In Vivo Kurtosis Imaging in Murine Cerebral Ischemia

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Introduction:
Diffusion weighted imaging (DWI) and the calculated apparent diffusion coefficient (D_{app}) are routinely used for the early diagnosis of stroke. Alterations of water mobility due to restrictions are proposed as an explanation for the decrease of D_{app} in ischemic tissue [1]. D_{app} is usually calculated by linear regression, assuming Gaussian diffusion. However, the water diffusion is non Gaussian if restrictions are present. Diffusion kurtosis imaging (DKI) is an extension of conventional DWI and a promising tool to visualize non Gaussian water diffusion, potentially generating a parameter reflecting tissue microstructure, such as cellular compartments and membranes [2,3]. However, only few reports exist to date, that investigate kurtosis in stroke patients [4,5,6] and to our knowledge, no animal experiments have been presented yet. Since animal experiments could in particular enable the controlled evaluation of different therapies, the aim of this study was to establish DKI in murine ischemic brain tissue and to investigate the characteristics of obtained parameters.

Materials and Methods:
Eight male *C57 black/6J* mice (Charles River, Germany) were measured 24 hours after middle cerebral artery occlusion (MCAo), induced as described by Orset et al. [7]. *In vivo* imaging was performed on a 9.4 T Biospec 94/20 USR (Bruker. Germany) small animal system equipped with 740 mT/m gradients and a ^{1}H surface cryogenic probe (Bruker, Germany). DK images were acquired using a respiratory triggered single-shot spin-echo echo-planar imaging (SS-EPI) sequence using the following parameters: Thirty gradient directions and seven b-values (b=0, 500, 1000, 1500, 2000, 2500, 3000 s/mm^2) along each direction, Δ/δ=10/2.5 ms, TR/TE=3000/21.5 ms, FOV=14x11 mm^2, matrix size=100x78, 12 slices with a slice thickness/spacing of 0.45/0.1 mm, bandwidth=300000 Hz, NEX=1, and a total acquisition time of 9 minutes. Additionally anatomical imaging was performed with a coronal T_2-weighted RARE sequence using the same geometry as the SS-EPI: TR/TE=3300/60 ms, echo train length=4, FOV=14x11 mm^2, matrix size=320x256, bandwidth=110000 Hz, NEX=4, and a total acquisition time of 4 minutes. The diffusion coefficient D_{app} and the apparent kurtosis K_{app} were obtained by fitting the signal S(b) as a function of the b-value using the Levenberg-Marquardt algorithm and the following equation: $\ln[S(b)/S(0)]=-b*D_{app}+1/6*b^2*D^2_{app}*K_{app}$. In addition the fractional anisotropy (FA) was calculated using the 2nd rank diffusion tensor model and the b-values=0 and 1000 s/mm^2. Regions of interest (ROIs) were defined in the ipsilateral ischemic lesion and the corresponding contralateral healthy tissue based on the T_2-weighted image. The values of the parameters extracted from these regions were tested for significant differences using a pair-wise Wilcoxen-Rank-Sum test.

Results:
Ischemic regions were identified in all mice brains and the mean lesion volume was 18.7±3.4 mm^3. Fig. 1a-e shows the characteristics of the MR images exemplarily for one mouse brain. The lesion is hyperintense compared to the contralateral region on the T_2-weighted image and on the diffusion weighted b_{3000} image. The kurtosis is increased, whereas the FA- and D_{app}-values are decreased in the ipsilateral ischemic region. The displayed findings on the parametric maps are verified by the mean values of the quantitative analysis, calculated individually for each mouse. Here the apparent diffusion coefficient (D_{app}=0.49±0.09 µm^2/ms vs. 0.75±0.05 µm^2/ms, P=0.0078), and the fractional anisotropy (FA=0.07±0.02 vs. 0.10±0.02, P=0.039) in the ischemic tissue are significantly decreased compared to the healthy contralateral tissue, whereas the kurtosis is significantly increased in the ipsilateral region (K_{app}=1.15±0.10 vs. 0.66±0.09, P=0.0078).

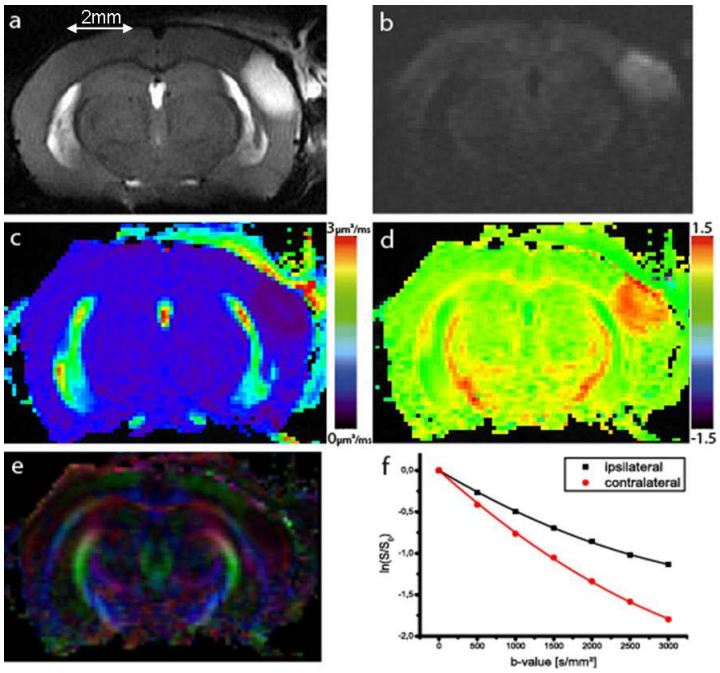

***Fig. 1**: Images of an exemplary mouse with induced MCAo. a: T_2-weighted, b: Diffusion weighted b_{3000} image, c: D_{app}-map, d: K_{app}-map, e: Color coded FA-map (red=left-right, green=anteroposterior, blue=craniocaudal). f: Mean signal as a function of the b-value and corresponding kurtosis fit in the ischemic and the contralateral region.*

Discussion:
Controlled DKI experiments were established in mice with MCAo for the first time. The results are in agreement with the findings of Lätt et al. [4] and Peeters et al. [6] who also reported an increase in K_{app} and a decrease in D_{app} in human acute stroke patients. Since in our animal setting, MRI acquisition can be performed 20 min after MCAo and the total measurement time in our study is about 15 min, the temporal evolution of the DKI parameters in the MCAo mouse can be investigated in detail, from hyper acute to chronic stroke. This will be evaluated in future research and may prove especially valuable when investigating the evolution of the kurtosis under different types of drug therapies.

References:
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