High-Resolution Diffusion Tensor Imaging of the Human Hippocampus

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INTRODUCTION

The hippocampus is a critical brain structure for learning and semantic memory formation that is pathologically-injured by many diverse neurological diseases such as epilepsy, ischemia, schizophrenia and Alzheimer's disease [1]. These diseases and normal aging can lead to hippocampal atrophy that is observable by conventional MRI studies, but it is sometimes difficult to distinguish among these processes without histological analysis of specific changes to neurons and axons within particular regions of the hippocampus. Diffusion tensor MRI (DTI) may be capable of detecting these disease-specific cytoarchitectural changes by measuring alterations in diffusivity and/or fractional anisotropy for individual hippocampal lamina. Unfortunately, at current clinical scanner field strengths (1.5 or 3.0-T), it is difficult to resolve individual lamina of the hippocampus with present DTI protocols. To better understand underlying MRI contrast of the healthy and injured hippocampus in present and future higher field clinical scanners, this study characterized DTI contrast in healthy human hippocampi autopsy specimens at 60-µm in-plane resolution at 14.1 T.

METHODS

8-mm coronal segments of hippocampal body were dissected from 5 autopsy specimens that were immersion-fixed in 20% formalin for 1 week and had postmortem intervals to fixation less than 24 hours. Only samples with no clinical or histological evidence for neuropathology were included in this study. Hippocampi were washed 4-5x with PBS (pH 7.4, 300 mOsm/kg) over 24 hrs, then immersed in Fluorinert™ and imaged using a 10-mm birdcage coil inside 600-MHz narrow-bore spectrometer. DTI datasets were obtained with 60x60x300-µm resolution using a multislice pulsed-gradient spin-echo sequence (TR/TE = 1500/34 ms). An image without diffusion-weighting was collected (NEX = 36), then 21 diffusion-weighted images (NEX = 12) were acquired with 415 mT/m diffusion gradients (diffusion time = 17 ms, b = 1250 s/mm^2) applied in directions determined by the tessellations of an icosahedron on a hemisphere. The resulting data were used to determine the apparent diffusion tensor at each voxel [2] from which mean diffusivity (<D>), fractional anisotropy (FA) and fiber direction were calculated [3]. The <D> and FA indices were compared statistically using an ANOVA. Data from this study were also used to create color fiber maps.

RESULTS

DTI at 60-µm in-plane resolution were obtained from 5 hippocampi autopsy specimens (mean age 55.6 ± 6.2 yrs) that were free of neuropathology and short postmortem fixation intervals (21.2 ± 5.7 hrs). The diffusion-weighted images used for this study had signal-to-noise ratios of 65.1 ± 35.9 at b = 0 s/mm^2 and 31.1 ± 13.0 at b = 1250 s/mm^2 [Fig. 1]. S_0, <D>, FA images and color fiber maps demonstrated the laminar anatomy of the hippocampus well [Fig. 2]. Mean diffusivity ranged from 1.21 ± 0.22 x 10^{-4} mm^2/s in the fimbria to 3.48 ± 0.72 x 10^{-4} mm^2/s in granule cells and the FA of the hippocampal lamina varied from 0.163 ± 0.016 in stratum oriens to 0.577 ± 0.121 in the fimbria. Some hippocampal regions could be distinguished from each other based on differences in <D> or FA (ANOVA, $P < 0.001$).

DISCUSSION

To our knowledge, this study provides the highest resolution DTI studies of the human hippocampus to date. DTI of human hippocampi autopsy specimens provides a wealth of microstructural information about specific anatomical lamina of the human hippocampus. Similar to recent DTI studies of rat hippocampi [4], these data in human hippocampi suggest that mean diffusivity may not be homogeneous in the central nervous system. The hippocampal lamina may be a unique exception to this commonly-held hypothesis since this phylogenetically-older structure contains regions almost exclusively populated by densely-packed neuronal cell bodies or acellular neuropil [1]. These unique cytoarchitectural features may also explain intermediate FA values for hippocampal lamina that are atypical for traditional gray and white matter structures. At this resolution the color fiber map also reveals several features not typically observed in clinical MRI of human hippocampus *in vivo*. For example, in stratum radiatum, the principal "fiber" orientation appears predominated by pyramidal neuron apical dendrites, whereas in stratum lacunosum-moleculare and oriens, fiber direction is dominated by axons with orientations perpendicular to the pyramidal neuron dendrites. Similarly the molecular layer fiber orientation is dominated by the dendritic trees of granule cells oriented parallel to the plane of the images. It is encouraging that these projections match anatomical descriptions [1] and provides preliminary evidence that high-resolution DTI of human samples may support future fiber-tracking studies of intrahippocampal pathways that are altered by disease (e.g. mossy fiber sprouting in epilepsy).

REFERENCES

1. Duvernoy Human Hippocampus: Functional Anatomy, Vascularization and Serial Sections with MRI (1998), 2. Basser et al. JMR B:247-254 (1994), 3. Basser NMR Biomed 8:333-344 (1995), 4. Shepherd et al. ISMRM 12:725 (2004) 5. Study funded by NIH RO1 NS36992 and P41 RR16105, 6. Thanks to Dan Plant for technical assistance.

Figure 1

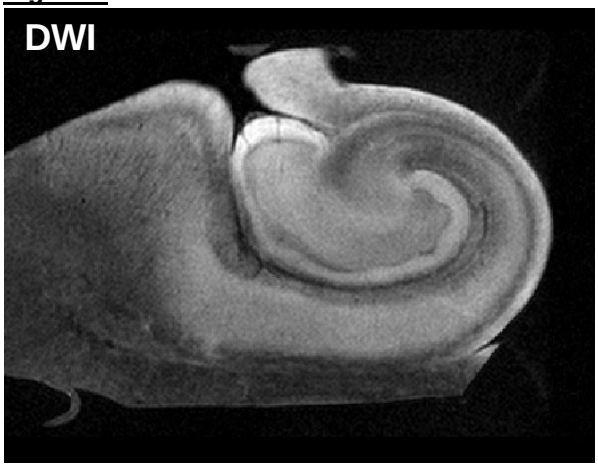

Figure 2