THE MAMMILLARY BODIES: TWO MEMORY SYSTEMS IN ONE?

Seralynne D. Vann and John P. Aggleton

Although the mammillary bodies have been implicated in amnesia perhaps for longer than any other single brain region, their role has remained elusive. It is now emerging that the difficulties in understanding the importance of the mammillary bodies for memory might stem from the tradition of treating the mammillary bodies as a single structure with a single function. This review will dissect the mammillary bodies and show how their component nuclei might have multiple functions that, nevertheless, are coordinated to give the impression of a unitary function.

EPISODIC MEMORY The recollection of events in an autobiographical context.

School of Psychology, Cardiff University, PO Box 901, Cardiff CF10 3YG, UK. Correspondence to S.D.V. e-mail: vannsd@cf.ac.uk doi:10.1038/nrn1299 lary bodies is that they might or might not be important for memory. This uncertainty persists even though pathology in this group of nuclei was noted in the amnesic Korsakoff's syndrome as long ago as 1896 (REF. 1), leading to the suggestion by Gamper² of a link between mammillary body pathology and memory loss. Rather than clarifying the situation, the intervening years have only created more uncertainty about the functions of this region. The task of understanding the mammillary bodies is not helped by the different ways in which these nuclei have been grouped and described. Another difficulty is that the term 'Korsakoff's syndrome' is sometimes used as a more general term for organic amnesia^{3,4} rather than for a specific class of amnesia (BOX 1).

One of the few things that is agreed about the mammil-

One agreed fact is that the mammillary bodies comprise several nuclei, each with distinct connections (FIG. 1). In spite of this consensus, attempts to understand the functions of the mammillary bodies have traditionally treated them as a single region. This unitary approach partly reflects the fact that the main nuclei within the mammillary bodies share common connections at the structural level (for example, with the hippocampus and anterior thalamic nuclei). This approach is reinforced by the fact that some investigative techniques do not have the resolution to differentiate between the various nuclei. Given that one of the most informative neuropsychological cases is the result of a snooker cue being pushed up the nostril into the base of the brain⁵, it is perhaps not surprising that anatomical resolution remains a problem.

This review brings together recent findings that show how the functions of these structures can be reinterpreted. The crucial advance is to treat the mammillary nuclei as parts of at least two related systems. Although these two systems have different functions, they can contribute to the same classes of learning. This complementary pattern of action helps to explain why some of the connections of the two systems are duplicated, and why the effects of damage to the two systems can seem similar. It is for the same reason that combined damage to the two systems is additive, giving the impression of a single function.

Perhaps the key advance that forced this reappraisal was the discovery of 'head direction' neurons in the lateral, but not the medial, mammillary nuclei of the rat⁶⁻⁸. The firing properties of these cells signal the direction in which the animal is facing. This discovery not only provides a specific role for one subregion of the mammillary nuclei but also forces a reconsideration of the roles of the remainder of this region. At the same time, new neuropsychological investigations (for example, see REE 9) have provided the strongest evidence yet that the mammillary bodies are important in EPISODIC MEMORY. To understand the impact and likely implications of this new evidence, it is first necessary to understand the anatomical connections of the mammillary bodies.

Box 1 | Korsakoff's syndrome and amnesia

The Russian clinician Sergei Sergeievich Korsakov first described the confusion and amnesia (both retrograde and anterograde) that are associated with nutritional (thiamine) deficiency (1887). This syndrome is most frequent in alcoholics but can have other causes^{119,120}. Wernicke's syndrome (1881) has a similar aetiology but relates to the nystagmus, confusion and ataxia that are sometimes associated with Korsakoff's syndrome. In this review, 'Korsakoff's syndrome' relates only to amnesias that result from nutritional deficiencies.

The pathology in Korsakoff's syndrome always involves the medial mammillary nucleus^{119,121} and sometimes the lateral mammillary nucleus¹²¹. There is almost invariably other pathology in periventricular regions, including the thalamus^{121–124}. The cerebral cortex can also show atrophy¹²⁵, and cortical functional imaging abnormalities might be the norm^{111,126}. Although in rare cases the pathology seems to be restricted to the mammillary bodies^{127,128}, these cases lack a detailed description of other susceptible areas.

mammillary body damage is not sufficient to account for all of the memory deficits that are associated with Korsakoff's syndrome. Severe retrograde amnesia is not seen in patients with mammillary body damage from other causes^{5,106,107}, and the confabulation that is seen in patients probably results from frontal-lobe dysfunction¹²⁹. Further evidence that mammillary body degeneration is not sufficient to induce the anterograde amnesia in Korsakoff's syndrome comes from studies of alcoholics with or without Wernicke's syndrome, in which mammillary body degeneration is sometimes found in the absence of amnesia^{121,130,131}. Such examples have led to differing claims that the best predictor of memory loss is pathology in the anterior thalamic nuclei¹³¹, the medial dorsal thalamic nucleus¹¹¹ or the midline thalamic nuclei^{123,132}. Given the variability in degree and sites of pathology, a careful quantitative analysis of cell loss in Korsakoff's syndrome is required. Using unbiased stereological techniques, Harding et al.¹³¹ compared patients with Korsakoff's syndrome, Wernicke's syndrome and alcoholism. They found that anterior thalamic nucleus pathology was the best predictor of memory loss¹³¹. Medial mammillary pathology was found in both Wernicke and Korsakoff cases, and was not specifically linked with amnesia.

This finding¹²¹ does not rule out a contribution from the mammillary bodies to amnesia, but indicates a primary role for the anterior thalamic nuclei. The most plausible account (see main text) is a threshold model in which partial medial mammillary body degeneration can accentuate the amnesic effects of anterior thalamic degeneration. There is some redundancy because the mammillary bodies project through the anterior thalamic nuclei. Medial dorsal thalamic damage could account for the executive deficits^{9,39} that are found in some cases. It is also assumed that extensive mammillary pathology is sufficient to induce a demonstrable memory loss, which accounts for possible cases with no anterior thalamic pathology^{121,127,133}. A related assumption is that the mammillary body damage in alcoholics and in Wernicke's syndrome (when there is no apparent memory loss) is incomplete¹³⁴. This combined mammillary body–anterior thalamic account might also explain why it has proved difficult to find a consistent relationship between mammillary body volume and memory loss^{130,131,134,135} — the presence of concurrent anterior thalamic pathology will outweigh the mammillary body effects.

Anatomy of the mammillary bodies

The mammillary bodies lie at the posterior margin of the hypothalamus at the base of the brain. Although some authors have included the adjacent supramammillary nucleus and the caudal parts of the tuberomammillary nucleus in the mammillary bodies (for discussion, see REFS 10,11), in accordance with most anatomists we do not. Even so, their proximity means that damage to the mammillary body region often includes these nuclei. For this reason, the type and extent of mammillary body damage is likely to be a crucial issue when attempting to resolve the outcome of different lesion studies. A specific example concerns the supramammillary nucleus. As this nucleus controls the frequency of hippocampal THETA RHYTHM¹², additional supramammillary body' lesions^{13,14}.

THETA RHYTHM Rhythmic neural activity with a frequency of 4–8 Hz.

Anatomists divide the mammalian mammillary bodies into two groups of nuclei — medial and lateral nuclei (FIG. 1). The medial group is larger and is composed of between one and five subnuclei. The number of subnuclei in the medial mammillary nucleus varies between species^{11,15} and between anatomists^{16,17}. Although the lateral mammillary nucleus contains the largest cells in the mammillary bodies, it is a much smaller structure. The volume of the lateral mammillary nucleus relative to the entire mammillary bodies remains relatively constant across many mammalian species: for example, it is 5.8% in the mouse, 6.6% in the rhesus monkey and 6.1% in a human infant¹¹. A third mammillary nucleus, the intercalatus, is sometimes recognized¹⁸, but there is disagreement about its description and status as a distinct nucleus^{10,19}. Intriguingly, some mammals, such as the porpoise (Phocaena phocaena), might have no lateral mammillary nucleus and no clearly differentiated medial mammillary nucleus¹⁵. Such findings have been used as evidence against a role for the mammillary bodies in memory.

Three sets of direct connections dominate mammillary body activity, and all show the same pattern of parallel connections with the lateral and medial mammillary nuclei (FIG. 2). One set (with the hippocampal formation) is only afferent to the mammillary bodies, the second (thalamic) is only efferent from the mammillary bodies, and the third (tegmental) is reciprocal. Dense hippocampal projections from the rostral (septal) subiculum pass through the postcommissural fornix to terminate in the medial mammillary nuclei. Other inputs to the medial mammillary nuclei arise from the medial entorhinal cortex. Parallel projections to the lateral mammillary nucleus arise from the presubiculum, parasubiculum and postsubiculum²⁰⁻²⁶. Another large tract, the mammillothalamic tract (or tract de Vic D'Azyr), emerges from the dorsal aspect of the mammillary bodies to carry fibres to the anterior thalamic nuclei. Whereas the medial mammillary nucleus projects ipsilaterally to the anterior medial and anterior ventral thalamic nuclei, the lateral mammillary nucleus projects bilaterally to the anterior dorsal thalamic nucleus^{27–29}. Finally, the lateral mammillary nuclei have reciprocal connections with the dorsal tegmental nucleus of Gudden, and the medial mammillary body has reciprocal connections with the ventral tegmental nucleus of Gudden^{30–32}. In addition, the medial and lateral mammillary nuclei project to slightly different parts of the reticular tegmental nucleus³³. Both lateral and medial mammillary bodies are also innervated by the supramammillary nuclei, the tuberomammillary nucleus and the septal region²¹. As far as can be determined, this overall pattern of connections, which has been most studied in the rat brain, is also found in the primate brain^{19,34,35}.

A number of key features emerge from this pattern of connections. First, the lateral and medial mammillary nuclei are connected with the same structures, but with different subregions in those structures (FIG. 2). Second, the hippocampus can directly influence

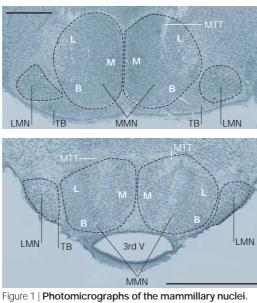


Figure 1 | Photomicrographs of the mammiliary nuclei. Nissl-stained coronal sections showing the mammillary nuclei in the cynomolgus monkey (*Macaca fascicularis*, top) and rat (bottom). The cytoarchitectonic divisions are taken from **REF. 18** for the monkey and **REF. 16** for the rat. 3rd V, third ventricle; B, pars basalis; L, pars lateralis; LMN, lateral mammillary nucleus; M, pars medialis; MMN, medial mammillary nucleus; MTT, mammillothalamic tract; TB, tuberomammillary nucleus. Scale bars, 1 mm.

mammillary body function, but the mammillary bodies can influence the hippocampus only indirectly, through the anterior thalamic nuclei. Third, the anterior thalamic nuclei are a crucial node for mammillary body influence on other brain areas. Fourth, the mammillary bodies are directly linked with brain regions (the hippocampus and anterior thalamic nuclei) that are thought to be vital for episodic memory³⁶. Consistent with this connectivity, damage to the main tracts (the fornix and mammillothalamic tract) that link the mammillary bodies with these structures is also strongly associated with anterograde amnesia^{9,37-39}. These findings are in accord with the notion of a memory system that involves a pathway from the hippocampus through the mammillary bodies to the anterior thalamus⁴⁰. Finally, the dual routes that link the hippocampus to the anterior thalamic nuclei (one direct, the other through the mammillary bodies) mean that lesion studies of mammillary body function might underestimate the importance of the mammillary bodies if the direct hippocampal-anterior thalamic connections can support similar functions.

Experimental mammillary lesions

The paucity of discrete mammillary body pathologies in humans (see later text) has led to animal studies in which selective lesions have been made in the mammillary bodies or the mammillothalamic tract. As the focus has been on memory tasks that relate to hippocampal function, many studies have examined spatial memory. Rodents with lesions of the mammillary bodies or mammillothalamic tract are impaired on tests of spatial alternation in the T-maze⁴¹⁻⁴⁹, spatial working memory in the radialarm maze task⁴⁹⁻⁵¹, reference memory in the MORRIS WATER MAZE⁵² (but see REF. 53) and working memory in the water maze^{49,53}. Monkeys with mammillary body lesions are also impaired on tests of spatial memory^{54,55}.

Attempts to explain these lesion-induced deficits have focused on evidence of increased susceptibility to proactive interference^{42,56}, increased sensitivity to retention intervals^{44,50,57} or impoverished spatial encoding⁴⁹. These three accounts are not mutually exclusive, as poor encoding could lead to increased disruption by delays or interference. Nevertheless, there are clear examples in which mammillary body lesions have had no apparent effect when interference levels were increased^{49,58,59} or when retention delays were extended^{49,53,58,59}. So, a general account based on interference or retention is not supported. For these reasons, the pattern of spatial deficits that is associated with mammillary body damage in rats can best be characterized as a failure of rapid Allocentric encoding⁴⁹ — that is, an impaired ability to learn a specific location within a cognitive map. This results in deficits being most evident at the initial stages of learning and most persistent when the animal is performing a spatial working memory task in which one-trial learning is at a premium and other (non-allocentric) spatial strategies are precluded^{49,53,60}. Consistent with this account, mammillary body lesions spare certain classes of spatial task, including conditional learning, in which an object is associated with a specific direction of body turn or location^{57,61}, and matching- or non-matching-to-position for levers in an automated apparatus^{58,59}. In these examples of sparing, the animals can gradually acquire a fixed spatial response^{57,61} or can use non-allocentric cues⁵⁸.

In view of the connections of the mammillary bodies, the deficits that arise from mammillary body lesions are assumed to reflect a disruption of the hippocampal projections to the anterior thalamus that pass through the mammillary bodies. Consistent with this view, lesions in each of these three structures can impair spatial memory tasks³⁶. However, spatial deficits after mammillary body damage are not as severe as those found after hippocampectomy⁶² and are typically less severe than those associated with anterior thalamic damage^{42,46,58}. Associated with this difference in severity is the impression that the effects of mammillary body lesions diminish with training^{42,49,60,63}. Although some of this recovery might reflect the inreasing use of alternate spatial strategies^{49,60}, it could also reflect the gradual recruitment of the direct pathway from the hippocampus to the anterior thalamic nuclei, so bypassing the mammillary bodies. At the same time, studies of the effects of lesions to the mammillothalamic tract have helped to confirm the normal importance of these pathways for spatial memory tasks in the rat^{45,48,49}.

The importance of the indirect route from the hippocampus to the anterior thalamic nuclei through the mammillary bodies is likely to be task dependent, so that for some classes of learning (when the mammillary body route is not replaceable) mammillary body and anterior thalamic lesions will have similar effects. Examples of this come from studies using an automated 'object-in-place'

MORRIS WATER MAZE A learning task in which an animal is placed in a pool filled with opaque water and has to learn to escape to a hidden platform that is placed at a constant position. The animal must learn to use distal cues, and the spatial relationship between them and the platform. Learning in this task involves the hippocampus.

ALLOCENTRIC Distal cues that provide geometric reference to current location.

REVIEWS

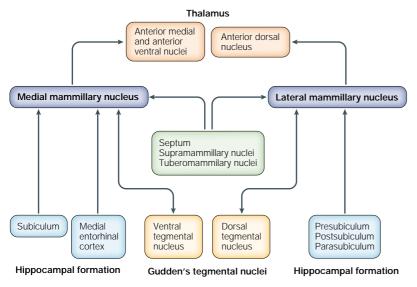


Figure 2 | Schematic figure of main direct connections of the lateral mammillary nucleus and the medial mammillary nucleus.

task⁶⁴, which tests scene discriminations. In the monkey, lesions in the fornix, mammillary bodies and anterior thalamic nuclei produced equivalent deficits on this visual task^{64,65}, which is thought to tax attributes of episodic memory. Similarly, lesions of the fornix, anterior thalamus and mammillary bodies in rats produced equivalent, abnormal processing of visual scenes in which the integration of object and place information is required⁴⁶. Surprisingly, all three lesions enhanced performance on this test of scene discrimination, a result that was interpreted as a failure to process all objects in a scene concurrently. These changes on tests of scene discrimination are again consistent with an encoding deficit. Finally, more evidence of a visual scene learning deficit comes from the finding that mammillothalamic tract lesions impair the initial acquisition of a visual contextual discrimination but spare the learning of a formally identical discrimination using thermal stimuli⁶³

An important limitation of these behavioural studies is that they do not distinguish between the contributions of different parts of the mammillary bodies. Although some conventional lesion studies have been more confined to the medial rather than the lateral mammillary nuclei (for example, see REFS 45,66), damage to the mammillothalamic tract will disconnect both nuclei. At present, there are no behavioural studies in which lesions have been confined to either the medial or lateral mammillary bodies. For this degree of anatomical resolution we have to turn to electrophysiological studies, in which the effects of lesions that are confined to the lateral mammillary nuclei have been studied.

Head direction cells

Head direction cells aid navigation by firing selectively when an animal is facing in a specific direction in the horizontal plane⁶⁷. Electrophysiological studies have found head direction cells not only in the lateral mammillary nucleus^{6–8} but also in a number of sites

directly connected with it (FIG. 3) — the anterior dorsal thalamic nucleus⁶⁸, the dorsal tegmental nucleus of Gudden⁶⁹ and the postsubiculum⁶⁷. The integrity of the lateral mammillary nucleus is necessary for the directional firing of the head direction cells in the anterior dorsal thalamic nucleus^{6,7}. The discovery that bilateral, but not unilateral, lesions of the lateral mammillary nuclei are required to abolish anterior thalamic head direction sensitivity⁷ is in accord with the bilateral projection from the lateral mammillary nucleus to the anterior dorsal nucleus. Consistent with this lesion finding, head direction signals in the lateral mammillary nucleus precede the signal in the anterior thalamus^{6,8}, again indicating that the lateral mammillary signal helps to drive the thalamic signal. As an indirect consequence of this, the lateral mammillary nuclei might have a pivotal role in the head direction circuit, as cells in the anterior dorsal nucleus are themselves necessary for the directional firing of head direction cells in the hippocampal formation (postsubiculum)⁷⁰. Therefore, damage to the lateral mammillary nuclei could affect head direction cells in both the anterior thalamic nuclei (directly) and the postsubiculum (indirectly). By contrast, lesions of the postsubiculum71 and the hippocampus⁷² do not affect head direction cells in the anterior thalamic nuclei, and so presumably also spare the mammillary signal.

The lateral mammillary nucleus, in conjunction with the dorsal tegmental nucleus of Gudden, is probably particularly important for transforming vestibular information to help signal head direction⁷³. Although vestibular information might not be crucial in generating head direction signals, its removal can abolish the directional sensitivity of head direction cells in the anterior thalamic nuclei⁷⁴. It is therefore assumed that the loss of this vestibular information accounts for the dependence of anterior thalamic head direction cells on lateral mammillary inputs. The lateral mammillary nucleus also contains cells that are sensitive to head pitch and to angular head velocity⁸ (FIG. 3), again implying a role in the integration of vestibular information. These cells are not, however, under the total control of vestibular information, as their head direction sensitivity can be influenced by visual stimuli⁸.

These electrophysiological findings raise the question of whether the loss of this head direction information is sufficient to account for all of the spatial learning deficits that follow typical mammillary body lesions (lesions of both the lateral and medial nuclei). This is a realistic question, given the correlative evidence that head direction information can help to guide spatial behaviour in the radial-arm maze⁷⁵ (but see REF. 76). Furthermore, there is evidence that head direction information and place information are closely coupled^{77,78}. The answer to this question remains unknown, as the appropriate lesion experiments have not been conducted. An example would be to test whether selective lateral mammillary nuclei lesions, which abolish the anterior thalamic head direction signal, are sufficient to induce spatial deficits comparable to those observed after complete mammillary body lesions. Nevertheless, inferences can

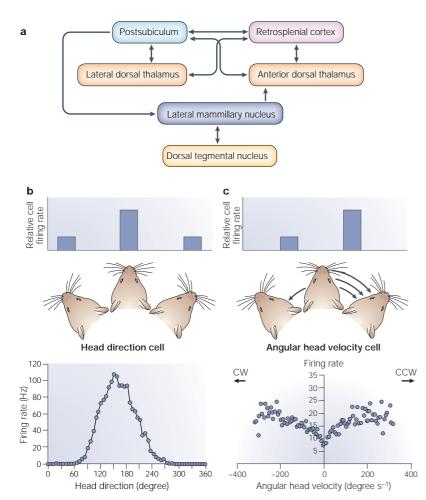


Figure 3 | The lateral mammillary nucleus and head direction information. a | Regions in the rodent brain that are involved in the head direction network. b | Recordings from a head direction cell in the lateral mammillary nucleus (data taken from REF.8). c | Recording from an angular velocity cell in the lateral mammillary nucleus (data taken from REF.136). This cell has a symmetrical firing pattern so that firing rates positively correlate with the velocity of head movement in both clockwise (CCW) and counterclockwise (CCW) directions.

be made from looking at the effects of selective lesions in the anterior thalamic nuclei, to which the lateral and medial mammillary nuclei have different patterns of projection (FIG. 2).

LONG-TERM POTENTIATION (LTP). An enduring increase in the amplitude of excitatory postsynaptic potentials as a result of high-frequency (tetanic) stimulation of afferent pathways. It is measured both as the amplitude of excitatory postsynaptic potentials and as the magnitude of the postsynaptic cell population spike. LTP is most often studied in the hippocampus and is often considered to be the cellular basis of learning and memory in vertebrates

Selective lesions involving the anterior dorsal thalamic nucleus^{79–82}, to which the lateral mammillary nucleus projects, produce impairments on spatial memory tasks in the radial-arm maze⁸⁰, T-maze⁷⁹ and water maze⁸¹. However, these deficits are less severe than those seen after lesions of the entire anterior thalamus⁷⁹⁻⁸¹. This additive effect indicates that the head direction system might not account for the entire deficit in animals with anterior thalamic lesions. In view of the dense inputs from the medial mammillary nucleus to the anterior medial and anterior ventral thalamic nuclei, it is likely that these parallel inputs also support spatial learning, and so explain the additive effects of different lesions in the anterior thalamic nuclei⁷⁹⁻⁸¹. Alternatively, the additional effects of these complete thalamic lesions might reflect direct interactions with the hippocampus.

Medial mammillary body and theta rhythm

Just as the dorsal tegmental. lateral mammillary and anterior dorsal thalamic nuclei form a system that relays one kind of information (head direction), so a parallel set of connections relays a different kind of signal theta activity. Theta activity refers to the regular burstfiring of cells which, en masse, can give rise to theta rhythm. Hippocampal theta rhythm has provoked particular interest, owing to its possible relationship with aspects of memory, including spatial processing in both rodents and primates^{83,84}. Recordings made in the medial mammillary nucleus reveal neurons that fire rhythmically in phase with hippocampal theta^{85,86}. These theta-related cells in the mammillary bodies seem to be driven by descending projections from the hippocampus (FIG. 4), and are especially correlated with the CA1 theta generators⁸⁷. The supramammillary nucleus has almost the opposite relationship as it helps to control the rhythmicity of hippocampal theta. Consistent with this difference, septal inactivation eliminates theta activity in the mammillary bodies but not in the adjacent supramammillary nucleus⁸⁸. For these reasons, the mammillary bodies are seen as relayers of hippocampal theta rhythm to the anterior thalamic nuclei and beyond.

Consistent with this view, electrophysiological studies in rats have found theta rhythm in the anterior thalamic nuclei⁸⁹. The cells that show theta discharge profiles are concentrated in the anterior ventral nucleus, to which the medial mammillary nucleus projects. Approximately 75% of the cells in the anterior ventral nucleus are thought to fire rhythmically in synchrony with hippocampal theta rhythm⁹⁰. Single units showing theta activity are also present in the tegmentum⁹¹, which is connected to the medial mammillary nucleus. Whereas the distinction between the medial and lateral mammillary nuclei, and their principal connections, seems almost complete for head direction cells, the same is not true for theta-related cells. So, the medial mammillary nucleus and the anterior ventral thalamic nucleus contain most theta-related cells, but a few are found in the lateral mammillary nucleus^{80,92} and the anterior dorsal thalamic nucleus⁸⁹.

As noted above, interest in theta has been boosted by its possible links with memory. For example, LONG-TERM POTENTIATION (LTP) in the hippocampus can best be elicited by stimulation at theta frequency⁹³. Furthermore, stimulation given on the positive phase of theta potentiates population responses in the hippocampus. It has therefore been proposed that theta rhythm acts as a 'significance signal', so that information arriving with theta activity is most likely to be stored⁹³. These findings can be linked to more specific theories of theta rhythm and its transmission around the diencephalon. One intriguing proposal is that the relaying of theta by the mammillary bodies might reduce interference by helping to separate encoding and retrieval⁹⁴. This would predict that mammillary body damage would increase proactive interference, a proposal that receives partial support⁹⁵ (but see REFS 49,58).

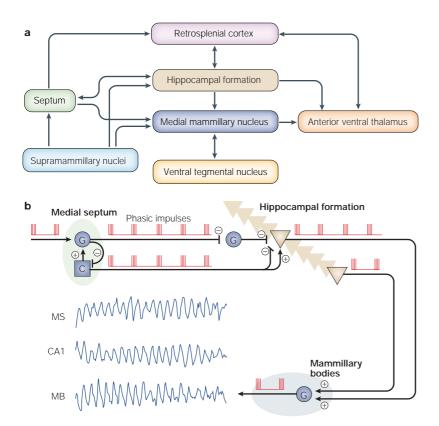


Figure 4 | **The medial mammillary nucleus and theta rhythm. a** | Some of the regions in the rodent brain that contain theta-responsive cells and their connections with respect to the medial mammillary nucleus. **b** | Some of the circuitry connecting the medial septum (MS) and hippocampus (CA1 field) to the mammillary bodies (MB) and its likely involvement in the generation of rhythmic theta activity. Phasic impulses enter the medial septum, which contains GABA (γ-aminobutyric acid) neurons (G) and cholinergic neurons (C). These inputs provide inhibitory (flat) and excitatory (arrow) connections to the hippocampal formation, which then relays phasic activity to the mammillary bodies. Note that the cholinergic cells, although they can fire in a phasic pattern, probably provide a mainly tonic input. Waveforms (blue traces) are concurrent phasic activity. The amplitudes of the three traces vary relative to each other, indicating that although the circuit shown controls the phasic pattern of firing in each structure, other influences determine how many cells in each structure are recruited to the phasic pattern. Figure provided by N. McNaughton, based on unpublished data supplied by L. Nerad.

To test whether the loss of the mammillary theta relay has a disruptive effect on learning, we need to turn to the outcome of selective lesions of the medial mammillary nuclei. Unfortunately, it is only possible to infer such lesion effects by examining the outcome of selective anterior thalamic lesions, with the caveat that the anterior thalamic nuclei have direct reciprocal connections with the hippocampus. Lesions centred on the anterior medial thalamic nucleus that do not involve the anterior dorsal nucleus produce mild deficits on tests of spatial working memory in the T-maze and radial-arm maze^{79,80}. Consistent with these findings, water-maze deficits were larger in rats with complete anterior thalamic lesions than in rats with combined anterior dorsal and anterior ventral lesions⁸¹. This indirect evidence supports the notion of a medial mammillary-anterior thalamic pathway that contributes to spatial learning, but does not provide definitive proof.

Clinical studies of normal memory

The focus up to this point has been on the distinctions between two mammillary body systems. Although clinical data on the effects of damage to this region do not permit this distinction, it is possible to address the question of whether the entire mammillary bodies are necessary for normal memory in humans and, if so, for which forms of memory they are needed.

Some of the most important information has come from a bizarre accident in which subject B.J. had a snooker cue pushed up his left nostril⁵. This resulted in bilateral damage to his mammillary bodies and some additional damage to adjacent hypothalamic nuclei and the pituitary (FIG. 5). The supramammillary nuclei and mammillothalamic tract might also have been involved^{5,96}. Although his other cognitive abilities remain intact, B.J. suffers a marked anterograde amnesia. His immediate recall of verbal and non-verbal material often seems normal, but his delayed recall of the same material is impaired⁹⁶. The latter problem is reflected in his low Delayed Memory Index score of 56 from the Wechsler Memory Scale-Revised (WMS-R). By contrast, B.J. performs within normal limits on many tests of recognition^{96,97}.

This pattern of memory loss can be compared with the more severe deficits found in Korsakoff's syndrome (BOX 1). These are typified by much poorer performance on the Wechsler General Memory Index⁹⁸, along with much more severe impairments of recognition memory⁹⁹. Finally, B.J.'s performance on tests of retrograde amnesia is largely intact, in contrast to that of patients with Korsakoff's syndrome⁹⁶.

Although B.J. is thankfully unique, there is a similar second case - N.A, who had a miniature fencing foil pushed up his right nostril¹⁰⁰. This resulted in bilateral loss of the mammillary bodies, along with more dorsal damage in the left thalamus¹⁰¹. The pattern of memory loss of N.A. is similar to that of B.J.⁵. Furthermore, consistent evidence has come from cases with tumours in the mammillary body region^{102,103}. A patient described by Tanaka et al.¹⁰³ developed moderate anterograde amnesia after tumour-associated damage to the region of the mammillary bodies. Like B.J., this patient was impaired for both verbal and non-verbal material, with delayed recall being most impaired (WMS-R Delayed Memory score 59). Another case¹⁰² had small, atrophic mammillary bodies but also some loss to the anterior pole of the temporal lobes. This patient again showed a selective impairment in memory, with recall being appreciably more affected than recognition¹⁰². Formal tests revealed that the patient was impaired on judgments of source and context¹⁰².

The restricted projection pattern from the mammillary bodies to the anterior thalamic nuclei means that if the mammillary bodies are vital for episodic memory then both the mammillothalamic tract and anterior thalamic nuclei will also be necessary. Analyses of the cognitive status of people who have suffered thalamic infarcts reveals that the best predictor of anterograde amnesia is pathology in the mammillothalamic tract, although in no case is the pathology confined to the tract^{9,39,104}.

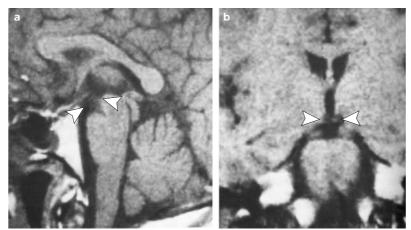


Figure 5 | Magnetic resonance scans showing the absence of the mammillary bodies in patient B.J. a | Sagittal scan. b | Coronal scan. Arrows, normal position of the mammillary bodies. Reproduced, with permission, from REF. 5 @ (1990) Oxford University Press.

Similarly, the prediction that anterior thalamic damage is sufficient to produce amnesia can not be confirmed, although there are occasional amnesic cases with damage centred on this region¹⁰⁵. Further evidence that additional diencephalic damage might be required to produce full amnesia comes from two cases with lesions to the mammillary bodies arising from surprasellar tumours¹⁰⁶. Magnetic resonance imaging (MRI) scans revealed that the mammillary bodies were obliterated by the tumours, but left only slight thalamic disruption¹⁰⁶. On many standard tests of learning, both cases performed well, and mild to moderate recall impairments only became evident on some subtests. Recognition was largely unaffected. The conclusion was that mammillary body damage can disrupt memory but is not sufficient to induce amnesia98.

Although the degree of memory impairment varies between cases, the overall pattern is remarkably consistent. The mammillary bodies are often necessary for normal episodic information, with deficits most evident after increased retention intervals. The severity of the memory loss is often less than that associated with other amnesic conditions (BOX 1) and this might reflect, in part, the sparing of the direct hippocampal-anterior thalamic link. Memories from before the injury96,106,107 and recognition memory^{96,102} are relatively spared. This sparing of recognition (see also REF. 108) supports dual-process models of recognition, which predict that selective damage to the hippocampal-mammillary body-anterior thalamic circuit will spare familiarity-based recognition but impair recall-based recognition³⁶. It is tempting to speculate as to whether the variations in the severity of the memory loss associated with mammillary body damage reflect the extent of total damage to the two putative (medial and lateral mammillary) systems. The problem is that in all of the above cases the lesion descriptions, which rely on MRI information, imply that all of the structure has been damaged. Furthermore, mammillothalamic tract damage will disconnect both the medial and lateral mammillary bodies. Other factors might include the extent of supramammillary involvement. It can only be hoped that future descriptions of the pathology in similar cases will make it possible to consider these factors.

Why does diencephalic amnesia exist?

This analysis of the mammillary bodies provides strong clues as to why diencephalic anterograde amnesia exists and to the relationship of this amnesia with temporallobe amnesia. If it is assumed that medial temporal-lobe amnesia and diencephalic amnesia are not independent, then there are at least two explanations for the causes of diencephalic amnesia. First, structures in the diencephalon contribute in a vital way to mnemonic processing through their direct and indirect projections to the medial temporal lobe. Second, damage to specific sites in the diencephalon disconnects interconnections between the temporal lobe and some other site such as the frontal lobe¹⁰⁹. A third possibility is that damage to key sites in the diencephalon results in widespread dysfunction in cortical regions, thereby disrupting memory^{110,111}. This disruptive action could be independent of the medial temporal lobe. In the case of the mammillary bodies, the evidence points most strongly to the first of these three possibilities (they contribute in a vital way to mnemonic processing through their direct and indirect projections to the temporal lobe). Indirect support comes from the discovery that anterior thalamic damage disrupts normal hippocampal activity^{112,113}. Similarly, a positron emission tomography study of the amnesic B.J. showed hippocampal hypoactivity in the hemisphere that received the largest amount of mammillary body damage⁹⁶. However, these three possibilities are not mutually exclusive and all could contribute to the final spectrum of diencephalic memory disorders, depending on the site and extent of pathology. Indeed, the evidence that mammillary body damage best reflects the first of these possibilities might explain why the amnesia associated with damage in this structure is often more selective than that found in other forms of diencephalic amnesia.

For the mammillary bodies, two contributions to memory have been proposed. The first concerns the formation of head direction signals. For this function it is thought that the lateral mammillary nucleus acts indirectly on the postsubiculum of the hippocampal formation⁶⁷. An obvious issue to be resolved is the question of how a signal that seems to be for navigation can become important for episodic memory. This has been addressed by a number of people who have pointed out that episodic memory is comprised of events that occur in a specific temporal and spatial context¹¹⁴. So, a process that aids the encoding or retrieval of context should be central to episodic memory. If head direction information and place information are closely coupled^{77,78,115}, then it is relatively easy to envisage how head direction signals could contribute to the formation of contextual scenes. Set against this view is evidence that damage to the anterior thalamic part of the head direction signal does not alter the stability of hippocampal place cells, although there is an increase in signal noise¹¹⁶. A slightly different idea is that the retrieval of spatial information, and therefore spatial episodes, requires the setting of a particular viewpoint¹¹⁷. This task requires

DIENCEPHALIC ANTEROGRADE AMNESIA Impaired learning of new declarative information following pathology in the medial thalamic or hypothalamic regions. the representation of head direction and, so, input from the head direction system. It is proposed that through interactions in the parietal cortex and retrosplenial cortex, information about current head direction makes it possible to translate allocentric representations into egocentric ones and vice versa¹¹⁷. This, in turn, could help the separation of distinctive episodes of information. One piece of evidence that is consistent with this general view is the finding that mammillary body damage can relatively spare recognition^{5,102}, a largely context-free form of information. A more direct test would be to examine the performance of patients with mammillary body damage on route-learning or spatial-memory tasks. The only spatial task that has been reported was a visual location task with patient B.J.⁹⁶. In this task, the participant is required to identify those items in a picture that had changed location. B.J. was significantly impaired on this task⁹⁰, a result that is consistent with a spatial-encoding deficit.

The medial mammillary nucleus is thought to be most crucial for the second of the two mnemonic roles, the relaying of theta. However, this role is assumed to depend on inputs from the hippocampus. This raises the question of whether the medial mammillary nucleus is merely a link in a chain of connections, ensuring the effective relaying of theta to other limbic sites, or whether the mammillary bodies add something unique to the processing of this signal. A potential problem with the idea of a chain of connections is that the outputs from the mammillary bodies are relayed by the anterior thalamic nuclei, which have their own hippocampal inputs, so making the mammillary bodies redundant. For this reason, there is a need to examine the second description — that the mammillary bodies add to the processing of the theta signal in a way that is independent of the hippocampus.

Concluding remarks

This review has emphasized the anatomical, electrophysiological and functional diversity within the mammillary bodies. At the same time it is assumed that the medial and lateral mammillary systems function in a synergistic way, as reflected by their common connections with the hippocampus, tegmentum and anterior thalamus. This cooperative activity raises the question of where the functions of these two systems might interact. Anatomically, the most plausible candidate regions are the retrosplenial cortex and the hippocampal formation, although this has not been formally examined. There is, in addition, the functional question of why head direction information and theta might have a special relationship. The answer to this presumably lies in the hippocampus, as so many of the effects of mammillary body damage mimic those of hippocampal damage, but to a lesser degree. One possibility concerns the rapid creation of distinct, separate spatial scenes.

It should finally be added that this review has described two parallel systems, but this might not be the limit. In particular, the projections from the medial mammillary nucleus to the anterior medial thalamic nuclei might need to be considered separately. This is because the anterior medial thalamic nucleus stands out from the rest of the anterior thalamic nuclei by virtue of its stronger connections with the anterior cingulate cortex and prefrontal cortex, and its lack of theta-related cells. In view of the high degree of topography in the mammillary body — anterior thalamic projections¹¹⁸ and the cytoarchitectonic variation within the medial mammillary nucleus — it is possible that an additional set of mammillary body functions remain to be uncovered

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Competing interests statement

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