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## Anterior hippocampus: the anatomy of perception, imagination and episodic memory

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### Abstract

The brain creates a model of the world around us. We can use this representation to perceive and comprehend what we see at any given moment, but also to vividly re-experience scenes from our past and imagine future (or even fanciful) scenarios. Recent work has shown that these cognitive functions — perception, imagination and recall of scenes and events — all engage the anterior hippocampus. Here we capitalise on new findings from functional neuroimaging to propose a model that links high-level cognitive functions to specific structures within the anterior hippocampus.

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The hippocampus is critical for learning, memory and cognition. It is one of the most studied brain structures in neuroscience and efforts to understand its functions continue apace. In particular there is considerable interest in functional differences between neural populations located at different points along its anterior–posterior axis<sup>1–5</sup>. A recent literature review<sup>3</sup> showed that, in addition to the gradients of gene expression and connectivity that vary along the length of the hippocampus, the anterior portion of the hippocampus (also known as the head, ventral or temporal region) can be distinguished from the intermediate and posterior sections (also known as the tail, dorsal or septal regions) by sharp changes in these functional characteristics.

The anterior hippocampus (and particularly that of humans) has proved to be difficult to study, as a result of its complex anatomy<sup>6</sup>. It has an intricate structure with unique cellular morphology and is positioned at the junction between the parahippocampal gyrus, the amygdala and posterior hippocampus. It has widespread connectivity and damage that includes the anterior hippocampus has a deleterious effect on learning, memory and navigation<sup>7–9</sup>. However, we are only beginning to understand its precise anatomy in humans<sup>10</sup> and consequently little is known about the specific structures within the anterior hippocampus that contribute to these important cognitive functions.

In this article, we focus on the human anterior hippocampus. We summarise current knowledge of its anatomy and highlight a striking consistency in the functional magnetic resonance imaging (fMRI) literature, which suggests that specific substructures within the

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anterior hippocampus make critical contributions to episodic memory, imagination and visual scene perception. Claims that the hippocampus (and the medial temporal lobes (MTL) more generally) performs functions beyond memory (such as visual perception) are heavily contested<sup>11</sup>, particularly because it is difficult to design experiments that unequivocally control for memory encoding and retrieval. By emphasising the importance of anatomical detail, and by reference to known connectivity across species, we propose a model of anterior hippocampal function that may help to clarify recent discussions of functional differences in the long axis of the hippocampus<sup>1–4</sup> as well as the relationship between visual perception and memory.

## Anterior hippocampus anatomy

In humans, the hippocampus is cradled by the parahippocampal gyrus which is positioned beneath it. The anterior part of the parahippocampal gyrus bends over and rests upon itself, forming the uncus. The various gyri that are visible on the brain's surface (Box 1) cover both the amygdala and the anterior portion of the hippocampus. Beneath this surface, the hippocampus is divided into cytoarchitecturally defined subfields. These are commonly thought of as being arranged in a canonical circuit, which can be visualised by slicing the main body of the hippocampus in cross section (Fig 1). In this circuit, the entorhinal cortex (EC), which is part of the neighbouring parahippocampal gyrus, projects to the dentate gyrus (DG), which in turn drives subfield CA3 then CA2, CA1 and the subiculum, before projecting back to EC. Also visible in this plane are regions related to, but distinct from the subiculum: the prosubiculum, presubiculum and parasubiculum. The prosubiculum is situated between CA1 and the subiculum. However, despite many differences between its connectivity and that of the subiculum<sup>12</sup>, these two regions are not normally separated in human neuroimaging due to the lack of borders visible with MRI. The presubiculum and parasubiculum are situated between the subiculum and the EC. These regions can be delineated with high resolution MRI<sup>10</sup> which offers new opportunities to study their functions in humans.

Understanding the arrangement of the subfields in the anterior hippocampus requires awareness of their three-dimensional shape. The main body of the hippocampus bends medially in its anterior portion (Fig 1a) to form the extraventricular part of anterior hippocampus, which is positioned within the uncus. As a result, CA1 and the subiculum must bend around a wider radius than the other subfields<sup>13</sup>. Thus, the most anterior portion of the hippocampus is dominated by CA1 and the subiculum (Fig 1b) whereas the more posterior part of the uncus contains only the DG and CA3-2 (Fig 1d). After the medial turn within the uncus, the subfields bend upwards, ascending vertically towards the amygdala (Fig 1b,c), which changes their orientation from the coronal to the axial plane.

Subfields within the uncus have cellular 'peculiarities'<sup>14</sup>: for example CA1 in the uncus - referred to as CA1' - has smaller and more densely packed neurons than CA1 in the body of the hippocampus<sup>13</sup> (note that CA1' is labelled uncal subiculum in an alternative nomenclature<sup>15</sup>). The vertical part of the uncus has particularly differentiated cytoarchitecture - for instance, vertical CA1' contains more densely packed pyramidal cell

bodies than horizontal CA1' or CA1 of the hippocampal body<sup>10</sup>. The functional implications of these cellular differences are unknown.

Although the subfields are usually studied in slices perpendicular to the hippocampal long axis (the coronal plane in humans, Figure 1b-e), connections also extend through the length of the hippocampus<sup>16,17</sup>. Within the coronal plane and with a slight anterior inclination, mossy fibres project from the DG to CA3, and upon reaching distal CA3 they change direction to extend 3-5 mm in the anterior direction<sup>17</sup>. By contrast, associational and local connections within the DG — which may have excitatory and inhibitory roles, respectively<sup>16</sup> — extend bidirectionally along much of the length of the hippocampus. The DG in the uncus is connected to the anterior DG in the main body of the hippocampus through these associational projections<sup>16</sup>. The connection from CA3 to CA1 (the Schaffer collaterals) and connections within CA3 also have longitudinal projections through most of the hippocampus<sup>17</sup>. Once again, the uncus is distinct, with the targets of projections of the uncus CA3 (CA3') being largely confined to CA3' and CA1'. The human hippocampus can therefore be divided into subfields in the main body of the hippocampus that are connected in cross-section and longitudinally, as well as modified subfields that comprise the uncus and have more limited connectivity with anterior hippocampus.

Importantly, there are differences in the hippocampal anatomy of different species. The uncus is particularly highly developed in primates, and the degree to which it is homologous to its counterpart in rodents is uncertain<sup>10,13</sup>. There are also differences in connectivity. Whereas rodents have commissural connections along the length of the hippocampus, in monkeys these connections are largely restricted to anterior regions, particularly the uncus<sup>18</sup>. Cells in the DG of the uncus project via the white matter of the fimbria or fornix, before crossing hemispheres via the ventral hippocampal commissure<sup>19</sup>, returning along the same pathway in the opposite hemisphere to terminate in contralateral uncus. Other regions associated with the hippocampus – presubiculum, EC and posterior parahippocampal cortex - connect across hemispheres via the dorsal hippocampal commissure. These findings point to a striking role for the anterior hippocampus in connecting the hippocampi of each hemisphere. It has been suggested that the ventral hippocampal commissure may not exist in humans<sup>20</sup>; however, there is a notable lack of research relating human hippocampal connectivity to that of non-human primates.

## Representing the environment

We can vividly re-experience past events, simulate future events and imagine fictitious scenarios, in addition to experiencing the environment we currently inhabit. To achieve this, we must be able to construct internal representations of environments based on incoming sensory information and/or prior experience. As we will argue, there is evidence that structures within the medial part of anterior hippocampus have a role in constructing these representations.

Decades of research, carried out primarily in rodents, has revealed several key cell types in the hippocampus and neighbouring structures that contribute to spatial processing. Place cells in CA1 represent an animal's location<sup>21</sup>, whereas grid cells in the EC, presubiculum

and parasubiculum may provide a metric-like framework for spatial representation<sup>22,23</sup>. Head direction cells, which represent the animal's heading relative to fixed landmarks, have been discovered in a number of interconnected regions including presubiculum, postsubiculum, anterodorsal thalamus, EC, retrosplenial cortex, mammillary bodies and thalamus<sup>23–25</sup>. More recently, boundary vector (border) cells, which represent the position of environmental boundaries, have been found in subiculum, presubiculum, parasubiculum and EC<sup>26</sup>. In humans, the hippocampus<sup>9,27,28</sup>, entorhinal<sup>29</sup> and retrosplenial cortices<sup>30</sup> have been implicated in fMRI and neuropsychological studies of spatial navigation.

The properties of place cells are modulated by their anterior-posterior position within the hippocampus. In rodents, anterior (ventral) place cells have firing fields that cover a larger area of space than posterior (dorsal) place fields<sup>31</sup>. The notion that the anterior hippocampus represents less specific information contributed to the proposal<sup>2</sup> that anterior–posterior differences in hippocampus can be understood as a gradient in level of detail, from coarse representations in anterior hippocampus to fine detail in the posterior. An alternative explanation comes from a recent finding<sup>32</sup> that an animal's precise location can be decoded from the activity of cell populations in anterior hippocampus, despite each individual cell only representing a larger area of the environment. Computer simulations demonstrated that this distributed representation in anterior hippocampus (which is no less precise than that of the posterior hippocampus) make it better suited to generalising across environments (pattern completion), whereas the smaller place fields in posterior hippocampus would be better at resisting interference from similar locations (pattern separation)<sup>33</sup>. Although this finding is still to be replicated, the general consensus is that having a spatially large-scale or generalisable representation of the environment depends upon the anterior hippocampus<sup>2,32</sup>.

Hippocampal cell populations involved in spatial processing represent both the current state of the animal, and also imagined future locations<sup>34–36</sup> and enable 'replay' of remembered past locations<sup>37</sup>. However, recent evidence suggests that a purely spatial account of hippocampal function is insufficient. For example, some aspects of allocentric spatial navigation are preserved in patients with bilateral hippocampal damage<sup>9,38</sup>, whereas these individuals exhibit a clear deficit in processing scenes<sup>39,40</sup>.

## Recalling and imagining scenes

Scenes are coherent object-containing spaces within which we can potentially operate. If scenes develop over time they may be referred to as events or episodes (however, a temporal dimension is not required in order to involve the hippocampus<sup>39,41</sup>). Tasks that require scenes or events to be imagined or recalled<sup>41–50</sup>, including those which involve navigation<sup>28</sup>, engage the hippocampus, with performance impaired or abolished following bilateral hippocampal lesions<sup>7–9</sup>.

It has been hypothesised that the hippocampus contributes to these tasks by providing a spatial representation (or model) of the scene being processed<sup>51,52</sup>. If so, common subregions within the hippocampus should be engaged by any task that involves the construction of scene representations. Indeed, as described below, there is a striking

consistency in the fMRI results across many studies in the literature, which differed in the tasks they employed but all involved naturalistic scenes. These studies reported activation of anterior hippocampus, and close examination of their findings reveals a common region of activation in the medial bank of the anterior hippocampus, which we refer to as amHipp (Figure 2a-j). Here we use a working definition of anterior hippocampus as the region having a MNI y-coordinate of less than or equal to -22 (ensuring complete coverage of the uncus) and we define amHipp functionally, as clusters of activated locations (voxels) that peak in the anterior hippocampus and exhibit a clear bias towards the medial half of the structure. Using this definition, it can be seen that a number of cognitive tasks engage amHipp (see below). Although several of these tasks, particularly those involving visual stimuli, also engage other parts of the hippocampus, amHipp appears to be the most consistently engaged subregion across studies and often shows the greatest effect size. Quantifying the proportion of studies which have found this specific region to be engaged for recall and imagination would require a formal meta-analysis, which would be complicated by the limited scanning resolution of some studies. However, our observation is that this finding is the norm rather than the exception. As we discuss below, high resolution MRI is starting to relate this fMRI activity to the precise underlying anatomy.

### Episodic memory and imagination

fMRI studies of episodic (autobiographical) memory, which require participants to vividly recall specific events from their past, generally find that a 'core network' of brain regions — including anterior hippocampus — is engaged<sup>53,54</sup> (Box 2). Activation within the hippocampus may be limited to amHipp. For example, when subjects were cued to imagine static atemporal scenes based on short descriptions, amHipp was the only part of the hippocampus to be significantly engaged, relative to a control condition in which participants imagined isolated static objects<sup>41</sup> (Figure 2a). Specific increases in amHipp activity were found in another study in which subjects constructed and elaborated upon past events and imagined future events<sup>42</sup> (Figure 2b). When participants recalled episodic memories and imagined fictitious events set in the past or future (based on recombined elements from episodic memories) the amHipp was again the only part of the hippocampus significantly engaged for imagination<sup>43</sup> and was part of a larger region activated during both imagination and recall (Figure 2c) whereas activation of posterior hippocampus was found specifically for vividly recalling real memories. Only amHipp was found to respond more strongly to imagining specific past or future events rather than general events<sup>44</sup> (Figure 2d), whereas the anterior lateral hippocampus distinguished past from future episodes. Autobiographical memory retrieval was also found to engage only amHipp<sup>45</sup> (Figure 2e) although other subregions of the hippocampus were responsive to whether retrieval was cued using a direct association with the cue or a strategy of searching through memories. A subsequent study sought to distinguish the initial construction stage of autobiographical memory recall from elaboration<sup>46</sup>, and within the hippocampus found solely amHipp engagement for construction (Figure 2f). Posterior hippocampus was engaged for elaboration, which connectivity analyses showed was also linked to areas processing visual stimuli. These studies suggest that despite different research questions, tasks and some points of divergence – including the extent of differences between recalling the past and imagining the future<sup>55</sup> and the relationship between imagination, novelty and encoding

(Box 3) - one common feature across studies was the engagement of amHipp, in addition to regions of the wider core network<sup>42,53,54,56</sup>.

The hippocampus may contribute to these tasks by linking elements of scenes in a coherent spatial representation, as suggested by studies in humans with bilateral hippocampal lesions. Self-reports from these patients demonstrate that they can fully comprehend the elements that should appear in an imagined scene, but cannot arrange them into a spatially coherent representation<sup>39,40</sup>. In one study, patients and control participants were asked to describe what they would see beyond the edges of a scene photograph<sup>40</sup>. The patients described relevant objects they would have expected to see, demonstrating preserved associational processing, but were specifically unable to describe how the extended scene would fit together and reported being unable to visualise it in their imagination. In another study<sup>57</sup>, patients with bilateral hippocampal damage were tested on their ability to reflect on “what might have been”. The patients could deconstruct a given narrative and then add, recombine and re-order narrative elements into a counterfactual alternative reality. However, detailed questioning showed that they had specific impairment in the spatial coherence of the mental representations needed to perform some aspects of the task. Although these patients rarely, if ever, have lesions limited to the anterior hippocampus, these findings have been instrumental in demonstrating a spatial scene-related role for the human hippocampus.

### Visual perception and posterior hippocampus

If the hippocampus is required for the internal representation of spatially coherent scenes or events, then it may also support perception by representing the environment currently being experienced. This contrasts with a long-standing theory of the hippocampus<sup>58</sup>, which holds that human MTL (including the hippocampus) is involved only in memory and that perception involves a separate system. Over the last two decades, this proposed separation has been challenged by converging functional and anatomical results across species (for reviews see REFs<sup>11,59,60</sup>).

Investigations into hippocampal involvement in scene perception have focussed on visual discrimination studies, in which subjects decide whether visually presented stimuli are identical or subtly different to each other or to a sample stimulus. Patients with bilateral hippocampal lesions cannot match morphed pictures of scenes to a sample, but are not impaired when other stimuli are used, such as faces and objects<sup>61</sup>. Responding to criticisms that this effect may be driven by learning over trials, a subsequent study<sup>62</sup> used trial-unique stimuli in an odd-one-out task. The patients had difficulty identifying non-matching scenes; however, this impairment was only apparent when the scene pictures were taken from different viewpoints. By contrast, they were able to match pictures of faces regardless of viewpoint. This is important because matching scenes from different viewpoints requires an internal global scene model, which we suggest is represented in the hippocampus. However, these results were not replicated in a separate group of subjects<sup>63</sup>, and another study involving four patients found only two to have impaired perception of the topology of virtual reality scenes<sup>64</sup>. Differences in the nature and extent of intra-hippocampal damage may help to explain these disparate functional outcomes<sup>65</sup> and emphasise the need to better understand intra-hippocampal anatomy and its mapping to function.

In healthy participants, the hippocampus consistently responds to visually presented scenes. Making an indoor/outdoor decision about scene photographs was sufficient to engage much of the length of the hippocampus, with the most consistent result across subjects found to be in amHipp66 (Figure 2g). In another study, when the spatial configuration of items within visually presented scenes was altered, amHipp was activated (Figure 2h)<sup>67</sup> together with a more anterior lateral region of hippocampus. This study did not identify posterior hippocampus activation. However, the posterior hippocampus was engaged during a scene discrimination task<sup>68</sup> and subregions of the hippocampus responded to viewing scenes, regardless of whether or not they were subsequently recalled<sup>69</sup> (Figure 2i), suggesting this does not relate to memory encoding. To probe which aspects of scenes the hippocampus responds to, a task was developed<sup>70,71</sup> in which scene discrimination based on global layout (“strength-based perception”) was dissociated from discrimination based on local visual features (“state-based perception”). The posterior hippocampus was involved specifically with strength-based perception, reinforcing the notion that it represents the configuration of the scene as a whole. Beyond discrimination studies, a recent experiment had participants passively view scenes and single isolated objects as they underwent fMRI scanning<sup>47</sup>. Activation of both amHipp and posterior hippocampus was observed in response to perceiving scenes, relative to perceiving isolated objects. When the same participants constructed scenes in their imagination, there was significant engagement of amHipp without evidence for posterior hippocampus activity. Thus, the posterior hippocampus appeared to be particularly responsive to visual perception, whereas amHipp was engaged by scenes regardless of whether they were generated internally or externally (Figure 2j). This study also showed that amHipp was engaged by novel scenes, whereas posterior hippocampus was engaged regardless of novelty - supporting the hypothesis that amHipp is involved with constructing an initial representation of the scene, whereas posterior hippocampus has a more specific visuospatial role.

Also of relevance to scene perception is Boundary extension<sup>72</sup> (BE), a cognitive phenomenon whereby people remember seeing more of a scene than was actually present in the original stimulus. This effect is attenuated in patients with hippocampal lesions<sup>40</sup> (see also REFs<sup>65,73</sup>). Of note, during an fMRI study in which healthy participants viewed scenes and experienced BE on half the trials, there was greater engagement of the posterior hippocampus during the viewing of scenes that induced BE<sup>74</sup>. The BE effect was not linked with amHipp activity during neuroimaging, potentially because scene perception (which was present in all conditions) always engages amHipp, regardless of whether BE is experienced.

The evidence that the hippocampus is engaged during scene perception is challenged by studies of patients with hippocampal lesions who can lucidly produce narratives to accompany visually presented cartoon images or photographs<sup>40,75</sup>. However, impairments become apparent when patients are asked to extend the scene beyond the edges of the picture into the imagination<sup>40</sup>. This suggests that a hippocampus-based model of the scene, constructed during visual perception, facilitates prediction beyond the edges of the view as well as beyond the sensory domain into imagination/recall. We predict that asking patients with hippocampal lesions challenging questions about visually presented scenes that could only be answered by possessing a coherent internal scene model might reveal impairments that are not evident in more general narrative description tasks.

The studies we have discussed, tapping into apparently distinct cognitive functions, share a common requirement to form internal representations of spatially coherent scenes. This, we suggest involves amHipp. The existence of amHipp as a distinct functional region was noted in a recent fMRI study<sup>47</sup> and lately by two studies which parcellated the hippocampus based on a meta-analysis of fMRI data<sup>76</sup> and functional connectivity<sup>77</sup>. Posterior hippocampus responds particularly strongly to visual scene perception, which may relate to its direct anatomical connections with parahippocampal and retrosplenial cortices<sup>78</sup>. How involvement of the posterior hippocampus with scene perception relates to its known role in navigation<sup>79</sup> is yet to be investigated. Interestingly, posterior hippocampal volume has been found to be reduced in blind people<sup>80,81</sup> with concomitant volume increases in anterior hippocampus<sup>81,82</sup> (although there are various possible explanations for this, such as differences in blind people's navigation performance<sup>82</sup>).

In suggesting functional differences between anterior and posterior hippocampus, it is important to note that these functions are not completely segregated. For instance, although the posterior hippocampus responds more strongly to visually perceiving scenes than imagining scenes<sup>47</sup>, there is evidence that it is engaged by imagination and recall<sup>48,49</sup>. All of these functions involve extrinsic connections that link the hippocampus to parahippocampal and perirhinal cortices<sup>83,84</sup>. There is also variability in the locus of hippocampal activation between studies, which may be explained by multiple factors including the age of recalled stimuli<sup>48,50</sup>, differences in task demands, differences in the definition of anterior versus posterior hippocampus and varying statistical thresholds. This variability, we suggest, makes the striking overlap in amHipp across studies all the more interesting.

## From scenes to subfields

To investigate which specific structures underlie the activation patterns observed in amHipp in neuroimaging studies, an experiment was recently conducted<sup>50</sup> in which subjects constructed novel naturalistic scenes in their imagination and recalled scene photographs from a week earlier while undergoing high resolution structural and functional MRI. The anterior presubiculum and parasubiculum were both activated by tasks involving specifically the construction and recall of scenes. There was also activation of the uncus when subjects recalled scenes first viewed a week earlier, and of the anterior subiculum when subjects constructed novel scenes. Effect sizes in anterior lateral hippocampus and posterior hippocampus were far smaller. These results suggest that engagement of amHipp in the studies using scene or event stimuli described above is likely to have been driven by activity in the presubiculum and parasubiculum, potentially in conjunction with anterior subiculum and the uncus.

## Anterior presubiculum and parasubiculum

The presubiculum and parasubiculum were engaged by both scene construction and scene recall<sup>50</sup>. These findings complement those of a recent study using high resolution fMRI in humans, which identified the peak activity for perceiving novel scenes to be in the presubiculum<sup>85</sup>. In rats, the presubiculum and parasubiculum contain grid cells and border



cells<sup>23</sup>, pointing to a spatial role for both regions. In monkeys, presubiculum at the level of the uncus projects to medial entorhinal cortex<sup>18</sup>, which is commonly associated with spatial function and where grid cells were first discovered in rodents<sup>22,86</sup>. Based on these findings, we hypothesise that the presubiculum and parasubiculum contribute to the spatial basis of scene representations in humans.

## Uncus

As described above<sup>50</sup>, the uncus is engaged when recalling scenes from a week prior to scanning. Although subfields within the uncus were not distinguished due to the limited spatial resolution of MRI, one striking property of this region is its inter-hemispheric connectivity. In non-human primates, the uncus of hippocampus sends and receives commissural connections<sup>18</sup>, which complement the even stronger commissural connections arising from presubiculum and terminating in contralateral medial EC. Little is known about the precise differences in hippocampal function between hemispheres beyond suggestions of general verbal or visuospatial distinctions<sup>87</sup> and the homology of inter-hemispheric connections between humans and primates is uncertain<sup>20</sup>. However, we speculate that recall of consolidated representations from memory may involve the integration of information from across regions located in both hemispheres and thus may be supported by connections terminating in the uncus.

The uncus is also well placed to mediate communication between the prefrontal cortex (PFC) and the rest of the hippocampus. In non-human primates, subfield CA1' projects directly to PFC, particularly medial areas BA25<sup>83,88</sup> and BA14<sup>88</sup>, with lighter projections to orbital PFC. There is an indirect pathway between CA1' and PFC via the amygdala – both prosubiculum and CA1' project to the basal nucleus<sup>89</sup> which in turn projects widely through medial PFC (BA 24, 25 and 32), lateral PFC (BA 12 and 45) and orbital PFC (BA 7a, 13b and 14)<sup>90</sup>. Functional neuroimaging studies in humans have also found that the PFC, particularly ventromedial PFC, is co-activated with anterior hippocampus (Box 2). Of particular relevance are studies implicating ventromedial PFC in memory consolidation<sup>48,91,92</sup>. Thus, the uncus and ventromedial PFC may be jointly involved in retrieving the elements of memories which have been consolidated, to be reconstructed as spatially coherent scenes by amHipp.

## Anterior subiculum

The subiculum is a main output structure of the hippocampus (although there are outgoing connections from various other parts of the hippocampus<sup>93</sup>). This region includes border cells<sup>26</sup>, pointing to a role in modelling the environment. The anterior subiculum is engaged when subjects imagine novel scenes<sup>50</sup>. In human fMRI, the subiculum and prosubiculum are not generally distinguishable, but differ in their connectivity. The subiculum projects to the mammillary bodies and retrosplenial cortex<sup>12</sup>, two regions closely involved with the representation of head direction. The prosubiculum, however, has reciprocal connections with targets including ventromedial PFC<sup>12</sup>.

## Methodological issues

Anterior hippocampus is particularly challenging to study using fMRI. A consensus has not yet been reached on the definition of the subfields at the resolution attainable with MRI although work is underway<sup>6</sup>. Weak contrast-to-noise ratio is a well-known problem in the anterior temporal lobes and may cause false negative results. Furthermore, the uncus is flanked by significant vasculature<sup>94</sup>. The influence of vasculature on fMRI interpretation has been questioned<sup>95</sup>, however this issue is not specific to the hippocampus. These concerns emphasise the importance of having well-matched control conditions and the need for precise anatomical detail as well as further research into neuro-vascular coupling.

## A model and future directions

Based on the available anatomical and functional data, we propose that the hippocampus (specifically amHipp) supports modelling of scenes. It can be driven ‘offline’ during imagination and recall in order to construct a spatially coherent scene representation. In addition, it continually constructs and refines a representation of the scene being experienced ‘online’, extending into the perceptual domain the notion of scene construction<sup>51,52</sup>. The presubiculum and parasubiculum provide a spatial basis for the elements of the scene, complemented by the uncus and anterior subiculum, which may mediate communication with other regions that represent the elements of the scene and generate vivid imagery. When visual stimulation is used to update one’s internal model, or when visual representations are vividly reinstated during recall, the posterior hippocampus is additionally engaged to process the scene’s visuospatial properties.

This model makes several predictions. First, there should be a novelty response to scenes in anterior hippocampus, reflecting the construction of the novel representation. This is supported by many findings<sup>2</sup> (Box 3) and helps to explain why scene novelty particularly engages amHipp<sup>47,67</sup>. Second, amHipp should be engaged when a spatially coherent representation of a scene needs to be constructed or used for simulating events. This is borne out by recent findings, including studies using simple visual scene perception tasks<sup>47,66</sup> as well as scene discrimination tasks, where patients with hippocampal lesions could distinguish scenes from the same angle but not different angles<sup>62</sup>. Third, amHipp will be placed under greater demand for recalling consolidated memories than very recent memories, because in the former case the scene must be constructed from a distributed representation across cortex. A recent study found greater amHipp response to recalling scenes encoded a week before scanning, compared to those encoded 30 minutes before scanning<sup>50</sup>. Consolidation findings do, however, differ across studies, which have used varying stimulus content, analysis techniques and durations of consolidation<sup>48,50,92,96–98</sup>. We argue that understanding the role of the uncus in recall will be key to unpacking these differences. Finally, the model predicts that patients with bilateral hippocampal lesions will have visual perceptual deficits, but only when probed in such a way as to demand a coherent internal model of their surroundings. More detailed neuropsychological studies should be able to evaluate the limits of visual scene perception in the presence of dysfunctional hippocampi.

By reformulating the current ‘perception versus memory’ debate with reference to the detailed anatomy of anterior hippocampus, we believe that increased explanatory power and more fruitful lines of inquiry can be forthcoming. Moreover, this proposal may help to clarify the discussion over functional differences in the long axis of the hippocampus, as well as providing anatomical detail to computational models of hippocampal function. For instance, one computational model of spatial memory and imagery<sup>99</sup> proposed that CA3 combines spatial information from boundary vector cells with object identity information in perirhinal cortex to facilitate pattern completion. The findings summarised here suggest that this point of integration between spatial and non-spatial information may be the presubiculum and/or parasubiculum in humans.

In our opinion, visual perception, imagination and episodic recall depend upon a common process – the creation of models of the world and the use of those models to plan scenarios and re-play memories. This, we suggest, offers a better way to understand the function of the hippocampus and reconcile apparently disparate findings in the literature. Nevertheless, there are numerous unanswered questions. What form does the spatial representation in the presubiculum and parasubiculum take? What visually-driven operations are performed by the posterior hippocampus and how do these relate to navigation? Most of all, we call for further studies capitalising on advances in high resolution fMRI in humans to understand the specific functional anatomy of the anterior hippocampus, as well as its functional connectivity with neighbouring structures. The uncus is particularly poorly understood, but the results reviewed here suggest it may play an important role in scene recall. High resolution neuroimaging experiments and analysis of gene expression<sup>100</sup> in humans could complement neuropsychological studies of patients and in vivo animal models, to improve our knowledge of this critical brain region.

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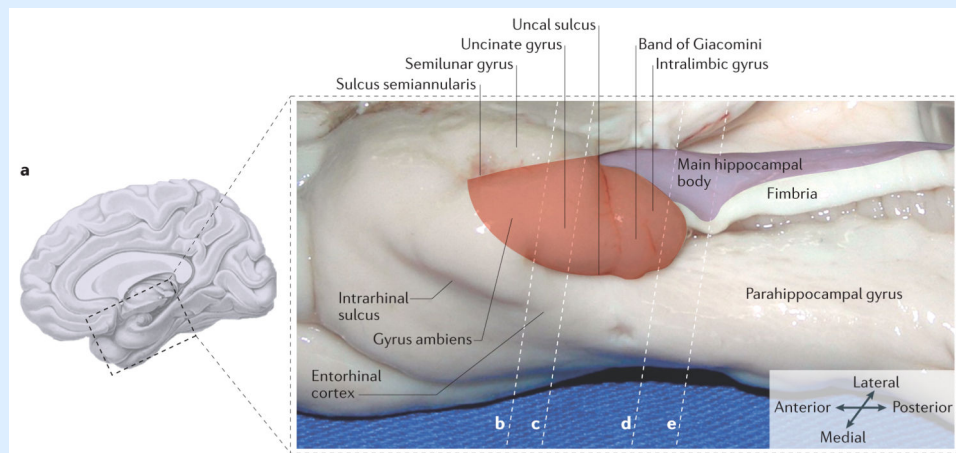
**Box 1****A tour of the anterior hippocampus**

The anterior hippocampus may be understood in terms of its cytoarchitecture (see main text) or in terms of the features that are visible on the brain's surface, which are summarised here based on previous observations<sup>10,13,94</sup>. (See the figure part a for context. Dashed lines labelled b-e correspond to the coronal slices shown in Fig 1).

Starting in parahippocampal gyrus and moving anteriorly (towards the left of the figure) the gyrus becomes the entorhinal cortex. Its approximate position is indicated for clarity, although its borders are not visible on the brain's surface (in coronal slices the entorhinal cortex appears approximately at the level of lateral geniculate nucleus<sup>101</sup>).

Parahippocampal gyrus then bends upwards, separated by the narrow intrarhinal sulcus from the gyrus ambiens above. The gyrus ambiens extends laterally to the sulcus semiannularis, which marks the lateral extent of the entorhinal cortex. Further lateral to this is the semilunar gyrus, which covers the medial portion of the amygdala and the most anterior part of the hippocampus.

The uncus of the hippocampus (marked on the figure by the orange shading) is part of the anterior parahippocampal gyrus that bends over and rests on itself, separated from entorhinal cortex below by the uncal sulcus. Moving posteriorly along the uncus (towards the right of the figure), the gyrus ambiens becomes the uncinete gyrus, which contains the hippocampal-amygdaloid transition area (HATA; Fig 1b,c). Next, the uncus becomes the band of Giacomini and finally the intralimbic gyrus, getting progressively smaller towards the posterior. The point at which the intralimbic gyrus is no longer visible in coronal section is a landmark for the posterior-most slice of the anterior hippocampus<sup>2</sup>. Thus, the anterior part of the uncus is formed of the uncinete gyrus, whereas the posterior consists of the band of Giacomini and the intralimbic gyrus. The main hippocampal body and fimbria are positioned lateral to the uncus. Part a adapted, with permission, from REF<sup>102</sup>. Photograph of a dissected brain adapted, with permission, from REF<sup>103</sup>.

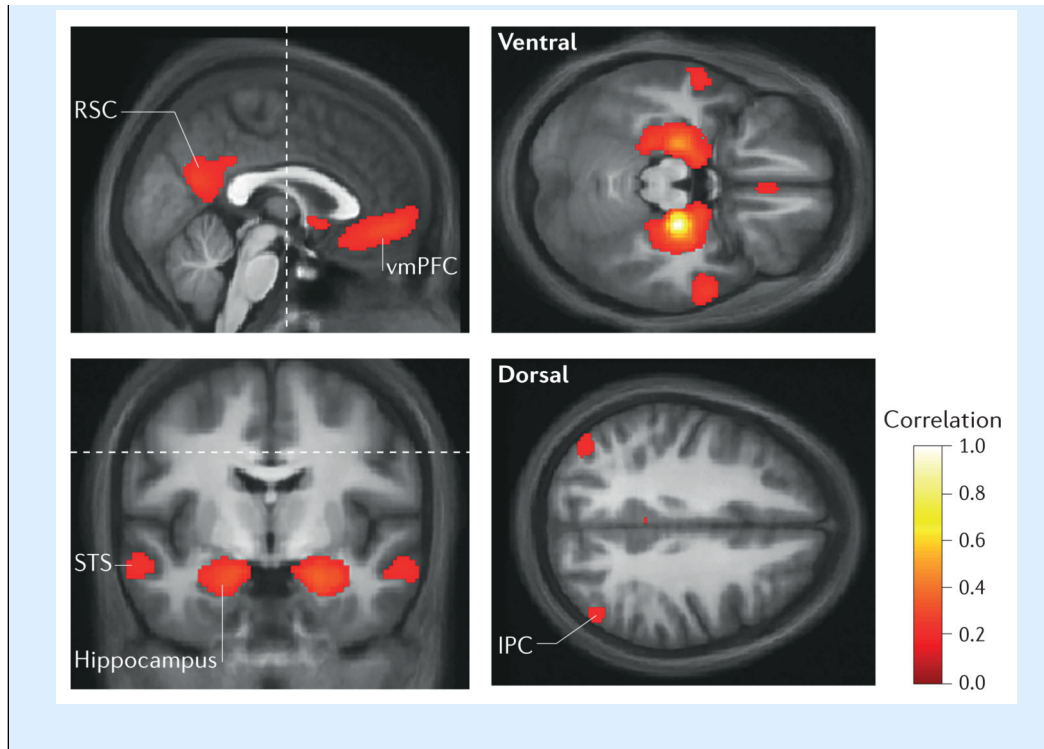


**Box 2****A core network for recall and imagination**

A recent study<sup>47</sup> showed that recalling and imagining scenes activates the anterior medial hippocampus (amHipp) as part of a well-established ‘core network’ of brain regions<sup>56</sup>. There are various suggestions as to what common function this network may serve<sup>56,104,105</sup>. It is similar to a set of regions found to be most active during rest periods, termed the ‘default mode network’ (DMN)<sup>106</sup>. The figure shows resting state fMRI activity (based on 1000 subjects at rest<sup>107,108</sup>, accessed via the Neurosynth meta-analysis tool<sup>109</sup> – see Further Information) illustrating regions that had activity that correlated with right amHipp. The colour scale indicates the strength of the correlations (Pearson correlations ( $r$ )) between the BOLD timeseries in each voxel and a seed voxel in the right amHipp (seed MNI co-ordinates 22,-20,-18;  $r > 0.2$ ). This demonstrates the association between the DMN and the amHipp. The DMN brain regions shown are the anterior superior temporal sulcus (STS), inferior parietal cortex (IPC), parahippocampal cortex (PHC), retrosplenial cortex (RSC), ventromedial prefrontal cortex (vmPFC) and the septal nuclei. In agreement with other authors<sup>110</sup>, we suggest that scene-related tasks such as recalling the past engage a similar set of brain regions as the DMN because they depend on common cognitive processes. When at rest, people often construct spatially coherent scenes, which may be generated in their imagination or recalled from their past. This gives rise to several testable predictions regarding the brain at rest. As patients with hippocampal lesions cannot imagine fictitious scenarios<sup>39,40</sup>, their mind-wandering behaviour should be limited to events in the present. Moreover, there should be changes within the DMN compared with healthy control subjects. Indeed the latter has been reported in amnesic patients with bilateral medial temporal lobe damage<sup>111</sup>.

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Further Information  
Neurosynth: <http://www.neurosynth.org/locations/>



**Box 3****Other functions of anterior hippocampus**

Evidence points to the hippocampus being a site of integration between spatial and non-spatial information. There are several key themes in the literature implicating anterior hippocampus.

**Anxiety and stress**

The anterior (ventral) hippocampus is associated with anxiety across species<sup>112</sup>. Contextual fear conditioning, in which a spatial location is associated with an aversive stimulus, is associated with activity in the anterior hippocampus in humans<sup>113,114</sup> and rodents (reviewed in REF<sup>115</sup>). The anterior dentate gyrus (DG) is the source of adult-born stem cells in the hippocampus<sup>116</sup> and stress-related decreases in neurogenesis in primates are accompanied by increases in depressive symptoms<sup>117</sup>. However, neuroimaging studies in humans which have tested for changes in hippocampal volume with depression suggest that there are more often changes in the posterior than the anterior volume<sup>118,119</sup>, potentially because neurogenesis effects are more difficult to measure in the anterior hippocampus<sup>119</sup>.

**Novelty and encoding**

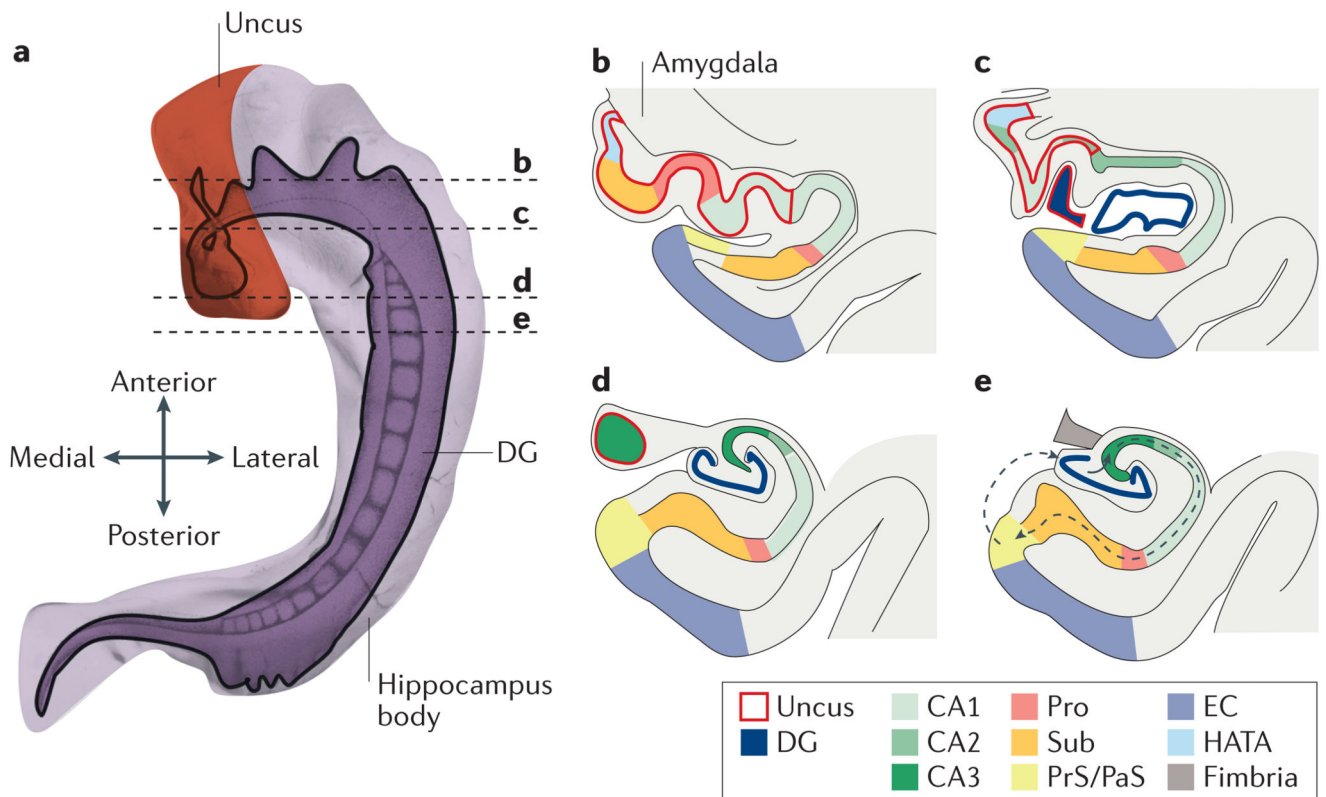
The anterior hippocampus responds to novelty, particularly for spatial stimuli. For instance, there is a stronger response to novel scene stimuli than to those that are more familiar<sup>120,121</sup> and the anterior hippocampus also responds to novel spatial configurations<sup>67</sup>. Moreover, it is engaged by associative novelty, in which novel stimuli are paired with familiar stimuli to form new associations or violate expectations<sup>122</sup>. It has also been suggested that the anterior hippocampus is involved with encoding memories<sup>123</sup> and has been found to respond more strongly to imagined scenarios that are subsequently remembered than to those that are forgotten<sup>124</sup>. However, successful encoding is not a prerequisite for anterior hippocampus engagement<sup>69</sup> or for its interaction with the core network<sup>124</sup> (Box 2) in response to scene or event stimuli.

**Decision-making**

Although beyond the scope of this article, the anterior hippocampus is associated with decision-making and representation of value, functions that might relate to its anatomical connections with prefrontal cortex. For instance, anterior hippocampus and amygdala were found to represent value and task-specific goals in spatial decision-making<sup>125,126</sup>.

**Summary**

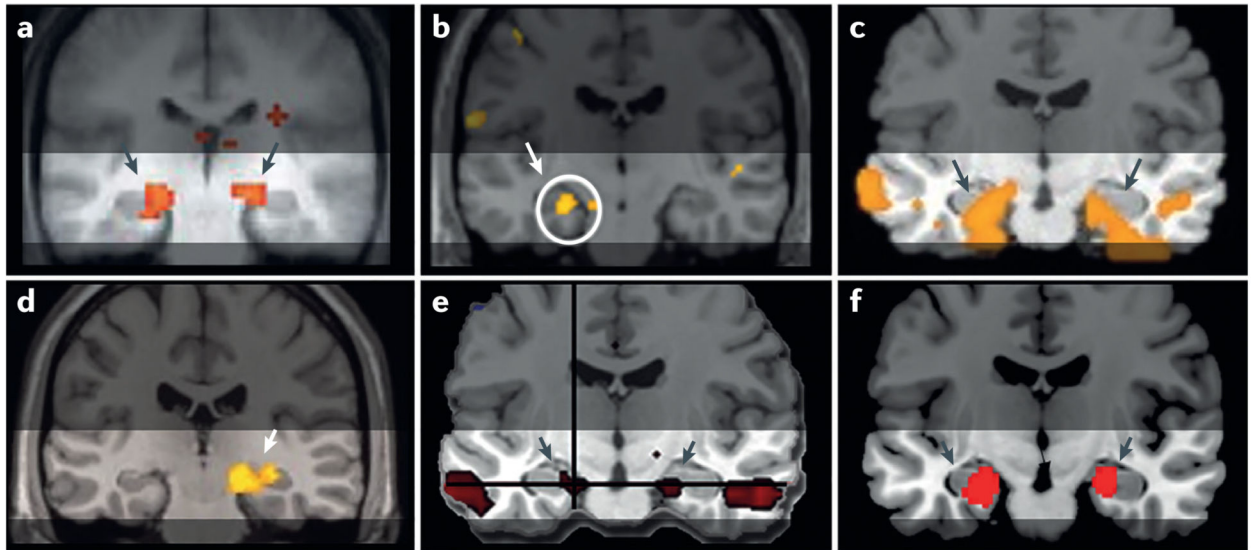
Here, we build upon the proposal that the hippocampus constructs representations of scenes<sup>52</sup>. This will necessarily occur when a stimulus is novel or not recently recalled, and may integrate non-spatial elements including emotional valence.



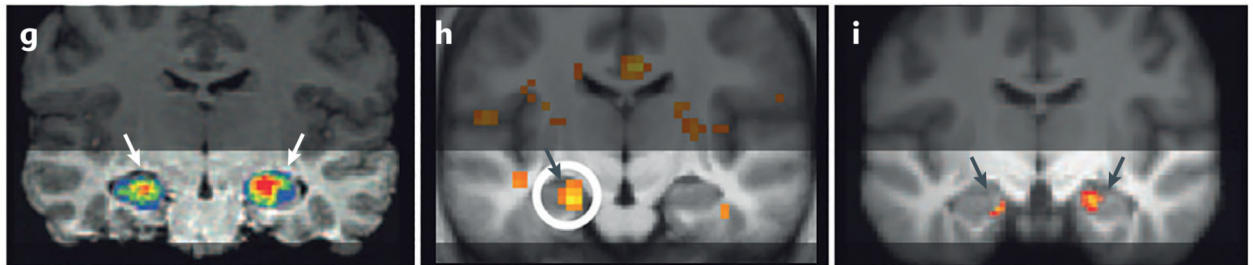
**Figure 1. Anatomy of the anterior hippocampus.**

**a** A schematic showing a dorsal view of the hippocampus with the dentate gyrus (DG) visible inside. The main hippocampus body as well as the uncus are indicated. **b-e** Coronal slices showing the hippocampal subfields in the anterior hippocampus. Red lines indicate subfields that are found within the uncus and which have distinct cytoarchitectural properties relative to the main body of the hippocampus. The slices in parts b and c are at the level of the uncinate gyrus, whereas slice d is at the level of the intralimbic gyrus. The arrows in part e indicate the flow of information in the canonical hippocampal circuit in the body of the hippocampus. Pro, prosubiculum; PrS/PaS, presubiculum and parasubiculum; EC, entorhinal cortex; HATA=hippocampal-amygdaloid transition area. Part a adapted from: REF94. Parts b-e adapted from REF10.

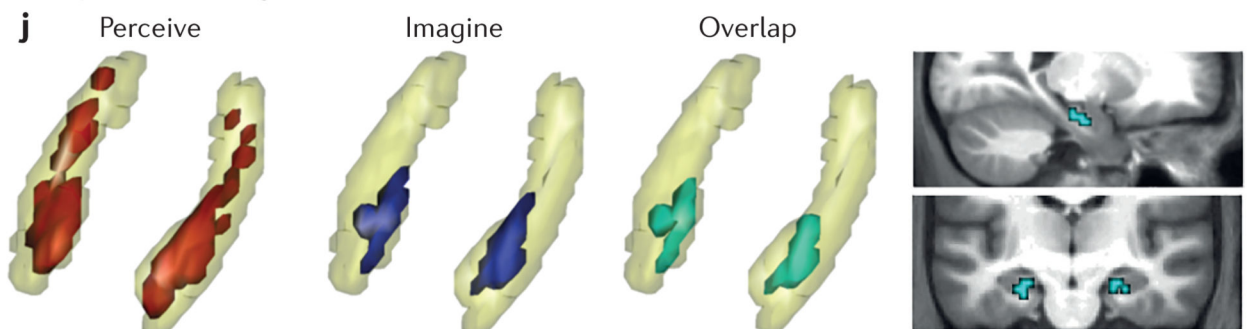
### Imagination and recall of scenes and/or events



### Perception of scenes and/or events



### Perception and imagination of scenes



**Figure 2. Activation of the anterior medial hippocampus during fMRI.**

**a-i** The images show the results of a selection of fMRI studies in which amHipp (arrows) was engaged by imagination and recall (a-f) and visual perception (g-i) of scenes and events. Coloured regions are those in which there was an increased haemodynamic response during each task (in part g, colours represent % of subjects ( $n=34$ ) with activation, range 50-80%). The tasks involved constructing static atemporal scenes<sup>41</sup>(a), constructing and elaborating upon imagined events<sup>42</sup> (b, white circle indicates the hippocampus), recalling past events and imagining events set in the past and future<sup>43</sup> (c), imagining specific rather than general

future events<sup>44</sup>(d), autobiographical memory retrieval<sup>45,46</sup> (e and f), viewing novel scenes relative to scrambled images<sup>66</sup> (g), viewing scenes in which an object had been moved relative to the background<sup>67</sup> (h, white circle indicates hippocampus) or correct versus incorrect scene oddity judgements<sup>69</sup> (i). **j** The overlap in activity between the perception and imagination of scenes. Hippocampal activation for scene perception relative to object perception is shown in red, activity for imagining scenes versus imagining objects is shown in blue and the overlap is shown in turquoise (also shown in sagittal and coronal slices)<sup>47</sup>. Part a modified, with permission from REF 41. Part b modified, with permission, from REF 42. Part c modified, with permission from REF 43. Part d modified, with permission, from REF 44. Part e modified, with permission, from REF 45. Part f modified, with permission from REF 46. Part g modified, with permission from REF 66. Part h modified, with permission from REF 67. Part i modified, with permission from REF 69. Part j modified, with permission from REF 47.