Review

Long-axis specialization of the human hippocampus

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Investigation of the hippocampus has historically focused on computations within the trisynaptic circuit. However, discovery of important anatomical and functional variability along its long axis has inspired recent proposals of long-axis functional specialization in both the animal and human literatures. Here, we review and evaluate these proposals. We suggest that various long-axis specializations arise out of differences between the anterior (aHPC) and posterior hippocampus (pHPC) in large-scale network connectivity, the organization of entorhinal grid cells, and subfield compositions that bias the aHPC and pHPC towards pattern completion and separation, respectively. The latter two differences give rise to a property, reflected in the expression of multiple other functional specializations, of coarse, global representations in anterior hippocampus and fine-grained, local representations in posterior hippocampus.

Introduction

The idea that the aHPC and pHPC (see Glossary) may serve different functions (i.e., long-axis specialization) emerged half a century ago [1,2] and growing appreciation of long-axis anatomical variation at present provides a theoretical rationale and impetus for exploring this topic. In a recent review of anatomical, genetic, and functional data drawn primarily from animal models, Fanselow and Dong established a case for specialization within the hippocampus in general, and for affective and cognitive specializations within anterior and posterior regions in particular [3]. However, many alternative specializations have been proposed, especially for humans, and the task of reconciling them remains. Here, we review these proposals in the context of human hippocampal anatomy and argue that variations in connectivity and subfield organization systematically influence the grain and nature of hippocampal memory representations.

We define aHPC and pHPC as the hippocampal segments obtained by bisecting the structure at the most posterior coronal plane containing the uncal apex (including cornu ammonis fields CA1–CA4, dentate gyrus/DG, and subiculum; see also Box 1). The rodent analogues of the aHPC and pHPC are the ventral and dorsal hippocampus, respectively; within the dorsal hippocampus, some also distinguish between intermediate and tail portions (e.g., [3–5]). Because human proposals do not yet distinguish between these segments, we will take a simpler, bisectional approach and revisit the issue in the synthesis section below.

Anatomical differentiation

Although the literature on human long-axis neuroanatomy is less developed than the analogous animal literature, it may help account for the functional segregation (see following section) observed in humans.

Internal variation

The aHPC includes intraventricular and uncal parts, the former extending from the pHPC and the latter from piriform cortex, featuring only superficial contiguity with the pHPC (for visualization, see Box 1 and [6]). Interestingly, the uncus is especially developed in humans and primates [6], raising the possibility of more sophisticated functions in the primate uncus. Although the interconnections of hippocampal subfields (i.e., the trisynaptic circuit) are repeated along the hippocampus, Malykhin *et al.* [7] found variations in their distribution in healthy adults, with a

Glossary

Anterior and posterior hippocampus: hippocampal segments defined by their position relative to the uncal apex on the long axis of the hippocampus [roughly the *y* axis of the anterior commissure–posterior commissure (AC–PC) space; see Box 1].
Neurogenesis: the creation of new neurons. Among adults, this process is thought to take place specifically in the subventricular zone and DG subregion of the hippocampus.
Place cells: hippocampal neurons that respond with a high firing rate when the organism is in a specific location.
Resting-state fMRI: neuroimaging technique for the assessment of possible neuronal interactions that involves measuring temporal correlations in blood oxygenation across brain regions while participants rest.
Tracer study: histological technique performed in animals in order to trace neuroanatomical connections by staining neuronal connections with dyes for *in vitro* examination.
Tractography: neuroimaging technique that enables one to trace neuroanatomical connections by measuring the asymmetry of brain water diffusion. Due to methodological limitations, tractography is sometimes combined with other approaches (e.g., post-mortem studies).
Trisynaptic circuit: pattern of neuroanatomical connections among CA1, CA3, and DG hippocampal subfields.
Ventral and dorsal hippocampus: in rodents, the long axis of the hippocampus is roughly aligned with the *z* axis. Accordingly, the ventral and dorsal rodent hippocampus are analogues of the human anterior and posterior hippocampus.

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Box 1. Strategies for long-axis segmentation of the hippocampus in human neuroimaging

Landmark-based segmentation

The hippocampus head is most accurately delineated using landmark-based hippocampus segmentation within individual brains. For this purpose, the uncal apex (red arrow in Figure I) is a distinctive, easily recognized marker and a prevailing standard in hippocampal volumetry. The aHPC also contains a non-uncal, intraventricular part (right of the uncus in Figure I) that contains an aHPC-pHPC boundary. However, the crucial point of transition in this lateral section is not known, agreed upon, or easily discernible from standard anatomical images. Moreover, the use of such a boundary would reduce the accuracy of uncal segmentation. For these reasons, we prefer the uncal apex as a standard for landmark-based segmentation.

Talairach/MNI coordinate-based segmentation

Brain images are often spatially transformed into MNI or Talairach 'standard' space during the course of analysis. Because no specific convention exists for describing effects as 'anterior' or 'posterior', these labels are used somewhat subjectively. For lack of an existing standard, we propose that foci at or anterior to $y = -21$ mm in MNI space ($y = -20$ mm in Talairach space) may be regarded as falling in the aHPC, as this coordinate incorporates the uncal apex in the MNI152 template and current neuroanatomical atlases [89].

Percentile-based axis segmentation

The hippocampus is sometimes described with respect to its medial axis or the *y* axis in AC–PC space, allowing localization within the hippocampus without the need for warping to standard space. One system defines the anterior 35% of the hippocampus as 'head', the middle 45% as 'body', and the final 25% as 'tail' [90]; another defines the aHPC as the structure's anterior third [91]. Notably, the head, when defined by the uncal apex in MNI space, extends 14 mm along the *y* axis; and the full hippocampus 41 mm. Therefore, the anterior 34.1% of the standard-space hippocampus is the aHPC; and percentile-based conventions correspond approximately to coordinate-based localization.

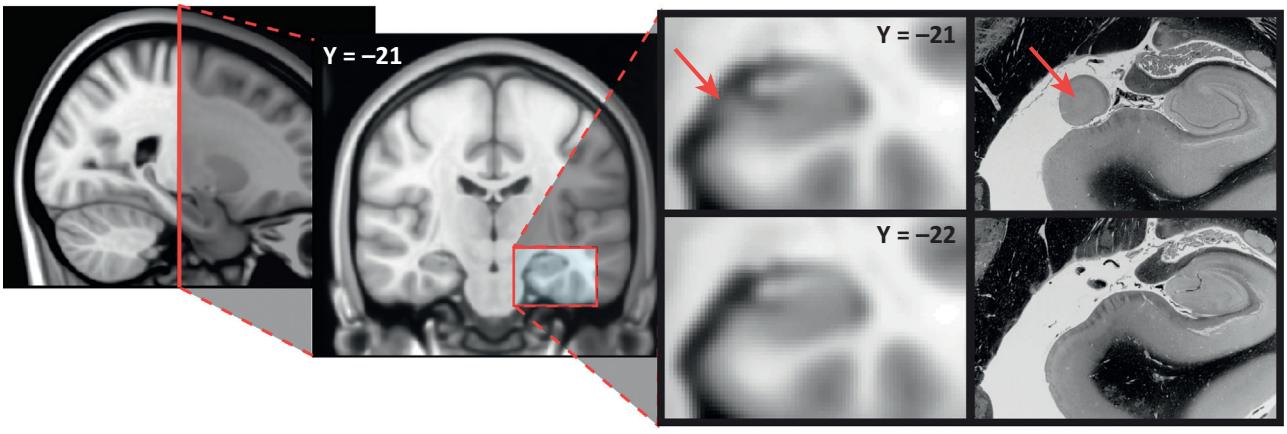

Figure I. Uncal apex landmark for long-axis segmentation. In defining the hippocampal head, most segmentation conventions use or approximate the position of the uncal apex (red arrow; visible at $y = -21$ on an MNI152 and neuroanatomical atlas; absent at $y = -22$). Atlas photos, right, are adapted, with permission, from [89].

lower proportion of DG in aHPC (~25%) than in pHPC (~38%) and a higher proportion of CA1–3 in aHPC (~50%) than in pHPC (~40%). The authors speculate that this distribution may influence local neurogenesis; we note that, alternatively, differences in neurogenesis could yield this outcome (Box 2).

Connectivity

Tracer studies are inappropriate in humans, but yield the most conclusive connectivity evidence. Such studies in animal models have revealed little to no direct connectivity between the ventral and dorsal hippocampus (rodents) or the aHPC and pHPC (monkeys) [3,8]; the segments even project to different entorhinal cortex (ERC) bands that are sparsely interconnected. In rodents, they may communicate indirectly via ERC connections to perirhinal cortex (PRC) and parahippocampal cortex (PHC), or via several other routes [3]. Thus, the neural circuits to which the segments belong are largely distinct.

Turning to human evidence, dissection has revealed direct connections between the aHPC and amygdalar nuclei [6]. The uncinate fasciculus joins the uncus and amygdala to the temporal pole, insula, gyrus rectus, and ventromedial prefrontal cortex (vmPFC) via reciprocal connections that traverse the temporal stem, as outlined by dissection tractography [9] and confirmed functionally through direct stimulation with depth electrodes [10]. Tractography has revealed a direct pathway, possibly unique to humans, that connects the fusiform cortex with the amygdala and the aHPC [11]. The aHPC is functionally linked to the ventral tegmental area (VTA) and the ventromedial nucleus accumbens shell [12,13], though rodent dorsal hippocampus also projects to the VTA via the nucleus accumbens core [3].

Most aHPC and pHPC communication with the cortex is mediated by reciprocal connections with medial versus intermediate and lateral bands of the ERC, respectively. The strongest ERC connections, PRC and PHC, likely fall in both bands (as in rodents [3]); however, functional coupling in humans is greatest between the aHPC and PRC and between the pHPC and PHC, as observed with standard-resolution functional MRI (fMRI) [14] and high-resolution fMRI [15]. Functional responses of the aHPC and pHPC – and corresponding ERC bands – to faces and scenes, respectively, confirm these connections in humans [16,17].

Other resting-state fMRI evidence has correlated aHPC signals with those of the amygdala, hypothalamus, and

Box 2. Neurogenesis along the long axis

Differences in neurogenesis

In the context of their discovery that the DG constitutes a larger proportion of human pHPC than aHPC, Malykhin and colleagues [7] suggest that this pattern may be of relevance to hippocampal neurogenesis, which takes place within the DG: although neurogenesis can be observed in the DG along the entire long axis, relatively high DG composition in the pHPC could reflect a greater capacity for neurogenesis in that segment. Because neurogenesis produces DG granule cells, we note that greater DG composition in the pHPC could also be caused by, as opposed to being a cause of, high rates of neurogenesis in that segment.

Also of possible relevance, human dissection reveals that choroid plexus coverage is thick over the pHPC, especially at its posterior extent, but terminates at the uncal apex, such that there is no choroid plexus over the aHPC [6]. Although growth factors secreted by the choroid plexus are only known to impact neurogenesis in the subventricular zone [92], it is interesting to speculate that they may also encourage neurogenesis locally in the pHPC, possibly contributing to the greater DG composition described above.

Consistent with human evidence that is suggestive of greater pHPC neurogenesis, histological evidence shows that, in rodents, greater numbers of new neurons are indeed born in the dorsal than the ventral hippocampus [93]. These newly born dorsal hippocampal neurons also mature more rapidly than their ventral hippocampal counterparts [93,94].

Potentially linked phenomena

Differences in aHPC and pHPC neurogenesis could contribute to other long-axis phenomena in humans. For example, they could help explain why longitudinal increases can be observed in pHPC volume in association with extensive spatial learning [50], whereas no longitudinal volume increases have yet been observed in the adult aHPC.

Greater capacity for pHPC neurogenesis could also coincide with findings that receptive fields rescale in the rodent medial ERC to reflect compression or expansion in the environment, a phenomenon observed in aHPC-connected, but not pHPC-connected segments of the ERC [63]. Therefore, whereas existing aHPC neurons may be easily adapted to environmental changes, changes involving pHPC representations may require new neurons. This requirement could be met by greater pHPC neurogenesis.

anterolateral temporal lobes; and pHPC signals with those of the cuneus, precuneus, anterior and posterior cingulate cortex, inferior parietal cortex, and parts of the thalamus [18]. Each such functional pairing corresponds to a known direct or entorhinally-mediated anatomical pathway in rodents [3,4]. Some known hippocampal connections, such as to the vmPFC (discussed above), are vulnerable to signal loss in fMRI and were not observed in these studies.

Functional segregation

An emotion vs cognition dichotomy is prominent in animal models of long-axis specialization [3] (but see [19]). In humans, however, there are many others (Table 1).

Motivational processing

Direct reciprocal links between the aHPC and the amygdala, insula, and vmPFC, as well as projections to the nucleus accumbens, offer the aHPC a privileged interface with motivational processing regions [12,20,21]. One proposed contribution of this interface is to enhance hippocampal memory for biologically relevant information [22]. Researchers have linked reward value to enhanced subsequent memory (Dm) effects in aHPC, VTA and nucleus accumbens [23] and meta-analysis reveals that the amygdala and the aHPC better predict Dm in the context of emotional rather than neutral stimuli [24], although such interactions are sometimes also found in the pHPC [25].

A related observation concerns sensitivity of the aHPC to partial novelty (e.g., altered object locations or sequences) [26–28] and invalid cues [29], both of which may correspond to 'mismatch detection' (i.e., violation of expectations). Completely novel stimuli (e.g., sentences, faces, scenes, and environments) also activate the aHPC and/or the amygdala [30–32], perhaps because 'mismatches' arise from their familiar elements. To the extent that mismatches indicate knowledge gaps, they signal a need for exploration and, because novelty responses activate the VTA and substantia nigra to elicit dopamine release (as reward does), some suggest that novelty has reward-like qualities that motivate exploration [22]. However, factors associated with familiarity may outweigh mnemonic benefits conferred by increased motivation [33].

Some studies hint at complementary pHPC contributions to negative emotional processing, possibly driven by reciprocal pHPC-amygdala connections via the ERC [4]. For example, one report revealed a correlation between trait anxiety and pHPC responses to threat [34]. Also, whereas meta-analysis links Dm effects primarily to the aHPC [24], several studies involving negative materials reveal enhanced Dm effects in both the aHPC and pHPC (e.g., [35]). Finally, pHPC volume moderates arousal by shock-associated stimuli [36], which also activate the pHPC relative to stimuli without shock [37], although control stimuli with associates are needed in future studies in order to distinguish emotion from general associative retrieval.

Encoding vs retrieval

An encoding/retrieval dichotomy was proposed on the basis of aHPC responses in studies of encoding and pHPC responses in studies of retrieval [38], and enjoyed support from the aforementioned link between the aHPC and novelty, which was once considered a requirement for encoding [39]. This proposal faced conflicting evidence from the outset [40], but received recent meta-analytic support [41]. Meta-analysis revealed that fMRI episodic memory encoding studies evoke aHPC foci more frequently than retrieval studies, and more frequently evoke encoding Dm effects in the aHPC than in the pHPC. By contrast, the peak hippocampal coordinate associated with subjective retrieval fell in the pHPC (albeit at the aHPC border).

Still, many individual reports do not fit this pattern and meta-analytic outcomes can reflect design conventions. Importantly, encoding experiments typically employ novel materials and novelty appears to determine encoding locus: one fMRI study revealed Dm effects in the aHPC for novel but not repeated stimuli, and the opposite pattern in the pHPC [42]. Also, mnemonic advantages of novel stimuli in older studies appear to arise from a design confound, in which familiar items are tested under more challenging conditions than novel ones [33]. Together, these findings indicate that an encoding/retrieval dichotomy cannot rely on findings that link the aHPC to novelty, as neither the aHPC nor novelty uniquely contributes to encoding. It is difficult to reconcile this dichotomy with these issues.

Table 1. Existing theoretical proposals for long-axis functional specialization in the human hippocampus

Functional specialization		Evidence for	Evidence against	Relevant connections
Anterior	**Posterior**			
Emotion/ motivation	Other cognition	• Modulation of aHPC function by reward/novelty (e.g., [26,32,95]) • Meta-analysis: emotionally-enhanced memory in the aHPC [24] • Converging evidence from animal literature [3]	• In rodents, the dorsal hippocampus also connects directly to the SNr/VTA reward system [3] • pHPC is associated with trait anxiety [34] and contributes to negative emotional memory [35–37]	• Direct aHPC connections to motivational processing regions (amygdala, vmPFC, nucleus accumbens) [6,10,12,18] • Indirect aHPC connections to the hypothalamus, substantia nigra, VTA [12,18] • In rodents, ERC-mediated connections between dorsal hippocampus and amygdala [4]
Encoding	Retrieval	• Meta-analysis: the aHPC is associated with encoding tasks and Dm; the pHPC is associated with retrieval tasks [38,41] • Taxi drivers with a small aHPC have difficulty encoding new spatial associations [52]	• Encoding activity is observed along the entire long axis [40] • Stimulus novelty determines long-axis locus of Dm effects [42] and most encoding studies use novel stimuli, which are associated with the aHPC (e.g., [26,32,95]) • Familiar stimuli are associated with both pHPC Dm effects and superior source memory [33,42]	• None in particular
Other cognition	Spatial memory	• Volumetric and fMRI neuroimaging studies have often linked the pHPC and not the aHPC to spatial memory and navigation [48–50] • In rodents and monkeys, more place cell reports implicate the dorsal/ pHPC [46,47], although those sites are also more frequently sampled	• Place cells have been found in the human aHPC [43] and the rodent ventral hippocampus [61] • Taxi drivers with a small aHPC have difficulty encoding new spatial associations [52] • aHPC activity is linked to the representation of relative landmark positions [65,66]	• ERC-mediated pHPC connections to the PHC and parietal lobe [14,15,18] • Thalamus-mediated pHPC connections to the cingulate gyrus [3,18]
Vestibular memory and navigation	Visual memory and navigation	• The aHPC has strong vestibular connections [9] • The blind have a larger aHPC and smaller pHPC than controls [56] • The aHPC responds to vestibular sensation in fMRI studies [54,55] • Populations with high vestibular input have a larger pHPC and smaller aHPC [58]	• The aHPC receives visual information from its PRC and fusiform connections [11,53] • Evidence from vestibular high-input populations could also be taken as evidence against this framework	• Strong aHPC-insula connections via the uncinate fasciculus and ERC [4,9] • Possible direct aHPC connection to the fusiform gyrus [11] • ERC-mediated pHPC connections to the PHC and parietal lobe [14,15,18]
Global spatial representations	Local spatial representations	• In rodents, receptive field sizes vary on the hippocampal long axis (smallest receptive fields occur dorsally) [61] • Upon environmental change, aHPC-connected ERC grid cells rescale, maintaining global information, whereas pHPC-connected ERC grid cells do not, retaining local information • pHPC activity is often found in studies that address exact position or local features (e.g., [19,31,45,49,59,60]) • aHPC activity is linked to the representation of relative landmark positions [65,66]	• The proposal requires formalization for adaptation to non-spatial measures of memory	• ERC-mediated pHPC connections to the PHC and parietal lobe [14,15,18] • Thalamus-mediated pHPC connections to the cingulate gyrus [3,18] • ERC-mediated aHPC connections to the PRC [14,15]
Gist	Detail	• Category-level hits with item-level errors are associated with increased aHPC activity [68] • Novel verbal gist, but not novel verbatim structure, is linked to aHPC activation [32] • PTSD is associated with pHPC volume loss and increased gist reliance [69,70] • pHPC volume is associated with recollection of source details [18]	• Definition of 'gist' too flexible	• Same aHPC and pHPC connections as above • Direct aHPC connections to vmPFC and temporal pole [9,10,14,18]

Spatial processing

Many cells within the hippocampus respond selectively to portions of the environment (c.f. landmark responses in PHC [43]). Collectively, such hippocampal place cells are thought to underlie internal 'maps' of the environment [44,45], implying a special role for the hippocampus in spatial memory and navigation. In non-human animals, these cells have been recorded primarily in the dorsal hippocampus (rodents) and the pHPC (monkeys) [46,47], although these locations, for surgical reasons, are also the most frequently recorded. In humans, responses to spatial manipulations are often localized in the pHPC and not the aHPC (e.g., [48,49]; adding spatial details to a representation of London is associated with increases in pHPC, but not aHPC, volume [50]; and the pHPC, but not the aHPC, has access through its connections to spatial information in PHC, cingulate, precuneus and visual cortices (Table 2). Consequently, many have proposed that the pHPC is especially important for spatial processing, whereas the aHPC may be important for episodic memory or other functions [48–51].

These proposals are undercut by evidence that the aHPC also plays a spatial role. Although less numerous, place cells are found in the aHPC [43] and smaller aHPC volumes in taxi drivers are associated with reduced performance on spatial tests [52]. Observations that the pHPC is implicated in recollection of details [18] and episodic memory for familiar or repeated items [42] further argue against segregation of episodic memory to the aHPC and spatial processing to the pHPC.

Vestibular vs visual processing

Because vestibular stimulation frequently results in aHPC activation, Hufner *et al.* [51] propose that vestibular information is represented there (supporting path integration), whereas visual information is used in the pHPC (supporting navigation using visual cues). They emphasize respective connections with vestibular and visual systems, although visual information does reach the aHPC via the PRC and fusiform gyrus [11,53]. Support for their view arises from fMRI studies that link vestibular sensation to aHPC activation (e.g., [54,55]) and volumetric changes in special populations: for example, individuals with congenital or late-onset blindness have larger aHPC and smaller pHPC volumes than controls [56] and enhanced, rather than reduced, ability to select a spatial layout that corresponds to a recently navigated maze [57]). No study on vestibular loss has explored long-axis effects, but populations with high vestibular input, such as ballet dancers, show decreased aHPC and increased pHPC volumes [58] (surprisingly, the opposite pattern to that seen in the blind).

Global vs local representations

In human fMRI studies, pHPC activations often concern local spatial details, such as the precise position of individual landmarks [31,49,59] and other local environmental features [45,60]. Similarly, in rats, ventral hippocampal cells have larger receptive fields and more correlated responses than in the dorsal hippocampus [61], just as dorsal hippocampal lesions impair fine, but not coarse, spatial discriminations [62]. This evidence suggests that ventral spatial representations are more global and dorsal representations more local. Such high-detail representations may be facilitated by continuous representations of space received from the PHC and parietal inputs to the pHPC. ERC inputs may also contribute: whereas grid cells in ventral hippocampus-connected portions of rodent medial ERC respond to compression of the environment with proportional rescaling of their receptive fields, thereby preserving global information, grid cells in dorsal hippocampus-connected portions [63] do not, thereby preserving local spatial detail at the cost of global coverage. By contrast, binding global features in the aHPC (e.g., the relative positions of landmarks) may be supported by object-based and possibly holistic information from its

Table 2. Confirmed and suspected long-range connections of human anterior and posterior hippocampus

Anterior hippocampus		Posterior hippocampus	
Confirmed in humans	**Observed in animals and suspected in humans**	**Observed in animals and suspected in humans**	**Confirmed in humans**
• Perirhinal cortex[a,b] • Amygdala[c,d] • Nucleus accumbens (shell)[e] • Hypothalamus[f] • Ventral tegmental area[e] • Anterior and lateral temporal lobe[a,c,f,g] • Insula[c,f] • Ventromedial prefrontal cortex[f] • Gyrus rectus[g] • Fusiform gyrus[h]	• Entorhinal cortex (medial band)[i] • Piriform cortex • Lateral septum (rostral and ventral parts) • Bed nuclei of stria terminalis	• Entorhinal cortex (intermediate and lateral bands)[i] • Nucleus accumbens (core)[i] • Thalamus (anterior part)[i] • Mammilary bodies • Caudoputamen • Lateral septum (caudal part) • Medial septal complex • Supramammilary nucleus • Ventral tegmental area	• Parahippocampal cortex[a,b] • Anterior cingulate cortex[g] • Posterior cingulate cortex[g] • Cuneus[g] • Precuneus[g] • Dorsolateral prefrontal cortex[g] • Inferior parietal lobe[g]

[a]Evoked fMRI [14].

[b]Resting-state fMRI [15].

[c]Evoked EEG [10].

[d]Dissection [6].

[e]Evoked fMRI [12].

[f]Dissection tractography [9].

[g]Resting-state fMRI [18].

[h]Tractography [11].

[i]Previously linked to either aHPC or pHPC, but without sufficient resolution to resolve within-structure subdivisions.

Box 3. Emerging functional specializations

Environmental reconfiguration
Recent data from rats [63] indicate a number of discrete modules along the ERC (which map onto the hippocampal long axis), with segments at each end behaving quite differently in response to environmental changes. Although place cells have been recorded in the human hippocampus (e.g., [43]), the data do not show whether human place cells share these properties.

Recent vs remote memory
Gilboa and colleagues [96] report a long-axis interaction of memory remoteness in a cued autobiographical recall task, with recent memories clustering in the aHPC and remote memories being distributed along the entire length. Similarly, Bonnici and colleagues [97] report a trend towards a long-axis interaction of remoteness in classifier accuracy, driven by better pHPC classification of remote memories. The authors speculate that the pattern may reflect the physical distribution of memories themselves [96] or that the pHPC supports event reconstruction, which is needed more for older memories [86]. These explanations underscore uncertainty about whether remoteness, or a correlate of remoteness, underlies this apparent dichotomy.

Temporal sequence
Reconstruction of movie scene order evokes aHPC activity beyond that induced by inference of their sequence without memory [98]. Also, in rats, the PRC and vmPFC (connections of ventral hippocampus) are needed for temporal memory [99]. However, the pHPC and PHC have also predicted encoding success for word sequences in human fMRI studies (in addition to the aHPC; [100]), which suggests a possible additional role for the pHPC. One interesting possibility is that the aHPC contributes configural structure to sequences through conceptual knowledge, whereas temporal information in the pHPC is continuous. Another possibility is that, because recently reported hippocampal 'time cells' behave like place cells [101], time could be represented in a corresponding aHPC-to-pHPC gradient of increasing precision.

Olfactory processing
In rodents, olfactory memory is impaired following ventral but not dorsal hippocampal lesions [102], just as rodent aHPC is directly connected with primary sensory areas and sensory inputs. In humans, direct aHPC connections are weaker, with no direct link to sensory inputs [103], although aHPC-piriform links cannot be ruled out. FMRI Dm effects for odors have been found in both aHPC and pHPC [104,105], just as ERC-mediated olfactory connections reach both segments in rats [4]. Uncal (aHPC) seizure foci are associated with olfactory auras, but these could plausibly arise from stimulation of the piriform cortex [103]. Because odor lacks sharp spatial or temporal boundaries [106], our model predicts an aHPC link will ultimately be confirmed.

Auditory processing
Although no formal auditory proposal has been advanced, recent studies that compare professional musicians to controls have revealed both increased left aHPC volume [107] and increased sensitivity to acoustic novelty in the aHPC [108].

PRC and fusiform gyrus connections [64]. Consistent with this idea, the pHPC is activated by retrieving exact local positions of landmarks, whereas the aHPC is activated by retrieving approximate or relative positions within a global framework (Evensmoen *et al.*, unpublished manuscript; [65,66]); and thinking of local spatial details from past life events, such as wedding seating arrangements, evokes more pHPC activation than thinking of the general location of those events, which evokes aHPC activation [19].

Semantic gist (schemas) vs detail

Other evidence supports long-axis separation of episodic detail and 'gist', defined as the essence of an event, or a schematic representation of it, lacking idiosyncratic detail. Gist, however, should not be confused with 'familiarity', which does not require the hippocampus, does not readily support associations, and is often recognized by the absence of associative details [67]. Although lacking in detail, gist memory nonetheless encompasses novel associations among semantic elements. Gist tends to be associated with the aHPC: for example, abstracting over large sets of items to create category-consistent false alarms – a measure of gist memory – is associated with increased aHPC activity [68]. Also, repetition of sentences with altered gist evokes aHPC responses, whereas repetition of sentences with preserved gist but altered syntactic structure does not [32]. Post-traumatic stress disorder (PTSD) is linked with both pHPC volume loss and increased reliance on gist memory [69,70]. By contrast, in healthy individuals, pHPC volume is positively correlated with memory for detailed contextual information [18]. Notably, the aHPC has direct and reciprocal connections with the anterior temporal lobes and vmPFC, providing access to semantic information that could be bound by aHPC into conceptual representations [71,72].

Synthesis

Overview

No framework for integrating these proposals is readily available, the evidence prevents us from definitively dismissing most of them, and still further proposals are poised to emerge (Box 3). How can these disparate accounts be accommodated? We propose that the aHPC and the pHPC have various *de facto* specializations based on their different connectivity, and that they also have properties pervading these specializations that derive from their subfield composition and connected ERC grid cells.

Proposed model

Most current accounts assume that the hippocampus plays an 'indexing' role (e.g., [73,74] and that what it indexes depends on its inputs. As the aHPC and pHPC feature largely non-overlapping sets of physical connections, their connectivity must distinguish what each segment can index and hence what it can represent (Figure 1). Also, within its limited set of physical connections, each segment interacts with constantly varying subsets of active cortical and subcortical systems. For example, the aHPC might receive schematic information from the temporal pole at one moment, and object information from the PRC a moment later. As such interactions likely alter the dynamics of each system [75], it is hardly surprising that the evidence links the aHPC and pHPC to many different functional specializations.

Internal to the hippocampus, cells in both segments share functional properties (e.g., place cells), just as the trisynaptic loop in both the aHPC and the pHPC performs the same operations. However, because of the influential role of the DG in pattern separation [76], low DG/CA ratios in the aHPC and high ratios in the pHPC seem likely to bias the segments towards pattern completion and separation,

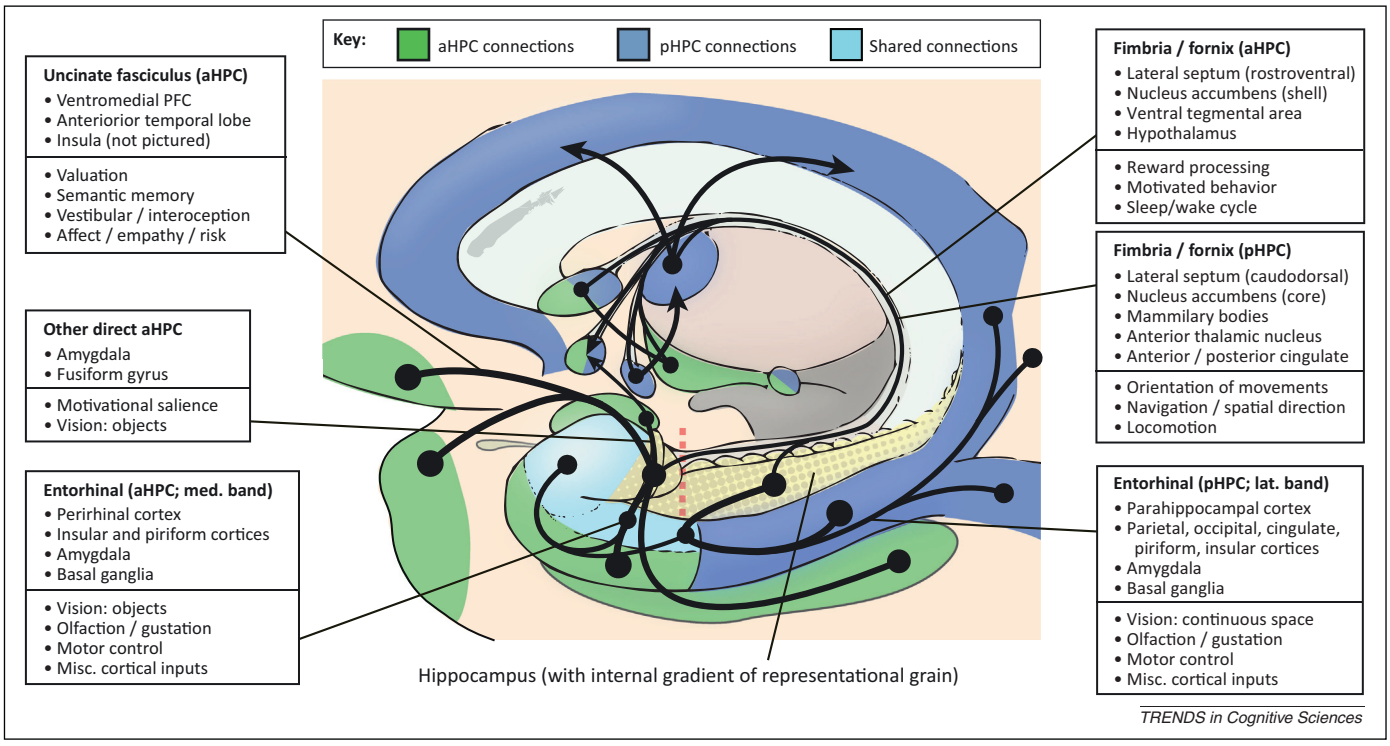

Figure 1. Model of long-axis hippocampal specialization. We posit that long-axis hippocampal specialization emerges based on two primary mechanisms. First, the aHPC and pHPC represent information internally at coarse and fine granularities, respectively. This pattern may arise on the basis of different DG/CA subfield ratios that influence the balance of pattern completion and pattern separation; inputs from the ERC that reflect similar grain differences; or both factors. Second, the aHPC and pHPC connect to different cortical and subcortical systems as depicted here. The basic operations of the hippocampus, applied to these various connections, produces an array of different 'functions' that involve the aHPC vs pHPC. Hippocampal connections (thick black lines) are depicted with reciprocal termination points (black dots). The aHPC and pHPC are separated by the plane that contains the uncal apex (dashed red line). The information hypothetically carried on each pathway is shown in boxes.

respectively. This bias could contribute to sharp pHPC representations (high match specificity) and broader aHPC representations (low match specificity). This gradient in the 'grain' of hippocampal representations would likely influence the nature of all information processed in the aHPC and pHPC, ranging from the size of spatial receptive fields [61] to the level of detail in events [19].*

This account predicts the finding in rodents of a dorsal-to-ventral gradient of increasing receptive field sizes [61]. However, this gradient could alternatively arise from connectivity with ERC grid cells, which feature a corresponding gradient of field sizes [77,78] and are thought to impose a spatial framework on incoming information (e.g., [79]). More likely, the mechanisms work in concert, with ERC grid cells facilitating cortical-hippocampus exchanges by converting information to or from spatial formats suited to the aHPC or pHPC (see [19,80], for discussion of spatial organization of non-spatial information). Further upstream, the PRC and PHC may further contribute to this translation by coding information in object or scene-based formats.

Taken together, these mechanisms could conspire to create unique aHPC and pHPC encoding environments, with the aHPC, anterior ERC and PRC coding information, whatever its form or origin, in terms of global spatial relations among entities (e.g., a sketch that describes general or relative positions of its features); and the pHPC, posterior ERC and PHC coding information in terms of precise positions within some continuous dimension (e.g., a detailed map drawn to scale). Extending this idea to a more autobiographical example, the aHPC might retain associative links between the principal actors, actions, and setting of an event; whereas the pHPC might retain the exact spatial or temporal context of the event, even when this information is tangential to the episode's theme. It should be noted, however, that the role of the hippocampus is believed to primarily concern associations and episodes, whereas properties of isolated objects are likely encoded in extra-hippocampal regions [53].

The various proposals for hippocampal specialization that we have reviewed share properties predicted by our model. For example, rewarding, relative to neutral, stimuli lead to relatively gist-like memories [81] and increased aHPC activity. By contrast, familiar, relative to novel, stimuli lead to enhanced contextual detail [42] and increased pHPC activity. Alignment of connections to the aHPC vs pHPC may be adaptively determined: for example, cortical systems processing information that pervades an environment (e.g., predator threat) may connect to the aHPC in order to take advantage of its coarse-grained representations. By contrast, those that concern focal portions of the environment (e.g., food cache location) may have developed connections to the pHPC.

Relation to other proposals

The connections of the aHPC and pHPC align approximately with those sets of regions specified in recent efforts to segment cortex into separate memory systems [82]. Ranganath and Ritchey distinguish between an anterior temporal

* Many investigators have assumed that pattern completion is involved primarily in retrieval and pattern separation, in encoding. By our model, however, either process may be implicated in encoding and retrieval, the determining factor being the 'grain' needed for the particular task.

(AT) and posterior medial (PM) system encompassing the amygdala, temporal pole and vmPFC versus thalamic nuclei, mammillary bodies, and dorsolateral/parietal elements of the default network, respectively. The authors characterize these systems as concerning familiarity, people, objects, and concepts (AT); and recollection, scenes, theory of mind, and 'situation models' of interactions between elements of an environment (PM). The data we have discussed are roughly in agreement with this partitioning scheme, suggesting that the AT and PM systems are indeed partitioned at the level of the hippocampus. Our proposal extends these ideas in addressing the manner in which the hippocampus connects to, and represents, information from these (and other) cortical systems.

Our ideas also align with the proposal of nested hierarchies in autobiographical memory that increase in abstraction and inclusiveness as one moves from sensory-perceptual-affective-conceptual episodic elements at the bottom to general events and lifetime periods at the top, which confer meaning, on lower levels. To access autobiographical details, one must first activate gist-like levels [83]. We suggest that the partial starting inputs of a memory search are more likely to cue gist-like aHPC representations than detailed, pattern-separated pHPC ones. Cortical reinstatement of such gist-like memories would reproduce the general mental context associated with an event, providing a better contextual match for a subsequent pHPC-mediated memory search for particular details. Consistent with these ideas, initially locating a memory implicates the aPHC, whereas later elaboration of its details implicates the pHPC [84–86]. Likewise, during navigation, the aHPC has been associated with initial global reinstatement of the environment and the pHPC with ongoing retrieval of local details [60].

The PHC and pHPC both contribute to fine perceptual discriminations among scenes (not objects), whereas the PRC performs object discrimination independently of the hippocampus [17]. This asymmetry can be understood in the context of our proposal: pHPC pattern separation facilitates discrimination in connected PHC, whereas aHPC pattern completion is not useful for discrimination. Along these lines, in the ongoing stream of scene imagery relayed to PHC during navigation, the important information concerns changes (updates to the environment). By contrast, relations among entities are often unstable across instances and the important information lies in the detection of patterns (e.g., game is often found at the water's edge). Accordingly, an object system tolerant of change (involving aHPC pattern completion) and a scene system sensitive to it (involving pHPC pattern separation) may be optimal from a survival perspective.

The notion of aHPC tolerance of altered inputs may seem at odds with its sensitivity to stimulus novelty. However, prediction error, which may underlie novelty responses, can be generated only where there are predictions. Familiar elements of novel inputs would be more likely to generate (incorrect) predictions in the aHPC, yielding mismatch responses. By contrast, repeated inputs would satisfy the coarse predictions of the aHPC, but also elicit more detailed predictions by the pHPC. When these latter predictions are violated by subtle changes (e.g., to context), pHPC mismatch responses would result. Consistent with these ideas, novel stimuli and initial schema formation activate the aHPC, whereas repeated stimuli in a novel task context and schema application activate the pHPC [42,87].

We had previously suggested that pHPC may play a special role in recollection memory on the basis of larger pHPC volumes predicting more subjective recollection and source memory in several experiments [18]. Notably, source memory in these experiments involved memory for specific details, just as recollection is often described to participants (who identify it subjectively) as concerning retrieval of specific details associated with the target memory. However, the current proposal predicts that recollection of gist-level associative details, which may be more difficult for participants to subjectively identify as specific details, will be linked with the aHPC rather than the pHPC.

Limitations

Human proposals and evidence do not typically address the intermediate hippocampus, likely because little is known about its properties. To limit free parameters for theoretical development, we have not distinguished the intermediate from the posterior hippocampus. Doing so may ultimately prove valuable: tracer studies suggest that it features diffuse entorhinally-mediated cortical connections incorporating elements preferred by the ventral and dorsal hippocampus [4]; ablation evidence suggests that one-trial spatial learning may require it [5]; it has distinctive genetic coding [3]; and, in humans, it features the smallest proportion of CA1–3 neurons [7]. One possibility is that its hybrid connectivity allows it to bridge properties of the aHPC and pHPC when their fusion is desirable. Along these lines, fMRI activations fell at the aHPC/pHPC boundary when either object sequence (requiring global aHPC processing) or location (requiring local pHPC processing) was novel, but not when both were novel [27].

Also, we have primarily discussed correlational data in order to relate aHPC and pHPC to behavior: most human evidence regresses volumetry against individual differences or neuroimaging data against design matrices. Evidence that supports causal inferences, such as patient data, is limited. Without such evidence, it remains possible that the hippocampal specialization in various domains is ancillary. We note, however, that patient evidence links the hippocampus to episodic memory more generally [88], pHPC volume loss in PTSD increases reliance on gist memory [69,70], and lesions to dorsal hippocampus specifically impair fine-grained spatial discriminations in rodents [62].

Finally, the boundaries drawn by our model between global and local representations are fuzzy, leaving open the criticism that our proposal is too vague. Additional complication arises from the possibility we have discussed of an intermediate zone in which distinctions between the aHPC and the pHPC are blurred. Further research will be required to establish clear boundary conditions.

Concluding remarks

The human hippocampus, like that of rodents and primates, features anatomically distinct anterior and posterior segments associated with various functional

Box 4. Questions for future research

- Can suspected direct and indirect connections to the aHPC and pHPC be confirmed? Many important connections observed in animals have not yet been directly observed in humans. Advanced neuroimaging methods and further post-mortem studies may soon make these observations possible.
- Can new evidence be provided to support 'emerging' specializations? Existing evidence hints at this possibility, but is problematic or incomplete (Box 3). Further investigation is needed to substantiate these proposals.
- Can increased pattern separation in the pHPC relative to the aHPC, as implied by greater DG composition in the pHPC, be confirmed? Observation of this relationship would support the gist-detail dichotomy and, more broadly, the idea of an internal mechanism for long-axis segregation.
- Is the routing of aHPC and pHPC connections to those segments adapted to the hypothesized properties of those segments? Comparison of 'ideal' and actual properties of a representation store may reveal that the connections of the aHPC and the pHPC are organized to take advantage of their respective properties.
- What are the properties of the intermediate hippocampus in humans? Initial indications suggest that it may share characteristics of both the aHPC and the pHPC, but its qualities are at present poorly understood.

specializations. To accommodate these data, we propose a model that assumes similarities and differences between the aHPC and the pHPC. In both, cellular properties and the trisynaptic circuit are similar, and the ERC imposes a spatial framework on cortical communication. However, the two regions represent information internally at different granularities. This phenomenon may be imposed by the ERC, which shows similar grain differences; by variation in subfield composition, which biases the aHPC towards pattern completion and the pHPC towards pattern separation; or by both factors. The aHPC and pHPC also connect with different cortical and subcortical systems, with their connectivity seemingly determined by whether such systems are better suited to coarse-grained (global) or fine-grained (local) information. More data will be needed to assess these possibilities (Box 4).

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