The anterior thalamic nuclei: core components of a tripartite episodic memory system

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Abstract| Standard models of episodic memory focus on hippocampal–parahippocampal interactions, with the neocortex supplying sensory information and providing a final repository of mnemonic representations. However, recent advances have shown that other regions make distinct and equally critical contributions to memory. In particular, there is growing evidence that the anterior thalamic nuclei have a number of key cognitive functions that contribute to episodic memory. In this article, we describe these findings and argue for a core, tripartite memory system, comprising a 'temporal lobe' stream (hippocampal centred) and a 'medial diencephalic' stream (anterior thalamic centred) that together act on shared cortical areas. We demonstrate how these distributed brain regions form complementary and necessary partnerships in episodic memory formation.

[H1] Introduction

Many theoretical and computational models of episodic memory ignore the influence of medial diencephalic sites, while emphasising hippocampal interactions with the cortex[1-5]. However, there is growing evidence that, by failing to account for the necessary and substantial contributions of medial diencephalic brain regions (most notably the anterior thalamic nuclei), such models are imbalanced and misleading.

The likely importance of the anterior thalamic nuclei for memory first emerged more than a century ago, when descriptions appeared[6-8] of the devastating amnesia following medial diencephalic damage. The consistent pattern of pathology adjacent to the third ventricle helped to highlight the potential significance of the anterior thalamic nuclei for human episodic memory – one's memory for day-to-day events. Subsequent animal studies have shown that the anterior thalamic nuclei play multiple, vital roles in aspects of cognition for

which their influence has frequently been underestimated, including for spatial processing, memory, and attention[9,10,11,12]. It is proposed that (like the hippocampus) the contributions of the anterior thalamic nuclei to the processing of spatial information are a requirement for the contextual processing and binding that is integral to the encoding and retrieval of episodic information[5,13-16], thereby allowing the representation of experiences in cognitive space[4,5].

The anterior thalamic nuclei often function in partnership with the hippocampus, with the two structures acting in parallel to effect plasticity in widespread areas of medial and midline cortex[17]. In addition, some of the spatial functions of the hippocampus rely on its inputs from the anterior thalamic nuclei[18-21]. However, there is also evidence for memory-related functions of the anterior thalamic nuclei that are independent of the hippocampus[9,10,22]. Consequently, the cognitive roles of these thalamic nuclei are not simply framed by the hippocampus, despite many overlapping areas of function.

In this article we outline a model that realigns the hippocampal formation, anterior thalamic nuclei, and cortex as necessary and co-equal partners within a tripartite mnemonic system, thereby highlighting vital, but relatively neglected, thalamic components of the brain's memory systems. The focus of the article is intentionally on the anterior thalamic nuclei in order to redress the balance of coverage given to each of the key elements of the model. Indeed, the hippocampal formation and its cortical interactions have been discussed in numerous reviews and models to which the reader is referred[4,5,15,16].

[H1] A brief history

One of the first formal descriptions of a persistent amnesic syndrome was published by Robert Lawson[23] in 1878. Summarising his observations of a series of patients with amnesia driven by alcohol abuse, Lawson wrote that the “feature of such cases which is sufficiently striking to give character to them is the almost absolute loss of memory for recent events”. Almost a decade later, the same alcohol-related amnesic syndrome was more famously described by Sergei Korsakoff[24], who noted that “especially characteristic is a derangement of memory and of the association of ideas”. Shortly thereafter, based on post-mortem studies, Hans Gudden[6] reported that “atrophy of the mammillary bodies appears to be a frequent finding in cases of alcohol neuritis with amnesia (and perhaps generally in chronic alcoholism)”. By the early 20th century, further post-mortem studies[7] confirmed the consistent mammillary body involvement in what had come to be known as Korsakoff syndrome,

alongside apparently more variable thalamic pathology (reviewed in REF[8]). The latter included changes in the anterior thalamic nuclei[8,25] (which comprise the anterodorsal, anteromedial, and anteroventral nuclei; **Fig. 1**). Linking these diencephalic pathologies is how the anterior thalamic nuclei form the principal target of mammillary body neurons[26,27]. It might, therefore, be supposed that the contributions of these two diencephalic sites (the anterior thalamic nuclei and the mammillary bodies) to episodic memory would have been intensively scrutinised. That is not what happened: instead, the hippocampus took centre stage.

In 1900, Vladimir Bekhterev[28] reported a possible link between hippocampal damage and memory loss in humans. However, it still took decades for this idea to become established (reviewed in REF[29]), with the landmark case of amnesic patient H.M.[30] playing a central role. Meanwhile, research into diencephalic amnesia remained severely hampered by the lack of a similar landmark case with confirmed, discrete pathology. Indeed, identifying such patients has remained problematic, mainly because of the twin difficulty of distinguishing individual diencephalic nuclei and determining potential disruption to fibres of passage when relying on non-invasive imaging. In contrast, studies linking hippocampal pathology and memory took advantage of the sensitivity of this structure to conditions such as anoxia[31-33] while its size and location enabled imaging studies. Perhaps just as detrimental for diencephalic amnesia has been the pervasive view that the mammillary bodies and anterior thalamic nuclei function as downstream enablers for the hippocampus[34-37] and are thereby of secondary importance. This perspective was first popularised in accounts of the 'Papez circuit', a loop of extended hippocampal connections that was previously thought to maintain emotions[34].

Hippocampal research was further galvanised by the parallel discoveries, in animal experiments, of place cells[38] (which fire selectively at certain locations), synaptic plasticity in the form of long-term potentiation[39], and confirmation that damage to the hippocampus severely disrupts performance in tests of spatial memory[40]. More recent studies have demonstrated a key role of hippocampal oscillations (rhythmic patterns of neuronal firing) for the optimisation of plasticity[41,42], while findings from intracranial recordings in the medial temporal lobe of epileptic patients have shown that theta oscillations are associated with navigation[43] and episodic recall[44-46]. Inevitably, therefore, investigations into the mechanism of episodic memory gravitated towards the hippocampus and were later refined by considering hippocampo–cortical interactions[15,41,47-49]. This hippocampal-centred approach

further reinforced the notion that the anterior thalamic nuclei merely serve as relays or have ill-specified roles in modulating or activating temporal lobe structures supporting memory[35-37,50].

[H1] Revisiting the anterior thalamic nuclei

To rebalance the situation outlined above, there is a pressing need to appreciate the distinct contributions of medial diencephalic sites to memory. Chief among these sites are the anterior thalamic nuclei. Over recent years, there has been a growing awareness that these nuclei can contribute to the cognitive changes associated with aging[51], mild cognitive impairment[52,53], various dementias[53-55], and, potentially, an array of other neurological and psychiatric disorders[56-58]. Meanwhile, the discovery of neurons within the rodent anterior thalamic nuclei that signal different types of spatial information (**Table 1**) has forced a further rethink regarding the significance of these nuclei in cognition[59].

[H2] Anterior thalamic connectivity

The anterior thalamic nuclei stand out among medial diencephalic structures as they receive dense, direct hippocampal and parahippocampal projections (**Fig. 2 ; Table 1)** from the subiculum, presubiculum, and postsubiculum, as well as providing direct return projections to the same sites[60-63]. Importantly, comparable sets of connections are present in rodents and nonhuman primates[64]. In addition, the rodent anterior thalamic nuclei receive sparse inputs from hippocampal area CA1[65], while sparse inhibitory projections from CA3[66] target the anterodorsal nucleus. Meanwhile, almost every mammillary body neuron is thought to innervate the anterior thalamic nuclei through the mammillothalamic tract[26,27]. Via this monosynaptic mammillary route, the subiculum, presubiculum, and postsubiculum provide additional, indirect influences on the anterior thalamus[27,64]. The anterior thalamic nuclei also have extensive reciprocal connections with retrosplenial and anterior cingulate cortices[64]. Consequently, the anterior thalamic nuclei interlink multiple cortical and subcortical areas strongly associated with memory, amnesia, and spatial processing[35,37,50,64,67].

[H2] Comparisons with other thalamic nuclei

Other medial diencephalic sites contribute to cognition[68]. Foremost among these are the thalamic nucleus reuniens and the dorsomedial thalamic nucleus (reviewed in REFs [69-71]). While both nucleus reuniens and the anterior thalamic nuclei support spatial learning and memory, anterior thalamic lesions have a wider impact in rats and are the more disruptive[71-75]. Although nucleus reuniens is also reciprocally connected with the hippocampus, including

direct inputs to CA1, it only receives sparse inputs from the mammillary bodies[76,77] and retrosplenial cortex[62] in rats. Furthermore, although the anterior thalamic nuclei and nucleus reuniens appear to be connected to overlapping cortical sites, the respective inputs from these regions are largely separated by topography and lamina[62], indicative of complementary functions. This difference can be seen in their respective importance for linking prefrontal (reuniens) and cingulate/retrosplenial regions (anterior thalamic nuclei) to the hippocampus[62,78]. In association with its prefrontal connections, the rodent nucleus reuniens assists spatial working memory[79], gating information to the hippocampus[80].

Meanwhile, the dorsomedial thalamic nucleus, which lacks direct hippocampal connections[81], is far less important for rodent spatial learning than the anterior thalamic nuclei[69,70,82]. Instead, through its dense, reciprocal connections with the prefrontal cortex, the dorsomedial nucleus supports a range of functions that rely upon the prefrontal cortex, including executive actions (reviewed in REFs[70,81]). The complementary actions of these adjacent thalamic nuclei (anterior, dorsomedial, reuniens) means that typical pathologies, which affect more than one thalamic nuclei, both increase the severity and breadth of cognitive impairments, while adding to the difficulty of discerning the roles of individual regions[70,83].

[H2] Hippocampal comparisons

To understand why the anterior thalamic nuclei deserve more attention it is helpful to make comparisons with the hippocampus. Numerous parallels emerge. Just as hippocampal tissue loss is principally responsible for temporal lobe amnesia[31-31], so the anterior thalamic nuclei are at the core of diencephalic amnesia. The relevant clinical evidence for the latter statement largely derives from two sources; studies of Korsakoff syndrome[8,25,84] and systematic analyses of diencephalic strokes[8,85,86]. The second approach repeatedly shows that mammillothalamic tract involvement is the best predictor of memory loss following thalamic infarcts[85,86], highlighting the importance of the anterior thalamic nuclei, the principal target of the mammillothalamic tract (**Figs. 1C, 2**).

Meanwhile, behavioural studies in rodents repeatedly show that anterior thalamic lesions cause spatial memory deficits that parallel those following hippocampal lesions[11,72,87-89]. These deficits are striking with respect to their range and severity[11]. Indeed, the consequences of anterior thalamic lesions on spatial memory tasks are often greater than those of lesions to other sites beyond the hippocampal formation[11,71,72,89-91]. A resulting question is, therefore, whether anterior thalamic lesions can be as disruptive as hippocampal damage. Unfortunately,

almost all evidence relating to this question is indirect, coming from comparisons of anterior thalamic lesions with lesions to the fornix, the principal tract containing extrinsic hippocampal fibres. For this reason, fornix lesions only partially replicate hippocampal damage[92,93].

While the effects of fornix lesions and anterior thalamic lesions on spatial memory tasks are sometimes similar [11,94-98], anterior thalamic damage can also be more disruptive[73,99]. For example, a geometric deficit in the framing of space[99] is seen after hippocampal and anterior thalamic (but not fornix) lesions[99,100]. Other relevant findings show that lesions of the fornix, hippocampal formation, and anterior thalamic nuclei all cause comparable deficits on tests of automated delayed nonmatching-to-sample in rats when using identical methodologies[98,101]. This equivalence is notable as the same spatial paradigm has advanced our appreciation of hippocampal memory functions[102]. At the same time, complete hippocampal formation lesions (which include the subiculum) appear more disruptive than anterior thalamic lesions for reinforced spatial alternation[11]. Interpretations of this difference should, however, be made with care as 'hippocampus proper' lesions, i.e., surgeries that spare the subiculum, are associated with more limited spatial deficits[103,104]. These findings raise the possibility that hippocampus proper lesions and anterior thalamic lesions could have equivalent disruptive effects.

[H2] Not just head-direction

With hindsight, the failure of the severe spatial memory deficits after anterior thalamic lesions to spark wider interest probably stems from the misguided sense that the contribution of this site was already known. Within the anterior thalamic nuclei, the anterodorsal nucleus has long been recognised as a key component of the 'head-direction system'[18,105,106], which provides compass-like directional signals to assist navigation[18]. Indeed, lesions involving the rat anterodorsal nucleus abolish parahippocampal head-direction signals[19] and disrupt the activity of 'grid' cells[20], which normally fire at regular, discrete locations forming hexagonally spaced fields that create a metric for local space[107]. In contrast, anterodorsal nucleus head-direction signals do not require the integrity of the hippocampus[108]. However, more recent work reveals that, while the loss of head-direction signals undoubtedly contributes to the spatial deficits observed following anterior thalamic lesions[20], the loss of other anterior thalamic functions plays its part[121,109]. Arguably, the clearest evidence comes from the demonstration in rats that disconnecting the ascending head-direction pathway (from the lateral mammillary nucleus to

the anterodorsal thalamic nucleus) only induces mild, transient spatial learning deficits[110,111]. These mild impairments are in marked contrast to the severe, persistent, mnemonic deficits seen after lesions involving all three anterior thalamic nuclei[11,12,89,112]. One important conclusion is that head-direction information is not a proxy for episodic memory processing[111].

It remains interesting to consider why attention remained firmly fixed on the hippocampus at the expense of the anterior thalamic nuclei given their demonstrable importance for spatial processing and memory. It seems most probable that the landmark discoveries of place cells and forms of synaptic plasticity, such as long-term potentiation (LTP), within the hippocampus[38,39] opened the way for a myriad of investigations into memory at the neuronal level at a time when no counterparts existed for the thalamus[113].

[H2] Spatial signalling and plasticity

The discovery of spatial cell-types beyond head-direction cells in the rat anterior and midline thalamus has more recently encouraged a broader conception of thalamic spatial signalling[59,114-116]. These anterior and midline thalamic spatial cells resemble the grid, place, and border cells (which signal the perimeter of an environment) found in the medial temporal lobe[114,115]. In addition, head-direction cells have been found more extensively across the anterior thalamic nuclei[59,116], i.e., beyond the anterodorsal nucleus. One feature of all of these thalamic spatial cells is the high-fidelity of the spatial information that they encode, undermining one previous suggestion that these nuclei merely enable some form of diffuse cortical arousal[117,118]. These discoveries are additionally significant because spatial processing provides a framework not only for navigation but also for an array of other cognitive processes. In particular, contextual information plays an integral role in episodic memory encoding and retrieval, while being particularly important for the visualization of information[4,14-16,47,119].

The hippocampus understandably remains a favoured target for studies of neuronal plasticity, although we are also beginning to appreciate the plasticity that takes place within medial thalamic nuclei. A feature of this plasticity is that its underlying mechanisms may depend on the fibres of origin. One set of experiments[120] examined the plastic responses of rat anterior thalamic synapses to different types (high- and low-frequency) of stimulation. These investigations revealed that basal synaptic transmission mediated by the mammillothalamic

tract undergoes stimulation-dependent, BDNF-mediated potentiation [120]. This pathway resulted in LTP of the thalamic field response, and was induced predominantly via high-frequency stimulation. By contrast, anterior thalamic long-term depression (LTD) of the field response could only be induced after low-frequency stimulation of the direct subiculum (hippocampal) projections to the anterior thalamic nuclei[120], which largely rely on the fornix. Hence, the two major tracts that mediate direct routes to the anterior thalamic nuclei (fornix vs mammillothalamic tract) exhibit opposing plasticity characteristics. This suggests the integration of hippocampal and mammillary body inputs depends on the pattern of prior activity in the fornix and mammillothalamic tract components of the circuit. Furthermore, evidence of the balancing effects of these parallel pathways upon anterior thalamic activity reinforces the notion that the anterior thalamic nuclei do not merely duplicate hippocampal functions, helping us to appreciate how they may make independent contributions to episodic memory consolidation, perhaps by offering complementary pathways to stabilise memory, allowing mnemonic streams that function in parallel and are partially independent of each other (**Fig 4**).

Deep-brain thalamic recordings in epileptic patients have added to our knowledge. Anterior thalamic activity has, for example, been linked to memory retrieval[121]. Meanwhile, a series of related studies describes how oscillatory activity in the anterior thalamic and dorsomedial thalamic nuclei correlates with memory performance[122-124]. For example, the presence of theta oscillation synchrony across neocortical and anterior thalamic areas, as well as cross-coupling with gamma oscillations, predicted subsequent memory for complex photographic scenes[122]. These findings have been incorporated into the hypothesis that the anterior thalamic nuclei promote the selection and coordination of task-relevant information during human memory formation[124]. A further implication is that the role of the anterior thalamic nuclei in memory encoding involves accessing information from widespread neocortical sources, including frontal areas[124].

Imaging studies, using both functional and structural MRI, have repeatedly highlighted hippocampal associations with spatial[125,126] and episodic[127-129] memory. Comparable imaging information concerning the anterior thalamic nuclei had been largely lacking, partly due to the difficulty of localising these nuclei in the human brain. Evidence of progress comes from the relatively few but growing number of MRI-based studies of cognition reporting activity-related signals in anterior thalamic regions[22,130-133]. fMRI studies of associative recognition[130],

as well as comparisons of familiarity with recollective based recognition[132], implicate anterior thalamic nuclei activity in the encoding[130] and recall[130,133] of episodic information. Moreover, advances in both structural and functional MRI[134-136] make it increasingly feasible to interrogate individual anterior thalamic nuclei (**Fig. 1**).

[H1] Separating the anterior thalamic nuclei

Evidence that distinct functional contributions are made by the three anterior thalamic nuclei has come from multiple levels of animal research (**Table 1**). For example, electrophysiological recordings in rats show different distributions of both spatial[59,114-116] and theta-modulated[137] cells across the three nuclei, while gene-transcription analyses show that each nucleus belongs to a different cluster of brain sites, each with individual gene expression profiles[138]. Extending these differences, the anatomical inputs to each individual nucleus[60,64] is distinct (**Fig. 2**). Meanwhile, lesion studies in rats repeatedly reveal that, while each nucleus contributes to spatial learning and memory, their combined impact is far greater than a lesion within any single nucleus[21,66,109,112,140,141].

The differences between the three principal anterior thalamic nuclei are most apparent for the anterodorsal nucleus, which — in addition to being the only nucleus to contain large numbers of head-direction cells — has distinct cytoarchitectural and connectomic properties (**Table 1**). The concentration of head-direction cells in this nucleus points to a principal role in navigation, allied to the growing appreciation that head-direction information can impact on other classes of spatial cells[20,142]. In addition, the firing of mouse anterodorsal neurons immediately before hippocampal sharp-wave ripples during non-REM sleep may signal previously experienced directions of movement[143], potentially contributing to consolidation. The finding that ~60% of rat anterodorsal units can be classified as head-direction cells[105] does, however, raise questions about the functional properties of the remaining cells. It is, therefore, of interest that optogenetic silencing of the inhibitory projection from hippocampal area CA3 to the anterodorsal nucleus disrupts contextual fear memory retrieval after extended delays[66], again pointing to a role in mnemonic consolidation.

Functional differences between the anteromedial and anteroventral nuclei are, at present, often speculative because few behavioural studies have sought to isolate these nuclei (**Table 1**). Of the anterior thalamic nuclei, in both rodent and primates the anteromedial nucleus has the most links with the medial prefrontal and anterior cingulate cortices, alongside further

connections with perirhinal cortex, dysgranular retrosplenial (area 30) cortex, and related visual areas[60,64,144-146]. The anteromedial nucleus also contains place cells and border cells, but few head-direction cells[59,114,115]. Targeted lesions of this nucleus give modest deficits on spatial working memory tasks[139,140], with further evidence of a selective contribution to the retrieval of spatial information[109]. Largely based on its frontal connectivity, it might be supposed that the anteromedial nucleus assists in the retrieval of high-interference information – that is, the separation of related target information[147,148]. Other potential roles for this region include the integration of item and contextual information in parahippocampal areas, while its anterior cingulate connections suggest that it may support aspects of attention[149] (**Fig. 3**). The combination of functions implies dynamic relations between differing cognitive processes; spatial processing and attention are deployed during episodic memory encoding and consolidation (as they are contributory processes to memory), but might function independently of memory during other tasks.

Meanwhile, the anteroventral nucleus is well connected with dorsal hippocampal, presubicular and postsubicular sites, along with the granular retrosplenial cortex (area 29)[60,64]. Its concentration of inputs from the rat distal subiculum[53] further underline its links with spatial processing[150,151]. The anteroventral nucleus also contains most of the theta-modulated neurons within the anterior thalamic nuclei[116,137], which are jointly influenced by fibres in the fornix[152] and the mammillothalamic tract[153]. These activation patterns contribute to cortical (retrosplenial) and hippocampal oscillations, affecting plasticity[124,153]. In animal studies, reversible lesions implicate the anteroventral nucleus in the encoding, consolidation, and retrieval of spatial information[109]. These widespread effects are consistent with this region have the role of a hub nucleus with access to multiple sources of spatial codes, suggesting a potential role in on-line location monitoring, as well as gating and updating spatial information[12,109,154].

The proposed functions of the different anterior thalamic nuclei provide a working framework with which to generate testable hypotheses, with the caveat that the distinctions are heavily based on rodent studies. Other considerations include the degree of communication between these different nuclei and whether this might diminish their individual differences. While there is no evidence for local pathways between the three thalamic nuclei, Golgi stains show that dendritic fields may extend across the nuclei[155], potentially blurring distinctions. Likewise, while the connectivity of the three nuclei clearly differs, this is often by degree

rather than absolute differences[60]. For example, the anteroventral nucleus may also contribute to attentional functions with the anterior cingulate cortex[146]. Similarly, while the anterodorsal nucleus is the principal site for head-direction cells, they are also present in the anteroventral nucleus[116]. It is, therefore, likely that the functional differences between the three nuclei will prove to be nuanced.

[H1] Models of function

[H2] Interactions with the hippocampal formation

Historically, researchers have often conceptualised anterior thalamic function within the context of its dense hippocampal and parahippocampal inputs[34-37], reinforced by evidence that damage to the fornix can cause anterograde amnesia in humans[156,157]. However, the fornix makes numerous connections outside the medial diencephalon, highlighting the need to isolate hippocampal–anterior thalamic interactions to investigate their functions.

One experimental solution was to combine unilateral lesions in the anterior thalamic nuclei with unilateral lesions in the hippocampus of the opposite hemisphere. While this disconnection method helped to confirm the importance of anterior thalamic–hippocampal interactions for rat spatial learning[158,159], it could not determine the direction of effect. More targeted chemogenetic methods in rats have disrupted only those hippocampal projections that arise in the dorsal subiculum and terminate in the anteromedial and anteroventral nuclei[21]. This was sufficient to impair performance in a spatial working memory task (T-maze alternation), but only after maze rotation to further tax allocentric processing[21]. While this procedure, which spares anterodorsal nucleus function, further highlights the significance of anterior thalamic contributions to memory beyond head-direction information, the resulting deficit was not as severe as that seen after complete anterior thalamic lesions[11,21], again pointing to additive roles of the three nuclei[139,140]. Meanwhile, optogenetic studies in rats have isolated subiculum cells with different targets, revealing that place-related firing is a feature of those subiculum neurons that innervate the anteroventral thalamus, as well as the medial mammillary bodies, retrosplenial cortex, and nucleus accumbens[160].

A complementary approach to study hippocampal–diencephalic connections in humans involves diffusion MRI, which has shown that changes in fornix properties are closely associated with levels of episodic memory[161-163], with further links to recollective-based

recognition[161] and navigation[164]. A valuable refinement has allowed the isolation of the postcommissural fornix (**Box 1**), which principally contains hippocampal projections to the anterior thalamic nuclei and mammillary bodies. Such studies have found correlations between the properties of this pathway and aspects of memory, including visual recall[165] and types of spatial learning[166], suggesting that the functions of the postcommissural fornix differ from those of the precommissural fornix (which links the hippocampus with septal, striatal, and frontal sites).

The reverse challenge is to understand the importance of anterior thalamic inputs to the hippocampal formation (**Table 1**). As described above, past analyses largely focussed on head-direction signals[19,20]. More recently, however, the wider significance of anterior thalamic influences on the dorsal hippocampal formation was revealed by the discovery that in rats both permanent and transient anterior thalamic lesions cause a cessation of spatial-responsive firing (place, head-direction, border, and grid cells) within the subiculum[154], combined with impaired spatial alternation memory. In the same study, permanent anterior thalamic lesions spared hippocampal CA1 place cell fields (but see also[106]). This is important because the very dense, plastic projections from CA1 to the subiculum[167] might otherwise have been assumed to be sufficient to ensure the effective function of spatial cells in the subiculum[1564]. It remains to be determined whether the observed subiculum silencing arises from the loss of the direct or indirect inputs from the anterior thalamus. However, a recent chemogenetic study showed the importance of the direct anterior thalamic projections to the rat dorsal hippocampal formation for spatial working memory[21]. Other insights come from evidence that stimulation of the anterior thalamic nuclei in epileptic patients can modulate hippocampal gamma activity[168].

[H2] Communications beyond the hippocampus

To substantiate the case that the anterior thalamic nuclei are independently critical for memory it is necessary to highlight their connections and potential functions that are not part of traditional hippocampal circuitry. Sites such as the prelimbic, anterior cingulate, and retrosplenial cortices project to the anterior thalamic nuclei, but largely fail to directly innervate the hippocampal formation[64,194-171]; trans-synaptic tracing in rats further confirms that the anterior thalamic nuclei form a major monosynaptic route from these cortical regions to the dorsal hippocampal formation[78]. Consequently, along with the nucleus reuniens[62,78], the

anterior thalamic nuclei provide a potentially important (but rarely recognised) subcortical route, allowing frontal sites to influence hippocampal activity.

When comparing respective subcortical afferents to the anterior thalamic nuclei and hippocampal formation, the mamillary bodies provide the most striking difference. The lateral mammillary nucleus projects to the anterodorsal nucleus, whereas the medial mammillary nucleus projects to the anteromedial and anteroventral nuclei[64]. In contrast, the mammillary bodies do not innervate the hippocampal formation. The finding that mammillothalamic tract lesions in rats, which disconnect the anterior thalamic nuclei, affect oscillatory activity and neuronal microstructure in the hippocampus[153] has been interpreted as indicating a suppression of learning-induced plasticity, set alongside changes in retrosplenial theta and immediate-early gene expression[153,172]. The latter findings add to the discovery that anterior thalamic lesions cause a persistent retrosplenial hypoactivity, as measured by immediate-early genes, alongside a wider de-regulation of retrosplenial gene transcription[173,174]. Additional attention has focused on the ascending tegmental inputs from Gudden's nuclei to the mammillary bodies, which contribute to spatial navigation and learning[172,178], but do not innervate the hippocampus. It is presumed that these same tegmental inputs have their principal actions via the anterior thalamic nuclei[175].

[H2] Widening our horizons

By moving from a hippocampal-centred view, a broader perspective emerges that is illustrated by the many convergent efferent projections from the anterior thalamic nuclei and hippocampal formation to cortical sites. Projections from both structures terminate in the retrosplenial cortex and parahippocampal region, as well as the anterior cingulate and prelimbic cortices[17,63,64,176-178]. The need to look beyond reciprocal anterior thalamic–hippocampal interactions also stems from fMRI analyses of the human 'default mode network'[179,180]. This network, which was initially closely linked with self-related (introspective) tasks[178], is also activated during spatial, mnemonic, and social cognitive tasks[181-184]. The default mode network is typically regarded as comprising several subsystems, including those in the medial prefrontal cortex, posteromedial parietal cortex, and medial temporal regions, with partial separation between different areas of cognitive engagement[18-183]. One focus has been the apparent overlap between medial temporal and midline components of the default mode network and those areas that are active when remembering the past[182,184,185], including constructing mental scenes from memory as well as imagining the

future[184,185]. This overlap extends to the distributed network of brain sites associated with anterograde amnesia[61]. Such findings have strongly influenced models of memory such as the 'constructive episodic simulation hypothesis'[185,186]. Rather than memory being a replay of the past, such models emphasise the predictive construction of relevant scene information[15,186].

Connectivity analyses show that the human anterior thalamic nuclei, along with some other thalamic nuclei[187,188], have close links with multiple components of the default mode network[187]. Furthermore, damage to the anterior thalamic nuclei disrupts activity in the default mode network[189], while deep-brain stimulation of the anterior thalamic nuclei in epileptics can modulate the same network[190]. Meanwhile, functional connectivity studies place the retrosplenial cortex as a key gateway between the medial temporal lobe and frontal default mode subsystems that support episodic memory[191], suggesting that anterior thalamic damage may impact on landmark and scene construction via its disruptive effects on retrosplenial cortex [68,173,174,192]. Interestingly, diffusion imaging suggests a relationship between precommissural fornix status and the episodic richness of past and future events, while a similar association was not found for the postcommissural fornix[193]. One interpretation of this finding is that anterior thalamic–retrosplenial, rather than hippocampal–anterior thalamic interactions have particular significance for scene construction.

Arguably more striking evidence of the independence of the anterior thalamic nuclei from the hippocampus is seen in their contributions to specific aspects of attention[10,22,149]. Selective lesions of the anterior thalamic nuclei impair the ability of rats to accelerate their learning over a series of closely related discriminations in which normal animals narrow their attention to the same reinforced stimulus dimension[10], while ignoring other cue types. Quite remarkably, these same thalamic lesions facilitate performance when the discriminations require a dimension switch[10]. This profile of altered performance, not associated with hippocampal dysfunction[194,195], points to an independent role for the anterior thalamic nuclei in cognition that contributes to learning and memory.

Subsequent chemogenetic studies have found that disrupting anterior cingulate–anteromedial thalamic nucleus interactions cause the same profile of learning deficits and facilitation on the same test of attention assisted learning[149]. One interpretation is that the anterior thalamic nuclei, along with the anterior cingulate cortex, normally help to maintain attention to previously rewarded stimulus categories, a role extending beyond spatial processing[149]. The

paradoxical, facilitated switching occurs because the lesioned rats fail to initially disengage from a stimulus dimension that subsequently becomes the rewarded dimension. Support for this interpretation comes from functional imaging and from evidence from patients with rostral thalamic damage[22,130], though these human studies lack the anatomical precision of the rodent analyses. If correct, these rodent and human findings reveal an anterior thalamic attentional system that opposes[196] the well-established actions of those prefrontal areas that normally enable flexible responding[197-199]. Indeed, a prefrontal-like pattern of lesion effects was observed on these same attentional tasks in rats with hippocampal damage[200], thereby contrasting with anterior thalamic lesion effects. These anterior thalamic actions on attention and memory may then facilitate a wide variety of learning tasks[9,201-205].

These same findings prompt renewed interest in earlier evidence that lesions to the anterior thalamic lead to a range of nonspatial problems[9,147,148,201,202]. Some, such as deficits in recency memory[147,148], may align with alterations in hippocampal function[203]. Others, such as changes in anxiety and increased motor activity might again be linked to disrupted hippocampal function but could also reflect changes in anterior cingulate action[204]. Meanwhile, studies of classical conditioning and discrimination learning in rabbits, which employed both electrophysiological recordings and lesion analyses, highlighted the importance of delayed anterior thalamic interactions with the retrosplenial cortex that emerged after initial learning of these nonspatial associative tasks was established[9,205]. These thalamo–cortical interactions, along with others involving the dorsomedial thalamic nucleus, were interpreted as supporting the associative attention to reward-related cues that emerges during different stages of discrimination learning[9,205]. Consequently, these findings again point to the significance of the anterior thalamic nuclei for attention based on experience, contributions that may influence a variety of learning tasks, including those involving episodic memory.

[H1] A new tripartite memory model

As outlined above, the anterior thalamic nuclei make independent, wider contributions to cognitive function beyond those framed by their hippocampal connections[68] (**Fig. 3**). Through these contributions, the multiple actions of the anterior thalamic nuclei together affect episodic memory. Thus, we suggest there is a need to develop broader models of episodic memory that incorporate medial diencephalic contributions to encoding and consolidation. While this more inclusive approach appears in some existing models[35,37,50], the roles of the anterior thalamic nuclei remain poorly specified.

In the model we present here, it is suggested that there is a hippocampal–cortical memory stream, and a medial diencephalic–cortical memory stream (with the anterior thalamic nuclei at its core). The hippocampal memory stream courses from the entorhinal cortex to the hippocampus proper (the dentate gyrus, CA3 and CA1), thence to the subiculum, and onwards to cortical sites (such as parahippocampal, prefrontal, and retrosplenial cortical sites), along with parallel CA1 projections to parahippocampal and prefrontal areas[177]. Meanwhile, the anterior thalamic nuclei project to the hippocampal formation (subiculum) and the parahippocampal and retrosplenial cortices, while receiving return inputs from the hippocampal formation (many via the mammillary bodies), retrosplenial, anterior cingulate, and prefrontal cortices. Both memory streams project to several cortical sites, including parahippocampal, prefrontal, and retrosplenial cortices, where synaptic plasticity supports memory consolidation (**Fig. 4**). These mnemonic streams are envisaged to operate in parallel, with activity in each stream being partially independent of the other stream. Critically, there are cortical zones where anatomical influences from both streams converge. Anterior thalamic nuclei- and hippocampus-dependent memory depends on these zones of interaction, where synchronous activity is required for mnemonic consolidation.

This tripartite model predicts that separate lesions to the hippocampal–cortical circuit or to the medial diencephalic–cortical circuit will cause approximately equivalent deficits in episodic memory, given the significance of synchronous cortical activity at the temporal lobe and medial diencephalic sites of convergence. Thus, damage to the specific cortical sites of convergence between these two streams will also cause memory impairments[67], providing further insights into memory consolidation[15,48,49].

While details of the respective synaptic actions of these two streams are beyond the scope of this review, recent reviews[206] describe how cortical layer 1 might be critical for long-term plasticity, reflecting the convergence of thalamic inputs with those from sites such as the hippocampal formation (either directly or via parahippocampal structures)[17,176,207]. The retrosplenial cortex is a likely candidate as it receives convergent projections from the anterior thalamic nuclei, hippocampal area CA1, and the dorsal subiculum[17,176]. Within retrosplenial cortex layer 1, opposing excitatory anteroventral nucleus and inhibitory CA1 actions have contrasting, vital effects on mouse contextual fear conditioning[17]. Furthermore, superficial vesicular glutamate transporter 1-expressing ($VGLUT1^{+}$) projections from the subiculum to

retrosplenial cortex may be involved in processing recent context memories, whereas corresponding VGLUT2^{+} projections to retrosplenial cortex contribute to their long-lasting storage[176]. Such findings reinforce the value of initially exploring joint hippocampal and anterior thalamic influences on cortical sites, while underlining how the anterior thalamic nuclei make independent contributions. Intriguingly, the anterior thalamic and dorsal subiculum projections strongly target small low-rheobase pyramidal cells in the retrosplenial cortex, while neighbouring regular-spiking cells are preferentially controlled by claustral and anterior cingulate inputs, sources of mostly non-spatial information[208]. Such analyses begin to reveal the true complexity of many of these cortical interactions.

[H1] Future challenges

Many issues remain. These include the need to test the potential significance of the anterior thalamic nuclei for landmark and scene construction, while determining whether converging hippocampal formation and anterior thalamic projections within retrosplenial cortex support these functions. A striking feature of the hippocampal projections to the retrosplenial cortex in rats is that approximately 50% of them collateralise so that the same neurons also innervate the mammillary bodies[209], creating a unique linkage across the anterior thalamic hub. Another issue arises from evidence pointing to an especially important role for the human anterior thalamic nuclei in recollective (associative), but not familiarity-based, episodic information[37,83]. Currently, the absence of patients with truly selective anterior thalamic pathology has stalled the ability to test this prediction. Perhaps for this same reason, the findings from thalamic stroke patients remain mixed[210-212]. There does, however, appear to be more agreement from initial fMRI studies[132,133], which find support for the recollection:familiarity distinction with respect to the anterior thalamic nuclei, but replications are required. Further issues concern the potential significance of the anterior thalamic nuclei for memory retrieval[109] and whether their roles are facilitated by their frontal connections[41,78,169].

Additional challenges involve making further comparisons with other components of the cognitive thalamus. For example, nucleus reuniens appears to be the principal thalamic relay to the rodent hippocampal formation from more rostral and ventral prefrontal cortical sites, while the anterior thalamic nuclei increasingly replace that role for cingulate and retrosplenial projections indirectly reaching the hippocampus[62,78]. The functional consequences of these differences require added examination. Other issues stem from growing evidence that the

anterior thalamic nuclei contribute to specific aspects of attention[22,149,201], a function that is potentially independent of the hippocampus but can still affect learning and memory. This impact on learning can be seen in how animals with anterior thalamic lesions fail to benefit from the repeated experience of prior, similar discriminations[10]. Human neuropsychological studies also point to deficits in executive function following rostral thalamic damage[130] that stem from the attentional demand. Related fMRI studies also suggest anterior thalamic influences on working memory[22] and point to contributions away from the medial temporal lobe[130,201]. It may prove relevant that recent diffusion imaging studies[213] suggest that the anterior thalamic nuclei are far more richly connected with prefrontal areas than often suspected from animal tracer studies. While dense reciprocal anterior cingulate–anterior thalamic interconnections have long been recognised[60-,64], there are increasing reasons to believe that the anterior thalamic nuclei not only receive information from distributed areas of prefrontal cortex[62,162], but may prove to act back upon these same areas, both directly and indirectly, to support cognition[124]. Determining these prefrontal contributions represents an important future challenge.

Our review prompts the question of whether the anterior thalamic nuclei have one paramount function that largely explains their significance for memory, or whether their importance arises from multiple contributions to memory, spatial processing, and attention. The present analysis strongly suggests the latter (**Fig. 3**). Furthermore, their widespread zones of prefrontal[124] and cingulate[9,64,17] influence create broader opportunities for these thalamic nuclei to contribute to collective mnemonic schemas, affective states, and avoidance learning[9,204,205,214], offering a variety of clinical opportunities for cognitive investigations. One example arises from how deep brain stimulation of the anterior thalamic nuclei in epileptic patients can improve a colour-matching working memory task[168]. Meanwhile optogenetic theta-burst stimulation of the rat anterior thalamic nuclei can rescue the spatial working memory deficit following mammillothalamic tract lesions[215] - findings that yet again underline the significance of these thalamic nuclei for cognition.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

Table 1 Contrasting properties of the three principal anterior thalamic nuclei

Property	Anterodorsal nucleus	Anteromedial nucleus	Anteroventral nucleus
Gene expression	Unique expression profile[138]	Expression profile corresponds to a cluster of 8 thalamic nuclei[138]	Expression profile corresponds to a cluster of 5 thalamic nuclei[138]
Electrophysiology	Head-direction cells predominate[105] Activity associated with hippocampal sharp wave ripples[143]	Place cells [59,115] and perimeter cells[114] identified	Head-direction cells (modest numbers)[116] Theta oscillations[116,137]
Cortical and hippocampal inputs*‡	Presubiculum[64,218] Postsubiculum[64,218] Hippocampal area CA3 (sparse)[66] Retrosplenial area 29[§64,219]	Dorsal subiculum (proximal)[61,64,218] CA1(sparse)[65] Retrosplenial area 30[64,220] Anterior cingulate cortex[60,146] Prelimbic cortex[60,146]	Dorsal subiculum (distal)[61,64,218] Retrosplenial area 29[64] Anterior cingulate cortex[60,146] Prelimbic cortex[60,146]
Subcortical inputs*‡	Lateral mammillary nucleus (bilateral)[27,217] Dorsal-most rostral reticular thalamic nucleus[216]	Medial mammillary nucleus (ipsilateral)[27,60,217] Upper half of the rostral reticular thalamic nucleus[216]	Medial mammillary nucleus (ipsilateral)[27,60,217] Dorsal rostral reticular thalamic nucleus[216]
Projection targets*	Presubiculum[64] Postsubiculum[64] Retrosplenial area 29 [64,117,219] (layers I, III and IV)	Subiculum (ventral)[63] Area 29[117,144, 219] (layers I and V; light input) Area 30[117,144,220] (layers I, V and VI) Prelimbic cortex [144] (layers I, III, IV and V) Anterior cingulate cortex[144] (layers I and V)	Subiculum (dorsal)[63] Area 29[17,117, 219] (layers I and IV) Area 30[117,220] (layer IV, light)
Transient lesion effects - passive avoidance	No effect[109]	Deficit in consolidation[109]	Deficits in consolidation and retrieval[109]
Transient lesion effects on spatial memory (Morris water maze)	Deficit in retrieval[109]	Deficit in retrieval[109]	Deficits in encoding, consolidation and retrieval[109]
Permanent lesions effects - spatial working memory	Deficit[141] (but included lateral dorsal nucleus damage)	Modest deficit[112,139,140]	Modest deficit[112,139,140]

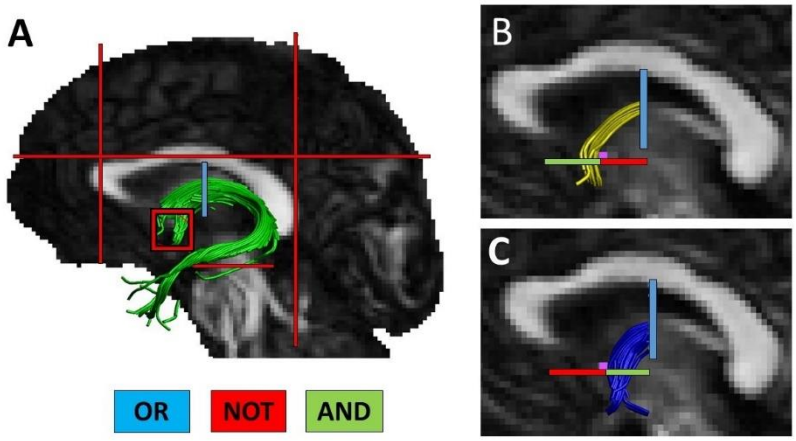
The information in the table is derived from rodent data. *Some very light connections are not included. ‡Note that few individual neurons innervate more than one anterior thalamic nucleus[52]. §Note that retrosplenial cortex comprises areas 29 and 30.

Figure 1. Location of the anterior thalamic nuclei. A, **B**. Visualisation of the anterodorsal (red), anteromedial (yellow), and anteroventral (green) nuclei, along with adjacent thalamic nuclei from MRI images[213]. Each columns shows axial (upper), coronal (mid), sagittal (lower) sections. Those on the left are overlaid on the MNI brain template with corresponding X, Y, and Z coordinates. Those are the right are corresponding 3D rendered views of the selected nuclei overlaid on a thalamic template. **C**. Dissection of the human brain[222] showing midline sagittal view of the medial temporal lobe (lower) and medial diencephalon (upper). The major tracts appear white. **D**. Location and arrangement of thalamic nuclei in the rat brain, with the anterior thalamic nuclei highlighted in colour[223] Abbreviations: 3V, third ventricle; AD, anterodorsal nucleus; AM, anteromedial nucleus; Amy, amygdala; ATN, anterior thalamic nuclei; AV, anteroventral nucleus; CeM, central medial nucleus; CL, centrolateral nucleus; F, fornix; IAM, interoanteromedial nucleus; ic, internal capsule; LD, laterodorsal nucleus; LGN lateral geniculate nucleus; LP, lateral posterior nucleus; Hb, habenula; HPC, hippocampus; MB, mammillary bodies; MD, mediodorsal nucleus; MGN, medial geniculate nucleus; MNI, Montral Neurological Institute; MTT, mammillothalamic tract; PC, paracentral nucleus; PCF, postcommissural fornix; Pf, parafascicular nucleus; PT, paratenial nucleus; Pul, pulvinar; PuM, medial pulvinar; PV, paraventricular nucleus; RE, nucleus reuniens; RT, reticular thalamic nucleus; sm, stria medullaris; st, stria terminalis; VA, ventral anterior nucleus; VL, ventrolateral nucleus; VM, ventromedial nucleus; VPL, ventral posterior nucleus, pars lateralis. (A, B. With permission from W. Grodd[213]; C, D permission from O'Mara[223]).

Fig. 2: **Principal connections of the anterior thalamic nuclei.** The main diagram depicts the connectivity of the rodent anteromedial nucleus (AM), the anteroventral nucleus (AV), and the anterodorsal (AD) thalamic nucleus [26,27,60-64,144-146,217,218]. The thickness of the arrows reflects the relative density of the various connections. Dashed arrows indicate connections that do not directly target the anterior thalamic nuclei (ATN) but are potentially important for their contribution to episodic memory. The schematic to the right includes key pathways considered in the text. AC, anterior cingulate cortex; CB, cingulum bundle; F, fornix; HPC, hippocampal formation; LMB, lateral mammillary nucleus; M Bodies, mamillary bodies; MPF, medial prefrontal cortex; MMB, medial mammillary nucleus; MPF, medial prefrontal cortex; MTT, mammillothalamic tract; PHC, parahippocampal region; RSP, retrosplenial cortex.

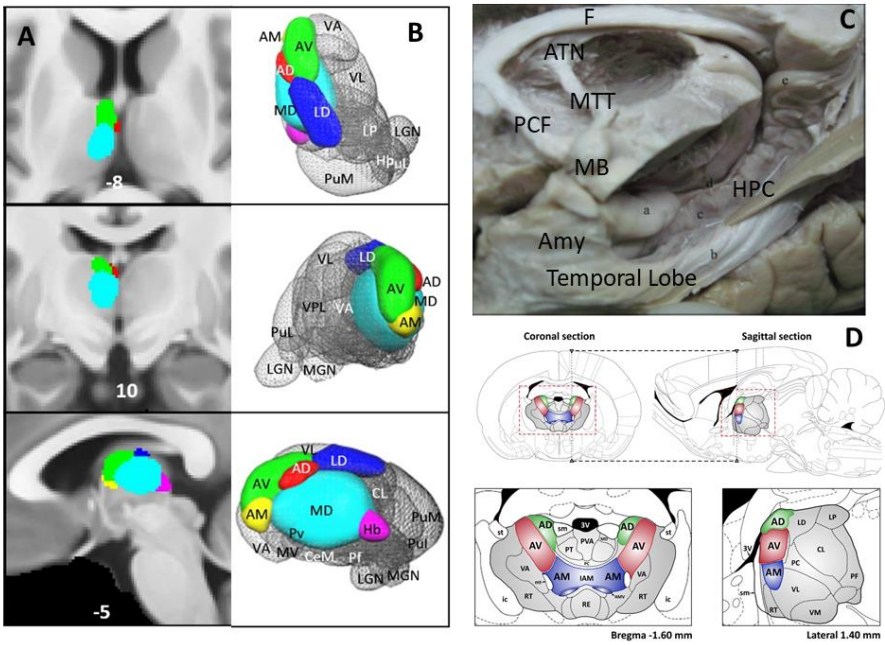
Fig. 3: Proposed anterior thalamic participation in cognition. Hypothesised mapping of three interleaving, interconnected, 'cognitive zones' of anterior thalamic nuclear influence. Each zone maps cognitive functions — spatial processing[18-21,37,50,59,87-89,94,105,109,124,154] attention[9,10,59,124,130,149], and memory [8,9,17,35,37,50,59,83-86,109,149]— to particular anterior nuclei (as confirmed by lesion, recording, anatomical tracing, or other evidence) illustrating their extensive contributions to multiple aspects of cognition. This mapping of functions implies fast-acting, dynamic relations between spatial processing, attentional, and mnemonic processes; spatial processing and attention are deployed during episodic memory encoding and consolidation (as they are contributory processes to memory), but equally they may well be independent of memory during other tasks. In sum, this figure illustrates that individual anterior thalamic nuclei participate in multiple, but particular, cognitive functions (namely, spatial processing, attention, and memory).

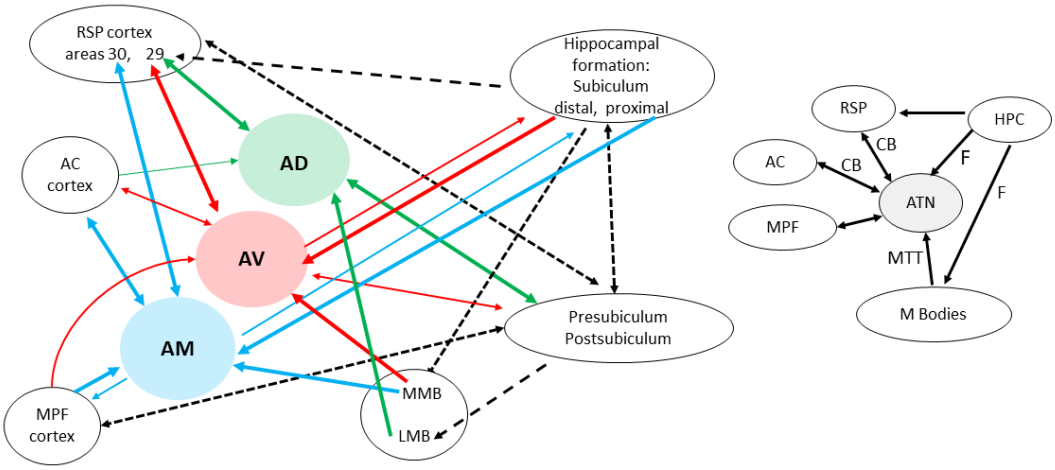
Fig. 4: A core, tripartite episodic memory system. An anatomically-simplified schematic of the parallel, interacting circuits supporting our model of a core, tripartite episodic memory system. According to the model, this system comprises a 'temporal lobe' stream (hippocampal-centred) and a 'medial diencephalic' stream (anterior thalamic-centred) that together act on independent and shared cortical areas (including parahippocampal, prefrontal, and retrosplenial cortices; note that more detailed connections are presented in **Fig. 2**). These mnemonic streams function in parallel and are partially independent of each other. There are cortical zones of anatomical overlap where projections from both streams converge; anterior thalamic nuclei-hippocampus dependent memory depends on these anatomical zones of interaction, where synchronous activity is required for mnemonic consolidation. The rules governing plasticity at many of the synapses in this circuit remain to be comprehensively investigated.

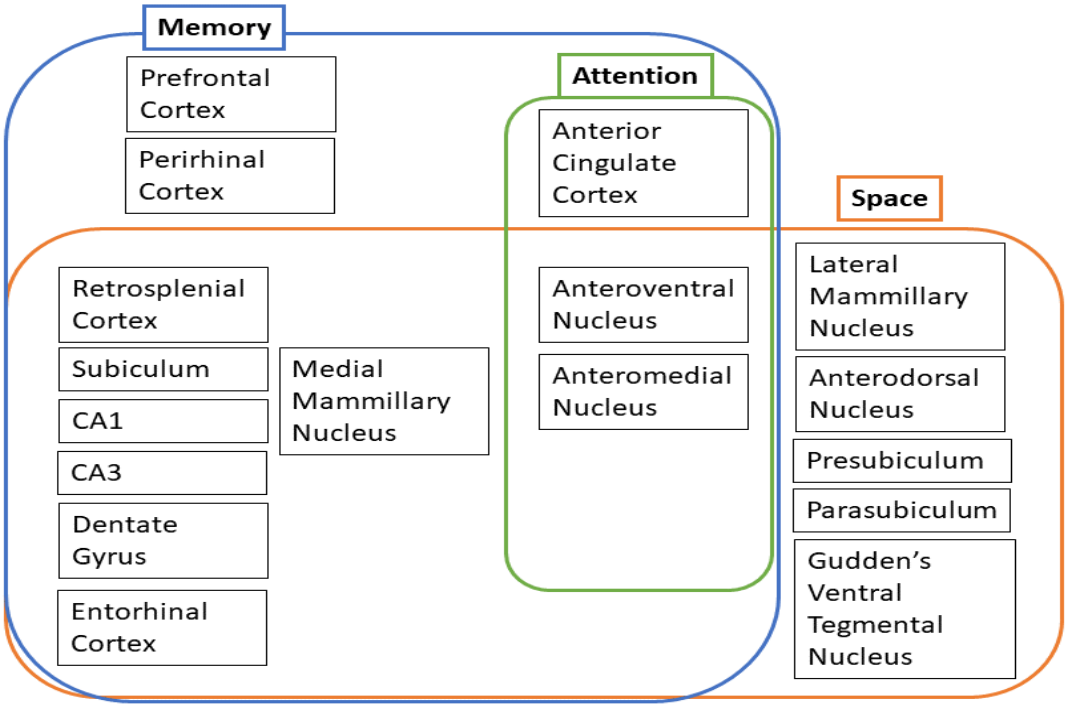


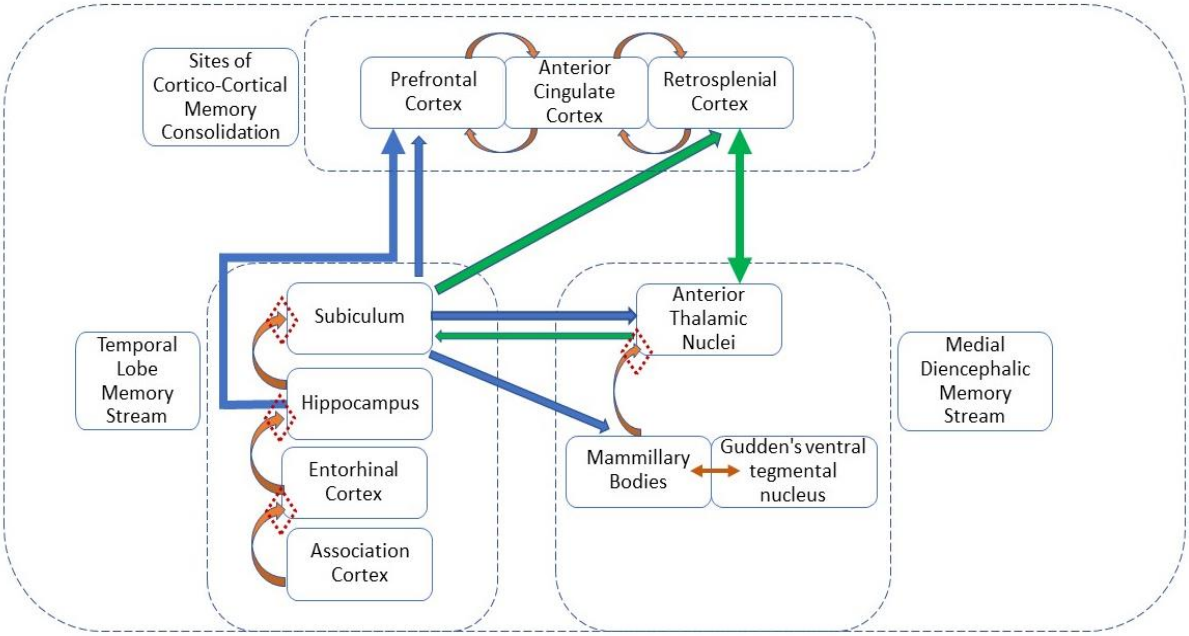
Box 1. Visualisation of fornix pathway and its subdivisions with diffusion imaging. Diffusion imaging has delivered insights into the properties of fibre pathways associated with the anterior thalamic nuclei and how they may change in disease states[84] or relate to individual variations in cognitive performance by healthy participants[161-166]. Diffusion imaging uses the movement of water molecules to reconstruct white matter pathways and changes in the patterns of diffusion can provide indirect insights into the structural status of the pathway. This technique makes it possible to not only reconstruct the fornix (see the figure, part **A** green) but also to separate those fibres that pass in front ('precommissural' B) and behind ('postcommissural' C) the anterior commissure (from[166] with permission). This separation is informative as anatomical studies[221] show that the postcommissural fornix contains most of the direct hippocampal projections to the anterior thalamic nuclei along with the indirect projections via the mammillary bodies. To isolate the precommissural fornix (B – see also **Fig 1C**), a 'NOT' gate (red) is placed immediately behind the anterior commissure (centre of red box in A and pink pixel in B and C). This NOT gate precludes those fibre streams passing behind the commissure. Meanwhile, the AND gate in front of the commissure ensures that just fibre

streams in this region are visualised. The converse arrangement isolates the postcommissural fornix (C). The OR gate makes it possible to identify those fibres in the body of the fornix that pass in front or behind the anterior commissure. In this way it is possible to distinguish hippocampal – prefrontal (precommissural fornix) influences from hippocampal – diencephalic (postcommissural fornix) influiences using non-invasive techniques.


A
B
C
D
AM
AV
VA
AD
VL
MD
LD
LP
LGN
HPuL
PuM
-8
VPL
PuL
MGN
10
CL
Pv
Hb
PuM
Pul
MV
CeM
Pf
-5
F
ATN
MTT
PCF
MB
HPC
Amy
Temporal Lobe
Coronal section
Sagittal section
Bregma -1.60 mm
Lateral 1.40 mm


RSP cortex
areas 30, 29
Hippocampal
formation:
Subiculum
distal, proximal
AC
cortex
AD
AV
AM
MPF
cortex
MMB
LMB
Presubiculum
Postsubiculum
RSP
HPC
CB
CB
F
F
AC
ATN
MPF
MTT
M Bodies


Memory
Prefrontal Cortex
Perirhinal Cortex
Attention
Anterior Cingulate Cortex
Space
Retrosplenial Cortex
Subiculum
CA1
CA3
Dentate Gyrus
Entorhinal Cortex
Medial Mammillary Nucleus
Anteroventral Nucleus
Anteromedial Nucleus
Lateral Mammillary Nucleus
Anterodorsal Nucleus
Presubiculum
Parasubiculum
Gudden's Ventral Tegmental Nucleus


Sites of Cortico-Cortical Memory Consolidation
Prefrontal Cortex
Anterior Cingulate Cortex
Retrosplenial Cortex
Temporal Lobe Memory Stream
Subiculum
Hippocampus
Entorhinal Cortex
Association Cortex
Anterior Thalamic Nuclei
Mammillary Bodies
Gudden's ventral tegmental nucleus
Medial Diencephalic Memory Stream