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BIOMARKERS

POSTER PRESENTATION

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NEUROIMAGING

Comparison of histological delineation of the entorhinal, perirhinal, ectorhinal, and parahippocampal cortices by different neuroanatomy laboratories

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Abstract

Background: The medial temporal lobe (MTL) cortex, located adjacent to the hippocampus, is crucial for memory and a hotspot of neurodegenerative processes (e.g., accumulation of tau tangles or TDP-43). Importantly, the MTL cortex comprises several

subregions with distinct functional, cytoarchitectonic, and macro-anatomical features (Fig. 1). *In vivo* imaging studies measuring atrophy or aggregates of pathologies in these subregions rely on various segmentation protocols. Comparability of these imaging studies is limited as segmentation protocols differ, which results from different macro-anatomical parcellations and cytoarchitectonic definitions of MTL subregions. Thus, it must be clarified to which extent definitions of MTL subregions overlap between neuroanatomists, to establish a harmonized MTL magnetic resonance imaging (MRI) segmentation protocol. We give an overview of cytoarchitectonic definitions of MTL cortex subregions provided by four neuroanatomists from independent laboratories.

Method: Four neuroanatomists performed annotations of the entorhinal cortex, Brodmann area (BA) 35, BA36, and the parahippocampal cortex on digital histology images. Nissl-stained series were acquired in three specimens (Fig. 2). Slices (50µm thick) were prepared perpendicular to the anterior commissure-posterior comimssure line spanning the entire longitudinal extent of the MTL cortex. Neuroanatomists annotated MTL cortex subdivisions on digitized (20X resolution) slices with 5mm spacing. Parcellations, terminology, and delineations were compared between neuroanatomists.

Result: Cytoarchitectonic features of the MTL cortex subregions are described in detail. Overall, we observed higher agreement in the definition of the entorhinal cortex and BA35, while definitions of BA36 and the parahippocampal cortex exhibited less overlap between neuroanatomists (Fig. 2). The degree of overlap of cytoarchitectonic definitions was reflected in the neuroanatomists' agreement on the respective delineations. Lower agreement on annotations was observed for transitional zones where gradual changes from one subregion to another occur (Fig. 3). Due to the gradual transition of features from, for example, proisocortex to periallocortex, border placement is difficult to determine according to the neuroanatomists.

Conclusion: The results highlight that definitions and parcellations of the MTL cortex are variable but increase understanding of why these differences arise. This sets a crucial foundation for a harmonized *in vivo* MRI segmentation protocol for cortical MTL subregions and the study of these regions in the context of dementia.

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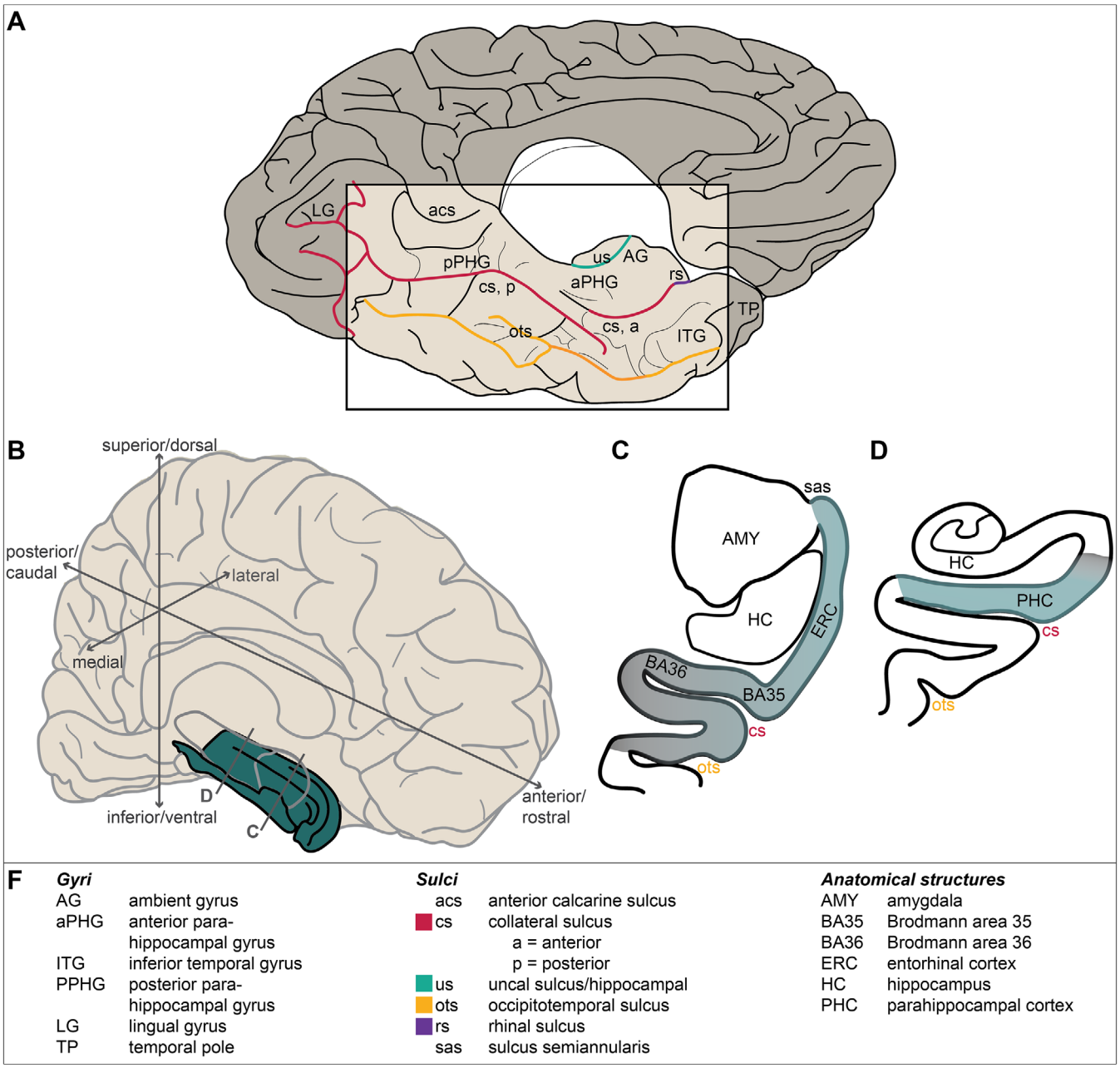

Fig. 1. Overview of the cortical medial temporal lobe structures.
A shows an inferior-medial view on the brain cut at the midline including labels for relevant gyri and sulci. **B** shows a 3D model of the MTL cortex (in dark green) from a medial view and indicates important terminology. **C** shows an anterior coronal section of the MTL cortex including the entorhinal cortex and Brodmann areas 35 and 36 labels. The gradient of color fill indicates certainty of borders (blue: higher agreement, gray: lower agreement). **D** shows a more posterior section of the MTL cortex showing the parahippocampal cortex. **F** explains the used terminology.

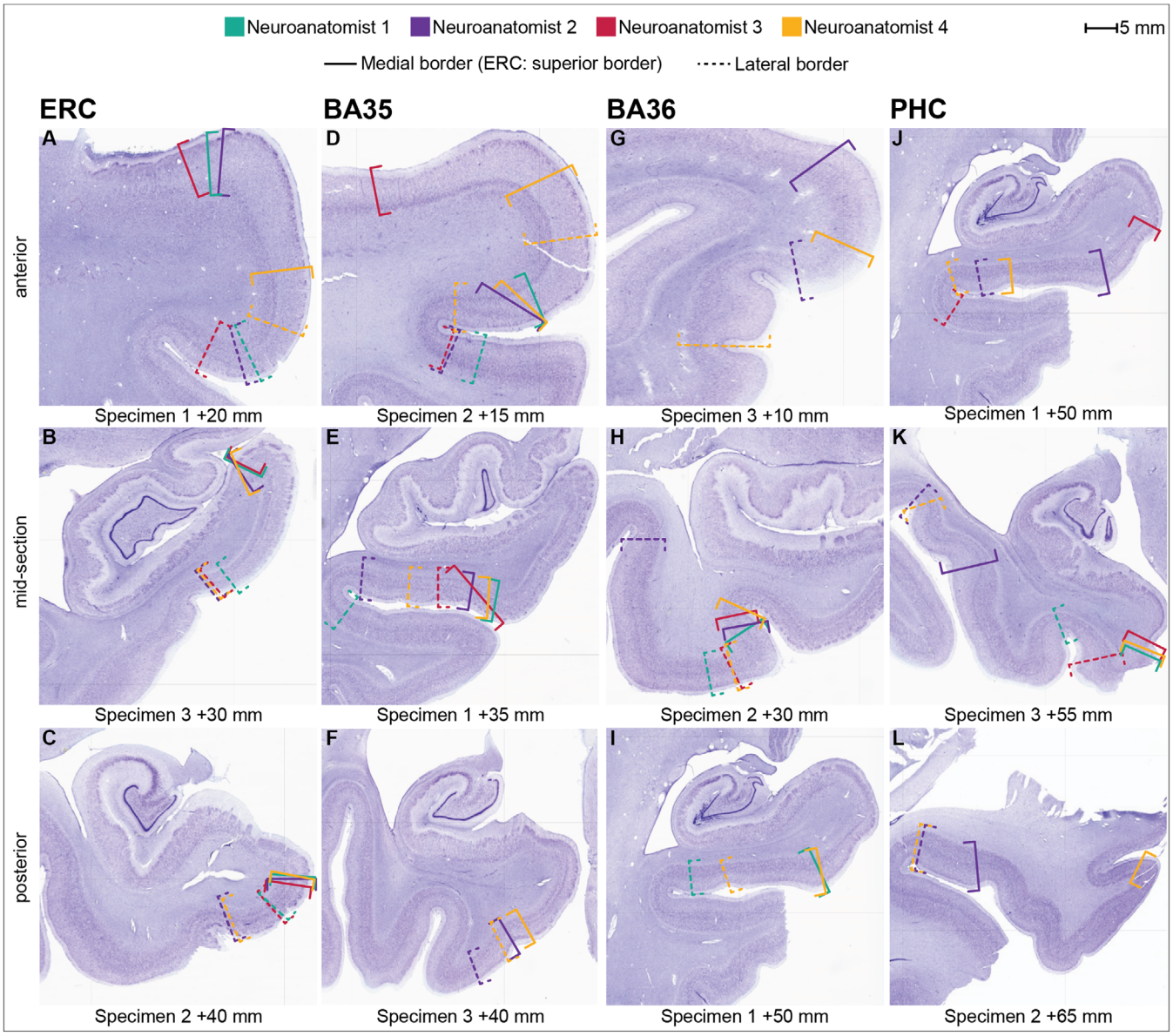

Fig. 2. Annotations of the neuroanatomists for anterior, mid-section, and posterior parts of all four medial temporal lobe cortex subregions show higher agreement in border placement for ERC and lower agreement for PHC. Mid-section annotations for BA35, BA36, and PHC show higher agreement than more anterior or posterior annotations. Millimeters under histology images indicate distance from the temporal pole.
Specimen 1: aged 90; male; right hemisphere; deep, continuous collateral sulcus; low ADNC; A1:B1:C0; Braak II.
Specimen 2: aged 66; female; left hemisphere; deep, discontinuous collateral sulcus; A0:B1:C0.
Specimen 3: aged 83; female; right hemisphere; shallow, discontinuous collateral sulcus; low ADNC & PSP; A1:B0:C0; minimal AD NFTs, 3+ tau (PSP).
Diagnosis and neuropathological staging were derived from contralateral sampling. No TDP-43 pathology in either specimen. A:B:C score: 0=no, 0.5=rare, 1=mild, 2=moderate, 3=severe (Hyman et al., 2012, Alz&Dem).
Abbreviations: A=Amyloid; AD=Alzheimer's disease; ADNC=Alzheimer's disease neuropathologic change; BA=Brodmann area; B=Braak; C=CERAD; ERC=entorhinal cortex; NFT=neurofibrillary tangles (AT8 staining); PHC=parahippocampal cortex; PSP=progressive supranuclear palsy.

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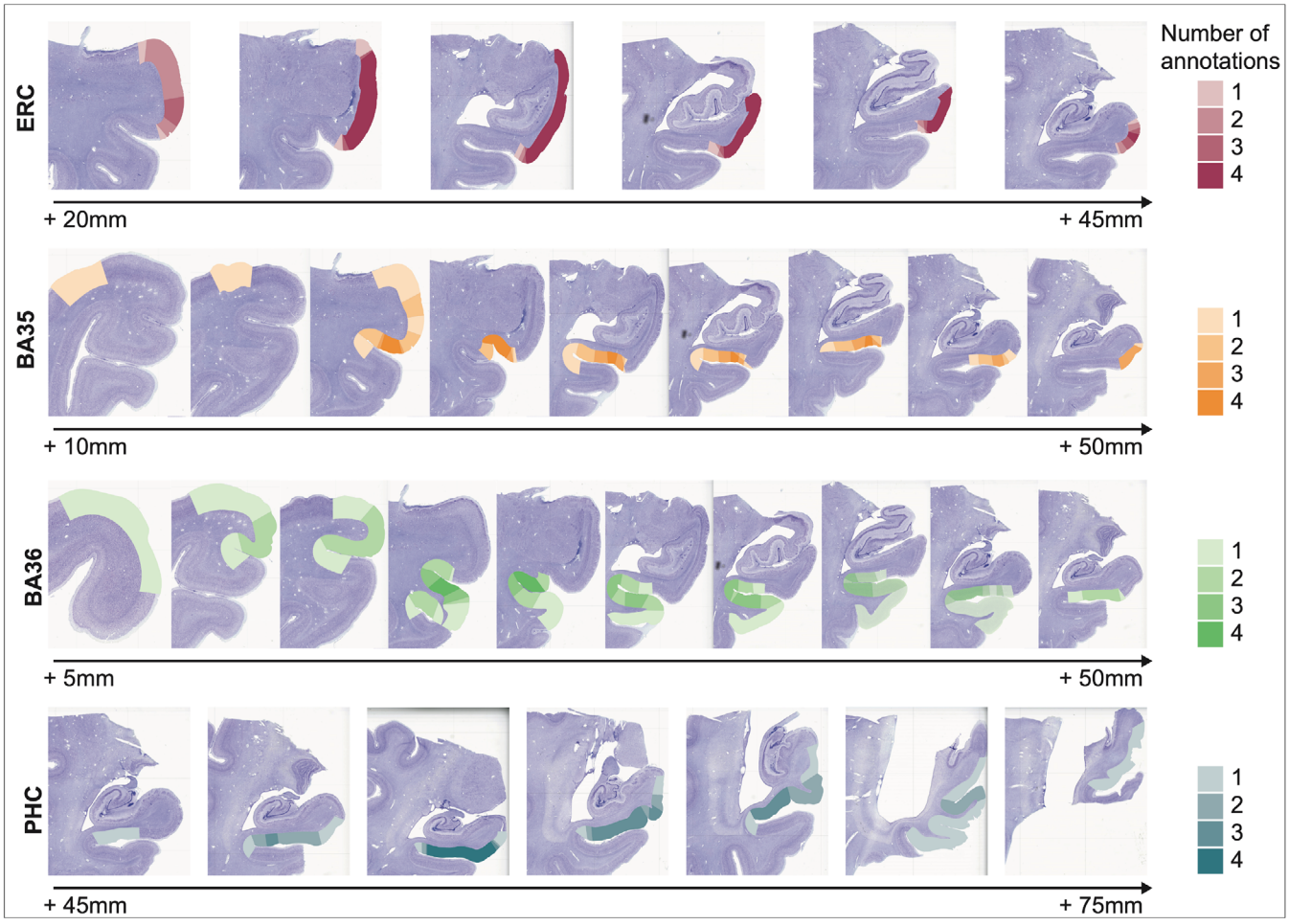

Fig. 3. Overview of border placement of all four parahippocampal subregions in Specimen 1 exemplifying more disagreement on transitional slices than on mid-section slices.
Millimeters below the arrows indicate the distance from the temporal pole.
Abbreviations: BA=Brodmann area; ERC=entorhinal cortex; PHC=parahippocampal cortex.