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Multi-template analysis of human perirhinal cortex in brain MRI: Explicitly accounting for anatomical variability

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ABSTRACT

Rational: The human perirhinal cortex (PRC) plays critical roles in episodic and semantic memory and visual perception. The PRC consists of Brodmann areas 35 and 36 (BA35, BA36). In Alzheimer's disease (AD), BA35 is the first cortical site affected by neurofibrillary tangle pathology, which is closely linked to neural injury in AD. Large anatomical variability, manifested in the form of different cortical folding and branching patterns, makes it difficult to segment the PRC in MRI scans. Pathology studies have found that in ~97% of specimens, the PRC falls into one of three discrete anatomical variants. However, current methods for PRC segmentation and morphometry in MRI are based on single-template approaches, which may not be able to accurately model these discrete variants

Methods: A multi-template analysis pipeline that explicitly accounts for anatomical variability is used to automatically label the PRC and measure its thickness in T2-weighted MRI scans. The pipeline uses multi-atlas segmentation to automatically label medial temporal lobe cortices including entorhinal cortex, PRC and the parahippocampal cortex. Pairwise registration between label maps and clustering based on residual dissimilarity after registration are used to construct separate templates for the anatomical variants of the PRC. An optimal path of deformations linking these templates is used to establish correspondences between all the subjects. Experimental evaluation focuses on the ability of single-template and multi-template analyses to detect differences in the thickness of medial temporal lobe cortices between patients with amnestic mild cognitive impairment (aMCI, n=41) and age-matched controls (n=44).

Results: The proposed technique is able to generate templates that recover the three dominant discrete variants of PRC and establish more meaningful correspondences between subjects than a single-template approach. The largest reduction in thickness associated with aMCI, in absolute terms, was found in left BA35 using both regional and summary thickness measures. Further, statistical maps of regional thickness difference between aMCI and controls revealed different patterns for the three anatomical variants.

Abbreviations: AD, Alzheimer's disease; ASHS, automatic segmentation of hippocampal subfields; AUC, area under the curve; aMCI, amnestic mild cognitive impairment; BA35 and BA36, Brodmann area 35 and 36; CA, cornu ammonis; CS, collateral sulcus; DG, dentate gyrus; DSC, Dice similarity coefficient; ERC, entorhinal cortex; FDR, false discovery rate; FWER, family-wise error rate; GDSC, generalized Dice similarity coefficient; GLM, general linear model; HD, Hausdorff distance; ICV, intracranial volume; MST, minimum spanning tree; MTL, medial temporal lobe; NC, normal control; NFT, neurofibrillary tangle; OTS, occipito-temporal sulcus; PHC, parahippocampal cortex; PPCA, probabilistic principal component analysis; PRC, perirhinal cortex; ROC, receiver operating curve; ST, single template; SUB, subiculum; SR, super-resolution; T1w, T1-weighted; T2w, T2-weighted; UT, unified template; VT, variant template

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1. Introduction

The human perirhinal cortex (PRC) is a cortical region in the anterior medial temporal lobe (MTL) encompassing Brodmann areas 35 and 36 (BA35 and BA36) (Ding and Van Hoesen, 2010; Suzuki and Amaral, 1994a, 1994b). The PRC receives input from the sensory association cortices (Jones and Powell, 1970). Its output is to the entorhinal cortex (ERC) and hippocampal subfields subiculum (SUB) and cornu ammonis 1 (CA1) (Van Hoesen and Pandya, 1975a, 1975b; Van Hoesen, 1982; Van Hoesen et al., 1972, 1975). Serving as a conduit between sensory inputs and MTL substructures associated with memory, the PRC plays an essential role in episodic memory, semantic memory (Murray and Richmond, 2001) and visual perceptual processing systems (Meunier et al., 1993; Murray and Richmond, 2001; Murray et al., 2005; Zola-Morgan et al., 1989).

The PRC is also an important region for observing effects of early Alzheimer's disease (AD) on the brain. The hallmark molecular pathologies of AD are extracellular amyloid plaques and intracellular neurofibrillary tangles (NFT). The latter are more directly linked to neurodegeneration in AD (Bennett et al., 2004; Gómez-Isla et al., 1997). The PRC is the first site in the cortex to be affected by NFT pathology, which appears first in the BA35 (also referred to as the "transentorhinal" region), then spreads out to the ERC, the hippocampus and, eventually, to the rest of the brain (Braak and Braak, 1995). Accurate quantification of the volume and thickness of the PRC (and BA35 in particular) from *in vivo* MRI has the potential to improve early AD diagnosis and disease progression monitoring in early stages, as well as to enhance brain-behavior studies of the MTL.

Despite its critical importance in AD and memory models, the PRC is surprisingly overlooked in the biomedical image analysis literature. This is likely due to challenges in accurately identifying its borders in MRI scans. The PRC and the adjacent MTL regions exhibit a large degree of anatomical variability, i.e. different cortical folding and branching patterns (Insausti et al., 1998), which affects the lateral borders of the PRC, making it difficult to perform accurate segmentation and morphometric analysis. Recently, Ding and Van Hoesen (2010) examined a large number of *ex vivo* human PRC specimens and described three discrete anatomical variants, defined by the depth and the branching pattern of the anterior portion of the collateral sulcus (CS) adjacent to the PRC (named CS_{PRC}, whereas the portion of the CS adjacent to parahippocampal cortex (PHC) is referred to as CS_{PHC}). These three variants accounted for 97% of all cases examined by Ding and Van Hoesen (2010). They are shown in Fig. 1A. Variant 1 has continuous CS_{PRC}; Variant 2 has discontinuous CS_{PRC} with the anterior branch of the CS_{PRC} shorter than the posterior branch; Variant 3 has discontinuous CS_{PRC} with the anterior CS_{PRC} branch longer than the posterior branch. According to Ding and Van Hoesen (2010) and Kivisaari et al. (2013), the borders and extent of BA35 and BA36 depend highly on the depth of CS_{PRC}. Where CS_{PRC} is deep (depth > 1.5 cm), the BA35 occupies a part of the medial bank (the example on the left in Fig. 1B), while for shallow portions of CS_{PRC}, the BA35 encompasses the whole medial bank, the fundus and even the lateral bank of CS_{PRC} (the example on the right in Fig. 1B). Difference in lateral boundaries of BA36 is even larger (Ding and Van Hoesen, 2010; Kivisaari et al., 2013). Since different variants have different depth patterns of CS_{PRC} along the anterior-posterior axis, the definition of the PRC borders differs substantially between them. Failure to account for this variability during segmentation can degrade the accuracy of subsequent morphometric analysis and reduce the utility of the PRC quantitative measures as an imaging biomarker.

Several manual protocols for labeling MTL cortical subregions (PRC, ERC, PHC) in MRI scans have been developed. They target different MRI acquisitions, including approximately $1.0\times1.0\times1.0$ mm^3 T1-weighted (T1w) 1.5 T and 3 T MRI (Insausti et al., 1998; Kivisaari et al., 2013); as well as oblique coronal T2-weighted (T2w) MRI with high in-plane resolution (0.5×0.5 mm^2 or smaller, usually obtained at the cost of increasing slice thickness and partial brain coverage) at 3 T (Duncan et al., 2014; Ekstrom et al., 2009; Libby et al., 2012; Olsen et al., 2009, 2013; Preston et al., 2010; Yushkevich et al., 2015b; Zeineh et al., 2001) and 7 T (Zeineh et al., 2012). Expert human raters can generate segmentations of the PRC that account for anatomical variability. However, labor intensive and time consuming manual segmentation is impractical for large-scale studies. Large neuroimaging studies of memory and dementia can benefit from accurate automatic segmentation of the MTL cortices. To our knowledge, only two automatic analysis pipelines for the PRC have been published so far (Augustinack et al., 2013; Yushkevich et al., 2015b). These methods rely on a single template to model the anatomical variation among the population. Augustinack et al. (2013) use high-resolution postmortem MRI from multiple specimens to build a single probabilistic template of the location of BA35, which is then used for segmentation and thickness measurement in *in vivo* T1w whole brain MRI within the FreeSurfer framework (Fischl, 2012). In our prior work (Yushkevich et al., 2010; Yushkevich et al., 2015b), multi-atlas segmentation with 29 expert-labeled *in vivo* T2w MRI scans is used to label the MTL cortical regions, including BA35 and BA36. A single template is subsequently constructed from the multi-atlas segmentation results and used to establish inter-subject correspondences and analyze regional thickness.

Directly using a single template to model anatomical variability of the PRC, either in the segmentation step (Augustinack et al., 2013) or in the thickness measurement step (Yushkevich et al., 2015b), may introduce errors in the analysis because the borders and extent of BA35 and BA36 depend on the pattern of CS_{PRC}. The goal of the current study is to develop a multi-template thickness analysis approach for the PRC that explicitly accounts for the existence of discrete anatomical variants. This paper extends work presented at the 17th international conference on Medical Image Computing and Computer Assisted Intervention (MICCAI) (Xie et al., 2014). That paper showed that by automatically clustering subjects into three groups based on the pairwise similarity in PRC shape and building separate templates to model the variation within each group, increased the sensitivity of the PRC thickness measures over the single-template approach in a cross-sectional comparison of amnestic mild cognitive impairment (aMCI) to normal aging. However, the lack of pointwise correspondences between templates limited the thickness analysis in Xie et al. (2014) to global summary measures. The current study addresses this limitation and performs regional (pointwise) thickness analysis in the multi-template context by establishing pointwise correspondences between multiple templates. Inter-template correspondences are computed, and a unified template linking the three templates of the PRC variants is derived using a graph-based approach that builds on the ideas from recent work on group-wise image registration using manifold learning (Hamm et al., 2010; Wolz et al., 2010; Wu et al., 2011). Additionally, the current study extends (Xie et al., 2014) by incorporating the super-resolution technique in Manjón et al. (2010a) into the automatic segmentation pipeline, which reduces step artifacts caused by large slice thickness of the T2w MRI scans used for high-resolution MTL imaging.

The proposed multi-template thickness analysis pipeline is evaluated in this paper in the context of aMCI, a group commonly conceptualized as enriched in patients at prodromal stage of AD (Petersen et al., 2009). First, the discriminative ability of the PRC summary thickness measures derived from the current pipeline is compared with volumetric measurements, thickness measures derived from the single-template approach (Yushkevich et al., 2015b) and FreeSurfer (Fischl, 2012). Second, we compare the localized effects of aMCI on the PRC using maps of regional thickness derived from the multi-template and single-template approaches. Third, statistical maps of regional thickness difference between aMCI and controls with templates of the three variants are computed separately and compared.

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