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Opinion

Surface-based hippocampal subfield segmentation

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Though it is often termed 'subcortical,' the hippocampus is composed of a folded 'archicortical' sheet contiguous with the neocortex. The human hippocampus varies considerably in its internal folding configuration, creating major challenges in interindividual alignment and parcellation into subfields. In this opinion article, we discuss surface-based methods that aim to explicitly model hippocampal folding, similar to methods used in the neocortex, allowing interindividual alignment in an unfolded or flat-mapped 2D space. Such an approach enables detailed morphological characterization, constrains the problem of subfield segmentation, and provides a way to visualize data without occlusions. We argue that, when applied to magnetic resonance imaging (MRI) data, such methods overcome pitfalls of more conventional manual or registration-based subfield segmentation approaches.

Challenges in defining hippocampal subfields

Hippocampal subfields are regions with stereotyped cellular composition that have come to the forefront of current research because of their promise in furthering both clinical and theoretical neuroscience research. Precise estimates of subfield locations can be used to test hypotheses about the relationship of subfield architecture and function via functional magnetic resonance imaging (fMRI) or other recording methods in humans [1–3]. Differences in subfield-specific integrity have been observed in many diseases or disease subtypes (e.g., [4–7]), and subfield-specific functions have been linked to distinct aspects of cognition (e.g., [8–10]). Thus, tremendous effort has gone into developing protocols to infer hippocampal subfields from *in vivo* MRI. A fundamental challenge in this endeavor is that the cellular composition that defines the subfields currently cannot be captured with such techniques.

In histology, there are typically sufficient microscale features available for an expert neuroanatomist to distinguish the subfields [1,11,12], providing ground truth reference materials. Thus, the challenge of subfield segmentation is primarily in establishing correspondence between tissues and image modalities. The simplest method to do this is linear alignment between a given image and a ground truth 2D or 3D reference atlas, as in rigid stereotaxic approaches. However, this does not account for interindividual differences in hippocampal anatomy, which, as we describe in this opinion article, can vary widely.

Currently, the issue of interindividual variability is addressed in one of three ways. First, manual segmentation aims to identify landmarks that remain consistently aligned to subfield boundaries despite interindividual differences. Second, alternatively, a reference atlas can be computationally deformed (or registered) to best fit a given subject, which is the workhorse of most automated segmentation methods. Third, novel surface-based methods aim to define hippocampal folding in 3D, which can then be mapped to a topologically constrained 2D space. In this opinion article, we argue that the latter approach holds unique promise because it is flexible to different variants

Highlights

The human hippocampus is composed of a folded archicortical sheet with its subfields containing unique cellular compositions.

Magnetic resonance imaging (MRI) is a promising way to study subfield functions and abnormalities in disease, but alignment to histologically defined subfield atlases is challenging due to extensive interindividual variability.

Surface-based methods allow alignment of topologically homologous tissues between individuals or from one individual to a histological reference.

Compared with manual or registration-based approaches, surface-based approaches provide new biologically valid constraints to subfield segmentation and do not suffer some of the technical limitations, such as out-of-plane sampling, of manual approaches.

In particular, such methods show promise in high-resolution imaging where assessing interindividual variability within the hippocampus is becoming increasingly feasible.

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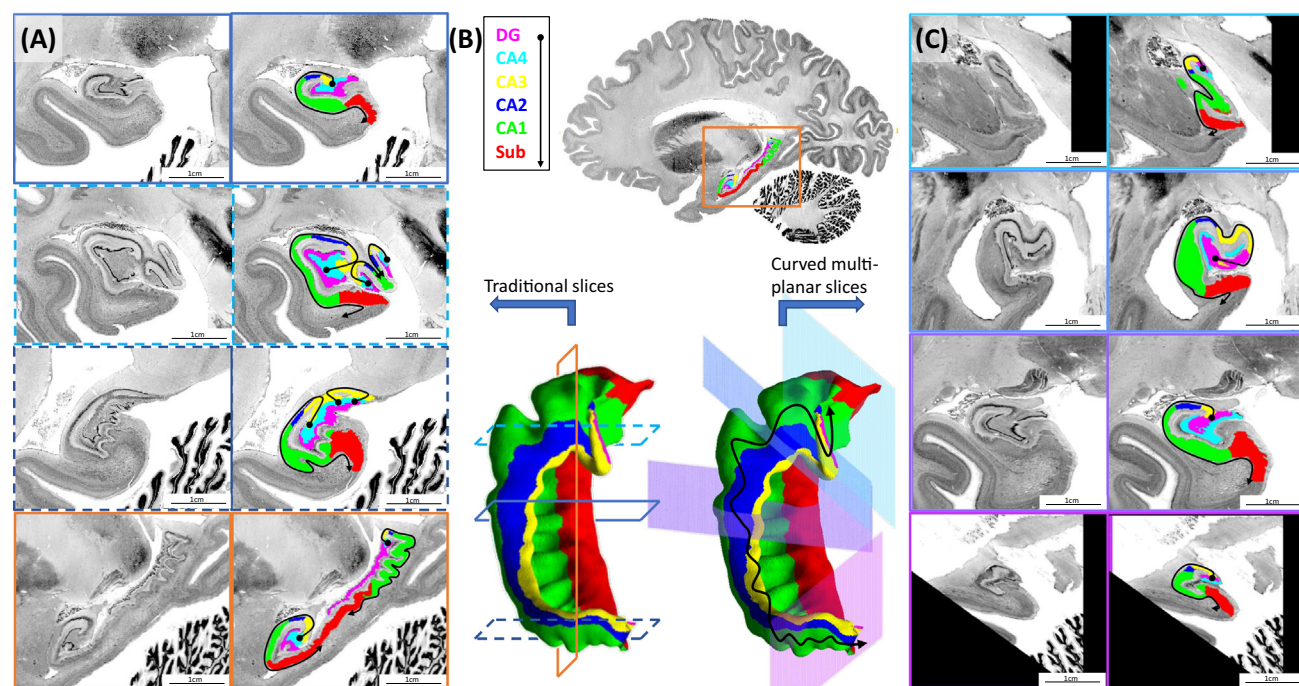[6]These authors shared senior authorship

of hippocampal folding and constrains alignment between individuals (or from one individual to a reference) in a biologically motivated manner. We see this approach as being aligned with the paradigm shift towards surface-based neocortical analysis methods that can accommodate different gyral and sulcal patterning [13].

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Relevant anatomy

Hippocampal subfields are principally defined by cyto-, myelo-, and chemoarchitectures using *ex vivo* histology, typically in the coronal plane (Figure 1A). When samples are taken from the body of the hippocampus (midway along the anterior–posterior extent), all subfields can be seen to follow a canonical topological ordering, which is shown at the top left of Figure 1A. Specifically, the subfields follow a curled C shape with dentate gyrus at the innermost terminus wrapped by cornu ammonis (CA) fields 4 through 1, followed by subiculum, which borders the medial temporal lobe neocortex.

It has been known for a long time that, in 3D, the hippocampal subfields are fully contiguous [1], even though this is often not apparent in individual slices (Figure 1A). To appreciate this contiguity, consideration of the full 3D extent of the hippocampus is required through either the context of neighboring slices in histology [11] or the application of 3D imaging methods such as MRI. In humans, all subfields follow a complex trajectory in 3D: The hippocampal tail (posterior) curves

Figure 1. Illustration of hippocampal subfield topology in traditional and multiplanar histological slices (data from [42] and segmentations from [20]). (A) Traditional hippocampal slices with and without subfields overlaid. Coronal slices through the hippocampal body (top) are the most commonly used orientation. In particular, slices through the hippocampal head (light blue broken outline) and tail (dark blue broken line) show discontinuities due to out-of-plane sampling. (B) Approximate locations of the coronal slices (outlined in unbroken or broken blue lines) are shown on the left-side 3D model of the hippocampus. A sagittal slice is shown in the full brain image on top (outlined in orange). Folds including digitations and medial curvature in the hippocampal head and tail are illustrated by the black line in the right-side 3D model. (C) Multiplanar resampled slices along the axis of hippocampal curvature with and without subfields overlaid. The color of each image outline corresponds to the location of its sampling on the right-side 3D hippocampal model in (B). The contiguity of subfields is shown by a black line and is consistent in all slices in (C) as described in classic neuroanatomy. Abbreviations: CA, cornu ammonis; DG, dentate gyrus; Sub, subiculum.

medially, and the hippocampal head (anterior) curves medially, posteriorly, and then superiorly, where it terminates on the amygdala. The contiguity of the subfields in each of these regions has been highlighted in recent anatomical work using multiplanar rather than coronal sampling [14], which we illustrate in Figure 1C and in the supplemental video (see the Supplemental information online) showing all slices. Digitations – smaller-scale folds in hippocampal tissue that resemble neocortical gyrifications – are sometimes seen approximately perpendicular to this curvature. This can be appreciated most easily on coronal slices in the hippocampal head or on sagittal slices in the hippocampal body, as exemplified in Figure 1A.

Both the presence of digitations and the extent of anterior–posterior curvature are difficult to assess using traditional histological methods alone, which are typically limited to sparse coronal slices. Only recently have these features become apparent using 3D neuroimaging such as ultra-high-resolution *in vivo* and *ex vivo* MRI. These methods have begun to reveal wide interindividual variability in the anterior–posterior curvature of the hippocampus and in the presence and prevalence of digitations (Figure 2) [11,15–17]. Early evidence suggests that the extent of digitation is linked to healthy aging [16] and memory [17].

Surface-based approaches

The logic of surface-based alignment is to account for interindividual differences in folding by projecting to a 2D flat or spherical surface. Parcellation or subfield segmentation performed in this unfolded space can then be projected back to the native space, an approach that has been highly successful in the neocortex (see [13] and Box 1 for further discussion). In the hippocampus, a similar unfolding entails the definition and removal of the inward curl of the subfields, hippocampal curvature along its anterior–posterior extent, and its digitations. Alignment between samples, or between one sample and a histological reference atlas, can then be performed by projecting to this unfolded space, regardless of variations in native folding configurations, as
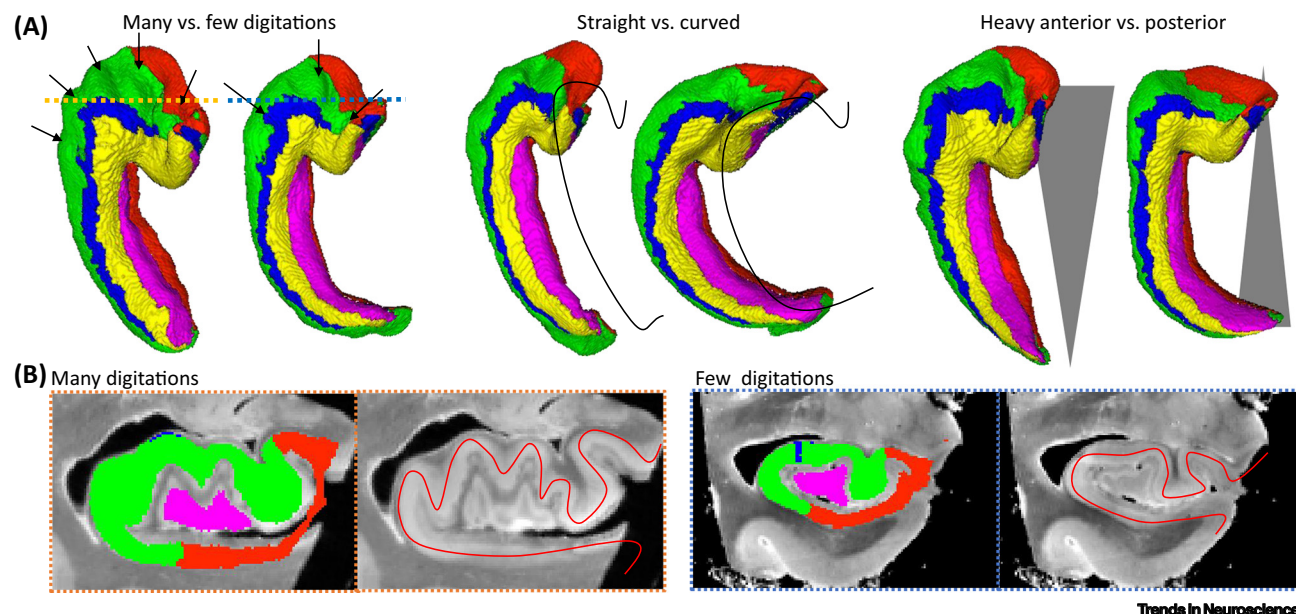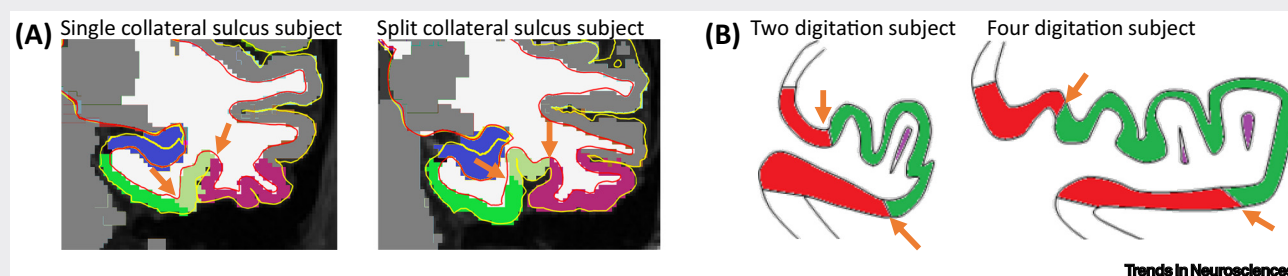

Figure 2. Variability in hippocampal morphology in six representative individuals as seen in magnetic resonance imaging (MRI) from [43] (same data and segmentations). (A) 3D models of manual subfield segmentations. (B) Coronal slices showing segmentations and underlying MRI data from the first two samples shown in (A) (location indicated by the orange and blue broken lines). Note that in addition to differences in the gross morphology of the hippocampus (A), there are differences in smaller-scale digitations [indicated by the red lines in (B)], which are not always well captured in manual segmentations.

Figure I. Comparison of different neocortical gyrification or hippocampal digitation patterns. (A) Single versus split collateral sulcus in two Human Connectome Project subjects [51] (same coronal slice following minimal preprocessing and parcellation using Freesurfer's surface-based APARC neocortical parcellation). Labels from left to right: hippocampus (blue), parahippocampal cortex (green), fusiform cortex (sage), and inferior temporal cortex (pink). (B) Two versus four digitations within the anterior hippocampus, based on illustrations from [11]. Labels: subiculum (red), CA1 (green), and dentate gyrus (purple). Orange arrows highlight topologically shifted boundaries between different subjects.

illustrated in Figure 3. Critically, homology of tissues between different individuals is thus established in unfolded space on the basis of topology and contiguity of tissue in 3D. In principle, surface-based approaches can accommodate any pattern of digitation and curvature within the hippocampus and potentially even abnormal cases such as hippocampal malrotations (or abnormal 3D shape) [18,19]. This is because, to our knowledge, no actual breaks in topology have been reported that would conflict with such an approach.

Several studies have used surface-based methods to flat map the hippocampus [15,20–23]. In its first implementations, Bookheimer and colleagues [21,22] performed manual subfield segmentation in native volumetric space before transforming the entire volume of the hippocampus, with its subfield labels, to an unfolded space via multidimensional scaling methods similar to those that have been used in the neocortex [24,25]. Other groups have employed similar combinations of manual and surface-based methods, but with flat mapping applied at the level of individual subfields, which are then 'stitched back together' to form a contiguous unfolded space [23]. In our own work [15,20], we have developed an approach that starts with unfolding of the entire hippocampal volume using a subject-specific coordinate framework, and then subfield segmentation is performed in unfolded space (Figure 3). All of these methods ([15,20–23]) allow measurement of detailed structural hippocampal features, such as thickness or surface area, by virtue of providing a dimension that can be estimated perpendicular to the axis of hippocampal folding. However, only some of these methods [15,20] explicitly leverage topology to register to a standardized space in which reference subfield boundaries are defined. The latter methods uniquely respect the topological contiguity of subfields and allow contiguity-constrained decisions about subfield boundaries in 2D rather than 3D. This constraint is well supported by the ontogeny of hippocampal subfields, which begin to differentiate within a flat archicortical sheet before their folding [1].
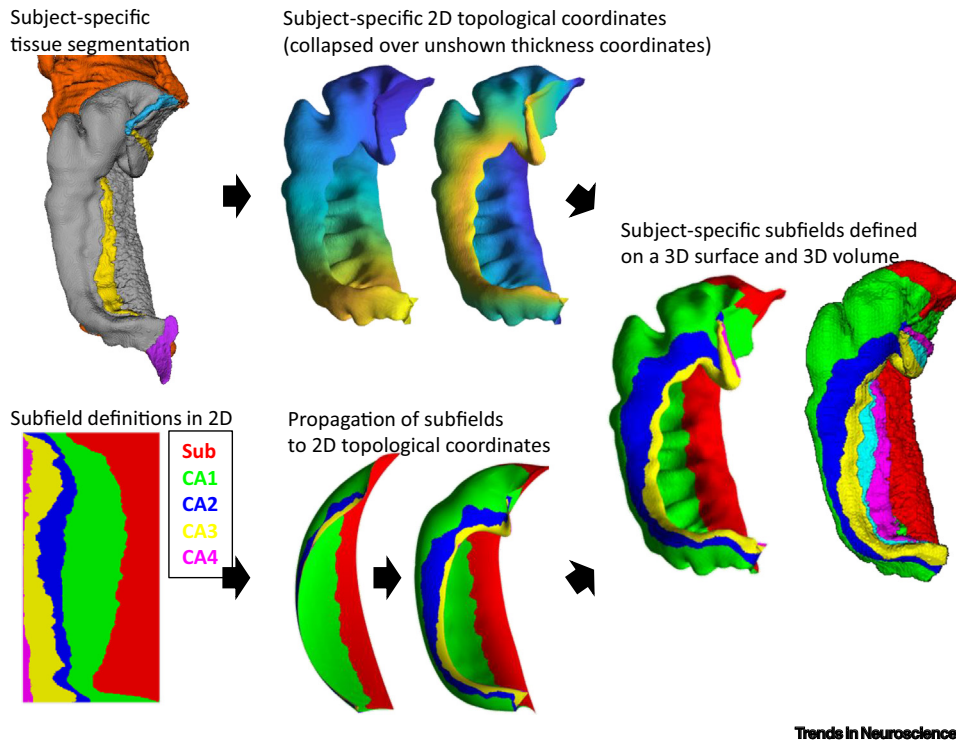
Figure 3. Surface-based representation of the hippocampal subfields as applied in [20] (same data and models). Gradients are imposed on hippocampal gray matter segmentations on the basis of where this tissue borders nearby structures (shown in one subject in the top left panel: hippocampal–amygdalar transition area in cyan, indusium griseum in purple, DG in yellow, and medial-temporal lobe cortex in orange, mostly inferior to and obscured by the hippocampus). These gradients act as a subject-specific coordinate system, allowing the hippocampus to be flat mapped to a standardized 2D space. Note that the DG was not included in this unfolded space due to its distinct topology (see [20] for discussion). Subfields can be defined in this standardized space, such as on the basis of 3D histology [20], and then can be propagated to each subject's native space. Abbreviations: CA, cornu ammonis; DG, dentate gyrus; Sub, subiculum.

Comparison with manual and registration-based segmentation methods

In general, manual protocols for subfield segmentation aim to provide heuristics for matching 2D coronal MRI slices to coronal histology slices via landmarks available in both modalities. Such key structures include the high myelin stratum lacunosum-moleculare and sometimes stratum radiatum (SLM or SRLM) [26] (unlabeled space between subfields in Figures 1 and 2). These structures appear collectively as a landmark visible in both histology (as containing few neurons and high myelin) and in MRI (given sufficient contrast and resolution). As such, it provides a potential intrahippocampal landmark to which subfield borders can be anchored. For example, the border between subiculum and CA1 may be defined as half of the medial–lateral extent of the SRLM [27]. Thus, variability in the subiculum–CA boundary is tied to variability in the visible SRLM via geometric rules. Many manual protocols have been proposed that leverage the SRLM or other structures but show considerable inconsistencies, giving rise to an ongoing international harmonization effort to address this issue [28–30].

There is growing evidence that subfield boundaries do not remain consistent in geometric position relative to the SRLM. Specifically, this alignment is highly dependent on the slice angle and distance along the anterior–posterior axis of the hippocampus [11,31]. Notably, because the hippocampal subfields curve medially (or out of plane) in most of the hippocampal head

and tail, their presence and position can vary drastically or appear discontiguous between coronal slices. This can readily be appreciated by comparing coronal slices with multiplanar slices in Figure 1. In addition, there is broad interindividual variability in the number and magnitude of digitations within the hippocampal head [11,20] as well as the hippocampal body and tail [15–17] (Figure 2). Digitations include the SRLM, and thus it is not yet clear whether geometric rules derived from the SRLM remain stable across variants with different digitation patterns. Many protocols simplify or do not label subfields in the head or tail because of these limitations (see [28] for overview).

Another approach to segmentation that is becoming increasingly popular involves computational methods. Such methods are advantageous because not only are they time-efficient and reproducible but also, in principle, they can use morphological 3D image features that would be out of plane to a histologist or manual rater of MRI images. Common approaches involve deformable registration of a given subject's hippocampus to a sufficiently detailed 3D reference material, which is constructed via a combination of densely sampled histology, *ex vivo* MRI, and/or manual *in vivo* annotations at very high resolution [12,32,33]. Recent and ongoing work enhances both the registration process and 3D reference materials used in these methods [12,27,33–35].

Given good-quality reference materials, computational approaches can account for the gross curvature seen in the hippocampal head and tail, as well as for subfield boundary differences along the anterior–posterior extent of the hippocampal body, without introducing challenges related to slice position or angle. However, variability in hippocampal digitations may not be well posed for registration-based approaches to segmentation. For example, it is not always clear what deformation should be applied to align a hippocampus with two anterior digitations to one with four anterior digitations (Figure 2B). In some cases, one reference digitation may become stretched over multiple target digitations or vice versa, creating major distortions and loss of anatomical detail in the resulting segmentation. Resulting 3D models may appear contiguous while still not accurately capturing the folding and topological shifting found in the underlying tissue. This is similar to the problem of registering the neocortex of individuals with variable gyrification or sulcal patterns, a problem that is discussed in Box 1.

Current and future directions

Currently, there is only indirect or incomplete evidence to suggest that surface-based subfield segmentation approaches outperform other approaches in MRI with histological validation. For example, within coronal slices of the hippocampal body, Steve and colleagues [36] measured histologically defined subfield boundaries as a percentage distance along the inward curl of the hippocampus (i.e., a 1D topological framework) and found high consistency across slices and across samples. This type of topological rule could replace more typical geometric rules, such as the subiculum–CA1 border being 'half the medial–lateral extent of the SRLM' (example described earlier), which may not remain consistent across the length of the hippocampal body [31]. Under a fully 3D approach (or 2D topology, as in the surface-based approaches advocated here), such rules are extended into the medially curved hippocampal head and tail. However, there is still limited evidence of whether topologically defined subfield boundaries remain consistent across individuals in the hippocampal head and tail (however, see [15]).

Additional differences in subfield boundaries beyond those accounted for by folding or topology do likely exist and could be envisioned as alternative or shifted boundaries in the unfolded space illustrated in Figure 3. Future *in vivo* work could leverage quantitative MRI (e.g., intracortical myelin or other measures that have been influential in recent neocortical

parcellations [37]) to account for topologically shifted differences in subfield boundary locations between individuals, similar in spirit to recent data-driven parcellation work [20,23,38–40]. Within histological studies that are considered ground truth, it can still be challenging to match subfield boundaries between slices, depending on issues such as slice angles, intersubject variability, or even different histologists (see [29] for discussion). These problems might be ameliorated by using surface-based approaches to consider the 3D context of a given histology slice or by weighing additional 3D quantitative MRI data. Such information could in turn determine to what extent ground truth subfield boundaries differ between subjects within a surface-based framework (for further discussion, see Outstanding questions).

An outstanding technical challenge with surface-based subfield segmentation approaches is that they require definition of different hippocampal folds. This is possible through detailed manual tissue segmentation within the hippocampus [15,20]. However, severe atrophy or sclerosis (e.g., [41]) and partial voluming with cysts can make the detection of intrahippocampal white matter structures challenging. These issues may reduce the feasibility of this approach in lower-resolution images (e.g., with voxel size >1 mm^3 isotropic or large slice thickness). Finally, to our knowledge, no actual breaks in topology have been observed that would conflict with the principles of a surface-based approach, even when applied at low resolution or in cases with severe atrophy or sclerosis. Thus, despite these limitations, it is our opinion that surface-based hippocampal segmentation offers the greatest flexibility in accounting for interindividual differences when high-resolution data are available, which is becoming increasingly feasible in the field at large.

Concluding remarks

We have examined recent evidence on the complex and variable folding found within the human hippocampus, which presents significant challenges for manual and registration-based subfield segmentation methods in MRI. Specifically, manual approaches may not adequately address the full 3D extent of the hippocampus, whereas registration-based approaches may be ill posed to address some types of morphological variability. Explicitly modelling the hippocampus as a folded surface and flat mapping it can account for this variability while also constraining the problem of subfield segmentation from 3D to 2D and providing additional detailed morphological information. This novel approach may reveal relationships between hippocampal subfield morphology, integrity in disease, and function.

Declaration of interests

The authors declare no competing interests.

Supplemental information

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Outstanding questions

External validation of a surface-based subfield segmentation approach is lacking and would require both a 3D model of hippocampal folding and same-subject histology, ideally sampled throughout the hippocampal head, body, and tail. Conversely, could 3D modelling of hippocampal folding and flat mapping account for variability seen within histology?

Manual subfield segmentation protocols often use anisotropic image acquisitions, but this can obscure medial curvature in the hippocampal head and tail and digitations in the hippocampal body. What is the optimal level of resolution and anisotropy, if any, to apply a surface-based method to these regions?

Computational unfolding of the hippocampus can be accomplished through manual segmentation of gray matter and the SRLM, which separates folds. Can this be reliably accomplished automatically?

Surface-based neocortical parcellation schemes can be modified to accommodate subject-specific features (e.g., intracortical myelin, gyrification, or thickness measures). Could such approaches further improve hippocampal surface-based subfield definition?

Do variants of hippocampal digitation fall into distinct clusters (e.g., two versus three versus four anterior digitations)? Recent work identifies digitations that continue into the hippocampal body and tail that vary in number and amplitude, raising the possibility of continuously varying morphologies.

Some evidence shows that having greater hippocampal digitation is linked to aspects of memory and healthy aging. Are other functions linked to hippocampal folding more generally? Might digitations and their functional associations both result from changes in tissue properties such as surface area or thickness?

Do surface-based methods offer any improvement in applications such as detection or localization of hippocampal pathology in neurological or psychiatric disorders over more conventional manual inspection, manual segmentation, or registration-based approaches?

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