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Review

The many dimensions of human hippocampal organization and (dys)function

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The internal organization of hippocampal formation has been studied for more than a century. Although early accounts emphasized its subfields along the medial–lateral axis, findings in recent decades have highlighted also the anterior-to-posterior (i.e., longitudinal) axis as a key contributor to this brain region's functional organization. Hence, understanding of hippocampal function likely demands characterizing both medial-to-lateral and anterior-to-posterior axes, an approach that has been concretized by recent advances in *in vivo* parcellation and gradient mapping techniques. Following a short historical overview, we review the evidence provided by these approaches in brain-mapping studies, as well as the perspectives they open for addressing the behavioral relevance of the interacting organizational axes in healthy and clinical populations.

Highlights

Magnetic resonance imaging–based parcellation of the hippocampal formation and gradient mapping are data-driven techniques that can capture many dimensions of hippocampal organization and provide readily usable outcomes.

Features of cortical architecture, such as local connectivity and microstructure, reveal differentiation within the hippocampal formation along the medial–lateral axis. This organizational dimension seemingly reflects local information-processing organization.

Neuroimaging markers tapping into hippocampal integration into large-scale networks (i.e., whole-brain connectivity) highlight the long-axis differentiation.

The long-axis organization corresponds to a molecular gradient and differential integration across distinct behavioral systems.

Capitalizing on gradients and parcellations maps, the long-axis organization of the hippocampal formation can be related to behavioral phenotypes in healthy and clinical populations.

The question of hippocampal organization

The hippocampal formation is a core brain region from a phylogeny standpoint (cf. the dual origin hypothesis of brain evolution [1]), as well as a key node of the human memory system, and is also a target of research in brain disorders such as Alzheimer's disease (AD) and temporal lobe epilepsy. The hippocampal formation is of interest to various fields of research, and numerous models and theories have been proposed regarding its organization, function, and relationship to behavior in the healthy and diseased brain. The traditional anatomical model subdivides the hippocampal formation into discrete subfields arranged along its mediolateral and ventrodorsal axes, including the cornu ammonis (CA1–4) subfields, the dentate gyrus, and the subiculum. The implementation of this model in human research, in particular in neuroimaging studies, is supported by the availability of cytoarchitecture maps (e.g., [2–4]), extensive guidelines for manual segmentation (e.g., [5]), and automated *in vivo* segmentation tools (e.g., [6,7]). Through these easily available anatomical maps and segmentation tools, the issue of subfield distinction has achieved a prominent role in the study of behavioral functions and pathophysiological processes.

More recently, the organization of the hippocampus along its longitudinal axis has gained considerable interest. Several hypotheses on this organizational pattern have been proposed, such as a tripartite model, differentiating a head from body and tail, and the distinction between the anterior and posterior parts [8]. On the basis of anatomical, genetic, and functional data, the relevance of this long-axis organization for behavior has been subject to vivid discussion. It appeared that the literature on human long-axis neuroanatomy was initially less developed than the analogous animal literature [9]. Addressing this point, we review how advances in neuroimaging markers of functional and anatomical connectivity, together with the development of parcellation and gradient-mapping approaches, have recently provided substantial empirical support for a differentiation of the hippocampal formation along the long axis [10–19]. It was pointed out a few years ago [20] that, in humans, discrete changes in molecular or anatomical organization along the hippocampal long axis have yet to be examined. Accordingly, we also review how recent resources, such as BigBrain [21–24] and genetic mapping, have driven progress in this research [25,26].

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Considering the interacting nature of these organizational dimensions, we show how they can be synergistically probed by both discrete (with subfield-to-subfield and head–body–tail differentiation) and dimensional approaches (with gradients running in mediolateral and long-axis directions). We also illustrate how such synergy may lead to a unified model of hippocampal organization, function, and pathology.

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Two main dimensions of hippocampal organization

Hippocampal subfields organization

Ex vivo investigations in both animal models and humans, as well as *in vivo* experiments in animal models, have led to the distinction of several hippocampal subfields. Despite many subfields and their finer subdivisions still being debated (Box 1), it seems generally acknowledged that the hippocampal formation (consisting of the hippocampus itself and the adjacent subiculum) can be subdivided into at least three parts: the CA fields comprising three or even four subfields (CA1–CA4), the dentate gyrus, and the subiculum (or subicular complex) (see Figure I in Box 1), [2,4,27]. Evidence for this organizational model is provided by differences in cytoarchitectonic profiles (see Box 1), as well as physiological findings that reveal different intrinsic connections of these subfields (i.e., within the hippocampal formation) or local ones (within the medial temporal lobe), such as the trisynaptic circuit [28]. This circuit encompasses the performant path system connecting the entorhinal cortex with the hippocampus, mossy fibers, and Schaffer collaterals. Recent studies have shown that all these pathways consist of multiple components: superficial sheets of fibers emanating from the entorhinal cortex project to the presubiculum and parasubiculum; intermixed transverse and long-axis angular bundle fibers perforate the subiculum and then project to the CA fields and dentate molecular layer; and a significant alvear component runs from the angular bundle to the CA fields [29]. These pathways are relevant not only in terms of information processing, but also for understanding disease progression. For instance, it is assumed that the perforant path system is often the first white matter pathway to degenerate in AD [30].

The subfield model has hence been well corroborated across techniques and species, using a variety of *ex vivo* analyses and invasive investigations. The practical implementation of this model for neuroimaging research became crucial in the context of positron emission tomography (PET) and magnetic resonance imaging (MRI) studies. Targeted examinations of imaging characteristics for hippocampal subfields became possible by the availability of cytoarchitectonic maps in stereotaxic Montreal Neurological Institute space [2,3], the continuous development of guidelines for manual delineation of subfields, in particular by the Hippocampal Subfield Group [5], and the development of automated segmentation tools (see Box 1 and [31] for a review). These resources and developments drove a vast literature of subfield-based studies in the healthy brain, such as with regard to genetic profiles (e.g., [32]), influence of environmental factors (e.g., [33]), and aging (e.g., [34]), but also in the diseased brain (cf. below).

The long-axis organization

The most robust support for an anterior–posterior division in the hippocampal formation comes from anatomical and electrophysiological recordings in rodents, showing a differentiation between ventral and dorsal subregions (corresponding to the anterior and posterior human hippocampus, respectively). These include differences in connectivity (for a review, see [20]) as well as in functional profiles (for a review, see [9]), leading, for instance, to an emotion versus cognition segregation hypothesis [41]. Evidence for an organizational pattern along the long axis is also further supported by gene expression studies in rodents and nonhuman primates (for reviews, see [20,42]).

In humans, neuroimaging studies using PET and later functional MRI (fMRI) have led to the 'encoding versus retrieval' hypothesis for the differentiation along the long axis of the hippocampus

Box 1. Hippocampal subfields

The hippocampal formation can be divided into at least three different anatomical parts: the CA fields, the subiculum, and the dentate gyrus. Beyond this broad distinction, finer subdivisions into specific subfields are likely possible but remain debated. Within the CA subregion, Lorente de Nó [35] identified four regions (i.e., CA1, CA2, CA3, and CA4). However, CA2 and CA4 are both not universally accepted as distinct subfields (e.g., [36–38]). One practical consequence of such scientific disagreements is that although a probabilistic map of CA2 can be found, for example, in the SPM Anatomy Toolbox, a corresponding segment is not available in the FreeSurfer automated segmentation of the hippocampus (Figure IB). These theoretical and practical discrepancies evidently complicate comparison and integration across studies. In the context of segmentation, different protocols may also have different reliability [39,40]. Furthermore, finer subdivisions within specific CA subfields, such as subfields within CA1 or the subiculum, have been proposed (see, e.g., [4]) but are still a matter of debate. Acknowledging these diverging viewpoints, one of the most recent mappings of hippocampal subfields can be found in [4]. Resulting from a combination of cytoarchitectonic and receptor architectonic features, the proposed map includes nine distinct regions: fascia dentata (a subregion of the dentate gyrus), CA1, CA2, CA3, CA4, prosubiculum, subiculum proper, presubiculum, and parasubiculum (Figure IA). All in all, microstructural investigations within the hippocampal formation suggest that one can differentiate distinct subfields, whose number diverges across studies, but that are typically aligned along the mediolateral and ventrodorsal axes in humans.

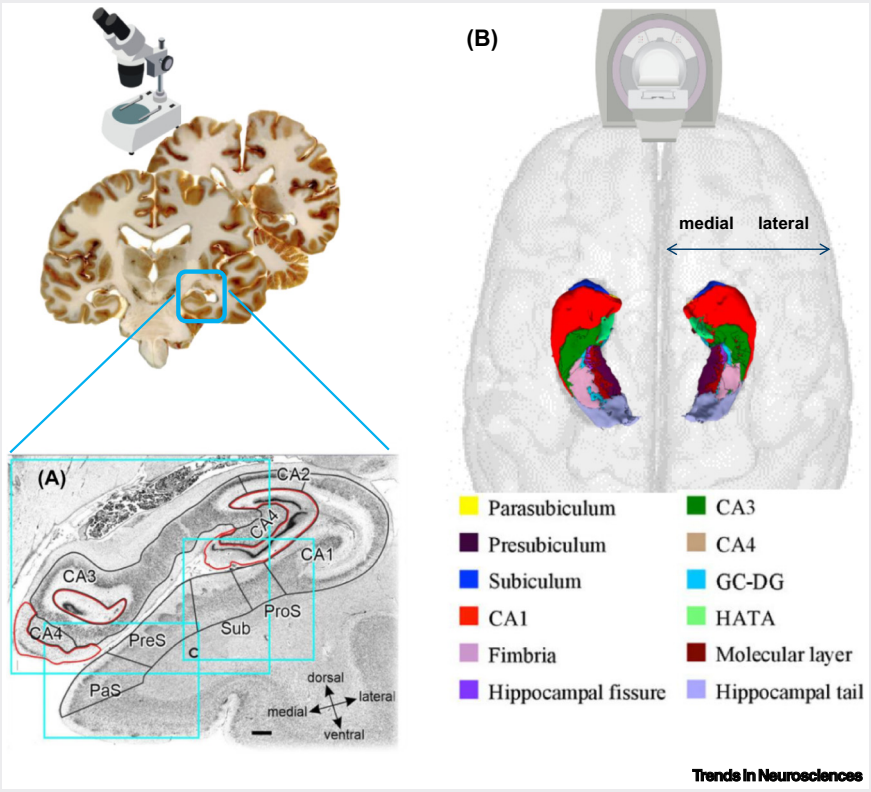

Figure I. Subfields within the human hippocampus and subiculum. (A) Multimodal mapping based on cytoarchitectonic and receptor architectonic features [4]. (B) Automated segmentation of an anatomical scan provided by FreeSurfer [81]. Abbreviations: CA, cornu ammonis; DG, dentate gyrus; GC-DG, granule cell layer of dentate gyrus; HATA, hippocampal-amygdaloid transition region.

(the hippocampal encoding/retrieval model [43,44]). The encoding and retrieval components of this hypothesis were later linked to engagement of the dorsal attention and the default model networks, respectively, leading to the hippocampal encoding/retrieval and network model [45]. In this hypothesis-driven framework, MRI was used to compare the connectivity profiles of *a priori* defined anterior versus posterior subregions. In particular, differences in connectivity profiles along the long

axis of the hippocampus were observed when examining functional connectivity based on resting-state fMRI [12,46], and also when probing anatomical connectivity through diffusion MRI [10].

Hence, the long-axis organization pattern has gathered increasing support from evidence in rodents and from hypothesis-driven activation and connectivity neuroimaging studies in humans. Nevertheless, to achieve a level of scientific validation comparable to the subfields model, the long-axis organizational pattern should be supported by data-driven investigations in humans and across different neurobiological features tapping into large-scale functional integration and behavioral systems organization. As described in the next section, this became possible by capitalizing on parcellation and gradient approaches.

Capturing hippocampal organization using data-driven approaches

Parcellation and gradient-mapping approaches provide summary representations of spatial variability in a dataset and can hence reveal the topographical patterns of large-scale integration provided by estimates of structural or functional connectivity (Box 2). They thus allow disentangling the differentiation of hippocampus (or subiculum) voxels with regard to their whole-brain connectivity profiles (which represent a multivariate pattern). Parcellation provides a spatial map of parcels (regions) that are internally as homogeneous as possible but at the same time maximally different from each other, whereas gradient mapping will reveal continuous dimensions in a latent space along which the connectivity profiles vary. Below, we first review studies that have applied parcellation approaches to connectivity data of the human hippocampal formation, followed by those that have used gradient methods on similar data. For the sake of comparison and discussion, we also report the few studies that have applied similar, data-driven approaches to markers of local hippocampal structure rather than connectivity patterns.

Hippocampal parcellations

Connectivity-based hippocampal parcellations

Different MRI-based measures can probe large-scale functional integration between distant brain regions and are hence commonly labeled as 'connectivity' markers. Early parcellation studies that probed functional connectivity in the human hippocampus/subiculum used estimates of coactivation across experiments (based on an approach known as meta-analytic connectivity modeling [52]). These studies strikingly highlighted a pattern of differentiation along the long axis, either when including both the hippocampus and the subiculum [15,18] or when focusing on the subiculum solely [11]. This long-axis organization appears to be a general feature of hippocampal functional integration, as a similar pattern was also found when using a different marker of

Box 2. Parcellation and gradient mapping techniques

In neuroimaging analyses, 'parcellation' is an umbrella term that covers a variety of approaches to delineate brain regions. For the sake of brevity, here we focus on parcellation using decomposition approaches (i.e., clustering or factorization, in contrast to border detection algorithms; for a review, see [47]). Gradient mapping techniques, however, often refer to 'dimensional decompositions' (such as principal component analysis or nonlinear variants such as diffusion map embedding [48,49]). Overall, parcellation and gradient mapping techniques can be applied to the same type of data and simplify spatial variations in a data-driven way. Notably, parcellation approaches focus on discretization into distinct but internally homogeneous regions, whereas gradient mapping identifies continuous axes of feature variation. For example, the pattern of functional connectivity of hippocampal voxels can be summarized by defining groups of voxels that show a similar pattern of connectivity, or, alternatively, it can be summarized as principal gradients along which the connectivity profile of the voxels varies. Generally, the first principal dimensions along which the voxels vary (explaining most variance) will determine the first levels of subdivisions. These approaches are often used in a data-driven framework – that is, without specifying *a priori* the number of clusters or principal gradients to be extracted from the data. Different metrics can evaluate the quality of fit in addition to assessments of reproducibility and correspondence with other neural features [50]. Additionally, a model selection approach based on statistical testing against a null model that preserves the geometrical features of the region of interest has recently been promoted to delineate potential borders and gradual transitions [19,51].

functional interactions, namely resting-state connectivity [15,53,54], as illustrated in Figure 1. This organizational dimension hence reflects the differential functional integration into whole-brain networks of hippocampal anterior and posterior regions, as illustrated in Figure 2 (see also [55]).

Despite some technical challenges (Box 3), a primary pattern of subdivision into three subregions reminiscent of the head–body–tail partitions of the hippocampus can be found throughout the current literature of parcellation studies based on functional connectivity. Only secondly, higher parcellation levels further subdivide this pattern into medial versus lateral parcels. Thus, parcellation studies confirmed that functional connectivity of the hippocampal formation differs across the long axis with a stable and relatively robust subdivision into a head, body, and tail (i.e., the tripartite model). Further subdivisions along the long axis could also be evidenced ([15]; see Figure 1), in particular with higher resolution [19], and it could be speculated that they partly

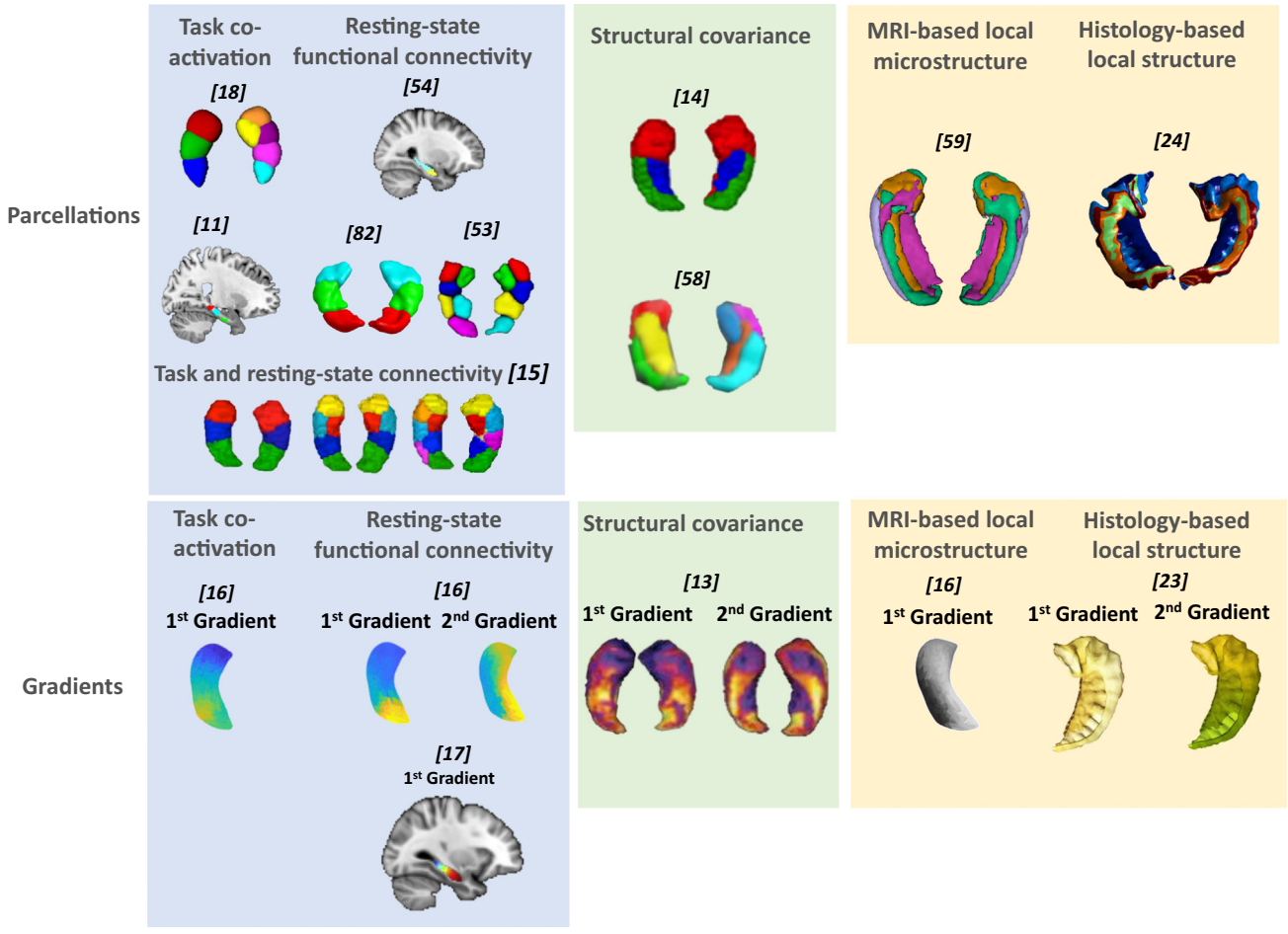

Figure 1. Parcellation and gradient patterns in the human hippocampal formation and its subcomponents. Parcellation and gradient studies probing functional connectivity, be it during task or at rest, primarily highlight a long-axis differentiation (left/blue panel). In contrast, studies probing local microstructure (such as laminar pattern and white matter microstructural features) primarily highlight a subfield-like differentiation along the medial–lateral and ventrodorsal axes (right/yellow panel). Interestingly, both dimensions of differentiation (long axis and medial–lateral) markedly appear in the pattern of hippocampal covariance with whole-brain structure. Notes: Reference [11] focuses on the subiculum. Reference [54] specifically examined a two-cluster subdivision of the right and left hippocampus, but only the right hippocampus is illustrated here. Reference [82] did not use a fully data-driven parcellation approach, but it used a semisupervized clustering technique. Reference [16] examined resting-state functional connectivity and T1/T2 ratio gradients separately in distinct subfields, but only the left subiculum is illustrated here. Abbreviation: MRI, magnetic resonance imaging. See also [13-15,17,18,23,24,53,58,59].

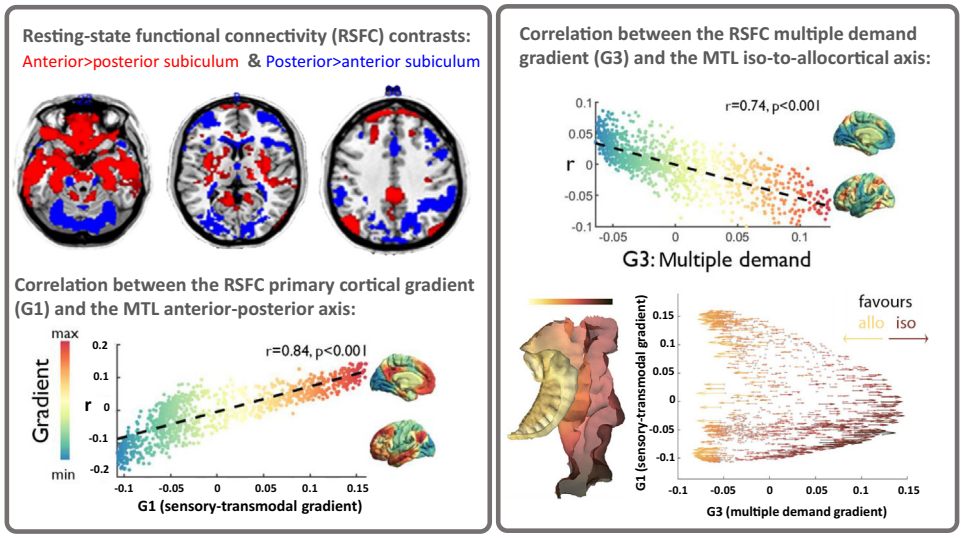

Figure 2. Relationships between hippocampal organization and functional brain organization at the macroscale. Anterior and posterior subregions (see Figure 1) show different preferential coupling across the brain (top left panel, from [11]). In particular, the differentiation along the anterior–posterior axis is primarily related to a transmodal to sensory primary gradient of cortical organization (bottom left panel, from [23]). In contrast, isocortical to allocortical organization (i.e., lateromedial differentiation) within the medial temporal lobe (MTL) is strongly related to a cortical 'multiple-demand' functional gradient (right panel, from [23]). The main organizational dimensions of the hippocampal formation are hence differentially related to the organizational dimensions of the rest of the human brain.

reflect gyrification of the hippocampus along the long axis (see [24] and hippocampal unfolding at high resolution in Figure 1). This emerging hypothesis should be further evaluated in future studies.

Although functional connectivity markers are popular estimates of large-scale integration, the latter can also be probed by examining structural covariance reflecting shared neurobiological properties (e.g., regions that are influenced by similar genetic, environmental, or metabolic factors) and/or contribution to the same behavioral systems [56,57]. This hybrid nature of structural covariance (neurobiological vs. behavioral) remarkably appeared when the hippocampal formation was parcellated into different subregions based on structural covariance patterns [14,58]. Although a primary differentiation between the head (or anterior) and the body-tail (two-thirds) region was revealed by these patterns, the latter region is further subdivided into medial and lateral segments strikingly resembling the subiculum versus CA fields (see Figure 1). This pattern contrasts with the functional tripartite model and demonstrates that structural variations to an important extent also follow microstructural territories despite being primarily segregated according to anterior versus posterior networks.

Local structure-based hippocampal parcellations

Recently, data-driven clustering has also been applied to features representing local structural properties of the human hippocampal formation. Typical markers of local microstructure offered by MRI techniques are T1/T2 ratio as a proxy of myelin, as well as estimates of white matter microstructure from diffusion-weighted imaging. Applying a non-negative matrix factorization approach to the combination of these features in the hippocampus revealed four stable components mainly organized along the medial–lateral and ventrodorsal axes in a subfield-like fashion [59] (see Figure 1). Nevertheless, a clear one-to-one mapping between the derived component

Box 3. Challenges raised by hippocampal parcellation and gradients

The elongated shape of the hippocampal formation and the intrinsic smoothness of MRI data are two technical factors that could potentially contribute to a primary gradient and clustering pattern along the longitudinal axis in MRI data [50]. It should be noted that when comparable parcellation techniques are applied to MRI data probing local microstructural features, the pattern of organization was characterized not along the longitudinal axis but along the medial–lateral axis [59]. Additionally, this issue can be directly investigated with a model selection approach based on statistical testing against a null model taken into the hippocampal geometry [18,50]. Such a framework confirmed the long-axis organization in functional connectivity [18], and this pattern was replicated at higher spatial resolution (7-Tesla data [18]). These recent findings suggest that the pattern of organization along the long axis, and in particular the tripartite subdivision, is genuinely related to large-scale functional connectivity as measured by fMRI and is not primarily driven by technical factors.

Nevertheless, when considering a range of different neurobiological features, it is likely that the hippocampus comprises a mixture of continuous gradients and discrete boundaries, as suggested in Figure 3. To examine that hypothesis, the robust identification in multimodal data of hybrid topographical representations that combine gradients and parcels would need a proper model selection. In that perspective, model selection could be used to determine whether a gradient or hard boundary provides the best fit to the data across different points of the topography. Such an approach would provide a potential path toward reconciling gradients and parcels in the hippocampus.

Although the primary long-axis gradient is consistently seen across different connectivity features, and to an important extent reproduces a head-body-tail model [16] as well as gene expression gradients [25], the second gradient is less easily characterized. It partly corresponds to the differentiation revealed by microstructural mapping, in particular when using MRI-based estimates of myelin [16] or laminar features [23]. Nevertheless, the overlap remains partial, being limited by noise in the data or reflecting the influence of additional, as yet unknown, neurobiological factors. Furthermore, despite most studies focusing on the first or the first and second gradients, additional gradients could be extracted from the data, and their neurobiological interpretation remains to be established.

Finally, interhemispheric asymmetry represents an important open question for future research. Despite a relatively similar pattern being generally observed in the right and left hippocampal formations with both parcellation or gradient mapping (see Figure 1), some differences across hemispheres have also been noted. For instance, different levels of partitions have been suggested to represent the left and right hippocampal organization optimally [18]. Furthermore, the left hippocampus often shows a more consistent topographical organization than the right across subjects or samples [13,16]. Such observations of hemispheric asymmetry currently remain anecdotal but call for future systematic investigations of the potential neurobiological factors and the related implications for the hippocampus/subiculum relationship to cognitive functions and behavioral phenotypes.

and the traditional, histologically defined subfields was not evident, preventing a straightforward link to classical neurobiological models.

In addition to MRI-based estimates, more direct investigations of hippocampal microstructure with automated approaches has been facilitated by the BigBrain initiative, which, for example, allows the characterization of laminar features [21]. A recent application of a clustering approach to laminar and morphological features (such as thickness, curvature, and gyrification) in BigBrain's hippocampal formation reveals again subregions arranged along the medial–lateral and ventrodorsal axes [24] (see Figure 1). This replicated the classical subfield model to some extent. Importantly, though, some changes in features along the long axis were also observed. In particular, anterior–posterior differences were qualitatively observed in gyrification in CA1, and in density in CA1 and CA4, hence raising the hypothesis of a relationship between gyrification and functional properties along the long axis.

Hippocampal gradients

Connectivity-based hippocampal gradients

In contrast to clustering approaches aiming for discrete subdivisions, gradient mapping techniques reveal continuous dimensions of brain organization [60] and can likewise be applied to MRI-derived connectivity estimates. As in a traditional eigenvector decomposition, the first gradient reflects the main dimension that captures the highest part of variance in the features (the connectivity profiles), whereas subsequent gradients explain successively lower amounts of variance. Several studies

have applied gradient mapping approaches to connectivity profiles of the hippocampal formation using the same features as discussed above for parcellation studies: resting-state functional connectivity [13,16,17,19], task coactivation profiles (with meta-analytic connectivity modeling) [13,16], and structural covariance [13,25] (see Figure 1). Across these studies, and regardless of the connectivity features, the emerging first organizational dimension systematically corresponds to a differentiation along the long axis, resonating well with the distinctions revealed by parcellation studies.

In turn, the topographical pattern of the second gradient is generally distributed along the medial–lateral and ventrodorsal axes. This second dimension of connectivity variance was revealed not only when the hippocampus and subiculum were analyzed together but also when focusing on specific subfields [13,16]. Moreover, when examining its microstructural differentiation patterns, a partial overlap with the spatial distribution of myelin estimates and subfield differentiation was shown [16] (see Box 3 for further discussion). Similarly, the within-subfield functional gradient in humans resonates with intrinsic functional gradients evidenced using invasive methods in rodents. For instance, a spatial signal gradient along the transverse axis of CA1 has been described in place cell firing within CA1 [61]. However, cross-species comparisons of within-subfields functional gradients is currently limited by the spatial resolution of methods for human studies (primarily MRI in this context).

Local structure-based hippocampal gradients

A recent study capitalized on the BigBrain data to assess cytoarchitectural transitions in the broader mesiotemporal lobe (MTL) [23]. The analyses support a consistent mediolateral gradient of cytoarchitecture differentiation, from parahippocampal isocortex toward hippocampal allocortex, and within the hippocampal formation, a cytoarchitecture-based gradient that recapitulates subfield-to-subfield variations in microstructure (see Figure 1). Interestingly, this mediolateral organization was found to also reflect patterns of intrinsic functional signal within the hippocampal circuitry (assessed using coregistered fMRI data). This study hence highlights again the local organization of information processing represented by this mediolateral pattern [23]. Further advancing our understanding of the relationships between topographical gradients and brain information processing, the isocortical-to-allocortical and anterior-to-posterior axes differentially contributed to distinct dimensions of the macroscale functional systems, as illustrated in Figure 2 [23]. Even though there was no apparent one-to-one mapping between organizational dimensions of the MTL and cortical networks or gradients, distinct hippocampal organizational dimensions differently mapped onto cortical gradients. In particular, the anterior-to-posterior progression along the hippocampal complex primarily correlated with the sensory to transmodal functional dimension. In contrast, and importantly, the isocortical-to-allocortical positions (i.e., mediolateral and ventrodorsal organization) was related to the relative contribution of the multiple-demand system, a system supporting complex tasks whose execution cannot rely on a predetermined schema (cf. Figure 2). Hence, recent developments have opened new perspectives to relate the hippocampal organizational dimensions to functional dimensions of information processing.

In sum, when parcellation and gradient mapping approaches are applied to connectivity patterns of the hippocampal formation, different superimposed organization patterns can be observed, as depicted in Figure 3. Generally, two main organizational dimensions appear: a primary pattern of subregions or gradients along the long axis and a secondary one along the medial–lateral and ventrodorsal axes. This latter organizational dimension appears primarily when these approaches are used to probe hippocampal local microstructure, be it estimated from MRI data or extracted from high-resolution *ex vivo* data. This pattern, in line with its local microstructural origin, is assumed to serve local information-processing flows possibly corresponding to different

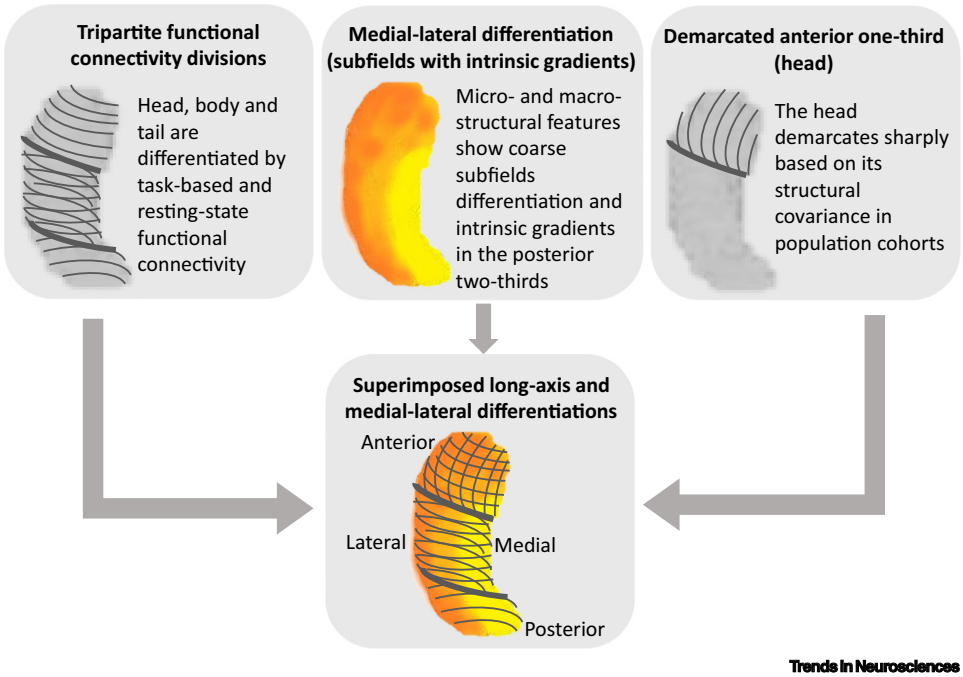

Figure 3. Schematic of superimposed differentiation patterns in human hippocampal formation. A tripartite subdivision corresponding to a head, body, and tail along the longitudinal axis is suggested by task-based and resting-state functional connectivity patterns. magnetic resonance imaging–based estimates of local microstructural and macrostructural features in turn highlight a medial–lateral and ventrodorsal differentiation separating the cornu ammonis complex from the subiculum complex, as well as intrinsic medial–lateral gradients (within subfield gradients). Finally, the head shows a specific whole-brain structural covariance in population cohorts. Superimposing these multiple differentiation patterns provides a holistic model to better understand hippocampal function and implications for clinical phenotypes.

processing requirements at the macroscale. In turn, the long-axis organizational pattern maps more directly into brain large-scale behavioral systems [55].

Relating hippocampal organization to phenotypes

Understanding hippocampal function and its relationship to behavior has long been a topic of interest in neuroscience (e.g., [62–64]). A substantial part of the related scientific literature has focused on developing theories of hippocampal function based on the subfield model, with the pattern separation theory (e.g., [65]) being a prominent example. Such computational models (in terms of pattern separation/completion processes) are typically anchored in local circuitry between subfields and build on experimental work in animal models. Nevertheless, they often fall short with regard to accounting for the variety and complexity of behavioral functions or psychological aspects in which the hippocampal formation is engaged [63,66]. Addressing this complexity requires a systemic view in which large-scale integration of the hippocampal formation into brainwide networks holds key information.

As the long-axis organization has increasingly gathered empirical support, several hypotheses have been proposed to explain its relevance for behavior, both in terms of a behavioral gradient and as a behavioral segregation (for reviews, see [9,20]). As noted, most of these theories live within a hypothesis-driven framework. For example, the famous encoding versus retrieval model was initially based on a selective review of the PET and fMRI activation literature [43] and was further reinforced by a targeted meta-analysis [45]. Nevertheless, examining behavioral

functions associated with activation along the long axis in a hypothesis-free context did not result in additional support of this theory. In contrast, the hypothesis of an emotion versus cognition gradient could be corroborated in a data-driven manner [15,16]. However, we would argue that it does not appear as an optimal conceptualization of functional differentiation, given a relative specificity for emotion processing in the anterior hippocampus but more widespread (i.e., unselective) associations for cognitive functions. Alternative conceptualizations based on large-scale behavioral decoding propose either a self-centric versus world-centric mode of processing [15] or a social and motivational system versus visuospatial cognition distinction [25]. These recent frameworks hence highlight the benefit of data-driven approaches of brain–behavior associations for generating new hypotheses.

The additional insight offered by such approaches might be particularly relevant when aiming to relate hippocampal organization to behavioral phenotypes in healthy and clinical populations. About a decade ago, a pathophysiological framework was proposed to relate specific diseases (corresponding to common diagnostic categories) to specific hippocampal subregions [67]. Importantly, and in line with the nosology of the previous decades, this framework postulated that current diagnostic categories indeed reflect distinct brain pathologies. It was hence suggested that specific regional vulnerability within the hippocampus differentiates AD, vascular disease, aging, depression, and post-traumatic stress disorder. Nevertheless, evidence for this view is inconsistent, and specific patterns of subfield alterations for different disorders do not clearly emerge from the (substantial) literature. In turn, a few studies have highlighted the role of the long-axis organization in interindividual variability, in particular in relation to behavioral phenotypes across childhood development (e.g., [68,69]) and aging (e.g., [70]). Furthermore, in young adults, different dimensions of the schizotypy risk phenotype were differently related to anterior versus posterior volume of hippocampal subfields [71]. This preclinical feature resonates well with differential alterations of anterior and posterior hippocampus in schizophrenia, where the anterior region is preferentially affected in the early stage [72–74]. Preferential atrophy in the hippocampus's head have also been reported in temporal lobe epilepsy [75,76], and functional decoupling of the anterior and posterior subregions has been evidenced in specific subtypes thereof [77]. Along the same line, the pattern of co-atrophy in dementia was recently shown to follow a differentiation along the long axis [14] (Figure 4). This suggests that the pattern of hippocampal–cortical codegeneration follows, to a large extent, functional coupling. In that regard, hippocampal anterior (self-oriented) and posterior (goal-oriented) networks may show opposite alterations in dementia, as increased medial temporal lobe connectivity to anterior networks has been associated with a decreased connectivity to posterior networks in patients with AD [78].

Finally, providing hints for the underlying neurobiological factors of interindividual differences along the long axis and their relationships with behavioral phenotype, a long-axis molecular gradient has recently been demonstrated (Figure 4) and has been related to large-scale behavioral systems [25,26]. In particular, cell type–specific expression of genes related to mood and affect have been found in the anterior hippocampus, whereas expression of genes related to cognitive functions have been identified in the posterior hippocampus [26]. Together, these observations highlight the relevance of the differentiation along the long axis for understanding interindividual differences in physiological phenotypes, but also in pathology and associated behavioral dysfunction.

Overall, the current literature points to relevant roles for both subfields and long-axis differences in hippocampal organization for interindividual differences and pathology. Considering both organizational dimensions simultaneously thus offers the opportunity to account for properties inherent to the computational infrastructure (related to local microstructural features), as well as features

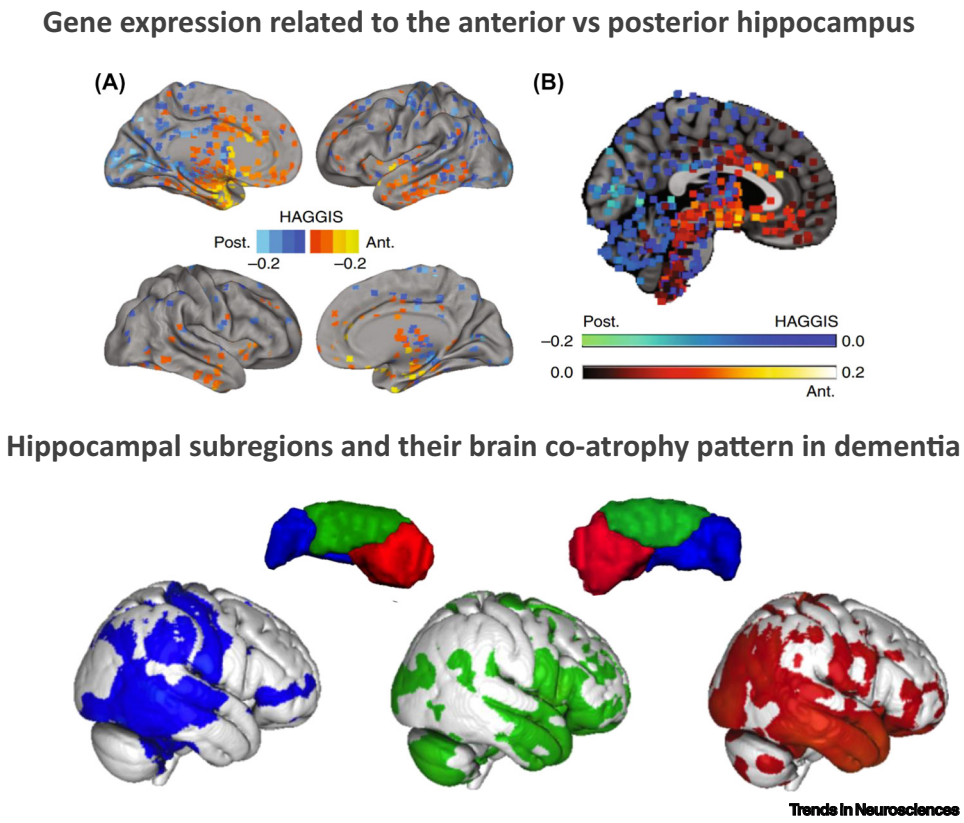

Figure 4. The relevance of hippocampal long-axis organization in relation to phenotype. (A and B) The *top panel* illustrates the molecular gradient along the long axis reported by [25] using a Hippocampal Axis Genomic Gradient Index of Similarity (HAGGIS), a value representing the degree to which the genomic signature of the hippocampal long axis is represented in the gene expression profile of a given nonhippocampal sample. Larger positive values represent greater genomic similarity to the anterior hippocampus, whereas smaller negative values represent greater genomic similarity to the posterior hippocampus. The bottom panel illustrates the differentiation of the left and right hippocampal formation into three subregions along the long axis based on their pattern of brain co-atrophy in Alzheimer's disease reported in [14].

reflecting network integration. Such a view has already been shown to characterize hippocampus structural changes with age (e.g., [79,80]). Further insight should be facilitated by parcellation and gradient-based representations that can be used to study pathophysiological aspects and the relationships between interindividual variability in hippocampal structure, function, and connectivity and interindividual variability in behavioral phenotype.

Concluding remarks and future perspectives

Adding to the well-established histological subfields of the human hippocampal formation, parcellation and gradient approaches capture at least two dimensions of organization in this brain region (and additional dimensions could be relevant; see Outstanding questions). Applying these approaches to local neurobiological features, such as local connectivity and microstructural properties, readily highlights a differentiation along the medial–lateral and ventrodorsal axes. In turn, applying these approaches to neurobiological features that tap into the integration of the hippocampal formation into large-scale networks and its relation to behavioral systems reveals a differentiation along the long axis. Accordingly, the medial–lateral and anterior-to-posterior axes could differentially contribute to distinct functional dimensions, with medial–lateral differentiation possibly relating to the relative contribution of the multiple-demand system and anterior-to-

Outstanding questions

Can the human hippocampal organization be further characterized by additional gradients/dimensions beyond the medial–lateral and longitudinal dimensions?

How do pathophysiological processes interact with the dimensions of hippocampal organization?

Can finer characterization of neurobiological alterations along both the medial–lateral and longitudinal dimensions improve diagnostics and/or treatment of brain disorders?

How do interindividual differences in hippocampal organization relate to interindividual differences in behavioral phenotype?

Are there interhemispheric differences in hippocampal organization?

How do fine long-axis subdivisions suggested by connectivity and structural features (such as gyrification) emerge across ontogenesis and phylogeny?

posterior position seemingly reflecting trade-offs between sensory/self-centric and transmodal function. When related to large-scale behavioral systems and related phenotypes, this latter dimension should reflect a differential involvement of emotional, motivational, and self-centric systems versus more integrative and word-oriented cognition. Parcellation maps and decomposition techniques have opened new perspectives to further investigate how this organization relates to behavioral phenotype, in particular in a transdiagnostic approach linking the dimensions of hippocampal organization to behavioral dimensions spanning across the healthy brain and disease categories.

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Declaration of interests

The authors declare no competing interests in relation to this work.

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