposed that the hippocampus–fornix–mamillary body pathway was critical for memory, and that both temporal lobe and diencephalic amnesia was the consequence of damage to different parts of the same system.

The intervening years have brought many challenges to this influential proposal. It has, for example, been argued that fornix damage in humans does not result in amnesia [27, 84] but see also [27]. It has also been claimed that damage to nucleus medialis dorsalis, a thalamic region not directly connected with the mamillary bodies, is responsible for the amnesia in Korsakoff's disease [79] and for other forms of diencephalic amnesia [44]. While the direct involvement of nucleus medialis dorsalis remains contentious [50, 53], a number of recent neuropathological analyses have stressed the contribution of fibre tracts rather than particular cell masses within the diencephalon [14, 52]. These tracts include the internal medullary lamina [14, 52] through which projections to nucleus medialis dorsalis...
pass. While these findings clearly question the original proposal of Delay and Brion [17], it is not clear how it should be revised or replaced.

Throughout this debate an additional diencephalic region, the anterior thalamic nuclei, has often been overlooked. There are, however, a number of important reasons why this region is likely to play a critical role in diencephalic memory processes. Perhaps the principal reason concerns its anatomical connections which link together key limbic areas. Although there is only limited, direct clinical evidence, a number of recent animal studies have indicated a close functional relationship between the anterior thalamus and limbic regions involved in memory. By focusing on the anterior thalamic nuclei it may prove possible to update the original notion of a hippocampal–fornix–mamillary body axis in a way that can accommodate much of the new evidence.

Anatomical considerations

The anterior thalamic nuclei can be subdivided into an anterior medial, anterior ventral, and anterior dorsal nucleus. The appearance and composition of these nuclei seem consistent across a wide range of mammalian species. There is, however, intriguing evidence that the anterior thalamic nuclei, unlike the mamillary bodies, have undergone a relative enlargement during human evolution [8]. While anatomists have sometimes also included the lateral dorsal thalamic nucleus as part of the anterior nuclei, this region will be treated as separate in the present discussion.

In order to understand the potential significance of the anterior thalamic nuclei it is first necessary to consider the connections of the mamillary bodies. It has long been known that the mamillary bodies receive dense projections from the hippocampus. These projections arise from the subicular complex and pass exclusively through the fornix to terminate in the medial mamillary nucleus [74], that part of the mamillary bodies most consistently affected in Korsakoff's disease. Additional hippocampal projections terminate in the lateral mamillary nucleus and the tuberomamillary nucleus. There do not appear to be any direct projections from the perirhinal or postrhinal cortices to the mamillary bodies [83].

While there are light projections from the mamillary region to the hippocampus (from the supra- and perimamillary nuclei), these do not arise from those areas receiving hippocampal inputs [78]. Furthermore, there is only very limited evidence to suggest that intra-mamillary connections may permit a reciprocal circuit [32]. Thus in order to trace the functional significance of the hippocampal–mamillary body projections it is necessary to consider the flow of "hippocampal" information leaving the mamillary bodies.

It is well established that a massive projection, forming the mamillothalamic tract, runs from the mamillary bodies to the anterior thalamic nuclei. Within this tract the medial mamillary nucleus projects ipsilaterally to the anterior medial and anterior ventral nuclei, while the lateral mamillary nucleus has a bilateral projection to the anterior dorsal nucleus [16, 68, 78]. These connections are not reciprocated. While the medial and lateral mamillary bodies also project to a number of midbrain sites, their only other limbic projection is to the medial septum [78]. The few direct cortical projections from the medial and lateral mamillary nuclei appear to terminate in the prefrontal cortex [41].

The anterior thalamic nuclei not only receive a massive input from the mamillary bodies, they also receive a dense, direct input from the hippocampus [2, 74]. This projection passes exclusively through the fornix [2]. It appears that the inputs to the anterior ventral nucleus arise predominantly from the pre- and parasubiculum, while those to the anterior medial nucleus arise predominantly in the subiculum [74]. Much lighter projections run to the
anterior dorsal nucleus. A laminar analysis indicates that essentially separate populations of subicular neurons project to the mamillary bodies and the anterior thalamic nucleus [19]. It should be added that the adjacent lateral dorsal thalamic nucleus also receives a hippocampal projection, but this has both a fornical and a nonfornical component [2, 54]. The anterior thalamic nuclei and the lateral dorsal nucleus not only receive a direct projection from the hippocampus, they also project back upon the hippocampus [18, 85]. This lighter, reciprocal connection terminates in the presubiculum [74] so completing a reciprocal circuit.

In addition, the anterior thalamic nuclei possesses significant, reciprocal connections with the cingulate region. Projections to the anterior thalamic nuclei appear to arise from all divisions of the cingulate cortex, but especially the retrosplenial division [35]. These afferents terminate throughout the anterior thalamic nuclei, with the anterior medial and anterior ventral nuclei receiving the majority [66]. The anterior thalamic nuclei are also the principal source of thalamic projections to certain cingulate regions. Substantial projections arise from the anterior medial nucleus to terminate in the posterior cingulate cortex (area 23), while dense inputs to the retrosplenial cortex (areas 29 and 30) arise from all three anterior nuclei, as well as the lateral dorsal nucleus [80]. In contrast, the anterior cingulate cortex (area 24) receives only a minor projection from the anterior thalamic nuclei. The potential significance of these anterior thalamic–cingulate connections lies in the fact that the various cingulate regions have complex, reciprocal connections with the hippocampal formation [74, 85]. In this way a second, indirect route is formed by which the hippocampus can interact with the anterior thalamic nuclei and vice versa.

From this analysis of hippocampal–diencephalic connections (Fig. 1) a number of key points emerge. (1) The fornix is the primary route by which the hippocampus can directly influence the medial diencephalon. (2) Despite the massive inputs from the hippocampus to the mamillary bodies there does not appear to be a reciprocal connection back to the hippocampus. (3) The mamillary bodies have only a limited array of output targets. (4) The anterior thalamic nuclei receive dense projections from both the mamillary bodies and the hippocampus. (5) The anterior thalamic nuclei project back to the hippocampus. (6) There is an additional reciprocal route between the hippocampus and the anterior thalamic nuclei, via the cingulate/retrosplenial cortices.

Fig. 1. Schematic diagram showing the anatomical relationship between the hippocampus and the anterior thalamic nuclei. Solid lines represent direct or indirect anterior thalamic afferents, dotted lines represent efferents. The heaviest projections are shown with thick lines.
It can therefore be seen that the anterior thalamic nuclei occupy a unique, pivotal position with respect to both direct and indirect hippocampal–diencephalic connections (Fig. 1). If damage to either the mamillary bodies or the mamillothalamic tract does contribute to amnesia, then it is difficult to escape the conclusion that the anterior thalamic nuclei must play an important role. Furthermore, the presence of hippocampal–anterior thalamic connections that are independent of the mamillary bodies means that the anterior thalamic nuclei may have a contribution beyond that dependent on the mamillary bodies.

**Neuropsychologicul considerations**

*Clinical evidence.* There is only a limited amount of clinical evidence that directly implicates the anterior thalamic nuclei in diencephalic amnesia, but a careful analysis reveals that connections to or from these nuclei are disrupted in many cases. In Korsakoff's disease, for example, the anterior thalamic and lateral dorsal nuclei are only sometimes affected [10, 79]. It is, however, known that the mamillary bodies almost invariably show shrinkage, demyelination, and gliosis. As a consequence a major input to the anterior thalamic nuclei is disrupted. Interpreting the pathology of alcoholic Korsakoff's disease has, however, proved particularly difficult as the pattern of memory loss may often reflect a combination of diencephalic and frontal damage [43, 69].

The other two main classes of diencephalic amnesia stem from the effects of third ventricular tumours and vascular accidents. Early reports describing third ventricular tumours emphasized the involvement of the mamillary body region [42], while later descriptions included cases centred around nucleus medialis dorsalis with apparent sparing of the mamillary bodies [44]. These findings do not, however, rule out an important contribution from the anterior thalamic nuclei. First, the frequency of mamillary body damage serves to implicate the anterior nuclei indirectly. Second, evidence that the raised intraventricular pressure associated with such tumours may be sufficient to produce an amnesic state [40] means that compression on the anterior thalamic nuclei could contribute to any memory loss.

There are now a large number of reports linking infarcts in the paramedial and polar thalamic arteries with memory loss [12, 14, 33]. The regions most typically invaded include nucleus medialis dorsalis, nucleus parafascicularis, nucleus centrum medianum, the mamillothalamic tract, and the internal medullary lamina [12, 14]. While the anterior thalamic nuclei are sometimes involved [31], they often appear to be spared. This is presumably because the anterior thalamic nuclei receive their blood supply from different arteries (branches of the choroidal vessels). Recent attempts to determine the common area of damage in such amnesic cases have identified a region involving both the mamillothalamic tract and the internal medullary lamina [14, 33, 52]. From this it has been argued that the amnesia results from a disconnection of mamillary body efferents combined with a loss of afferents to nucleus medialis dorsalis [14, 33]. This interpretation clearly places the anterior thalamic nuclei in a key position as they represent the disconnected target from the mamillary bodies. Furthermore, damage to this common area may disrupt other subcortical afferents to the anterior thalamus [70], and may also cut thalamic efferents to the cingulate region [63]. As a consequence, such vascular accidents may do more than just disconnect the anterior thalamic nuclei from the mamillary bodies.

Surgical lesions have been directed at the anterior thalamic nuclei in a small number of patients. Of particular interest is the case of a woman in whom lesions of the anterior thalamic nuclei were made during treatment for chronic depression [51]. Her death, as a
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result of suicide, made it possible to confirm that the surgery had bilaterally destroyed the anterior thalamic nuclei but had spared the mamillary bodies and much of nucleus medialis dorsalis. Following her surgery it was noted that she suffered confusion for both time and place. Her recent memory was described as being "quite impaired" and she would often get lost in the hospital [51]. While the report implies that her "severe" memory loss improved after about a month, no objective evidence is provided to support this claim (for much of the time she refused to take memory tests). She died 6 weeks after her final surgery. HASSLER [36] also described a case in which stereotaxic lesions of the anterior thalamic nuclei resulted in a severe, but temporary, amnesia. Finally, it was noted that the extension of a medial thalamic lesion into the anterior thalamic nuclei could reinstate a transient disorientation of time and memory [71].

In view of the proposal that the anterior thalamic nuclei are important because of their reciprocal hippocampal connections, it is relevant to consider whether damage to either the fornix or the cingulate region can lead to memory dysfunctions. While the effects of fornix damage have often proved contentious [27, 29, 75], a number of recent cases have helped to indicate that fornix damage can lead to anterograde amnesia [11, 27, 30, 38, 76]. As has been pointed out [27], those cases with no apparent memory loss may reflect sparing of fornical tissue, lack of adequate neuropsychological testing, or the presence of a prior neurological condition that itself led to memory dysfunction and so masked the effects of fornix damage. Further support that fornix damage may be sufficient to produce amnesia comes from the pattern of memory deficits seen after fornix transection in monkeys [26].

As fibres from the anterior thalamic nuclei pass through the cingulate region, as well as relay there, en route to the hippocampus it might be predicted that cingulate damage should also lead to memory loss. It could further be argued that posterior cingulate/retrosplenial lesions are likely to have the greatest impact as damage here may both disconnect anterior cingulate/anterior thalamic fibres passing to the hippocampus, as well as removing that part of the cingulate cortex with the densest anterior thalamic projections. This prediction seems to be borne out by recent reports of amnesia associated with posterior cingulate/retrosplenial damage [15, 77]. In contrast, anterior cingulate lesions are associated with only a transient disorganisation of memories [81].

In summary, it can be seen that a great deal of the clinical data is consistent with the proposal that damage to those structures or pathways that link the anterior thalamus with the hippocampus impairs memory for new events. The underlying assumption of a closely integrated temporal–diencephalic memory system (Fig. 1) accords with recent PET data from amnesic subjects [22]. These findings have shown that in both temporal lobe and diencephalic amnesics there is an overall metabolic depression that includes the hippocampus, the thalamus, and the cingulate gyrus [22].

Experimental evidence: monkeys. In view of the many limitations in the clinical data, it is not surprising that some researchers have attempted to model diencephalic amnesia in monkeys. Many of these studies have focused on recognition memory, using the now familiar delayed nonmatching-to-sample paradigm. While such research has confirmed that diencephalic lesions can impair memory, it has not yet been possible to determine the contributions of individual thalamic nuclei.

Studies using monkeys have shown that medial thalamic lesions involving the medial dorsal, midline, and anterior thalamic nuclei produce marked recognition impairments consistent with amnesia [7]. Furthermore, removal of either the rostral half of this area (centred around the anterior thalamic nuclei) or the caudal half of this area (centred around
the medial dorsal nucleus) produces a significant, although somewhat milder, recognition deficit [7, 88]. In a single case it was also found that bilateral damage to the region of the mamillothalamic tract also produced a mild recognition deficit [7]. As lesions in the mamillary bodies appear to produce even milder deficits on the delayed nonmatching-to-sample task [6, 89], it would suggest that the rostral thalamic lesion effect is not totally dependent on disrupting mamillary body efferents.

While these results are intriguing there are some important limitations. The most obvious has been the failure to produce truly selective diencephalic lesions. This arises from the difficulty in precisely locating or accessing the various nuclei. Thus, those surgeries using a dorsal approach have often damaged parts of the fornix [6, 7, 89], while those using a ventral approach have resulted in extensive unilateral damage to the basal temporal lobe [38, 89]. A further difficulty is posed by damage to fibres of passage. Finally, it has to be remembered that damage to the anterior thalamic nuclei or the mamillothalamic tract typically results in retrograde degeneration in the mamillary bodies. As a consequence it may be extremely difficult to determine the source of any resultant impairment.

The need to examine the effects of selective anterior thalamic lesions using methods that minimise damage to fibres of passage led to a series of experiments into the effects of limbic lesions in rats. The effects of various, discrete lesions were compared using a spatial test of working memory, delayed nonmatching-to-position (DNMP). This test was selected because such tasks are sensitive to hippocampal dysfunction [20, 21, 61] and because it is possible to derive a wide array of performance measures with which to analyse the nature of any deficit [65]. Although some of the results from these experiments have already been published [4, 5], new analyses are provided that give a more comprehensive picture of the lesions' effects. The important issue of whether any of the observed deficits can be regarded as delay-dependent (see Ref. [62]) is also examined in particular detail.

**EXPERIMENT 1**

**A direct comparison of the effects of fornix, mamillary body, and anterior thalamic lesions on delayed nonmatching-to-position by rats**

The basic findings have been published [5] and for this reason many of the experimental details are only described briefly. The task procedure and the data analyses are, however, described in more depth as it is necessary to understand these in order to appreciate the findings. In all cases naive rats were first trained on the task, they then received surgery and postoperative performance was compared. In the delayed nonmatching-to-position task (DNMP) the animal presses a sample lever and then, after a variable delay, is rewarded for pressing the opposite lever in a two lever box (Fig. 2). By requiring the rat to respond on a central panel during the retention interval it is possible to restrict the use of mediating strategies.

All rats were trained in an operant chamber fitted with two retractable levers and a central food magazine [5]. Following a standard pretraining regime (see Ref. [5]) the rats were trained to respond to the following sequence of events (see Fig. 2). After a 10 sec inter-trial interval, either the left or the right hand lever emerged; the stimulus light above it was also illuminated providing an extra cue. The rat had to respond to the lever (within 10 sec), upon which the lever was retracted and the magazine tray illuminated. The subject had to approach the tray and repeatedly operate the magazine flap. Both levers then emerged, and the stimulus lights above them were illuminated. If the rat responded on the lever that had
not been the sample (nonmatch) it was rewarded with a 45 mg food pellet. Incorrect responses, or a failure to respond, resulted in a “time-out” of 10 sec.

Delays were added between the sample and choice lever presentations once rats had learned the basic task. Now, magazine responses following the sample presentation were ineffective (but were recorded) until the appropriate delay interval had lapsed; the first response after this resulted in the choice levers being presented, providing this response occurred within 10 sec of the end of the delay. The length of the delays were progressively increased until each rat was receiving 96 trials in which retention delays of 0, 2, 4, 8, 16 and 32 sec were presented in a balanced order. Following this training procedure all rats received surgery, and approximately 3 weeks after surgery retesting began. For the first 6 sessions the
delays were as before surgery, but for sessions 7–11 the retention delays were 0, 4, 8, 16, 32 and 64 sec.

Following surgery the study consisted of three experimental groups and three control groups. The fornix lesions (FNX1, n = 9) were made by radiofrequency, while the mamillary body (MAM, n = 7) and anterior thalamic (ATH, n = 10) lesions were made by the injection of 0.12 ml N methyl d aspartic acid (NMDA). The control animals (CONT1) had surgeries that matched the three experimental groups except that no lesion was produced (total n = 15). The lesions were very much as intended and Fig. 3 depicts the largest and the smallest of the lesions in each of the three experimental groups. Further details concerning the surgical procedures and histological findings have been published [5]. It is important to note that while the anterior thalamic surgeries produced substantial bilateral damage in the anterior medial nucleus, the medial half of the anterior ventral nucleus, and parts of the paraventricular and parataenial nuclei (Fig. 3), there was no evidence of retrograde degeneration in the mamillary bodies.

Data analysis

The analyses could be divided into three categories; accuracy measures, bias indices, and general responsivity [23, 65].

The accuracy measures were percent correct and two indices derived from nonparametric signal detection models [23, 65], \( A' \) and SI (sensitivity index). Two measures of bias, \( B'' \) and RI, were also calculated. The first of these, \( B'' \), reflects perceptual bias, while RI (responsivity index) is more a measure of response bias [23]. A further measure of bias, \( l_y \), contrasts accuracy between the two levers [5]. Finally, estimates of general responsivity were also recorded. These included (a) latency to respond to the sample lever, (b) latency to make the first magazine response ("nose-poke"), (c) rate of responding to the magazine flap, or nose-pokes/s, excluding the 0 sec delay condition, (d) choice (and average choice) latencies and (e) the number of missed trials.

These data were transformed as appropriate (arcsin: all accuracy and bias indices; logarithmic: latencies; square-root: misses) and analysed by parametric analysis of variance (ANOVA). When the F-ratios were significant the means were compared by the Newman–Keuls procedure.

Results

The data consistently showed that both the FNX1 and ATH groups were impaired while the performance of the MAM animals was normal. The initial analyses compared the mean percent correct scores of the four groups over all of the post operative sessions (Fig. 4). These data were divided between those days using delays of 0–32 sec (sessions 1–6) and those using delays of 0–64 sec (sessions 7–11). Both sets of comparisons revealed clear group effects (sessions 1–6, \( F (3, 37) = 6.63, P < 0.01 \); sessions 7–11, \( F (3, 37) = 7.16, P < 0.001 \)), reflecting the poorer performance of the ATH and FNX1 groups. Subsequent Newman–Keuls tests indicated that both the ATH and the FNX1 groups performed worse than either the CONT1 or the MAM groups (all \( P < 0.05 \), both sets of sessions).

More detailed analyses using the pooled data from sessions 1 and 11 (selected at random) provided the same story. While the MAM group was unimpaired, both the ATH and FNX1 groups showed comparable deficits. Precisely the same pattern of results was obtained from sessions 1 and 4 although these are not detailed here [5].
Accuracy measures. For percent correct (Fig. 5) there was both a lesion effect \(F(3, 37) = 5.63, P = 0.003\) and a delay effect \(F(5, 185) = 182.0, P < 0.001\), but there was no significant interaction \(F(15, 185) = 1.423, P = 0.141\). Both the ATH and FNX1 groups, but not the MAM group, were impaired relative to the CONT1 group \((P < 0.01,\) Newman–Keuls procedure). The ATH and FNX1 groups did not differ from each other. A similar pattern of results was found for both A' and SI (the sensitivity index). Thus for A' there was a lesion \(F(3, 37) = 8.8, P < 0.001\) and a delay \(F(5, 185) = 86.74, P < 0.001\) effect. Now, the ATH and FNX1 groups were impaired compared to both the controls (both \(P < 0.001\)) and the MAM group \((P < 0.01\) and \(P < 0.05\), respectively). The SI results also showed that there was a lesion \(F(3, 37) = 7.43, P < 0.001\) and a delay effect \(F(5, 185) = 128.72, P < 0.001\). While both the ATH and FNX1 groups differed from the control scores, only the ATH group differed from the MAM animals \((P < 0.05)\).
Bias indices. Of three bias indicators only Iy yielded clear evidence of differential bias [lesion effect $F(3, 37)=3.99$, $P=0.015$]. Iy, which compares accuracy between the two levers, indicated that with longer delays the FNX1 group were particularly prone to make more of their correct responses on just one lever and that the extent of this bias was greater than that in the CONT1 ($P<0.01$) and ATH ($P<0.05$) groups. There were no group differences for the other two indices $B^*$ and $R_1$ (perceptual and response bias, respectively). Lastly, there were no group differences on any of the measures of general responsivity.

Discussion

A consistent pattern of results was obtained as lesions in the mamillary bodies had no apparent effect on performance of the delayed nonmatching-to-position task, while damage to either the fornix or the anterior thalamic nuclei resulted in comparable deficits. The only
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Evidence of a difference between the fornix and anterior thalamic groups arose from the lever bias measure $I_y$, the fornix animals showing greater bias (i.e. relatively more incorrect responses on a given lever) with increasing retention intervals. The finding that both the fornix and anterior thalamic rats showed normal levels of accuracy (percent correct, $A'$, SI) at the shortest retention interval ('0' sec, which in practice is between 1 and 2 sec delay) and that there were no group differences in the measures of general responsivity, are both consistent with a deficit affecting the ability to identify or remember the position of the lever.

A further clue as to the nature of the lesion deficit concerns the effect of delay. The notion that hippocampal system damage can bring about the faster forgetting of some material has long been prevalent, although recent studies have disputed this view and highlighted the need to have appropriately transformed data [62]. While the group by delay interactions for percent correct, $A'$, and SI were not significant in the present study this is perhaps misleading as all three analyses included the mamillary body group, a set of animals that contributed no relevant information. Reanalysis of the accuracy measures (arcsine transformed) following removal of the mamillary body group now suggested clearer interaction effects (percent correct, $P = 0.029$; SI, $P = 0.078$; $A'$, $P = 0.131$). The combined probability of these three group by delay interactions could also be calculated ($X^2 = 16.22$, $P = 0.013$). While these findings are consistent with a mild delay-dependent effect, i.e. evidence of faster forgetting, it is also apparent that large numbers of subjects may be required before any such effects are clear-cut.

This is not the first study to show that anterior thalamic lesions can mimic some of the effects of fornical damage. Deficits have been found in experiments using rewarded alternation in a T-maze [39] and the Morris maze [73], although in both cases the anterior thalamic deficit was not as severe as that seen after fornix transection. It is also the case that in some studies anterior thalamic lesions have had no apparent effect on spatial tasks known to be sensitive to fornix damage [9, 34]. This range of results can, however, be seen as consistent with the fact that the fornix projects to a range of sites other than the anterior thalamic nuclei and the mamillary bodies. Furthermore, the fornix is also an important source of afferent fibres to the hippocampus. For these reasons one would not always expect the effects of anterior thalamic damage to echo the effects of fornix transection.

The significance of the present results lies in the fact that for at least one spatial task, in which the impact of floor effects can be discounted, the deficits associated with fornix transection and anterior thalamic damage were found to be equivalent. The normal performance of the mamillary body group highlights the important point that the mnemonic functioning of the anterior thalamic nuclei need not depend on its input from the mamillary bodies. The implied significance of the direct hippocampus–fornix–anterior thalamic route has, in turn, obvious relevance for the interpretation of the pathology in anterograde amnesia.

The next study set out to compare the effects of fornix transection with hippocampectomy on the same delayed nonmatching-to-position task. It has been shown that hippocampectomy disrupts delayed nonmatching-to-position [20, 21], but it is not known whether hippocampectomy and fornicoctomy produce similar deficits. This is an important next step as the fornix is only one of several routes by which the hippocampus can directly influence the functioning of other limbic regions and so there may be an array of nonfornical outputs that support delayed nonmatching-to-position. If, however, it is discovered that the effects of these surgeries are equivalent then it will strengthen the significance of the fornix and hence, indirectly, the potential significance of the anterior thalamic nuclei.
EXPERIMENT 2

Comparing the effects of fornix transections and hippocampectomy on delayed nonmatching-to-position by rats

The experimental design and procedure was the same as that for the preceding experiment. The only difference was that the animals were trained and retested with retention delays of 0, 2, 4, 8, 16 and 32 sec for a total of 20 postoperative sessions. The study consisted of 11 rats with aspiration lesions of the hippocampus (HIP), 12 rats with fornix lesions (FNX2), and a surgical control group (CONT2) of 16 rats. Details of the surgical procedures and histological outcomes have been published [4]. Figure 3, which depicts the largest and the smallest of the HIP lesions, illustrates the completeness of the lesions.

Results

The data analyses were very similar to those used in Experiment 1, comparisons now being based on post-operative sessions 10, 15, and 20. Evidence that these were representative sessions comes from Fig. 6 which shows the mean performance of each group over the post-operative period. This figure also highlights the basic finding of the study, that while both the HIP and FNX2 groups were impaired on the DNMP task there was no evidence that these two groups differed from each other.

Fig. 6. Experiment 2. Mean percent correct over each of the 20 postoperative sessions, across all six delays, for the hippocampal (HIP), fimbria/fornix (FNX2), and surgical control (CONT2) groups.

Accuracy measures. For the percent correct scores the group \( F(2, 36) = 7.64, P = 0.002 \), delay \( F(5, 180) = 124.98, P < 0.001 \), and day \( F(2, 72) = 6.99, P = 0.002 \) main factor terms were all significant (Fig. 7). Subsequent analyses indicated that both HIP and FNX2 groups were impaired compared to controls (CONT2), but they did not differ from each other. The group by delay interaction was not significant \( F(10, 180) = 1.58, P = 0.13 \).

The A' measure provided the same pattern of results as the percent corrects with the group \( F(2, 36) = 4.41, P = 0.019 \), delay \( F(5, 180) = 81.26, P < 0.001 \), and day \( F(2, 72) = 8.11, P = 0.001 \) terms all being significant (Fig. 7). Once again, the HIP and FNX2 groups were impaired relative to the CONT2 group, and once again there was no clear group by delay interaction \( F(10, 180) = 1.30 \). A similar pattern of results was obtained with the measure, SI. There were significant main effects for the group \( F(2, 36) = 4.79 \), delay
Fig. 7. Experiment 2. Accuracy measures (percent correct, $A'$, $S_I$) as a function of lesion and delay. Data from postoperative sessions 10, 15, and 20 have been combined. All scores have been converted to read from 0 to 100. Groups as Fig. 6.

$[F(5, 180) = 39.80, P < 0.001]$, and day $[F(2, 72) = 4.11, P = 0.02]$ terms, but for this index there was also a significant lesion by delay interaction $[F(10, 180) = 2.01, P < 0.05]$.

Bias indices. There were no group effects for the index $I_y$, nor were any of the interaction terms significant. There were, however, both delay and day effects (both $P < 0.001$). Exactly the same pattern of results was found for the response bias measure $R$. Analysis of the perceptual bias measure $B''$ did, however, reveal a significant group effect $[F(2, 36) = 9.99, P < 0.001]$. While both the HIP and FNX2 groups showed greater bias than the control subjects, this was most marked in the HIP group.

General responsivity. There were no group differences on any of the measures of general responsivity, i.e. latency to sample, latency to make the first magazine response, choice latency, magazine response rate, number of misses.

Discussion

This second experiment both confirmed that cutting the fornix impairs delayed nonmatching-to-position and indicated that extensive lesions of the hippocampus (including the hippocampus proper, dentate gyrus, and much of the subicular complex) produce a deficit that is both qualitatively and quantitatively similar to fornix transection. It would therefore appear that the hippocampal involvement in this task is dependent on its fornical connections. Furthermore, comparisons with the control animals strongly indicated that neither motor nor other non-specific motivational factors contributed to the impairments in either the hippocampal or the fornix animals.

The general finding, that the effects of fornix transection and hippocampectomy were equivalent, was supported not only by the various measures of accuracy but also by the measures of bias. The only exception was the evidence that while both the hippocampal and fornix animals showed a change in the perceptual bias measure $B''$, this change was greater in the hippocampectomized animals. This, in turn, suggests that both groups were more conservative in their choice, requiring more “signalness” [23] to respond, and that this effect was most marked in the hippocampal group. While there were indications that hippocampal system damage produced delay-related deficits, this was only significant for index $A'$.

Furthermore, calculating the combined probability of the group by delay interactions for all...
three accuracy measures suggested only a mild, but significant, effect \( (X^2 = 13.99, \ P < 0.05) \). Thus the results from both experiments indicate that while damage to the hippocampal system can bring about slightly faster “forgetting”, this is most likely a secondary consequence of the main lesion effect.

Surprisingly few previous studies have directly compared the behavioural effects of fornical and hippocampal lesions in rats. Although there are problems arising from floor effects the weight of evidence indicates that these surgeries produce very similar deficits. Thus caparable studies using the radial-arm maze \([60]\), T-maze alternation \([1, 3]\), the Morris water maze \([55, 56]\), and concurrent discrimination learning \([82]\), all indicate that fornix transection and hippocampectomy can have equally disruptive effects. It can be seen that the present study, which used a variety of retention delays to avoid floor effects, is consistent with this pattern of results.

These results may be compared with those from a number of studies using monkeys. These latter studies, using tasks such as delayed nonmatching-to-sample \([49, 87]\), concurrent discrimination learning \([49, 57, 87]\), and the retention or reversal of object discriminations \([48, 86, 89]\), all indicate that hippocampectomy is more disruptive than fornixotomy. A part of this apparent species difference may reflect the fact that they all relate to nonspatial tests of memory. Support for this comes from evidence that spatial reversal learning is similarly disrupted in monkeys with either hippocampal or fornical damage \([45, 46]\).

A further difference, however, concerns the respective surgeries used in the different species. In the rat the hippocampus is reached by a dorsal approach and it is often possible to produce little additional damage. In the monkey it has been necessary to approach the hippocampus via the ventral temporal lobe. The use of aspiration techniques has meant that many hippocampectomies have also involved adjacent temporal tissue. Recent evidence that damage to this tissue can disrupt visual learning tasks \([28, 58, 89]\), even when no gross pathology is observed in extrahippocampal areas \([28]\), suggest that many of the preceding differences between the effects of hippocampal and fornical lesion in monkeys reflect the involvement of additional cortical damage. It would therefore be predicted that more selective hippocampal lesions in monkeys should produce small impairments on these nonspatial tasks and that the effects of fornixotomy and hippocampectomy would appear more comparable. Evidence that this is indeed the case comes from recent studies into the effects of ischemic and stereotaxic hippocampal damage in monkeys \([72]\). Unfortunately, as the lesions in both studies were only partial this matter remains unresolved at present.

**GENERAL DISCUSSION**

The findings from the two experiments, which used almost identical test procedures, may be combined. These indicate that lesions to the anterior thalamic nuclei, the fornix, and the hippocampus can all produce clear performance deficits on the delayed nonmatching-to-position task. Furthermore, comparisons using the two fornix groups revealed that the severity and nature of the deficits in the three groups was very similar. In contrast, damage to the mamillary bodies had no apparent effect \([5]\). These findings not only underline the importance of the fornix, they also point to a quite different relationship between the anterior thalamic nuclei and the mamillary bodies to that often supposed. That is, the direct projections to the anterior thalamic nuclei from the hippocampus may often play a more critical role than the indirect projections via the mamillary bodies. Whether this is just the case for a specific subset of mnemonic tasks remains to be determined, but as has already
been pointed out, this relationship is consistent with the anatomical connections of the two regions.

The effects of hippocampal system damage may be contrasted with damage to the thalamic nucleus medialis dorsalis. This nucleus is of particular interest as data from a variety of sources have implicated it in diencephalic amnesia [7, 44, 88]. In a recent experiment [59] we examined the effects of neurotoxic medialis dorsalis lesions on the performance of rats that had learnt the delayed nonmatching-to-position task prior to surgery. We also examined the effects of such surgery on delayed nonmatching-to-position acquisition by naive rats. Although the NMDA lesions damaged between 70 and 100% of the nucleus, they had no effect on either acquisition or subsequent performance. This contrast with the effects of fornix damage is further highlighted by a separate study [39] showing that neurotoxic lesions of medialis dorsalis can impair the acquisition of a nonspatial test of working memory (delayed nonmatching-to-sample, Fig. 8). These results provide a double dissociation with the effects of fornix damage as the latter surgery does not impair delayed nonmatching-to-sample acquisition [67]. Indeed, the fornix lesions resulted in a more rapid acquisition of the delayed nonmatching-to-sample task (Fig. 8). The different outcomes of these tests of spatial and nonspatial working memory clearly serve to highlight the qualitatively different contributions of nucleus medialis dorsalis and the fornix to memory processes.

![Fig. 8. Acquisition performance of rats with either fornix (FNX) or medialis dorsalis (MD) lesions on a nonspatial delayed nonmatching-to-sample (DNMS) task (see Refs 1381 and 1651). The scores represent the median number of trials to reach a criterion score of 80% over 50 trials. While animals with MD lesions are impaired, those with fornix lesions show a facilitation of performance (* P<0.05).](image)

If the present findings are to be extended to the primate brain one would expect similar deficits in monkeys with hippocampal system damage. Although the same delayed nonmatching-to-position task has not been used with monkeys, the task does share many features with both "delayed alternation" and "delayed response" tasks. The finding that hippocampectomy usually impairs delayed alternation performance [45, 64] would therefore seem consistent with the present results. But, in contrast, monkeys with hippocampal system damage often appear to perform normally on delayed response tasks [13, 46-48]. Before this is seen as a critical species difference it should be noted that the delayed nonmatching-to-position procedure required the rat to make repetitive nose-pokes on a central panel during the retention period, and so reduce the likelihood of positional strategies that may help solve the task. A comparable control procedure has not been used.
when testing delayed response in monkeys with hippocampal lesions. Furthermore, monkeys are standardly tested with only very short retention delays (often only up to 5 sec) while in the present delayed nonmatching-to-position task rats were tested over much greater delays. On those occasions that hippocampectomized monkeys have been given longer delays more distinct deficits have been observed ([87, 89] but see Ref. [13]). A final anomaly concerns the report that fornixotomy need not affect delayed response in monkeys [89], even with delays of 30 sec. Inspection of this study does, however, reveal that the two monkeys receiving complete fornix transection via a direct neurosurgical approach were markedly impaired, suggesting that fornixotomy can produce performance deficits.

In summary, it has been found that one particular spatial test for working memory, delayed nonmatching-to-position, provides clear evidence that the anterior thalamic nuclei can have an important role in memory. While this role can be closely linked with the fornical inputs to this nucleus, it does not appear to rely on afferents from the mamillary bodies. When this finding is combined with a re-analysis of anatomical and clinical evidence concerning diencephalic amnesia, it can be seen that there is considerable support for the notion that anterior thalamic nucleus dysfunction plays an important role in diencephalic amnesia. It now remains to test this possibility more directly using a wider variety of learning tasks and extending the studies from rats to nonhuman primates.

The present findings also support the notion that medial temporal amnesia and diencephalic amnesia should be regarded as closely related phenomena. This does not, however, mean that they need appear identical: Clearly diencephalic processing must be contributing something new to the incoming limbic information and hence the consequences of selective damage in these two regions may differ. This naturally leads to the final question of what it is that anterior thalamic activity adds to the information relayed from the hippocampus. Very little is presently known about such activity, although studies of avoidance learning by rabbits reinforce the view that it is necessary to consider the anterior thalamic nuclei in the context of both their hippocampal and cingulate connections [24, 25]. These avoidance studies have also led to the proposal that the connections between the anterior thalamic nuclei and the posterior cingulate cortex form part of a mnemonic system that maintains representations of persistent and repeating task events [24, 25]. In contrast, the present delayed nonmatching-to-position studies indicate that the anterior thalamic nuclei are involved in the processing of relatively brief, inconsistent events. Clearly there is a need to resolve these apparent differences and so uncover the contributions of the anterior thalamic–cingulate connections to new learning.

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