

# Feasibility of in-vivo high-resolution MRI of hippocampus substructures at 7 T

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**[Introduction]** Neurodegenerative disorders, such as Alzheimer's disease, affect hippocampal morphology and subregional structures<sup>1</sup> (see the anatomy in **Fig. 1**). Yet, no in-vivo imaging of human hippocampal subregional structures (or substructures) has been successfully achieved, mainly due to the technical limitations of available MR methods to image the small-size and deep location of the hippocampus<sup>2</sup>. With the recent advancement of high-field MR techniques, the gross hippocampal subregions (e.g., cornu ammonis, subiculum) can be imaged at a submillimeter spatial resolution<sup>3,4</sup>. Differentiation of hippocampal substructures (e.g., neuronal cells), however, remains difficult unlike the subcortical layer IV profile in the visual cortex<sup>5,6</sup>, presumably because of the lack of coil sensitivity to the hippocampus location. In this study, we investigated the feasibility/limitation of differentiating hippocampal substructures using in-vivo high-resolution MRI at 7 T with a multi-receiver head coil. The head coil sensitivity to the hippocampus and resolvability of the substructures were systematically examined by comparing them with ex-vivo MRI of a hippocampus specimen using a small single-loop surface coil.

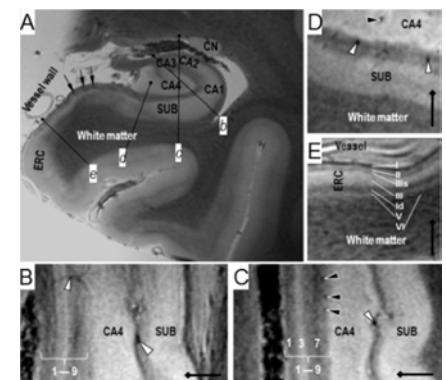
**[Methods and materials]** All scans were performed using a 7 T scanner (Siemens Medical Solutions, Germany). One subject and one brain specimen (immersed in a plastic bag filled with a formalin solution) were used for the hippocampal anatomy study. All procedures followed the guidelines of the approved IRB. A homogenous spherical saline phantom (dia. 150 mm) was used to measure sensitivity of the surface (dia. 40 mm) and the head coil (dia. 210 mm; 1-ch Tx/Rx, 8-ch Rx) under the same experimental conditions. **Ex-vivo MRI of hippocampus:** A high-resolution MR image of the hippocampal anatomy was acquired using a surface coil with 3D GRE; flip angle 15°, TR/TE 400/20 ms, isotropic resolution 100  $\mu\text{m}^3$ , and acquisition time 15 hours<sup>7</sup>. The high-resolution image was used as a reference of hippocampal subregional and substructural anatomy, particularly in the ERC (**Fig. 1**). For the comparison of ex-vivo hippocampal MRI using the two RF coils (e.g., single-loop small coil, head coil), the brain sample was tightly fixed to the head coil and the hippocampus was positioned to the coil center (Left in **Fig. 2**). The surface coil was installed directly under the hippocampus. 3D GRE was applied with the following imaging parameters: flip angle 15°, TR/TE 50/20 ms, isotropic resolution 100  $\mu\text{m}^3$  and acquisition time 1.5 hours (more practical imaging condition toward in-vivo human study). **In-vivo MRI of hippocampus:** The subject's head was fixed by adding form pads between the head and the coil frame. The longitudinal axis and direction of the hippocampus were identified by using the localizer images. High-resolution hippocampal MR images were acquired during free breathing in oblique coronal orientation (perpendicular to the long axis of hippocampus).  $T_2^*$ -weighted multi-slice 2D GRE images were acquired; flip angle 30°, TR/TE 750/17.8 ms, resolution 220  $\times$  220  $\times$  2,000  $\mu\text{m}^3$ , 19 slices, and total acquisition time 13 minutes – TE was empirically chosen showing the best contrast in the hippocampus.

**Data analysis:** 3D data were reconstructed in arbitrary orientation to visualize the hippocampus substructures; cells in CA and layer profiles in ERC. The SNR image map was calculated using the ratio of pixel intensity and the standard deviation of noise in the background. The visibility of hippocampal substructures was visually inspected.

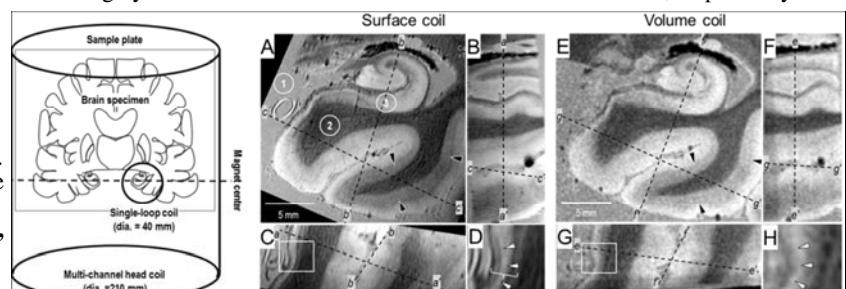
**[Results and conclusions]** In the phantom study, the head coil produced high signals only around the surface of the phantom (> 300), but SNR at the hippocampus location was around 90, which was ~15 less than that of the surface coil. The ex-vivo hippocampal MR image with the head coil was overall noisier than that with the surface coil; relative SNR in white and gray matter were measured as ~13 vs. ~19 and ~28 vs. ~40, respectively (region of ② and ③ in **Fig. 2A**). In CA3 and SUB, the different cells were not clearly discerned with the head coil (compare **Figs. 1C, 2B, 2F**). Particularly, the low SNR of the image with the head coil reduced the substructural resolution in the ERC (**Figs. 2C, D vs. G, H**). Only layer III of the ERC with the head coil could be nearly visualized with higher intensity from other layers (white arrowheads in **Figs. 2D, H**). In the human subject, the white band was clearly visible in the ERC (white arrowheads in **Fig. 3**), which corresponded with the layer III in the ex-vivo hippocampus MR image (**Figs. 2D, H**).

In conclusion, we achieved in-vivo high-resolution MRI of hippocampal subregional morphology using a multi-receiver coil at 7 T. Despite the increase of coil sensitivity to hippocampal depth, the full resolution of structural details of hippocampal subregions was limited. The limit of current in-vivo MRI of human hippocampus was investigated by comparing ex-vivo hippocampal MRI with a highly-sensitive single-loop surface coil. The current in-vivo high-resolution MRI of human hippocampus at 7 T could visualize the layer III profile in ERC.

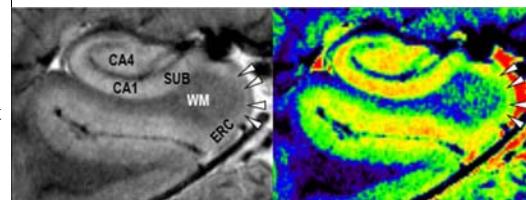
**[Reference]** 1. Small et al., *Nature Reviews, Neurosci*, 2011. 2. van Strien et al., *Nature Reviews, Neurosci*, 2012. 3. Cho et al., *ISMRM*, 2008. 4. Wise et al., *Neuroimage*, 2012. 5. Moon et al., *ISMRM*, 2009. 6. Duyn et al., *PNAS*, 2007. 7. Fischl et al., *Neuroimage*, 2009. [Acknowledgement] This study was supported by NIH grant R21 NS064448-01A1.



**Fig. 1** Ex-vivo high-resolution MRI of hippocampus. A, Axial. B – E, Cut-view images in CA3, CA2, SUB and ERC. Black arrows indicate possible ERC islands. White arrowheads point the vessels and black arrowheads represent possible 'plaques'. Number 1 to 9 represents the layers of different neurons. Abbreviations; CA1 – 3;cornu ammonis, SUB;subiculum, ERC; entorhinal cortex.



**Fig. 2** (Left panel) Experimental setup of ex-vivo hippocampal MRI comparison study with a surface and a head coil. (Right panels) Hippocampus MRI with a surface and a head volume coil. A and E, Coronal view of hippocampus body. Black arrowheads indicate the layer in medial occipitotemporal gyrus. B & F, D & H, View following b – b' & f – f' and c – c' & g – g' in A and E. D and H, Magnified ERC of white rectangular in C and G.



**Fig. 3** ERC substructures in in-vivo 7 T MRI. (Left panel) gray and (Right) color image. White arrowheads indicate the intensity-enhanced layer III of ERC. Note that the ERC layer III profile can be visualized in in-vivo high-resolution MRI at 7 T.