Towards Optimization of Diffusion Kurtosis Imaging to Study Brain Changes with Age

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Introduction

Diffusion kurtosis imaging (DKI) is an extension of diffusion tensor imaging (DTI) which provides an estimate of the kurtosis tensor in addition to the diffusion tensor [1,2]. Diffusion kurtosis is of interest because it is believed to be an index of tissue microstructural complexity [3].

DKI is more sensitive to noise, motion and other image artefacts than DTI since it requires the estimation of a larger number of parameters.

Our main goal is to optimize the DKI analysis pipeline to provide reliable measures for the large collaborative ageing project CamCAN (Cambridge Centre for Ageing and Neuroscience).

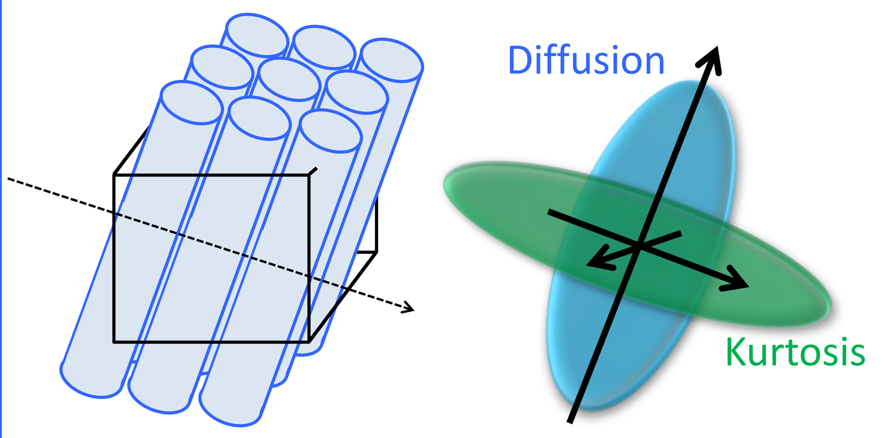

Fig.1 – Example of a white matter voxel (**A**) and the geometrical presentation of Diffusion and Kurtosis Tensors (**B**).

In this study, we will compare different fitting procedures to estimate the quantitative parameters for DKI. Secondly, the optimal value of FWHM for the Gaussian kernel used to reduce the impact of noise and image artefacts on the diffusion weighted (DW) images is investigated.

Methods

After acquisition of several DW images using at least 22 different diffusion gradient directions $\boldsymbol{n}=(n_1, n_2, n_3)$ and at least 3 b values, the elements D_{ij} of the 3x3 diffusion tensor and the elements W_{ijkl} of the 3x3x3x3 Kurtosis tensor can be estimated voxel by voxel using the equation:

$$S(\boldsymbol{n},b) = S_0 \exp\left[-b\sum_{i=1}^{3}\sum_{j=1}^{3} n_i n_j D_{ij} + \frac{1}{6}b^2(MD)^2 \sum_{i=1}^{3}\sum_{j=1}^{3}\sum_{k=1}^{3}\sum_{l=1}^{3} n_i n_j n_k n_l W_{ijkl}\right] \quad \text{(Eq.1)}$$

where S is the DW signal given a gradient direction $\boldsymbol{n}$ and value b, S_0 the voxel intensity if $b = 0$ s/mm^2, and MD the mean diffusivity over all 3D spatial directions.

Fitting procedures

- Eq. 1 can be converted to a linear framework applying a log-transformation, and then, assuming that the variance of each log-transformed DW intensity is the same, D_{ij} and W_{ijkl} can be extracted by using a ordinary linear squares (**OLS**) solution [4].
- The weighted linear squares (**WLS**) solution is also obtained from the linear framework, but now the variance σ of each log-transformed DW intensity is approximated by $\sigma = \sigma_s/S$, where σ_s is the variance of the non-log-transformed DW intensity [5].
- In the non-linear least squares (**NLS**) case, the tensors are estimated directly from Eq. 1 using iterative methods as the Levenberg-Marquardt non-linear regression [5].
- As suggested by Tabesh et al. in 2011 [6], the constrained linear squares (**CLS**) is formulated as a constrained linear least squares, where constraints ensure that values of kurtosis and diffusion are physically and biologically plausible.
- In this study a simple method for estimating the mean diffusion MD and mean kurtosis MK is proposed - the direct linear squares (**DLS**) fit. In this approach instead of estimating the individual elements of the tensors, MD and MK are directly estimated from the equation:

$$S = S_0 exp\left[-b.MD + \tfrac{1}{6}b^2 MD^2 MK\right] \quad \text{(Eq.2)}$$

Data and subjects

The different fitting procedures were tested on:

- DW simulated data from typical values of white matter diffusion and kurtosis tensors [7]. To test the noise effects on each type of fit, the simulated data are corrupted with different levels of Rician noise [5].
- Prefrontal brain data (Fig.2) for two groups of subjects: 14 young adults (mean age 26.2, sd 3.9) and 14 middle aged adults (mean age 53.4, sd 2.0). Data was filtered with a Gaussian kernel to reduce the impact of noise, motion and other artefacts. Different Gaussian kernel sizes are tested to assess the optimal value of FWHM, defined as the one which results on least implausible values of diffusion and kurtosis and is more sensitive to the age differences between the two groups. To analyze separately white and gray matter voxels, the prefrontal regions are segmented using SPM (Statistical Parametric Mapping, University College London, UK)

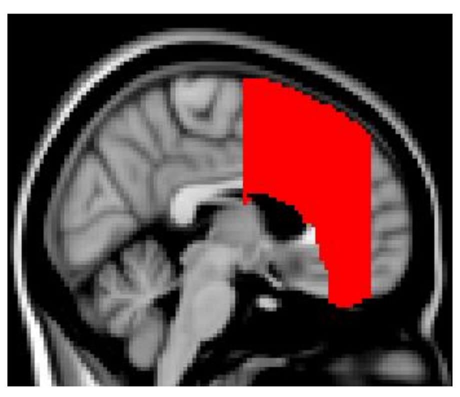

Fig. 2– Prefrontal region used for this study

Both synthetic and real data were based on 63 DW-images (3 for b-value 0, and 30 directions for b-values 1000 and 2000s/mm^2). DW-images were acquired on a 3T Siemens Trio using a Twice Refocused Spin Echo sequence.

Results 1: DKI Fitting

- WLS and NLS (data not shown) have performances similar to the OLS method
- Fig.3 shows that values of kurtosis are more sensitive to noise than values of diffusion. In particular the histograms of MK for OLS and DLS show negative values which are biologically implausible [6].
- CLS is the method that shows values of kurtosis with less variability, however it gives values that are positively biased.
- With the increase of noise level (Fig. 4), OLS fit results in a large number of MK underestimated values, while CLS seems to overestimate them. Despite producing some implausible values, DLS is the method that seems to be less sensitive to increasing noise levels.

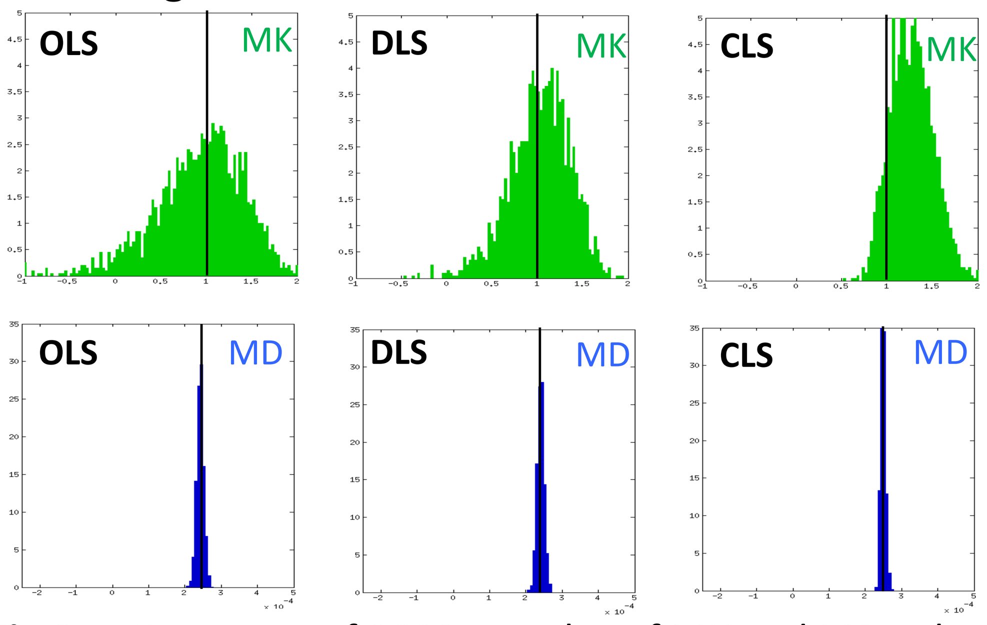

Fig.3 – Histogram of 2000 samples of MK and MD values estimated from OLS, DLS and CLS. The values were extracted from simulated data corrupted by Rician noise with standard deviation of 1. Histogram are plotted in the interval [-a, 2a], where a is the expected values of kurtosis and diffusion which are marked with the back lines on each panel of the Figure.

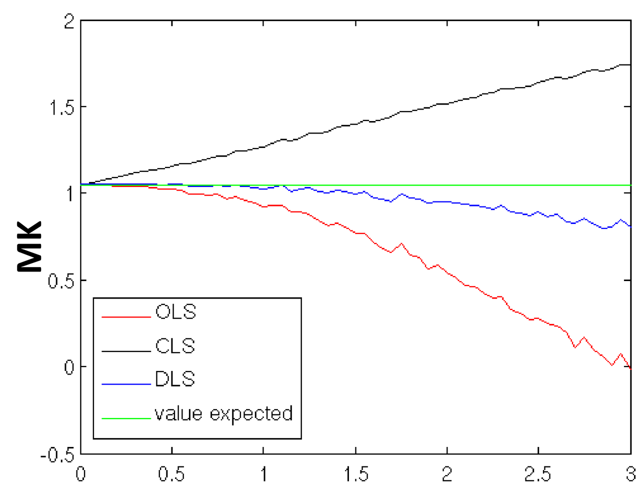

Fig.4 – Mean value of MK vs Rician noise standard deviation. Each value was computed with the mean of 2000 simulated values.

Results 2: Pre-processing

- For all 28 subjects, Fig.5 shows that a Gaussian kernel larger than 2mm successfully eliminates the implausible values of MK.
- Increasing the size of the kernel (Fig. 6) MK values increase which is related to the decrease of negative values produced by OLS.
- By using a kernel of 2.5 mm, MD and MK seem to be sensitive to age differences for both white and gray matter in prefrontal brain regions (Fig. 6).
- The example in Fig.7 shows that accurate data can be obtain by combining a accurate DKI fit with a proper filter.

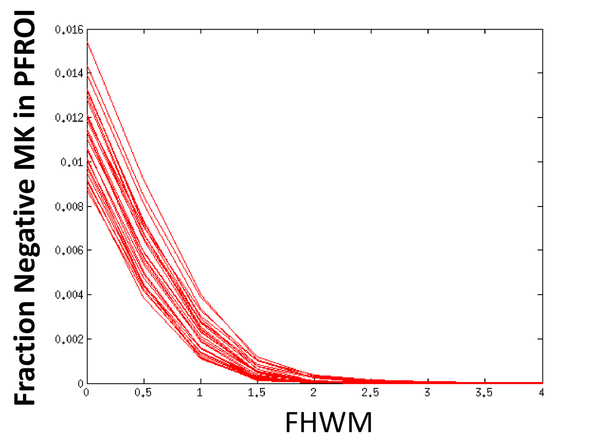

Fig.5 – Fraction of negative values of MK shown in the prefrontal ROI for all 28 subjects vs Gaussian kernel size. MK values were extracted using OLS.

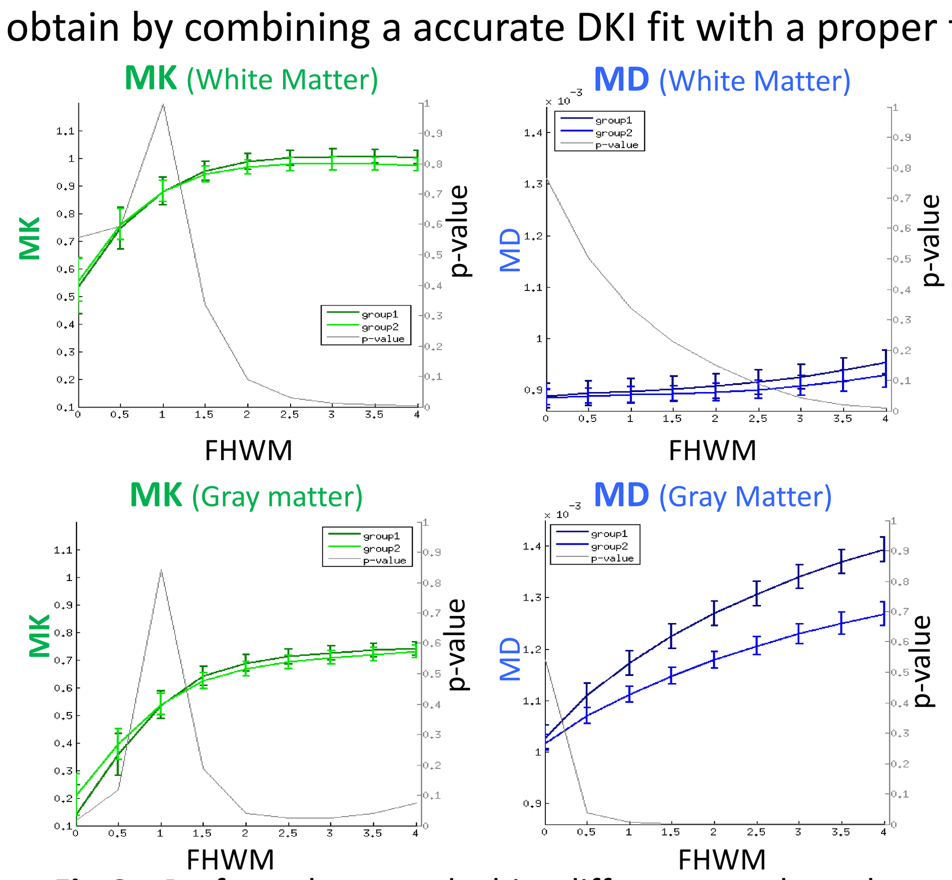

Fig.6 – Prefrontal gray and white differences vs kernel FWHM. MK and MD values are estimated using OLS. p-values of the differences between the two groups are computed using 2-sample t-test.

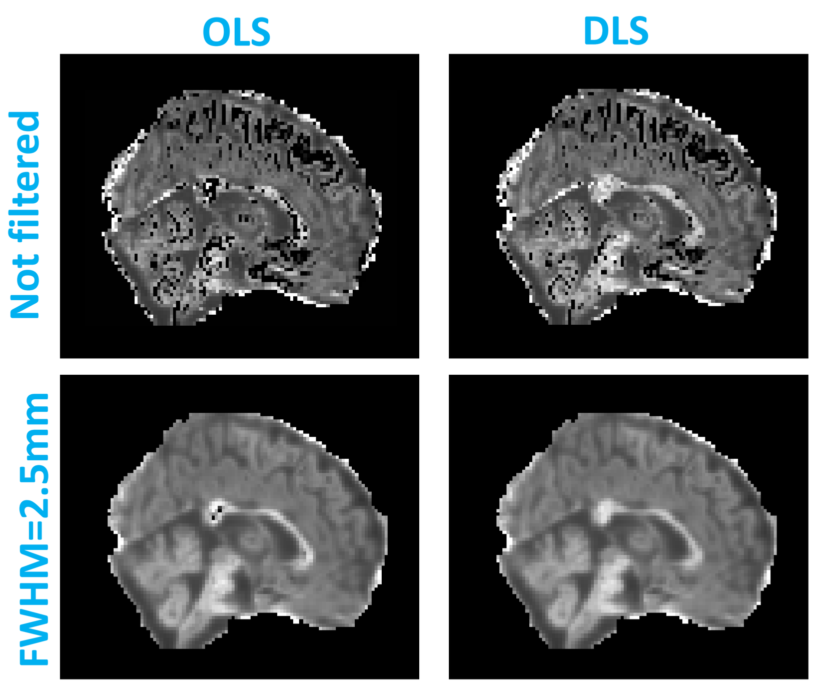

Fig.7- MK maps of the same sagittal slice using different pre-processing and parameter extraction procedures.

Discussion/Conclusion

- We show that DKI parameters are more sensitive to noise than DTI. Noise can have a larger impact in the curve's concavity, which is related to Kurtosis (see the quadratic term in Eq.1 and 2), than to its slop, which is related to diffusion.
- For the analysis performed on simulated data, we observe that even small amounts of noise have dramatic effects on the estimates for all tested methods. For example Fig.1 corresponds to SNR=100 which corresponds to signal quality normally not achieved by modern clinical scanners. Therefore, DKI fitting procedures should not be used without proper pre-processing steps as applying the Gaussian filter with kernel size of 2.5mm.
- In contrast to DTI studies [4,5], our data suggests that OLS, WLS, and NLS have similar accuracy on DKI. In addition, while the constrains of CLS seem to produce biased MK values, DLS is less sensitive to the increase of noise levels.
- In summary, we show the importance of developing robust methods pipelines for DKI: Kurtosis imaging is able to detect changes between the age groups if a proper combination of robust pre-processing and fitting methods are applied.

References

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