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POSTER PRESENTATION

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NEUROIMAGING

# A harmonized, histology-based protocol for selection of medial temporal lobe cortical subregion ranges on magnetic resonance imaging

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## Abstract

**Background:** The medial temporal lobe (MTL) has distinct cortical subregions that are differentially vulnerable to pathology and neurodegeneration in diseases such as Alzheimer's disease. However, previous protocols for segmentation of MTL cortical subregions on magnetic resonance imaging (MRI) vary substantially across research groups, and have been informed by different cytoarchitectonic definitions, precluding consistent interpretations. The Hippocampal Subfields Group aims to create a harmonized, histology-based protocol for segmentation of MTL cortical subregions that can reliably be applied to T2-weighted MRI with high in-plane resolution.

**Method:** Nissl-stained sections from the temporal lobes of three human specimens (66-90 years old; 2 female) were annotated by four expert neuroanatomists for the following MTL subregions: entorhinal cortex (ERC), Brodmann's Area 35 (BA35; largely corresponding to "transentorhinal" cortex), Brodmann's Area 36 (BA36), and parahippocampal cortex (PHC). On each histology section, the number of annotations and the spatial overlap of annotations were analyzed to determine the consensus of the anterior to posterior range of each structure. Gross anatomical landmarks, detectable on MRI and reliably corresponding with each range, were then selected to create an MRI ranging protocol. Feasibility of this MRI protocol was tested by two independent raters across four MRI scans (two healthy adults, two older adults), and agreement in range selection was assessed using Cohen's kappa statistic.

**Result:** The proposed MTL ranging protocol is shown in **Fig. 1**, and corresponding histology data substantiating the protocol is shown in **Fig. 2.** MRI-visible gross anatomical landmarks that reliably corresponded with the anterior or posterior range of each subregion on histology included the anterior-most appearance of the collateral sulcus (**Fig. 3A**), hippocampal head (**Fig. 3B**), hippocampal body, and anterior calcarine fissure (**Fig. 3C**). This protocol demonstrated high feasibility when applied to MRI, with average kappa values of $0.75 \pm 0.07$, representing a "substantial" level of agreement of range selection.

**Conclusion:** Future directions include obtaining consensus on this protocol from the larger research community through a Delphi procedure, and expansion of the protocol to include slice-by-slice segmentation guidelines for full delineation. This harmonized, histology-based protocol will facilitate critical research on MTL subregion vulnerability and their contributions to memory deficits in Alzheimer's disease.

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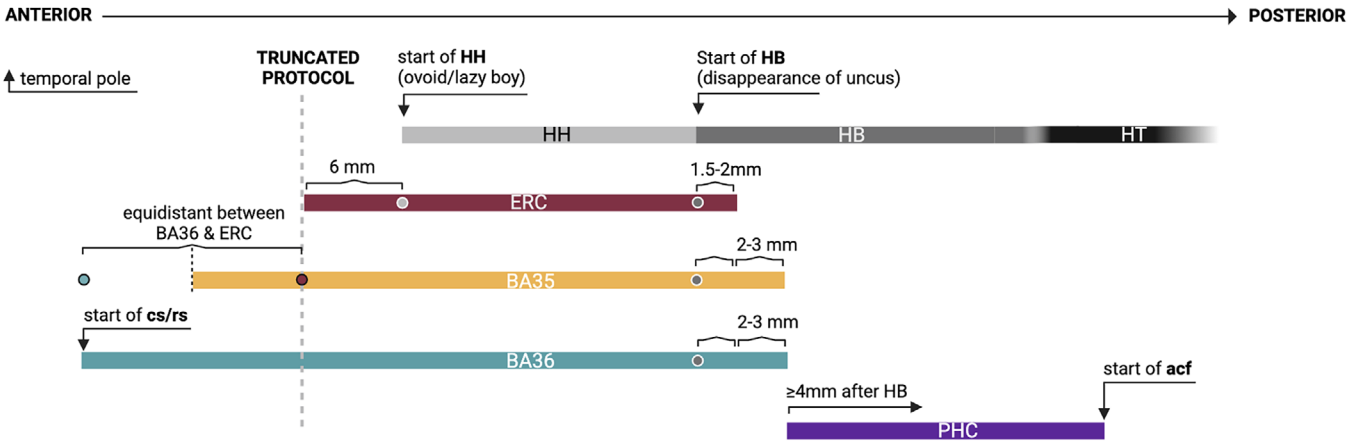


**Figure 1. Ranging protocol of medial temporal lobe cortex subregions.** This protocol was developed to be applied to T2-weighted MRI with high in-plane resolution with full coverage to the temporal pole. The anterior range of Brodmann's Area 36 (BA36; teal) is the most anterior slice in which the collateral sulcus (cs) or rhinal sulcus (rs), if it exists, appears. The anterior range of the entorhinal cortex (ERC; maroon) is 6mm anterior to the anterior appearance of the hippocampal head (HH). The anterior range of Brodmann's Area 35 (BA35; yellow) is equidistant between the anterior range of BA36 and the anterior range of ERC. The posterior range of ERC is 1.5-2mm posterior to the start of the hippocampal body (HB), dependent on slice thickness. The posterior range of both BA36 and BA35 is 4-4.5mm posterior to the HB (dependent on slice thickness). The anterior range of PHC is the first slice posterior to the posterior range of BA35 and BA36. Finally, the posterior range of parahippocampal cortex (PHC; purple) is one slice anterior to the anterior-most appearance of the anterior calcarine fissure (acf). For scans without full field of view coverage of the anterior temporal pole, precluding identification of the anterior appearance of the collateral/rhinal sulcus, the "Truncated Protocol" (indicated by the dotted line) is followed, in which the anterior range of BA35 and BA36 are artificially set to 6mm anterior to the hippocampal head, consistent with the anterior range of ERC.

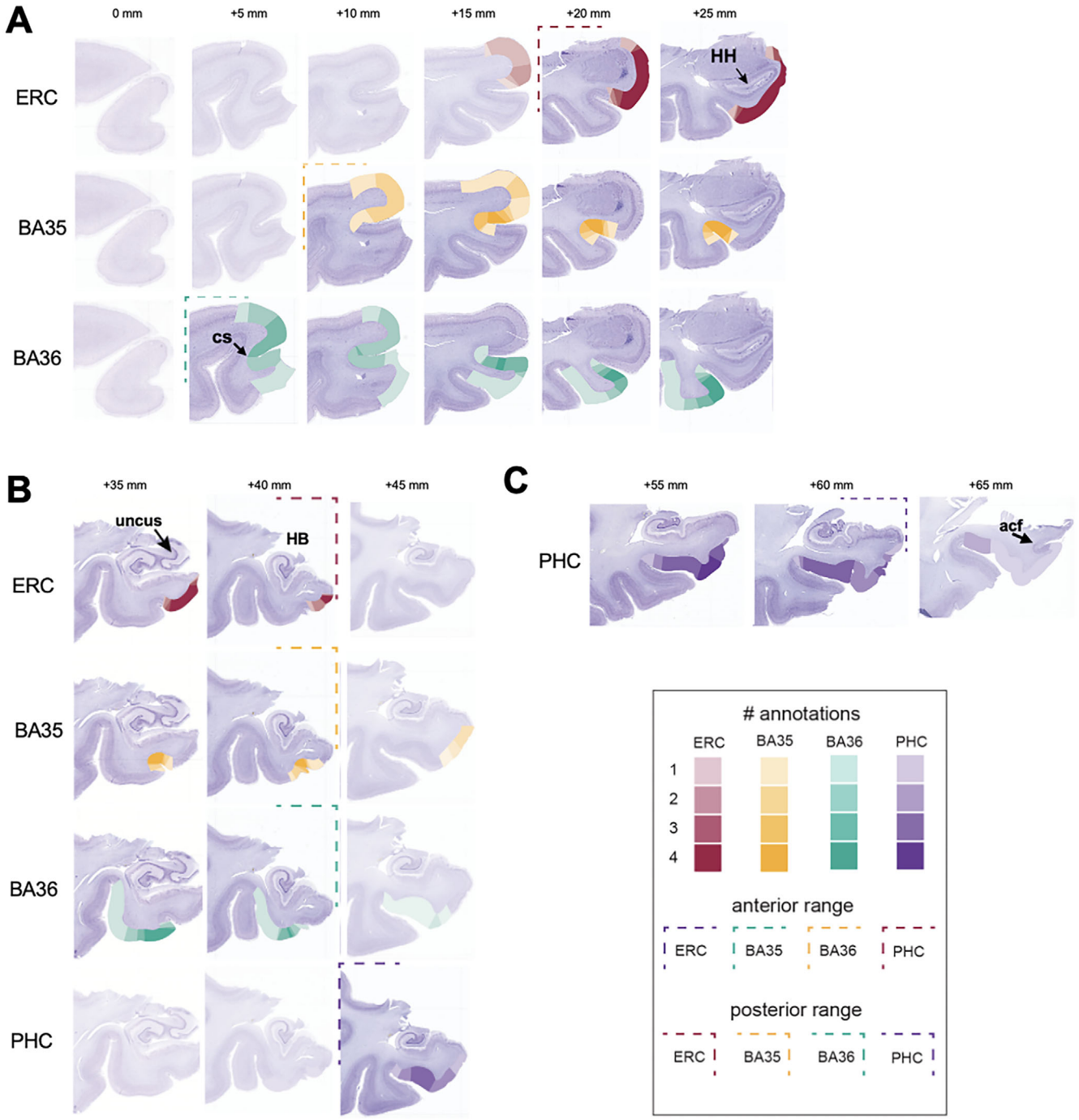


**Figure 2. Histology data supporting the medial temporal lobe cortex ranging protocol.** Images depict nissl-stained histology sections acquired for one specimen. Slices were annotated every 5 mm starting from the temporal pole (0mm). Darker colors indicate more overlap of annotations by neuroanatomists. Dotted corners indicate anterior or posterior range applied to histology. **A** Anterior ranges of entorhinal cortex (ERC; red), Brodmann's Area 35 (BA35; yellow), and Brodmann's Area 36 (BA36; maroon), with corresponding MRI-visible landmarks of collateral sulcus (cs) and the hippocampal head (HH). **B** Transition zone at the appearance of the hippocampal body (HB), corresponding to the posterior range of ERC, BA35, and BA36, and anterior range of the parahippocampal cortex (PHC; purple). **C** Posterior range of the PHC, with the corresponding landmark of the anterior calcarine fissure (acf).

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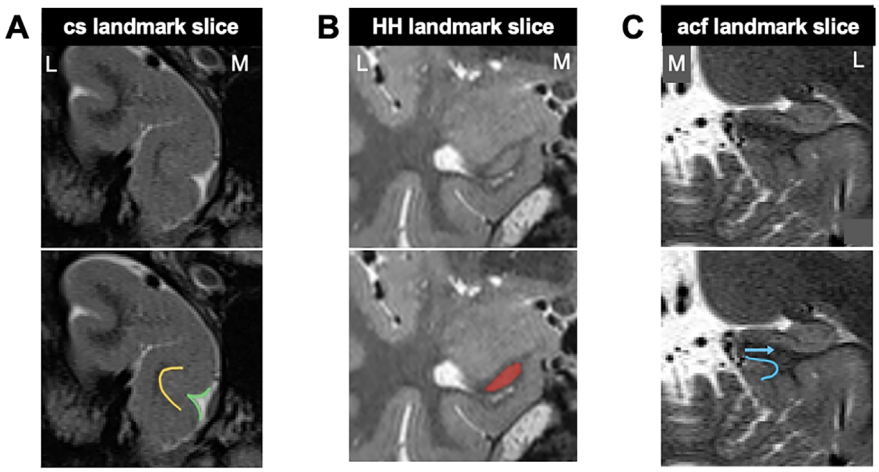


**Figure 3. Key MRI-visible anatomical landmarks for the ranging protocol.** The proposed protocol uses anatomical landmarks visible on MRI that are informed by histology to guide the anterior and posterior ranges of each medial temporal lobe (MTL) subregion. Key landmarks include (**A**) collateral sulcus (cs), which informs the anterior range of Brodmann's Area 36 (BA36); (**B**) hippocampal head (HH), which informs the anterior range of entorhinal cortex (ERC); hippocampal body (unpictured), which informs the posterior range of ERC, BA36, and Brodmann's Area 35 (BA35), and the anterior range of of parahippocampal cortex (PHC); (**C**) anterior calcarine fissure (acf), which informs the posterior range PHC. All images shown are T2-weighted images with high in plane resolution (~0.4mm x 0.4mm). The top panels show the unmarked landmark image, while the bottom panel shows the defining features to guide landmark slice selection. L, lateral; M, medial.