DKI visualizes hippocampal alterations in the chronic mild stress ratmodel

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Background

Depression is a widespread pathology in the modern world. But despite the high prevalence and mortality, little is known about the pathophysiology and aetiology. A significant risk factor however is the occurrence of stressful life events. A well established animal model of depression is the chronic mild stress (CMS) rat model. Repeated exposure to mild and unpredictable stressors has been shown to produce behavioral changes that resemble core features of human major depression and to induce changes of hippocampal neurogenesis and synaptic plasticity. [1,2] In addition, microstructural white matter changes are also associated with depression. We hypothesize that these changes are reflected in the diffusion properties of the tissue water which could then be detectable by diffusion weighted MRI. The recently developed diffusion kurtosis imaging (DKI) complements the diffusion tensor imaging (DTI) to detect small diffusion differences by quantifying the non-Gaussian nature of the diffusion process in biological tissue. Because tissue complexity results in non-Gaussian behavior, DKI can be considered a measure of tissue's microstructure. [3, 4] In this study we focused on changes of neurogenesis and neuroconnectivity in the hippocampus and structural alterations of the major white matter (corpus callosum and capsula externa). The outcome of this study contributes to the development of DKI as a sensitive tool for early detection and accurate evaluation of microstructural and neuroconnectional changes of gray and white matter structures and to the elucidation of the pathogenesis of depression.

Material & Methods

In this study we used a total of 23 rats, including 8 control and 15 CMS rats. [1] All rats were anaesthetized using isoflurane (1.5-2%) and were monitored carefully to maintain constant physiological parameters during measurements. The experiments were conducted on a 9.4T Bruker Biospec (Ettlingen, Germany). The imaging protocol included DKI scans which used 30 gradient directions and 7 b-values (0-2800s/mm²). Images were collected with a multi-slice spin echo 2-shot EPI sequence using following parameters: TR/TE=3000/25ms, δ=5ms, Δ=12ms, acquisition matrix=128*64, FOV=35*17.5mm², slice thickness=1mm, NEX=4. After realignment of the DW images with SPM5 diffusion II toolbox, diffusion kurtosis tensor and diffusion tensor derived parametric maps (MK, RK, AK, KA, MD, RD, AD, FA; see also figure 1) were computed (Matlab). Anatomy-based region of interest analysis of the hippocampus, a grey matter structure, and the corpus callosum and capsula externa, white matter structures - which were delineated on 5 and 7 slices respectively - was performed using AMIRA (Mercury Computer systems, San Diego, USA). Non-parametric statistical analysis testing for differences of diffusion parameters between control and CMS rats was performed using SPSS 14.0 (SPSS Inc. Chicago, USA).

Results

Mean kurtosis ($p<0.05$) and radial kurtosis ($p<0.05$) were significantly decreased in the hippocampus of the CMS rats as compared to the control rats. (Figure 2) Other DTI and DKI derived parameters didn't show significant differences. In the delineated white matter no significant differences were found in any of the DKI and DTI derived parameters.

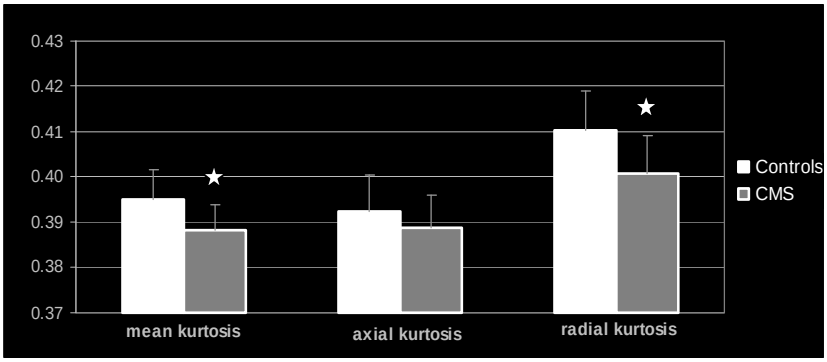

Figure 2. Diagram of the average mean kurtosis, axial kurtosis and radial kurtosis of the delineated hippocampus in control and chronic mild stress (CMS) rats. (☆: $p<0.05$)

Discussion

The decrease of mean and radial kurtosis might reflect the stress-induced CA3 apical dendrite atrophy, dendritic regression in granule and CA1 pyramidal cells and reduction of mossy fiber terminals volume and surface area. Since CMS decreases neurogenesis and possibly induces cell atrophy, the structure of the different hippocampal cell layers might be disrupted. [1, 5] Changes of radial kurtosis, but not axial kurtosis, suggests preservation of the layered structure, however, the coherence of the layers might be degraded. Delineation of other (sub)regions will be completed in the near future and will give additional spatial information to the kurtosis changes. In conclusion, in our study we found significant changes of mean and radial kurtosis in grey matter whereas no DTI derived parameters varied between control and CMS rats, suggesting a higher sensitivity of DKI in comparison to DTI.

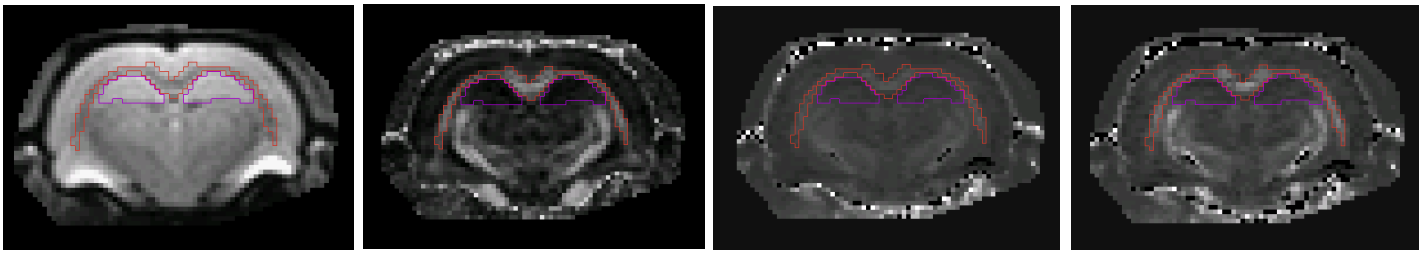

Figure 1. From left to right: original EPI image with the according fractional anisotropy, mean kurtosis and radial kurtosis maps with ROI delineation of the hippocampus and the corpus callosum and capsula externa

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