

Re-evaluating the role of the mammillary bodies in memory

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ABSTRACT

Although the mammillary bodies were among the first brain regions to be implicated in amnesia, the functional importance of this structure for memory has been questioned over the intervening years. Recent patient studies have, however, re-established the mammillary bodies, and their projections to the anterior thalamus via the mammillothalamic tract, as being crucial for recollective memory. Complementary animal research has also made substantial advances in recent years by determining the electrophysiological, neurochemical, anatomical and functional properties of the mammillary bodies. Mammillary body and mammillothalamic tract lesions in rats impair performance on a number of spatial memory tasks and these deficits are consistent with impoverished spatial encoding. The mammillary bodies have traditionally been considered a hippocampal relay which is consistent with the equivalent deficits seen following lesions of the mammillary bodies or their major efferents, the mammillothalamic tract. However, recent findings suggest that the mammillary bodies may have a role in memory that is independent of their hippocampal formation afferents; instead, the ventral tegmental nucleus of Gudden could be providing critical mammillary body inputs needed to support mnemonic processes. Finally, it is now apparent that the medial and lateral mammillary nuclei should be considered separately and initial research indicates that the medial mammillary nucleus is predominantly responsible for the spatial memory deficits following mammillary body lesions in rats.

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1. Introduction

The mammillary bodies have a number of features that single them out as prime targets for research into episodic memory in humans and episodic-like memory in rodents. The first is historical: it is over one hundred years since Gudden (1896) first noted mammillary body atrophy in cases of memory loss, making it arguably the very first brain region implicated in amnesia. Despite this fact, remarkably little research has been conducted on this structure over the intervening years. The second feature is anatomical: the mammillary bodies comprise just two major nuclear groups (medial and lateral), with a limited array of cell types in each. The third is connective: the mammillary bodies have major connections with a limited number of structures. These connections are largely via major fiber tracts (i.e. postcommissural fornix, mammillothalamic tract, mammillotegmental tract, mammillary peduncle), making it possible to make selective disconnections of mammillary body inputs and outputs. The presence of mammillary body atrophy in a number of conditions, including Korsakoff's syndrome (Kopelman, 1995; Victor, Adams, & Collins, 1989), colloid cysts in the third ventricle (Denby et al., 2009), Alzheimer's disease

(Callen, Black, Gao, Caldwell, & Szalai, 2001; Copenhagen et al., 2006; Grossi, Lopez, & Martinez, 1989), schizophrenia (Bernstein et al., 2007; Briess, Cotter, Doshi, & Everall, 1998), heart failure (Kumar et al., 2009), and sleep apnea (Kumar et al., 2008), emphasizes the growing need to clarify the functional importance of this structure.

Until recently, uncertainty regarding the importance of the mammillary bodies for human memory held back research into this region. Most obviously, neuropathological studies of Korsakoff's syndrome, one of the most common causes of amnesia, had failed to establish the extent to which mammillary body atrophy contributes to the memory loss in this condition (Harding, Halliday, Caine, & Kril, 2000; Kopelman, 1995; Vann & Aggleton, 2004; Victor et al., 1989). This uncertain picture has changed dramatically in recent years. One key discovery was that damage to the mammillothalamic tract provides the sole, consistent predictor of whether a thalamic stroke will cause anterograde amnesia (Carlesimo et al., 2007; Clarke et al., 1994; Graff-Radford, Tranel, Van Hoesen, & Brandt, 1990; Van der Werf, Jolles, Witter, & Uylings, 2003; Van der Werf, Scheltens, et al., 2003; Van der Werf, Witter, Uylings, & Jolles, 2000; von Cramon, Hebel, & Schuri, 1985; Yoneoka et al., 2004). The mammillothalamic tract is a major fiber tract formed by the unidirectional projections that arise from every mammillary body neuron to terminate in the anterior thalamus (Guillery, 1955; Vann, Saunders, & Aggleton, 2007). While it is most likely

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that damage to other medial diencephalic sites contributes to diencephalic amnesia (e.g. intralaminar nuclei/medial dorsal nucleus), the pathway from the mammillary bodies to the anterior thalamus seems to be of paramount importance. More recently, a study of patients who had undergone surgery for the removal of colloid cysts revealed the mammillary bodies to be the only site consistently linked to recollective memory impairments (Tsivilis et al., 2008; Vann et al., 2009). Patients, who were matched on all factors other than the degree of mammillary body atrophy, differed significantly on measures of recollection but not familiarity-based recognition (Tsivilis et al., 2008; Vann et al., 2009), consistent with some dual-process models of memory (e.g. Aggleton & Brown, 1999). While all these patient studies have implicated the mammillary bodies in human cognitive processes, pathology outside of the mammillary bodies and possible co-existing etiologies might limit any definitive interpretations. Due to the size and position of the mammillary bodies, current functional imaging techniques are unsuitable for investigating this structure in healthy controls. These limitations in human mammillary body research make animal models all the more valuable.

At present, most accounts describing the role of the mammillary bodies in memory emphasize the importance of the hippocampal inputs to the region; indeed the mammillary bodies are often referred to as part of an “extended hippocampal system” (Aggleton & Brown, 1999; Delay & Brion, 1969; Gaffan, 1992; Gaffan, 2001). Remarkably, the mammillary bodies appear to lack interneurons (Veazey, Amaral, & Cowan, 1982b) and every mammillary neuron is thought to project to the thalamus (e.g. Guillery, 1955; Vann et al., 2007); properties that have reinforced the idea of the structure simply acting as a relay. Within this extended hippocampal system, the proposed functional importance of the mammillary bodies and mammillothalamic tract is to relay hippocampal inputs to the anterior thalamic nuclei and from there to the cingulate cortex (Barbizet, 1963; Delay & Brion, 1969) or the prefrontal cortex (Warrington & Weiskrantz, 1982). Memory impairments following mammillary body lesions would, therefore, reflect the disconnection of either the cingulate cortex or prefrontal cortex from these hippocampal inputs. An alternative model combines these two accounts of mammillary body function by proposing that diencephalic damage causes widespread cortical dysfunction, again due to a loss of hippocampal inputs, and this is responsible for subsequent memory impairment (Mair, Warrington, & Weiskrantz, 1979; Paller, 1997; Vann & Aggleton, 2004). However, because the hippocampus projects directly to the anterior thalamic nuclei (Aggleton, Desimone, & Mishkin, 1986; Poletti & Creswell, 1977), prefrontal cortex (Jay, Glowinski, & Thierry, 1989) and cingulate cortex (Meibach & Siegel, 1977b), it must be assumed that the hippocampal formation–mammillary body projections are providing unique information or these indirect pathways would seem redundant; this is possible as the majority of the hippocampal formation efferents arise from different populations of cells within the subicular complex and CA1 (Aggleton, Vann, & Saunders, 2005; Jay et al., 1989; Namura, Takada, Kikuchi, & Mizuno, 1994; Saunders, Mishkin, & Aggleton, 2005; Witter, Groenewegen, Lopes da Silva, & Lohman, 1989).

The similarity in mammillary body structure and connections across species make animal studies of this brain region particularly relevant. However, the size and/or type of mammillary body lesions in some studies have made it, on occasion, difficult to interpret lesion effects. For example, electrolytic or radiofrequency lesions (e.g. Harper, McLean, & Dalrymple-Alford, 1994; Santin, Rubio, Begega, & Arias, 1999; Saravis, Sziklas, & Petrides, 1990; Sharp & Koester, 2008a, 2008b; Sziklas & Petrides, 1993; Tonkiss & Rawlins, 1992) will also damage the large number of fiber tracts in the vicinity of the mammillary bodies (Nauta & Haymaker, 1969). If the lesions are too large they will encroach

upon adjacent structures, most likely the supramammillary nuclei which are situated immediately dorsal to the mammillary bodies (e.g. Saravis et al., 1990; Sharp & Koester, 2008a, 2008b; Sziklas & Petrides, 1998). As the supramammillary nuclei have been implicated in hippocampal theta and may also contribute to spatial memory (e.g. Aranda, Santin, Begega, Aguirre, & Arias, 2006; Pan & McNaughton, 1997, 2002, 2004; Vann, Brown, & Aggleton, 2000), additional damage to this structure makes the subsequent interpretation of mammillary body lesion effects problematic. Finally, if insufficient detail is given regarding the size and location of the lesions (e.g. Sharp & Koester, 2008a, 2008b) and the extent of disconnection following mammillothalamic tract lesions is not determined (e.g. Sharp & Koester, 2008a, 2008b; Vann & Aggleton, 2003; Vann, Honey, & Aggleton, 2003) it becomes increasingly difficult to attribute subsequent effects or lack of effects with any confidence. These issues highlight the need to make the best use of animal models by making discrete lesions, determining the extent of any fiber disconnections, and providing sufficient detail regarding the extent of pathology. Despite some of these limitations, animal studies have been invaluable in advancing our knowledge about the mammillary bodies. In the following sections the anatomical, electrophysiological, and functional properties of the mammillary bodies, as revealed by these studies, will be detailed. Current models of mammillary body function will then be re-evaluated in light of more recent findings.

2. Anatomy

The mammillary bodies comprise two main nuclei: medial and lateral. The medial mammillary nucleus is the larger of the two nuclei with the lateral mammillary nuclei accounting for about 6% of the entire structure across species (Guillery, 1955; Rose, 1939). The medial mammillary nucleus has been divided further into between one and six subregions depending on species and anatomist (Allen & Hopkins, 1988; Rose, 1939). However, the most commonly used distinctions across species are pars lateralis, pars medialis, and pars basalis (Fig. 1). While the medial and lateral mammillary nuclei differ in terms of their cell morphology, within each nucleus there appears to be only one cell type (Cajal, 1911; Veazey et al., 1982b). The neurons in the lateral mammillary nucleus are much larger than the very small neurons found in the pars lateralis of the medial nucleus and the intermediate size cells in pars medialis (see Fig. 1). Interestingly, all mammillary body cells appear to be projection cells (Powell & Cowan, 1954; Takeuchi, Allen, & Hopkins, 1985) with no apparent interneurons (Veazey et al., 1982b).

The mammillary bodies have major connections with only a limited number of structures (Fig. 2). The principal mammillary body inputs are from the hippocampal formation (via the post-commissural fornix) and from the tegmental nuclei of Gudden (via the mammillary peduncle). Their main outputs are to the anterior thalamic nuclei (via the mammillothalamic tract) and to the tegmental nuclei of Gudden (via the mammillotegmental tract); some of these projections arise from collateral axons (Hayakawa & Zyo, 1989). The lateral and medial mammillary nuclei are connected to the same overall structures but different subregions within those structures, thus forming two parallel systems (Vann & Aggleton, 2004). With regards to the hippocampal formation afferents, the medial mammillary nucleus receives inputs from the dorsal, ventral and intermediate subiculum and medial entorhinal cortex while the lateral mammillary nucleus is innervated by projections from the presubiculum, postsubiculum, and parasubiculum (Allen & Hopkins, 1989; Meibach & Siegel, 1977a; Shibata, 1988; Swanson & Cowan, 1977; Van Groen & Wyss, 1990). In terms of the anterior thalamic projections, the medial mammil-

lary nuclei project unilaterally to the anterior medial and anterior ventral thalamic nuclei whereas the lateral mammillary nuclei project bilaterally to the anterodorsal thalamic nuclei (Cruce, 1975; Seki & Zyo, 1984; Vann et al., 2007). The medial mammillary

nucleus has reciprocal connections with the ventral tegmental nucleus of Gudden and the lateral mammillary nucleus has reciprocal connections with the dorsal tegmental nucleus of Gudden (Cruce, 1977; Hayakawa & Zyo, 1984, 1985, 1989; Veazey, Amaral, & Cowan, 1982a). Both medial and lateral mammillary nuclei are innervated by the supramammillary nucleus, the tuberomammillary nucleus and the septal region (Cajal, 1911; Fry & Cowan, 1972; Gonzalo-Ruiz, Alonso, Sanz, & Llinas, 1992a; Hayakawa & Zyo, 1989; Shibata, 1989) and both medial and lateral mammillary nuclei project to separate but adjacent parts of the nucleus reticularis tegmenti ponti and pontine nuclei (Cruce, 1977; Takeuchi et al., 1985); these projections are of interest as they provide a mechanism for the mammillary bodies to influence visual and vestibular processes (Allen & Hopkins, 1990; Hopkins, 2005). The prefrontal cortex appears to be the only region where the parallel lateral and mammillary connections are not upheld as the prefrontal cortex projects solely to the medial mammillary nucleus (Allen & Hopkins, 1989).

Although the mammillary bodies receive both excitatory and inhibitory inputs, their major outputs appear to be solely excitatory. The mammillary bodies receive excitatory inputs from the hippocampal formation; these projection use either glutamate or aspartate (Storm-Mathisen & Woxen Opsahl, 1978) as well as neurotensin (Kiyama et al., 1986; Sakamoto et al., 1986). The inputs from the prefrontal cortex are also excitatory (Allen & Hopkins, 1989). The projections from the tegmental nuclei are inhibitory, using GABA and leu-enkephalin (Allen & Hopkins, 1989; Gonzalo-Ruiz, Romero, Sanz, & Morte, 1999; Gonzalo-Ruiz, Sanz-Anquela, & Spencer, 1993; Hayakawa & Zyo, 1991; Wirtshafter & Stratford, 1993). The mammillary bodies also receive a dopaminergic input from the nearby supramammillary nuclei (Gonzalo-Ruiz, Alonso, Sanz, & Llinas, 1992b). The mammillary body efferents to both the tegmental nuclei and the anterior thalamic nuclei are excitatory (Allen & Hopkins, 1990; Gonzalo-Ruiz, Morte, & Sanz, 1998). The projections to the anterior thalamic nuclei use glutamate, aspartate (Gonzalo-Ruiz et al., 1998), enkephalins (Fujii, Senba, Kiyama, Ueda, & Tohyama, 1987; Gonzalo-Ruiz et al., 1998) and cholecystokinin (Kiyama et al., 1984).

3. Electrophysiology

Consistent with their different anatomical properties and connections, the lateral and medial mammillary nuclei also have very different electrophysiological properties which have been assessed both *in vitro* and *in vivo*. Recent electrophysiological discoveries have been extremely instrumental in developing models of mammillary body function.

3.1. *In vitro*

Using an *in vitro* slice preparation, Alonso and Llinas found neurons in the medial mammillary nucleus that have intrinsic pacemaker properties and these are mediated by calcium-dependent mechanisms (Alonso & Llinas, 1992). Although there only appears to be one cell type within the medial mammillary nucleus (Cajal, 1911; Veazey et al., 1982b), there are several electrophysiologically distinct cell populations within this structure which differ in terms of their spike burst generation. The lateral mammillary neurons are also able to switch from tonic repetitive firing to a low threshold-bursting pattern and, as with the medial mammillary neurons, this response is calcium-dependent (Llinas & Alonso, 1992). Unlike the cells in the medial mammillary nuclei, the lateral mammillary neurons appear electrophysiologically homogenous (Llinas & Alonso, 1992).

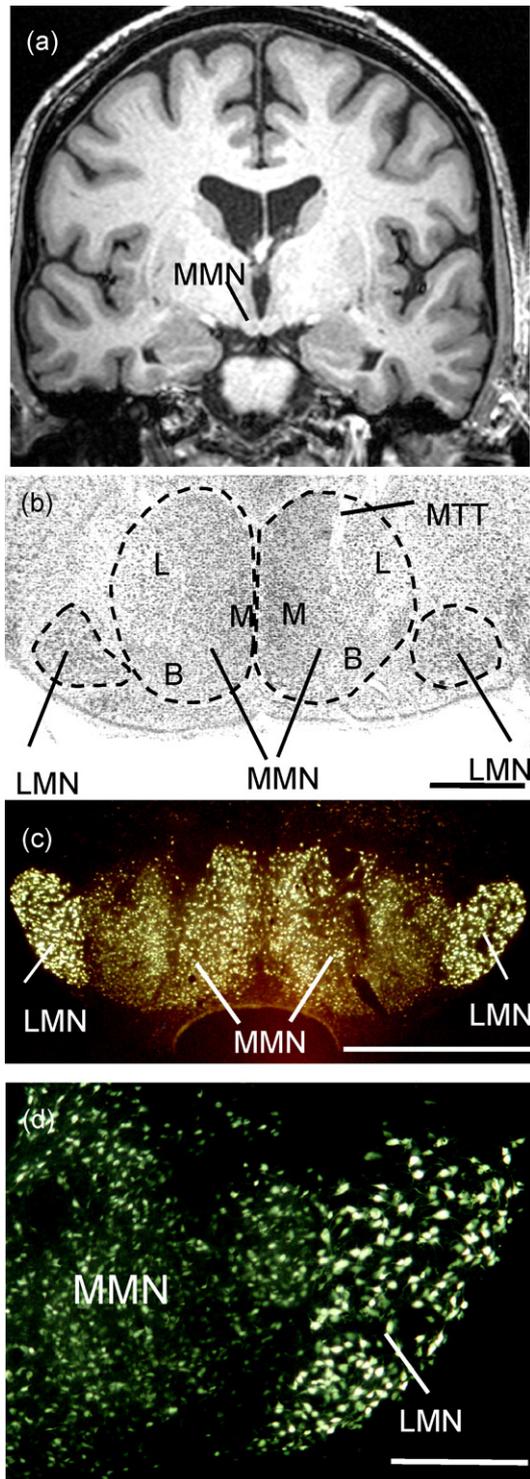


Fig. 1. a. Magnetic resonance scan showing human mammillary bodies in the coronal plane. b. Nissl-stained coronal section showing the mammillary nuclei in the cynomolgus monkey (*Macaca fascicularis*). c. Coronal section showing mammillary nuclei in the rat (Fluorogold). d. High-power photomicrograph showing lateral mammillary nucleus and pars lateralis of the medial mammillary nucleus. B, pars basalis, L, pars lateralis, LMN, lateral mammillary nucleus; M, pars medialis; MMN, medial mammillary nucleus; MTT, mammillothalamic tract. Scale bar for b and c, 1 mm; Scale bar for d, 0.25 mm.

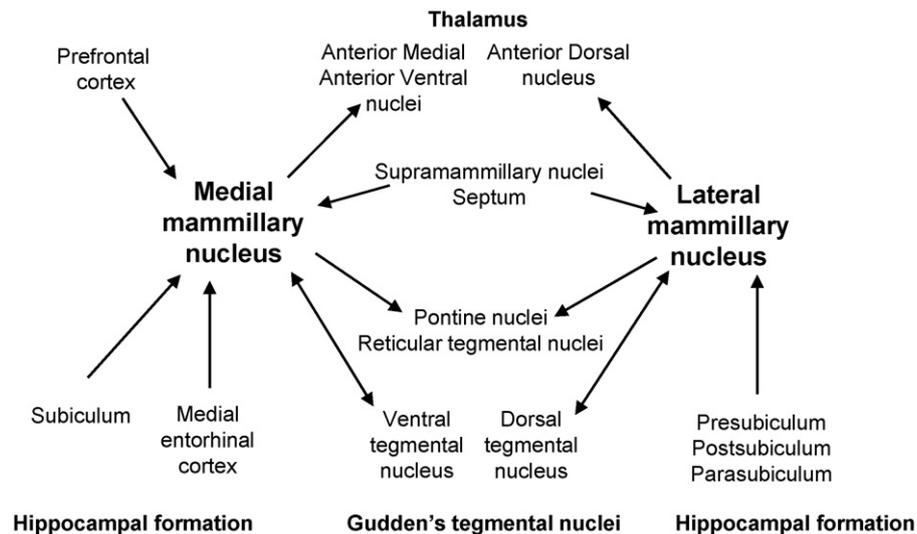


Fig. 2. The main direct connections of the medial and lateral mammillary nuclei.

3.2. *In vivo*

3.2.1. *Lateral mammillary nucleus*

Both head-direction cells and angular velocity cells have been reported in the lateral mammillary nucleus (Blair, Cho, & Sharp, 1998; Stackman & Taube, 1998). Head-direction cells and angular velocity cells fire differentially depending on the rat's head-direction (Taube, Muller, & Ranck, 1990) or velocity of head movements (Stackman & Taube, 1998), respectively. The lateral mammillary nuclei are connected with a number of other head-direction regions and they are instrumental in the generation and maintenance of the head-direction signal throughout the head-direction circuit. The lateral mammillary nucleus requires the inputs from dorsal tegmental nucleus of Gudden to generate the head-direction signal (Bassett, Tullman, & Taube, 2007). In turn, the head-direction signal in both the anterodorsal thalamic nucleus (Bassett et al., 2007) and postsubiculum (Sharp & Koester, 2008b) are dependent on the integrity of the lateral mammillary nuclei. While there are cells that show theta discharge profiles in the lateral mammillary nuclei, these cells only account for a small proportion of the total cell numbers in this structure (Blair et al., 1998; Stackman & Taube, 1998).

3.2.2. *Medial mammillary nucleus*

While there are no head-direction cells in the medial mammillary nucleus, approximately one third of cells respond to angular head velocity (Sharp & Turner-Williams, 2005). However, unlike the angular head velocity cells in the lateral mammillary nuclei, which fire irrespective of the direction in which the animal's head is turning (Stackman & Taube, 1998), the cells in the medial mammillary nuclei fire differentially for clockwise and anticlockwise movements (Sharp & Turner-Williams, 2005). In addition, over half of the cells in the medial mammillary nucleus correlate with running speed, such that their firing rate increases with greater running velocity (Sharp & Turner-Williams, 2005). Finally, nearly all cells in the medial mammillary nucleus modulate their firing rate at a frequency of theta (Bland, Konopacki, Kirk, Oddie, & Dickson, 1995; Kirk, 1998; Kirk, Oddie, Konopacki, & Bland, 1996; Kocsis & Vertes, 1994; Sharp & Turner-Williams, 2005). The current view is that medial mammillary nucleus theta is driven by the CA1 field of the hippocampus as theta-related cells in the medial mammillary nuclei show a strong correlation with CA1 theta (Kocsis & Vertes, 1994). In addition, septal procaine infusion that attenuates hip-

poampal theta also attenuates medial mammillary body theta thus providing further evidence that medial mammillary body theta is driven by descending projections from the septo-hippocampal system (Kirk et al., 1996). One proposal is that the medial mammillary bodies act as a relay of hippocampal theta, passing it along the diencephalon and back to the hippocampus, thus forming a re-entrant loop which is necessary for successful encoding (Kirk & Mackay, 2003).

More recently, the ventral tegmental nucleus of Gudden has been linked to mammillary body theta. As described earlier, the medial mammillary nucleus has reciprocal connections with the ventral tegmental nucleus of Gudden, and all cells in this structure fire rhythmically and highly coherently with hippocampal theta (Kocsis, Di Prisco, & Vertes, 2001). One account is that the ventral tegmental nucleus of Gudden moderates the hippocampal-driven rhythmic firing in the medial mammillary (Kocsis et al., 2001; Vertes, Hoover, & Viana Di Prisco, 2004). A more radical account is that the Gudden's ventral tegmental nucleus is a generator of hippocampal theta as rhythmic-bursting recordings from this tegmental nucleus occur 1 or 2 s prior to the onset of hippocampal theta (Bassant & Poindessous-Jazat, 2001). In addition, Gudden's ventral tegmental nucleus recordings show similar properties to the rhythmic discharges seen in the medial septum/diagonal band (Apartis, Poindessous-Jazat, Lamour, & Bassant, 1998). However, lesions of the supramammillary nuclei, which may also involve the mammillary bodies or mammillothalamic tract, can disrupt some aspects of hippocampal theta but do not eliminate it completely (Sharp & Koester, 2008a; Thinschmidt, Kinney, & Kocsis, 1995). As Gudden's ventral tegmental nucleus would presumably act on hippocampal theta via the mammillary bodies and/or supramammillary nuclei, it seems unlikely that this tegmental nucleus generates hippocampal theta, although it could act as a modulator.

Finally, the projections from the mammillary bodies to the anterior thalamic nuclei are necessary for the excitatory training-induced activity in the anteroventral thalamic nucleus that occurs when rabbits learn a conditional avoidance discrimination (Gabriel et al., 1995). Not only are the mammillary body projections to the anterior thalamic nuclei necessary for these behavior-induced changes in anteroventral nucleus activity, but they are also needed for the spontaneous baseline unit activity normally seen in the anteroventral thalamic nucleus (Gabriel et al., 1995). This finding demonstrates the importance of mammillary body efferents for normal anterior thalamic function.

4. Behavioral lesion studies

4.1. Rodents

As current models of mammillary body function emphasize their hippocampal formation inputs, the majority of behavioral lesion studies in rodents have focused on spatial memory. Mammillary body lesions, in both mice and rats, disrupt performance on reinforced and spontaneous T-maze alternation (Aggleton, Neave, Nagle, & Hunt, 1995; Beracochea & Jaffard, 1987,1990; Gaffan, Bannerman, Warburton, & Aggleton, 2001; Rosenstock, Field, & Greene, 1977; Vann & Aggleton, 2003). Impairments are found both during the standard task, where animals are given a separate sample and test trial, and also during continuous alternation which increases task demands (Aggleton et al., 1995; Field, Rosenstock, King, & Greene, 1978; Vann & Aggleton, 2003). Lesions of the main mammillary body efferents, the mammillothalamic tract and mammillotegmental tract, also disrupt T-maze performance (Field et al., 1978; Vann & Aggleton, 2003).

Tasks in the water-maze have also been used to assess the importance of the mammillary bodies for allocentric spatial memory. These tasks prevent the use of intra-maze cues, such as odor trails, which can in some instances mask impairments. For the reference memory task in the water-maze, the platform remains in the same place in the water-maze throughout testing thus resulting in very low levels of proactive interference. Sutherland and Rodriguez found rats with mammillary body lesions to be slower at learning a platform position, although this impairment disappeared with training (Sutherland & Rodriguez, 1989). However, a later study reported no effect of mammillary body lesions on the reference memory task (Santin et al., 1999). The working memory task (delayed matching-to-place) in the water-maze differs in that the platform is in a different position during each session so that animals have to rapidly learn the new spatial location within a session. Mammillary body lesions reliably produce robust, long-lasting impairments on the working memory task in the water-maze (Santin et al., 1999; Vann & Aggleton, 2003). In addition, lesions of the mammillary bodies or mammillothalamic tract produce equivalent impairments on this task (Vann & Aggleton, 2003). The size of impairment on these spatial memory tasks appears to be dependent on prior experience as pre-surgical training can improve performance on reinforced alternation (Rosenstock et al., 1977) and the reference memory task in the water-maze (Sutherland & Rodriguez, 1989).

Another widely used paradigm to assess spatial memory is the radial-arm-maze task. The “working memory” version of this task requires animals to enter all arms to retrieve a reward, such as a sugar pellet; to do this most effectively animals should not re-enter previously entered arms. Animals, therefore, have to keep track of the arms they have entered within a session. Rats with mammillary body lesions and mammillothalamic tract lesions are impaired on this task (Jarrard, Okaichi, Steward, & Goldschmidt, 1984; Neave, Nagle, & Aggleton, 1997; Sziklas & Petrides, 1993; Vann & Aggleton, 2003) and this impairment reflects the ineffective use of distal allocentric cues (Vann & Aggleton, 2003). Using a modified task in the radial-arm-maze, designed to assess memory for “lists”, mammillary body lesions disrupt both the primacy and recency effects shown by normal animals on this task (Harper, Dalrymple-Alford, & McLean, 1993). In contrast to the frequently reported spatial memory impairments, mammillary body lesions in rats do not affect object recognition (Aggleton et al., 1995), again consistent with some dual-models of recognition memory (e.g. Aggleton & Brown, 1999) and findings from patient studies (Kapur et al., 1994; Tsivilis et al., 2008; Vann et al., 2009).

The standard tasks in the T-maze, water-maze and radial-arm-maze require animals to use distal spatial cues to navigate

in the environment; however, mammillary body lesion effects are not restricted to tasks that involve navigation. Mammillary body lesions facilitate rats' performance on a visual discrimination task where animals are required to discriminate simultaneously between two scenes that contain different combinations of the same objects and positions (Gaffan et al., 2001). Mammillary body lesions also facilitate performance when animals are required to discriminate between familiar and less familiar objects, and familiar and less familiar object-position compounds, but have no effect when animals are required to discriminate familiar positions from less familiar positions (Gaffan et al., 2001). A possible explanation put forward for this facilitation was that animals with mammillary body lesions were less likely to process the whole scene and instead process one object at a time which would give them an advantage on certain trial types (Gaffan et al., 2001). Mammillothalamic tract lesions in rats impair acquisition of a visuo-spatial but not non-spatial conditional discrimination task in an operant box (Vann et al., 2003). For this task, animals have to respond differentially to stimuli (light/sound) depending on which visual-spatial context (spotted/striped walls) or non-spatial context (hot/cold) they are in, in order to receive a reward. A similar contextual impairment was found in mice with mammillary body lesions; they were impaired on contextual fear conditioning, but not auditory conditioning, in a comparable manner to dorsal hippocampal lesions (Celerier, Pierard, & Beracochea, 2004). Mice were presented with an auditory cue (conditioned stimulus) followed by a shock (unconditioned stimulus) in a conditioning chamber. Mammillary body lesioned mice exhibited the freezing response when given the conditioned stimulus in a neutral environment but not when placed back in the previously experienced conditioning chamber, that is, they responded to the auditory cue but not the context (Celerier et al., 2004). Finally, mammillothalamic tracts lesions in rabbits impair the acquisition of a discriminative avoidance task where animals have to learn to step into a wheel on hearing one tone to avoid a shock whilst ignoring a different tone which does not predict a shock (Gabriel et al., 1995).

Although mammillothalamic tract lesions impair visuo-spatial contextual discrimination (Vann et al., 2003), mammillary body lesions do not affect all conditional tasks. For example, mammillary body lesions do not affect the acquisition of a visuo-spatial conditional associative learning task where animals have to acquire associations between visual stimuli and spatial locations (Sziklas & Petrides, 1993; Sziklas, Petrides, & Leri, 1996). The lack of impairment on these tasks could be due to animals requiring extensive training in order to acquire the task. In the Vann et al. study (2003), the mammillothalamic tract impairment was only found in the very first stages of training such that any deficits on the conditional associative task could be masked by slow acquisition (Sziklas & Petrides, 1993).

One of the first theories of mammillary body function was that they form part of a circuit that underlies emotion (MacLean, 1949; Papez, 1937). There continues to be support for this theory and it has been proposed that emotional disturbances, resulting from mammillary body pathology, may contribute to subsequent memory impairments (Beracochea, 2005). Mice with mammillary body lesions spend more time in the open arms of an elevated plus than control animals suggesting that mammillary body lesions reduce anxiety levels (Beracochea & Krazem, 1991). In addition, mammillary body lesions increase the rate of responding during the punished, but not unpunished, period in a continuous reinforcement conflict schedule (Shibata, Kataoka, Yamashita, & Ueki, 1986). A similar effect was found when benzodiazepines were injected directly into the mammillary bodies (Kataoka, Shibata, Gomita, & Ueki, 1982) suggesting that in both manipulations the animals were less affected by aversive stimuli; this effect appears to be moderated by noradrenaline (Kataoka, Shibata, Yamashita, &

Ueki, 1987). It is possible that the anxiolytic effects of mammillary body lesions are due to the high density of benzodiazepine receptors in this structure (Young & Kuhar, 1980). A proposal put forward by Beracochea (2005) is that animals with mammillary body lesions are less anxious and, therefore, less emotionally aroused; this results in the animals processing relevant stimuli less well. This proposal is consistent with pharmacological studies that have shown that administering a benzodiazepine receptor inverse agonist to mice with mammillary body lesions increases fear reactivity (so that they now behave similarly to controls) and reverses observed memory impairments on an alternation task (Beracochea, Krazem, & Jaffard, 1995). In addition, administering diazepam reduces neuronal activity in the mammillary bodies as measured by glucose utilization (Ableitner, Wuster, & Herz, 1985). However, mammillary body lesions do not disrupt the acquisition of all emotion-related learning as they do not impair conditioned taste aversion (Sziklas & Petrides, 1993) or basic fear-avoidance (e.g. Celerier et al., 2004).

Finally, there is some evidence that the mammillary bodies are important for temporal processing in addition to spatial processing. Tonkiss and Rawlins (1992) showed that mammillary body lesions impair performance on tasks that require animals to delay their response to a stimulus for a minimum time (DRL tasks). DRL tasks are hippocampal-dependent (Clark & Isaacson, 1965; Sinden, Rawlins, Gray, & Jarrard, 1986) and the ability to delay a response is disrupted in amnesics (Oscar-Berman, Zola-Morgan, Oberg, & Bonner, 1982) and monkeys with hippocampal lesions (Jackson & Gergen, 1970). However, it is possible that deficits observed on DRL tasks could reflect impairments in either temporal judgment or response inhibition.

4.2. Medial vs lateral mammillary body lesions

Lesions of the mammillary bodies typically involve the medial mammillary nuclei more than the lateral mammillary nuclei (e.g. Beracochea & Jaffard, 1987, 1995; Field et al., 1978; Rosenstock et al., 1977; Santin et al., 1999; Sziklas & Petrides, 1993). In addition, discrete lesions of the mammillothalamic tract can selectively disconnect medial mammillary nucleus efferents (Vann & Aggleton, 2003, 2004) and it is the medial mammillary nucleus that is always affected in Korsakoff syndrome (Kopelman, 1995; Victor et al., 1989). While it is, therefore, apparent that the medial mammillary nucleus is implicated in memory, the importance of the lateral mammillary nucleus is less clear. There are very few studies that have assessed lesions restricted to the lateral mammillary nuclei and there is only one study that has assessed the behavioral effects of these lesions (Vann, 2005). This study found that rats with lesions restricted to the lateral mammillary nuclei were unimpaired on a spatial alternation task in the T-maze which is sensitive to complete mammillary body lesions (Vann & Aggleton, 2003). While the lateral mammillary nucleus lesions impaired performance on the working memory task in the water-maze this effect was only transient (Vann, 2005) unlike the robust deficits seen following mammillary body and mammillothalamic tract lesions (Vann & Aggleton, 2003). From these findings, it is evident that the loss of lateral mammillary nuclei cannot account for all the effects seen following complete mammillary nucleus lesions. In addition, it would appear that spatial memory impairments seen following mammillary body lesions cannot simply be explained in terms of loss of head-direction information.

4.3. Non-human primates

To date, the majority of mammillary body lesion studies have been carried out on rodents with very few studies in monkeys; this is in part due to the size and position of the mammillary

body lesions in primates which make them a difficult target for surgery. However, from the few studies that are available, the impairments across species appear consistent. Mammillary body lesions in monkeys leave recognition memory intact while affecting performance on a spatial discrimination task (Aggleton & Mishkin, 1985). Similarly, Holmes et al. reported a mammillary body lesion induced impairment on spatial reversal learning but not object reversal learning (Holmes, Jacobson, Stein, & Butters, 1983). Finally, mammillary body lesions impair monkeys ability to learn new object-in-place scenes; the mammillary body lesion effects were comparable to those seen following fornix lesions (Parker & Gaffan, 1997b).

4.4. Accounts of mammillary body lesion deficits

Several explanations have been put forward to explain the memory deficits resulting from mammillary body lesions: increased sensitivity to proactive interference, that is, difficulty in separating events (Aggleton et al., 1995; Beracochea & Jaffard, 1990; Jaffard, Beracochea, & Cho, 1991); increased rate of forgetting (Beracochea & Jaffard, 1987; Rosenstock et al., 1977; Saravis et al., 1990; Sziklas & Petrides, 1998; Tako, Beracochea, & Jaffard, 1988); impaired encoding (Butters, 1985; Vann & Aggleton, 2003; Vann et al., 2003); impaired retrieval (Lhermitte & Signoret, 1972; Warrington & Weiskrantz, 1974); and impaired emotion-memory interactions (Beracochea, 2005). These explanations are not, however, mutually exclusive. While there is evidence supporting each of these accounts, there are cases where animals with mammillary body lesion are not differentially affected by increased interference (Aggleton, Keith, & Sahgal, 1991; Harper et al., 1994; Vann & Aggleton, 2003) or increased retention delays (Aggleton et al., 1991; Harper et al., 1994; Santin et al., 1999; Vann & Aggleton, 2003). These findings make it difficult to provide a simple explanation based on interference or retention. Instead, mammillary body lesion effects are most consistent with impaired rapid allocentric encoding, such that deficits are most clearly seen during initial stages of learning or when animals have to perform a spatial working memory tasks that preclude the use of non-allocentric spatial strategies. This interpretation would account for deficits on tasks such as the working memory task in the water-maze and would explain the lack of impairment on certain spatial conditioning tasks. There is also evidence that mammillary body lesion deficits reflect impaired retrieval processes. For example, Beracochea et al., have shown that the performance of mice with mammillary body damage on T-maze alternation can be improved by changing the context within a T-maze during the test trial (Beracochea, Lescaudron, Tako, Verna, & Jaffard, 1987; Tako et al., 1988). They suggest that changing the context increases arousal levels in the animal which facilitates retrieval processes (Beracochea & Jaffard, 1987; Tako et al., 1988). In addition, rats trained on the DRL procedure and subsequently given a mammillary body lesion became less efficient on the task, although their performance was superior to rats given mammillary body lesions before any DRL training (Tonkiss & Rawlins, 1992). However, this decline in DRL performance following mammillary body lesions may reflect a decreased ability to inhibit responses rather than a retrieval deficit *per se*. Finally, as described earlier, mammillary body lesions have been reported to have an anxiolytic effect so Beracochea (2005) proposed that mammillary body lesions result in animals being less emotionally aroused; this reduced arousal would result in animals processing relevant stimuli less well which would affect subsequent memory (Beracochea, 2005). It is unlikely that mammillary body lesion effects reflect the disruption of a single process, instead, the mammillary bodies may contribute to several processes required to support memory and this may be dependent on specific task demands and output targets.

4.5. Animal models of Korsakoff's syndrome

Animal models of Korsakoff's syndrome have provided further insights into mammillary body function. These animal models are the result of either chronically administered ethanol or treatment with the thiamine antagonist, pyriethamine. In the same way as patients with Korsakoff's syndrome, the pathology in the pyriethamine-induced thiamine deficiency (PTD) rat model is diffuse and, in addition to diencephalic damage, there is widespread cortical and thalamic damage as well as damage to major white matter tracts including the corpus callosum and internal capsule (Langlais, Mandel, & Mair, 1992). Rats and cats treated with pyriethamine are impaired on spatial alternation (Irle & Markowitsch, 1982; Mair, Anderson, Langlais, & McEntee, 1985) and the reference memory task in the water-maze (Langlais et al., 1992). Pyriethamine-induced thiamine deficiency in rats also disrupts hippocampal and cortical acetylcholine and noradrenalin levels (Mair et al., 1985; Pires, Pereira, Oliveira-Silva, Franco, & Ribeiro, 2005; Roland & Savage, 2007; Savage, Chang, & Gold, 2003). In addition, chronic administration of alcohol in mice produces medial mammillary atrophy and impairs spatial memory (Tako, Beracochea, Lescaudron, & Jaffard, 1991). The spatial memory impairments and hippocampal dysfunction reported in these Korsakoff models are consistent with the effects of more discrete mammillary body or mammillothalamic tract lesions. Therefore, despite the additional pathology in these models, the pattern of deficits is likely to be attributable, in the most part, to the medial diencephalic atrophy.

4.6. Functional gene imaging in normal animals

There are very few studies that have used functional gene imaging to assess specific contributions of the mammillary bodies. This is partly due to very low levels of expression of the immediate-early genes *c-fos* and *zif268* in the mammillary bodies, both at baseline and following appetitive learning tasks (e.g. Amin, Pearce, Brown, & Aggleton, 2006; Jenkins, Amin, Brown, & Aggleton, 2006; Vann, Brown, & Aggleton, 2000; Vann, Brown, Erichsen, & Aggleton, 2000). In one study, where changes in *c-Fos* levels could be assessed, the authors reported increases in immediate-early gene expression in the lateral, but not medial, mammillary nucleus in animals that had undergone contextual and auditory fear conditioning (Conejo, Gonzalez-Pardo, Lopez, Cantora, & Arias, 2007). An earlier study used 2-deoxyglucose as a marker of activity and found increased metabolic activity in the mammillary bodies of monkeys that performed a spatial working memory task compared to monkeys that performed a control task (Friedman, Janas, & Goldman-Rakic, 1990).

4.7. Distal effects of mammillary body lesions

As traditional theories consider the mammillary bodies to form part of a hippocampal relay, it would be expected that disconnecting this relay would affect distal brain sites. Consistent with this prediction, the integrity of the mammillary bodies appears to be essential for the normal functioning of other key structures implicated in memory. For example, retrosplenial and hippocampal hypoactivity are regularly seen in Korsakoff's syndrome patients (Caulo et al., 2005; Joyce et al., 1994; Reed et al., 2003). Reduced hippocampal activity was also reported in patient BJ; this patient suffered mammillary damage following an intranasal penetration injury and, therefore, had more restricted pathology than that seen in Korsakoff's syndrome (Kapur et al., 1994). These findings are consistent with the distal hypoactivity seen in animal models of diencephalic amnesia. Mammillary body lesions in mice disrupt cholinergic activity, as measured by sodium-dependent high affini-

ty choline uptake, in both the hippocampus and frontal cortex; this reduction in cholinergic levels is found irrespective of whether animals were taken from the home-cage or actively exploring a maze (Beracochea et al., 1995b). Similar results were found in rats with mammillothalamic tract lesions which selectively disrupted the efferents from the medial mammillary nucleus to the anterior thalamic nuclei (Vann & Albasser, 2009). These lesions resulted in hypoactivity, as measured by the immediate-early gene *c-fos*, in the hippocampus, retrosplenial cortex and prefrontal cortex (Vann & Albasser, 2009). In this way, mammillothalamic tract damage has selective, indirect effects upon multiple regions thought to be critical for the encoding and recall of episodic memory. In the past there have been problems dissociating involvement of the frontal lobe in diencephalic amnesia as additional damage to the mediodorsal thalamus would result in a loss of frontal projections and direct damage to the frontal cortex can occur in cases of Korsakoff's syndrome. This immediate-early gene study shows that prelimbic dysfunction can occur in a model of diencephalic amnesia without direct deafferentation or damage (Vann & Albasser, 2009).

5. Lesions of major mammillary body afferents and efferents

5.1. Mammillary body, anterior thalamic and fornix lesions

Traditional models of mammillary body function emphasize the fornix–mammillary body–thalamic system. As mammillothalamic tract lesions produce largely equivalent effects to mammillary body lesions (e.g. Vann & Aggleton, 2003) it appears that the mammillary bodies exert their role on spatial memory via their projections to the anterior thalamic nuclei. Within the mammillary bodies' role as a relay the comparative effects of mammillary body, anterior thalamic and fornix lesions become particularly relevant. When anterior thalamic lesions produce greater effects than mammillary body lesion effects, it is presumed that the direct projections from the subicular complex to the anterior thalamic nuclei are sufficient to support this task, although this would not preclude an additional contribution from the mammillary body projections in normal animals.

There are occasions where mammillary body lesions have had no effect on tasks that are sensitive to either anterior thalamic, hippocampal or fornix lesions. For example, mammillary body lesions do not affect performance on an automated delayed non-matching-to-position task, where animals are required to select the lever in the choice stage that was not presented in the sample phase (Aggleton et al., 1991; Harper et al., 1994), despite this task being sensitive to both fornix and anterior thalamic nuclei lesions (Aggleton et al., 1991; Harper et al., 1994). In addition, while mammillary body lesions disrupt the acquisition of the reference memory task in the water-maze, animals were able to learn the platform position and perform normally on a probe trial (Sutherland & Rodriguez, 1989); this is in contrast to rats with either anterior thalamic nuclei or fornix lesions where they were impaired throughout training and on the probe trial (Sutherland & Rodriguez, 1989). Mammillary body lesions are also less disruptive on the standard T-maze task than anterior thalamic or fornix lesions (Aggleton et al., 1995; Gaffan et al., 2001). Finally, mammillary body lesions do not disrupt performance on a task that requires animals to form associations between visual stimuli and spatial locations (Sziklas & Petrides, 2000) even though this task is sensitive to hippocampal (Sziklas, Lebel, & Petrides, 1998; Sziklas et al., 1996) and anterior thalamic nuclei lesions (Sziklas & Petrides, 1999). However, these tasks are not sensitive to fornix lesions (Dumont, Petrides, & Sziklas, 2007) or retrosplenial cortex lesions (St-Laurent, Petrides, & Sziklas, 2009) so it is not clear which functional circuit is necessary for this task.

In contrast, there are instances where mammillary body, anterior thalamic and fornix lesions have equivalent effects, consistent with a fornix–mammillary body–anterior thalamic nucleus pathway. On the continuous alternation procedure in the T-maze, which increases proactive interference and task difficulty, mammillary body and anterior thalamic nuclei lesions are equivalently impaired but less so than fornix lesion rats (Aggleton et al., 1995). With subsequent delays, all lesion groups show an equivalent impairment (Aggleton et al., 1995). This suggests mammillary body lesion effects are only milder than anterior thalamic and fornix lesions when there are fewer task demands. Mammillary body, anterior thalamic and fornix lesions result in equivalent levels of facilitation on a constant-negative discrimination task (Gaffan et al., 2001). Likewise, mammillary body, anterior thalamic, and fornix lesions result in equivalent levels of performance on a scene-learning and object-in-place task in monkeys (Parker & Gaffan, 1997a, 1997b).

Comparisons can also be made between the effects of these lesions on immediate-early gene expression in distal brain sites. The hypoactivity seen in the hippocampus, retrosplenial cortex and prefrontal cortex following mammillothalamic tract lesions (Vann & Albasser, 2009) is remarkably similar to that seen following anterior thalamic nuclei lesions (Jenkins, Dias, Amin, & Aggleton, 2002; Jenkins et al., 2002b) and this is consistent with these anterior thalamic effects being driven by the loss of their mammillary body efferents. However, the striking decrease in Fos in the retrosplenial cortex following either anterior thalamic or mammillothalamic tract lesions is in contrast to the much smaller effects following fornix lesions (Vann, Brown, Erichsen, et al., 2000). The implication from this is that the retrosplenial hypoactivity resulting from loss of mammillary body efferents cannot solely be explained in terms of an indirect loss of hippocampal/fornical inputs, but that the mammillary bodies have an additional, independent contribution.

5.2. Descending postcommissural fornix lesions

Although fornix lesions disconnect the mammillary bodies from their hippocampal formation inputs, they also disconnect a large number of additional hippocampal efferents and afferents (Nauta, 1956; Poletti & Creswell, 1977; Saunders & Aggleton, 2007; Swanson & Cowan, 1977; Vann, Brown, Erichsen, et al., 2000). It is, therefore, difficult to use findings from complete fornix lesion studies to specifically assess the importance of the hippocampal formation–mammillary projections. While there have been a couple of studies that have targeted the postcommissural fornix these have all been at the level of the septum which would disconnect a number of other sites (Henderson & Greene, 1977; Thomas, 1978; Tonkiss, Feldon, & Rawlins, 1990). Recently, the hippocampal formation–mammillary projections have been targeted selectively by making a lesion of the descending postcommissural fornix at a level caudal to the anterior thalamus; retrograde tracers were subsequently used to confirm the completeness of the intended disconnection and the preservation of the hippocampal formation–anterior thalamic projections (Vann, 2009a). On standard tests of spatial memory, these descending postcommissural fornix lesions produce either no effect or only mild impairments and these lesions appear much less disruptive than lesions of the mammillary bodies or mammillothalamic tract (Vann, 2009a). This discrepancy between postcommissural and mammillary body effects is consistent with earlier findings where mammillary body lesions were significantly more disruptive than lesions of the descending postcommissural fornix on a DRL task (Tonkiss & Rawlins, 1992).

5.3. Gudden's ventral tegmental nucleus lesions

Findings from the immediate-early gene study and postcommissural fornix lesion study are not consistent with the mammillary

bodies simply acting as a hippocampal relay. Attention must, therefore, be directed towards the remaining mammillary body inputs, and the largest of these inputs comes from the tegmental nuclei of Gudden. As the medial mammillary nuclei seem to be predominantly responsible for mammillary body effects on memory, the ventral tegmental nucleus of Gudden becomes of particular interest. The functions of this brain structure have been largely overlooked but a recent study found that selective excitotoxic ventral tegmental nucleus lesions result in robust deficits on various spatial memory tasks, including working memory in the water-maze, T-maze alternation, and working memory in the radial-arm-maze (Vann, 2009b); these tasks are all sensitive to mammillary body and mammillothalamic tract lesions (Vann & Aggleton, 2003). In contrast, rats with ventral tegmental nucleus of Gudden lesions performed normally on a visually cued task in the water-maze and on the acquisition and reversal of an egocentric turning task in a cross-maze indicating that the spatial memory deficits were not a reflection of sensori-motor disturbances, motivational or gross learning impairments (Vann, 2009b). In addition, neurochemical assessments confirmed that the lesion effects were not a result of the loss of cholinergic projections from the adjacent laterodorsal tegmental nucleus or the loss of serotonergic raphe nuclei neurons (Vann, 2009b). These lesion effects are consistent with a small number of previous median raphe nuclei lesion studies that have unintentionally included the ventral tegmental nucleus of Gudden. For example, electrolytic lesions that included Gudden's ventral tegmental nucleus region impaired delayed alternation and radial-arm-maze performance (Asin & Fibiger, 1984; Wirtshafter & Asin, 1983), although there was additional damage to fibers of passage and adjacent fiber bundles. A study of excitotoxic median raphe nuclei lesions reported a significant correlation between the extent of ventral tegmental nucleus damage and the number of errors made on a reinforced T-maze task (Asin & Fibiger, 1984) although, again, there was extensive raphe cell loss. Finally, there is a report of a man with amnesia that was attributed to pathology in the ventral tegmental nucleus of Gudden area (Goldberg et al., 1981). One suggestion is that Gudden's ventral tegmental nucleus acts as an inhibitory feedback loop, with the mammillary bodies, and controls the transfer of information from the hippocampal formation to the anterior thalamic nuclei (Wirtshafter & Stratford, 1993). However, this account is not consistent with the descending postcommissural fornix lesions having such a small effect (see previous section) compared to mammillary body or Gudden's ventral tegmental lesions.

6. Re-evaluating mammillary models of memory

Despite some previous uncertainty it is now apparent, from both patient and animal studies, that the mammillary bodies are important for memory. The mammillary bodies comprise two main nuclei, medial and lateral, which differ in terms of their cell morphology, electrophysiology and connections. The lateral mammillary nucleus forms part of the head-direction system while the medial mammillary nucleus is situated within a "theta-related" system. It is likely that these two nuclei are also functionally distinct. The medial mammillary bodies, and their projections to the anterior thalamus, are necessary for spatial memory and normal hippocampal, retrosplenial and prefrontal function. Although lateral mammillary body lesions have only mild effects on standard spatial tasks they may contribute to additional aspects of spatial memory and/or navigation in normal animals.

Mammillary body lesion-induced deficits appear largely consistent across species and seem to reflect impoverished spatial encoding, although this does not preclude the mammillary bodies supporting other aspects of memory. Current theories of mammillary body function emphasize the hippocampal

formation–fornix–mammillary body pathway (Aggleton & Brown, 1999; Delay & Brion, 1969; Gaffan, 1992) with the mammillary bodies being considered part of the “extended hippocampal system”. However, recent findings are inconsistent with this traditional view, that the hippocampal formation drives the medial diencephalon via the fornix and, in fact, the reverse may be true. It is possible that the diencephalon has a role in memory that is largely independent of its hippocampal formation inputs and instead provides critical indirect hippocampal inputs that are required for normal, integrated memory. Within this revised model of mammillary body function the inputs from the tegmental nuclei of Gudden may prove critical.

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