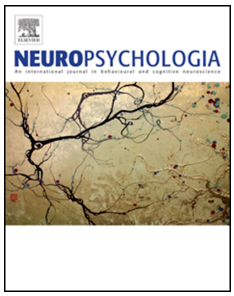

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PII: S0028-3932(23)00262-2

DOI: https://doi.org/10.1016/j.neuropsychologia.2023.108728

Reference: NSY 108728

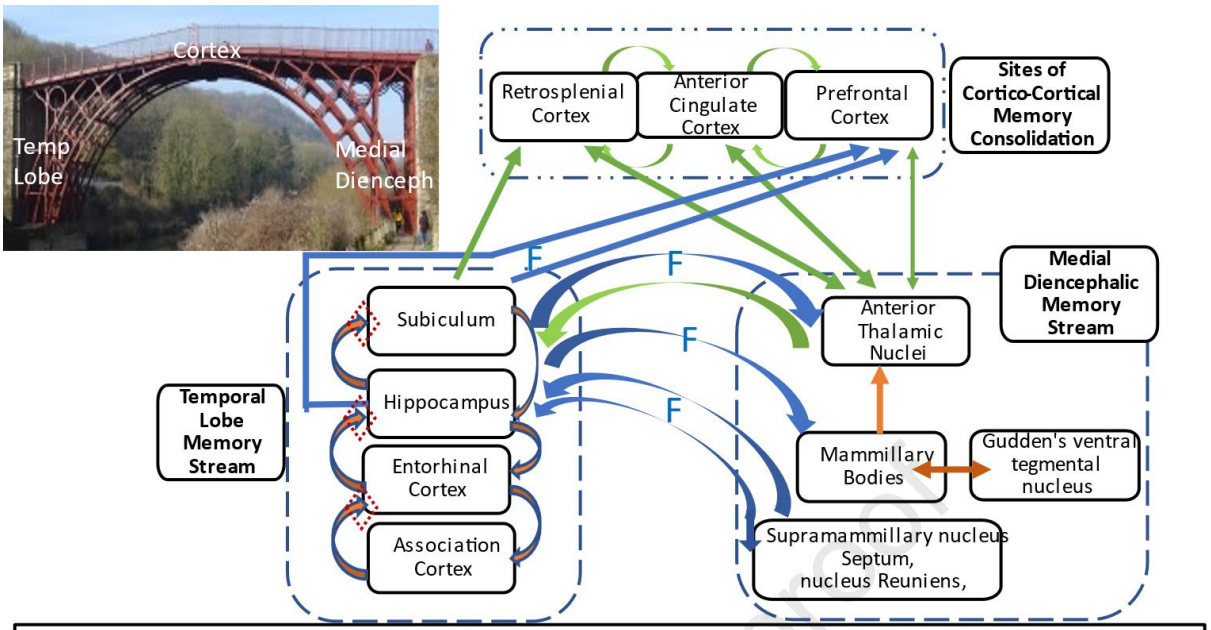
To appear in: *Neuropsychologia*

Received Date: 26 July 2023

Revised Date: 25 October 2023

Accepted Date: 3 November 2023

Please cite this article as: Aggleton, J.P., Vann, S.D., O'Mara, S.M., Converging diencephalic and hippocampal supports for episodic memory, *Neuropsychologia* (2023), doi: https://doi.org/10.1016/j.neuropsychologia.2023.108728.



Memory consolidation across subcortical and cortical sites is facilitated by activity-dependent synaptic plasticity in parallel and interacting circuits. These sites include a temporal lobe memory stream, a medial diencephalic memory stream, and areas of cortico-cortical memory consolidation. (Top left: the historic iron bridge at Ironbridge *-By Tk420 - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=87987570*)

Converging diencephalic and hippocampal supports for episodic memory

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Abstract

To understand the neural basis of episodic memory it is necessary to appreciate the significance of the fornix. This pathway creates a direct link between those temporal lobe and medial diencephalic sites responsible for anterograde amnesia. A collaboration with Andrew Mayes made it possible to recruit and scan 38 patients with colloid cysts in the third ventricle, a condition associated with variable fornix damage. Complete fornix loss was seen in three patients, who suffered chronic long-term memory problems. Volumetric analyses involving all 38 patients then revealed a highly consistent relationship between mammillary body volume and the recall of episodic memory. That relationship was not seen for working memory or tests of recognition memory. Three different methods all supported a dissociation between recollective-based recognition (impaired) and familiarity-based recognition (spared). This dissociation helped to show how the mammillary body-anterior thalamic nuclei axis, as well as the hippocampus, is vital for episodic memory yet is not required for familiarity-based recognition. These findings set the scene for a reformulation of temporal lobe and diencephalic amnesia. In this revised model, these two regions converge on overlapping cortical areas, including retrosplenial cortex. The united actions of the hippocampal formation and the anterior thalamic nuclei on these cortical areas enable episodic memory encoding and consolidation, impacting on subsequent recall.

Keywords: Amnesia, fornix, hippocampus, mammillary bodies, retrosplenial cortex, thalamus

Highlights:

Dissociation of recall from recognition in closely matched patient groups
Mammillary body atrophy predicts levels of episodic memory recall
Deconstruction of Papez circuit
Diencephalic and temporal lobe sites create vital supports in unified memory system
Spotlight on convergent inputs to medial cortical areas for consolidation

Introduction

To paraphrase an insight of Leonardo Da Vinci, an arch consists of two weaknesses which, leaning one against the other, make a strength (Richter, 1970). This same insight describes how and why medial temporal lobe and medial diencephalic structures interact to support episodic memory. In reaching this conclusion, we have to thank Andrew Mayes repeatedly for his pioneering work in understanding these complex relationships.

A good place to start is the fornix. The Latin word for an arch is fornix, an appropriate name for the major tract that arcs between the hippocampal formation and a range of distal brain sites. Among its many constituent pathways, the fornix contains reciprocal connections with the septum, as well as direct hippocampal projections from the subiculum and the CA1 field to various hypothalamic and thalamic nuclei, along with inputs to medial and orbital parts of prefrontal cortex (Poletti & Creswell, 1977; Barbas & Blatt, 1995; Bubb et al., 2017). Some of the densest hippocampal projections appear to terminate in the mammillary bodies and the anterior thalamic nuclei. While in the rodent brain some hippocampal fibres take a nonfornical route to reach the anterior thalamic nuclei, in the primate brain the fornix appears to be the sole pathway for the hippocampal projections to both the anterior thalamic nuclei and the mammillary bodies (Dillingham et al., 2015; Bubb et al., 2017).

Given our understanding of the core pathologies responsible for temporal lobe amnesia (the hippocampal formation) and diencephalic amnesia (the mammillary bodies and anterior thalamic nuclei), it is immediately apparent that the fornix creates a bridge between these two syndromes.

Understanding the relationship between these two forms of anterograde amnesia is a necessary step in mapping out the neural systems that support episodic memory. For this reason, it is important to determine the effects of fornix damage on human memory. If fornix damage has little or no effect on memory, we can probably conclude that temporal lobe amnesia and diencephalic amnesia are largely separate entities. If fornix damage produces obvious memory deficits, it becomes increasingly likely that these two amnesic syndromes are functionally linked.

One obstacle had been the lack of patients with relatively selective fornix damage. Much of the early information came from surgical interventions in cases of epilepsy. A review of such patients concluded that fornix damage had little or no effect on memory (Garcia-Bengochea & Friedman, 1987; also, Woolsey & Nelson, 1975). This conclusion was, however, later challenged (Gaffan & Gaffan, 1991). One concern is that the patients with epilepsy had already suffered a loss of memory prior to their surgery, masking the impact of the fornix intervention. This legitimate concern could not be resolved given the lack of formal test data. The solution was to look again at whether fornix damage could cause anterograde amnesia.

Colloid cyst patients and memory:

There is a rare condition in which a colloid cyst develops in the third ventricle. This type of benign tumour typically sits just under the fornix and may adhere itself to the tract (Figure 1). Such cysts are life threatening, and so are typically removed. In some patients the actions of the cyst and its surgical removal result in damage to the fornix. Preliminary studies based on small numbers of colloid cyst cases had indicated that such damage could cause chronic memory problems (Hodges & Carpenter, 1991; Gaffan et al., 1991; McMacken et al., 1995; Aggleton et al., 2000). As colloid cysts are rare these studies were based on just a handful of subjects, limiting the strength of any conclusion. Another problem is that colloid cysts affect more than just the fornix, e.g., they cause considerable ventricular dilation. Consequently, there is the need for closely matched controls.

Two centres (Andrew Mayes/ Daniela Montaldi and John Aggleton/ Seralynne Vann) combined resources to study colloid cyst patients. Just like the arch, the sum of the two centres proved to be far greater than the two component parts. From the outset, Andrew insisted that three

elements would be vital for the success of this project. First, to recruit far more cases than had been previously studied. Second, to complete extensive cognitive testing, the results of which could be integrated with MRI findings. Third, to make detailed, structural MRI images using the same scanner and protocol throughout in order to maximise comparability between cases. Another key decision was to refine the MRI protocols to help image the fornix and the mammillary bodies (Denby et al., 2008, 2009). As it turned out, mammillary body volume (Figure 2) proved to be especially informative in this condition.

Across the UK, we enlisted a remarkable total of 74 patients with colloid cysts in the third ventricle. Of these, 62 patients completed cognitive testing, of which 38 were scanned (Tsivilis et al., 2008). Of the 38 patients, only three appeared to have a complete, bilateral fornix disconnection. All three showed persistent, long-term memory deficits (Figure 3). For example, their scores on the Delayed Logical memory test from the Wechsler Memory Scale III (WMSIII) were all below the first percentile (Tsivilis et al., 2008). The loss of episodic memory was marked and persistent, significantly affecting their quality of life.

Attention then focussed on the full cohort of 38 colloid cyst patients with MRI data. Thirteen different brain areas were analysed, with the goal of correlating cognitive performance with the volume of each area. The WMSIII has eight memory indices. For twelve of the brain areas studied, which included the hippocampus, fornix, temporal lobe, various prefrontal cortex regions, and the lateral ventricles, there was not a single significant correlation between the volume of an area and any of the eight WMSIII memory index scores.

The thirteenth area, the mammillary bodies, showed a very different profile. Remarkably, mammillary body volume correlated with seven of the eight WMSIII memory indices (Tsivilis et al., 2008). The seven indices, all of which taxed long-term memory, included ‘immediate memory’ and ‘general memory’ (Figure 4 a). The sole exception was working memory. This separation agrees with factor analyses of the WMSIII, which point to distinct working memory, auditory memory, and visual memory, components (Millis et al., 1999). Furthermore, tests of working memory are often spared in anterograde amnesia (Yonelinas, 2013).

Two areas were notable for *not* correlating with the WMSIII memory indices in the colloid cyst cases (Tsivilis et al., 2008). The first was the hippocampus, even though this structure was reduced in volume in the patients. This hippocampal shrinkage was probably a reaction to the enlargement of the lateral ventricles, rather than reflecting any intrinsic hippocampal atrophy. Despite the loss of fornix fibres, cutting this pathway does not cause retrograde neuronal degeneration in the hippocampus (Aggleton et al., 1986).

The other notable area that did not appear to correlate with the WMSIII memory indices was the fornix, which decreased in volume by a mean of 30% (Tsivilis et al., 2008). While fornix volume correlated with a small number of memory subtests, it did not correlate with any of the eight WMSIII indices, nor did it correlate with any components of the Doors and People Test (Baddeley et al., 2006). One explanation might be that overall tract volume is a poor measure, and that the smallest cross-sectional area may better reflect disconnection. However, when the smallest cross-sectional fornix area was measured, no significant difference was found between the colloid cyst patients and 20 normal controls, and only about 5% of the patients had abnormally small cross-sectional area estimates (Denby et al., 2008). Given the weak association between memory and the various fornix measures, the spotlight returned to the mammillary bodies, whose volume correlated with all of the WMSII memory recall indices, along with all of the recall measures from the Doors and People Test (Tsivilis et al., 2008).

Most of the colloid cyst patients appeared to have shrunken mammillary body volumes (Figure 2). For example, over two thirds of the cases had mammillary body volumes that were more than one standard deviation below the control mean (Denby et al., 2009). While one contributing cause may be the loss of some fornical inputs, which will partially shrink the mammillary bodies (Loftus et al., 2000), this is unlikely to be the full explanation. For example, the extent of mammillary body atrophy in many of the cases was far greater than that seen after complete hippocampal disconnection (Loftus et al., 2000), yet only three cases suffered bilateral severance of the fornices (Tsivilis et al., 2008), i.e., the degree of mammillary body atrophy exceed that associated with the observed fornix damage.

Additional potential causes of mammillary body shrinkage include the effects of increased direct pressure within the third ventricle. A likely consequences is increased pressure on the anterior thalamic nuclei, which sit adjacent to the colloid cyst. Damage to the anterior thalamic nuclei not only causes retrograde degeneration in the mammillary bodies (Aggleton & Mishkin, 1983), but may also be sufficient to impair episodic memory (Harding et al., 2000; Aggleton, 2008; Carlesimo et al., 2011; Aggleton & O'Mara, 2022). Inspection showed that this thalamic area was often distorted, but for the same reason it was not possible to determine meaningful volumetric measurements.

The emerging conclusion is that the changes in memory performance observed in the colloid cyst patients largely reflected mammillary body atrophy, along with any anterior thalamic pathology. This conclusion gains support from descriptions of patients with damage centred on the mammillary bodies caused by tumours, trauma, or infarcts. These rare patients consistently show memory problems (e.g., Dusoir et al., 1990; Tanaka et al., 1997; Hildebrandt et al., 2001; Male & Zand, 2017) although, in some instances there can also be a recovery of memory (Tanaka et al., 1997; Kapur et al., 1998).

It is, of course, the case that the fornix contains an array of other hippocampal connections that are presumed to assist cognition. These connections include those to the medial and orbital prefrontal cortex, as well as those from the septum and the supramammillary nucleus to the hippocampal formation (McNaughton & Vann, 2022). While their partial interruption presumably adds to the impact of colloid cysts, the consistent correlations with mammillary body volume point to the primary significance of the mammillary body-anterior thalamic axis in this particular group of patients.

A striking feature of the colloid cyst patients was that recall was disrupted appreciably more than recognition memory (Tsivilis et al., 2008). A disproportionate impact on memory recall had also been reported in previous studies of colloid cyst patients with fornix damage (Gaffan et al., 1991; McMackin et al., 1995; Aggleton et al., 2000). Likewise, some patients with direct mammillary body damage also show a far greater loss of memory recall than recognition (Dusoir et al., 1990; Hildebrandt et al., 2001).

The recall:recognition difference in the colloid cyst cohort became especially compelling when the patients were divided into two groups (Tsivilis et al., 2008). The eleven patients with the smallest mammillary body volumes were compared to the eleven patients with the largest mammillary body volumes, i.e., those in whom the mammillary body volumes appeared closest to normal (Figure 2). This comparison was unusually well-balanced as the two patient groups did not differ in age, time since surgery, extent of lateral ventricular dilation, IQ scores, working memory performance, or type of surgical approach used to reach the cyst (Tsivilis et al., 2008; Vann et al., 2009). Of the structures measured, the only volume differences between the two groups were in the mammillary bodies (inevitably) and the fornix.

A recall index and a recognition index were derived from the standardised scores for the various memory tests administered, including the WMSIII, the Doors and People Test, and the Warrington Recognition Test (Figure 4b). Those patients with smaller mammillary bodies were clearly impaired on recall but performed within normal levels for recognition (Tsivilis et al., 2008). This same pattern of results was found when just considering the data from the Doors and People Test (Figure 4c). This additional result is informative as the Doors and People Test is designed so that the recall and recognition components are of comparable difficulty for normal individuals (Baddeley et al., 2008), i.e., the sparing of recognition was not due to using tests that were easier than those for recall.

One interpretation of the results, based on dual-process models of recognition, is that the mammillary-related pathology impaired recollective-based recognition but spared familiarity-based recognition. To test for this possibility, two additional cognitive tests were administered to 26 colloid cyst patients (Vann et al., 2009). One test (R/K) contrasted the frequency of recognition judgements that were subjectively based on a feeling of recollection (R, remember) with those based on a feeling of familiarity (K, knowing). For this comparison, the patient group was separated into the nine with the smallest mammillary bodies and the nine with the largest (i.e., near-normal sized) mammillary bodies (Vann et al., 2009). While familiarity (knowing) was at a comparable level across the two groups, recollection (remembering) was markedly depressed in those with smaller mammillary bodies (Figure 5A). A very similar pattern was

found when levels of confidence were used to create ROC (Receiver Operating Characteristics) curves to help distinguish familiarity from recollection (Figure 5C, D). Again, those with the smallest mammillary bodies did not differ from those with near-normal mammillary bodies on measures of familiarity, but they showed reduced measures of recollection (Vann et al., 2009).

A third strategy took the data from all 62 colloid cyst patients who had completed the full cognitive battery, irrespective of whether they had taken part in the MRI scanning. Structural equation modelling then determined the best fitting model for the patterns of cognitive performance (Vann et al., 2009). The two-factor model in which one latent variable (recollection) contributes to both recall and recognition, whereas a second latent variable (familiarity) only contributes to recognition, fitted the data well and appeared superior to other potential models. Applying this model to the patient subgroups (Figure 5B) not only corroborated the R/K and ROC data, but also used a different operationalization of recollection and familiarity, while still reaching the same conclusion (Vann et al., 2009).

The cognitive profile of the colloid cyst patients bore an obvious parallel to a patient with hippocampal damage previously described by Andrew Mayes. Patient Y.R., whose hippocampal volume, was reduced bilaterally by around 45% (relative to age-matched controls), showed frequent deficits on recall but often solved tests of item recognition at normal levels (Mayes et al., 2002). Further analyses indicated a sparing of familiarity that contrasted with a loss of recall (Mayes et al., 2004; Holdstock et al., 2019).

While not every patient with hippocampal damage has this same cognitive profile, it was observed again in the amnesic patient K.N. (Aggleton et al., 2005). Andrew Mayes assisted our analysis of K.N. who had suffered a 50% bilateral reduction of hippocampal volume following meningitis. His General Memory Index from the WMSIII was at the 0.1 percentile level, yet he showed relative sparing on tests of recognition. A similar pattern was seen for the recall (impaired) and recognition (spared) components of the Doors and People Test. Of particular relevance is that K.N. received exactly the same R/K and ROC protocols as used for the colloid cyst patients. These analyses reinforced the conclusion that K.N. displayed intact familiarity but

deficient recollective-based recognition (Aggleton et al., 2005), i.e., a profile that matched those colloid cyst patients with small mammillary bodies.

Together, these findings strengthened the belief that familiarity-based and recollective-based recognition can be dissociated, with only recollective recognition depending on fornix-diencephalic interactions. Subsequent research by Andrew Mayes, which involved both patient studies (e.g., Bastin et al., 2004) and fMRI studies of normal populations (e.g., Montaldi et al., 2006; Kafkas et al., 2020), proved integral in fleshing out the complementary systems for familiarity-based and recollective-based memory. In addition, he helped to account for apparent discrepancies in the neuropsychological findings from different groups (Montaldi & Mayes, 2010).

Building a strong arch from two weaker supports

The rationale for our colloid cyst study was to understand the relationships between those temporal lobe and diencephalic structures that support episodic memory. Initially, the pattern of results seemed to match the concept of a mnemonic loop involving hippocampal projections to the mammillary bodies, via the fornix, and thence to the anterior thalamic nuclei, with return projections (direct and indirect) from the anterior thalamic nuclei back to the hippocampal formation (Delay & Brion, 1969; Aggleton & Brown, 1999) – a loop often better known as Papez circuit (Papez, 1937).

Given this match, it might seem surprising to now propose a model based on an arch, rather than a circle (Aggleton & O'Mara, 2022). But, it has long been apparent that a circular loop may be of restricted value, aside from coordinating activity, e.g., oscillations along a sequence of sites. This same explanation also largely fails to explain why this coordination is needed, unless the sites beyond the hippocampus are providing something lacking in the medial temporal lobe. In other words, the medial diencephalon becomes both part of an extended-hippocampal circuit while also playing a vital, independent role that then interlocks with the hippocampal formation. It is this duality that has made unpicking these pathways for memory so complex.

This change in perspective begins by placing more emphasis on the separate contributions of the hippocampal formation and the mammillary/anterior thalamic axis, despite their important interconnections. The two arch supports (one the temporal lobe memory system, the other the medial diencephalic memory system) then converge on a select group of cortical areas, most notably the anterior and posterior cingulate cortices, the latter including retrosplenial cortex (Figure 6).

One reason for this reformulation is anatomical. The traditional hippocampal-diencephalic-cingulate circuit emphasizes a flow of information that is a largely in one direction, from the hippocampal formation to the mamillary bodies, to the anterior thalamic nuclei, to the posterior cingulate/retrosplenial cortices, and back to the parahippocampal and hippocampal regions. An obvious problem is that there are dense return connections from the posterior cingulate region, including retrosplenial cortex, back to the anterior thalamic nuclei (Shibata & Yukie, 2003; Bubb et al., 2017). Furthermore, while the direct projections from retrosplenial cortex to the hippocampal formation are only very light (Kobayashi & Amaral, 2007), there are dense, direct projections from the hippocampal formation to the retrosplenial cortex and adjacent posterior cingulate areas (Kobayashi & Amaral, 2003; Aggleton et al., 2012), i.e., dense hippocampal efferents that oppose Papez circuit. It has also been shown in rodents that many of the hippocampal projections to retrosplenial cortex collaterise, also terminating in the mammillary bodies (Kinnavane et al., 2018). These examples highlight how the traditional circular flow is very much a misrepresentation.

Another difficulty with the concept of a strict circular memory circuit emerges when considering the impact of damage to its constituent pathways. One prediction is that the disconnection of each part of the loop should cause amnesia. At first sight this prediction appears to be strongly supported. As already described, fornix damage can cause an anterograde amnesia, as also appears to be the case when the mammillothalamic tract is compromised by strokes (Carlesimo et al., 2011). More direct mammillary body damage is also associated with anterograde amnesia, although its severity and persistence can vary (Dusoir et al., 1990; Kapur et al., 1998; Hildebrandt et al., 2001).

Complications arise when considering the next tract, namely the cingulum bundle. This major brain tract is the principal route by which the anterior thalamus projects directly and indirectly to the hippocampal formation. The cingulum bundle also conveys a great many other connections (Mufson & Pandya, 1984; Bubb et al., 2018). Despite its strategic importance, loss of the cingulum bundle in humans is not associated with amnesia (Bubb et al., 2018). Similarly, the effects of cingulum bundle lesions on rodent spatial learning are typically mild (Bubb et al., 2018), being far less severe than those associated with either hippocampal damage or anterior thalamic damage.

It remains possible that the modest effects of cingulum damage reflect how the fibres reaching and leaving the cingulum bundle fan out, as well as how tract composition changes along its length. One example of the former consists of the anterior thalamic radiations which, as the name suggests, are very diffuse (Shah et al., 2012). Likewise, the cingulate cortex-anterior thalamic connections join and leave the cingulum bundle at multiple points, with those leaving the cingulate region for the thalamus only briefly joining the cingulum bundle. Consequently, there may be no single site that when damaged will produce an effective cingulum disconnection (Bubb et al., 2018). In addition, many of the hippocampal projections to retrosplenial cortex pass through the posterior presubiculum and, consequently, do not involve the cingulum (Aggleton et al., 2012). This anatomical explanation remains untested, highlighting the need to know much more about information processing beyond the anterior thalamic nuclei, including the importance of the cingulum bundle.

After taking a fresh look at this same 'circuit' it becomes increasingly evident that the retrosplenial/posterior cingulate region emerges as a key target for both the diencephalic and hippocampal sides of this network (Aggleton & O'Mara, 2022). The significance of the retrosplenial/posterior cingulate region is highlighted by how unilateral pathology in this region can cause topographical difficulties while bilateral pathology can cause anterograde amnesia (Maguire, 2001; Vann et al., 2009). Other reasons to focus on the retrosplenial region include the results from an MRI analysis of 53 stroke patients with anterograde amnesia (Ferguson et al., 2019). Many of these amnesic patients had pathologies that affected the hippocampal formation or the medial diencephalon, but a large subgroup had pathologies elsewhere in the brain. Based

on resting state connectivity data, the shared hub for the 53 amnesic cases was the subiculum-retrosplenial cortex continuum (Ferguson et al., 2019). Furthermore, the retrosplenial cortex is a key component of the default mode network (Kaboodvand et al., 2018), which is increasingly implicated in memory processes (Kaefer et al., 2022). Retrosplenial contributions to this network are modulated by both the hippocampus (Kaboodvand et al., 2018) and the anterior thalamic nuclei (Jones et al., 2011; Middlebrooks et al., 2020).

Animal research also highlights the significance of convergent actions on retrosplenial cortex. Optogenetic studies with rodents show how the direct hippocampal projections to retrosplenial cortex play a key role in the formation and persistence of spatial learning (Yamawaki et al., 2019a,b). Meanwhile, crossed-lesion studies implicate anterior thalamic-retrosplenial cortex interactions for spatial learning (Sutherland & Hoesing, 1993). Past models have tended to emphasise the significance of both the hippocampal and anterior thalamic systems for encoding (e.g., Aggleton & Brown, 1999), reflecting their joint importance for spatial framing, as evidenced by the array of spatially responsive cell types in both regions (O'Mara & Aggleton, 2019). Instead, there are increasing reasons to highlight their added importance for consolidation (McNaughton & Vann, 2022).

Current models of long-term memory consolidation consistently emphasise the importance of hippocampal influences on the cerebral cortex (Barry & Maguire, 2019). One likely mechanism involves sharp wave ripples. These are bouts of high frequency neuronal activity that are thought to facilitate communication between the hippocampus and cortex, where they support episodic memory consolidation (Buzsáki, 2015). It is particularly relevant that sharp wave ripples are not only present in the hippocampus, but via the subiculum, their analogues exist in retrosplenial cortex (Nitzan et al., 2020). The finding that head-direction cells in the anterodorsal nucleus display close coupling with hippocampal sharp wave ripples (Viejo & Peyrache, 2020), adds to the likelihood of converging actions on retrosplenial cortex involving sharp wave ripples.

Other hippocampal oscillatory patterns, including theta, are also conveyed to retrosplenial cortex, adding to the belief that this area coordinates information transfer to the neocortex for episodic memory and spatial cognition (Alexander et al., 2018; Karimi Abadchi et al., 2020). However,

not all retrosplenial theta is hippocampal-dependent, as there is also synchronous theta in the anteroventral thalamic nucleus and the retrosplenial cortex that is independent of the hippocampus (Talk et al., 2004), adding to the potential significance of convergent anterior thalamic/hippocampal actions on cortical consolidation.

Reinforcing these proposals is the finding of spatial engrams within the rodent retrosplenial cortex. These engrams have been identified using a variety of methods (Cowensage et al., 2014; Milczarek et al., 2018; de Sousa et al., 2019). One method involves tagging c-*fos* activated neurons in retrosplenial cortex (Cowansage et al., 2014; de Sousa et al., 2019). It is, therefore, notable that lesions in the anterior thalamic nuclei and the hippocampal formation both result in a dramatic loss of c-*fos*, as well as *zif268*, activity in retrosplenial cortex (Jenkins et al., 2004; Albasser et al., 2007).

Consistent with a role in persistent memory storage these retrosplenial engrams tend to be slower to develop (Milczarek & Vann, 2020) and can become independent of the hippocampus (Cowansage et al., 2014). One emerging concept is that the retrosplenial cortex helps to broadcast mnemonic information to other cortical sites, including the anterior cingulate cortex (de Sousa et al., 2019; Figure 6). This proposal may prove especially relevant as the anterior thalamic nuclei have dense reciprocal connections with both the anterior cingulate and retrosplenial regions.

From these findings, two separate supports for episodic memory emerge: one from the temporal lobe, the other from the medial diencephalon. Together these supports combine to create a stronger structure. The top of this structure is formed by cortical regions, with retrosplenial cortex providing one of the keystones. Another important region is the anterior cingulate area, which is anatomically far more closely linked with the anterior thalamic nuclei than the hippocampus, and again provides a cortical site for memory consolidation (Frankland et al., 2004; Einarsson & Nader, 2012). The parahippocampal region also receives inputs from both the anterior thalamic nuclei and hippocampal formation, but here it is the hippocampus that dominates.

As already observed, an implicit feature of this realignment is that the mammillary bodies/anterior thalamic nuclei have cognitive functions that are independent from those of the hippocampal formation. It has long been known that the mammillary-anterior thalamic pathway is a vital provider of head-direction information, a key component of our navigational systems (Taube, 2007). It has also been proposed that the mammillary bodies convey oscillations to the anterior thalamic nuclei and, from there, to frontal and cingulate cortical areas to boost engram consolidation (Sweeney-Reed et al., 2021; McNaughton & Vann, 2022). Evidence includes the discovery that mammillothalamic lesions reduce theta frequency in the hippocampus and also disrupt hippocampal-retrosplenial coupling (Dillingham et al., 2019), while theta stimulation of the anterior thalamic nuclei can ameliorate the effects of mammillothalamic tract lesions on spatial working memory in rats (Barnett et al., 2021).

Other likely contributions to cognition reflect the strategic placement of the anterior thalamic nuclei (Aggleton et al., 2010). One example is how, along with nucleus reuniens, the anterior thalamic nuclei provide complementary routes for prefrontal influences on the hippocampal formation (Prasad & Chudasama, 2013). The significance of these routes is heightened by the realisation that nucleus reuniens and the anterior thalamic nuclei share many gross similarities in their connectivity and functions, yet the fine details consistently differ (Mathiasen et al., 2020).

Furthermore, both rodent and human studies strongly suggest that the anterior thalamic nuclei have an important role in reinforcement-guided attention, which aids learning. In particular, the anterior thalamic nuclei are needed to help guide attention to stimulus features that consistently predict reward, their loss markedly disrupting ‘set-learning’ (Wright et al., 2015). Not only does this rodent thalamic function appear quite distinct from hippocampal actions, but experiments using Designer Receptors Exclusively Activated by Designer Drugs (DREADDS) have revealed the importance of the direct anterior thalamic–anterior cingulate interactions for this same attention-guided learning (Bubb et al., 2021). Importantly, these animal findings closely match the outcome of human neuroimaging and neuropsychological studies into the contributions of the anterior thalamic region to attention and learning Bourbon-Teles et al., 2014; Geier et al., 2020).

The emerging model creates a rich network of medial temporal-medial cortical-medial diencephalic interactions for episodic memory. At the same time, it is important not to overlook the significance of the various direct hippocampal-medial diencephalic pathways that involve the fornix. This perspective began with Andrew Mayes wanting to discover why the fornices might be critical for memory. Indeed, evidence, largely based on colloid cyst patients, indicates that the severity of the amnesia associated with complete fornix disruption is often comparable to that seen after bilateral hippocampal damage.

In a comprehensive review, IQ and WMS General Memory scores were listed for patients that had either suffered pathology centred in the hippocampus or the fornix (Spiers et al., 2001). These scores made it possible to directly compare the IQ-MQ difference for the 10 cases with fornix pathology and 27 cases with hippocampal pathology. (The hippocampal pathology typically arose from ischaemia, anoxia, or epilepsy – those cases with herpes encephalitis were excluded as the pathology in this condition is often widespread, while the few developmental amnesics were also excluded).

The mean IQ-MQ difference for the Hippocampal amnesics was 29.5, while that for the Fornix amnesics was 22.6. There was no evidence of a statistical difference between the respective scores (t =1.18) and there was considerable overlap. In other words, the anterograde amnesias were of similar severity. It was also possible to consider the three colloid cyst cases with complete fornix disconnection from the study with Andrew Mayes (Tsivilis et al., 2008). Their FSIQ-WMSIII General Memory Index difference scores were 20, 37, and 33, making them highly comparable to the previous hippocampal and fornix cases. In other words, the severity of the anterograde amnesias following fornix damage and hippocampal damage seems very similar. This brings us back to the issue of the direct hippocampal-medial diencephalic interactions.

Studies with rats using DREADDS have helped to confirm that selectively disrupting the direct hippocampal projections to the anterior thalamic nuclei, as well as the direct anterior thalamic projections to the hippocampal formation, impairs performance on a spatial learning task when it involves the flexible use of spatial cues (Nelson et al., 2020). Furthermore, it has been shown that anterior thalamic integrity is necessary for spatial signalling by subiculum neurons (Frost et

al., 2021). Consequently, any model of episodic memory still needs to retain these direct anterior thalamic–hippocampal interactions. In addition, the fornix contains projections from the medial septal nucleus and the supramammillary nucleus, which have critical roles in generating and modulating theta (Vann & McNaughton, 2022). Other fornical connections involve nucleus reuniens, which contributes to spatial processing and cognition (Dolleman et al., 2019). The fornix is also likely to the sole route for the direct projections from the CA1 field and the subiculum to prefrontal cortex (Aggleton et al., 2015).

To incorporate these various influences, it becomes necessary to integrate two models that emerge from a consideration of the direct and indirect hippocampal – medial diencephalic interactions. In this perspective, we largely emphasise how the anterior thalamic nuclei and hippocampus may be seen as two vital pillars that support a cortical arch. In this way, the joint regions support encoding and consolidation. This model does not, however, fully replace the more traditional models based around direct hippocampal – diencephalic interconnections involving the fornix. One difference is the greater emphasis on both hippocampal efferents and afferents that occupy this tract, i.e., their two-way interactions (Vann & McNaughton, 2022). Together, these direct fornical interconnections provide vital struts for the two pillars, making it possible for the hippocampus and medial diencephalon to operate effectively. The resulting complex framework, an arch with supporting cross-struts, engages cortical regions during both encoding and consolidation, actions that enable the subsequent retrieval of episodic memory (Figure 6).

Funding: This work was supported by the U.K. Medical Research Council (grant G0001371) and by the Wellcome Trust (grant 103722/Z14/Z). SDV is funded by a Wellcome Trust Senior Research Fellowship (WT212273/Z/18).

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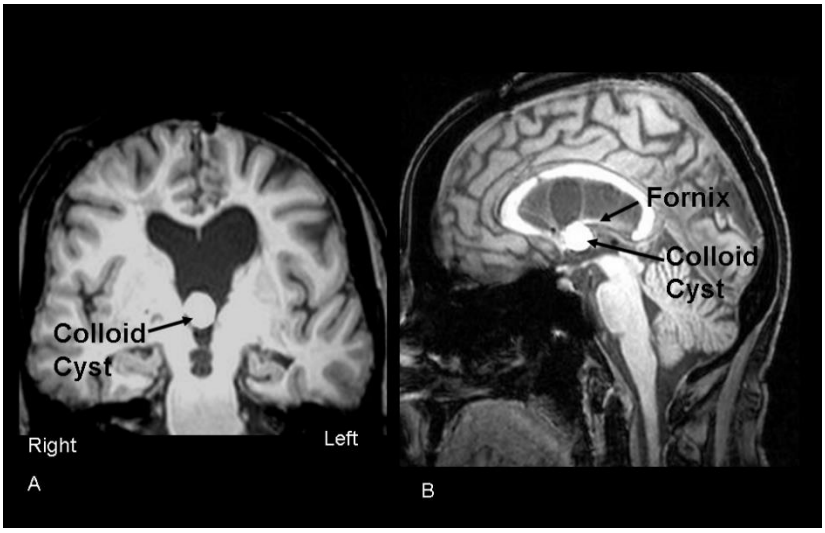

Figure 1A, coronal; **1B**, sagittal. Structural MRIs showing appearance of a colloid cyst in third ventricle. In Figure 1A the fornix appears absent as a result of the cyst. Ventricular dilation and thalamic distortion are also evident.

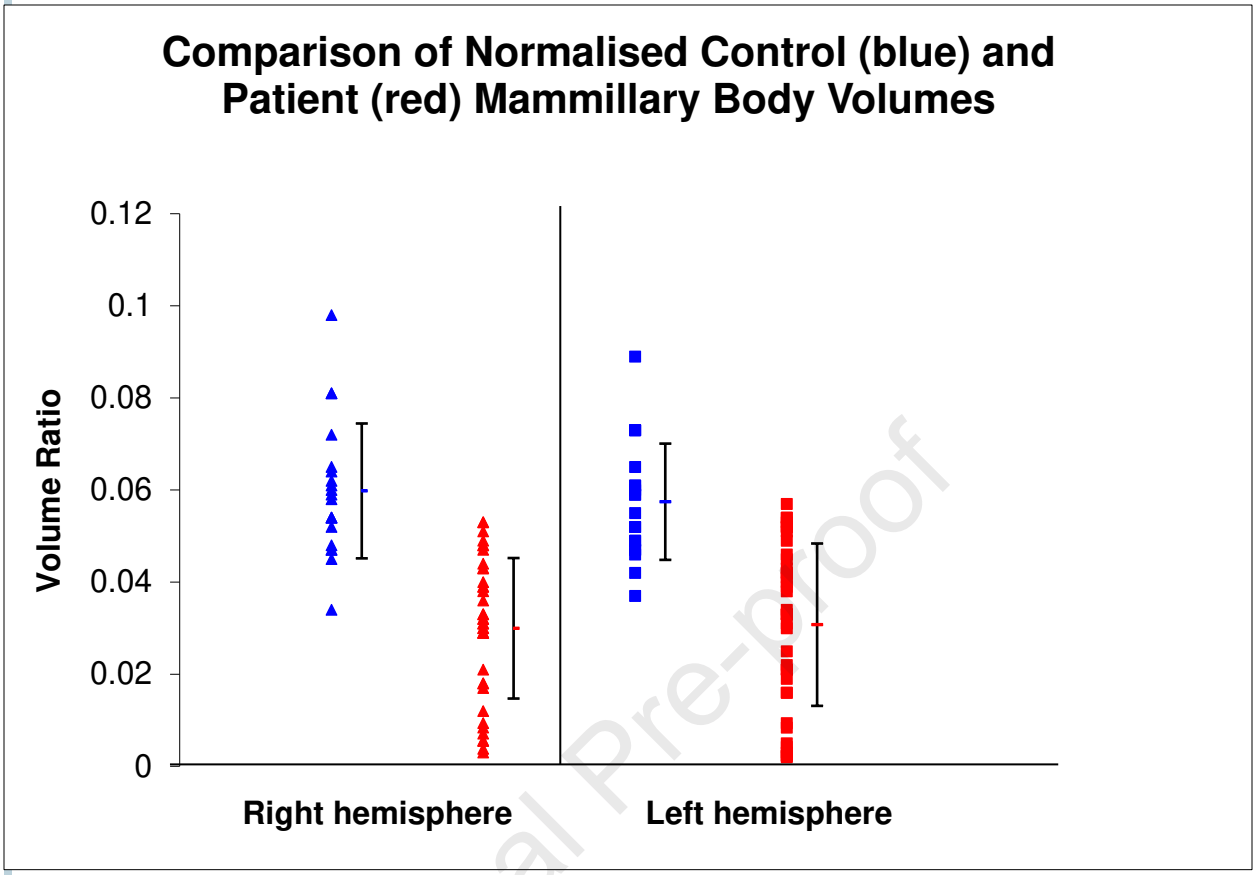

Figure 2. Distribution of control and patient mammillary body volumes (normalised by intracranial volume). The patient volumes are from after their surgeries. The data are shown for each hemisphere, the scale bars represent the standard deviation. For 31/38 (right hemisphere) and 28/38 (left hemisphere), the patient volumes were >1 SD below that of the control means. (Adapted from Denby et al., 2009)

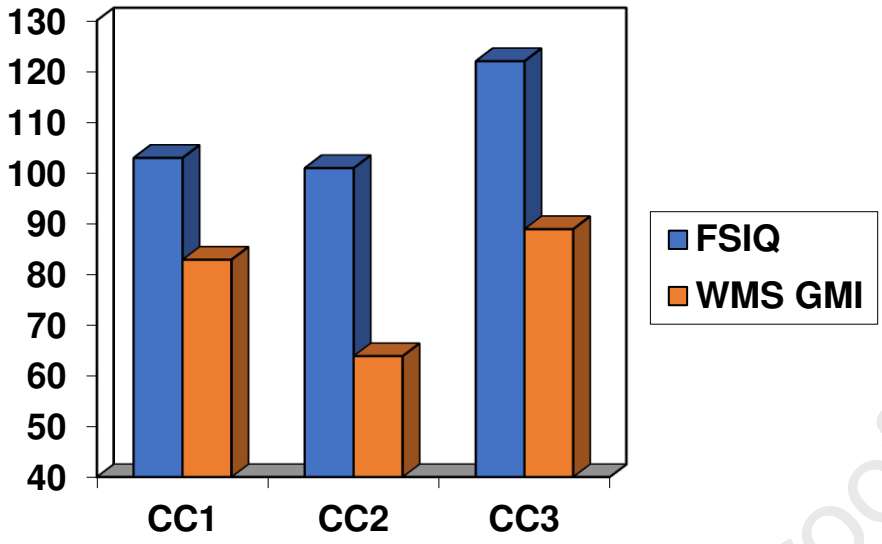

Figure 3. Cognitive performance of the three colloid cyst cases with complete fornix section from Tsivilis et al. (2008). FSIQ, Wechsler full-scale IQ score; WMS GMI, Wechsler Memory Scale III, general memory index.

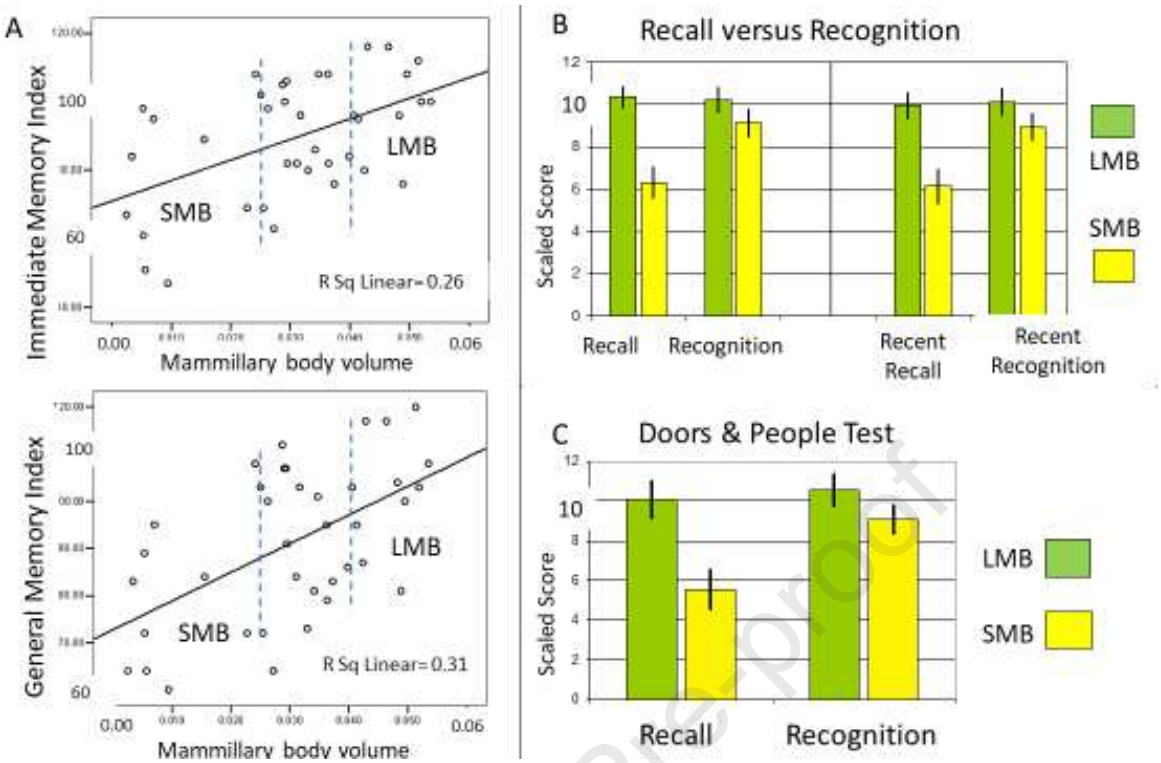

Figure 4 (**A**) Scatter plots showing the positive relationship between mammillary body volume (ICV-normalized) and the immediate memory index (upper) and general memory (lower) index of the WMS-III for 38 patients following colloid cyst removal (from Tsivilis et al., 2008). (**B**) Means (± s.e.m.) of the combined recall and combined recognition index scores for the larger (LMB, n=11) and smaller (SMB, n=11) mammillary body volume groups. The same findings for the recent recall and recent recognition index scores are shown to the right. (**C**) Mean (± s.e.m.) scaled recall and recognition scores from the Doors and People test for the LMB and SMB groups. The two recall tests and the two recognition tests have been combined. For both **B** and **C**, the normal population mean score is 10.

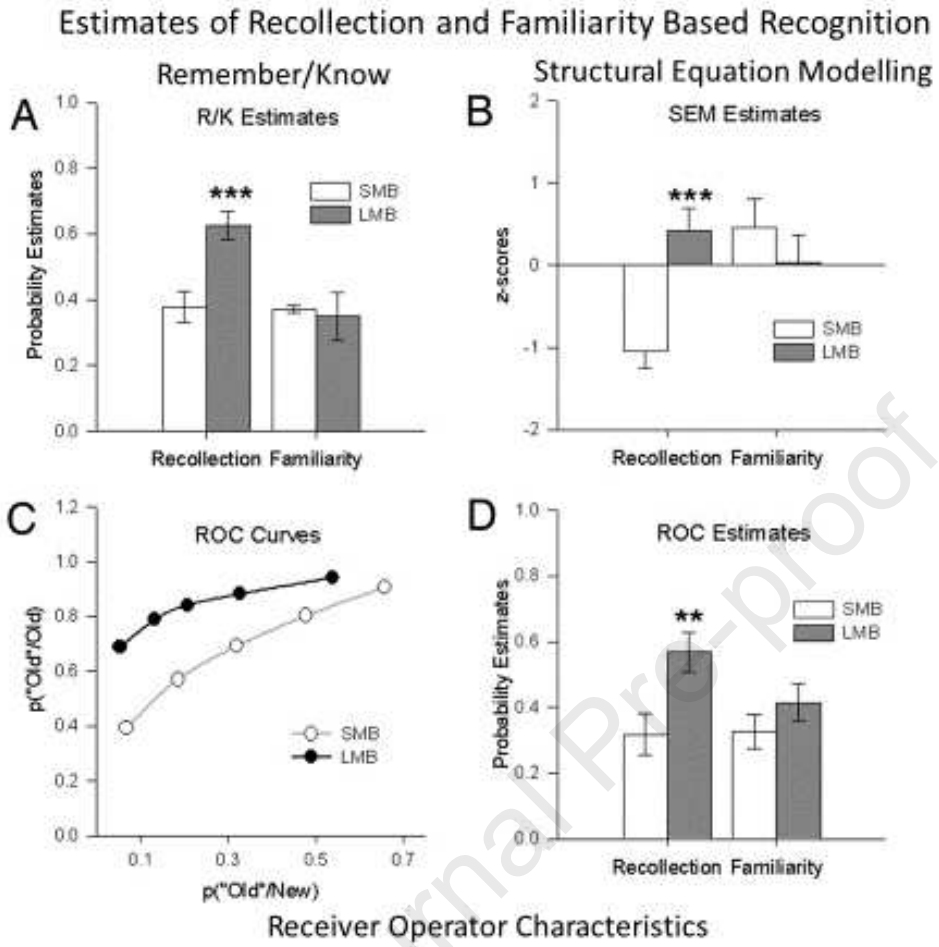

Figure 5. Derived probability estimates of 'recollection' and 'familiarity' for the small mammillary body volume (SMB) and larger (near-normal) mammillary body volume (LMB) groups, drawn from the cohort of post-surgery colloid cyst patients. Data in histograms are presented as means+/- standard error of the mean. A) Estimates from the Remember/Know (R/K) procedure. (B) Estimates from structural equation modelling (SEM). (C) Receiver operating characteristic (ROC) curve. (D) Estimates derived from ROC procedure. **, $p<0.01$; ***, $p<0.005$. (From Vann et al., 2009)

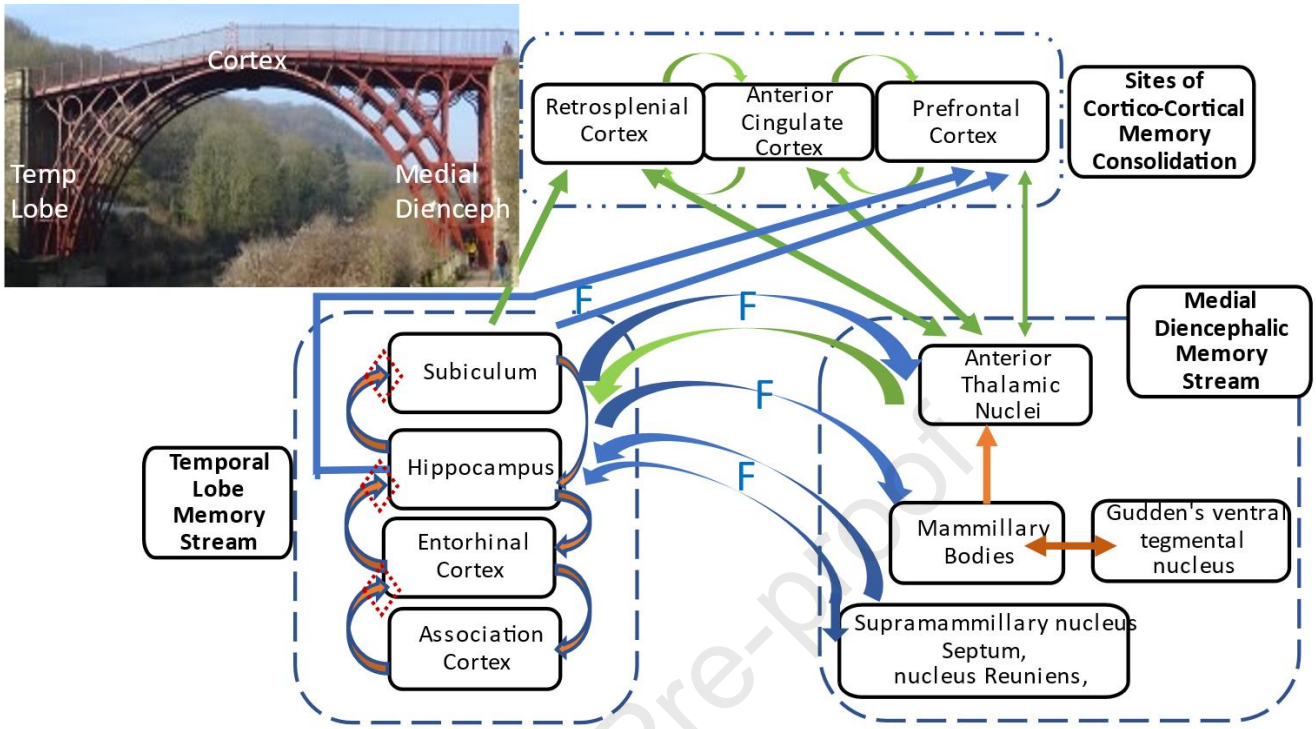

Figure 6. Memory consolidation across subcortical and cortical sites is facilitated by activity-dependent synaptic plasticity in parallel and interacting circuits. These sites include a temporal lobe memory stream (Temp Lobe), a medial diencephalic memory stream (Med Dienceph), and areas of cortico-cortical memory consolidation. The blue arrows show those projections that join the fornix (F). Meanwhile, the connections in green occupy parts of the cingulum bundle. Top left: the historic iron bridge at Ironbridge. (*By Tk420 - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=87987570*)

All three authors had an equal role in planning and writing this manuscript. JPA and SDV made additional contributions to the studies with colloid cyst patients, being involved in their funding and execution.