Towards an Early Prognosis of Alzheimer's Disease: Probing the Diffusion Characteristics of the Entorhinal Cortex and Perforant Pathway with Turboprop-DTI

M. Gui[1], A. Solodkin[2], J. A. Mastrianni[2], K. Arfanakis[1]

[1]Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, Illinois, United States, [2]Department of Neurology, University of Chicago, Chicago, Illinois, United States

Introduction: Early diagnosis of Alzheimer's disease (AD) is of great significance, since the neuronal death that accompanies AD is non-reversible and any potential therapies will provide the greatest benefit only when little loss of neurons has occurred. Neurofibrillary tangles (NFT) and neuritic plaques, hallmark lesions of AD, appear first in the entorhinal cortex (EC) and cause degeneration of the perforant pathway (PP) [1]. This results to isolation of the hippocampal formation from the remainder of the cerebral cortex, and leads to impairment of memory and other cognitive functions [1]. Therefore, early AD may be diagnosed through detection of the pathological changes in the EC and PP. Diffusion tensor imaging (DTI) is a powerful tool that can be used to study the microstructural characteristics of brain tissue non-invasively. However, conventional spin-echo echo-planar DTI (SE-EPI-DTI) acquisitions suffer from severe susceptibility-related artifacts in regions near field inhomogeneities, such as those in the inferior medial temporal lobe, near the EC and PP. In contrast, Turboprop-DTI, is based on the gradient and spin-echo (GRASE) sequence, and is relatively immune to susceptibility artifacts [2]. In this study, Turboprop-DTI was used to investigate the diffusion properties of the EC and PP in patients with AD and mild cognitive impairment (MCI). Significant differences in mean diffusivity and diffusion anisotropy were observed in the EC and PP of AD patients when compared to normal controls. No significant differences were detected in the corticospinal tract (CST). The diffusion characteristics in the EC and PP of some of the MCI subjects appeared similar to those of the AD patients and significantly different to those of normal controls. For the rest of the MCI subjects the diffusion properties of the EC and PP appeared normal. It was also shown that conventional volume measurements of the EC/PP and hippocampus were not as sensitive in separating AD patients from normal controls as the DTI characteristics of the EC and PP.

Methods: Nine MCI subjects, nine AD patients and nineteen age-matched normal controls participated in this study. All of the scans were performed on a 3T GE MRI scanner (Waukesha, WI). A T_1-weighted 3D MP-RAGE sequence was used to acquire high-resolution anatomical images of the brain. Turboprop-DTI data were also acquired using the following parameters: TR= 3500ms, FOV= 24cm x 24cm, 256x256 image matrix, 25 contiguous slices perpendicular to the long axis of the hippocampus, 3mm slice thickness, 16 blades, 8 spin-echoes per blade, turbofactor of 5 (thus 40 lines per blade), 12 diffusion directions, b=900s/mm^2, scan time=13mins 4secs. High resolution T_2-weighted and proton-density weighted images were also acquired. Maps of fractional anisotropy (FA) and trace of the diffusion tensor (proportional to mean diffusivity) were produced. An expert brain anatomist manually selected four volumes of interest (VOIs), in the left and right CST and EC/PP, based on the T_1, T_2-weighted and proton density images. The selected VOIs were overlaid onto the FA and trace maps. Measurements from homologous VOIs in the two hemispheres were combined and the mean FA, trace and their standard deviations were calculated for all structures in all subjects. The volumes of the EC/PP and the hippocampus (bilaterally) were measured based on the high-resolution T_1-weighted data, using slices oriented perpendicular to the intercommissural line [3]. The coronal intracranial area at the level of the anterior commissure was measured and used for normalization of the volumetric data [4].

To investigate possible differences between the diffusion properties of normal controls and those of AD or MCI patients, linear regression models were fitted to the data, including age as an additional parameter. Only differences with $p<0.05$ were considered significant. Similar statistical analysis was performed for the volume measurements. Pearson's correlation coefficient was computed between the DTI measurements and the size of the VOIs for all structures.

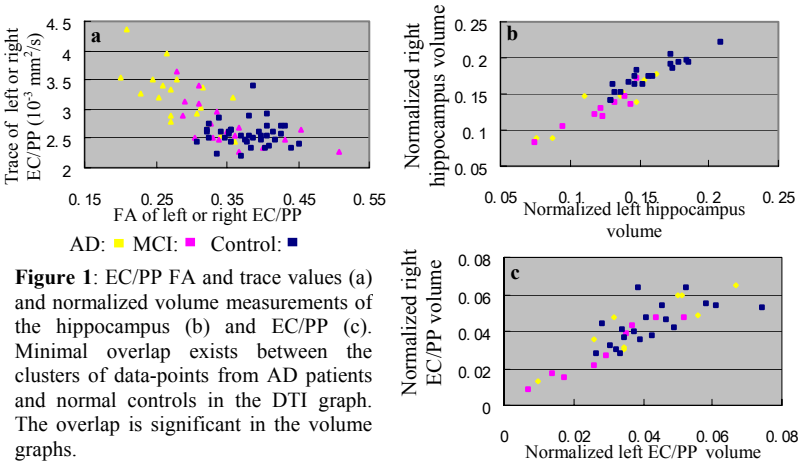

Figure 1: EC/PP FA and trace values (a) and normalized volume measurements of the hippocampus (b) and EC/PP (c). Minimal overlap exists between the clusters of data-points from AD patients and normal controls in the DTI graph. The overlap is significant in the volume graphs.

Results: A significant increase of trace ($p<0.00005$) and decrease of FA ($p<0.00005$) were observed in the EC/PP of AD patients compared to normal controls (Fig.1a). In contrast, no significant difference was detected in the FA or trace of CST between AD patients and normal controls. Also, no significant correlation existed between the sizes of the VOIs and the FA or trace values in any of the structures, suggesting that the DTI measurements were independent of the VOIs' size. The diffusion characteristics of EC/PP in three of the MCI subjects were significantly different from those of normal controls. In Figure 1a, the data-points that correspond to the trace and FA values from the left and right EC/PP of these 3 MCI subjects are located within the cluster of data-points from the AD patients. The remaining 6 MCI subjects had EC/PP diffusion properties that were similar to those of normal controls (Fig.1a). The volume of the hippocampus was significantly lower in the MCI and AD patients than in normal controls (Fig.1b). No significant difference was detected in the volume of EC/PP between normal controls, MCI and AD patients (Fig.1c). In the graph of DTI measurements from the EC/PP, there was minimal overlap between the clusters of data-points from AD patients and normal controls. The overlap was significant in the graphs of hippocampus and EC/PP volumes (Fig.1).

Discussion: The earliest neuropathological changes of AD appear in the EC and PP. In this study, changes in the diffusion characteristics of the EC/PP in patients with AD compared to normal controls were successfully detected using Turboprop-DTI. The FA and trace of EC/PP were more sensitive measures for identifying AD abnormalities than the measurements of hippocampus and EC/PP volumes. Furthermore, the EC/PP diffusion properties for some of the MCI subjects were similar to those of AD patients. This may indicate that these MCI subjects are more probable to develop AD than the remaining MCI subjects. Therefore, we hypothesize that DTI measurements in the EC/PP may allow early diagnosis of AD. To test this hypothesis, longitudinal studies will be performed using conventional volume measurements and DTI.

Reference: [1] Van Hoesen GW, et.al., Ann NY Acad Sci 1994;747:12-35. [2] Pipe JG, ISMRM 2002:p.435. [3] Frisoni GB, et.al., Neurology 1999;52:91-100. [4] Laakso MP, et.al., Neurobiol Aging 1998;19:23-31.