Ultra-high Resolution In-vivo 7.0T Structural Imaging of the Human Endfolial Pathway

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Introduction: The hippocampus is a very important structure in memory formation and retrieval, as well as in various neurological disorders such as Alzheimer's disease, epilepsy and depression. It is composed of many intricate subregions making it difficult to study the anatomical changes that take place during disease. The hippocampal hilus may have unique neuroanatomy in humans compared to monkeys and rodents, with field CA3h greatly enlarged in humans compared to rodents, and a white-matter pathway called the endfolial pathway possibly only present in humans. Anatomically, the endfolial pathway consists of myelinated axons of field CA3h that originate in the hippocampal hilus and travel superomedially, just inferior to the alveus, possibly part of the Schafer system [1]. In this study we have used newly developed 7.0T whole brain imaging that can achieve 0.4mm isotropic images to study *in vivo* the anatomy of the hippocampal hilus.

Methods Eight subjects provided written informed consent in accordance with Stanford's IRB, and were scanned on a GE 7.0 T Discovery MR950 whole-body scanner using a 32-channel receive quadrature transmit coil (Nova Medical). We acquired 8 increments of phase-cycled bSSFP and averaged them together after motion correcting (3D FIESTA, coronal, freq S/I, TR 8.2ms, TE 4.1ms, FA 25deg, NEX 0.5, BW 62kHz, FOV 17cm, 420x420 reconstructed to 512x512, 0.4mm isotropic acquisition, 480 slices, ARC 1.75x1.75, scan time 5:11 per phase cycle, image registration described in [2]). A detailed hippocampal subregional segmentation was performed according to anatomic atlases segmenting the following regions: CA3h, CA3, CA2, CA 1, SRLM (stratum radiatum lacunosum moleculare), alveus, fornix, and subiculum along with its molecular layer. [3]. We also segmented a hypointense structure centrally within the hilus that resembled the endfolial pathway [1]. To validate that this hypointense signal represented the endfolial pathway, we acquired 0.1mm isotropic 8-phase cycle bSSFP on an excised specimen (Fig 2C), and then sectioned and stained the specimen for myelin using an anti-myelin basic protein antibody (SMI 94) (Fig 2D). A structure tensor analysis was calculated on the myelin-stained section (Fig 2E) to show directionality of the underlying fibers.

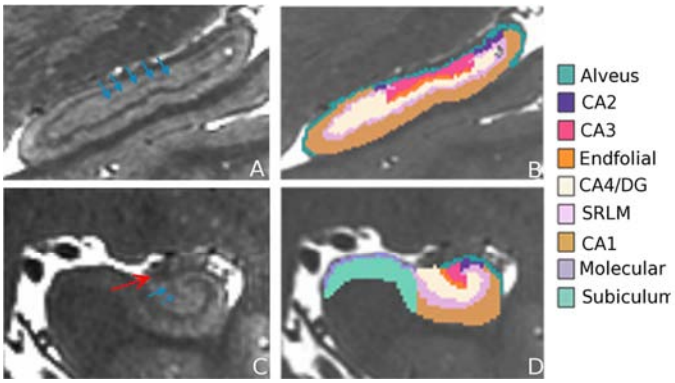

Figure 1: A/C) Sagittal/coronal plane showing hippocampus (blue arrows – endfolial, red – fimbria), B/D) overlayed with ROIs

	L	R
CA2	**29 ± 3**	**24 ± 7**
CA3	**51 ±14**	**63 ± 9**
EF	**21 ± 1**	**19 ± 0.8**
CA3h/DG	**188 ± 22**	**167 ± 24**
SRLM	**481± 63**	**492 ± 90**
CA1	**276 ± 11**	**264 ± 31**

Table 1: Volumes in mm^3

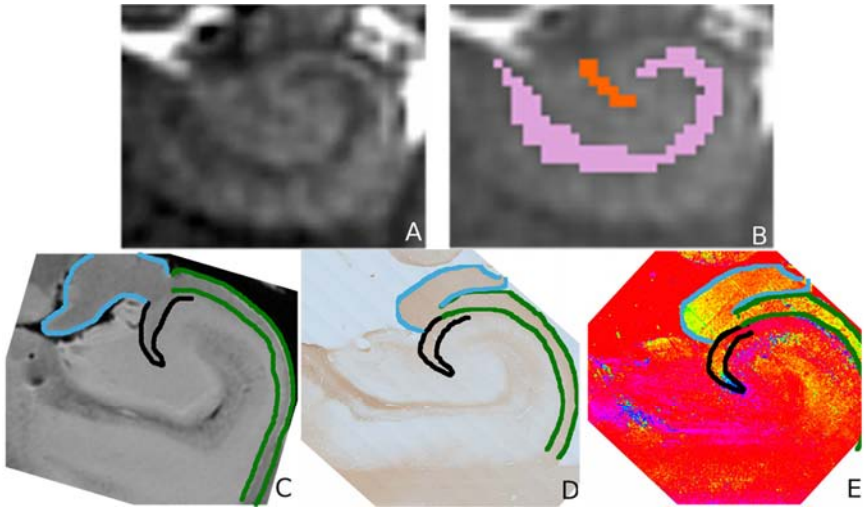

Figure 2: A and B are in vivo bSSFP scans. C. bSSFP scan of an excised hippocampal specimen D. Myelin stained section and E structural tensor map showing the endfolial pathway (black outline), alveus (green outline) and the fimbria (blue outline).

Results: Figure 1 shows the intricate details of hippocampal subregions. In all 8 subjects, we identified a hypointense region medial to the SRLM layer and centrally within the hilus (blue arrows in Fig 1A & C) which was consistent in location with the endfolial pathway described by Lim et al., 1997 [1]. It was lighter in signal intensity than the adjacent fornix on MRI. The volume was about 1/20th that of SRLM, with no left-right differences present. Excised imaging demonstrated that the same structure was similarly hyperintense compared with the fornix and contiguous with the stratum oriens. The myelin stain and structural orientation map (Fig 2D & E) confirms that the endfolial pathway does not join the alveus but traverses along its undersurface [1].

Conclusions: The endfolial pathway is a central pathway in the hippocampus, possibly unique to humans, and poorly described, with unknown relevance in neurodegenerative disorders. It can be consistently visualized within the hippocampal body *in* vivo using high-field MRI. Now that it can be visualized noninvasively, we can study its function and alterations in neurodegeneration.

References: 1. Lim, Chun, et al. Journal of Comparative Neurology 385.3 (1997): 352-371. 2. Zeineh, Michael M., et al. Journal of Investigative Radiology (2014). 3. Zeineh, Michael M., et al. NeuroImage 62.3 (2012): 2065-2082. **Acknowledgements:** GE Healthcare.