Mapping hippocampal connectivity of the live mouse brain with localized high resolution HARDI

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Target audience: Researchers working on *in vivo* diffusion MRI acquisition, fiber tracking, and brain connectivity

Purpose: While diffusion MRI (dMRI) based tractography have been successfully applied to reconstruct major white matter pathways, its *application* to map local neuronal circuits in the gray matter has not been fully investigated. The complex tissue structures in gray matter structures, e.g. interdigitation of axons and neurons, pose an obstacle to resolving their inner connections using dMRI. In this study, we investigated whether high-resolution HARDI could map local connectivity in the mouse hippocampus, which plays an important role in memory. Our approach combined localized imaging technique and fast imaging sequence to achieve fast HARDI of the mouse hippocampus *in vivo*. Group-averaged tractography results based on the high resolution HARDI data were then compared with tracer based histological data.

Methods: Five 3-month old C57BL/6J mice were imaged on a Bruker horizontal 11.7T system with a quadrature volume transmitter and a planar surface receive-only coil. Localization of the hippocampus was achieved by spatially selective excitation RF pulses, which was detailed in our previous study [1] based on the LCLTA pulses [2]. The designed pulses were combined with a 3D diffusion weighted gradient spin echo (DW-GRASE) sequence. Imaging parameters were: TE/TR = 23/500ms, NEX=2, 60 diffusion directions, b = 2500 s/mm^2, and 0.1 mm isotropic resolution. A localized field of excitation (FOE) was set to include the right hippocampus and its surrounding cortical regions. Scan time was 2.5 hours. Diffusion MRI data were analyzed using MRtrix [3]. Hippocampal tracking results in individual brain were averaged after co-registering the dataset to a template, and the connectivity profile were closely examined with tracer studies from the Allen brain connectivity atlas [4].

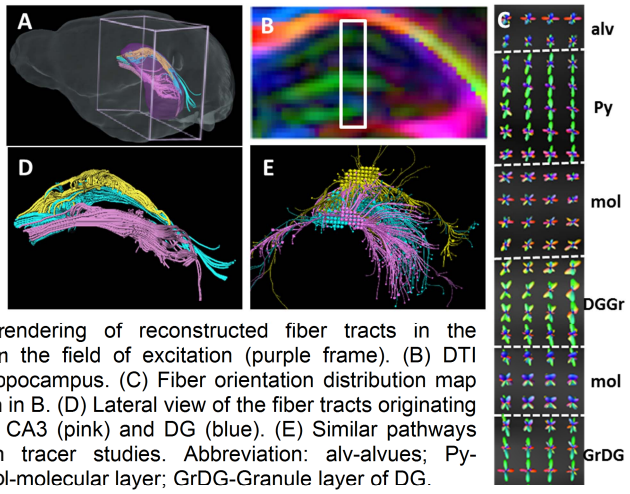

Fig. 1: (A) 3D rendering of reconstructed fiber tracts in the hippocampus within the field of excitation (purple frame). (B) DTI colormap of the hippocampus. (C) Fiber orientation distribution map of a selected region in B. (D) Lateral view of the fiber tracts originating from CA1 (yellow), CA3 (pink) and DG (blue). (E) Similar pathways reconstructed from tracer studies. Abbreviation: alv-alvues; Py-Pyramidal layer; mol-molecular layer; GrDG-Granule layer of DG.

Results: At 0.1 mm isotropic resolution, the layered structures in the hippocampus could be visualized in the direction-encoded colormap (Fig. 1B), and the fiber orientation in these layers was reconstructed using spherical deconvolution (Fig. 1C). For example, Fig. 1C shows the radially orientated fibers in the pyramidal cell layer of the CA1 and the granule cell layer of the dentate gyrus (DG), and fiber crossing in molecular layers of CA1 and DG. Deterministic fiber tracking was performed within the hippocampus, with the tracking seeds selected to be in sites comparable to the tracer injection sites in the Allen brain connectivity atlas. Fig. 1D-E showed the HARDI-based fiber tracts originated from CA1, CA3 and DG resembled the pathways reconstructed from the tracer data. Probabilistic fiber tracking was performed in the same fashion to generate track density maps, which were then averaged (n=5) to produce group average track density maps and compared with the tracer flurorescent density on the stained sections (Fig. 2). Track density maps for seeds in the CA1 and DG were comparable to the tracer-based results, whereas tract density maps for seeds in the CA3 showed some differences in the anterior CA1 region (yellow arrow).

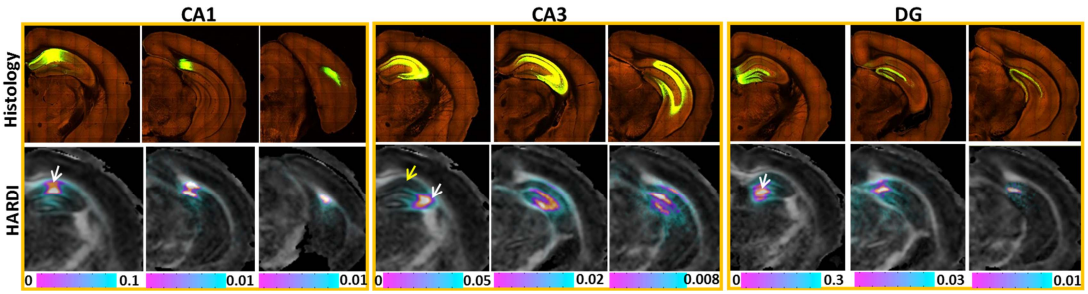

Fig. 2: Group-averaged (n=5) track density maps based on probabilistic fiber tracking, with the tracking seeds in CA1, CA3 and DG (indicated by the white arrows). The results are compared to tracer based data from the Allen brain connectivity atlas.

Discussion and conclusion: Previous post-mortem studies have demonstrated that high-resolution dMRI can reveal microstructural organization in several gray matter regions [5,6]. *In vivo* studies are emerging, e.g. Zeineh et al. [7] showed tractography in the human medial temporal lobe using high-resolution DTI with a 2D DW-EPI sequence. Using the localized 3D high-resolution HARDI approach, we could visualize the hippocampal microstructure *in vivo* in unprecedented detail and reconstruct several hippocampal connections, which could be useful for longitudinal studies of the hippocampal deficits at the network level. Using the tracer-based connectivity data as the gold standard, our results showed the capability of dMRI in resolving gray matter circuitry and its limitations.

References: 1) ISMRM 2013: 707. 2) JMR 1989 82(3): 571-87. 3) Neuroimage 2007 35(4): 1495-72. 4) Nucleic Acids Res. 2013 41(1): 996-1008. 5) Neuroimage 2002 15(4): 892-901. 6) Cereb Cortex 2012 doi:10.1093/cercor/bhs311. 7) Neuroimage 2012 62(3): 2065-82.