CHAPTER 5

CHARACTERIZATION OF WHITE AND GRAY MATTERS IN HEALTHY BRAIN: AN IN-VIVO DIFFUSION KURTOSIS IMAGING STUDY

5.1 Introduction

DW-MRI is used to measure the Brownian motion or diffusion of water molecules in tissues by calculating the diffusion coefficients. Diffusion in tissues is generally anisotropic and it is modelled using a diffusion ellipsoid which is a 3 x 3 tensor. Diffusion MRI using the tensor model is called DTI [2]. DTI derived metrics such as MD, FA, RD and AD are used for finding the average of diffusion coefficients in 3 principal directions, the anisotropic nature of diffusion, diffusion along the fibre and perpendicular to the fibre respectively. The tissue micro-structure and micro-dynamics can be characterized well by knowing these diffusion properties [81–83].

While DTI assumes Gaussian model, in DKI the non-Gaussian nature of diffusion is quantified [3, 13, 48], since in reality, the water diffusion is actually restricted due to the diffusion barriers like cell membranes and organelles [84]. DKI has been shown to be potentially more sensitive than DTI for detecting micro-structural changes with the use of DKI derived metrics such as MK, FAK, RK and AK. Various studies for DKI have been performed in the recent years for characterizing the human brain regions.
and also in evaluating brain disorders such as Multiple Sclerosis, Parkinson’s Disease, Alzheimer Disease and Gliomas [63, 65–67].

In a recent work by Jimmy Latt et al [4], the DTI and DKI parameters are determined for a large number of anatomically defined regions (26 regions) in the healthy brain. The study states that a positive correlation is observed between FA and MK for the WM. Extending the correlation studies in this work, we estimated the values of correlation between FA and MK in WM and GM for healthy human brain. Multiple methods to compute the correlation values such as,

1. Pearson’s correlation coefficient
2. Linear Regression using Least Squares
3. Linear Regression using Block based Weighted Least Squares

have been utilized to illustrate the consistency of the hypothesis. It is observed that the difference in correlation values for WM and GM is substantial.

The chapter is organized as follows. Section II describes the studies in literature that illustrate the utilities of DTI and DKI in human brain studies. Next, in Section III, methods and materials used are presented, which details the data utilized and the analysis performed. Results of the experiments are presented in Section IV which is followed by Discussion in Section V. Finally, in Section VI, the conclusions are presented.

5.2 Materials and Method

5.2.1 Theory

Diffusion parameters MD, FA and MK were studied in this work for healthy brain regions. A brief introduction on the DTI and DKI models are given below. Detailed
explanation of these diffusion models can be referred in 1.

5.2.1.1 DTI

In diffusion weighted MRI, a diffusion weighting is used to magnify the amount of signal attenuation caused by diffusion [17]. The diffusion coefficient of tissue, D, can then be derived by comparing the diffusion weighted signal \( S(b) \) at certain diffusion weighting, \( b \ (s/mm^2) \), to the non-diffusion weighted signal \( S_0 \) using a linear equation:

\[
ln\left[\frac{S(b)}{S(0)}\right] = -bD_{app}
\]  
(Eqn 5.1)

where

\[
D_{app} = Dx^2 = \sum_{i,j=1}^{3} D_{ij}x_ix_j
\]  
(Eqn 5.2)

is ADC along the gradient direction, \( x = (x_1, x_2, x_3) \) which is an unit vector,

\[
b = (\gamma*\delta*g)^2(\Delta - \frac{\delta}{3})
\]  
(Eqn 5.3)

and \( g \) is the gradient strength in \((mT/mm)\), \( \gamma \) is the proton gyromagnetic ratio, \( \delta \) is a pulse duration in seconds, \( \Delta \) is a time interval between the centres of the diffusion sensitizing gradient pulse in seconds, and \( D \) is a symmetric second order tensor with elements \( D_{ij}, i, j = 1, 2, 3 \). By applying gradients in different directions the diffusion coefficient along 3 principal axes can be calculated. One of the DTI parameters, MD which characterizes the average diffusivity is calculated as:

\[
MD = (\lambda_1 + \lambda_2 + \lambda_3)/3
\]  
(Eqn 5.4)
where $\lambda_1$, $\lambda_2$ and $\lambda_3$ are the Eigenvalues resulting from the Eigen decomposition of the diffusion tensor. FA can be calculated using MD:

$$FA = \sqrt{\frac{3[(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2]}{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$$  
(Eqn 5.5)

The range of FA is [0,1] where 0 means completely isotropic diffusion and 1 for highly anisotropic diffusion.

### 5.2.1.2 DKI

In DKI both $(D_{app})$ and $(K_{app})$ along each applied diffusion gradient direction are estimated by fitting the following equation with multiple DW signals acquired using a range of b-values:

$$\ln\left[\frac{S(b)}{S(0)}\right] = -bD_{app} + \left(\frac{1}{6}\right)b^2D_{app}^2K_{app}$$  
(Eqn 5.6)

The mean kurtosis, MK is measured as:

$$MK = \frac{1}{n}\sum_{i=1}^{n}(K_{app})_i$$  
(Eqn 5.7)

where $(K_{app})_i$ is the $(K_{app})$ along $i^{th}$ direction and ‘n’ is the total number of directions in which diffusion measurements are carried out.

### 5.2.2 Data Acquisition

All datasets were acquired using a Philips Achieva 3 Tesla (T) scanner (Philips Medical Systems, Best, The Netherlands). DKI image acquisition was performed using a PGSE sequence with echo-planar imaging (EPI) with the following scanning parameters: TR/TE=4000ms/90ms; Slices = 25; Image Resolution = 2 x 2 x 3.5 mm$^3$; Acqui-
Position Duration = 10 minutes. Diffusion encoding was applied in 15 directions with 5 b-values 0, 400, 800, 1600 and 3200 s/mm\(^2\). The studies were performed on datasets from 9 healthy subjects in the age range of 25-55 years with informed consent. The size of the data acquired is 112 x 112 x 25 x 61 for each of the subject.

### 5.2.3 Parameters Mapping

The apparent diffusion and kurtosis coefficients were calculated to obtain the diffusional tensor and kurtosis tensor by least squares linear fitting using equation (6), which were used to derive FA and MK (equations (5) and (7)) using in-house MATLAB (MathWorks, Natick, MA, USA) programs based on the theory presented in [2,3]. A representative image from the first subject in each of the b-values for a given gradient direction (0.289, -0.699, -0.653) is shown in Figure FC5.1. The FA and MK parametric maps for the 2 subjects of 2 different ages such as 25 and 35 are shown in Figure FC5.2. ROIs were manually drawn for WM and GM in the original images and the corresponding voxels are analysed for FA and MK values. The regional values of obtained FA and MK for a single subject are presented in Table TC5.1 which are consistent with the previous study [4].

### 5.2.4 Data Analysis

The FA and MK values are calculated in the manually marked ROIs for WM and GM. Correlation measures between FA and MK are calculated for WM and GM ROIs separately. The correlation coefficients are computed using the following 3 different ways [85] in order to check the consistency of the values over the entire nine datasets.

1. Pearson’s Correlation Coefficient

2. Linear Least Squares Line Fitting for z-scores transformed data points
3. Line Fitting Using Block based Weighted Least Squares for z-scores transformed data points

5.2.4.1 Pearson’s Correlation Coefficient

Pearson’s Correlation Coefficient, $\rho$ which is a measure of the linear correlation between two variables $X$ and $Y$. In our case, the two variables are FA and MK. $\rho$ is calculated as per the below formula:

$$\rho(FA, MK) = \frac{\text{cov}(FA, MK)}{\sigma_{FA} \ast \sigma_{MK}}$$  \hspace{1cm} (Eqn 5.8)

A value of +1 for $\rho$ indicates maximum positive correlation, 0 is no correlation, and -1 denotes maximum negative correlation.

Figure FC5.1: Representative image from a real dataset for each of the b-values for slice = 10

5.2.4.2 Linear Least Squares Line Fitting

A simple linear regression is performed by using least squares method to find the correlation between FA and MK. The slope of the regression line which best fits the
Figure FC5.2: Representative FA and MK maps for 2 different subjects for a fixed slice (slice = 13); (a) and (c) - FA maps for subjects 2 and 5 respectively; (b) and (d) - MK maps for subjects 2 and 5 respectively

data points in the scatterplot is calculated to understand the correlation pattern between FA and MK. In order to better estimate the value of the correlation coefficient based on the scatterplot, the data points have to be transformed to z-scores [85]. This is because, the Correlation Coefficient, $\rho$ is the slope of the regression line when both the X and Y variables have been converted to z-scores. The larger the size of the correlation coefficient, the steeper the slope. In our analysis, the FA and MK are converted initially to corresponding z-scores, $FA_z$ and $MK_z$. The z-scores transformation is given below,

$$X_{iz} = \frac{\mu_X - X_i}{\sigma_X}$$  \hspace{1cm} (Eqn 5.9)

where $\mu_X$ is the mean of X and $\sigma_X$ is the sample standard deviation. The two significant characteristics are: (1) the correlation coefficient is invariant under a linear transformation of either X and/or Y, and (2) the slope of the regression line when both X and Y have been transformed to z-scores is the correlation coefficient. Using $FA_z$ and $MK_z$, the slope and the corresponding angle in degrees can be calculated by best fitting a line using least squares method.
5.2.4.3 Line Fitting Using Block based Weighted Least Squares

In this method, the slope of the regression line is calculated by assigning weights to each of the data points and the line fitting is done using weighted least squares approach. The steps involved in finding the slope are as below,

1. Calculate z-scores of FA and MK
2. Compute the weights for every voxel of the ROI
3. Perform Line Fitting using weighted least squares method

Computation of Weights for voxels: The weights to be associated with each of the voxel of a ROI is computed as below,

1. Divide the whole area within the scatterplot between $FA_z$ and $MK_z$ into four quadrants, as shown in Figure FC5.3
2. Count the number of voxels belonging to each of the quadrants
3. The weightage accorded to a voxel is proportional to the count of voxels in that particular quadrant where the voxel lies.

Table TC5.1: Computed FA and MK values for WM and GM, based on the procedure given in [2] and [3], to show the consistency of the values with respect to previous work published [4]
5.3 Results

ROIs are manually drawn for WM and GM. These regions were defined on the FA and MK images while using the T2-weighted image for anatomic reference. The correlation values are computed voxelwise for every voxel belonging to WM and GM between FA and MK using the different methods. The total number of voxels picked from FA and MK maps for WM and GM regions are in the range of 100 ± 50 for each of the subject. The computed correlation values are presented in Table TC5.2 and Table TC5.3 for WM and GM respectively, along with the angle of the corresponding regression line in degrees. The scatterplots of WM and GM plotted for $FA_\zeta$ and $MK_\zeta$ are shown in Figures FC5.4 and FC5.5 respectively.
Table TC5.2: Correlation measures between FA and MK for WM

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Pearson’s Correlation Coefficient</th>
<th>Least Squares Line Fitting</th>
<th>Block based Weighted Least Squares</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Slope of regression line(z-score)</td>
<td>Angle of regression line(Degrees)</td>
</tr>
<tr>
<td>1</td>
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<td>0.9015</td>
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<tr>
<td>2</td>
<td>0.9126</td>
<td>0.9126</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>0.8783</td>
<td>0.8783</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>0.9233</td>
<td>0.9233</td>
<td>42</td>
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<td>5</td>
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<td>0.9512</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
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<td>0.8856</td>
<td>41</td>
</tr>
<tr>
<td>7</td>
<td>0.9215</td>
<td>0.9215</td>
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</tr>
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<td>0.8764</td>
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</tr>
<tr>
<td>9</td>
<td>0.8955</td>
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<td>42</td>
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Table TC5.3: Correlation measures between FA and MK for GM

<table>
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<tr>
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<th>Least Squares Line Fitting</th>
<th>Block based Weighted Least Squares</th>
</tr>
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<td>Angle of regression line(Degrees)</td>
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<tr>
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<tr>
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<td>35</td>
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<tr>
<td>8</td>
<td>0.5672</td>
<td>0.5672</td>
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<tr>
<td>9</td>
<td>0.4581</td>
<td>0.4581</td>
<td>25</td>
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Figure FC5.4: Representative Scatterplot of WM plotted for $FA_z$ and $MK_z$ for a real dataset

### 5.4 Discussion

We demonstrated that correlation analysis of DTI and DKI metrics enabled differentiation of WM and GM. As illustrated in the correlation measures from different
methods in Table TC5.2 and Table TC5.3, there is a substantial difference between WM and GM regions. The correlation coefficients between FA and MK for WM is high in the range of 0.8 to 0.9, whereas the correlation coefficients between FA and MK for GM is relatively low in the range of 0.28 to 0.76. This could be a potential tool for segmentation of WM and GM.

The angle of the regression line gives an idea on the amount of deviation of the correlation from the maximum positive correlation value of 1 whose corresponding angle is 45 degrees. On analysing these angles, the values for WM are in the range of 40 to 44 which is approximately near to 45 degrees. In the case of GM, the angles of regression line corresponding to nine subjects are in the range of 16 to 37.

Weighted least squares method of line fitting also shows similar kind of differentiation in the correlation measures between WM and GM. The correlation coefficients of weighted least squares method are same as that of least squares method for GM, whereas in case of WM, the weighted least squares method seems to strengthen the correlation in regions of good correlation and weakens the correlation in regions of lower correlation.
5.4.1 Future Scope

The preliminary findings are reported in this study for a sample size of nine normal subjects. The correlation analysis could be extended in the future with increased sample size to produce new results and also to strengthen the obtained results. Moreover, the correlation measure could be used for automating segmentation of WM and GM. As the correlation analysis is done on DTI and DKI derived metrics which has the ability to provide quantitative information about tissue micro-structure, the automatic segmentation based on this approach may improve the reliability of segmentation of WM and GM.

5.5 Conclusion

The study mainly focussed on finding the correlation between DTI and DKI parameters for characterizing the brain regions such as WM and GM of healthy human brain. The diffusion weighted images obtained on nine healthy subjects are used in this study. Parameters such as MK and FA were estimated for the two brain regions, WM and GM. Correlation analysis was performed between MK and FA in WM and GM. Significant differences in correlation results were observed for WM and GM. These preliminary findings indicate that this correlation measure could be used to characterize WM and GM regions in normal human brain and also in segmentation of WM and GM. In addition, this indicates a promising potential for diagnostic imaging of gray and white matter in discriminating pathologies.