# Functional organisation of the hippocampal longitudinal axis

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**The precise functional role of the hippocampus remains a topic of much debate. According to a dominant view, the dorsal/posterior hippocampus is implicated in memory and spatial navigation and the ventral/anterior hippocampus mediates anxiety-related behaviours. However, this 'dichotomy view' may need revision. Gene expression studies demonstrate multiple functional domains along the hippocampal long axis, which often exhibit sharply demarcated borders. By contrast, anatomical studies and electrophysiological recordings in rodents suggest that the long-axis is organized along a gradient. Together, these observations suggest a model in which functional long-axis gradients are superimposed on discrete functional domains. This model provides a potential framework to explain and test the multiple functions ascribed to the hippocampus.**

The hippocampus is a medial temporal lobe structure critically involved in episodic memory and spatial navigation[1-7]. Its long, curved form is present across all mammalian orders and runs along a dorsal (septal) to ventral (temporal) axis in rodents, corresponding to a posterior-to-anterior axis in humans (FIG. 1a-b). The same basic intrinsic circuitry is maintained throughout the long axis and across species (FIG. 1c). Despite this conserved intrinsic circuitry, the dorsal and ventral portions have different connectivities with cortical and subcortical areas, and this has long posed a question as to whether the hippocampus is functionally uniform along this axis. Here we review cross-species data that show how the seemingly disparate functions ascribed to the hippocampus can be accommodated by a model in which different functional properties exist along the longitudinal axis.

The severe memory impairment suffered by patient H.M. following bilateral hippocampal resection[1] led to intensive study[8] of patients and animal models with hippocampal damage, with an ensuing characterisation of hippocampal function in terms of declarative memory[2], encompassing both episodic and semantic memory. At the same time, however, evidence emerged for a hippocampal role in spatial memory, based on the discovery of hippocampal 'place cells'[9,10] and the demonstration that hippocampal lesions impair spatial memory[4]. Both the declarative memory hypothesis[11] and the spatial mapping hypothesis[12] of hippocampal function proposed a unitary model in which the entire hippocampus is dedicated

to a single, general type of memory. In light of subsequent evidence for a hippocampal role in emotional memory[13], an alternative model that could account for different types of memory is that each type of memory depends on separate intrahippocampal circuits; this raises the question of whether these circuits are segregated or superimposed[14].

In one anatomical framework, functionally distinct hippocampal circuits are segregated along the dorsoventral hippocampal axis. Indeed, early rodent electrophysiological studies indicated dissociable response properties in dorsal *vs*. ventral hippocampus[15-16], and early lesion studies suggested that behaviour was differentially affected by dorsal and ventral hippocampal lesions[17-20]. These early studies did not, however, distinguish between the location and the volume of the lesion. Subsequent work[21-22] which did make this distinction showed that restricted dorsal hippocampal lesions, but not similarly sized ventral lesions, impaired spatial learning. A role for the hippocampus in emotional responses[23] was proposed to reside in the more ventral parts of the hippocampus, on the basis of more dense ventral than dorsal connectivity with the amygdala[24-25] and hypothalamic endocrine and autonomic nuclei[26], and the selective ventral hippocampal role in the endocrine stress response[27]. The ensuing view, which has dominated the field ever since, has been that dorsal parts of the hippocampus (DH) mediate cognitive functions — particularly spatial memory — whereas ventral portions of the hippocampus (VH) are involved in emotional responses[28-29].

This 'dorsal–ventral dichotomy view' was, in part, based on observations that emphasized segregation of inputs to the hippocampus. However, differences in connectivity with cortical and subcortical structures along the dorsoventral axis of the hippocampus are gradual rather than absolute[30], which suggests that functional differences along the long axis may also follow gradient-like organisation[31]. Furthermore, recent gene expression data indicate that there are multiple, discretised dorsal–ventral subdivisions along the hippocampal long-axis[32]. Thus, given this potentially more complex hippocampal long-axis functional organisation[14], the currently accepted dorsal–ventral dichotomy model requires revision.

In this Review, we first describe anatomical findings in rodents that suggest there are multiple long-axis functional gradients. We then review evidence from rodent gene expression data indicating that discrete genetic domains are superimposed on this graded long-axis organisation. We then discuss — using data from studies in animals and humans — how these anatomical and genetic patterns may result in patterns of long-axis functional specialisation, particularly in terms of spatial processing, emotional responses, action and episodic memory. The evidence for multiple levels of longitudinal functional organisation should change our view of the hippocampus and is critical to understanding the role of the hippocampus in cognition.

## Hippocampal long-axis anatomy in rodents

### *Gradients in hippocampal–cortical connectivity*

In terms of cortical input in rodents, a dorsolateral to ventromedial gradient of origin in the entorhinal cortex (EC) corresponds to a dorsoventral axis of termination in the hippocampus[33-35] (FIG. 2a). This topography is smooth, without abrupt transitions in EC–hippocampal projections. The cortical input to the EC is itself topographically arranged (FIG. 2a) and this mapping is maintained in EC–hippocampal inputs. Taking the rat cingulate cortex as an example[36], information arising from the infralimbic (IL) and prelimbic (PL) cortex will, via input to the ventromedial parts of the EC, primarily reach ventral parts of the hippocampus. By contrast, projections from the PL cortex targeting intermediate parts of the EC influence

the hippocampus at intermediate dorsoventral levels. The remaining parts of the cingulate cortex — anterior cingulate and retrosplenial (RS) cortices — primarily target dorsal and lateral parts of the EC, which subsequently project to dorsal parts of the hippocampus[36]. The hippocampus thus receives a transition of projections from the cingulate cortex along its long axis: cingulate areas involved in emotional regulation (IL and PL) project more ventrally, and cingulate areas involved in spatial processing (RS) project more dorsally. Importantly, this transition of projections is continuous rather than discretised. Furthermore, reciprocating projections from the CA1 and subiculum to the EC show a topographical organisation similar to the EC–hippocampal inputs[37].

*Gradients in hippocampal–subcortical connectivity*

Hippocampal connectivity with multiple subcortical structures also shows dorsoventral topographical gradients. Taking the topography of the major hippocampal output to the lateral septum (LS)[26] as an example, the dorsal half of the hippocampus projects to a very small dorsal part of the LS, whereas progressively more-ventral parts of the hippocampus innervate progressively larger parts of the LS more ventrally (FIG. 2b). Adjacent hippocampal areas along the longitudinal axis innervate distinct, though overlapping regions of the LS[38]. Thus, although individual LS neurons receive inputs from a dorsoventral 'patch' of hippocampal pyramidal cells[38], the projection on the whole has a topographically graded organisation. Critically, this topographically graded organization is preserved in LS projections to the hypothalamus. This implies that different hippocampal regions along the longitudinal axis map topographically onto different hypothalamic regions involved in behavioural, endocrine and autonomic responses associated with specific goal-oriented behaviours[26] (FIG. 2b). Hippocampal connectivity with the nucleus accumbens[39] (NAc) and amygdala[40] also follows a topographical pattern, with progressively more ventral hippocampal portions projecting to progressively more medial parts of both of these subcortical structures (FIG. 2c).

Interestingly, these topographical gradients appear to arise during embryonic neurogenesis[41]. Although neurogenesis occurs simultaneously along the hippocampal dorsoventral axis, the dorsal hippocampus projects to those zones in target structures in which cells were generated earlier, whereas progressively more ventral parts project to zones in which cells were generated later. For example, the dorsal hippocampus projects to a zone in the LS that contains earlier formed, medially placed LS cells, whereas the ventral hippocampus — which is geometrically further away from the LS — projects to lateral-septum zones containing later-formed, laterally placed cells[41].

The density of neuromodulator projections to the hippocampus also changes along the long axis (Supplementary Box 1). Whether these changes are gradual, step-like or abrupt has not been studied in detail, but a clear pattern of stronger projections of monoamine systems to more ventral parts of the hippocampus is apparent. Thus, in general, the dorsoventral organisation of extrinsic connectivity is one of gradual transitions of topographically organised projections, which does not show a dichotomous segregation into discrete dorsal *vs*. ventral portions.

## Gene expression along the long axis

The development of an unbiased transcriptional map of the mouse hippocampus, using genome-scale *in situ* hybridization[42] has provided detailed molecular evidence for a discretised dorsal–ventral pattern of gene expression[29,32,43]. Importantly, genetic domains are

not defined by expression of any single gene but, rather, by the combined overlap of many gene expression domains[32]. Thus, the overlap of many genes with common expression boundaries gives rise to genetic domains with clearly demarcated borders[32]. Boundaries between domains can be reciprocal, in that individual genes delineate a given boundary from each side (FIG. 3a) [32]. Multiple segregated molecular subdomains, each with a unique complement of expressed genes, have been demonstrated along the long axis. A first study demonstrated 9 domains within CA3[32], and other studies showed that DG[29] and CA1[43] are segregated into three major molecular domains: dorsal, intermediate and ventral (with ventral CA1 domain comprising 4 subdomains). Importantly, the molecular differentiation along the longitudinal axis is not simply dorsal *vs*. ventral, *i.e.* there is no evidence for a boundary that divides the long-axis into two portions. If the 9 expression domains in CA3 can be simplified into dorsal, intermediate and ventral parts, similar to CA1 and DG[29], this could suggest a tripartite model of the long axis. Such a tripartite model has been recently corroborated in a developmental gene expression study in rats[44]. Nevertheless, the exact number of domains along the long axis, and whether these are hierarchically organised, is currently unknown[14].

The interesting challenge ahead will be to assess whether these patterns of molecular expression translate into specific functional properties along the hippocampal long axis. The expression profiles of genes encoding adhesion molecules and ion channels[32,43] may determine intrinsic electrophysiological properties of discrete hippocampal neuronal populations, such as the differences in neuronal excitability[45] and synaptic plasticity[46-47] that have been detected along the long axis. For example, hyperpolarisation-activated cation channels HCN1 and HCN2, which mediate hyperpolarization-activated currents ($I_h$) currents, exhibit dorsoventral expression differences[48] and are important for a spatial function that is dorsoventrally graded[49-51]. In general, neurotransmitter receptor expression varies across the long axis for the majority of transmitter systems (Supplementary Table 1). Studies combining genetic and anatomical techniques in the rodent brain have begun to reveal that neuronal circuits, both within the hippocampus[52-53] and between hippocampus and lateral septum[43], share common gene expression patterns, which indicates overlap between anatomical and genetic levels of organisation along the long axis. Importantly, however, in contrast to the anatomical homologies between the rodent and primate hippocampus described in Box 1, the recently developed transcriptional atlas of the adult human brain[54] indicates that there are differences in gene regulation between mouse and human hippocampus. The molecular organisation along the hippocampal long axis in primates, and whether this is similar to mice[32,43], remains to be examined.

**Reconciling molecular and anatomical data**

How can the molecular data indicating sharp expression boundaries along the long axis that are common to many genes be reconciled with the anatomical data showing extrinsic connectivity gradients along the long axis? Two points are important in answering this question. First, at the level of individual genes, there are various long-axis expression patterns, including gradual changes, step-like changes and sharp transitions[32]. Second, although extrinsic hippocampal connectivity appears to follow a smooth, graded topographical organisation, sharp demarcations of intrinsic connectivity along the long-axis have also been observed. For example, the two major longitudinal association fibre systems in the hippocampal formation — the longitudinal axon collaterals of CA3 pyramidal cells and the longitudinally-oriented axons of DG mossy cells — show extensive axon divergence within the dorsal two-thirds and within the ventral third of rat hippocampus, but few fibres

cross between these subdivisions[30,55-58] (FIG. 3b). That is, the division between these areas in terms of intrinsic connectivity is relatively abrupt. Similarly, in monkeys there are extensive *vs*. limited interconnections in the posterior two-thirds *vs*. the anterior third of the hippocampus, respectively[59] (FIG. 3b), although the boundary, in terms of intrinsic connectivity, between these hippocampal portions is less marked than that in rodents.

In humans, discrete changes in molecular or anatomical organisation along the hippocampal long axis have yet to be examined. However, one study showed abrupt transitions in electrophysiological properties along this axis in humans[60]. Specifically, measurements at adjacent contacts (on multi-contact depth electrodes) showed an abrupt decrease in coherence at approximately the transition between anterior third and posterior two thirds of the hippocampus[60]. Similarly, in rats theta-wave coherence is relatively high between dorsal and intermediate sites, but substantially less between dorsal and ventral sites[61] (FIG. 3c). It will be important to determine whether this decrease in coherence coincides with the locus on the long axis at which intrinsic connectivity shows the partition described above[58-59].

Together, the data suggest that there are different types of longitudinal organisation — both gradual gradients and discrete sharply-demarcated domains — that appear to be superimposed at both the anatomical and mRNA levels (FIG. 4). Next we review how these various patterns of long-axis organisation may be expressed functionally.

## Functional organization of the long axis

### *Spatial processing in rodents*

The representation of location by hippocampal place cells is non-topographic[3]. A local cluster of place cells in the rodent DH can cover most of a spatial environment[62]. Initial evidence suggested that relatively small segments of the DH (a quarter or less of total hippocampal volume) are sufficient to encode spatial memory[22]. However, if the original spatial encoding occurs in the context of a normal hippocampus, retrieval requires the entire dorsal two-thirds of the hippocampus (*i.e.*, including parts of the VH), suggesting a more distributed — or graded — mode of action in a normal hippocampus during spatial learning[63]. Thus, these lesion studies suggested the possibility that normal rats engage an extensive hippocampal network — located in the dorsal 70% of the hippocampus — during encoding and retrieval of spatial memory, whereas more limited networks within this dorsal region can be used for encoding in rats with partial hippocampal lesions[63].

Does the ventral hippocampus have a role in spatial processing? Initial data indicated that the proportion of ventral hippocampal cells expressing place fields was markedly lower than that of DH, and that ventral place cells having lower spatial selectivity[64]. More recent data demonstrate that the relative size of place fields in area CA3 increases almost linearly with position from the dorsal hippocampal pole (where place fields are ~1m) to the ventral pole (where place field size approaches 10m) (Fig 5a)[31]. This finding not only highlights a role for the VH in the processing of large-scale spatial information, it also implies a functional gradient along the hippocampal longitudinal axis (as opposed to a dorsal–ventral dichotomy). That is, the VH may subserve similar spatial processing functions as the DH, but at a larger spatial scale. Such a representation of space at multiple scales has computational advantages in the sense that a gradient for space accommodates both spatial resolution and spatial contiguity. A further recent observation regarding place cells is that when rodents locomote in a constant location, place cells firing fields are defined by time instead of location[65-67], posing the interesting question of whether such ‘time fields’ expand from dorsal to ventral[68] similar to place fields.

Place cells participate in multiple, independent spatial representations[69-70], whereas the more recently discovered entorhinal grid cells[71] encode a universal metric of the spatial map. Grid-cell firing locations define a periodic triangular or hexagonal array covering the animal's entire environment[71], and they are anchored to external cues and maintained when the cue is removed and with ongoing changes in the animal's speed and direction[71]. The spatial selectivity of place cells may be linked to inputs from grid cells[72-76]. Critically, the increase in the size of place fields along the hippocampal dorsoventral axis[31,64,77] is mirrored by an increase in the spacing between grid-cell firing locations from the dorsomedial to the ventrolateral medial EC[71,78-79]. In contrast to the gradual dorsoventral increase in place-field size, the observed spatial gradient in medial EC grid size shows discrete, step-like increases[80]. However, although the scale of place cells increases gradually from dorsal to ventral on average, this does not rule out the existence of discrete transitions like those observed in entorhinal cortex[80]. If increase in place-field scale turns out not to be continuous, it will be important to determine whether this scale changes abruptly with transitions between genetic domains. Assuming for now that the place-field scale is indeed continuous, inputs from different medial EC functional modules could, in theory, be combined[76,81] to give rise to the observed longitudinal spatial gradient[75]. Specifically, EC modules of increasing spatial scale show considerable anatomical overlap in the dorsal-to-ventral axis of the EC[80], suggesting that there may be overlap of module inputs to hippocampus, even if inputs come from the same dorsoventral EC level. Future studies will determine whether grid-cell modules in the medial EC distribute evenly across the hippocampus, or connect to modules in hippocampus, or whether there is complete convergence. With respect to the organisation of the hippocampal long axis more generally, the gradient in place-field size illustrates that, despite numerous molecular and anatomical domains having distinct boundaries, a combination of hippocampal afferent signals may engender gradually changing functional properties (FIG. 4).

*Spatial processing in primates*

Does the dependence of spatial processing on dorsal portions of the hippocampus in rodents extrapolate to posterior portions of the hippocampus in primates? The majority of primate data pertaining to functional long-axis organisation comes from human structural and functional MRI (fMRI) studies. It should be kept in mind that technical factors may differentially influence fMRI and voxel-based volumetric measures for anterior *vs*. posterior portions of human hippocampus. fMRI susceptibility artefact and signal drop-out may affect the anterior medial temporal lobe more than posterior medial temporal lobe[82] (although protocols exist to correct this[83]). In addition, posterior hippocampus is approximately half the cross-sectional area than the larger anterior hippocampal head, such that activated cluster size and degree of post-acquisition spatial smoothing may influence statistical effects differentially along the long-axis.

Despite these potential limitations, fMRI studies in humans have demonstrated a relationship between activation[7,84-85] and structural change[86] in the posterior hippocampus with navigation, and are therefore broadly in keeping with the dependence of spatial function on dorsal portions of the hippocampus in rodents. However, neuroimaging results are typically reported as anatomically focal effects that exceed a particular statistical threshold, and simply demonstrating an effect to be located at a specific long-axis locus does not exclude an effect just below that statistical threshold at another locus. Although most studies report responses in either anterior or posterior hippocampus, some studies demonstrate functional double dissociations between long-axis loci, and these are particularly informative[6,87]. Thus, in further support of a posterior hippocampal specialisation for space processing, one reported

double dissociation is that accurate way-finding activates posterior, but not anterior, hippocampus[84], whereas activity in anterior, but not posterior, hippocampus correlated with the formation of a survey representation of a new virtual-reality environment[84] (see also [88-89]). A recent fMRI study[90] reported a long-axis dissociation in terms of spatial size and complexity. Participants navigated through three virtual mazes (small with 6 corridors; large with 6 corridors; large with 14 corridors), and then, during scanning, were presented images of landmarks from these mazes and asked to retrieve to which maze they pertained. Anterior hippocampal activation scaled with the number of corridors (complexity), whereas posterior responses were larger for larger mazes. The interpretation of these data is limited, however, by the fact that for all mazes, participants navigated almost exclusively along border paths, and there was no measure of how much spatial retrieval was evoked by correct landmark retrieval (cf. [91]).

Electrophysiological evidence for posterior hippocampal involvement in spatial processing in primates is limited. One non-human primate study using a spatial delayed matching-to-sample task demonstrated greater activity during the delay period in posterior hippocampus than in anterior hippocampus[92]. Although intracranial recordings in humans have provided evidence for place-cell-like responses during navigation[93], the relative distribution of these cells along the long axis, and how their responses vary as a function of environment size, has yet to be determined. However, recent electrophysiology data from non-human primates reveal grid-like cell properties in the posterior EC. The study showed that spatial scale varied as a function of distance from the rhinal sulcus[94] (which is equivalent to the dorsomedial-to-ventrolateral axis in rodent medial EC), suggesting that spatial scale may also vary along the primate hippocampal long axis (FIG. 5b).

How does spatial scale representation observed in rodents increase or change across species? Developments in human fMRI, such as hippocampal MRI unfolding[95] and high-resolution fMRI techniques[96-97], combined with within-scanner virtual reality applications[84-85], may provide the technical advances that are required to confirm whether there is a linear representation of spatial scale along the human hippocampal long axis. It will be particularly interesting to assess whether humans show the same spatial precision as that expressed in the rat DH (<1 m at the dorsal pole[31]), and conversely, whether spatial scale extends beyond the 10 m expressed in the rat VH[31], given the much larger home range of humans *vs*. rats. By contrast, no species may need grids larger than a few meters because grid maps are likely to be local and fragmented in all realistic environments[98]. An important point to note, however, is that humans are obviously not locomoting during fMRI scanning, and this might influence the scale of the place fields during scanning, similar to what has been observed in rodents locomoting by train instead of walking themselves[99]. Studies in monkeys have also been limited for practical reasons: thus far these have involved head fixation[94]. As a result, grid-like cells in monkeys[94] observed in these studies differ from rodent grid cells[71] in that they follow eye position, rather than the animal's movement in space. Thus, future studies could perform recordings in freely-moving monkeys to test whether spatial scale is comparable to that observed in rodents.

*Emotion*

Anatomical evidence demonstrates that the reciprocal connectivity between the amygdala on the one hand and CA1 and the subiculum on the other hand is largely confined to the ventral two thirds[40,100-102]. This is particularly striking in a study which reported that only the dorsal-most portion of the hippocampus does not innervate the amygdala[40]. This connectivity is topographically organized along the longitudinal hippocampal axis, so that the ventral-to-

dorsal axis of origin of the projection in CA1 and subiculum is associated with a medial-to-lateral axis of termination in the amygdala[40,102] (FIG. 2c). In view of the specific roles for individual amygdala nuclei, this pattern of connectivity could explain the emotion-related functions of hippocampal regions along the dorsoventral axis. For example, the basolateral amygdala, which has a crucial role in fear learning[103], receives inputs from a considerable extent of the dorsoventral long-axis[40,102] (FIG. 2c). This may explain the inconsistent findings in rodent fear conditioning studies following lesions or inactivation of either dorsal or ventral hippocampus[29,104-106] (in which some studies find effects of dorsal not ventral lesions, and vice versa). That is, the effects on conditioned fear may be a function of the locus of the hippocampal lesion with respect to the dorsoventral hippocampus to mediolateral amygdala topography. It should be noted that the origin of the homologous hippocampus–amygdala topographical projections in primates is more restricted in the sense that amygdala-projecting neurons are focally restricted to the most anterior (uncal) CA1 and prosubiculum[107]. This may explain why fMRI activations associated with emotional memory in humans are primarily anterior[108-109] (but see ref. [110]).

In contrast to evidence for both DH and VH involvement in conditioned fear, there is growing evidence that the ventral hippocampus, but not the dorsal hippocampus, plays a role in mediating unconditioned fear behaviour[28,111-112]. An initial study[111] demonstrated that ventral, but not dorsal, hippocampal lesions reduce defensive fear responses during exposure to the elevated plus maze (an unconditioned threatening environment). The fact that selective amygdala lesions did not reduce defensive responses[111] suggests that the ventral hippocampus may influence unconditioned fear expression independently of the amygdala, namely through direct VH projections to downstream neuroendocrine and behavioral control systems in the hypothalamus[26] (FIG. 2b). With respect to longitudinal organisation, the critical observation is that lesion data for unconditioned emotional response show an anatomically marked ventral-dorsal hippocampal distinction: lesions of the dorsal two-thirds of the hippocampus not affecting fear expression, whereas small lesions in the ventral one-third did[111]. The hippocampal role in unconditioned emotional responses may thus be segregated to a ventral functional portion.

Given the model of longitudinal organisation we propose, in which demarcated domains are superimposed on functional gradients (FIG. 4), it is particularly interesting to consider the role of this ventral portion in unconditioned emotional responses in the context of the hippocampal gradient for space processing[31]. In non-spatial tasks, such as tone–shock fear conditioning, place-cell responses to non-spatial stimuli, such as the auditory tone that predicts the shock[113], are only observed when the animal is in that cell's place field. Thus, having larger place fields in the ventral hippocampal portion, which is strongly linked to defensive behaviour-related circuitry of the hypothalamus[26,101], may be evolutionary advantageous. That is, it is obviously advantageous to detect approaching danger as far away as possible, and distant danger may require fewer computational steps within these larger fields of the ventral hippocampus. However, it is not yet known whether this 'emotional' portion of the hippocampus has a dorsal border that is defined by molecular transitions[29,32,43], by abrupt changes in longitudinal association fibre anatomy[58], or is anatomically circumscribed to a particular level of topographical VH–LS–hypothalamic connections[26].

*Action and motivation*

Although no gross, permanent motor deficits arise after bilateral hippocampal lesions, an association between hippocampal activity and motor acts has long been described[3,114]. In non-human primates, movement-related responses have been reported in anterior, but not middle

or posterior, hippocampus[92]. Although human intracranial recordings[115] and fMRI[116] studies have demonstrated various motor-evoked hippocampal responses, differences in these responses along the human long axis have yet to be examined. In rodents, ventral, but not dorsal, hippocampal stimulation increases locomotion[117-118] by engaging the NAc and mesolimbic dopamine (DA) system[119-121], whereas inhibiting VH decreases locomotion[104]. This relationship with the NAc is also relevant to the observation that reward- or goal-directed functions localise to ventral parts of rodent hippocampus[122-123] and to the anterior human hippocampus[124], given that the ventral striatum — in particular the NAc — is considered the 'limbic–motor interface' at which motivation- and emotion-related processing gains access to the motor system[125-126].

The rodent studies discussed above[117-121] examined dorsal *vs*. ventral functional dissociations, but the anatomical connectivity between the hippocampus and NAc in fact shows a graded topography[39]. In view of this topography, it was suggested that the intermediate hippocampus, lying between the dorsal and ventral poles, is the site where accurate place encoding (which is strongest in DH) 'meets' connections (which are strongest in the VH) with behavioural control areas, including prefrontal cortex and nucleus accumbens[127] (FIG. 2). Selective lesions along the long axis have demonstrated that the intermediate hippocampus is critical for rapid place learning and the subsequent use of this encoded information to guide navigational performance[127]. However, it should be noted (in view of the anatomical orientation of the intrinsic hippocampal circuitry) that after selective lesioning, the remaining dorsal, intermediate and ventral portions of the hippocampus will differ in their composition of subfields. Thus, intermediate tissue blocks are more likely to comprise complete trisynaptic circuits than blocks from the poles, and this could bias the interpretation of such studies in terms of the functional relevance of the intermediate hippocampus.

*Episodic memory*

An early suggestion[128], based on human positron emission tomography (PET) data, proposed an dissociation between anterior and posterior hippocampus for episodic-memory encoding and retrieval, respectively (but see ref [129]). Furthermore, anterior hippocampal responses to novel (*vs*. familiar) stimuli have been frequently reported[6,130-132] (but see [133]) and some studies showed a double dissociation between anterior responses to novelty and posterior responses to previously encountered stimuli[6,130]. Given that novelty and familiarity detection may be components of memory encoding and retrieval processes, respectively[6,130,134], these data could be taken as support for a dissociation between encoding and retrieval within the hippocampus[128]. However, a caveat to these proposed dissociations is that single-unit data and neuronal-network models indicate that it is extremely unlikely that different hippocampal cells, *i.e.*, anterior *vs*. posterior cells, are involved in encoding versus retrieval of a particular memory. This is because a memory is recalled by reactivating the very same neuronal network that was formed during the encoding of the event[91,135-137], so that encoding and retrieval occur in parallel, possibly on alternating theta cycles[137-139].

One recent suggestion[140] — based on an extrapolation of the ventral-dorsal increasing resolution gradient in the rodent representation of topographical space — is that in humans, episodic memories follow a similar gradient in terms of level of detail, *i.e.*, the degree of context specificity and/or richness in detail with which that memory can be retrieved. Indeed, retrieval of detailed spatial[141] or autobiographical[142] memory has been observed to engage posterior hippocampus, whereas anterior hippocampus may be more involved in coarse, 'gist-like' memory[140]. A demonstration that this organisation follows a gradient-like pattern akin to

place representation has yet to be provided, and a clear challenge will be how to define a metric by which to quantify the richness or detail of episodic memories.

*Forming non-sequential, higher-order connections*

A highly consistent observation in human memory neuroimaging is that tasks requiring semantic processing engage the anterior hippocampus[129,143-144]. There is evidence of double dissociation between semantic processing in the anterior hippocampus and non-semantic processing in the posterior hippocampus [143,145] (the term 'relational' memory[146] has been used for the former, but we use semantic memory here, given that all memory could be viewed as relational). One example of semantic processing that requires flexible expression of memory is transitive inference[147]. Human studies showing that transitive inference activates the anterior hippocampus[148-149] (FIG. 6a) are underpinned by earlier demonstration that hippocampal lesions impair transitive inference in rodents[147]. This led to the suggestion that the hippocampus is critical for the linking of episodic memories into semantic networks in order to abstract the common features — spatial and nonspatial — among related memories and to mediate flexible memory expression and inferential reasoning[150]. Although initial lesion data linking the hippocampus to transitive inference involved the entire dorsoventral extent[147], a recent electrophysiological study reported that neurons in the ventral CA3 possess the response characteristics that are required to enable flexible memory encoding that span different contexts[151]. Whereas neuron ensembles in the dorsal CA3 rapidly associated the identity of specific objects with locations, successively more-ventral neurons were reported to increasingly generalise over object-sampling events involving specific objects and locations within a spatial context, whilst still distinguishing between different spatial contexts[151].

What response properties of ventral hippocampal neurons might facilitate the formation of higher-order memory representations? One possible mechanism emerges from the relationship between place-cell oscillating frequency and place-field size[152]. Every place cell oscillates faster than the population theta rhythm, which brings about a frequency-interference pattern known as phase precession[153]. Phase precession enables a compressed representation of temporal structure to be expressed within single theta cycles (the compression dynamic[154]). Given the size of place fields, several place cells are active together in each theta cycle, such that the compression dynamic potentially allows not only adjacent but also more distant neuronal assemblies to be linked, as long as they consistently co-occur in the same theta cycles. The oscillation frequency of place cells decreases along the dorsal–ventral axis, whereas the size of place fields increases[31,77,122]. Thus, larger place-field size ventrally theoretically provides more opportunities for neurons with distant place fields (that is, in the ventral hippocampus) to fire together in the same theta cycle than in the dorsal hippocampus[5,155]. As such, the ventral hippocampal portion may be specially suited for the formation of non-sequential or higher-order links between memory representations that could provide the flexibility needed for efficient navigation and detour planning[5,155]. Although this suggestion is derived from studies on spatial processing, it could be extrapolated to semantic function: if locations are assumed to be analogous to items, and we assume that dorsal–ventral differences in place-cell properties extrapolate to the human anterior–posterior axis, a larger field size anteriorly provides a potential explanation for the anterior locus of semantic processing responses in human hippocampus (FIG. 6b). Semantic memory obviously involves considerably more than just linking remote locations or time points, but this mechanism for creating higher-order memory representations potentially underpins aspects of semantic memory formation.

## Clinical implications

We propose a model of hippocampal functional organisation which superimposes long-axis gradients and discrete functional domains (FIG. 4). Can we use this model of longitudinal organisation to make specific predictions about the clinical manifestations of hippocampal damage along the long axis in humans? Hippocampal structural abnormalities are observed in a wide range of diseases[156]. With developments in human hippocampal volumetric techniques[157] and the application of functional imaging to patient populations, evidence is emerging for anterior–posterior differences in the relative severity of hippocampal structural and functional changes in a variety of psychiatric and neurological conditions[158] (although the caveats in interpreting long-axis differences described earlier also apply here). For a number of these conditions, preclinical animal models have considerable predictive value regarding the relative severity of anterior vs. posterior pathology observed in patients (Table 1). In addition, the locus of pathology on the long axis is associated with specific cognitive impairments (for example, schizophrenia is associated with anterior hippocampal pathology and with impaired transitive inference[159-160]) as well as with clinical manifestations of particular diseases. For example, in view of the greater connectivity between ventral (anterior) hippocampus and endocrine hypothalamic nuclei[26], impaired hormonal regulation by the hypothalamus (such as hyponataraemic polydypsia reported in schizophrenia patients with decreased AH volume[161-163]) may be a common finding in patients with AH damage — this is something that has been relatively under-investigated in medial temporal lobe epilepsy[164-166]. Furthermore, given the role of VH[111] — and ventral DG in particular[167] — in models of innate anxiety, this region could prove an important future target for a range of neurotic disorders. Lastly, assuming genetic subdomains are found in human hippocampus, one important future challenge for clinical research will be to determine whether these subdomains can be characterised non-invasively with current MR techniques, and whether the genetic composition of these subdomains can be related to specific pathologies.

## Conclusions and future directions

Two patterns of functional organisation appear to be superimposed on the hippocampal long axis: gradual and discrete transitions. At present, this framework can accommodate some of the multiple, and disparate, functions that have been ascribed to the hippocampus. However, for future studies to disambiguate the relative contributions of different genetic domains and different levels along functional gradients to a given behaviour, a novel approach with high anatomical precision is required. The huge advance in understanding hippocampal molecular anatomy enables this information to be used to allow highly specific targeted genetic manipulation of a particular region of the hippocampus (*e.g.* the ventral third of a specific CA subfield). A variety of transgenic tools can be applied to stimulate or block activity in that region with tight temporal control relative to an experimental paradigm. Thus, this experimental approach provides an avenue toward functional manipulation that could determine whether a specific domain of the hippocampus is necessary or sufficient to subserve a particular behaviour, and the mechanism through which this is achieved.

**Glossary**

Place cells: pyramidal cells that fire in specific locations, with spatially restricted firing patterns that are maintained on memory retention trials

Episodic memory: Long-term memory for events or episodes that is accessible to conscious recollection.

Hippocampus: in animal studies, the term describes dentate gyrus (DG) and CA subfields. In human fMRI studies, the term typically includes DG, CA subfields and subiculum (except in high-resolution fMRI).

Semantic memory: Long-term memory for facts that is accessible to conscious recollection.

Callosal mammals: mammals with a corpus callosum. In acallosal mammals, such as the opossum, the dorsal portion of the hippocampus extends into the frontal lobe.

Theta rhythm: A prominent 4–10 Hz oscillation in the hippocampal local field potential (LFP) studied most in rodents but also present in humans.

Transitive inference: If A is paired with B, and B paired with C, the transitive inference is A with C.

Theta phase precession: the phenomenon that when a rat first enters the field of firing of a place cell, spiking occurs at late phases, but shifts to earlier theta phases as the rat moves through the place field.

Adult neurogenesis: the production of new neurons within the brain of an adult animal. Adult neurogenesis is primarily confined to the subventricular zone and the subgranular zone of the DG.

Ischaemia: a restriction in blood supply, leading to lack of oxygen delivery.

Hippocampal MRI unfolding: The application of cortical unfolding techniques to high-resolution MR images of hippocampus. Structural images are segmented and the gray matter surface extracted and stretched until it is a two-dimensional flat surface.

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**Box 1. Is the rodent ventral-dorsal axis homologous to the primate anterior-posterior axis?**

There are obvious macroscopic differences between the rodent hippocampus and the primate hippocampus. Therefore, we consider whether the rodent ventral-dorsal axis is homologous to an anterior-posterior axis in non-human primates and humans (FIG. 1).

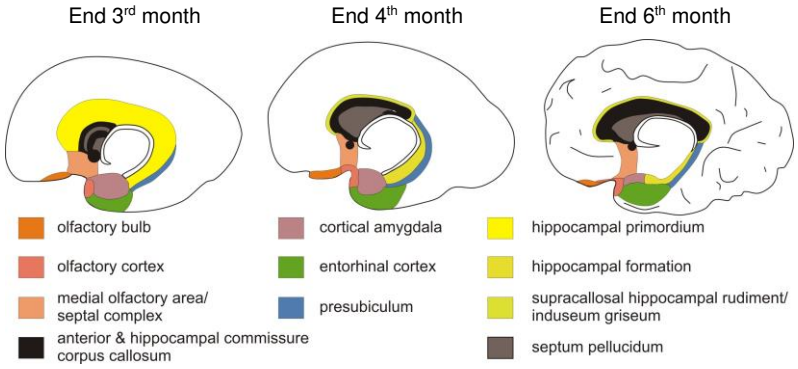
One obvious difference lies in the orientation of the hippocampal long axis in rodents versus humans. This difference probably relates to the fact that in non-primate callosal mammals, the major portion of dorsal hippocampus is tucked under the caudal section of the corpus callosum, whereas this subcallosal flexure diminishes from prosimian to simian species to being practically absent in human, presumably because of forward growth of the temporal lobe[168]. That is, the ventral hippocampus appears to have been 'pulled' downwards and forwards in primates to occupy a position in the anterior medial temporal lobe, thereby changing the long axis orientation.

A second macroscopic difference is that the rodent hippocampus cross-sectional area is relatively uniform along the long axis, whereas the anterior hippocampus has expanded relative to the posterior hippocampus in primates, particularly in humans[169]. One speculative phylogenetic account for this involves the entorhinal cortex, which in all mammals has a close topological relationship with ventral/anterior hippocampus (FIG. 1b). With forward growth of the temporal lobe, the entorhinal cortex moved from its occipital lobe position in lower-order mammals to a rostral location in the primate anterior-medial temporal lobe, where it has expanded considerably compared to other components of the uncus[168]. Thus, the expansion of the entorhinal cortex and its more anterior position in the temporal lobe in primates may have accompanied the expansion of the anterior hippocampus, such that a greater portion of hippocampal tissue becomes located anteriorly. This observation poses several currently unanswered questions such as what is the functional gain/loss of increased size of anterior hippocampus, and is this at the expense of posterior functions in humans? What would an increased number of anterior cells be good for? Can the posterior functions be done with the small number of cells that *e.g.* a rodent dorsal hippocampus has?

The rodent and primate hippocampus also differ in terms of embryonic development[170]. Species that have an evolutionary relationship typically share the early stages of embryonic development but differ in later stages. Indeed, during early embryonic development, the human hippocampus resembles that of the rat, running dorsal-ventral with the dorsal portion lying above the diencephalon[171]. At approximately the 14-week stage and coincident with the development of the corpus callosum, the dorsal (supracallosal) hippocampus in humans begins massive involution and remains only as a rudimentary thin band above the corpus callosum (the indusium griseum)[171-172]. By contrast, the ventral embryological portion develops to form the length of the human hippocampus[171-172]. The figure illustrates the embryological development of human hippocampus. Note massive involution of dorsal (supracallosal) hippocampal primordium. Involution of the supracallosal part of the hippocampus also occurs in rodents, although the indusium griseum is far less conspicuous than in humans. This leaves open a possibility that the extent of involution of the dorsal embryological hippocampal portion differs between species, and one may therefore wonder whether a homologue of rat dorsal hippocampus is present in the human brain or whether the human posterior hippocampus instead corresponds, phylogenetically, to rodent intermediate hippocampal portions.

Notwithstanding these differences, a cross-species comparison of anatomical connectivity provides evidence that the primate hippocampal long axis may be homologous to that of the rat. Indeed, output connectivity of the primate hippocampus with subcortical areas

— including nucleus accumbens[173] — follows a graded topography similar to that in rodents[174] (but note longitudinally restricted vs. distributed hippocampal-amygdala projections in primates and rodents, respectively[107,175]). Input connectivity from entorhinal cortex to DG also follow a graded mapping that is analogous to that in rats[34-35], with an anteromedial–posterolateral EC axis corresponding to an anterior–posterior DG termination[176-178]. For example, the pattern of connectivity between cingulate cortex and hippocampus in primates is similar to that in rats, in the sense that anterior hippocampus is more strongly connected with anterior regions and medial frontal cortex, and connections with posterior cingulate (including retrosplenial cortex) are stronger with posterior hippocampus[179-180]. Figure is adapted from ref. [171].



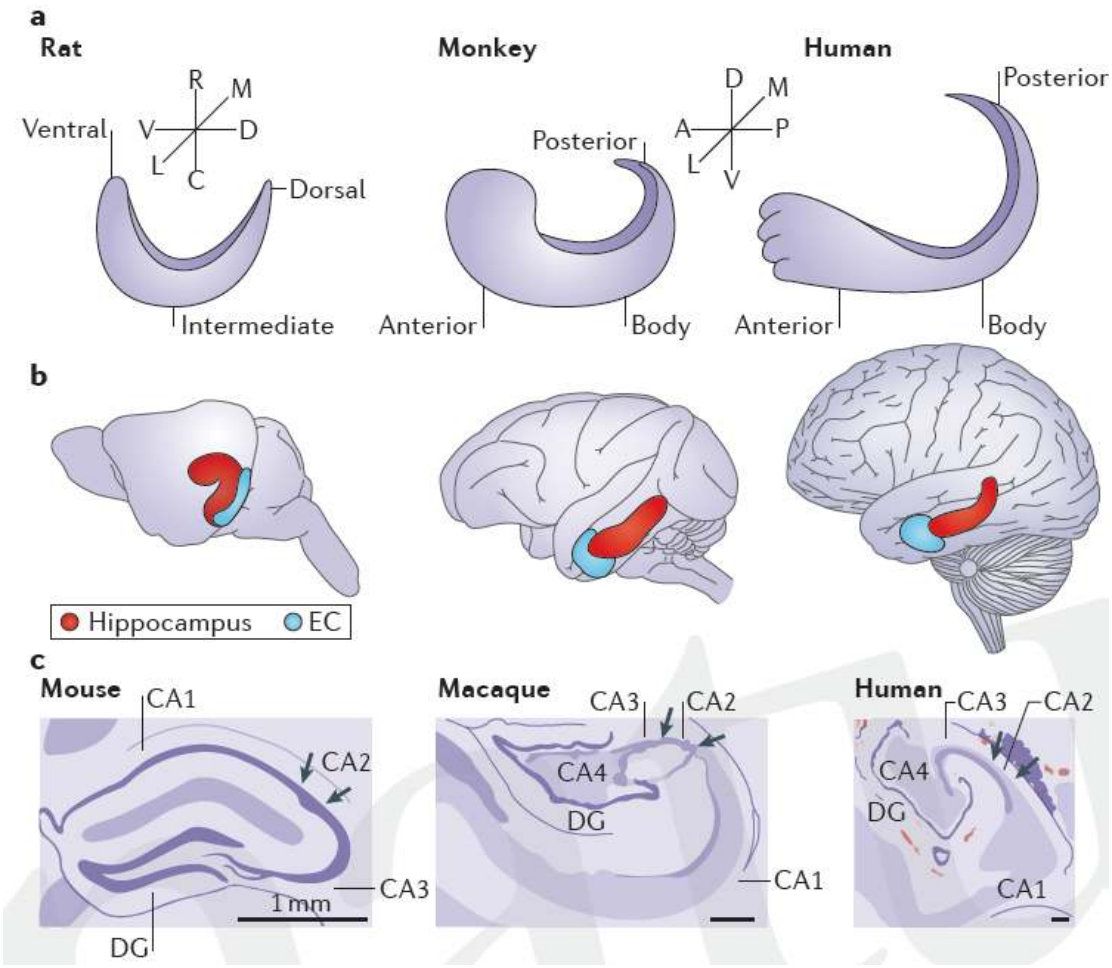



**Figure 1. Cross-species comparative hippocampal anatomy.**
(a) Schematic illustrations of the orientation of the hippocampal long-axis in rat, macaque monkey and human. The longitudinal axis is described as ventro-dorsal in rodents, and antero-posterior in primates (also referred to as rostro-caudal in non-human primates). There is currently no precise anatomical definition for a dorsal/posterior portion relative to a ventral/anterior one, although in general topologically, the former is positioned close to the retrosplenial cortex and the latter close to the amygdaloid complex. Note that a 90º rotation is required for the rat hippocampus to have the same orientation as that of primates. In primates, the anterior extreme is curved rostro-medially to form the uncus. (b) The full long-axis of the hippocampus (red) can be seen in semi-transparent brains of rat, macaque monkey and human, with entorhinal cortex shown in blue. (c) Nissl cross-section in mouse, rhesus and human hippocampus. Scale bars: 1mm. Panel (c) adapted (or reproduced, depending on whether we use photos or drawings) from [54].

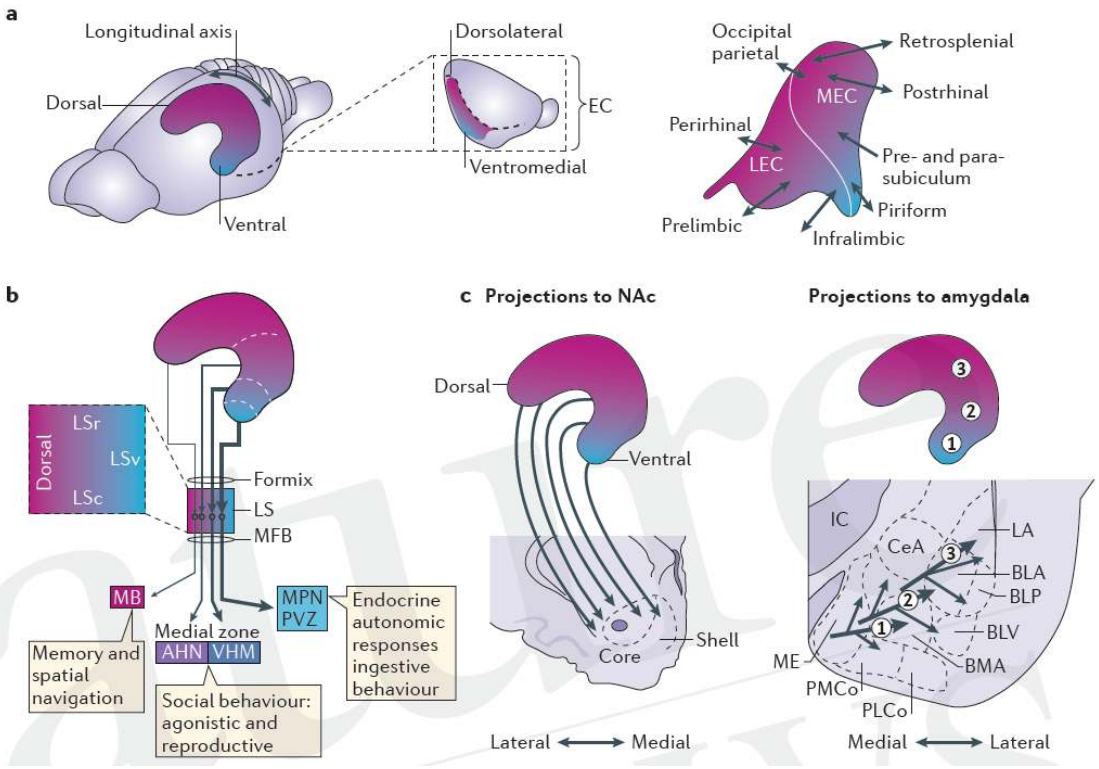



**Figure 2. Extrinsic connectivity gradients.**
(a) Left panel: representation of the topographical arrangement of entorhinal–hippocampal reciprocal connections in rodents. A dorsolateral band of the entorhinal cortex (magenta) is preferentially connected to the dorsal hippocampus (DH). Increasingly more ventral and medial bands of entorhinal cortex (purple to blue) are connected to increasingly more ventral levels of the hippocampus. (right panel). Right panel: an enlarged EC indicating the topology of its major cortical connectivity. The white line indicates the border between lateral (L) and medial (M) EC. (b) The hippocampal output to the lateral septum (LS) and hypothalamus. The LS can be divided into rostral (LSr), caudal (LSc) and ventral (LSv). The most ventral tip of CA1/subiculum (blue) projects to LSv, which projects to the medial preoptic nucleus (MPN) and hypothalamic periventricular zone (PVZ). More-ventral parts of the CA1-subiculum field project to the LSr, which in turn projects to hypothalamic medial zone nuclei, including anterior (AHN) and ventromedial (VMH) hypothalamic nuclei. The dorsal subiculum (red) sends a small projection to dorsal LS, which is relayed to the mammillary body (MB). The thickness of the arrows indicates the projection density. (c) Topographical gradient of projections from the hippocampus to the medial (shell) to lateral (core) portions of the NAc (left) and the medial to lateral portions of the amygdala (right). Note the absence of projections from the DH and the relative lack of innervation of the central nucleus of the amygdala. Abbreviations: mfb, medial forebrain bundle; BMA, anterior basomedial nucleus; BLA, anterior basolateral nucleus; BLP, posterior basolateral nucleus; BLV, ventral basolateral nucleus; Ce, central nucleus; La, lateral nucleus; Me, medial nucleus; PMCo, posteromedial cortical nucleus; rf, rhinal fissure. Part a, right panel, adapted from[181]; part c, bottom right panel, is adapted from ref [40].

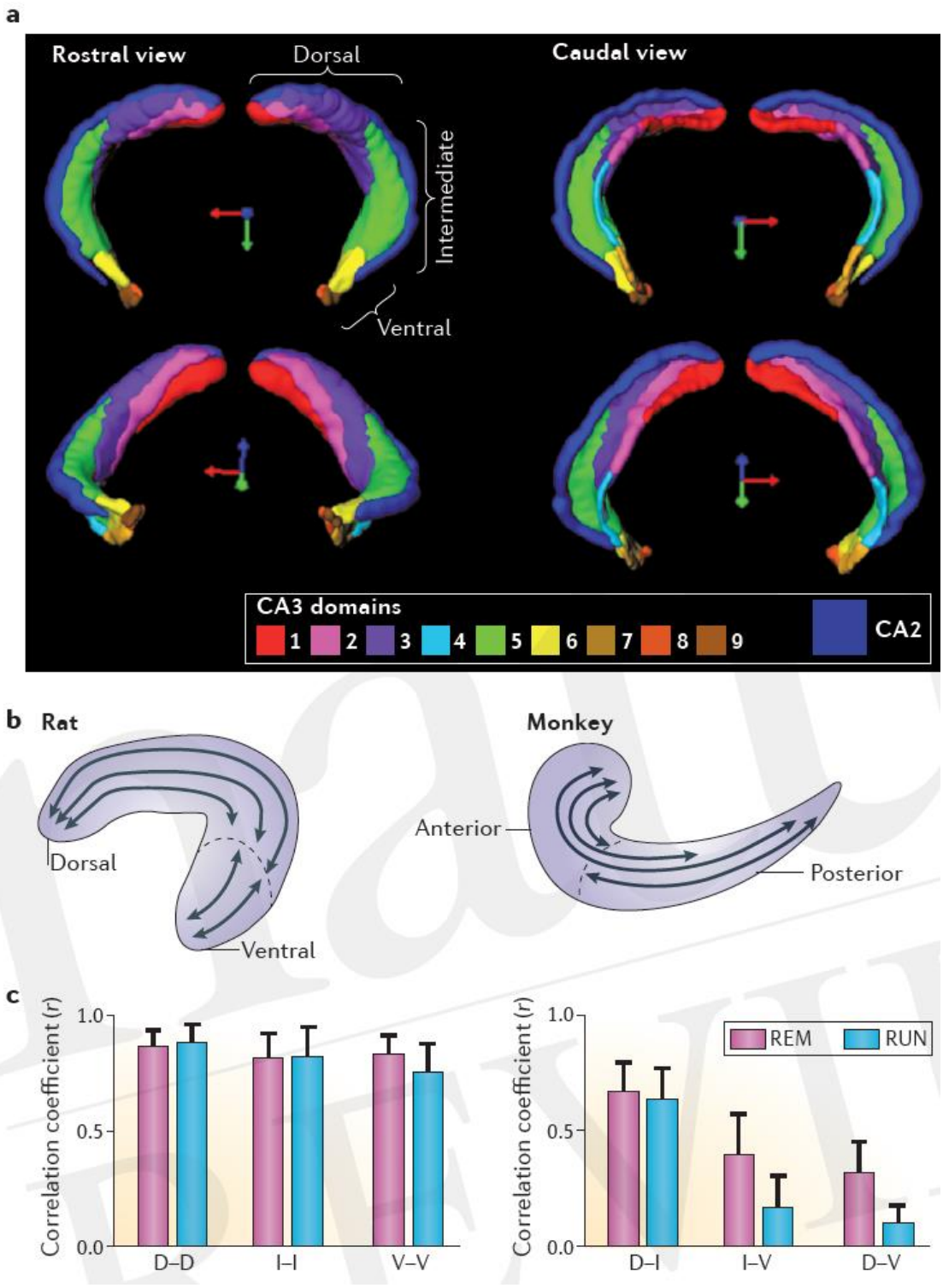



**Figure 3. Discrete transitions in molecular, anatomical and functional organisation of the hippocampal long axis.**

(a) Discrete gene expression domains in CA3 are defined by reciprocal, non-overlapping boundaries. Colour-coded 3D models of 9 gene expression-based subdivisions of CA3 are shown in rostral and caudal views at two different orientations (3D orientation bars: lateral, red; ventral, green; rostral, blue). Suggested boundaries for collapsing the 9 domains into 3

domains (ventral, intermediate and dorsal) are indicated in the top left 3D model. Note, however, that there are substantially different patterns within each of the dorsal, intermediate and ventral domains, and that these are sharp boundaries in some cases. The CA2 is indicated in dark blue. (b) Extensive *vs*. limited intrinsic connections in monkey and rat hippocampus. In monkeys (right), projections from CA3 to CA1 and CA3 at the level of the uncus are restricted to the anterior portions of the hippocampus (representative origins of projections are shown as circles). In rats (left) the longitudinal ipsilateral extent of associational fibres from dentate hilus is shown. The boundary between posterior/dorsal two-thirds *vs*. anterior/ventral third of hippocampus is indicated schematically by dotted lines. Note that this line is interrupted in the right panel to indicate that this boundary is less discrete in monkeys than in rodents[58,59]. (c) Coherence decreases along the longitudinal axis. Theta power correlations between dorsal (D), intermediate (I) and ventral (V) sites in the CA1 pyramidal layer during running (RUN) and REM sleep. Power–power correlations are high within the same portions (left) and significantly decrease between ventral *vs*. intermediate and dorsal sites (right). Panel a is based on data from [32], panel b is adapted from [59] ; panel (c) adapted from [61].

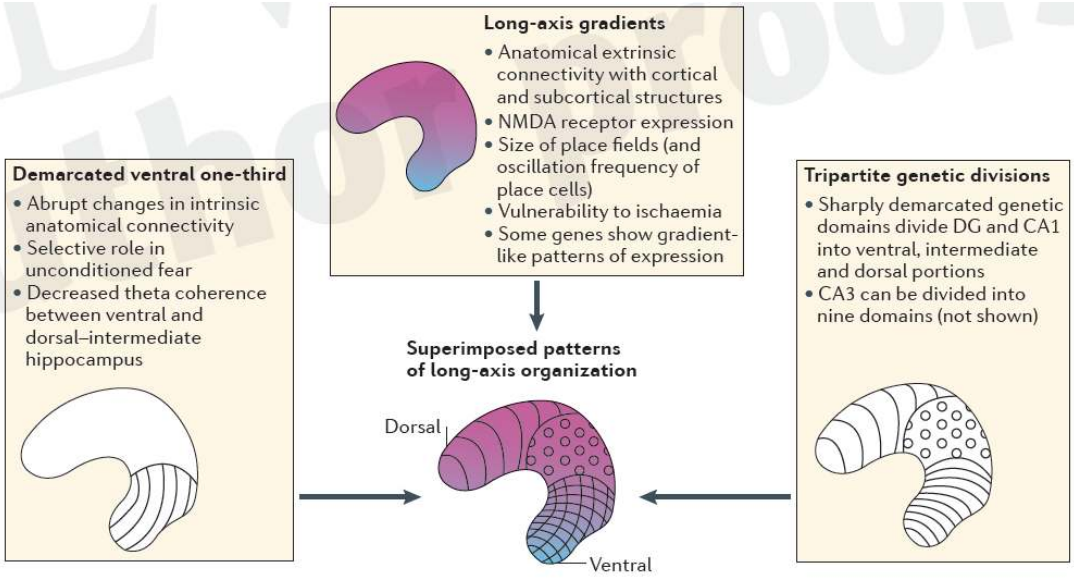



**Figure 4. Schematic of superimposed patterns of long-axis organisation.** Behavioural, recording and intrinsic-connectivity studies have suggested a functional distinction between the ventral third of the hippocampus versus the dorsal two-thirds. Other studies have revealed gradual changes along the hippocampus in terms of extrinsic connectivity, NMDA receptor expression and place fields size, whereas recent gene expression studies indicate that there are three sharply demarcated portions of the hippocampus. Superimposing these three organizational patterns results in a new model of functional organization along the hippocampal long axis.

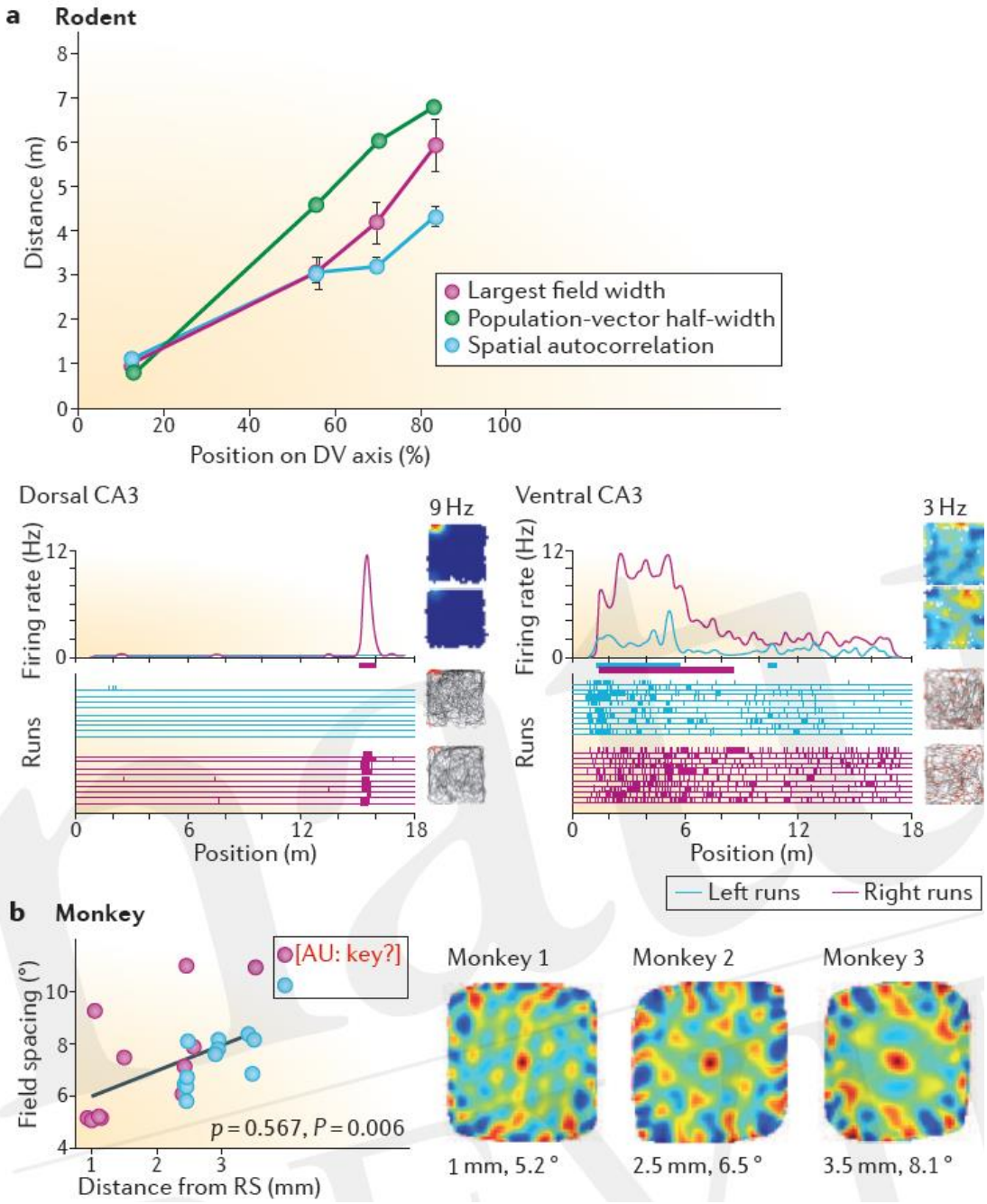



**Figure 5. Gradients for space in the medial temporal lobe in rodent and monkey.**
(a). Monotonic relationship between spatial scale and position along the dorsoventral hippocampal axis (top). Spatial scale is expressed as the half-width of the correlated band of the population vector, the average width of the largest place field of individual cells, and the estimated field width. The lower panels show place fields of example pyramidal cells in the dorsal (left) and ventral (right) CA3 of rats during running on an 18 m track. Smoothed spike density function indicates that the firing rate is a function of position. The horizontal bar indicates the estimated place field (left runs, magenta; right runs, cyan). Below the graphs are raster plots showing the density of spikes on individual laps. Each vertical tic indicates one spike and each horizontal line shows one lap. To the right of each panel are rate maps and trajectories (top pairs and bottom pairs, respectively) with individual spikes from repeated trials in two-dimensional enclosures (1 m × 1 m). Rate maps are colour-coded with red as

maximum and blue as 0 Hz, with peak rate indicated at the top. Trajectories are shown as black traces with positions of individual spikes shown as red dots on top of the trajectory. (b) Left, grid-cell spacing increased with distance from the rhinal sulcus (r.s.). Blue and red circles identify the grid cells from each of two monkeys. Note that these grid cells are from head-fixed monkeys and that firing is defined by view position rather than by position in the room. Right, autocorrelations for representative grid cells recorded at different locations medial to the rhinal sulcus in three monkeys. The distance from r.s. (mm) and field spacing (deg) are indicated below. Part a is adapted from [31]; part b is adapted from [94].

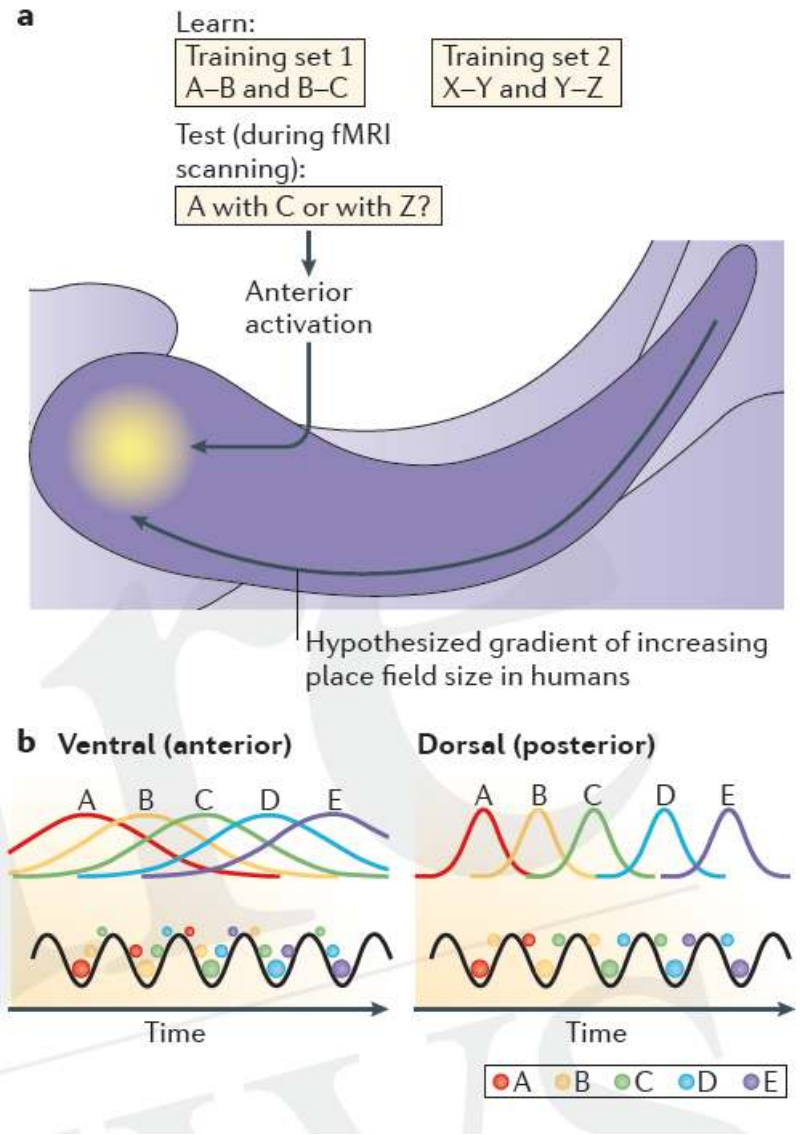



**Figure 6. Forming non-sequential, higher-order connections in human hippocampus.** Schematic to illustrate a putative mechanism by which the human anterior hippocampus is able to form non-sequential connections that enable flexible cognitive processes such as transitive inference. (a) fMRI studies demonstrate increased anterior hippocampal responses when subjects infer the correct transitive inference (e.g. A–C is correct if previous pairings were A–B and B–C), relative to simple recognition of previously learned pairs of non-overlapping visual stimuli. (b) Interleaved neuronal sequences in the ventral/anterior (left) and dorsal/posterior (right) hippocampus. The coloured Gaussian curves represent place fields of 5 cell assemblies in ventral/anterior and 5 cell assemblies in dorsal/posterior hippocampus. Together, the place fields could pertain to locations A-E, or (speculatively) a sequence of items A-E. Note the longer 'tails' of the fields in ventral/anterior hippocampus. Below the place fields are shown circles representing spiking activity from each cell assembly that represents the items in the sequence A-E. The spiking activity precesses gradually from the end to the beginning of the theta cycle (the size of the circle indicates the firing rates of the hypothesized assemblies). Each item is defined by the most active cell assembly that fires at the trough of the theta cycle (e.g., C is defined by the assembly depicted by the green place

field), and is embedded in the temporal context of previous and subsequent items. Portions of the sequence A-E are replicated repeatedly within individual theta cycles. Note that longer sequences are accommodated ventrally/anteriorly. The formation of assembly sequences within theta cycles could reflect a strengthening of connections not only between adjacent items (e.g., C-D) but also between nonadjacent (e.g., A-E; B-D) items, thereby enabling transitive inference to be made[5,155]. Part a is based on data from [148] and [149]. (b) is based on [155] and [5].

**Table 1. Examples of pathologies in which long-axis differences in preclinical animal studies provide insights into the locus of hippocampal damage in different patient populations.**

| Condition | Abnormality along hippocampal long axis |
|---|---|
| **Medial temporal lobe epilepsy** | *Animal*<br>Greater spontaneous epileptiform bursting in VH than DH[15,182].<br>*Human*<br>Chronic intracranial recordings in patients indicate seizure initiation more frequent from AH than PH[183].<br>Neuronal loss greater in AH than PH[184-186] (expressed as anterior-posterior gradient[184]). |
| **Depression** | *Animal*<br>Behavioural effects of chronic anti-depressant treatment are critically dependent on neurogenesis in the adult hippocampus[187], with suggestion that this occurs in VH[188].<br>*Human*<br>Post-mortem studies on patients with major depressive disorder show that anti-depressants increase neurogenesis in anterior dentate gyrus[189]. |
| **Schizophrenia** | *Animal*<br>VH lesions is an animal model of several features of schizophrenia[190]<br>Schizophrenia-related biomarkers are present in VH at birth[44]<br>*Human*<br>Increasingly viewed as primary pathology being in AH[158], but considerable evidence for PH abnormality e.g.[191-192] |
| **Ischaemia** | *Animal*<br>Ventral to dorsal increase in hippocampal vulnerability to ischaemia[193].<br>May be related to an increasing gradient for NMDA receptor expression from ventral-to-dorsal in area CA1[194] and proposed role of NMDA activation in hypoxic excitotoxicity[195].<br>Cerebral blood flow is greater in VH than DH during reperfusion following ischemia, which may contribute to DH damage[196].<br>*Human*<br>↓ PH volume in patients who had had cardiac arrest with successful subsequent resuscitation[197] (but note previous reports of cardiac arrest-induced ischaemia affecting entire hippocampal long-axis[198]). |