Preclinical Study of Stroke using T2relaxometry and Diffusion Weighted Imaging

Dushyant Kumar[1,2], Peter Ludewig[3], Ashish Raj[4], Tim Magnus[3], Jens Fiehler[1], Christoph Heesen[5], Susanne Siemonsen[1,2], and Jan Sedlacik[1]

[1]Neuroradiology, University Medical Center, Hamburg, Hamburg, Germany, [2]Multiple Sclerosis Imaging Center, University Medical Center, Hamburg, Hamburg, Germany, [3]Neurology, University Medical Center, Hamburg, Hamburg, Germany, [4]Radiology, Weill Cornell Medical College, Newyork, New York, United States, [5]Institute for Neuroimmunology and Clinical MS Research, University Medical Center, Hamburg, Hamburg, Germany

Target Audience: Physicist, clinical and pre-clinical stroke researchers, researchers and medical practitioners interested in T2 relaxometry.

Introduction: Stroke is a devastating neurological disease second only to cardiac ischemia as a cause of death and disability worldwide. Traditionally, preclinical stroke research focuses on gray matter (**GM**); however, this may be because most of experiments use rodents, in which white matter (**WM**) constitutes only about 14% of total brain volume; in human, WM is about 50% of brain volume [1]. WM lesions are shown to have prognostic values in predicting stroke occurrence and recurrence in patients [2,3]. Though T2 weighted (**T2W**) images could be used to detect the WM lesion and stroke core, it lacks in specificity regarding the underlying mechanism and it's difficult to predict the individual risk of deterioration. To gain better understanding of stroke lesion progression, we applied quantitative T2 relaxometry (**QT2R**) and diffusion weighted imaging in a common mouse stroke model.

Data and Methods: Six mice underwent transient middle cerebral artery occlusion (tMCAo), which is a well-accepted model of re-canalization after ischemic stroke. All experiments were performed at 7T (Bruker) scanner. All mice underwent DWI, T2W-TSE and QT2R imaging. The QT2R data was acquired using 2D CPMG sequence with the following parameters: axial FOV = 20 mm, matrix size = 128x96, partial phase FOV factor = 0.75, receiver bandwidth = 454 kHz, # slices = 8, slice thickness = 0.5 mm, TR = 2000 ms, # echoes = 32, echo spacing = 5.4 ms, only even echoes were further evaluated as these even echoes are not affected by B1-error for the CPMG sequence, acquisition time = 30 min.

Data Processing: The utility of QT2R in clinical practice is limited by prohibitively long acquisition time and high SNR requirement (~500) of data inversion model [4]. Though conventional regularization [5] in temporal domain improves the stability of the solution, it's insufficient at moderate SNR of (150-200). Inverting QT2R data for animal model is particularly challenging given simultaneous requirement of high SNR and high resolution. The noise robustness of QT2R analysis was improved using multi-voxel spatial regularization (**MVSR**) method as described in [6] which imposes the well founded assumption that tissue specific characteristics vary smoothly in a local neighborhood of 3 x 3 voxels. We have implemented a modified scheme.

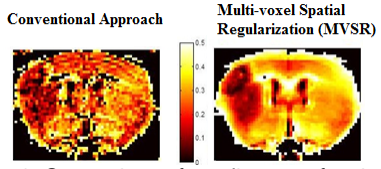

Fig.1. Comparison of myelin water fraction maps obtained with the conventional and multi-voxel spatial regularization algorithms. Notice the improved depiction of anatomic structure and stroke core due to MVSR algorithm.

Assuming the underlying T2 distribution consists of discrete T2 points logarithmically chosen over a range of relevant T2 values, the signal at any echo time TE_k for a single voxel is given by: $\mathbf{y} = \mathbf{Ax} + \boldsymbol{\varepsilon}$, with $\mathbf{A}_{ki} = \exp(-TE_k/T_2(i))$ and $\mathbf{y}$ is echo data in column form and $\mathbf{x}$ is a column vector consisting of all volume fractions α_i for respective T2 values of T2(i), and $\boldsymbol{\varepsilon}$ denotes the noise vector (white Gaussian). The corresponding multiple voxels forward equation can be written as: $\bar{y} = A_{ex}\bar{x} + \bar{\varepsilon}; \bar{x} \geq 0$ where the single-voxel quantities $\mathbf{x}$, $\mathbf{y}$, $\boldsymbol{\varepsilon}$ are collected into multi-voxel column vectors and the diagonal blocks of the block diagonal matrix $\mathbf{A}_{ex}$ is the matrix $\mathbf{A}$. To improve the noise robustness of reconstruction, the prior expectations regarding the spatial smoothness of tissue organizations is being introduced using a spatial regularization approach which minimizes $\left\|A_{ex}\bar{x} - \bar{y}\right\|^2 + M_T\left\|\bar{x}\right\|^2 + \mu_S\left\|D_S\bar{x}\right\|^2 ; x \geq 0 \quad (1)$ where M_T is the diagonal matrix with voxelwise temporal regularization μ_T along its diagonal and μ_S is spatial regularization parameter. The first term is the data fidelity term, while the second term is the conventional temporal regularization term which penalizes large values in inferred T2 distributions. The third term imposes spatial constraints. Matrix D_S is a first difference operator whose norm $\| D_S\bar{x} \|$ penalizes non-smooth solutions. To achieve the minimization as formulated in (1), T2 scale was splitted into three ranges (myelin: 5-50 ms; intra/extra cell. water: 55-120 ms; exp. free water: 125-600 ms) and then 17 points on linear scale were chosen in each range. This choice or range ensured that none of three ranges are over-regularized. The optimum values of temporal regularization constant μ_T are allowed to vary voxelwise and are chosen by L-curve method as described in [6]. The spatial regularization parameter μ_S is assumed to be spatially invariant constant for a particular data and is chosen using a supervised trial and error strategy as described in [6]. The contributions of T2 points between 5 ms- 50 ms are assumed to be due to myelin. The myelin water fraction is the value of myelin contribution normalized with respect to the overall contribution.

Results and Discussion: Myelin water fraction maps were reconstructed using the conventional regularization [5, 6] vs using MVSR approach as described in [6]. The MVSR method resulted in improved depiction of anatomical structures and stroke cores (Fig.1).

In columns 1 and 2 of Fig.2, absolute signal contributions of short T2, i.e. myelin, and long T2, i.e. intra cellular and interstitial water, tissue compartments are plotted rather than their normalized values. The loss of myelin and accompanying edema contribution is evident from corresponding signal contribution of myelin (Fig.2-column 1) and remaining long T2 compartment (Fig.2-column 2), respectively. Furthermore, myelin damage within stroke cores is evident from day-1 and remains unchanged to day-3 (Tab.1). Drops in the apparent diffusion coefficient (**ADC**) (Fig.2-column 3 and Tab.1) in stroke lesions, are most likely attributed to damage in axonal structures, do not exactly match to myelin damage. While ADC-maps on day-1 show small ADC drops in stroke cores, the drops in ADC values on day 3 are very pronounced and match closely to stroke core depicted in T2-W and myelin signal contribution. Based on these observation, we infer that while the myelin loss occurs at the initial stage of the stroke; the loss of axon occurs at much later stage (day 3 for current study).

All mice	Myelin	ADC drop
Day-1	0.63±0.01	0.14± 0.03
Day-3	0.60±0.01	0.24± 0.02

Table 1: Mean difference (%) and standard deviation of myelin signal contribution and ADC values between stroke core and corresponding region in healthy hemisphere.

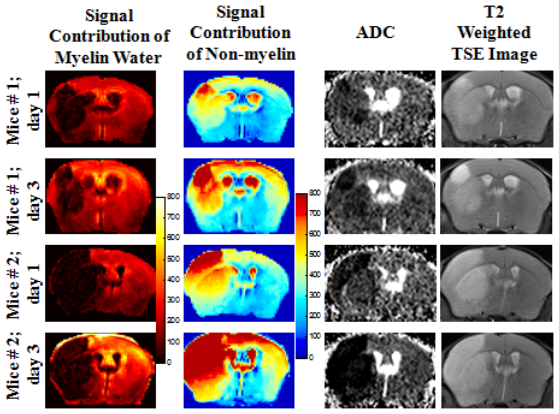

Fig.2. Myelin water contribution (column 1) and edema contribution (column 2) compared against ADC map and T2-W TSE image.

Conclusions: Our preliminary results demonstrate that the feasibility of QT2R analysis at moderate SNR (~200). We also demonstrate using animal model that by combining ADC data to QT2R analysis, it may be possible to gain better understanding of the progression of stroke lesions. Further investigations and the histopathological verification are planned in near future.

References: [1] Zhang et al, Proc. Natl. Acad. Sci. USA, **97,** 2000. [2] Yamauchi et al, J. Neurol. Neurosurg. Psychiatry, **72**, 2002 [3] Goldberg et al, Stroke, **34**, 2003 [4] Graham et al, Magn. Reson. in Med., 35(3), 1996 [5] Whittall et al, J. Magn. Reson. **84**, 1989. [6] Kumar et al, Magn. Reson. in Med., 68(5), 2012.