High resolution ex vivo diffusion kurtosis imaging of chronic perilesional brain changes in a rat stroke model

Umesh Rudrapatna[1], Pavel Yanev[1], Karsten Ruscher[2], Annette van der Toorn[1], Tadeusz Wieloch[2], and Rick Dijkhuizen[1]

[1]*Biomedical MR Imaging and Spectroscopy Group, Image Sciences Institute, University Medical Center Utrecht, Utrecht, Netherlands,* [2]*Laboratory for Experimental Brain Research, Department of Clinical Sciences Lund, Lund University, Lund, Sweden*

Introduction: Understanding of plasticity mechanisms that follow ischemic brain injury is important for determining recovery-enhancing treatment strategies for patients in the chronic phase of stroke. For the past few years, DTI has been a popular method for elucidating microstructural characteristics of such mechanisms. Though DTI provides ample information regarding white matter structures, its role in deducing changes in grey matter regions has been limited. Given that perilesional grey matter undergoes significant microstructural changes following stroke[1], a contrast mechanism that can be made sensitive to such changes is highly desirable. Recently, diffusion kurtosis imaging (DKI), which was proposed as an extension to DTI, has been shown to potentially suit this need.[2,3] Its ability to capture the non-Gaussian nature of diffusion has been shown to exhibit enhanced sensitivity to microstructural changes.[4] Besides, the standard DTI parameters can also be obtained with this procedure. Thus, the application of DKI in stroke research is being keenly pursued.[5] Here, we present results from a high-resolution ex-vivo DKI study following chronic experimental stroke in rats. In this study, we aimed to determine if DKI parameters in perilesional grey matter structures exhibit markedly different contrast from DTI parameters 8 weeks post-stroke.

Methods: Male Wistar rats (n=8) were mechanically ventilated with air and 2% isoflurane. Focal cerebral ischemia was induced by 105-min middle cerebral artery occlusion (MCAO) with an intraluminal filament.[6] After a recovery period of 8 weeks, the animals were sacrificed and perfusion-fixed with paraformaldehyde. After overnight post-fixation at 4°C, intact skulls were cold stored in phosphate-buffered saline with sodium azide. DKI acquisitions of the brains inside the intact skull were performed on a 9.4T magnet (Varian Inc.), equipped with a gradient insert capable of operating at 100G/cm, using a 2d-multislice EPI sequence with scan parameters TR:3.4s, TE:26ms, Interleaves:10, FOV:20x30x11mm, Matrix size:100x150x55 (ROxPExSlices) (isotropic resolution of 200µm). Diffusion weighting was performed in 30 optimized directions[7] (δ=3.63ms, Δ=13.67ms). Four b-values (1125, 2250, 3375 and 4500 s/mm^2) were used and 4 b=0 scans were placed at the beginning and in the middle of each session. Seven averages of these 128 (30x4 +8) 3d-datasets were obtained in a period of 8.5hrs.

Analysis: DKI and DTI fits were performed on the reconstructed data.[8,9] The DKI and DTI parameters were visually inspected in each brain and perilesional regions of sensorimotor cortex and striatum and homologous regions in the healthy contralateral hemisphere were carefully delineated by an expert observer. Data from these regions were used in repeated measures ANOVA to test if the DTI and DKI parameters in the homologous regions showed significant differences. Ratio tests[10] were performed on the same data to assess to what extent the various parameters are capable of discriminating the possible tissue changes that had occurred in these areas.

Results: Fig.1 shows single slice post-stroke brain maps of FA and MD (DTI fit) in comparison with a combined contrast involving FA (DKI fit), mean kurtosis (MK) and perpendicular kurtosis, along with the perilesional ROIs chosen for the analysis. Fig. 2a, 2b and 2c show box-plots obtained from ROI analysis of Fractional Anisotropy (FA), Mean Diffusivity (MD) and the three Kurtosis parameters (Means, Parallel and Perpendicular Kurtosis), respectively, along with significance scores from ANOVA. Fig. 3 shows the ipsi- vs. contralateral ratio estimates and their 95% confidence intervals for each of the parameters in the two ROIs. The results clearly demonstrate that the parameters obtained with DKI fits revealed enhanced contrast in perilesional cortex and striatum in comparison to the homologous regions on the contralateral side, which was strongest for mean kurtosis. However, the FA and MD resulting from DTI fits did not highlight significant difference in parameters in the two hemispheres.

Discussion and Conclusion: Our results are in line with previous observations that kurtosis parameters may serve as a more robust marker for grey matter changes as compared to MD. This has been attributed to the relative insensitivity of kurtosis measures to partial volume effects.[11] Although generally accepted principles exist, causes for changes in kurtosis and diffusion parameters at chronic time points after stroke are essentially unknown. If we assume that kurtosis is a characteristic of the diversity of diffusion that occurs intra- and extra-cellularly, and take into account the two component water exchange model[12], we can speculate on the changes we observe in the perilesional cortex and striatum. These areas undergo active remodeling at acute as well as chronic stages after cerebral ischemia. The remodeling processes, such as neuronal sprouting, gliosis, angiogenesis, etc., may significantly increase local tissue heterogeneity, leading to higher values of kurtosis parameters. Our data point out that DKI allows detection of structural plasticity in brains recovering from ischemic injury, which may help to unravel the processes involved in stroke recovery. However, the underlying biological mechanisms of the alteration in tissue kurtosis parameters still need to be elucidated.

References: 1) Schaechter et al, Brain 2006;129:2722-33 2) Jensen et al., Magn Reson Med 2005;53:1432-40 3) Lu et al., NMR Biomed 2006;19:236-47 4) Cheung et al., Neuroimage 2009;45:386-92 5) Jensen et al., NMR Biomed 2011;24:452–7 6) Longa et al., Stroke 1989;20:84–91 7) Cook et al., J Magn Reson Imaging 2007;25:1051-8 8) Tabesh et al., Magn Reson Med 2011;65:823-36 9) FDT toolbox, FSL 10) pairwise CI 0.1-19, R package 11) Hu et al., ISMRM Book of Abstracts 2008 (3325) 12) Kärger et al., Adv Magn Reson 1988;12:1-89

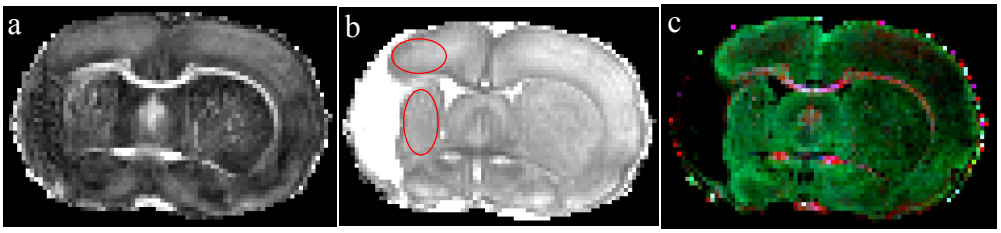


Fig.1. Representative maps of a post-stroke brain slice. a. FA (DTI) b. MD (DTI), c. RGB image of FA (DKI) in red, Mean Kurtosis (Green) and Perpendicular Kurtosis (Blue) from the same slice. The red ellipses on MD show the typical perilesional cortical and striatal ROIs for ROI based analysis.

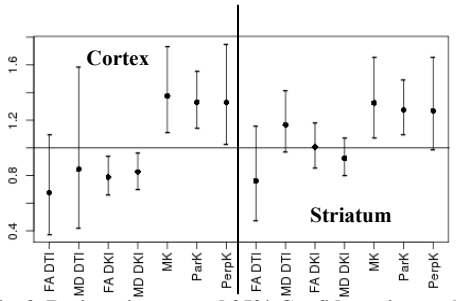
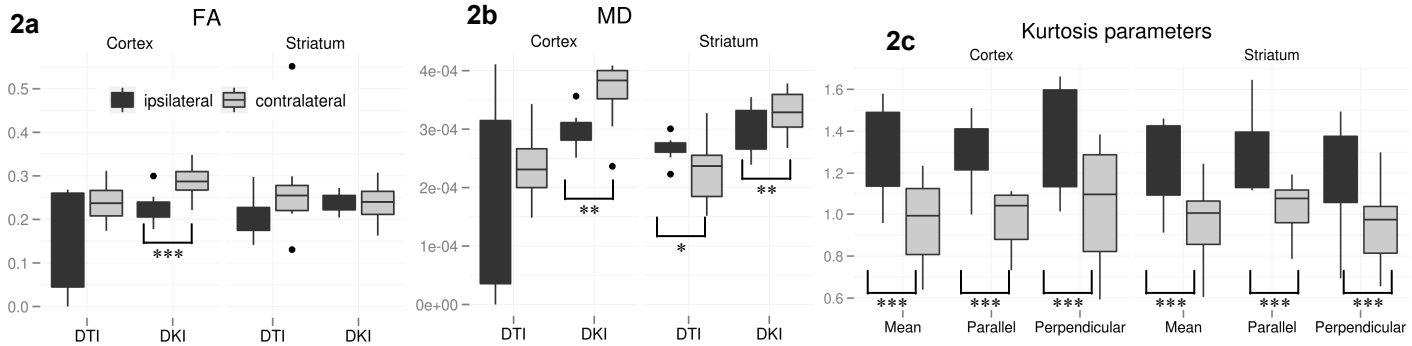


Fig. 3. Ratio estimates and 95% Confidence intervals.



DTI and DKI parameters in perilesional (ipsilateral) cortex and striatum, and homologous regions in contralateral hemisphere. p: 0 * 0.001 ** 0.01* 0.05**