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Quantitative comparison of 21 protocols for labeling hippocampal subfields and parahippocampal subregions in in vivo MRI: Towards a harmonized segmentation protocol

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ABSTRACT

Objective: An increasing number of human in vivo magnetic resonance imaging (MRI) studies have focused on examining the structure and function of the subfields of the hippocampal formation (the dentate gyrus, CA fields 1−3, and the subiculum) and subregions of the parahippocampal gyrus (entorhinal, perirhinal, and parahippocampal cortices). The ability to interpret the results of such studies and to relate them to each other would be improved if a common standard existed for labeling hippocampal subfields and parahippocampal subregions. Currently, research groups label different subsets of structures and use different rules, landmarks, and cues to define their anatomical extents. This paper characterizes, both qualitatively and quantitatively, the variability in the existing manual segmentation protocols for labeling hippocampal and parahippocampal substructures in MRI, with the goal of guiding subsequent work on developing a harmonized substructure segmentation protocol.
Method: MRI scans of a single healthy adult human subject were acquired both at 3 T and 7 T. Representatives from 21 research groups applied their respective manual segmentation protocols to the MRI modalities of their choice. The resulting set of 21 segmentations was analyzed in a common anatomical space to quantify similarity and identify areas of agreement.
Results: The differences between the 21 protocols include the region within which segmentation is performed, the set of anatomical labels used, and the extents of specific anatomical labels. The greatest overall disagreement among the protocols is at the CA1/subiculum boundary, and disagreement across all structures is greatest in the anterior portion of the hippocampal formation relative to the body and tail.
Conclusions: The combined examination of the 21 protocols in the same dataset suggests possible strategies towards developing a harmonized subfield segmentation protocol and facilitates comparison between published studies.

Introduction

The medial temporal lobe (MTL) is a complex brain region of enormous interest in research on memory, aging, psychiatric disorders, and neurodegenerative diseases. Within the MTL, the subfields of the hippocampus (cornu Ammonis fields CA1—CA4, dentate gyrus, subiculum) and the adjacent cortical subregions of the parahippocampal gyrus (entorhinal cortex, perirhinal cortex, and parahippocampal cortex) are understood to subserve different functions in the memory system (Squire et al., 2004; Moscovitch et al., 2006; Bakker et al., 2008; Wolk et al., 2011). Different psychiatric and neurological disorders are known to affect hippocampal subfields and MTL cortical subregions differently, selectively, and in a complex progression (Braak & Braak, 1995; Arnold et al., 1995; Simić et al., 1997; de Lanerolle et al., 2003; West et al., 2004; Lucassen et al., 2006; Small et al., 2011). The non-uniformity of MTL involvement in normal brain function and in disease makes in vivo interrogation of the structural and functional properties of hippocampal subfields and parahippocampal subregions highly desirable. Recent advances in MRI technology have made it possible to visualize the hippocampal region with increasing detail, leading a growing number of researchers to attempt to label and quantify small substructures using in vivo MRI (Insausti et al., 1998; Small et al., 2000; Zeineh et al., 2001, 2003; Wang et al., 2003, 2006, 2010; Apostolova et al., 2006; Mueller et al., 2007; Mueller & Weiner, 2009; Van Leemput et al., 2009; Ekstrom et al., 2009; Fischl et al., 2009; Malykhin et al., 2010; Kerchner et al., 2010; Preston et al., 2010; Prudent et al., 2010; Yassa et al., 2010; La Joie et al., 2010, 2013; Hanseeuw et al., 2011; Henry et al., 2011; Bonnici et al., 2012; Wisse et al., 2012; Pluta et al., 2012; Teicher et al., 2012; Libby et al., 2012; Bender et al., 2013; Winterburn et al., 2013; Olsen et al., 2013; Kirov et al., 2013; Augustinack et al., 2013; Palombo et al., 2013; Pereira et al., 2013).

However, the anatomy of the human MTL is complex and variable, and the boundaries between different subfields have been described in the neuroanatomy literature using cytoarchitectonic features that require histological staining and microscopic resolution to visualize (Lorente de Nó, 1934; Rosene & Van Hoesen, 1987; Gloor, 1997; Insausti & Amaral, 2004; Duvernoy, 2005; Amaral & Lavenex, 2007; van Strien et al., 2012). Even at that resolution, neuroanatomical references do not always agree on the definition and boundaries of subfields. Any protocol that attempts to label these substructures in MRI, regardless of resolution, has to employ some combination of image intensity cues, known anatomical landmarks, and geometrical rules to define boundaries between substructures. A substantial number of manual segmentation protocols have been published in the last few years, and up to now, no common set of rules has been adopted by the research community. Indeed, different groups partition the MTL into different subsets of substructures, with different rules used to define each substructure, and different extents of the region within which the substructures are labeled. For example, one protocol may combine all CA subfields into a single label, draw the boundary between CA1 and subiculum at the medial-most extent of the dentate gyrus, and exclude the hippocampal head and tail from the segmentation. Another protocol may group CA3 and the dentate gyrus into one label and draw the CA1/subiculum boundary in a more lateral location, while also labeling the full extent of the hippocampus. Such variability among protocols makes comparisons between the results reported by different research groups difficult.

In this paper, we take the first step towards quantitatively and qualitatively characterizing the differences between the hippocampal subfield and parahippocampal subregion segmentation protocols used in the in vivo imaging community. We do so by having 21 research groups apply their manual segmentation protocols to label the left MTL of the same subject, which makes it possible for the segmentations to be compared on a voxel by voxel basis. Since different groups have used different MRI field strengths and different MRI contrast mechanisms to develop their protocols, the single subject in this study was scanned using three different MRI protocols (T1-weighted 3 T MRI, T2-weighted 3 T MRI, and T2-weighted 7 T MRI), and participating research groups chose the images that best fitted the MRI modality targeted by their respective protocols. We report on the differences in label sets used by the different protocols, provide voxel-wise maps of inter-protocol agreement, and identify substructure boundaries where there is most disagreement between protocols.

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