Investigation of the Cytoarchitectural Changes in Ischemic Infarction using Cerebral Microenviroment Modeling (CMM)

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Introduction: Diffusional kurtosis imaging (DKI) is a promising tool for ischemic stroke assessment[1-3]. A prior animal DKI study showed that the diffusional kurtosis of ischemic tissue remains elevated during subacute ischemia even with pseudonormalization of diffusivity[1]. However, the biophysical interpretation of these bulk diffusion MRI (dMRI) metrics remains a challenge. Here, we employ a new analysis technique, termed cerebral microenvironment modeling (CMM), which generalizes our proposed method[4] to include specific microstructural properties of cortical tissue.

Methods: CMM idealizes neural tissue as consisting of two non-exchanging compartments, a non-Gaussian confined- (CC) and Gaussian open- (OC) compartment. The CC represents water confined in neurites (i.e. axons and dendrites) that are idealized as infinitely long, narrow cylinders. The OC represents all other water that yields a detectable signal. The non-Gaussianity of the CC stems from a distribution of neurite orientations. CMM parameters were obtained such that $C \equiv \sum_{j=1}^{N}\left|S_{\exp}(\mathbf{g}_j)/S_{\exp}(0) - S_{CMM}(\mathbf{g}_j)\right|/N$ is minimized. $S_{\exp}$ is the measured dMRI signal, $S_{CMM}(\mathbf{g}_j) = f\exp\left[-\mathbf{g}_j^T\mathbf{D}^{CC}\mathbf{g}_j + \left(\mathbf{g}_j^T\mathbf{D}^{CC}\mathbf{g}_j\right)^2 K_{cc}/6\right] + (1-f)\exp\left[-\mathbf{g}_j^T\mathbf{D}^{OC}\mathbf{g}_j\right]$ with $\mathbf{g}_j$ being diffusion gradient encoding vector, and $\mathbf{D}^{CC}$ and $\mathbf{D}^{OC}$ being the diffusion tensor (DT) of CC and OC, respectively. Specific microstructural properties such as apparent neurite density (f), diffusivity ($D_{CC} = \mathrm{Tr}(\mathbf{D}^{CC})$), diffusional kurtosis (K_{CC}) and fractional anisotropy (FA_{CC}) of the CC can then be estimated.

Experiment and post-processing Focal ischemia in the forelimb region of the sensorimotor cortex (SMC) was induced in 3 groups of Long-Evans rats (3 - 4 month-old) using endothelin-1 as previously established[5]. dMRI experiments were performed on each group of animals at 2 time points: pre- (N=15) and post-surgery (at 2 (N=4), 24 (N=7) and 72 (N=4) hrs after stroke, respectively). All animals were scanned on a 7T Bruker Biospec scanner. Diffusion-weighted images were acquired with 3 b-values (650, 1300, 2000 s/mm^2) along 30 directions using TR/TE=4750/32.5ms, matrix=128x128, resolution=0.23x0.23x1mm^3, and NEX=2. Diffusion and kurtosis tensors were calculated with Diffusional Kurtosis Estimator (DKE)[6], and CMM parameters were computed using in house C and MATLAB programs. Multi-slice regions-of-interest (ROIs) were manually drawn in the infarct (ipsi) and contralateral hemisphere (contra).

Results and Discussion: Fig.1 shows the mean diffusivity (MD), mean kurtosis (MK), D_{CC}, K_{CC}, f and FA_{CC} maps of a representative rat at pre- (left) and 24hr post-surgery (right). **Fig.2** illustrates the longitudinal change in various diffusion parameters of all animals in the infarct (ipsi) and contralateral hemisphere (contra). All post-surgery (pos) measurements were divided by those of pre-surgery (pre) of the corresponding hemisphere. Consistent with a previous study[1], the kurtosis of the infarct remains higher than normal during subacute ischemia, amid pseudonormalization of diffusivity. According to our new CMM, the biophysical mechanism underlying this phenomenon may be the result of an increase in apparent neurite density (f). However it is important to recall that CMM is nominally based on a two-compartment model without water exchange between CC and OC. This approximation may be expected to hold reasonably well for myelinated axons, but less so for unmyelinated axons and dendrites in cortex due to water exchange. The well-known residence time of water in a compartment is $T_{CC} = V/PS$, where P is the neurite plasma membrane permeability, S is the neurite surface area and V is the neurite volume. In other words, the factors that contribute to the increase in f observed in the current study could be three-fold: 1) increase in the actual neurite or cell density, or increase in T_{CC} due to 2) the decrease in the P or 3) increase in the volume to surface ratio (V/S) of the neurites. During acute ischemia (<= 24hrs), increase in f may be due, at least in part, to dendritic beading[7] as the V/S of beaded neurites is considerably larger than that of intact neurites. On the other hand, the increase in f during subacute ischemia (> 24hrs) may be due to decrease in P. In conclusion, we have demonstrated how CMM may be used to investigate potential biophysical mechanisms underlying the change in diffusional kurtosis along the course of ischemia.

References: **1.** Hui et al. *Brain research.* 2012;1451:100-109. **2.** Hui et al. *Stroke* 2012;43(11):2968-2973. **3.** Jensen et al. *NMR Biomed.* 2011;24(5):452-457. **4.** Fieremans et al. *Neuroimage.* 2011;58(1):177-188. **5.** Adkins et al. *Neuroscience.* 2004;128(3):473-486. **6.** Tabesh et al. *Magn Reson Med.* 2011;65(3):823-836. **7.** Murphy et al. *J Neurosci* 2008;28(7):1756-1772.

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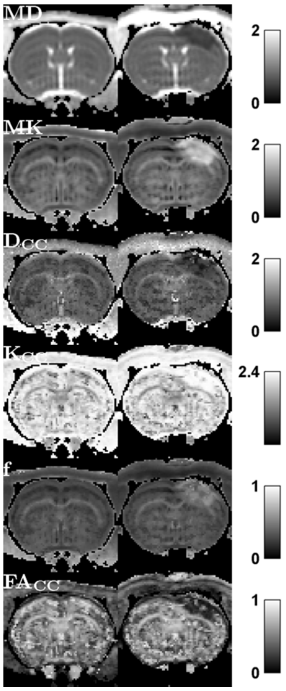

Fig. 1 MD, MK, D_{CC}, K_{CC}, f and FA_{CC} maps of a representative rat at pre- (left) and 24hr post-surgery (right).

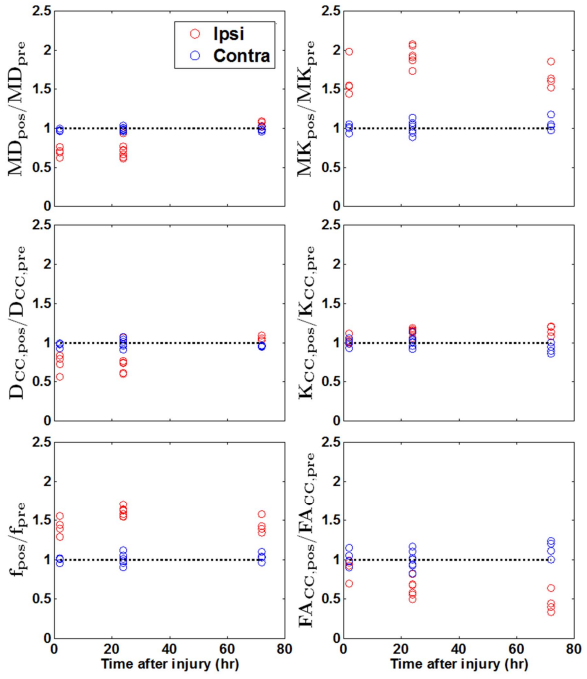

Fig. 2 ROI measurements of various diffusion parameters of all animals in the infarct (ipsi) and contralateral hemisphere (contra). All post-surgery (pos) values were normalized by those of pre-surgery (pre) of the corresponding hemisphere.