Diffusion tensor imaging detects white matter and gray matter changes in a mouse model for Alzheimer

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Introduction

Alzheimer's Disease (AD) is primarily a disorder of brain metabolism. Disturbances in the amyloid metabolism can lead to the formation of amyloid plaques in the brain with selective vulnerability of cortex and hippocampus. This causes degeneration of neurons but also affects axons. Therefore it is reasonable to anticipate that white matter is also damaged.

Changes in the microstructural organization of the brain are reflected in the molecular motion of tissue water and detectable by MR diffusion measurements. It was our aim to use MR diffusion measurements and more in particular diffusion tensor imaging (DTI) to discern and quantify disturbed brain connectivity and validate this tool as a potential biomarker of AD-associated pathology. We focused on mouse models which were generated according to a recent identification of an Austrian mutation in the amyloid presursor protein (APP_Au). This mouse model exceptionally shows intracellular diffuse plaques, different from the extracellular dense-core plaques.

Materials and Methods

APP_Au transgenic mouse models (n=4) at the age of 20 months were compared with aged matched controls (n=4). All mice were anaesthetized using 5% isoflurane (Forene®) for induction and 0.4%-0.8% for maintenance in a mixture of O2:N2O (3:7) at a flow rate of 600ml/min. Refined monitoring systems allowed us to maintain the physiological parameters within strict boundaries: 37.0±0.2°C for body temperature (Kent, UK), 150±20 for breaths per minute and 3.5±0.5% for the end-tidal CO2 (Capstar-100, Linton Instruments, UK). All MR experiments were performed on a 7T horizontal bore magnet (Bruker) using multi-slice DTI-EPI, a circular surface coil and diffusion sensitizing gradients along 30 directions. On a pixel-by-pixel basis, the fractional anisotropy (FA, value between 0 and 1) was derived using software written in Matlab (MathWorks, Natick, MA, USA). After the generation of the parameter maps, anatomy-based ROI analysis was performed on selected grey matter structures and white matter tracts. The Mann-Whitney test - a non-parametric test - was used to detect significant differences.

Results

Note the strong similarity of anatomic features on the FA maps (figure 1B) compared with the raw EPI image-slice (Figure 1A). Pixels containing high anisotropy are displayed in white. In stead of a magnitude, also a directional character can be ascribed to each pixel on a color map (figure 1C). FA values in the cerebellum and corpus callosum of APP_Au mice were significantly reduced as compared to control values. Not only white matter was affected but also cortical and hippocampal anisotropy was significantly reduced (table 1). The mean diffusion remained unaltered.

Discussion

Reduced FA in white matter tracts in the APP_Au mice reflects loss of neuronal connectivity. This can be due to demyelinisation, lowered axonal density or fiber reorganization. The relative high spatial resolution of the EPI acquisitions allowed to demonstrate the apparently low anisotropy of gray matter and to identify a reduced FA in the cortex and the hippocampus. These changes reflect destruction of the underlying cellular architecture which accompanies the diffuse plaques present in the neocortex and the hippocampus (unpublished data) in this new AD model.

Diffusion tensor visualization is increasingly used as a promising technology for investigating neurological diseases. Among these techniques, fiber tracking is most attractive but careful interpretation is needed, since in general, some degree of anisotropy must exist for the tracking algorithms to work. Most algorithms stop where diffusion anisotropy is apparently strongly reduced. Also fiber crossing and partial volume effects remain critical issues. Therefore, we stick to calculation of FA to infer changes in tissue morphology caused by AD. In this way, gray and white matter structural abnormalities are quantitatively approached.

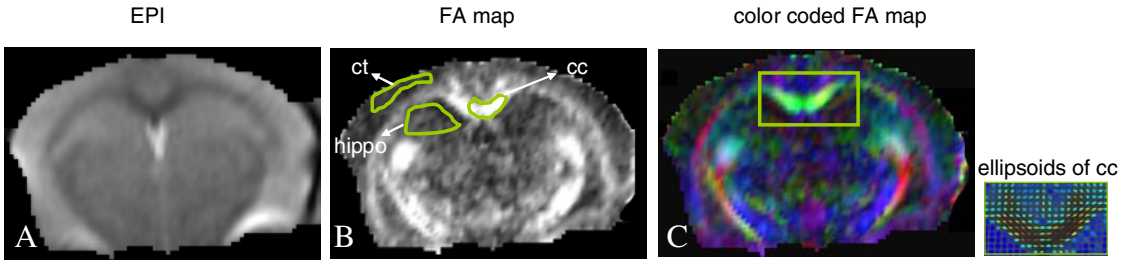

Figure1: (A) raw EPI image (136µm*136µm) with the according FA map (B) with illustration of ROI delineation (ct) cortex, (cc) corpus callosum, (hippo) hipocampus. The colors in C helpt to visualize direction in stead of magnitude. Another representation of the diffusion tensor by means of ellipsoids is shown in the zoomed detail of the cc.Isotropic voxels are represented by a spherical element while linear or planar shaped elements indicate some degree of anisotropy.

FA	controls	APP_Au
cc	0.64 ± 0.03	0.50 ± 0.04
cb	0.34 ± 0.09	0.25 ± 0.07
ct	0.22 ± 0.04	0.18 ± 0.02
hp	0.22 ± 0.04	0.17 ± 0.05

Table 1: Mean FA values are decreased in the APP_Au models for the following regions: (cc) corpus callosum (cb) cerebellum (ct) cortex (hp) hippocampus.