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## Towards the assessment of myelination using time-dependent diffusion MRI indices.

Abib O. Y. Alimi<sup>1</sup>, Alexandra Petiet<sup>2</sup>, Mathieu Santin<sup>2</sup>, Anne-Charlotte Philippe<sup>2</sup>, Stephane Lehericy<sup>2,3</sup>, Rachid Deriche<sup>1</sup>, and Demian Wassermann<sup>1,4</sup>

<sup>1</sup>Université Côte d'Azur, Inria, Valbonne, France, <sup>2</sup>Institut du Cerveau et de la Moelle épinière – ICM, Centre de NeuroImagerie de Recherche – CENIR, Paris, France, <sup>3</sup>Sorbonne Universités, UPMC Univ Paris 06, Inserm U1127, CNRS UMR 7225, Paris, France, <sup>4</sup>Inria, CEA, Université Paris-Saclay, Paris, France

### Synopsis

We study the sensitivity of time-dependent diffusion MRI indices or  $q\tau$ -indices to demyelination in the mouse brain. For this, we acquire *in vivo* four-dimensional diffusion-weighted images -varying over gradient strength, direction and diffusion time- and estimate the  $q\tau$ -indices from the corpus callosum. First order Taylor approximation of each index gives fitting coefficients  $\alpha$  and  $\beta$  whose variance we investigate. Results indicate that, cuprizone intoxication affects mainly index coefficient  $\beta$  by introducing inequality of variances between the two mice groups, most significantly in the splenium and that MSD increases and RTOP decreases over diffusion time  $\tau$ .

### Introduction

Time-dependent diffusion is increasingly becoming popular among the diffusion MRI (dMRI) community<sup>1,2,3,4</sup>. We propose, for the very first time to our knowledge, to explore the potential of the time-dependent diffusion microstructure indices ( $q\tau$ -indices) as accurate biomarkers in order to understand and efficiently treat myelin-related pathologies, *in vivo* and non invasively. Here, as a preliminary study, we use the cuprizone mouse model<sup>5,6</sup> to investigate the sensitivity of the  $q\tau$ -indices to demyelination in the corpus callosum. We acquire *in vivo* time-varying diffusion-weighted images using the sparse four-dimensional diffusion signal represented in terms of functional basis<sup>4</sup>, taking into consideration both the tree-dimensional  $q$ -space and diffusion time  $\tau$ .

### Methods

In this study, we consider the time-dependent dMRI indices<sup>4</sup>. These microstructure indices correspond to the three-dimensional  $q$ -space scalar indices<sup>7,8</sup> evaluated over diffusion time  $\tau$ . That is, the time-dependent Return-To-Origin Probability (RTOP), Return-To-Axis Probability (RTAP), Return-To-Plane Probability (RTPP) and Mean Squared Displacement (MSD). These are referred to as  $q\tau$ -indices and are estimated using the sparse four-dimensional diffusion signal representation. For illustration, we focus on MSD and RTOP in this preliminary study.

*Index coefficients approximation:* To compare the  $q\tau$ -indices from the corpus callosum regions of the two mice groups, each index is formulated as a function of time  $\tau$ :  $index(\tau)$ . Then, in the logarithmic scale illustrated in Fig. 2, the first order Taylor approximation of  $\log(index(\tau))$  fits a linear function of  $\log \tau$ ,  $\alpha \log \tau + \log \beta$  to  $\log(index(\tau))$ . For each  $q\tau$ -index, the coefficients  $\alpha$  and  $\log \beta$  are estimated by a least square approach then the exponent of the linear line is taken

$$index(\tau) \simeq \exp(\alpha \log \tau + \log \beta + \Omega(\log \tau)) = \beta \tau^\alpha \Omega(\log \tau) \quad (1)$$

Given an index,  $\alpha$  and  $\log \beta$  respectively correspond to the slope and intercept of the linear system that best fits the index in the log scale.

*In vivo acquisitions:* We acquire *in vivo* diffusion images of the brains of controls and cuprizone-treated mice on a 11.7 Tesla Bruker scanner. We use the  $q\tau$ -dMRI acquisition scheme<sup>4</sup> defined in  $q\tau$  space so as to account for both three-dimensional  $q$ -space and diffusion time  $\tau$ , but with drastically less  $q\tau$ -samples using the relaxed probabilistic model<sup>9</sup> for down-sampling purpose. The data consist of  $80 \times 160 \times 5$  voxels of size  $0.1 \times 0.1 \times 0.5$  mm<sup>3</sup> for a total of 515 diffusion-weighted images from each mouse.

*Data preparation:* We use FSL's eddy to correct the data from eddy currents and motion artifacts. We then manually create a mask from the fractional anisotropy (FA) map, as pictured in Fig. 1, to segment the corpus callosum and separate three regions of interest: genu, body and splenium.

### Results and discussion

Fig. 2 indicates that, at short diffusion  $\tau$ , time-dependent  $q\tau$ -indices are approximated by the first order Taylor in the logarithmic scale. To assess cuprizone effects on  $q\tau$ -indices, our analysis focuses on the derived  $\beta$  coefficients. Results concerning the slope  $\alpha$  are discarded since  $\alpha$  does not vary very notably between mice groups. As cuprizone induces myeline changes mainly in the corpus callosum, we test the homogeneity of

variances of  $\beta$  estimated from MSD and RTOP. In Fig. 3, for both  $q\tau$ -indices, difference of variances is significant in the splenium of the corpus callosum. It is the same in the body for MSD but no significant inhomogeneity is observed elsewhere. Fig. 4 supports this trend by showing large variances of  $\beta$  between mice groups, more specifically in the splenium, considering both  $q\tau$ -indices. Overall,  $\beta$  coefficients of indices determined from the splenium are the most impacted as expected because this region is the most readily affected by cuprizone<sup>10</sup>. Moreover, MSD increases and RTOP decreases over time, see Fig. 2. Indeed as diffusion  $\tau$  increases, spins have more time to diffuse, traveling longer distances and reducing their chance to return at the origin<sup>7</sup>.

## Conclusion

This abstract presents our preliminary results of the potential of time-dependent dMRI  $q\tau$ -indices as *in vivo* biomarkers for myeline-related pathologies through the cuprizone mouse model. We focused on the cuprizone effects on the variance of  $\beta$  coefficient derived from time-dependent MSD and RTOP indices. First order Taylor approximation of each  $q\tau$ -index gives fitting coefficients  $\alpha$  and  $\beta$  whose physical or physiological meanings are still unknown, however they can be used to quantify the changes caused by cuprizone-induced demyelination.

## Acknowledgements

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## Figures



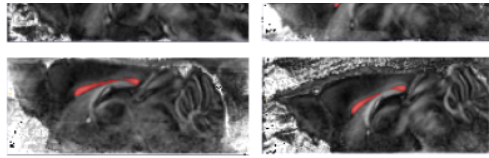


Figure 1. Illustrations of segmentation of the corpus callosum, colored in red from the FA map, of mice brains selected from the control group (top) and the cuprizone-treated group (bottom), respectively.

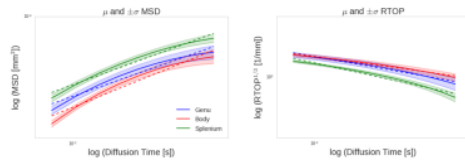


Figure 2. Mean and standard deviation of MSD and RTOP estimated from the genu, the body and the splenium of the corpus callosum. In each region, the qt-index is fitted in the logarithmic scale by a linear function (dashed line) of  $\log(\tau)$  derived from the first order Taylor approximation.

	MSD	RTOP
	W	
Splenium	8.988*	9.81*
Body	16.016*	0.7
Genu	0.006	1.82

\*  $p < 0.05$  Bonferroni corrected  
degrees of freedom :  $k-1=1$ ,  $N-k=17$

Figure 3. Levene's test for equality of variances of estimated  $\beta$  between controls and cuprizone-fed mice. After Bonferroni correction, significant results are highlighted in cyan ( $p < 0.05$ ).

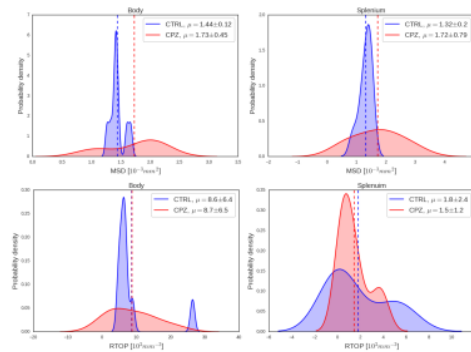


Figure 4. Histogram comparison of variances of approximated  $\beta$  coefficients: inhomogeneities of variances are observed between mice groups. The vertical lines indicate the mean of each distribution.