NeuroImage 167 (2018) 408–418

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Unfolding the hippocampus: An intrinsic coordinate system for subfield segmentations and quantitative mapping

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ARTICLE INFO

Keywords:
Hippocampus
Hippocampal subfields
Uncus
Magnetic resonance imaging
7 Tesla
Ultra-high field MRI
Morphometry
Segmentation
Computational anatomy

ABSTRACT

The hippocampus, like the neocortex, has a morphological structure that is complex and variable in its folding pattern, especially in the hippocampal head. The current study presents a computational method to unfold hippocampal grey matter, with a particular focus on the hippocampal head where complexity is highest due to medial curving of the structure and the variable presence of digitations. This unfolding was performed on segmentations from high-resolution, T2-weighted 7T MRI data from 12 healthy participants and one surgical patient with epilepsy whose resected hippocampal tissue was used for histological validation. We traced a critical image feature composed of the hippocampal sulcus and stratum radiatum lacunosum-moleculare, (SRLM) in these images, then employed user-guided semi-automated techniques to detect and subsequently unfold the surrounding hippocampal grey matter. This unfolding was performed by solving Laplace's equation in three dimensions of interest (long-axis, proximal-distal, and laminar). The resulting 'unfolded coordinate space' provides an intuitive way of mapping the hippocampal subfields in 2D space (long-axis and proximal-distal), such that similar borders can be applied in the head, body, and tail of the hippocampus independently of variability in folding. This unfolded coordinate space was employed to map intracortical myelin and thickness in relation to subfield borders, which revealed intracortical myelin differences that closely follow the subfield borders used here. Examination of a histological resected tissue sample from a patient with epilepsy reveals that our unfolded coordinate system has biological validity, and that subfield segmentations applied in this space are able to capture features not seen in manual tracing protocols.

Introduction

Researchers often distinguish the hippocampus from neocortex but the hippocampus, in fact, also has a cortical composition sometimes referred to as archicortex due to its wide evolutionary preservation (e.g. Duvernoy et al., 2013). Like the neocortex, the hippocampus shows variable gyrification, often referred to as digitations or pseudo-digitations in the anterior hippocampal head and more posterior body/tail, respectively. This variability creates major challenges for cross-participant alignment and segmentation. This is particularly of interest given the recent controversy over segmentation of the hippocampus into subfields in MR data, which are not sensitive to most cytoarchitectonic features that define the subfields (for an overview of this controversy see Yushkevich et al., 2015 and harmonization efforts by Wisse et al., 2017).

Though present in the rest of the hippocampus, digitations are most

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https://doi.org/10.1016/j.neuroimage.2017.11.054
Received 6 June 2017; Received in revised form 9 November 2017; Accepted 22 November 2017
Available online 23 November 2017

prominent in the hippocampal head. This structural feature is a significant challenge for subfield segmentation protocols and as such most protocols do not segment this region, or do not honour its complex and variable structure (see Yushkevich et al., 2015). Ding and Van Hoesen (2015) recently provided detailed descriptions of the hippocampal head including three different morphologies (2, 3, or 4 digitations). However, there are observed cases with even more digitations that continue through the hippocampal body (see also Gao and Ver Hoef, 2016) and cases with differences in the amount of medial curvature of the uncus. Dalton et al. (2017) and Berron et al. (2017) have recently published protocols leveraging Ding & Van Hoesen's descriptions. These protocols collapse across different morphologies and deal primarily with one canonical case. This may produce results that are close to the ground truth under different morphologies as well. However, differences in folding will cause a topological shift and so each subfield border should shift in turn. Thus, attempting to impose borders without considering topology creates challenges in subjects with different degrees of folding, or different rotations or positions within the medial-temporal lobe (e.g. varying degrees of dysplasia), similar to the challenge of aligning the neocortex in participants with variable gyrification.

In the neocortex, the challenge of inter-subject alignment in cases of variable gyrification have been largely overcome by using topology-preserving surface-based alignment (Dale et al., 1999; Fischl et al., 1999a, 1999b, 2001), which has led to the development of powerful methods for parcellation (e.g. Glasser et al., 2016). These types of methods have not yet been applied to the archicortex of the hippocampus. However, several studies reported by Bookheimer and colleagues have implemented a technique that is similar but used primarily for visualizing results rather than as an analysis technique (see Ekstrom et al., 2009; Zeineh et al., 2003; and also in 7T MRI Suthana et al., 2015). Under their protocol, delineation of medial temporal neocortex and hippocampus is performed in the subject's native space and conformal mapping is used to flatten this tissue, such that results can be viewed in a single plane. However, this protocol does not make use of some of the advantageous features used in neocortical surface-based analysis: it does not use a standardized set of coordinate points, segmentation is performed based on a geometric landmarks in native space (i.e. prior to any surface-based alignment). Although the folded topology in the hippocampal body is captured, the digitations and medial curvature of the hippocampal head and tail do not appear to be separately delineated – instead they are labelled using a similar coronal scheme as the hippocampal body. As a consequence, topology is not fully preserved in these areas.

Goals of the current study

The current study aimed to examine the topological structure and ontogeny of the hippocampus in order to develop a two-dimensional coordinate system for alignment and segmentation of variably folded hippocampi across individuals, similar to surface-based alignment methods used in the neocortex. Specific structural features we identified and aimed to account for are the medial folding forming the classic hippocampal C-shape (or inverse C-shape depending on hemisphere and orientation), long-axis and uncal curvature, digitations, and inter-individual variability in each of these features (further detailed in the next section). After tracing each of these features in 7T T2-weighted MR images, we applied the Laplace equation to divide hippocampal archicortex into a set of standardized long-axis and proximal-distal coordinates using anatomically motivated boundary structures that are topologically continuous with the hippocampus. We applied a segmentation of the hippocampus based on the histological samples used by Ding and Van Hoesen (2015) under the framework of this two dimensional, topology-preserving coordinate space, which we then validated by comparison to quantitative MR measures of intracortical myelin and thickness, as well by direct comparison to a surgically resected tissue sample from a patient with epilepsy (i.e. comparison of preoperative segmentation to postoperative histology).

Critical structural features we aim to accommodate

During development, the hippocampus originates from a single flat tissue, which in addition to its long-axis curvature, also folds medially upon itself forming a C-shape while differentiating into the various subfields (Duvernoy et al., 2013; Williams, 1995; Smith, 1897) (Fig. 1A). This developmental characteristic has several interesting consequences for the structure of the adult hippocampus: all subfields make up adjacent segments of a contiguous tissue segment (though the dentate gyrus makes up a distinct tissue but keeps a consistent position at the distal edge of the CA fields). The sulcus, or 'crease', around which this folding occurs can be visualized in histology as the hippocampal sulcus, or in MRI as the 'dark band' or stratum radiatum and lacunosum-moleculare (SRLM or SLM in the subiculum). It is named after the high-myelin laminae thought to be driving its MRI contrast (Kerchner et al., 2010; Thomas et al., 2008, and others), although no extant work has ruled out contributions of non-penetrating blood vessels within the hippocampal sulcus. Many subfield segmentation protocols rely on this image feature in the hippocampal body. In the current study we aimed to capture the SRLM in the hippocampal head and tail as well, which we then critically leveraged to differentiate the folds of the entire hippocampus, preserving its topology.

Recent histological evidence from Ding and Van Hoesen (2015) offers a new morphological characterization of the hippocampal head, which we also aimed to respect in our unfolded coordinate space. A main finding in this characterization was the documentation of considerable interindividual differences in digitations (i.e. folding, similar to the gyrification of neocortex) in the hippocampal head, varying from 2 to 4 digitations, with additional pseudo-digitations sometimes found along the lateral and inferior sides of the hippocampal body and tail. Ding & Van Hoesen also delineated the subfields in detail in the uncus - a part of the hippocampal head that curves medially, and then superiorly (see Fig. 1B). In line with Duvernoy et al.'s (2013) characterization, Ding & Van Hoesen showed that all subfields of the hippocampus contiguously follow this curvature through the hippocampal head and have their natural anterior termination not in the absolute anterior tip of the hippocampus, but rather in the more medial and posterior vertical component of the uncus (Fig. 1B, red line terminating in 'vert. unc'). As the subfields curve into the uncus, their borders also shift such that the

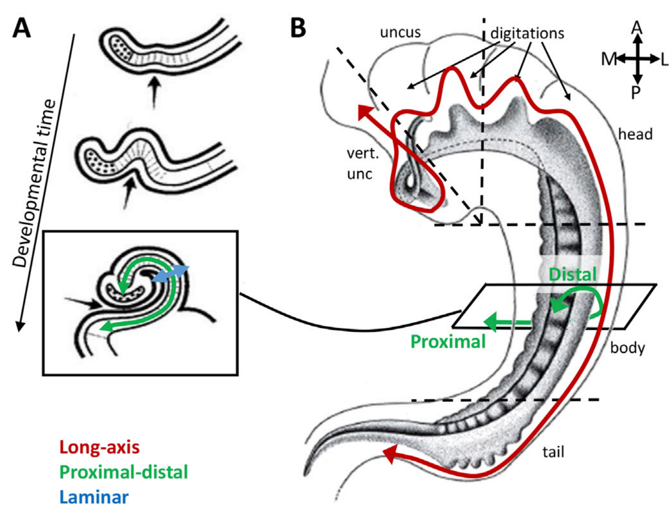

Fig. 1. Ontogeny and anatomy of the hippocampus. A) Coronal sections of the initially flat tissue of the hippocampus folding medially during development, forming the hippocampal sulcus (indicated by black arrow). B) Fully developed hippocampus seen from above, showing the long-axis curvature in the head and tail and anterior digitations. Dotted lines roughly indicate commonly used long-axis divisions of the hippocampus. Both images adapted with permission from (Duvernoy et al., 2013).