Diffusion Kurtosis Imaging in Temporal Lobe Epilepsy

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Abstract

Epilepsy constitutes one of the most common neurological clinicopathological entities affecting approximately 1% of the general population. Temporal lobe epilepsy (TLE) represents by far the most common form of medically intractable focal epilepsy in adults. Surgical resection is the common form of treatment when lesions are clearly delineated, either from patient’s magnetic resonance imaging (MRI) structural scans or by invasive seizure monitoring techniques (e.g., intracranial EEG) for patients with non-lesional MRI scans. Increasing numbers of studies have suggested that TLE is more of a network disorder, therefore full delineation of pathological tissue is difficult resulting in incomplete resection, possibly contributing to long-term recurrence of seizures after surgery. Diffusion MRI, an advanced MRI technique that is sensitive to the tissue at the microstructural level, has been studied, hoping to detect subtle microstructural changes related to TLE.

In this thesis, we investigated the ability of a diffusion MRI model, called diffusion kurtosis imaging, (DKI) to quantify TLE patients brain microstructure. Each chapter discusses the method developed to accomplish this, beginning with Chapter 1 giving the general background and the motivation behind this thesis. Chapter 2 develops a method of assessing the reproducibility in whole-brain high-resolution DKI at varying b-values. A shorter protocol was identified with comparable precision as the protocol with three b-values, supporting DKI for aiding clinical tools to assess brain tissue microstructure. Chapter 3 focuses on identifying microstructural abnormalities in the white matter (WM) and grey matter (GM) of the temporal pole, a region underappreciated in TLE patients. The method developed combining DKI measurements and tract-specific analysis uncovered temporal pole microstructural abnormalities in TLE patients (includes non-lesional TLE patients) compared to healthy controls. The work described in Chapter 4 explores a machine learning approach to lateralize TLE patients, demonstrating that DKI-based classifiers obtained slight increase in their general accuracy for GM region. Finally, Chapter 5 discusses the contributions of the thesis and provide suggestions for future research.
Temporal lobe epilepsy is a medical condition that affects the temporal lobe region of the brain, and is commonly treated with anti-epileptic drugs. However, for some of the TLE patients who do not respond to medication, surgery is the preferred method of treatment. Before surgery is performed, the seizure focus must be identified. Magnetic resonance imaging is a technique that has been used to image TLE patients, but sometimes the scans of these patients are reported as being normal (i.e., no sign of abnormality). Therefore, more invasive monitoring techniques must be employed to isolate the seizure focus. Following surgery, long-term follow up has indicated that seizures recur in some of these patients. Several studies have attributed this to in-complete resection of abnormal brain areas, which may not be confined solely to the temporal lobe.

In this thesis, we investigated an advanced MRI technique, commonly known as diffusion MRI, that detects the movement of water in the brain, to provide indirect information relating to the underlying microstructure. Using the signal measured with diffusion MRI, many models have been developed to quantify the microstructure property. One such model is called diffusion kurtosis imaging (DKI), which aims to quantify the complex tissue microstructure.

Chapter 1 provides more detailed background and motivation behind this thesis; Chapter 2 discusses our approach to assess the precision of the DKI model. It was concluded that high precision can still be achieved within reasonable scan time, supporting the use of DKI for clinical application. Chapter 3 describes the method developed to detect microstructural changes
within the temporal pole region of the temporal lobe in TLE patients. Basically, we extracted DKI measurements along two WM fiber bundles connected to the temporal pole and the deep grey matter. Our findings demonstrated that by combining DKI and other analysis techniques, diffusion abnormalities related to TLE can be uncovered within the temporal pole. Chapter 4 focuses on a machine learning approach for classifying a cohort of TLE patients into left or right TLE according to the side on which the lesions are detected. The overall accuracy measurements demonstrated that DKI based classifiers have slightly better performance in the GM region compared to DTI classifiers. Finally, the thesis ends with Chapter 5, which provides general conclusions and plans for future work.
To say that the white matter is but a uniform substance like wax in which there is no hidden contrivance, would be too low an opinion of nature’s finest masterpiece. We are assured that wherever in the body there are fibers, they everywhere adopt a certain arrangement among themselves, created more or less according to the functions for which they are intended. If the substance is everywhere of fibers, as, in fact, it appears to be in several places, you must admit that these fibers have been arranged with great skill, since all the diversity of our sensation and our movements depends upon this. We admire the skillful construction of the fibers in each muscle; how much more then ought we to admire it in the brain, where each of these fibers, confined in a small space, functions without confusion and without disorder.

NICOLAS STENO, 1669
Co-Authorship Statement

This thesis integrates several manuscripts (i.e., published or in preparation for submission) that stem from work discussed in each chapters. The following are details of authors and collaborators contributions in each chapters work.

Dr. Terry Peters and Dr. Ali Khan co-supervised the overall projects comprising this thesis. The Chapter 2 work was carried out in collaboration with Dr. Roy Haast, Tristan, Farah, Dr. Corey Baron, Terry and Ali. The Human Connectome Project and 3D diffusion phantom data were used for this study. The DKI reproducibility and fitting quality project was jointly conceived by Loxlan, Terry and Ali. Loxlan designed and implemented the methods being evaluated in this work, including writing the code for generating the DKI quantitative maps and calculating the reproducibility measurements, designing the protocol for phantom imaging at 9.4T, preprocessing and analysing the data. Tristan and Farah assisted in the manufacture and preparation of the phantom for scanning. Roy contributed in providing an initial code for surface analysis and also helped in the statistical analysis. Based on this work, Loxlan wrote and published a manuscript in the Journal of Magnetic Resonance Imaging, with the help from Roy and revisions from Corey, Terry and Ali.

The work in Chapter 3 was carried out in collaboration with Dr. Roy Haast, Dr. Seyed Mirsattari, Dr. Michael Jurkiewicz, Terry and Ali. Temporal lobe epilepsy patient data from the Ontario Brain Institute Epilepsy Program database were used for this study. The temporal pole DKI analysis framework was jointly conceived by Loxlan and Ali. Loxlan designed and implemented the methods being evaluated in this work, which included writing the code for generating the DKI quantitative maps and anatomically constrained tractography incorporating binary mask manually created by Ali. Loxlan also ran the preprocessing and performed tract-specific analysis and mapping of the DKI maps to different cortical depths using an initial code provided by Roy. Roy also contributed with the sampling of DKI measurements in the
different cortical surfaces as well as to the statistical analysis. Seyed and Michael collected and provided clinical interpretation of the data acquired. Based on this work, Loxlan has prepared a manuscript to be submitted to the journal Epilepsia, with the help from Roy and revisions from Terry, Seyed and Ali.

Finally, the work presented in Chapter 4 was carried out in collaboration with Terry and Ali. The TLE patients data used in Chapter 3 work was also used for this project. Loxlan and Ali jointly conceived this project. Generation of DKI quantitative maps and writing the code that performed a multiclass classification task that was trained on features selected using a class specific feature selection method, were performed by Loxlan. Ali contributed in the extraction of features (i.e., mean values from anatomical regions of interest). Seyed helped in collection and clinical interpretation of the data acquired. At the time of writing this thesis, Loxlan has prepared a draft manuscript for submission to the journal PLOS ONE, with revisions from Terry, Seyed and Ali.
Acknowledgments

My wholehearted appreciation goes to my co-supervisor and mentor, Dr. Terry Peters, for giving me the opportunity to continue my graduate studies in his world-class laboratory. His invaluable insights, guidance and support throughout my PhD study is truly immeasurable. Terry always has time to listen to matters related to both work and outside of work, and has incredible patience. I am humbled to have had the opportunity to work and learn from Terry, an experience that has influenced many aspects of my life.

My deep gratitude also goes to my co-supervisor Dr. Ali Khan. Ali provided the guidance I needed from the very beginning of my graduate studies in Robarts Research Institute. It was a privilege to have had those informal one-on-one discussions with him anywhere within the Robarts building in the early days of my studies. I am mostly grateful to have had the opportunity to be part of his new laboratory, this not only helped me grow more into the computational neuroimaging realm, but has also been inspiring. At times when faced with constraints that required changes to my initial plans, his insights and guidance were invaluable. Truly a memorable experience that I will always be grateful for. Ali, thank you!

In no specific order, I would also like to acknowledge all those that helped me through this journey. Thank you to Dr. Roy Haast, Dr. Seyed Mirsattari, Dr. Corey Baron, Dr. Robert Bartha and Dr. Robert Hammond, for your time given to our countless valuable scientific discussions. Also my sincere thank you to all the members of Dr. Kahn’s Computational Imaging lab and Dr. Peters’ VASST lab, for those insightful discussions inside and outside of work and most importantly the friendship. A special thank you to Dr. Jayarathne for being a great friend to me and my family.

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Finally, my heart felt gratitude to my best friend, my beautiful wife, Euphrasia, for her endless love and support. Always standing beside me, even putting aside her career plans to help me realize my academic dreams. Her time invested in discussing science, careers, faith, life together or just listening to me talk about kurtosis imaging is priceless. Most importantly, I am eternally grateful for her tireless effort to keep our family functioning day in day out. The love of our two beautiful children (David and Lazennia) has always grounded me emotionally and filled me with motivation. I would also like to say thank you to my parents and parents in-law for the love and words of encouragements during my studies. And above all, a big thank you to the Supreme Provider, the Almighty God.

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Chapter 1

Introduction

1.1 Overview

This chapter provides a brief introduction to temporal lobe epilepsy (TLE) and the role of neuroimaging as the preferred diagnostic tool. It sets the stage for the discussion of various magnetic resonance imaging (MRI) based research in TLE and motivates the use of an advance diffusion MRI technique: diffusion kurtosis imaging, the central theme of this thesis. In addition, a brief overview of existing diffusion MRI image analysis techniques is provided to support the advanced techniques used throughout the work in the thesis. The chapter concludes with a description of the goals and scope of this thesis and a summary of each subsequent chapter.

1.2 Temporal Lobe Epilepsy Definition and General Characteristics

Epilepsy is one of the oldest neurological condition known to mankind, affecting 50 million individuals across the age spectrum [10]. The condition is characterized by two or multiple recurrent seizures, with unidentified cause [102]. This class of patients has a risk of premature death, seizure-related injuries, psycho-social dysfunction and a general reduction in quality of
life [86]. In addition, epilepsy patients can suffer from a wide range of side effects and co-morbidities including cognitive impairment (e.g., memory loss), mood disorders (e.g., depression), risk of sudden unexpected death, and the potential to develop status epilepticus, where the brain is unable to control seizures and may lead to permanent brain damage [154, 17]. Epileptic seizures are episodes of abnormal neuronal activity resulting in neurological dysfunction [52]. The International League Against Epilepsy (ILAE) in 1981 categorized seizures into two main groups: partial or general seizures, based on their clinical type and interictal electroencephalography findings. The partial (or focal) seizures are characterized as seizures originating in a particular area of the brain and can be further subdivided into simple partial (no alteration in consciousness) and complex partial seizures (alteration of consciousness). On the other hand, generalized seizures conceptually involves the entire brain (both hemispheres) simultaneously [10].

Following the classification of seizure types, in 1985, the ILAE defined TLE as a condition characterized by recurrent, unprovoked seizures originating from the medial or lateral temporal lobe (Figure 1.1 and 1.2). TLE represents the most common form of medically intractable or
Figure 1.2: The medial temporal lobe consists of the hippocampal formation (blue-green), superiorly, and the parahippocampal gyrus, inferiorly, which consist of the parahippocampal (off-white), entorhinal (brown) and perirhinal (yellow) cortices. Adapted from [109].

drug-resistant (i.e., unresponsive to anti-epileptic drugs (AEDs)) [15] focal epilepsy in adults [58] and can be etiologically divided into two broad categories: mesial temporal lobe epilepsy (MTLE) and neocortical temporal lobe epilepsy (NTLE) [106].

MTLE involves the medial or internal structures of the temporal lobe with seizures originating from the hippocampus, amygdala or entorhinal cortex Figure 1.2. MTLE accounts for almost 80% of all temporal lobe seizures and its common pathophysiological substrate are hippocampal (HS) or mesial temporal sclerosis (MTS) which are characterized by apoptosis of pyramidal neurons in the hippocampus (cornu ammonis and dentate gyrus). Others could include infections (meningitis or encephalitis), traumatic brain injury, cerebral tumours or stroke [18, 19]. TLE can affect the outer parts of the temporal lobe. A recently recognized entity is called NTLE, or lateral temporal lobe epilepsy, although to date the condition is not well characterized. Occasionally, patients can have MTS (or HS) in addition to neocortical pathologies and are therefore referred to as having ‘dual pathology’. Some of the potential pathophysio-
logical substrates that could cause NTLE are: tumours (astrocytomas, gangliogliomas, meningioma, and dysembryonic neuroepithelial tumour (DNET)); vascular malformations; malformation of cortical development (focal cortical dysplasia); stroke; trauma or infections [18, 19].

Surgery has been the treatment of choice for most of TLE patients. However, surgical candidacy depends on how fully the lesions are delineated. Surgical resection may offer post-operative seizure freedom up to 2 years in 60-80% of patients with drug-resistant TLE, while longer-term follow-up studies show less favorable results, supporting the notion that TLE is a network disorder [20, 141]. Diagnosis of TLE can be very invasive. For example, the current gold standard for outlining lesions in TLE patients is through the use of intracranial electroencephalography (iEEG) to identify the epileptogenic zone (EZ). The EZ is either determined from measurements with scalp electrodes, or invasively by deploying intracranial monitoring subdural strips or stereotactic EEG (SEEG) electrodes [83, 129]. The prevention of recurrent seizures is critical for minimizing the cognitive and psychiatric comorbidities of epilepsy, and to maintain an acceptable quality of life. Ideally, invasive interventions for localizing the EZ could be substituted with less invasive, or ideally, non-invasive diagnosing protocols that are sufficiently sensitive to detect the presence of subtle alterations of the brain’s state. One important non-invasive imaging modality that will be discussed in detail in the subsequent sections is, magnetic resonance imaging (MRI).

1.3 Magnetic Resonance Imaging in Temporal Lobe Epilepsy

Here we discuss the basic principles of MRI and the conventional contrast used in diagnosing TLE.

1.3.1 T1, T2 and proton density weighted imaging

The brain consists of 80 percent water, and therefore the basic particle of interest in MRI is the hydrogen proton (H\(^1\)) in the water molecules. H\(^1\) posses a magnetic dipole (Figure 1.3A), often referred to a spin. Magnetic resonance imaging of the human brain relies on the manipulation of these H\(^1\) nuclei or other nuclei with magnetic moments, using a combination of a strong
static magnetic field ($B_0$), a variable radiofrequency (RF) field and magnetic field gradient ($B_1$). The $H^1$s in the water molecule are randomly oriented in the absence of an external magnetic field, with a net magnetization of zero. In a typical MRI scan, $B_0$ is applied, aligning the $H^1$s either of parallel or anti-parallel to $B_0$ (Figure 1.3C). The protons at the lower energy state are easily forced to align with the $B_0$ (e.g., usually defined as the z-direction), while those at a higher energy state point in the opposite direction to $B_0$. The protons anti-parallel to each other cancel out, leaving a small number in alignment with the $B_0$, creating an overall net magnetization or magnetization vector ($M$). This resultant vector ($M$) precesses around the direction of $B_0$, in a process called Larmor precession. The angular frequency of the precession is given by the following simple relationship,

$$\omega = \gamma B_0,$$

(1.1)

where $B_0$ is the main magnetic field to which the spins are exposed, and the gyromagnetic ratio $\gamma$, is a constant that is specific to the atomic nucleus and which for hydrogen proton is 42.58 MHz.T$^{-1}$. $M$ can be manipulated by applying an RF field commonly referred to as an RF

![Figure 1.3: (A) a hydrogen proton behaves like a tiny bar magnet, (B) represents the arbitrary precession of the hydrogen protons in the absence of a strong magnetic field, $B_0$. However when $B_0$ (thick red arrow) is present (C), hydrogen protons with high energy points in the opposite direction to $B_0$ while low energy protons will align with $B_0$. The oppositely aligned protons cancel out, yielding a net magnetization vector $M$.](image-url)
pulse at the appropriate frequency (i.e., Larmor frequency). The RF pulse has two purposes: it is used to both excite and refocus the spins. By applying the excitation RF pulse perpendicular to the $\mathbf{B}_0$ tuned at the Larmor frequency, $\mathbf{M}$ is forced into the x-y plane (transverse plane) whose normal is in the direction of $\mathbf{B}_0$ (Figure 1.4). The chosen flip angle determines how far $\mathbf{M}$ is forced away from $\mathbf{B}_0$. Due to the magnetic field inhomogeneity and spin-spin interactions, the spins precess around the direction of $\mathbf{B}_0$ at different frequencies reducing the $\mathbf{M}$, in a phenomenon known as ‘dephasing’, as illustrated in Figure 1.4. To correct the out-of-phase spins, a refocusing RF pulse (e.g., 180°) can be applied. The spins eventually realign resulting in a signal pulse whose maximum occurs at the point of maximum re-phasing (i.e., at echo time, $\text{TE}$). This results in a net transverse magnetization ($\mathbf{M}_{xy}$). Any disruption of this signal (i.e., loss of $\mathbf{M}_{xy}$), results in an exponential decay of the signal (known as T2 relaxation). Eventually, $\mathbf{M}$ returns to its initial position, (i.e., realigning with $\mathbf{B}_0$ or regrowth of longitudinal magnetization). This results in an exponential regrowth of the signal (known as T1 relaxation).

In a ‘spin echo’ pulse sequence, the signal is measured at the echo time ($\text{TE}$) after the refocusing RF pulse, and the procedure is repeated at the repetition time ($\text{TR}$). Other common pulse sequences that do not use a refocusing RF pulse, are called ‘gradient echo’ sequences. Finally, the $\mathbf{B}_1$ field or simply the gradient, creates linear changes to the $\mathbf{B}_0$ along x-, y- and z-planes. Generally, gradients have three main functions; for slice selection, image encoding (i.e., frequency and phase encoding) and diffusion weighting (covered in detail in the later section). As a result, the spins precess at different frequencies and phases at different locations, generating unique signals that are eventually stored in a data array called ‘k-space’. Fourier transformation of k-space values then allows the reconstruction of the tissue in Cartesian coordinates in the image space.

Since MRI primarily manipulates protons, the signal can also be weighted to reflect the actual density of protons ($\rho_0$) (i.e., an intermediate sequence sharing some features of both T1 and T2), commonly known as proton density weighted image. These respective signals (i.e., T1, T2 and $\rho_0$) depict a tissue type (i.e., there is a variation in the brightness of the
white matter WM, grey matter GM and cerebrospinal fluid (CSF)) and generally vary with sequence parameters (e.g., TE and TR). Nearly all MR image display tissue contrasts that depend on these tissue properties; density of protons and the two relaxation times, T1 and T2 simultaneously. Another commonly used structural MRI sequence employed in the diagnosis of TLE, is fluid attenuation inversion recovery (FLAIR). The sequence aims to remove signal from the CSF in the resulting images. In order to null the signal from CSF, the inversion time of the FLAIR pulse sequence is adjusted such that at equilibrium there is no $M_{xy}$ of fluid. Therefore FLAIR images appear similar to T2 weighted images with brighter GM than WM except that CSF is dark instead of bright. Furthermore, functional information of the brain can be measured using functional MRI (FMRI). The FMRI technique aims at tracking local changes in oxygenated blood supply in response to external stimuli (e.g., auditory). This information is important to guide surgery in TLE, to avoided or minimize cognitive deficits, as language and memory areas commonly overlap with TLE lesions.

**1.3.2 Structural MRI biomarkers of TLE**

Given its non-invasive nature as well as the wide range of available image contrasts [29], MRI has been the preferred diagnostic imaging tool for TLE. Here, structural MR imaging is primarily used to delineate structural abnormalities that underlie the clinical phenotype. For example, MRI is highly sensitive for detecting brain tissue lesions related to TLE and may have clinical manifestations similar to those seen for MTLE HS, such as tumors, dysplasias, vascular malformations and other lesions, including temporal lobe encephaloceles (Figure 1.5). Some of the common MRI features in HS from visual inspection include [29]:

- the presence of hippocampal atrophy — change of hippocampal size and shape. An oval shape is considered normal, while flatter and inclined appearance is abnormal
- increase in T2/FLAIR signal — present in the hippocampus, amygdala, and lateral temporal lobe WM
- the loss of internal structure — abnormal hippocampal structure as a consequence of
Figure 1.4: Schematic of spin dephasing. The excitation RF pulse (e.g., $90^\circ$) rotates the spins or longitudinal net magnetization $M$ into the x-y plane. Differences in spins precession frequency (dephasing) causes $M$ to reduce. To re-phase the spins, a refocusing RF pulse can be applied, (e.g., $180^\circ$) at TE/2 after the excitation pulse. The out-of-phase spins are flipped about their axis, putting the slower spins (orange) in front of more faster precessing spins (red). Over sometime, the faster spins catch up to the slower spins, so at time TE all spins are back in phase. This type of sequence is called spin echo and ($M_{xy}$) reflects the total magnetization of all in phase spins.

neuronal loss and gliosis

- asymmetry of the horns of the lateral ventricles
- atrophy of the anterior temporal lobe
- atrophy of the ipsilateral fornix and mammillary bodies

Although such lesions can be easily delineated in approximately two thirds of the patients, contributing to a favorable surgical outcome, the remainder of TLE patients exhibit no structural abnormalities in their MRI scans. This poses difficulties in proper diagnosis and surgical planning [130] and promotes the use of more advanced MRI techniques such as diffusion-weighted MRI (dMRI) to highlight complementary properties related to the tissue’s microstructure.
Figure 1.5: Two T1-weighted inversion recovery and a T2-weighted coronal images (top row) showing a left hippocampus with an abnormal shape and loss of internal structure (open arrow). And a T1-weighted and two FLAIR sagittal images (bottom row) showing a small left anterior temporal encephalocele (white arrows) in a patient with left TLE. Adapted from [29].

1.3.3 Diffusion weighted imaging

The three primary image contrasts T1, T2 and $\rho_0$ discussed above provide essential information at the macroscopic level of the brain tissue. However, these image contrasts fail to provide insight into the geometric architecture of the brain, or in other words, on the arrangement of neurons and their connectivity. This important information could increase our understanding of different diseases and processes of the brain. Diffusion weighted imaging (DWI) allows us to probe tissue structure at different length scales, that is, levels of hierarchical architectural organization. DWI is the clinical workhorse of stroke imaging, where hyper-intensity in diffusion weighted images helps isolate cerebral infraction in the brain. In addition, DWI has been widely used in research studies of the WM and its connectivity in the living brain. A more recent area of research is called microstructure-imaging, which aims to estimate and map microscopic properties of brain tissue in vivo, using models that link these properties to diffusion MRI signal [3]. This thesis discusses one of these models which aims to quantify complex
What is diffusion?

In 1855, Adolf Eugene Fick was the first to describe the diffusion of molecules, a phenomenon which is nowadays known as Fick’s Law, that states that molecules in a high concentration region will slowly expand to a region of lower concentration. This expansion is also called ‘mutual diffusion’ [48]. For example, if a perfume bottle is opened at a corner of a closed room, the perfume odor gradually permeates the room, because the molecules have diffused from one side of the room (i.e., with a higher concentration) to the other (i.e., a region with a lower concentration). Another type of diffusion known as ‘self-diffusion’ or (Brownian motion), was first observed by Robert Brown in 1828 [24]. He noticed pollen grains suspended in water under his microscope moving randomly without any apparent cause. Later, in 1905, Albert Einstein first formally described this molecular self-diffusion phenomena [43]. To illustrate his idea, let us imagine we have $N$ water molecules at time $t = 0$. After some time $\Delta$ we measure the water molecules’ individual displacements. We then count the number of molecules $n$ with the same displacement $x$, and plot the data on a histogram of the relative number of molecules ($n/N$) versus displacement distance $x$. We expect to see a Gaussian (or normal) distribution since most of the molecules will have a shorter displacement while only few will have longer displacement. Einstein described this concept as the likelihood, or probability, of a single particle to move a certain distance as a displacement distribution [43]. In a homogeneous medium, we assumes that the water molecules are free to move in any direction (free diffusion) as in our imaginary experiment above. The diffusion process of water molecules in this scenario will have a Gaussian distribution. In general, the Gaussian functions is given by,

$$f(x) = \frac{1}{\sigma \sqrt{2\pi}} e^{-x^2/2\sigma^2}$$  \hspace{1cm}(1.2)$$

where $\sigma^2$ is the variance which determines the dispersion of the Gaussian distribution, and $x$ is the displacement of water molecules. The likelihood of displacement is proportional to the
diffusivity coefficient explained by Einstein’s equation [43] as the following,

$$\sigma^2 = 2Dt$$  \hspace{1cm} (1.3)

where \( D \) denotes the diffusion coefficient which characterizes the viscosity of the medium, or how easy the molecules can move, and \( t \) indicates the time taken for the molecules to displace (i.e., diffusion time). To estimate the population of water molecule movement in a given time, we substitute \( \sigma^2 \) in Equation 1.2 with Equation 1.3, which yields,

$$P(x, t) = \frac{1}{\sqrt{4\pi D t}} e^{-x^2/4Dt}$$  \hspace{1cm} (1.4)

Understanding this molecular movement (or diffusion) and the ability to measure it, can provide us indirect information on the microstructure of living tissue and forms the basis of diffusion MRI. Diffusion MRI is primarily concerned with the inherent mobility of water molecules in tissue. Before describing the methods to measure diffusion of water molecules in the brain tissue using MRI, it is important to briefly discuss the biophysical properties of diffusion in the living brain tissue.

**Diffusion in the human brain**

In the brain, the cerebrospinal fluid can be considered as a free diffusion medium with diffusing water particles following a Gaussian distribution. As such, Einstein’s equation holds in this case. However, this is rarely the case in biological tissue, because of boundaries imposed by micro-architectural features, such as cell membranes and organelles, that hinder and restrict the mobility of water molecules. Therefore, Einstein’s equation does not hold in the neuroanatomical environment due to the assumption related to free or isotropic diffusion. To account for this, the diffusion coefficient derived from the MRI measurement is termed apparent diffusion coefficient (ADC) [97].

Diffusion is characterized by the geometry and composition of the intra- and extracellular
space as illustrated in Figure 1.6. The axons are insulated by the lipid bilayer of the myelin membrane, which forms a boundary between the interior and exterior of the cells. It also forms an impermeable barrier to the diffusion of water particles. Outside the cell, interstitial fluid similar to CSF forms a thin layer around the cell. While the diffusion is freer outside the cells, in areas of increased distance between cells (e.g., the green diffusion path moving around axon A in Figure 1.6a), tightly packed cells increases viscosity, which reduces the diffusion of water and hence the protons of the hydrogen nuclei (e.g., the green diffusion path moving between tightly packed axons A, B and C in Figure 1.6b) [125]. In addition, diffusion also declines when protons encounter macromolecules in the extracellular matrix and on the neuronal membranes. Nevertheless, the proton displacement distribution due to diffusion in the extracellular space can be approximated reasonably well by Equation 1.4 irrespective of the time the protons are diffusing. This equation is sometimes called the Gaussian diffusion propagator.

On the other hand, although the intra-cellular fluid is dominated by water, the cytoskeletal filaments composed of microfilaments and microtubules prevent free diffusion of protons, resulting in a drastic decline of the diffusion coefficient. Therefore the use of a Gaussian ap-
proximation of diffusion in this environment is questionable, since at some point it breaks down when diffusion is highly restricted (e.g., the magenta diffusion path inside axon B in Figure 1.6a), in which case the distribution becomes non-Gaussian. In WM, the neurons are more structured, forming long fibre bundles, giving rise to directionality in the diffusing protons. For example, in Figure 1.6b the protons have a preferential direction of diffusion (i.e., along the fibres than perpendicular direction) and which is described as anisotropic diffusion. Therefore, the diffusion along the fibre bundles can be easily quantified using Gaussian distribution compared to the restricted diffusion in the perpendicular direction. The anisotropic diffusion along the WM fibres is affected by the diameter, density and myelination of the neurons.

![Figure 1.7: Schematics of basics fibre configurations in the white matter: (a) linear, (b) bending, (c) fanning, (d) crossing, (e) kissing and (f) tangential view of the cortical GM with its layers (I-VI). Adapted from [84].](image)

Another factor that influences the diffusion pattern in the WM is the complex configuration of the fibre bundles, commonly known as the ‘crossing fibre issue’ (Figure 1.7) [135]. The configuration includes the actual crossing fibres (Figure 1.7d interdigitating fibres and (e) simply two distinct fibre bundles brushing past each other). In addition, fibre bundles can be parallel to each other (Figure 1.7a), simply bending in a common direction, (Figure 1.7b) or diverging (fanning) into different directions (Figure 1.7c). Any combination of these configurations can
also lead to alteration of diffusion anisotropy.

The diffusion in GM is less anisotropic compared to that in WM, which can be attributed largely to its composition (i.e., cell bodies of both neurons and glial cells). Fibre bundle forming axons originating from the GM include long range fibres that connect various parts of the brain, and short range fibres that connect different cortical structures. Moreover, almost all dendritic processes are found in the GM and are characterized by their organization, especially in the neocortex. As illustrated in Figure 1.7f, the neocortex is subdivided into six distinct layers, each with fibres highly orchestrated corresponding to their functions. The two common fibre arrangement are radial (provides connection between the adjacent layers and distant regions) and tangential (provides lateral connections). The fibre density varies across the different layers.

During the time frame of the diffusion weighting (ms) (more on this in the next section), diffusion of protons is influenced by microscopic structures in a limited (µm) range. Most significantly, the contributions of all these properties are averaged over a (typical) voxel size of $1 - 2\text{mm}^3$. This makes basic dMRI non-specific with respect to individual microstructural features. Figures 1.6 and 1.7 illustrate how cells can hinder the random motion of water molecules in the brain tissue. The better we characterize the diffusion properties within the underlying microstructure, the better we can understand the structural and functional aspects of the human brain. More importantly we will be able to probe the brain with higher accuracy to identify regions exhibiting abnormal behaviour.

**Measuring diffusion with MRI**

Diffusion magnetic resonance imaging provides a unique opportunity to non-invasively characterize the brain microstructure *in vivo*. To appreciate how the signal from the random movement of water molecules can be measured with MRI, please refer to section 1.3.1. It is possible to sensitize MRI sequences to the diffusion processes discussed above. The ‘spin echo’ (Figure 1.4) technique as first proposed by Edwin Hahn in 1950 [67], stated that the dephasing due to magnetic field inhomogeneities can be corrected by applying a second RF pulse at 180°, re-
sulting in the signal (echo) being regenerated. The echo time is twice the time between the two RF pulses (i.e., first RF pulse at 90° and second RF at 180°). Hahn noticed that the reduction in the spin echo signal intensity was due to molecular diffusion. A few years later in 1954, Carr and Purcell formally described a method to measure the signal that was reduced due to diffusivity motion [27]. Their technique introduced an additional magnetic gradient field to linearly modulate the main field in one or more of the three orthogonal directions, resulting in a slight increase of the observed main magnetic field at one extreme, and a slight decrease at the other. The spins at different location then begin to experience different magnetic fields and precess at different angular frequencies gradually acquiring different relative phase shifts depending on their location. Stronger gradients produce larger phase shifts and consequently they are more sensitive to diffusion. The addition of the gradient modifies the Larmor frequency Equation 1.1 initially experienced when only $B_0$ is applied, as described below.

$$\omega = \gamma B_0 + \gamma Gx,$$  

(1.5)

where $Gx$ is the strength of the applied gradient in the x direction. The idea introduced by Carr and Purcell applied a constant magnetic field gradient throughout the entire spin echo experiment. In this setup, spins at position $x$ at a particular time $\tau$ experience a magnetic field $B_0 + Gx(t)$. Therefore, a spin located at point $x$ for a very short time $\tau'$ before moving to another location will experience a phase shift given by the following expression,

$$\phi(x(t)) = -\gamma(B_0 + Gx(t))\tau'$$  

(1.6)

due to the change in Larmor frequency effected by the applied constant gradient. A decade later, Stejskal and Tanner introduced the pulsed-gradient spin echo (PGSE) technique [128]. They proposed the replacement of the Carr and Purcell constant magnetic field gradient with short-duration gradient pulses, which can be triggered immediately following the RF pulses as
illustrated in Figure 1.8. With this idea it was possible to identify the difference between the pulse duration $\delta$ (encoding time) and the diffusion time ($\Delta$) (i.e., separation of the two gradient pulses, Figure 1.8). In this setting, the spins’ net phase change due to the first gradient can be easily computed by

$$\phi_1 = -qx_1$$  (1.7)

and the net phase shift due to the second gradient is given by

$$\phi_2 = -qx_2$$  (1.8)

where $q = \gamma \delta G$. The 180° RF pulse is applied before the second gradient to correct the phase shift induced by the first gradient pulse. However, the spins that did not remain at the same location along the applied gradient axis during the two gradient pulses do not return to their initial state, resulting in a net phase difference ($\phi_2 - \phi_1$). These spins experience a total phase shift during the second gradient pulse, resulting in a decrease in intensity of the measured MR signal (Figure 1.8 Diffusion). Hence, the resultant images have regions with low signal (appear darker) when diffusion is high in the direction of the applied gradient. The important measurement is the fractional signal loss given by the Stejskal-Tanner equation,

$$S = S_0 e^{-bD}$$  (1.9)

where $S$ and $S_0$ denote the echo signal acquired when a pulsed gradient magnetic field is triggered and the signal without the pulse gradient (commonly known as $B0$ image), respectively, $b$ is a function of the applied gradient strength ($G$), duration of the pulse gradient ($\delta$) and the time between the two gradient pulses ($\Delta$). According to the Stejskal-Tanner formulation in the
Figure 1.8: A schematic of the PGSE MR technique introduced by Stejskal and Tanner. The time between two strong diffusion-sensitizing gradients ($G_{\text{diffusion}}$) applied on either side of the applied RF $180^\circ$-pulse, $(\Delta)$ can range from 10ms to few hundred of milliseconds. The phases of stationary spins are unaffected by the ($G_{\text{diffusion}}$) pair since any phase accumulation from the first gradient lobe is reversed by the second. However, some diffusing spins move into different locations between the first and second lobes, falling out of phase and losing signal (spins in the dotted red box). The ($G_{\text{diffusion}}$) duration, $(\delta)$, may be anywhere between a few milliseconds to $(\Delta)$.

In the context of a basic PGSE sequence, the value of $b$ commonly known as ‘b-value’ is given by,

$$b = (\gamma G \delta)^2 (\Delta - \frac{\delta}{3})$$  \hspace{1cm} (1.10)

The ability of MRI to measure diffusion along a predetermined direction enables us to extract vital information relating to the underlying anatomical architecture of living tissue. The section 1.3.4 below discusses how we can represent the diffusion directionality using a tensor, which
provides an intuitive model to visualize the diffusion MR signal in 3D.

**Practical considerations for DWI**

Strong, rapidly switching diffusion gradients tend to induce eddy currents in the electrically conductive components of the MRI scanner, which can produce additional unwanted magnetic fields that slowly decay after the diffusion weighted gradients are turned off. If these lingering fields overlap with the detected signal, unwanted image distortion can occur. Therefore, to achieve accurate quantitative results, the eddy current effects needs to be corrected. Distortions due to eddy currents can be corrected by using affine transformations of distorted DWIs to a nondistorted, non-diffusion weighted, reference volume of the same subject which is usually the $B_0$ volume (i.e., the non-diffusion weighted image, see Equation 1.9). In addition, DWI is commonly acquired by a modified spin echo sequence called ‘echo-planar imaging’ (EPI), and artifacts related to this type of sequence can also be minimized with parallel acquisition approaches and non-linear registration methods [50] [89].

### 1.3.4 3D modeling of diffusion signal

In the following subsection, well known diffusion tensor imaging (DTI) [13] and its extension diffusion kurtosis imaging (DKI) [74] models are described, with the latter topic forming the central focus of this thesis. Towards the end of the section, other specific models relevant to this thesis are also introduced. If we can characterize the way water molecules diffuse in various tissue architectures, we can acquire important information relating to living tissue indirectly without sacrificing the organism. This is the goal of most diffusion modeling techniques.

### 1.3.5 Diffusion tensor imaging

In isotropic diffusion as described in the previous section, the protons basically diffuse equally in all directions, a phenomenon that is observed predominently in the extracellular space where fibre bundles are loosely packed. This type of diffusion can be represented using a sphere. Since a sphere has a constant diameter in all directions, we require only one diffusion constant
(\(D\)) to describe isotropic diffusion. On the other hand, when there are closely packed linear axons, diffusion is said to be anisotropic (see Figure 1.6b), (i.e., the protons tend to diffuse in an ordered fashion). In this scenario, an ellipsoid can be used to describe the diffusion, and three axes are required to describe such a shape, with the longest defining its principle axis.

**Basics of DTI formulation**

To properly orient this ellipsoid (Figure 1.9) in 3D space, we require six parameters. The first three are the lengths of the orthogonal principle axes, and are commonly known as the eigenvalues (\(\lambda_1\), \(\lambda_2\) and \(\lambda_3\)). The other three parameters are the three unit vectors, called eigenvectors, (\(v_1\), \(v_2\) and \(v_3\)) needed to define the orientation of the three principle axes respectively. The diffusion tensor is often thought of in terms of this ellipsoid. The surface represents the distance the protons will diffuse with equal probability. The three eigenvalues correspond to the three diffusivity values along the three principle axes, and their lengths are determined by the diffusion distance in a given time, \(t\) as shown in Equation 1.3. Hence the principle axes of the diffusion tensor are scaled with respect to the square root of the eigenvalues (see Figure 1.9). In this representation of diffusion, the orientation of the diffusion tensor is aligned with the principle eigenvector (\(v_1\)) which is the vector corresponding to the largest eigenvalue (\(\lambda_1\)).

*Figure 1.9: Schematic of a diffusion tensor ellipsoid in an anisotropic environment (parallel bundle of axons). The three principle axes are given by the eigenvectors \((v_1, v_2\) and \(v_3\)) and are scaled according to the square root of the corresponding eigenvalues \((\lambda_1, \lambda_2\) and \(\lambda_3\)). The eigenvalues are sorted according to their magnitude, such that \(\lambda_1 \geq \lambda_2 \geq \lambda_3\). Diffusion is greatest in the direction of the primary eigenvector \(v_1\) resulting in an ellipsoid.*
It is assumed that the $v_1$ is collinear to the dominant fibre bundle orientation in a given diffusion weighted voxel. The six parameters can be represented using a 3 X 3 tensor commonly known as the diffusion tensor as the following,

$$D = \begin{bmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{yx} & D_{yy} & D_{yz} \\
D_{zx} & D_{zy} & D_{zz}
\end{bmatrix} \quad (1.11)$$

Due to the symmetry of the diffusion tensor ($D_{yx} = D_{xy}$) a minimum of 6 diffusion weighted images, each acquired with different orientations are required. As more DWI or orientations are acquired, the estimation accuracy increases accordingly [97].

**Diffusion tensor derived parameters**

From the diffusion tensor (Equation 1.11), important parameters are extracted which quantify the diffusion properties in a voxel. The two most common of these are the mean diffusivity (MD) and fractional anisotropy (FA), as they characterize the overall diffusion properties within an imaging voxel. Mean diffusivity describes the average diffusion in a given voxel and its defined as,

$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \quad (1.12)$$

where $\lambda_1$, $\lambda_2$ and $\lambda_3$ are the eigenvalues of the diffusion tensor. In regions of isotropic diffusion, MD is high and in areas of anisotropic diffusion MD tends to be lower. Fractional anisotropy describes the degree of non-isotropic diffusion and reflects the preferred direction of diffusion in a given voxel and its defined as,

$$FA = \sqrt{\frac{1}{2} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}} \quad (1.13)$$
Fractional anisotropy is scaled between 0 and 1. In regions of free diffusion (e.g., CSF) FA tends to be lower compared to FA measured in the WM.

The other two quantitative parameters derived from DTI are axial diffusivity (AD) and radial diffusivity (RD). Axial diffusivity describes the diffusion in the axial direction and its equal to the largest eigenvalue ($\lambda_1$), whereas RD is the diffusion perpendicular to the axial diffusion and is equal to the mean of the two smaller eigenvalues ($\lambda_2$ and $\lambda_3$).

**DTI in temporal lobe epilepsy**

Diffusion abnormalities in several WM structures in TLE patients have been reported for more than a decade. One of the first studies reported reduced FA in the external capsule and corpus callosum in patients with TLE when compared with control subjects [9]. Since then, many studies have expanded on the extent of DTI abnormalities in the WM of patients with TLE. A study on patients with non-lesional MRI (nlTLE) was conducted on children by Govindan, *et al.* (2008) [61]. DTI measurements were obtained from four fibre bundles (i.e., uncinate, arcuate, inferior longitudinal fasciculi and corticospinal tract). Their results indicated abnormal water diffusion in the four tracts, including temporal lobe and extra-temporal regions. A subsequent study looking also at nlTLE was performed by Concha, *et al.* (2009) [34]. This study attempted to determine whether WM abnormalities are related to the presence of MTS, or whether they are also present in nlTLE. DTI was used to assess tract integrity of the fornix, cingulum, external capsules and the corpus callosum. Their findings provided considerable evidence supporting the idea that DTI abnormalities are more pronounced in patients with radiological evidence of MTS than in patients with nlTLE [34]. A recent study [103] performed a meta-analysis that included 13 cross-sectional studies and confirmed the existence of temporal and extra-temporal white matter DTI abnormalities. The evidence showed that reductions of FA and increases of MD are most prominent in WM structures (i.e., uncinate and arcuate fasciculi, cingulum and external capsule) closely related to the epileptogenic temporal lobe. Contralateral structures and the corpus callosum were also affected, albeit to a lesser degree. Furthermore, there seems to be a centrifugal decrease of the degree of abnormalities as tracts
extend away from the epileptogenic temporal lobe [103].

**Challenges with DTI**

Although DTI is non-invasive and can infer the microstructure *in vivo*, it has a major challenge limiting its full applicability in clinical workflows [135]. DTI is based on the assumption that water diffusion in the brain is unrestricted or free. In reality, the complex intracellular and extracellular *in vivo* environment (e.g., see Figure 1.7) can cause the diffusion of water molecules to deviate considerably from this pattern [124]. Therefore, DTI derived parameters including tractography (more on this in later sections) are a degraded representation of the microstructure integrity. This DTI shortcoming fueled the development of various models, one of which is called, diffusion kurtosis imaging (DKI) [74].

**1.3.6 Diffusion kurtosis imaging**

Diffusion kurtosis imaging is an expansion of DTI, where the diffusion tensor is estimated together with a 4th-order 3D kurtosis tensor. This approach attempts to characterise the degree to which diffusion deviates from Gaussian behaviour, for which kurtosis ($K$) is zero. Kurtosis is a dimensionless statistic and mathematically can take values from positive where the displacement distribution curve has a more sharply peaked profile or negative Kurtosis with the distribution least peaked. Although mathematically kurtosis can have negative values, biological tissues have been shown to only exhibit positive kurtosis [150].

**Basics of DKI formulation**

Distributions can be mathematically defined using cumulants ($k_i$) [74] [150]. In particular, the first three cumulants can be expressed in terms of the central moments of the distribution, (i.e., $k_1$, $k_2$ and $k_3$ are equal to $\mu$ (mean), $\mu_2$ (variance) and $\mu_3$ (skewness), respectively), in which the latter quantifies the asymmetry of normal distribution. Kurtosis can be derived using the second and fourth central moments (i.e., $\mu_2$ and $\mu_4$), or equivalently with the second and fourth
cumulants (i.e., $k_2, k_4$), as given by:

$$K = \frac{\mu_4}{\mu_2^2} - 3 = \frac{k_4}{k_2^2},$$  \hspace{1cm} (1.14)

where $K$ is a dimensionless metric that describe the deviation of distribution from the normal distribution (i.e., when $K = 0$). Consider a PGSE sequence (see Figure 1.8) that applies diffusion encoding gradients with infinitesimally short duration $\delta$ and amplitude $G$. The expression of the relationship between the diffusion signal decay and the diffusion coefficient can be derived as a summation of the cumulants $k_n$,

$$\ln \frac{S(G)}{S_0} = \sum_{n=1}^{\infty} k_n \frac{(\gamma G \delta)^n}{n!},$$  \hspace{1cm} (1.15)

expanding Equation 1.15 and omitting all the odd cumulants yields,

$$\ln \frac{S(G)}{S_0} = -k_2 \frac{(\gamma G \delta)^2}{2!} + k_4 \frac{(\gamma G \delta)^4}{4!} + k_6 \frac{(\gamma G \delta)^6}{6!} + ...$$  \hspace{1cm} (1.16)

given that diffusion coefficient for free diffusion is (see Equation 1.3),

$$D = \frac{\sigma^2}{2\Delta} = \frac{k_2}{2\Delta},$$  \hspace{1cm} (1.17)

equation 1.14 can be rewritten as,

$$k_4 = 4K\Delta^2 D^2.$$  \hspace{1cm} (1.18)

Substituting $k_2$ and $k_4$ in Equation 1.16 with Equations 1.17 and 1.18 respectively, and truncating the third term and above gives,

$$\ln \frac{S(G)}{S_0} = -\gamma^2 G^2 \delta^2 D \Delta + \frac{\gamma^4 G^4 \delta^4 D^2 \Delta^2 K}{6}.$$  \hspace{1cm} (1.19)
The diffusion weighting factor $b$ (b-value) in the PGSE sequence, when applying infinitesimally short diffusion encoding gradients $\delta$ and amplitude $G$ is given by [150],

$$b = \gamma^2 G^2 \delta^2 \Delta,$$

(1.20)

Finally the relationship between the diffusion weighted signal and the $b$-value for a gradient direction can be approximated by substituting Equation 1.20 into 1.19,

$$\ln \frac{S(b)}{S_0} = -bD + \frac{b^2D^2K}{6},$$

(1.21)

where $D$ and $K$ represent the apparent diffusivity and apparent diffusion kurtosis values respectively. Note that both $D$ and $K$ are estimated in the second term of the kurtosis method. Therefore, by acquiring diffusion weighted signals from multiple $b$-values, $D$ and $K$ can be estimated simultaneously along a specific diffusion direction by fitting Equation 1.21.

### Kurtosis tensor derived parameters

In an isotropic environment, the distribution of apparent diffusivity ($D$) in the second term of (Equation 1.21) is represented as a 2nd-order 3D diffusivity tensor as in traditional DTI as discussed earlier. The DTI parameters can also be calculated following the conventional DTI approach. For a 3D anisotropic medium, kurtosis has to be defined by a 3 X 3 X 3 X 3 matrix which can be represented as 4th-order 3D kurtosis tensor ($W_{ijkl}$) to fully characterize non-Gaussian behaviour of the diffusion tensor. Therefore the $K$ estimated along an arbitrary direction using Equation 1.21 is related to $W_{ijkl}$ by,

$$K = \frac{MD^2}{D^2} \sum_{i=1}^{3} \sum_{j=1}^{3} \sum_{k=1}^{3} \sum_{l=1}^{3} n_in_jn_kn_lW_{ijkl}$$

(1.22)

where $n_i$ is the $i$th element of the diffusion direction. Analogous with the diffusion tensor, the kurtosis tensor is symmetric, therefore it can be fully described with only 15 independent elements [91]. The most common derived metric related to kurtosis tensor is the mean kurtosis.
(MK), which is the mean kurtosis value along all uniformly distributed diffusion directions and its given by,

\[ MK = \frac{1}{n} \sum_{i=1}^{n} (K_i). \]  

(1.23)

Mean kurtosis only measures the overall kurtosis without any directional specificity. More recent development has shown that directional kurtosis is possible by transforming the kurtosis tensor from standard Cartesian coordinate system to a different coordinate system as illustrated in Figure 1.10. The kurtosis values along the eigenvectors \( v_1, v_2 \) and \( v_3 \) of the diffusion tensor are \( K_1, K_2 \) and \( K_3 \) respectively. The other two parameters used for quantifying the kurtosis in the axial and radial directions are axial kurtosis (AK) and radial kurtosis (RK) respectively, which are formulated as,

\[ AK = K_1 \]  

(1.24)

Figure 1.10: Illustrating the 3D kurtosis distribution as a 4th-order 3D kurtosis tensor as described in Equation 1.22. Note that for simplicity, kurtosis tensor is shown as a oblate ellipsoid (orange). The diffusivity ellipsoid (red) with \( v_1, v_2 \) and \( v_3 \) as the eigenvectors of the 2nd-order 3D diffusivity tensor.
and

\[ RK = \frac{K_2 + K_3}{2}. \]  

(1.25)

In addition, the anisotropy of directional kurtosis (Kfa) is calculated similar to DTI FA.

\[ Kfa = \sqrt{\frac{3}{2}} \frac{\sqrt{(K_1 - \bar{K})^2 + (K_2 - \bar{K})^2 + (K_3 - \bar{K})^2}}{\sqrt{K_1^2 + K_2^2 + K_3^2}}, \]  

(1.26)

where \( \bar{K} \) is the mean of the kurtosis \( K_1, K_2 \) and \( K_3 \) along the three respective diffusion tensor eigenvectors.

**DKI in temporal lobe epilepsy**

A preliminary study comparing DKI with DTI in nTLE patients was performed on children by Gao, *et al.* (2012) [56]. The findings of this study indicated that MK was much more sensitive to DTI parameters. This was a preliminary study for DKI application in nTLE and little information was given as to why they found elevation in MK in the white matter. Another study [21] investigating the use of DKI was carried out on mixed TLE patients of which only five had normal MRI findings. Whole brain voxel-wise statistical analysis was performed on DKI and DTI parametric maps to compare patients with TLE and controls. The DTI findings were parallel to previous studies, generally demonstrating a reduction in FA and an increase in MD mostly at the temporal lobe ipsilateral to seizure onset. On the other hand, there was significant reduction in mean, axial and radial kurtosis, but not restricted to the seizure onset area [21]. Another study looked at WM tract-specific analysis [60], by evaluating measures along each tract, to possibly identify abnormalities localised to specific tract subregions. Compared with healthy controls, subjects with TLE demonstrated pathological changes in circumscribed regions of the fornix, parahippocampal area, uncinate fasciculus, arcuate fasciculus and inferior longitudinal fasciculus. Several of these abnormalities were detected only with DKI metrics compared to the DTI metrics. Further work is still needed to improve on these preliminary
findings to help understand the relationship of DKI in TLE, particularly in drug resistant TLE patients with or without neuroradiological signs in their structural MRI scans.

**Challenges with DKI**

As seen in the second term of (Equation 1.21), both $K$ and $D$ are estimated in the DKI technique, therefore there are 22 unknown variables (i.e., 6 for DTI, 15 for DKI as well as a non-diffusion weighted image $S_0$). This means at least 22 diffusion weighted images acquired in 15 different gradient directions with two b-values, one of which is slightly higher than that required for traditional DTI fitting [150]. Therefore, DKI has more variables to fit compared to DTI, possibly leading to over fitting and poor reproducibility. Moreover, the acquisition time will also increase as the number of b-values increase, limiting DKI for clinical applications. However, one of the studies discussed in this thesis (Chapter 2) has shown that high spatial resolution DKI can still be achieved in a scanning time clinically feasible [76].

### 1.3.7 Fibre orientation distribution function

The DTI and DKI techniques discussed above do not naturally distinguish different fibre configurations (see Figure 1.7). In the investigation of structural connectivity, it is important to know the exact direction(s) of the underlying fibre bundle. This is possible with the PGSE sequence, since it enables probing diffusion in multiple directions. We know that, $P$ (Equation 1.4), the probability distribution of the water particles during the diffusion time (in order of milliseconds), fully characterizes the diffusion process in the underlying tissue. In many cases, the aim is to visualize the preferred direction of diffusion which likely corresponds to the underlying fibre. A common approach is to compute the relative magnitude of the water particle displacements, or $P$, over all directions, and then radially integrate $P$, to obtain the diffusion orientation distribution function (dODF). The dODF characterizes the diffusion process itself or in other-words, it is the probability of diffusing water particle moving in a certain direction. To make inferences relating to the underlying fibre distribution in an imaging voxel, a metric called fibre orientation distribution function (FOD) is calculated. The FOD is a probability dis-
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Distributions on the sphere, where each point on the sphere corresponds to a unique fibre orientation [66].

**Tractography**

As seen in the previous sections, the peak in the FOD or the primary eigenvector in DTI, provides information relating to the WM fibre bundle orientation within a voxel. The FOD is often employed to resolve multiple fibres with varying orientations or crossing fibres (see Figure 1.7). To appreciate the orientation of the fibres and their relationships with neighboring voxels and other WM fibre bundles or more remote structures as in GM, a computer aided 3D tracking technique called tractography is used. There are two common methods used in tractography: deterministic and probabilistic. The salient property that distinguishes these two tractography method is how fibre directions in a voxel are selected for streamline propagation. Deterministic tractography assumes a single preferential diffusion direction (i.e., indicated by the main eigenvector from DTI or the peak in the FOD) in each voxel, and by applying a streamlining algorithm a tract is produced. In contrast, instead of using a single FOD pick, the probabilistic method calculates the distribution of fibre orientations to select the direction of tracking. Generally, the two tractography methods require seed voxels to initialize tracking, which can be supplied via a registered template [88].

1.4 Group-wise dMRI Parameters Comparison Methods

The following subsections briefly highlight some of the common dMRI parameter analysis methods, in particular voxel-based morphometry (VBM), tract-base spatial statistics (TBSS), region of interest (ROI) and introduce the new track specific analysis. Before looking into these analysis techniques, a quick summary of the common image registration approach is given, since registration is an important step that must be applied before most group-wise comparison of local dMRI measurements are performed.
1.4.1 Cross-subject image registration

Registration is the spatial alignment of two images, an input and a reference image. The input image contents are moved around within the image matrix to find the closest match with the reference image. The two images can be from a same subject or two different subjects, or a subject and a template (i.e., a image commonly build form averaging multiple subjects).

There are basically two main types of registrations, linear and nonlinear. In linear registration, the motions applied to the input image are limited to translation, rotations, scaling and shear, and these motions are applied to the entire input image and tend to be robust and accurate for aligning images from the same subject. However, linear registration is generally not very accurate for aligning two images from different subjects, due to differences in shapes and sizes of the brain. Therefore, nonlinear registration is mostly used to align images from different subjects or subject to a template. Nonlinear registration allows for more local warps instead of the global or whole image motions achieved with linear registration. Generally, this type of registration is first initialized by linear registration to find a global match of the two images, before very fine and complex warps are made to achieve a final alignment. The approach (linear + nonlinear registration) is common in diffusion MRI analysis studies. The preferred method is to register subjects’ FA images to standard template such as MNI152-T1 weighted average image or a more study-specific template.

1.4.2 Voxel-based morphometry

The VBM technique aims to detect local tissue differences between groups (e.g., patients vs controls) by performing voxel-wise comparisons using quantitative images. The main challenge faced in various studies applying VBM on structural MRI data, is to guarantee that any given voxel in the final space (i.e., the space where voxel-wise statistical analysis is performed) for each subject corresponds to the same anatomical region. In dMRI based VBM analysis, subjects’ FA images are commonly used for registering to a standard template. However, it is observed that, differences in certain parts of the brain (e.g., ventricular sizes or shape) be-
between patients and controls have led to shifts in fibre bundles causing misalignment between
the groups. This phenomenon has sometimes led to misinterpretation of the results with voxel-
wise analysis [118]. In addition, the arbitrary choice of smoothing can improve detection of
alterations in the microstructure if the degree of smoothing is matched to the spatial properties
of the anatomical structure of interest. The challenge is that, prior information relating to the
structure of interest is limited, and there is no standard way to choose the extent of smooth-
ing. Moreover, applying different smoothing extent increases partial volume effects. The main
challenge here is that, dMRI data are sensitive to the microscopic structures of the brain tissue,
and comparison between groups at this level relies heavily on the accurate alignment of these
microscopic structures. Any misalignment in the data severely influences the interpretability,
leading to incorrect conclusions. Although, some studies have tried to deploy post-hoc analy-
sis to address VBM issues, it is clear that in dMRI, VBM is not sufficiently sensitive to detect
focal pathology in subjects with relatively subtle tissue microstructural changes [80], such as
cortical neuronal loss and hippocampal sclerosis [46]. Therefore, VBM is not considered to be
an adequate stand-alone technique for detecting focal lesions [93].

1.4.3 Tract-based spatial statistics

The TBSS technique attempts to address the alignment and smoothing problems in a fully
automated manner [120]. TBSS is achieved by first registering an individual subject’s FA
images to a common space using nonlinear registration. At this stage perfect alignment is
not required. The next step is to estimate the group mean FA skeleton (representation of the
WM fibre bundles cores), which is achieved by creating an average FA image from all the
aligned individual subject’s FA images to remove any non-maximum values perpendicular to
the local tract structure. Also removed are areas of low mean FA and or high inter-subject
variability. The following step is to project the individual subject’s aligned FA images onto
the skeleton, filling it with values from corresponding tract in each subject FA image. Finally,
voxel-wise statistical analysis is carried out across subjects on the skeleton-space FA maps.
The same approach can be used to project other quantitative maps (e.g., MK from DKI) onto the skeleton for statistical analysis. TBSS may be an improvement over conventional VBA. However, similar to VBA, the TBSS technique cannot ensure that any voxel along a tract length corresponds to the same tract across subjects [136].

### 1.4.4 Region of interest and tractography based methods

Region of interest analysis is a widely used method for the analysis of diffusion MRI data. This technique is used to compare local diffusion parameters across subjects or groups (i.e., patients vs controls). The ROI analysis method involves an anatomically defined region, either based on anatomical borders or a geometrical shape. These regions are used to extract quantitative measurements from DKI or other diffusion MRI techniques, which can later be analyzed statistically. The ROI analysis can be performed either automatically by aligning all subjects to a template, or by manual delineation.

A more sophisticated approach uses tractography to identify voxels to take quantitative measurements between groups or subjects. This method uses manually drawn ROIs in standard space for bundles of interest and constrains tracking to the respective bundles. The tracking is seeded from the ROIs, then the resulting bundle is averaged across subject to generate the bundle mask. Finally, summary statistics are carried out on all voxels from the quantitative metrics within the mask.

The challenge is that the ROIs are defined in a standard space and tracking is therefore carried out in this space, which means the final results still rely on the accuracy of the individual metrics (e.g., DKI parametric maps) alignment to the template. In addition, diffusion measurements are averaged across the entire tract length, this ignores possible variations in diffusion properties along the tract. To account for this, approach such as ‘along-tract analysis’ has been developed [153]. This technique uses fibre bundles derived from tractography and quantitative metrics estimated with dMRI models (e.g., MD from DTI) are sampled along the bundle length. Since this method is robust in addressing the alignment problem across sub-
jects, a specific along-tract analysis was incorporated in some of the work discussed in this thesis (see Chapter 3). Furthermore, new emerging techniques are now able to automatically identify and cluster fibre bundles from whole brain tractography and provide alternative to the TBSS approach discussed above [104].

1.5 Thesis Objectives

Diffusion tensor imaging has been used to quantify diffusion properties in TLE patients brain microstructure. However, its inherent assumption of free water diffusion is widely considered to be inadequate for fully quantifying diffusion within the complex microstructure of the human brain tissue. On the other hand, the DKI method aims to characterize the restricted and hindered diffusion environment while also measuring the free diffusion properties in the underlying tissue microstructure. Preliminary studies have shown DKI to better detect diffusion abnormalities in TLE patients compared to traditional DTI. Given these factors, the objectives of this thesis is to:

1. Evaluate the reproducibility of high spatial resolution DKI at different gradient strengths,
2. Investigate the ability of DKI to detect diffusion abnormalities in the temporal pole of lesional and non-lesional MRI TLE subjects, and
3. Assess the added value of DKI in lateralization of TLE patients using machine learning.

1.6 Thesis Outline

Three studies are conducted to systematically address the objectives listed in section 1.5. These studies incorporate a DWI dataset acquired locally from a 3T MRI system, high spatial resolution DWI dataset from the open source Human Connectome Project (HCP) database and a diffusion phantom dataset. A short summary of each chapter is given below.

- Chapter 2 —Investigating DKI reproducibility at higher spatial resolution with phantom validation. This work aims to evaluate the reproducibility (test-retest reliability) and
quality of fit of high spatial resolution (1.25mm isotropic) DKI. We examined tissue-
specific coefficients of variation and fitting residuals as function of b-values for whole-
brain WM, including specific WM fibre bundles, and cortical GM, as well as across
lobes. In addition, we verified the in vivo findings using tissue-mimicking phantoms.
The study demonstrates that high reproducibility can still be achieved within a reason-
able scan time, specifically with a sequence employing only two b-values (i.e., b-value
= 1000, 3000 s/mm$^2$), supporting the potential of DKI for aiding clinical tools in detect-
ing microstructural changes.

- **Chapter 3 —Probing the temporal pole microstructure of TLE patients using DKI.**
The following study aims to employ DKI to quantify complex microstructure to detect
diffusion anomalies in TLE patients, and more specifically, to evaluate the sensitivity
of DKI to detect anomalous regions along the inferior longitudinal (ILF) and uncinate
fasciculus (Unc) fibre bundles connected to the temporal pole in lesional MRI (‘MRI+’) and
non-lesional MRI (‘MRI-’) TLE patients. In addition, the connected temporopolar
cortex was also investigated for abnormalities. The study showed that DKI was able to
detect possible microstructural changes in the anterior WM connected to temporal pole
and within the cortex in both MRI+ and MRI- subjects not clearly visible using DTI
metrics.

- **Chapter 4 —Diffusion kurtosis imaging based characterization of TLE patients.** In
this chapter, we sought to evaluate the added value of a DKI imaging protocol by assess-
ing how well diffusion metrics (tensor-based and kurtosis-based) perform in a machine
learning application to classify epilepsy patient groups and controls. We employed a
multiclass classification approach, and examined how the regions and metrics chosen by
the feature selection algorithm relate to clinical findings. The study demonstrates that
DKI has potential in detecting subtle changes in the brain regions, suggesting alteration
in water diffusion, possibly induced by cytoarchitecture changes related to epilepsy.
• **Chapter 5 — Conclusion.** Finally, this chapter presents a summary of this thesis contributions and suggestions for future directions.
Chapter 2

High Spatial Resolution Diffusion Kurtosis Imaging Reproducibility

2.1 Overview

This Chapter is adopted from the following manuscript titled, *Evaluating High Spatial Resolution Diffusion Kurtosis Imaging at 3T: Reproducibility and Quality of Fit* [76] which is published in the Journal of Magnetic Resonance Imaging. The main focus is to verify the reproducibility and fitting quality of high resolution DKI protocol.

2.2 Introduction

Diffusion tensor imaging (DTI) is a non-invasive method to estimate water particle’s apparent diffusion in the brain [12]. Since its first use, DTI has evolved tremendously, in particular with faster acquisition times, making it better suitable for clinical imaging purposes [12, 70]. Common quantitative parameters derived from DTI include: fractional anisotropy (FA), which describes the amount of anisotropic diffusion and reflects the preferred direction of diffusion; mean diffusivity (MD), the average diffusion; axial diffusivity (AD), the diffusion in the axial direction; and radial diffusivity (RD), the diffusion perpendicular to the axial diffusion [135]. While these DTI metrics are useful, the technique is based on the assumption that diffusion
of water particles in tissue microstructure follows a Gaussian distribution [135]. Although a Gaussian distribution is predominantly observed in regions of coherent fiber bundles, DTI fails to adequately quantify water motion in most parts of the brain with complex cytoarchitecture such as in the cerebral cortex and in areas of white matter (WM) with substantial fiber crossings [135]. These microstructural properties cause water diffusion to considerably deviate from a Gaussian shape. This has been evident in imaging techniques like q-space imaging, which employs many acquisitions that include both high and low b-values in order to estimate the full diffusion displacement, but with the trade-off of longer scan time [135, 33].

Diffusion kurtosis imaging (DKI) was introduced to accommodate the shortcomings of DTI and better characterize non-Gaussian diffusion behaviour with a protocol that uses a modest increase in the number of b-values that are used in DTI [74]. DKI is derived from expanding the standard diffusion signal equation in powers of b-value (see Equation 2.1). Therefore, both diffusion and kurtosis tensors can be estimated to provide mean kurtosis (MK); axial kurtosis (AK); radial kurtosis (RK) in addition to the DTI metrics [74, 150]. Since the introduction of these parameters, they have been used across several clinical populations including Parkinson’s and Alzheimer’s patients, but also for (early) assessment of stroke, traumatic brain injury, epilepsy and numerous other clinical studies [8, 71, 63, 21, 113].

Despite the benefits of DKI as a non-invasive tool for delineating microstructural alterations due to diseases or microstructural complexity, the technique requires at least one additional shell of acquisitions than the single shell required for DTI. DKI also has more parameters to fit than DTI, which, depending on the acquisition (e.g., minimum of 15 directions for standard DKI protocol), could lead to overfitting of the data, poor reproducibility (test-retest reliability), and limited use in clinical practice [124]. Additionally, in order to capture the non-Gaussian diffusion behaviour of water molecules in biological tissues, b-values larger than those employed in DTI are required [74]. However, higher b-values not only lower the signal-to-noise ratio (SNR) of the respective image volumes, affecting the reproducibility of the calculated parameters, but also increase acquisition time [134, 47, 107]. In order for DKI to be integrated
into clinical workflows, the reproducibility of its estimated parameters in different tissue types with different microstructural properties has to be established. A previous study has assessed DKI reproducibility with different b-values and fitting algorithms, but was limited to 3 mm isotropic spatial resolution, and concentrated on MK in selected WM and grey matter (GM) voxels only [32]. A more recent study specifically focused on test-retest reliability of high spatial resolution data, looked at test-retest reliability of DKI 1.75 mm isotropic spatial resolution only, but were unable to utilize 1.25 mm resolution imaging due to insufficient SNR [116]. Although this was a first study to evaluate DKI at high spatial resolution in vivo, the study only focused on whole-brain WM and the effect of different b-values in different tissue types was not assessed. Since DKI has the ability to characterize microstructure in less anisotropic environments such as GM, it is important to fully investigate DKI reproducibility in these areas, which could also aid our understanding of neurodegenerative diseases, including aging, that are associated with GM abnormalities [74, 26, 108]. The aim of the study was to evaluate the test-retest reliability of the following: (i) high resolution (1.25 mm isotropic spatial resolution) DKI estimated parameters over the entire brain including specific WM and GM regions of interest (ROIs), and (ii) DKI parameters on fiber phantoms that mimic WM fiber configuration, specifically to investigate whether acquisitions with fewer shells, but differing maximum b-value, could provide reproducible parameters with reduced scanning time.

2.3 Materials and Methods

2.3.1 Image acquisition

In vivo imaging

A total of 44 subjects (31 female, age 22-35) from the test-retest Human Connectome Project (HCP) database were included in this study. Diffusion weighted imaging (DWI) data were acquired twice for all subjects across two separate sessions (average of 5 ± 3 months apart) using a high-quality image acquisition protocol and a modified Siemens (Erlangen, Germany) Skyra 3T scanner [123]. DWI acquisition parameters included repetition time/echo time (TR)/(TE) =
5520/89.5 ms, multiband factor = 3, phase partial Fourier = 6/8 without in-plane acceleration, and nominal isotropic voxel size of 1.25 mm\(^3\). A total of 288 images were acquired in each DWI dataset (acquired in both left-to-right and right-to-left phase-encoding polarities for echo-planar imaging (EPI) distortion correction), including 18 baseline images with low diffusion weighting b-values = 5 s/mm\(^2\) and 270 diffusion weighted images or diffusion gradient directions evenly distributed across three shells of b-values = 1000, 2000, 3000 s/mm\(^2\). Acquisition for each shell took 9 minutes and 50 seconds, totalling up to 29 minutes and 30 seconds for the full DWI acquisition. The data were preprocessed following HCP’s “minimal preprocessing” pipeline, which included brain masking, motion correction, eddy current correction and EPI distortion correction [59].

**Phantom imaging**

We constructed four groups of three phantoms each to compare across specific crossing angles of 0°, 30°, 60°, and 90°, and to verify the *in vivo* results. For this we used a 3D printing protocol developed in a previous study that entails fused deposition modeling 3D printing with a composite material consisting of rubber-elastomeric polymer and a polyvinyl alcohol (PVA) component (PORO-LAY) [100]. Each of the 12 phantoms were 11 mm in radius with 100 µm layers of parallel lines with alternating orientations mimicking brain microstructure with crossing fibres (see Appendix A Figure A.5). Following immersion in water for 168 hours to allow the PVA to dissolve exposing the microstructure, the phantoms were stacked in a test tube with distilled water before imaging with a 9.4T Bruker (Billerica, MA) scanner, following the HCP *in vivo* protocol’s number of directions per shell. The other imaging parameters include TE/TR=37/2500 ms, field of view (FOV) = 200 x 200 mm\(^2\), 0.7 mm isotropic in-plane resolution, 6 axial slices (3 mm, one per phantom), and scan time 8.5 minutes per each of 2 scans to cover all phantoms. This was repeated twice to facilitate test-retest reliability measurements (the sample was not removed between scans).
2.3.2 Image processing

In vivo

For both test and retest data of each subject, two subsets of data were selected from the original three shell dataset to assess DKI reproducibility as a function of b-values used. The second dataset included only b-values = 1000, 3000 s/mm$^2$, while a third only b-values = 1000, 2000 s/mm$^2$. Note that the b-values = 0 s/mm$^2$ was included in both datasets. Three separate fitting procedures were conducted using the open source software diffusion imaging in Python (DIPY v1.0) to generate corresponding DKI parametric maps for each b-value dataset and timepoint (i.e., test-retest). It is important to note that during DKI fitting, the diffusion tensor $D$ and diffusion kurtosis $K$ are calculated simultaneously (see Equation 2.1), where $K$ characterizes the deviation from Gaussian diffusion [74]. $S$ corresponds to the diffusion weighted image at $b \neq 0$ and $S_0$ is non-diffusion weighted image at $b = 0$.

\[
\ln \frac{S}{S_0} = -bD + \frac{(bD)^2K}{6},
\]  

(2.1)

The DKI metrics include: DTI MD, AD and RD. In addition, we obtained the three kurtosis metrics: MK, the average of the kurtosis overall diffusion directions; AK, the kurtosis in the axial direction, and RK, the kurtosis perpendicular to the axial direction. To allow group analyses, we used the MRtrix v3.0 functions: ‘dwi2fod’ to generate individual fiber orientation dispersion (FOD) maps and ‘population_template’ to compute an unbiased group-average FOD template from the individual subject’s FODs. To minimize variability between the subjects’ scans (test and retest data), we performed a rigid registration between subject’s FODs bringing all FODs into test data space.

The calculated transformations were also applied to the respective DKI maps. Then the FODs from the first test dataset for each subject were registered to the FOD template, the calculated warps were then used to warp each subject’s DKI maps including maps from retest
data in test data space to the template space.

For white matter region-based analyses, the JHU-ICBM-labels atlas in MNI152 space was transformed to the FOD template via transformation obtained from FSL v6.0.2 ‘flirt’ registration of the MNI (6th generation) template to b = 0 image extracted from the FOD template [96]. For whole-brain WM analysis, the transformed JHU-ICBM-labels atlas was used as WM mask, restricting analysis within the deep WM only, that is, within the WM axonal bundles. The MNI152 to FOD template transformation was also used for transforming selected WM ROIs from the JHU-ICBM-labels atlas.

We selected these white matter ROIs (see Appendix A Figure A.1, (CiC-Cingulum Cingulate, CiH-Cingulum Hippocampus, Fx-Fornix, SFOF-Superior Fronto Occipital Fasciculus, SLF- Superior Longitudinal Fasciculus and Unc-Uncinate Fasciculus) since they are commonly implicated in neurological disorders [115]. In addition, for GM analyses of the individual lobes (FL-Frontal Lobe, PL-Parietal Lobe, LL-Limbic Lobe, TL-Temporal Lobe and OL-Occipital Lobe) of the population-average, landmark and surface-based (PALS) atlas of the human cerebral cortex, we mapped all the individual subject’s coregistered maps onto the ‘fsaverage’ surface space [51, 137].

To do so we used the DWI-based data that were registered to the anatomical space following the HCP’s ‘minimal preprocessing’ pipeline [59]. Then, FreeSurfer’s ‘mri_vol2surf’ function was used to project the anatomical space DKI maps onto the fsaverage surface by calculating the vertex-wise (i.e., per individual data point on the surface mesh) averages across cortical depths (i.e., WM to pial surface direction). To minimize partial voluming effects with WM and CSF, we only averaged across voxels within 20-80% of the estimated cortical thickness, within each of the five lobes from the PALS atlas (see Appendix A Figure A.1).

**Phantom**

For the phantom’s test-retest data, masks were manually created (L.K., 4 yrs of experience) for the images from each of the 12 phantoms to remove regions with air bubbles. Then the original test-retest data were used for selecting two subsets of data with two shells each, similar to the
procedure performed for the *in vivo* dataset. Following this, FODs were generated for each subset including the original data with three shells. We then rigidly registered the retest to the test data to minimize any variability between the scans, and the warp fields obtained were used to transform the calculated DKI maps. These steps were also similar to the *in vivo* dataset workflow, with the exception of the transformation to the WM and GM template spaces.

### 2.3.3 Image analysis

To evaluate reproducibility, we calculated the voxel- (both *in vivo* and phantom data) and vertex-wise (*in vivo* data only) within-subject coefficient of variation (CoV). The CoV (i.e., the standard deviation to mean ratio) was determined for the individual parametric maps and estimated from the test-retest data within each of the three datasets: original (b-values = 1000, 2000, 3000 s/mm$^2$) will be referred to as dataset A and the two selected datasets (b-values = 1000, 3000 s/mm$^2$ and b-values = 1000, 2000 s/mm$^2$), which will be referred to has datasets B and C, respectively. A representative axial slice was extracted for visual inspection of individual DKI maps from each of the test-retest dataset (A, B, and C). In addition, to check for any potential bias in our analysis, we performed Pearson correlation tests of the calculated values between the DKI parametric maps derived from each dataset. Moreover, to evaluate DKI fitting quality, we calculated the mean absolute residuals ($R$), which represent the difference between the modeled and diffusion-weighted signals (see Equation 2.2) for each dataset (i.e., varying b-values) [135]. Large residuals indicate the presence either of potential artefacts in the acquired data, or that the applied method is unable to characterize the observed signal accurately [135]. Therefore, to gauge the quality of the DKI estimation of the measured signals, mean residual maps $R$ for each voxel for individual DWIs were calculated,

$$R = \frac{1}{N} \sum_{n=1}^{N} \left| \frac{S}{S_0} - e^{-bD + \frac{1}{6}b^2D^2} \right|,$$

(2.2)

where $N$ is the number of DWIs, $S$ and $S_0$ are the diffusion and non-diffusion weighted
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images respectively, and $D$ and $K$ are the estimated diffusion and kurtosis tensor with the diffusion weighting $b$ [98]. Note that in addition to $K$, $D$ is also estimated in the kurtosis method, as outlined by Jensen et al. [74]. All statistical analysis was carried out using the scipy package (v1.4.1) for Python.

Statistical analysis

Differences in CoV between datasets and individual parameters were statistically evaluated using repeated measures analysis of variance (ANOVA, corrected for multiple comparisons using Bonferroni, age and sex), and followed up by tests of simple main effects in case of statistical interactions (using $\alpha = 0.05$) as implemented in SPSS (v.23, IBM, Armonk, NY) (Figure 2.1).

Figure 2.1: General workflow. Preprocessed HCP test-retest data were used for the study. A population-based template was created from the subjects’ FOD images. Then the individual subject’s generated DKI maps were coregistered before warping into the FOD template space. The WM JHU-ICBM-labels atlas was coregistered to the template, facilitating CoV analysis in WM ROIs and whole-brain WM. For GM analysis, the coregistered subject’s maps are mapped onto Freesurfer’s fsaverage space; following this, CoV analysis was performed for selected ROI surfaces.
Figure 2.2: The test-retest datasets, (b-values = 1000-3000 s/mm$^2$) 1$^{st}$ column (dataset A) and the two derived datasets (b-values = 1000 & 3000) 2$^{nd}$ column (dataset B) and (b-values = 1000 & 2000 s/mm$^2$) 3$^{rd}$ column (dataset C). Shown is a representative axial slice for all generated DKI maps including the DTI maps estimated with DKI method from an individual subject.

2.4 Results

For the in vivo study, Figure 2.2 shows a representative axial slice for all the DKI estimated parameters from each of the test-retest datasets (columns). Figures 2.3 and 2.4 report the CoV analysis of the WM, while Figures 2.5 and 2.6 represent GM CoV analysis and evaluation of whole-brain and WM ROIs fitting quality, respectively. Figures 2.7 and 2.8 show the CoV and fitting quality analysis of the phantom data.
Figure 2.3: Mean voxel-wise within-subject CoV for MK mapped onto the FOD template (A) and within the WM for all the maps (B). All maps were generated from dataset A (blue) (b-values = 1000-3000 s/mm$^2$), dataset B (orange) (b-values = 1000 & 3000 s/mm$^2$), and dataset C (green) (b-values = 1000 & 2000 s/mm$^2$). The dotted line is placed at 20% CoV for reference. Notice in (A), the superficial WM (the area that fills the space between the deep WM and the cortex) is masked out, enabling extraction of CoV within the main WM axonal bundles only.

2.4.1 In vivo imaging

Parameter reproducibility

Initial visual inspection of a representative subject’s parametric maps shows a closer resemblance for the DKI parametric maps (MK, AK and RK) between datasets A and B, compared
to dataset C (Figure 2.2). Lower differences are seen for the DTI maps calculated from the DKI technique. More specifically, the heat maps in Figure 2.3A indicate the variation in the MK metric within the whole-brain WM mask. While the CoV for datasets A and B is comparable, dataset C differs strongly from the other two, with more regions around the ventricles having higher CoV (~ 20%). As a result, mean within-subject CoV varies significantly between datasets ($F_{2,82} = 12.80, p < 0.001$; Figure 2.3B). Datasets A (in blue) and B (orange) are more comparable (CoV < 10%; simple mean effects: $p > 0.05$) compared to C (green) with CoV > 10%, $p < 0.05$ for the DKI metrics. Moreover, test-retest variability is significantly different between parametric maps ($F_{2,82} = 24.80, p < 0.001$). In general, lower differences between datasets are seen among the DTI metrics (MD, AD and RD) estimated from DKI, as indicated by a significant dataset*modality interaction effect ($F_{2,82} = 5.92, p < 0.005$). A similar trend across datasets is apparent for the within-subject CoV in the selected WM ROIs ($F_{2,82} = 6.68, p < 0.005$; Figure 2.4). In datasets A and B, the mean CoV ranges from 5-15% compared to dataset C, with a more dispersed CoV as high as ~ 40% seen in the RK metric. CoV does not differ between selected WM bundles ($F_{5,205} = 1.48, p > 0.05$). In addition, we note a high Pearson correlation coefficient ($r \sim 1$) between all the three datasets in their DKI mean parametric values in the whole-brain and selected WM ROIs, as shown in the Appendix A Figures A.2 and A.3. The heat maps in Figure 2.5A indicate the within-subject variation for the MK cortical surface data and shows a similar, but stronger, behaviour across datasets ($F_{2,82} = 96.62, p < 0.001$) as seen for the WM results (Figures 2.3 and 2.4). We observed widespread higher CoV (~ 20%) in the cortex from the dataset C, in contrast to A vs. B. This pattern is consistent across each of the five lobes (Figure 2.5B). The within-subject CoV varied strongly between lobes ($F_{4,164} = 4.298, p < 0.005$). However, higher variability is observed for the DKI maps, ranging from 10-28% ($F_{1,41} = 50.94, p < 0.001$), with the highest in the limbic lobe from the dataset C compared to the A and B datasets with CoV in between 5-15%. Contrary to the higher CoV in dataset C for the DKI maps, only a slight increase in reproducibility was observed in the estimated DTI maps between the three datasets (dataset*modality interaction
effect, $F_{2,82} = 101.15, p < 0.001$). Although there were differences in the CoV values across the three datasets (A, B, and C), we note a high Pearson correlation coefficient ($r \sim 1$) between all the three datasets in their DKI mean parametric values as shown in Appendix A Figure A.4.

**Quality of fitting**

Figure 2.6A shows the kurtosis tensor residuals calculated for each subject’s DWIs (averaged across whole-brain voxels). Based on the whole-brain data, the quality of fitting appears to be consistent across datasets ($F_{2,82} = 0.498, p > 0.05$). Two subjects (encircled in red) are characterized by higher residuals across the three datasets, with dataset C characterized by highest residuals. Figure 2.6B presents the residuals averaged within the selected WM ROIs. Dataset B is characterized by the lowest residuals, compared to A and C ($F_{2,82} = 48.70, p < 0.001$), while compared to the other WM ROIs, the SFOF had the highest fitting residuals ($p < 0.001$).

### 2.4.2 Phantom studies

**Parameter reproducibility**

In line with the *in vivo* CoV analyses (Figures 2.3 and 2.4), CoV varies significantly between datasets for the phantom acquisitions ($F_{2,16} = 29.83, p < 0.001$), with lowest CoV observed for A and B, compared to C. DTI maps were characterized by significant lower CoV ($p < 0.05$) and different patterns across datasets ($F_{2,16} = 22.13, p < 0.001$), as shown in Figure 2.7. Interestingly, although dataset C values were consistently higher across the DKI maps across the different phantoms (i.e., characterized by different crossing angles), the lowest CoV was observed for the 60° phantom in all the maps from the respective datasets (n.s.). The mean parametric values for MK and MD are shown in Appendix A Table A.1; we observed all datasets having a high Pearson correlation coefficient ($r \sim 1$) except for the 60° phantom in dataset C with an outlier.
Figure 2.4: Mean voxel-wise within-subject CoV within the WM ROIs (CiC-Cingulum Cingulate, CiH-Cingulum Hippocampus, Fx-Fornix, SFOF-Superior Fronto Occipital Fasciculus, SLF-Superior Longitudinal Fasciculus, and Unc-Uncinate Fasciculus). All maps were generated from the datasets; dataset A (blue) (b-values = 1000-3000 s/mm$^2$), dataset B (orange) (b-values = 1000 & 3000 s/mm$^2$), and dataset C (green) (b-values = 1000 & 2000 s/mm$^2$). The dotted line is placed at 20% CoV for reference.

Quality of fitting

The goodness of fit test for each of the phantoms representing varying fiber orientations is shown in Figure 2.8, where we observe the same trend with datasets A and B having lower fitting residuals compared to dataset C ($F_{2,16} = 810.7$, $p < 0.001$). Finally, the phantoms with 60° crossing angles had the lowest DKI fitting residuals across all the three datasets, similar to what is seen in Figure 2.7 ($F_{3,8} = 7.270$, $p < 0.05$).
2.5 Discussion

In this study, we explored the reproducibility and fitting quality for all DKI-based estimated parameters at varying b-values used in a test-retest scenario for high spatial resolution data acquisitions. The key finding in this study was that DKI using only two b-values – the lowest and highest b-values (1000, 3000 s/mm$^2$) of the HCP dataset – is a satisfactory approach. In other words, an additional third b-value (i.e., b-value = 2000 s/mm$^2$) has a limited beneficial effect on the reproducibility to quantify the different tissue types (WM and GM). These findings were further verified with 3D printed brain microstructure-mimicking phantoms. Importantly, compared to the b-values = 1000, 2000, 3000 s/mm$^2$ approach, the derived b-values = 1000, 3000 s/mm$^2$ protocol offers the advantage of reduced scanning with comparable reproducibility.

2.5.1 DKI reproducibility and fitting quality in in vivo imaging

In the WM, the CoV for the DKI estimated parameters was comparable between the original dataset with three shells and the dataset B with two shells (b-values = 1000, 3000 s/mm$^2$), with CoVs <10% except for a slight increase in RK. This finding corresponds to a previous study that looked only at MK reproducibility and accuracy in selected voxels with respect to b-values and fitting algorithms in in vivo and ex vivo datasets [32]. The authors concluded that in the WM the protocols with maximum b-values ($b_{\text{max}}$) ranging from 2500 to 3000 s/mm$^2$ and applying weighted linear least square (WLS) fitting achieved the highest accuracy. It was also observed that in selected voxels, the variability of the microstructure influenced the accuracy and reproducibility for each $b_{\text{max}}$. This is in line with what we examined in both whole-brain WM and across selected WM bundles. We also observed that there was lower variability within most of the selected bundles, including the larger known bundles like SLF and Unc for the datasets with $b_{\text{max}} = 3000$ s/mm$^2$ (datasets A and B) compared to $b_{\text{max}} = 2000$ s/mm$^2$ dataset (dataset C), except for a slight increase of CoV in the CiC.

These larger bundles are known to have higher crossing or bending configurations, suggesting that higher b-value acquisition could be beneficial for DKI to quantify non-Gaussian
diffusion in WM regions with more complex fiber configurations [135]. However, the SFOF results deviate from this hypothesis, with higher fitting residuals (i.e., lower quality of DKI fitting). This could be reflective of the label’s specific location, since SFOF is more coherent in the middle segment and disperses at the ends [11].

Moreover, better representation of SFOF is seen to be achieved using data-driven approaches like tractography [11]; therefore, the high residuals could be related to the inaccu-
Figure 2.6: Residuals from DKI fitting averaged across voxels for individual subject’s DWIs from each of the three datasets: A (blue) (b-values = 1000-3000 s/mm²), dataset B (orange) (b-values = 1000 & 3000 s/mm²), and dataset C (green) (b-values = 1000 & 2000 s/mm²) (A). ROI residuals from DKI fitting averaged across voxels for individual DWIs from each of the three datasets: A, B, and C (B).

racy of hand-segmented labels. For the GM, we focused on the five lobes and determined the average DKI CoV across cortical depths (i.e., from WM to the pial surface). Although DKI reproducibility was lower in GM compared to whole-brain WM, potentially due to partial volume effects [87, 152], a similar trend was noticed between the dataset A and the dataset B, both achieving CoVs ranging from 10-15%. Dataset C had higher interscan variability across the five lobes in all the maps.

In contrast to the frontal, parietal, occipital and limbic lobes, the temporal lobe has lower CoV across all the DKI maps. This might allude to the structural composition of the tempo-
ral lobe itself compared to the other four lobes of the brain [137]. As seen in both animal and human studies, the entorhinal cortex within the temporal lobe, which constitutes the major gateway between the hippocampal formation and the neocortex, is characterized by polysynaptic fan cells (i.e., especially within layer II) [147]. The complexity of these cells could contribute to higher kurtosis within the temporal cortex, allowing DKI to better quantify this region. In addition, an earlier study using neurite orientation dispersion and density imaging (NODDI) revealed higher neurite (dendrites and axons) density values, indicative of more branching complexity in dendrites within the temporal cortex compared to other cortical regions [55]. This suggests that DKI datasets with $b_{max} = 3000 \text{ s/mm}^2$ could especially be helpful for the quantification of a highly dispersed region such as the temporal lobe. Therefore, the differences in the reproducibility of each datasets across the lobes, in particular between dataset C and the two $b_{max} = 3000 \text{ s/mm}^2$ datasets (A and B), could be also due to the variability of the cytoarchitecture in individual lobes composition and functions [138]. Furthermore, possible signal dropouts in this region may have introduced consistently low values contributing to less variation between test-retest data. To verify the quality of kurtosis tensor fitting, we determined the fitting residuals as the difference between the measured and the predicted DWI signal, where higher residuals correspond to lower quality of fitting [98]. In general, we observed comparable fitting results between datasets A and B, while dataset C has slightly higher residuals across the brain. From the calculated fitting residuals in the whole-brain, we found that two subjects had high residuals across the three datasets, this could be due to motion artifact.

On the other hand, in the WM ROIs, lower residuals were observed with dataset B compared to A and C, indicating the possibility of lower signal in the acquisition with a $b_{max}$ of 2000 s/mm², rendering it less adequate for DKI fitting. In addition, although we employed the preprocessed HCP dataset for the current study, subtle imaging artifacts (e.g., head movement, eddy-current, inhomogeneity of magnetic susceptibility, etc.) could remain present in the underlying data that potentially affect the fitting quality [59].

Furthermore, to check for any bias in our in vivo analysis, we also performed a pairwise
correlation coefficient (r) test (see Appendix A Figures A.2, A.3 and A.4) for each subject between DKI parametric values from the three datasets. The findings suggested a high correlation (r \sim 1) between all datasets, with consistent correlation between the \( b_{\text{max}} = 3000 \text{ s/mm}^2 \) datasets in both WM and GM. The DKI \( b_{\text{max}} \) dependencies observed in this study had been seen previously, where approximation of signal intensity with DKI up to b-values of about 5000 \text{ s/mm}^2 had been examined \[32, 73\]. But the downside of deploying higher b-values is the reduced SNR for these data and lower reproducibility, thus limiting the clinical feasibility of these acquisition approaches \[32, 54\].

Figure 2.7: Mean voxel-wise within-scans CoV determined across the phantoms with varying fiber crossings (0°, 30°, 60°, and 90°). All maps generated from dataset A (blue) (b-values = 1000-3000 s/mm\(^2\)) and the derived datasets, B (orange) (b-values = 1000 \& 3000 s/mm\(^2\)), and C (green) (b-values = 1000 \& 2000 s/mm\(^2\)), respectively.
Figure 2.8: Fitting residuals averaged across voxels for individual DWIs in each of the phantoms with varying fiber crossings (0°, 30°, 60°, and 90°). This was determined for each of the three datasets: A (blue) (b-values = 1000-3000 s/mm²), B (orange) (b-values = 1000 & 3000 s/mm²), and C (green) (b-values = 1000 & 2000 s/mm²), respectively.

In addition, the kurtosis method used here breaks down for $b_{\text{max}} > 3000$ s/mm², where you would have to use higher orders of the cumulant expansion (i.e., up to $b^3$ instead of $b^2$) [32]. Therefore, it has been observed that better fitting accuracy is achieved up to $b_{\text{max}} = 3000$ s/mm², while $b_{\text{max}} > 3000$ s/mm² shows poor fitting quality [91]. A major difference of this study, compared to previous work that evaluated DKI test-retest reliability, is the conclusion that adding another b-value shell between the protocol with b-values = 1000, 3000 s/mm² does not provide much benefit. This also implies that a lower acquisition time (i.e., by a time equivalent to a single shell acquisition) may be achieved, increasing the potential of DKI for clinical applicability. Nevertheless, the CoV observed within the WM and GM could increase in a clinical MRI system and limit the clinical applicability of DKI. Therefore, to apply the DKI protocol with b-values = 1000, 3000 s/mm² in a clinical setting, further investigation of the current findings is warranted. This could, for example, include investigations with larger
subject cohorts, acquired across multiple sites and different clinical MRI systems. Although there are transitional steps before DKI could qualify as a clinical decision making tool, the suggested investigations could help further verify DKI as a useful medical research tool [149, 101].

### 2.5.2 Verifying DKI reproducibility and fitting quality with phantom data

Similar to the *in vivo* analysis of the whole-brain WM, selected WM bundles and GM, the reproducibility in the protocols with $b_{max} = 3000 \text{s/mm}^2$ (datasets A and B) was higher in phantoms with fibers crossing at 30, 60 and 90 degrees. This indicates that $b_{max} = 3000 \text{s/mm}^2$ could be needed to quantify varying microstructure complexity underlying different tissue types, including WM fiber bundles of complex geometry. This is more evident in the MK, AK, and RK maps.

MK remains almost stable in terms of reproducibility across the different fiber crossings compared to the other maps, including DKI-derived DTI metrics [142]. However, we also observed a lower variability in the 60° phantoms in all the datasets, which could be related to DKI’s ability to resolve fibers close to this configuration, but further analysis (outside the scope of the current study) is necessary to support this hypothesis. We have found the mean CoV for separately printed 3D phantoms with identical crossing angles to be between 2 and 8%, depending on the DKI parameter. Accordingly, the apparent dependence on the crossing angle is likely a result in variabilities of the phantom manufacturing process. In contrast to the *in vivo* data, lower CoV values (difference of 12-18%) are observed in the phantom data; these could reflect the differences in the complexity of the two data types. The fiber orientations represented in the phantoms outline a simplified fiber arrangement in a given voxel and do not capture the complexity of fiber orientations that could be present in the WM [135]. Also, the phantoms are not subject to physiological variation between scans, such as pulsatile brain motion.

In addition, we assessed the goodness of fit in the ground truth data. These findings follow
the same pattern as seen in our CoV results. The three shells dataset b-values = 1000, 2000, 3000 s/mm² (dataset A) and two shells dataset b-values = 1000, 3000 s/mm² (dataset B) maintained lower fitting residuals across the phantoms. On the other hand, higher residuals were seen in the other two shells dataset b-values = 1000, 2000 s/mm² (dataset C). These findings indicate that DKI is robust for quantifying diffusion of water molecules reliably in heterogeneous microstructural environments while maintaining clinical feasibility. Specifically, the kurtosis values in fibers with smaller crossing angles are low. This is due to the intrinsic AK for these fibers being almost negligible (∼0), thus inflating the CoV. On the other hand, fibers with larger crossing angles have higher kurtosis values, since fiber dispersion is a source of kurtosis [126]. There were also small differences in the residuals between different fiber configurations. This is likely due to the fact that the 0 and 30 degree phantoms were observed to have slightly higher $b = 0$ signal intensity, which stemmed from a slightly higher water density. Since the residual is in signal units (a.u.), this translates to a slightly higher residual. Nevertheless, the DKI parameters from datasets with $b_{max} = 3000$ s/mm² show strong reproducibility as the fiber’s angle of crossing increased compared to the more coherent fibers ($0°$), while maintaining high DKI fitting quality across the phantoms [135].

2.5.3 Limitations

Our results may not be readily comparable to a more typical, clinical MRI setup. The current data were acquired using a modified 3T MRI system. This HCP scanner employs more powerful gradients to achieve the high spatial resolution (1.25mm isotropic) for the DWI data [59]. Future work may investigate this potential beneficial effect of HCP’s custom hardware setup and interscanner variability. Moreover, the test-retest interval varies across subjects (average of 5 ± 3 months). However, we assume this effect on the kurtosis parameters reproducibility to be minimal, as the brain’s structural configuration is not expected to change much within this time span. In contrast, phantoms were not moved between scans, thereby not changing partial volume effects and keeping CoVs low. Nevertheless, the phantom observations were in agree-
ment with the *in vivo* results. A larger cohort increasing the age range could provide stronger statistical power. Furthermore, the atlas-based ROIs and their ability to only capture the core part of the tracts may have influenced our WM ROI analysis. Finally, we employed the WLF algorithm, since it was considered to give optimum results [32], therefore did not compare the effects of different fitting algorithms.

### 2.6 Conclusion

We have demonstrated that DKI reproducibility and quality of fitting depends on the maximum b-value used. Comparable reproducibility can be achieved with three (b-values = 1000, 2000, 3000 s/mm$^2$) and the two (b-values = 1000, 3000 s/mm$^2$) shell protocols, the latter having the advantage of shorter scan time. In contrast, the more common acquisition strategy (i.e., b-values =1000, 2000 s/mm$^2$) is characterized by higher interscan variability. Although DKI has proven to be capable of characterizing non-Gaussian diffusion patterns in the brain (which is evident in ~90% of the WM voxels) [135], the inherent challenges of longer scan time compared to the traditional DTI might limit its potential use in clinical workflow. The test-retest reliability of DKI observed in this study with the b-values = 1000, 3000 s/mm$^2$ dataset in both WM and GM, and further verified on ground truth data, indicate that high reproducibility can still be achieved within a reasonable scan time, supporting DKI for clinical purposes. We propose that investigating the efficacy of the three protocols, especially the derived two shells (b-values = 1000, 3000 s/mm$^2$) protocol in delineating subtle changes due to pathology in the patient cohort, would be an appropriate future research direction.
Chapter 3

Probing the Temporal Pole Microstructure

3.1 Overview

This Chapter is adopted from the following manuscript in preparation, titled, The Role of the Temporal Pole in Temporal Lobe Epilepsy: A Diffusion Kurtosis Imaging Study, for submission to the journal Epilepsia. The aim of the work discuss in this chapter is two-fold: To evaluate the sensitivity of DKI to detect abnormalities — (i) at specific segments along the two association WM fiber bundles (i.e., inferior longitudinal fasciculus (ILF) and uncinate fasciculus (Unc)) connected to the temporal pole (TP) and (ii) in the connected temporopolar cortex in TLE patients including non-lesional MRI patients.

3.2 Introduction

Temporal lobe epilepsy (TLE) is the most common form of medically intractable focal epilepsy in adults [45, 58]. In most of these patients, the seizure onset zone lies within the mesial temporal lobe, which in 70% of the cases is induced by mesial temporal sclerosis (MTS), including hippocampal sclerosis [30]. Studies have shown that, in clearly delineated MTS using both MRI (i.e., in MRI positive or ‘MRI+’ patients) and scalp EEG, nearly 80% of patients are seizure free after resective surgery [1]. Nevertheless, full delineation of pathological tissue can be challenging since seizures are not always exclusive to the hippocampus but may rather
originates from extrahippocampal structures [30]. Thus, the epileptogenic zone may extend beyond the atrophic mesial temporal structures, which may explain long-term recurrence of seizures after selective resections [16]. A growing amount of clinical investigations suggest that, among other extrahippocampal structures possibly involved in seizure, the temporal pole (TP, i.e., Brodmann’s Area [BA] 38 or anterior temporal lobe) could play an important and potentially underappreciated role in TLE [1, 131]. The TP is connected to the three temporal gyri, while the two association fibers that terminates at the TP provide connection to the prefrontal cortex (i.e., uncinate fasciculus (Unc)) and amygdala and hippocampus (i.e., inferior longitudinal fasciculus (ILF)), consequently associating with a number of functions including memory [148, 28]. Also, diffusion-weighted imaging (DWI) studies have consistently shown TLE to be a network disorder with possible microstructural alterations in the temporal and extra-temporal white matter (WM) fiber bundles. Diffusion anomalies have also been detected in the cortical grey matter (GM) and superficial white matter (SWM, i.e., the WM area directly bordering the GM) [90, 146, 122]. Each of these separate studies found microstructural irregularities in the temporal pole, as depicted in the change of diffusion tensor imaging (DTI) parameters and decreased fiber density measured with neurite orientation dispersion and density imaging. Despite these promising findings using DWI, a substantial portion of TLE patients (~30%) — often referred to as non-lesional (MRI-negative, or ‘MRI-’) patients — do not show lesions in their MRI scans, which can complicate the presurgical workup in these cases.

Although DTI is an elegant tool with relatively straightforward imaging requirements, a considerable number of studies have shown it to be inadequate for quantifying regions with complex fiber configurations (e.g., crossing fibers) [135]. As such, a technique called diffusion kurtosis imaging (DKI) was developed to address the DTI shortcomings that prevent it from accurately quantifying complex microstructure [74]. DKI enables the measurement of free diffusion (i.e., via its derived DTI metrics) and restricted diffusion within complex microstructure as it provides the common mean diffusivity (MD) and fractional anisotropy (FA) parameters as well as different kurtosis measures, namely mean kurtosis (MK); radial kurtosis (RK); axial
kurtosis (AK); and kurtosis fractional anisotropy (Kfa) [74, 150]. These DKI-derived metrics have shown to be sensitive to WM network and GM abnormalities associated with TLE [21, 60]. Furthermore, DKI can also be used to calculate specific microstructural compartments such as the ratio of axonal water content and the total water content per voxel, also known as axonal water fraction (AWF) [92, 49]. Therefore, DKI could provide a complementary and more comprehensive characterization of diffusion in complex tissue environments, and potentially be more sensitive to diffusion anomalies in TLE patients compared to the more commonly employed DTI acquisition. However, the benefit of DKI for detecting subtle alterations in the microstructure of the TP in TLE, and MRI- in particular, has yet to be established.

The work described in this paper aims to evaluate the sensitivity of DKI to detect abnormalities at specific regions along the two association WM fiber bundles, ILF and Unc connected to the TP and the connected temporopolar cortex in MRI+ and MRI- TLE patients. We believe that better understanding of the microstructural properties of the TP in TLE patients could improve planning of the resective surgery and its outcome.

3.3 Materials and Methods

3.3.1 Subjects

Of the 24 TLE patients recruited in this study (9 females, mean age ± SD = 32 ± 10 years), 10 were considered MRI- (i.e., patients that do not show any signs of lesions in their structural scans) (4 females, 27 ± 6 years). The study was approved by the research and ethics board at Western University and informed consent was obtained from all patients and 23 healthy control subjects (14 female, 36 ± 15 years) prior to their recruitment in the study, in accordance with the Declaration of Helsinki. The patient cohort was selected based on their seizure semiology, and preoperative MRI and intracranial EEG (iEEG) findings. Thirteen patients had undergone temporal lobectomy (i.e., 6 right and 7 left hemisphere) and further investigation with post-surgical pathology confirmed the presence of MTS and gliosis in more than 75% of these patients. A detailed description of the demographic and clinical information for patients
in this study is provided in the Table 3.1.

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</table>

DNET: Dysembryoplastic Neuroepithelial Tumor, FCD: Focal Cortical Dysplasia, L-Left, R-Right, MTS: Mesial Temporal Sclerosis, NL: non-normal MRI, NF/Nr: Post-Surgery Follow-ups, Sz: Seizure, and *: Not a Surgical Candidate, N/A: not available

### 3.3.2 MRI acquisition and processing

All subjects were scanned using a 3T MRI system (Siemens Prisma, Erlangen Germany) with a 32-channel head coil. The scanning protocol included the acquisition of structural images using a magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence (repetition time/echo time TR/TE = 5000/2.98 ms, 700 ms TI, FOV = 256 x 256 mm², 1 mm isotropic voxel size). In addition, a multiband echo-planar imaging (EPI) sequence with acceleration factor = 3 was used to acquire diffusion-weighted images (DWI). The DWI acquisition includes b=0, 1300, 2600 s/mm², 130 diffusion-encoding directions acquired twice with left-right, right-left phase encoding directions, TR/TE = 2800/66.80ms, FOV = 224 x 224 mm², and 2 mm isotropic voxel size. The acquired diffusion weighted images were corrected for EPI readout and eddy current distortions using *topup* [6] and *eddy* [7] from FSL [121]. Correction of Gibbs’ ringing artifact was performed by determining optimal sub-voxel shifts within the neighborhood of sharp edges in the image [81], while noise reduction was achieved by separating the signal from the noise in the image via local noise estimation (MRtrix3’s *dwidenoise*) [133, 139].
3.3.3 Calculations of DKI parameters

The preprocessed DWIs were used as input to the open source Diffusion Kurtosis Estimator (DKE) software package to calculate the DKI parameters (MK, AK, RK, Kfa) including MD and FA derived from DKI [127]. In addition, we modelled the AWF metric from the kurtosis tensor using the DKE software [49].

3.3.4 Automated white matter fiber quantification

The automated fiber-tract quantification (AFQ) software [153] was used to quantify the WM fiber bundles of interest (i.e., ILF and Unc). The basic AFQ four step procedure were executed: (i) fiber tractography, (ii) fiber tract segmentation using two waypoint regions of interest (ROIs), (iii) fiber tract refinement via a probabilistic fiber tract atlas and (iv) sampling diffusion measurements at 100 equidistant points along the tract length between two waypoints. To accommodate complex fiber configurations (i.e., fiber crossings) we modified the steps (i) and (ii) of the AFQ workflow and each of these steps are described in the following respective subsections.

Fiber tracking and segmentation

We used the anatomically constrained tracking (ACT) algorithm [119] implemented in MRtrix3 software [133]. In ACT, the first step is to calculate a response function, which was estimated from the pre-processed DWIs using *dwi2response* (with ‘dhollander’ algorithm for multi-shell data) [40]. In the second step, the estimated response functions for individual DWIs were used to calculate the fiber orientation function (FOD) using *dwi2fod*. The FODs were separately calculated for the three tissue types (i.e., WM, GM and cerebrospinal fluid (CSF)) using the multi-shell multi-tissue constrained spherical deconvolution (CSD) method (*msmt_csd*) [75]. To allow for group comparison, the subjects WM FODs were imputed to the population_template function to generate an unbiased group average FOD template, to which the respective subject’s FODs were warped. In order to deploy the ACT algorithm, additional anatomical information is required to guide the termination and acceptance/rejection criteria during fiber tracking in
Individual subject’s T1 images were segmented into five tissue types (‘5TT’), namely: WM, subcortical GM, GM and CSF, and the optional tissue type (i.e., pathological tissue, which was excluded here), using the 5ttgen fsl command. The 5ttgen fsl command uses the FSL FIRST and FAST segmentation functions to separate the four mandatory tissue types. To minimize tracking into the deep GM, we generated a WM-GM interface mask by inputting the 5TT segmented anatomical image into the 5ttgmwmi command. The resulting WM-GM interface mask was used as the seed point for tracking. To further guide fiber tracking, extra parameters were supplied to the MRtrix tckgen function responsible for tractography, following the six criteria described by [119]. These parameters influence the streamlines in two ways; when to terminate them and when they are either accepted or rejected based on their biological plausibility. Since tracking was seeded in the WM-GM interface, two waypoints manually created for the bundles ILF and Unc were input as part of step 3 of the devised six steps, as described by [119]. For each bundle we manually created an inclusion and exclusion waypoint ROI for both hemispheres. These waypoint ROIs were defined in MNI152 space and then transformed to the FOD template using FSL’s FLIRT. Finally, for tracking we used the tckgen iFOD2 algorithm, which is capable of reconstructing fibers with complex configurations [132]. We used the following additional tckgen settings and inputs: step size 0.8mm, min. length = 8mm, max. length = 250 mm, max. number of streamlines = 10,000, unidirectional, include = inclusion ROI, exclude = exclusion ROI and seeding and cropped at WM-GM interface, with latter crop streamline more precisely as they cross WM-GM interface.

Fiber tracts refinement and cleaning

The segmented tracts using our manually created waypoint ROIs were refined by comparing each candidate fiber bundle (i.e., ILF and Unc) to their respective probability maps provided within the AFQ tool [153]. As part of the AFQ processing, the probability maps are transformed into subject space (or FOD template space). The ILF and Unc are assigned scores based on the probability values of the voxels through which they pass. Any trajectories with low probability scores are discarded. Finally, the selected ILF and Unc bundles should pass
through the two predefined AFQ waypoint ROIs and also conform to the shape of the respective tract’s probability map. In addition, the fiber tracts are cleaned further by determining the core of the fiber tracts to identify and remove any stray fibers. Basically a fiber is represented as a 3D Gaussian distribution, and any outliers in the distribution are discarded (see Figure 3.1 for an example of the processed tracts).

![Figure 3.1: Showing the two WM bundles of interest, inferior longitudinal (green) and uncinate fasciculus (yellow) for a representative healthy subject. Generated using anatomically constrained tractography.](image)

**Sampling diffusion measurements along WM tract lengths**

The diffusion measurements were sampled along the ILF and Unc fiber cores at 100 equidistant points, which provided the respective tract profiles for each DKI maps (MK, AK, RK, Kfa, MD, FA and AWF) from individual subjects, and from which the diffusion status in the WM can be inferred. Furthermore, to verify that diffusion profiling was restricted to WM, we calculated the signed distance to the WM-GM boundary for each WM voxel, with negative values indicating proper sampling. For group-wise statistical analyses, each patient group was separated according to the side of lesion for MRI+ subjects, and the side of seizure focus for MRI-subjects (i.e., separated according to side ipsilateral to the epileptogenic temporal lobe), and their AFQ results were used as input to the Permutation Analysis of Linear Models (PALM)
toolbox. In addition, geometrical properties of the tract profiles were represented using the first four statistical moments: mean (i.e., mean of quantitative values, mean(y) and center of gravity in the x-direction, mean(x)), standard deviation (SD), skewness (skew) and kurtosis (kurt) [5].

3.3.5 Correlation between combined DKI metrics and seizure duration

Since DKI quantifies both the Gaussian component of diffusion (i.e., DTI metrics) and the non-Gaussian component (i.e., DKI metrics), we performed a combined DKI quantitative analysis. In addition, we incorporated the patient’s seizure duration (i.e., time between age of onset and age at scan) to investigate its correlation with different combinations of the DKI metrics.

3.3.6 Tract-based cortical analysis

To quantify diffusion profiles along the ILF and Unc to pial GM axis — referred to forthwith as tract-based cortical analysis (TCA) — we mapped all the individual subject’s DKI maps onto a series of cortical surfaces. First, a surface-based representation of the cortex was constructed using FreeSurfer’s recon-all pipeline and the MPRAGE T1w volume. The resulting WM surface was then used to obtain the additional cortical surfaces using FreeSurfer’s mris function. These were positioned at different depth fractions based on the estimated local (i.e, vertex-wise) cortical thickness, starting with a ‘superficial’ WM surface (-5% of cortical thickness with respect to WM-GM boundary) up to the pial GM (+90% of cortical thickness) with steps of 5%, resulting in a total of 15 surfaces while maintaining smoothness and self-intersection constraints. FreeSurfer’s mri_vol2surf function was then used to project the anatomical space DKI maps onto each of the generated surfaces. We obtained cortical surface maps up to 90% of the estimated cortical thickness, however due to limiting voxel size and partial voluming, only values up to 50% are considered for interpretation. Finally, vertex-wise DKI data were averaged within the rostral middle frontal (RMF, Unc) and temporal pole (ILF + Unc) cortical regions (defined by FreeSurfer’s cortical parcellation) at each depth fraction per subject to allow comparison of profiles across groups. The RMF was included to serve as
a baseline, as we expected little to no effects relating to TLE in this area. Similar to the WM analysis, for group-wise statistical analyses, each patient group (i.e., MRI+ and MRI-) was separated according to side ipsilateral to the epileptogenic temporal lobe.

### 3.3.7 Statistical analysis

The PALM toolbox was used to statistically assess group-wise differences in terms of WM profiles for each of the individual DKI-derived and WM distance maps [144]. A total of N=5000 permutations was used together with a cluster-wise t-statistic threshold of 3.1, while correcting for multiple comparisons (i.e., locations along the bundle) using the familywise error (FWE, q-FWE = 0.05), as well as age and sex effects. Output p-values were saved as $-\log_{10}(p)$ for visualization. The *statsmodels* (v0.12.2) Python package was used for the comparison of WM profile shapes across groups using one-way analysis of variance (ANOVA), and between bundles (within subjects) using repeated measures ANOVA. As for the WM bundles, age and sex were accounted for by including them in the statistical models. Similarly, ANOVA testing was used for contrasting WM bundle summary scores between MRI+ and MRI- as well as diffusion parameter maps, while linear regression was used for testing the correlation with disease duration.

### 3.4 Results

#### 3.4.1 White matter quantitative profiling

DKI quantitative profiles and corresponding z-scores (shown as heat maps) for the MRI+ subjects, compared to the healthy controls, are shown in Figure 3.2A and 3.2B respectively. Ipsilateral to the seizure focus, significant differences were observed between MRI+ and controls ($p < 0.005$) towards the most anterior (i.e., position 100) of the left ILF for MK, RK, AK, AWF and MD. A comparable, but slightly weaker, pattern was observed in Unc for the left MRI+ patients, with significant changes observed closer to the temporopolar cortex area in MD ($p < 0.005$) and MK, RK, AK and AWF ($p < 0.05$). For illustrative purposes, the corresponding
$p$-values for the microstructural alterations based on MK were mapped along the respective 3D renderings of the fiber bundles (Figure 3.2B). As such, it can be observed that MK for the left ILF ($p < 0.005$) and Unc ($p < 0.05$), differ most near the ipsilateral, anterior segments of the bundles (i.e., proximal to the temporopolar cortex). For the ipsilateral right temporal lobe, only AWF indicated possible microstructural alterations in the ILF ($p < 0.05$), otherwise weak or insignificant differences were detected in the ipsilateral right temporal lobe of the MRI+ group.

Figure 3.2: MRI+ patients vs controls. Showing only ILF MK and AWF profiles for ipsilateral left and right temporal lobe (A, top row) and corresponding $p$-values corrected for multiple comparisons using FWER, age and sex (A, bottom row). Heat maps show z-scores for all DKI derived maps, for ILF (B, top row) and for Unc (B, bottom row). To visualize the profile differences at corresponding anatomical locations along the bundles (0-100), the $p$-values are rendered onto the respective fiber bundles, showing here for MK only. Note that only results from the side ipsilateral to the epileptogenic temporal lobe are shown for each bundle.

For MRI- patients, noticeable differences were observed based on the DKI quantitative measurements, in particular MK, RK and AWF, ipsilateral to the seizure focus (as confirmed with iEEG), in line with the MRI+ patients and as indicated in Figure 3.3. Although no signif-
significant differences were detected after FWER corrections, indicators of possible changes along the WM bundles were mostly found at their most anterior parts in left TLE subjects, similar to what was observed with MRI+ group (Figure 3.3B).

Figure 3.3: MRI- patients vs controls. Showing only ILF MK and AWF profiles for ipsilateral left and right temporal lobe (A, top row) and corrected for multiple comparisons using FWER, age and sex p-values (A, bottom row). The heat maps show z-scores for all DKI maps including DTI MD and FA estimated with DKI, for left and right ILF (B, top row) and for left and right Unc (B, bottom row). Note that only results from the side ipsilateral to the epileptogenic temporal lobe are shown for each bundle.

The profiles calculated from the distance maps from the two (i.e., MRI+ and MRI-) patient groups and the controls as shown in Figure 3.4, clearly indicate all DKI quantitative sampling were exclusively within the WM (i.e., negative distance, Figure 3.4A, top row). One thing to note however, is the difference in the mean distance profiles from the WM to the WM-GM interface observed between the patients groups and the controls shown in Figure 3.4A, as well as demonstrated on the heat maps (Figure 3.4B), in particular ipsilateral left temporal lobe ILF and Unc (MRI+) and ipsilateral left temporal lobe ILF and right Unc for the MRI- group.
Figure 3.4: WM to GM distance profiles for MRI+ and MRI- ipsilateral left temporal lobe ILF (A, top row) and corrected for multiple comparisons using FWER, age and sex p-values (A, bottom row). The heat maps show z-scores from the distance profiles for ipsilateral left and right temporal lobe ILF (B, top row) and for ipsilateral left and right temporal lobe Unc (B, bottom row).

3.4.2 White matter profile’s shape analysis

Geometrical properties of the quantitative profiles showed possible differences between the two bundles (ILF and Unc), as shown in Figure 3.5. To demonstrate the distribution of the average of the diffusion kurtosis along all diffusion directions [124] we are showing MK only and AWF as a measure of possible changes in axonal density. A more subtle and variable difference is observed between the patient groups compared to control’s profile shapes as depicted in their skew, kurt, mean(y) and mean(x) distributions. However, in both MRI+ and MRI- groups, the SD for the two WM bundles MK (Figure 3.5A) and AWF (Figure 3.5B) values show consistent dissimilarity compared to controls.
3.4.3 White matter correlational analyses

When combining the DTI metrics estimated with DKI (i.e., MK+MD and Kfa+FA), we observed significant ($p < 0.05$) differences between the two patients groups (i.e., MRI+ vs MRI-) at the left anterior parts proximal to the temporopolar cortex (i.e., points 80-100) of the WM bundles within the ipsilateral temporal lobe (Figure 3.6A, top row). Higher, but not significant z-scores were also observed when combining MK+MD in ILF and Unc from the ipsilateral left temporal lobe, compared to the combination of Kfa+FA. We also observed a linear relationship with MK+MD in the anterior ILF with epilepsy duration as shown in (Figure 3.6A, bottom row), though based on visual judgement, a smaller change is noted with Kfa+FA values. A similar pattern is exhibited within the anterior Unc, showing slight difference between the patients groups with longer seizure activity. No significant changes were detected between
patient groups and WM bundles when averaging across sampling points 0-80. Nevertheless, in line with the observations for the anterior portions of the bundles, strongest effects were observed for the ipsilateral left temporal lobe data. Here, MRI+ patients were characterized by largest differences, driven primarily by the MK+MD parameters (Figure 3.6B, top row). A more comparable difference was noticed in the ipsilateral right temporal lobe between the patients groups’ MK+MD measurements. The DKI combined quantitative values show increased differences with persisting seizure in patients, with more distinct MK+MD changes in both ipsilateral temporal lobes (Figure 3.6B, bottom row).

### 3.4.4 Tract-based cortical analysis

We observed consistently strong differences at the temporopolar cortex tissue transition area (i.e., superficial WM towards WM-GM) between the controls and MRI+ group (Figure 3.7B, top row) for the MK, RK and AWF maps. In the MRI- group, we also see notable DKI differences, except for MD. In general, z-scores gradually change to zero while moving towards the pial surface. For both patient groups, almost no differences were observed at the RMF region (Figure 3.7B, bottom row).

### 3.5 Discussion

In this study we combined the anatomically constrained tractography using multi-shell CSD with DKI to compare diffusional properties along (i) the ILF and Uncinate, two major WM fiber bundles connecting the temporal pole with other cortical regions, as well as (ii) the WM to the transition area of the temporal pole, between healthy controls and TLE patients. Most importantly, we found prominent diffusion profile differences closer to the anterior portions of both bundles within the side ipsilateral to the epileptogenic temporal lobe. In addition, diffusion anomalies were detected within the temporal pole cortex ipsilateral to the epileptogenic temporal lobe and were more pronounced in the DKI measurements of the TP compared to the reference RMF. This is the first study to combine ACT using multi-shell CSD to overcome limitations imposed by complex fiber configurations (e.g., crossing fibers), AFQ for tract profiling
Figure 3.6: Combined DKI parameter analysis. The bar plots (top row, A) show z-scores ($K_{fa}$ + FA, green) and ($MK + MD$, orange) for MRI+ and MRI- patients vs controls calculated within the ipsilateral temporal lobe for ILF (left columns) and Unc using values extracted from sampling points (80-100). The correlation of combined DKI quantitative values within ipsilateral left and right temporal lobe and seizure duration is given on the scatter plots (bottom row, A), with MRI+ (•) and MRI- (×). B, combined DKI parameter analysis, values extracted from sampling points (0-80). Between contrast (i.e., $MK+MD$ vs $Kfa+FA$) and effect size shows FWER, age and sex p-values.

and DKI to characterize tissue microstructure by taking into account non-Gaussian diffusion behavior. Furthermore, depth-dependent DKI measurements were extracted to uncover possible diffusion abnormalities from superficial WM towards the pial surface of the TP.
Figure 3.7: General workflow — cortical diffusion profiling (A). The DKI quantitative values (e.g. MK, left A) are projected onto the temporopolar surfaces at varying depth, starting from the superficial WM (middle A, red) towards the pial surface (purple). Finally, quantitative measurements of the temporopolar cortex microstructure are extracted as depth-dependent profiles (right A). Comparison of cortical microstructure between patients and controls is shown in (B). Each heatmap shows z-scores for all DKI parameters extracted from the superficial WM (i.e., -0.5) towards the pial surface (0.9). The top row shows MRI+ patients vs controls (left columns) and MRI- patients vs controls (right columns) calculated within the temporopolar cortex of the side ipsilateral to the epileptogenic temporal lobe, similarly the bottom row presents rostral middle temporal. Note: The increased MK values towards the pial (A, line plot) show a possibility of CSF influence, so care should be taken when interpreting these results.

3.5.1 White matter quantitative profiling

Based on the diffusion profiles dissimilarities towards the anterior segments of the bundles, more prominent differences are noticeable for the ipsilateral left epileptogenic temporal lobe
across the MRI+ patients, in particular with regards to MK, RK, AK (i.e., decrease) and MD (increase). These findings are in line with a previous study which looked at DKI- and DTI-based metrics along specific WM tracts of left TLE subjects [60]. Moreover, as a surrogate marker for axonal density, the decrease in AWF showed potential axonal degradation in the left side ipsilateral to the epileptogenic temporal lobe in MRI+ patients, which has been a common find in TLE patients with MTS [112, 20]. We also observed a decrease in DKI parameters and increase in DKI-based MD towards left TP in both of the bundles ipsilateral to seizure focus in the MRI+ group. The differences in diffusion abnormalities between the left and right TLE patients, as categorized by seizure onset zone, is in accordance with a previous voxel-based study demonstrating widespread and prominent DTI abnormalities in patients with MTS and left hemispheric onset, while right MRI+ patients exhibited no detectable changes [117]. This suggests that DKI could serve as a complementary approach to detect subtle changes in the WM fiber bundles connected to the TP. In addition, the observed reduction in the distance of the patients’ WM fiber bundles to the WM-GM boundary could be attributed to the presence of ectopic WM neurons (i.e., WM neurons in abnormal locations, mostly found in the subcortical region) which increase in density in brain specimens of TLE patients compared to controls [44]. Identifying abnormalities at specific locations along the ILF and Unc prior to surgery in TLE, particularly in MRI+ subjects, could be used to guide the procedure by more completely identifying seizure onset zone and the region to be resected, potentially resulting in improved outcomes. However, although the current findings demonstrate DKI potential to measure diffusion in patients, it strongly motivates further evaluation with larger patient cohort.

### 3.5.2 White matter profiles shape analysis

Tract profile analysis of the MK and AWF values along WM bundles (i.e., between sampling points 0-100), indicated that ILF and Unc ipsilateral to seizure focus have a wider SD in the MRI+ group (more pronounced in Unc). Here, SD represents the variation along the y-axis of the profiles, implying that MK and AWF appear to vary more along points 0-100 for the MRI+,
but are more ‘flat’ for the MRI+ patients, compared to controls. This observation could correspond to the considerable evidence of dispersed diffusion abnormalities observed in MRI- patients compared to those with TLE patients having radiological evidence of MTS (i.e., MRI+) [112, 77]. In addition, a smaller SD of the AWF data for the MRI+ patients could also suggest diffusion anomalies related to degradation of spatial specificity of microstructural properties along the WM pathways compared to the more variable changes exhibited with MRI- patients. Furthermore, between the bundles, Unc shows greater deviations than ILF in the MRI- patients, in concordance to a previous tract base study, which found a significant reduction in the Unc, that was more pronounced in the anterior temporal lobe [60]. These differences observed in the DKI parameter distribution, specifically SD, is in agreement with the WM profiling analysis indicating potential diffusional changes due to patterns of neuronal loss and gliosis, particularly observed in patients with MTS [20].

3.5.3 White matter correlational analysis

The complementary properties of the MK and MD (i.e., restricted vs. free diffusion) parameters were utilized by combining their respective z-scores. In agreement to the WM findings, a significant difference at the anterior portion of the bundles between the two patient types (MRI+ vs MRI-) was observed. MK+MD demonstrated potential microstructural changes in the ipsilateral left epileptogenic temporal lobe, where MRI+ showed stronger differences compared to MRI- group especially towards the anterior segments of the two fiber bundles (i.e., from sampling point 80 right to the most anterior point 100). Similar, but milder diffusional changes were reflected in the MK+MD values within the more posterior segments (i.e., points 0-80) of the ILF and Unc, with noticeable differences with left TLE patients compared to controls. This goes along with a previous study that demonstrated a centrifugal decrease of DTI-based abnormalities as WM networks extend away from the epileptogenic temporal lobe [112, 36]. Furthermore, there was a relationship between the MK+MD measurements and seizure duration in the two patient groups (MRI+ and MRI-). The detected progressive diffusion anomalies
suggest gradual microstructural changes due to persistent seizure activities [79]. This pattern was also noted in a DTI-base study, with MD strongly correlating with seizure duration [31]. Although MK+MD showed clear differences compared to Kfa+FA, there were no significant differences between these combined DKI parameters (i.e., MK+MD vs Kfa+FA). Nevertheless, since MK and MD are average measurements along all diffusion weighting directions in restricted and free diffusion environments respectively, we expected MK+MD to provide a comprehensive characterization of diffusion properties depicting tissue integrity. On the other hand, FA depicts the preferred direction of diffusion and can reduce drastically in areas of crossing fibers or often in regions of coherent WM [68]. Therefore by combining FA and Kfa, complementary information regarding tissue microstructure could be derived [68].

3.5.4 Tract-based cortical analysis

The present findings indicated that MK and RK can detect microstructure anomalies within the temporopolar cortex in MRI+, and to some extent within the MRI- patients compared to a reference region (i.e., RMF). Although TLE appears to be characterized by a network of abnormalities [21], we expected RMF to have minimal association with the temporopolar cortex changes due to seizure activities. Besides the observations related to MK and RK, the changes in AWF indicate potential neuronal loss. This could be due to seizure activities originating either at the temporopolar cortex or the medial temporal lobe structures (e.g. hippocampus) [30]. These findings support previous work which detected neurons and dendritic changes in the temporopolar cortex in TLE patients [146]. Parallel to this study and in support of our findings, a number of earlier imaging- and histology-based studies have also identified reduction in neuronal density and gliosis within the superficial WM and temporopolar cortex [85, 22]. Furthermore, the WM-GM boundary diffusion anomalies could be related to the blurring of this area, commonly attributed to various causes (e.g. developmental cortical abnormalities, gliosis or myelin alterations) [44, 57]. Based on the current results, DKI could serve as a complementary approach to detect subtle microstructural alterations within the temporopolar
cortex. Understanding the role of TP in TLE is important to inform resection, which could help to minimize seizure recurrence due to insufficient resection [69].

3.5.5 Limitations

The diffusion anomalous along the WM fiber bundles connecting TP and the connected temporopolar cortex detected with DKI measurements indicated DKI’s ability to quantify subtle alterations of the microstructure in TLE patients. However, future work may include larger cohort patients groups (MRI+ and MRI-) to validate these findings. The spatial resolution (2 mm isotropic) of the DWI used in this study is approximately equivalent to the cortical thickness [72]. Therefore, the current findings could still be affected by partial volume effects near CSF. As such, data closer to the pial surface (i.e., sampling depth > 0.5) were not taken into consideration. Nevertheless, as we were particularly interested in the WM-GM transition area, the current TCA is still valid to reveal trends in terms of microstructural differences in the TLE patients. Moreover, statistical results were corrected for age and sex to minimize their influence on the patient vs. control differences. However, age- and sex-matched samples could avoid any residual differences in diffusion characteristics due to aging or gender [105, 151].

3.6 Conclusion

The current study demonstrated that the combination of ACT multi-shell tracking, AFQ and DKI could serve as a complementary approach to detect subtle microstructural alterations within the anterior segments of the two association WM fiber bundles connected to the temporal pole. In addition, depth dependent DKI measurements could aid in uncovering diffusion abnormalities in the temporopolar cortex. Furthermore, since the DKI acquisition and precision have shown to be clinically feasible [76], the methods developed in this study could be easily implemented in a clinical workflow. Finally, while the study was based on a limited patient cohort it provides solid preliminary data upon which to base a more comprehensive investigation. Identification of anomalies along the WM bundles segments and specific depths within the temporopolar cortex before surgery could help inform the planning of selective resection to
improve outcome, particularly in MRI-patients.
Chapter 4

Characterization of Temporal Lobe Epilepsy Patients

4.1 Overview

This Chapter is adopted from the following manuscript in preparation, titled, *Assessing the added value of diffusion kurtosis imaging in detecting microstructural changes in patients with temporal lobe epilepsy*, for submission to the journal PLOS ONE. The main focus of this work is to investigate DKI ability to lateralize TLE subjects using a machine learning approach.

4.2 Introduction

Temporal lobe epilepsy (TLE) represents the most common form of medically intractable focal epilepsy in adults [58] and is often associated with a lesion in the hippocampus, amygdala or entorhinal cortex characterized by specific patterns of neuronal loss and gliosis, which is commonly referred to as mesial temporal sclerosis (MTS) [20]. The current gold standard to identify the epileptogenic zone in TLE patients is through the use of intracranial electroencephalography (iEEG) and can be very invasive [83]. Although it is evident that lesions that are easily delineated with MRI have a better outcome after surgery, a third of epilepsy patients exhibit no structural abnormalities in their MRI scans, which poses difficulties for proper
Diagnosis and surgical planning [99].

Diffusion MRI (dMRI), primarily concerned with the inherent mobility of water molecules (Brownian motion) in tissue has been studied to non-invasively image TLE patients, aiming to better detect subtle changes in brain tissue. The widely known diffusion tensor imaging (DTI) approach, which describes the water diffusion process in tissue using a 2\textsuperscript{nd}-order 3D diffusivity tensor, where the three diffusivity eigenvectors correspond to the axes of a tri-axial diffusivity ellipsoid, is one of the simplest means of quantifying this diffusion process. The main quantitative parameters derived from DTI are fractional anisotropy (FA), which describes the amount of anisotropic diffusion in the preferred direction of diffusion; mean diffusivity (MD), the average diffusion, axial diffusivity (AD) the diffusion in the axial direction; and radial diffusivity (RD), the diffusion perpendicular to the axial diffusion [135]. For more than a decade, studies based on DTI in quantifying brain microstructure of TLE patients have shown diffusion abnormalities in several white matter structures closely related to the epileptogenic temporal lobe. One of the first studies [9] found a reduction in FA in selected voxels within the external and internal capsule and the corpus callosum of TLE patients. Since that time many other groups have expanded on the extent of DTI abnormalities in the white matter of patients with TLE [35, 34, 53]. Although some of the findings between these studies had some degree of variability, which could be due to variability in the patient cohort and analysis techniques, they all agreed that abnormalities in TLE are more of a network disorder, affecting widespread white matter regions, even in patients with unilateral MTS [62]. It has been hypothesized that the changes in DTI parameters (increased MD and reduction in FA) mostly observed in several white matter regions are caused by degeneration of axons (increased extra-axonal space) and possible demyelination in the axons [112]. Although DTI is a potential non-invasive imaging tool, it is not without its own challenges. This technique assumes unrestricted water diffusion characterized by a Gaussian distribution, a mathematical model describing a normative bell-curve distribution of water particle diffusion. In reality, the complex intracellular and extracellular environment \textit{in vivo} causes the diffusion of water molecules to deviate considerably
from this model. Moreover, it has been demonstrated that when using higher b-values in the
diffusion imaging sequence, the simplified 2\textsuperscript{nd}-order 3D diffusivity tensor is unable to fully
characterize relatively isotropic tissue such as grey matter (GM) [150]. This phenomenon is
also observed in the white matter (WM) when there is substantial crossing or diverging fibers
[135].

Based on the above, a statistical method like diffusion kurtosis imaging (DKI), a 4\textsuperscript{th}-order
tensor approach which is a straight forward extension of the 2\textsuperscript{nd}-order method (DTI), has been
developed, aimed at providing a better characterization of water diffusion properties [74]. The
derived DKI metrics are, mean kurtosis (MK), kurtosis fractional anisotropy (Kfa), axial kurtosis
(AK) and radial kurtosis (RD), all of which are analogous to the derived DTI metrics. Also
derived from this 4\textsuperscript{th}-order tensor are the traditional DTI metrics, referred henceforth as FA\textsubscript{2},
MD\textsubscript{2}, AD\textsubscript{2}, and RD\textsubscript{2}. A preliminary study performing region of interest (ROI) analysis compar-
ning DTI and DKI found MD, AD, and AK to reduce in WM while MD and MK increased
in GM but failed to detect widespread detection, contradicting previous findings [56]. Subse-
quently studies performing voxel-wise analysis in a heterogeneous juvenile patient cohort [155]
and adult ITLE patients group [21] demonstrated a reduction in FA and an increase in MD,
along with a reduction in MK and RK in left temporal, bilateral orbitofrontal and frontopari-
etal white matter. In GM they found increased MD and RD but a reduction in MK, AK, and
RK in varying regions. Although these findings reinforce DKI as more sensitive to anomalies
associated with TLE than DTI, the ability of DKI to identify microstructural changes specific
to certain TLE types (ITLE and rTLE), when comparing to healthy controls, is unclear. A more
recent study used machine learning approach to detect ITLE patients [38]. Although this study
exemplified the potential of DKI in distinguishing TLE patients from healthy controls, their
analysis was based on ITLE patients only. In addition, there is a possible inherent distinction in
different TLE types in their pathological effects on the temporal lobe or connected brain struc-
tures which could be used to classify ITLE and rTLE vs. healthy controls [78]. Therefore, the
goal of this study was to use multiclass classification to investigate the added value of DKI in
identifying heterogeneous TLE patient cohorts (iTLE and rTLE) compared to healthy controls based on consistently detected regional changes. The most frequently detected regions were assessed according to their clinical significance to TLE. Furthermore, the performance from DKI based classifiers were compared to the more traditional technique (DTI).

4.3 Materials and Methods

4.3.1 Subjects

Thirty-eight individuals were assessed in this study, 21 of whom were healthy controls (14 females, mean age ± SD = 38 ± 14 years) and 17 TLE patients (5 females, 34 ± 12 years). The study was approved by the research and ethics board and informed consent was obtained from all patients and healthy control subjects prior to their recruitment in the study. The patient cohort was selected based on (i) clinically diagnosed TLE based on seizure semiology, preoperative MRI findings and iEEG findings and (ii) epileptic activity localized on one side (not both sides) of the temporal lobe. Thirteen of whom had undergone temporal lobectomy (6 right and 7 left) and investigation with post-surgical pathology confirmed the presence of mesial temporal sclerosis and gliosis in more than 75% of patients. The inclusion criteria for the control group were: (i) no record of neurological disorder or brain injury and (ii) normal conventional MRI findings. A detailed description of the demographic and clinical information for patients included in this study is provided in Table 4.1.

4.3.2 Image acquisition and processing

All subjects were scanned using a 3T MRI system (Siemens Prisma, Erlangan Germany) with a 32-channel head coil. The scanning protocol included the acquisition of structural images using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (5000/2.98 ms TR/TE, 700ms inversion pulse (TI), field of view (FOV) = 256 x 256 mm², matrix size = 256 x 256, section thickness =1 mm and 176 sagittal sections). In addition, a multiband echo-planar sequence was used to acquire diffusion-weighted images (b=0, 1300, 2600 s/mm²,
### Table 4.1: Clinical characteristics of patients with left and right temporal lobe epilepsy.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Hand</th>
<th>Invasive EEG</th>
<th>Duration (years)</th>
<th>MRI</th>
<th>Hipp.path</th>
<th>Neo.path</th>
<th>Post-Sx, Sz- outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>M</td>
<td>R</td>
<td>L Temporal Lobe</td>
<td>1</td>
<td>L Hippocampus atrophy</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>M</td>
<td>R</td>
<td>L Hemisphere (Diffuse)</td>
<td>11</td>
<td>L MTS</td>
<td>MT and FCD 3b</td>
<td>Gliosis</td>
<td>Engel Class IIA</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>M</td>
<td>R</td>
<td>L Anterior Temporal Lobe</td>
<td>2</td>
<td>N</td>
<td>Gliosis</td>
<td>Gliosis</td>
<td>Engel Class IB</td>
</tr>
<tr>
<td>4</td>
<td>51</td>
<td>F</td>
<td>R</td>
<td>R Anterior Temporal Lobe</td>
<td>40</td>
<td>R MTS</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>M</td>
<td>R</td>
<td>L Fronto-Temporal R Insula and Temporal Lobe</td>
<td>48</td>
<td>L MTS</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>M</td>
<td>R</td>
<td>Temporal Lobe</td>
<td>4</td>
<td>N</td>
<td>Gliosis</td>
<td>Gliosis</td>
<td>Engel Class IA</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>F</td>
<td>R</td>
<td>R Temporal Lobe</td>
<td>12</td>
<td>R amygdala FCD</td>
<td>Gliosis</td>
<td>Gliosis</td>
<td>Engel Class IA</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>M</td>
<td>R</td>
<td>R Temporal Lobe</td>
<td>26</td>
<td>DNET</td>
<td>Glioneuronal tumor, FCD, MTS and Gliosis</td>
<td>Glioneuronal tumor, FCD, MTS and Gliosis</td>
<td>Engel Class IIA</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>M</td>
<td>R</td>
<td>R Temporal Lobe</td>
<td>35</td>
<td>R MTS</td>
<td>MTS and Gliosis</td>
<td>MTS and Gliosis</td>
<td>NF</td>
</tr>
<tr>
<td>10</td>
<td>18</td>
<td>M</td>
<td>R</td>
<td>L Insula and Temporal Lobe</td>
<td>6</td>
<td>L Temporal FCD</td>
<td>Arachnoid cyst and Focal scars</td>
<td>Gangliocytoma and Gliosis</td>
<td>Engel Class IIIA</td>
</tr>
<tr>
<td>11</td>
<td>42</td>
<td>M</td>
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<td>L Temporal Lobe</td>
<td>7</td>
<td>L MTS</td>
<td>Gliosis</td>
<td>Gliosis</td>
<td>Engel Class IIA</td>
</tr>
<tr>
<td>12</td>
<td>28</td>
<td>F</td>
<td>R</td>
<td>R Temporal Lobe</td>
<td>2</td>
<td>N</td>
<td>Gliosis</td>
<td>Leptomeningeal fibrosis and Gliosis</td>
<td>Engel Class IIA</td>
</tr>
<tr>
<td>13</td>
<td>21</td>
<td>M</td>
<td>R</td>
<td>L Temporal Lobe</td>
<td>2</td>
<td>N</td>
<td>Gliosis</td>
<td>Gliosis</td>
<td>Engel Class IIIA</td>
</tr>
<tr>
<td>14</td>
<td>23</td>
<td>M</td>
<td>L</td>
<td>R Temporal lobe</td>
<td>4</td>
<td>N</td>
<td>Gliosis</td>
<td>Gliosis</td>
<td>NF</td>
</tr>
<tr>
<td>15</td>
<td>36</td>
<td>F</td>
<td>R</td>
<td>R Temporal lobe</td>
<td>16</td>
<td>R MTS</td>
<td>MTS</td>
<td>Gliosis</td>
<td>NF</td>
</tr>
<tr>
<td>16</td>
<td>29</td>
<td>M</td>
<td>R</td>
<td>L Anterior Temporal Lobe</td>
<td>5</td>
<td>N</td>
<td>Gliosis</td>
<td>Gliosis</td>
<td>NF</td>
</tr>
<tr>
<td>17</td>
<td>31</td>
<td>F</td>
<td>R</td>
<td>L Temporal Lobe</td>
<td>27</td>
<td>L MTS</td>
<td>MTS</td>
<td>Gliosis</td>
<td>NF</td>
</tr>
</tbody>
</table>

DNET- Dysembryoplastic Neuroepithelial Tumor, FCD-Focal Cortical Dysplasia, L-Left, MTS -Mesial Temporal Scleroses, N- normal MRI, NF-No Post-Surgery Follow-ups, Pt-Patient, R-Right, Sx-Surgery, Sz-Seizure, and *- Not a Surgical Candidate

130 diffusion-encoding directions acquired twice with left-right, right-left phase encoding directions, 2800/66.80 ms TR/TE, FOV =224 x 224 mm², slice thickness = 2 mm, multiband accelerating factor =3, phase partial Fourier encoding = 0.75 and 72 axial sections with acquisition time of 10.45 min). The acquired diffusion weighted images were corrected for echo planar imaging and eddy current distortion using topup [6] and eddy [7] from FSL [121]. Correction of Gibbs’ ringing artifact was performed by determining optimal sub-voxel shifts within the neighborhood of sharp edges in the image [81], while noise reduction was achieved by separating the signal from the noise in the image via local noise estimation (MRtrix3 dwidenoise) [139]. Diffusion and kurtosis measurements were obtained using Diffusion Kurtosis Estima-
tor, an open source tool [127]. Diffusion and diffusional kurtosis tensors were fitted for \( b=0, 1300, \) and \( 2600 \text{ s/mm}^2 \) to each voxel of the diffusion-weighted images. To avoid any biases due to different \( b \)-values, or the number of gradient directions we fitted DTI with the same number of \( b \)-values. In addition, according to recent studies, the diffusion statistics from the kurtosis model are expected to have better accuracy compared to the ones calculated from the traditional DTI fitting via single non-zero \( b \)-value [140]. The following DTI and DKI parametric maps were generated: FA, MD, AD, and RD from DTI, and \( \text{FA}_2, \text{Kfa}, \text{MD}_2, \text{MK}, \text{AD}_2, \text{AK}, \text{RD}_2, \) and RK from DKI. For WM analysis, the pre-processed data were registered to the JHU-ICBM-DTI-81 white matter based labels atlas [96] in MNI space containing 48 regions using NiftyReg registration tool [94]. And for grey matter analysis, 68 cortical and 12 subcortical region of interest (ROI) were parcellated from the respective parametric maps using FreeSurfer [110]. Then mean values from these ROIs were extracted as features using the FreeSurfer function mri_segstats (Figure 4.1). The ROIs mean values were used as features for training multiple binary support vector machine (SVM) classifiers, this is discussed in detail in the following section.

### 4.3.3 Support vector machine multiclass classification

A SVM is a supervised machine learning algorithm, trained using the input data (features) and used to predict discrete responses [4]. SVM is traditionally used for binary classification problems, so to deal with multiclass problems we used the error correcting output code (ECOC) technique to recast the problem into smaller binary classification tasks and then combine the binary classifier outputs to solve the initial multiclass problem [42]. The ECOC technique is broken down into two steps: encoding and decoding. In the encoding step, a discrete decomposition matrix (coding matrix) is designed (Table. 4.2) for the given problem. Each row of the coding matrix is a sequence of bits (code word) representing each class, where each bit identifies the membership of the class to a classifier. A ‘0’, is considered not a member, ‘-1’ is considered as negative class and ‘1’ is considered as positive class of each respective clas-
Figure 4.1: Illustrates the general workflow of the multiclass classification using error correcting output code (ECOC) technique. The pre-processing to feature extraction steps are executed only once. The coding matrix defines the binary classifiers trained after its feature selection. In the encoding step, each classifier outputs a binary code that is combined to form message, which is then decoded by comparing it to each class code word with the closes match as the final prediction. Validation is performed using the test sample, then the performance metrics are calculated using the hit or miss counts. Each of these steps are described in detail.

sifiers. When an unlabelled test sample is input, each classifier casts a vote to one of the two meta-classes (-1 or 1) used in training. The output or encoded bit from each binary classifier is then combined forming an $x$-bit code called message. This message is then decoded in the decoding step. To do this, each bit in the message is compared to its corresponding bit in each class code word, the test sample is assigned to a class with the closest code word according to some form of distance measure.

To achieve this, a coding matrix was custom designed to suit our clinical problem, where each of the columns ($h_l$, $l = 1:4$) and rows, represent total of 4 binary SVM classifiers and 3 classes respectively (Table 4.2). The classifier ($h_1$) was built to discriminate between ITLE and rTLE, while two other classifiers discriminated between controls with ITLE and rTLE respectively ($h_2, h_3$), and one classifier ($h_4$) to discriminate between controls and all patients.
This allows training of classifiers on more homogeneous sets, while still allowing the combined set of predictions to be used to classify each individual.

**Table 4.2:** Custom designed coding matrix, rows are classes (controls (ctrl), left-TLE patients (lTLE) and right-TLE patients (rTLE) with their respective code word, e.g., ‘0 -1 -1 -1’ for class ctrl. The columns are the individual binary classifiers (\(h_l\), \(l = 1:4\)). A ‘0’ means the corresponding class is not included in training, ‘-1’ is considered as the negative class and ‘1’ as a positive class of the respective classifier.

<table>
<thead>
<tr>
<th></th>
<th>(h_1)</th>
<th>(h_2)</th>
<th>(h_3)</th>
<th>(h_4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ctrl</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>lTLE</td>
<td>-1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>rTLE</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**4.3.4 Data preparation for classifier training**

The first step before training a classifier is to perform feature extraction. As mentioned in the previous section, the extracted mean values from each of the anatomical regions from the respective parametric maps from DTI and DKI were used as the features. To evaluate the added value of DKI, we trained the DTI based classifiers on features extracted from the traditional DTI parametric maps, while DKI based classifiers were trained from the combination of features extracted from DKI parametric maps. The following were the respective combinations: \(\text{FA}_2\) and \(\text{Kfa}\) (\(\text{FA}_2\text{Kfa}\)), \(\text{MD}_2\) and \(\text{MK}\) (\(\text{MD}_2\text{MK}\)), \(\text{AD}_2\) and \(\text{AK}\) (\(\text{AD}_2\text{AK}\)) and \(\text{RD}_2\) and \(\text{RK}\) (\(\text{RD}_2\text{RK}\)).

The second step is feature selection, an important part of the workflow, since a selected subset of features or anatomical regions not only helps the accuracy of the classifier, but also reduces the number of regions required to localize the discriminative regions between the three classes. We employed a wrapper method [64] with forward feature selection using an SVM classifier [65]. The usual multiclass feature selection (MFS) method is normally applied to the black box of multiclass SVM and it selects the same feature subset for every binary classifier to maximize the average accuracy over all classes. In this study, we applied feature selection for individual classifiers \(h_l\) (Figure 4.2, Individual Feature Selection) defined in our coding matrix (Table 4.2). This technique has been shown to improve performance compared to traditional
MFS [37].

**Figure 4.2:** Demonstrate the individual feature selection method, where feature selection was performed for the individual classifier $h_l$, $l = 1:4$, the features were previously extracted mean values from anatomical regions or ROIs. The selected subset was then used for training the respective SVM classifier ($h_l$-SVM). Finally, the binary output from each of the four SVM classifiers is combined using the ECOC technique to predict the class.

### 4.3.5 Training and testing the classifier

To train the classifier we first subsample the training set by leaving a single subject out every time creating $j$ folds for a training set of size $j$ (Figure 4.1). We employed the sequential forward feature selection algorithm on each fold with respect to each individual binary classifier. Starting from an empty feature set, feature subsets from each of the features not yet selected were sequentially added according to the criterion value determined by the algorithm. For each candidate feature subset, we performed k-fold cross-validation (i.e., randomly dividing data into k-folds of approximately equal size, one as validation set, and the others as training sets). The evaluated feature subset was then used for training the respective classifier (Figure 4.2). After training all four classifiers ($h_l$-SVM) each time, a 4-bit message is encoded (Figure 4.2), each bit represent a classifier’s prediction (as discussed above, 1 for positive class or -1 for negative class). To decode the message we simply calculate the Jaccard distance (JD) (see
Equation 4.2) between the respective class code and the encoded message, the class with the least distance is selected as the final prediction. We validated the final prediction by testing it on the left out test subject $i$ (Figure 4.1) and updated a confusion matrix. This process was iterated until all thirty-eight subjects were classified. From the confusion matrix, the accuracy, sensitivity, and specificity were determined for each of the DTI and DKI classifiers (Table 4.3 & Table 4.4).

To calculate JD, the Jaccard index ($JI$) is first determined, as given in the following general expression,

$$JI = \frac{|S_1 \cap S_2|}{|S_1 \cup S_2|}$$  \hspace{1cm} (4.1)

Here the $S_1$ and $S_2$ are sets one and two, respectively. The Jaccard distance is given by the following equation,

$$JD = 1 - JI$$  \hspace{1cm} (4.2)

The Figure 4.3 illustrates how JD is calculated following Equations (4.1 and 4.2) above.

### 4.4 Results

#### 4.4.1 Multiclass classification based on white matter

As shown in Table 4.3, to assess the ability of DKI to detect microstructural changes in the white matter in different TLE types, we compared the performance of DKI and DTI classifiers trained with features extracted from WM as follows: MD vs MD$_2$MK, AD vs AD$_2$AK and RD vs RD$_2$RK. Generally, both DTI and DKI based classifiers (MD, MD$_2$MK, AD, and RD$_2$RK) had the highest overall accuracy of 92.1%. On the other hand, FA$_2$Kfa had the lowest accuracy of 78.9% while FA scoring 86.8%.
Figure 4.3: The decoding step. After the four binary classifiers \( (h_i) \) are trained, their encoded binary outputs are combined giving a 4-bit message (e.g., ‘-1 -1 -1 -1’). To decode this message the ‘Jaccard distance’ \( JD \) from the respective class code word (e.g., ‘0 -1 -1 -1’ for class ctrl) and the message is determined. For example, to calculate \( JD \) for the above encoded message ‘-1 -1 -1 -1’ and each class code word, each bit in the message is compared to the corresponding bit in the respective class code word. A match is a point and the sum is divided by the total number of bits. For this illustration, the control class is selected since 3 of its bits matched with the encoded code, by dividing the 3 with number of bits (4) gives \( JD = 0.75 \), and subtracting from 1 gives \( JD = 0.25 \), the least distance of the three classes.

### 4.4.2 Multiclass classification based on grey matter

We performed a similar comparison as in the white matter to assess the added value of DKI in detecting microstructural changes in the cortical area in different TLE types. As shown in Table 4.4, it was observed that DKI classifiers had slight increase in their performance compared to DTI, scoring highest overall accuracy of 92.1\% across all its classifiers while MD and AD scored 89.5\% and RD scored 86.8\%.

### 4.4.3 Discriminative regions of interest in the white matter

As shown in Figure 4.4 for MD vs MD2MK classifiers, the regions detected >50 % of the time were considered consistent, indicative of possible microstructural changes and these regions are shown on the registered coronal slices in Figure 4.6. Refer to Appendix B Figure B.3 (A-C) for FA vs FA2Kfa, AD vs AD2AK and RD vs RD2RK classifiers. It was observed that both DKI and DTI based classifiers consistently detected widespread abnormalities. In addition, we observed some regions highly detected by one or the other of the two methods (DTI or
Table 4.3: Comparison of overall classification accuracy, sensitivity, and specificity based on white matter between the following classifiers; MD vs MD_{2MK}, FA vs FA_{2Kfa}, AD vs AD_{2AK} and RD vs RD_{2RK}.

<table>
<thead>
<tr>
<th>Classifier</th>
<th>Class</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Overall Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>control</td>
<td>100</td>
<td>87.5</td>
<td>92.1</td>
</tr>
<tr>
<td>MD</td>
<td>left-TLE</td>
<td>75</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>right-TLE</td>
<td>88.9</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>95.2</td>
<td>90.9</td>
<td></td>
</tr>
<tr>
<td>MD_{2MK}</td>
<td>left-TLE</td>
<td>87.5</td>
<td>87.5</td>
<td>92.1</td>
</tr>
<tr>
<td></td>
<td>right-TLE</td>
<td>88.9</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td>control</td>
<td>95.2</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td></td>
<td>left-TLE</td>
<td>62.5</td>
<td>83.3</td>
<td>86.8</td>
</tr>
<tr>
<td></td>
<td>right-TLE</td>
<td>88.9</td>
<td>88.9</td>
<td></td>
</tr>
<tr>
<td>FA_{2Kfa}</td>
<td>control</td>
<td>95.2</td>
<td>76.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>left-TLE</td>
<td>37.5</td>
<td>75</td>
<td>78.9</td>
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<tr>
<td></td>
<td>right-TLE</td>
<td>77.8</td>
<td>87.5</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>control</td>
<td>100</td>
<td>87.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>left-TLE</td>
<td>87.5</td>
<td>100</td>
<td>92.1</td>
</tr>
<tr>
<td></td>
<td>right-TLE</td>
<td>77.8</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>100</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>AD_{2AK}</td>
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<td>87.5</td>
<td>100</td>
<td>89.5</td>
</tr>
<tr>
<td></td>
<td>right-TLE</td>
<td>66.7</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>RD</td>
<td>control</td>
<td>100</td>
<td>87.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>left-TLE</td>
<td>62.5</td>
<td>100</td>
<td>89.5</td>
</tr>
<tr>
<td></td>
<td>right-TLE</td>
<td>88.9</td>
<td>88.9</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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</tr>
<tr>
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<td>87.5</td>
<td>92.1</td>
</tr>
<tr>
<td></td>
<td>right-TLE</td>
<td>77.8</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

DKI). For example, only DKI was able to detect the SS_L which include the associative fibers, inferior longitudinal fasciculus and inferior fronto-occipital fasciculus. For full names of the white matter regions abbreviated in the Figure 4.4 and the Appendix B Figure B.1 see Appendix B Table B.1, the acronyms and names are consistent with the JHU-ICBM-DTI-81 white matter labels atlas [96].

### 4.4.4 Discriminative regions of interest in the grey matter

Again we see the same trend in the grey matter. As shown in Figure 4.5, showing only the MD vs MD_{2MK} classifier (see Figure B.2 for AD_{2AK} and RD vs RD_{2RK} classifiers). To visualize
Table 4.4: Classification accuracy, sensitivity and specificity based on grey matter between the following classifiers; MD vs \(MD_2MK\), AD vs \(AD_2AK\) and RD vs \(RD_2RK\).

<table>
<thead>
<tr>
<th>Classifier</th>
<th>Class</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Overall Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>control</td>
<td>100</td>
<td>91.3</td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>left-TLE</td>
<td>75.0</td>
<td>100</td>
<td>89.5</td>
</tr>
<tr>
<td></td>
<td>right-TLE</td>
<td>77.8</td>
<td>77.8</td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>control</td>
<td>100</td>
<td>91.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>left-TLE</td>
<td>75.0</td>
<td>100</td>
<td>92.1</td>
</tr>
<tr>
<td></td>
<td>right-TLE</td>
<td>88.9</td>
<td>88.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>95.2</td>
<td>90.9</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>left-TLE</td>
<td>87.5</td>
<td>87.5</td>
<td>89.5</td>
</tr>
<tr>
<td></td>
<td>right-TLE</td>
<td>77.8</td>
<td>87.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>100</td>
<td>91.3</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>left-TLE</td>
<td>87.5</td>
<td>100</td>
<td>92.1</td>
</tr>
<tr>
<td></td>
<td>right-TLE</td>
<td>77.8</td>
<td>87.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>100</td>
<td>80.8</td>
<td></td>
</tr>
<tr>
<td>RD</td>
<td>left-TLE</td>
<td>75</td>
<td>100</td>
<td>86.8</td>
</tr>
<tr>
<td></td>
<td>right-TLE</td>
<td>66.7</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>95.2</td>
<td>95.2</td>
<td></td>
</tr>
<tr>
<td>RD</td>
<td>left-TLE</td>
<td>87.5</td>
<td>87.5</td>
<td>92.1</td>
</tr>
<tr>
<td></td>
<td>right-TLE</td>
<td>88.9</td>
<td>88.9</td>
<td></td>
</tr>
</tbody>
</table>

the spatial location of the detected regions the ROIs were overlayed on the registered coronal slices shown in Figure 4.6 (see Appendix B Figure B.3 for rest of the classifiers). Although there were some extrahippocampal regions only detected by DTI or DKI, for example, DKI was able to pick the left temporal pole and right entorhinal cortex consistently compared to DTI, both techniques detected widespread abnormalities. It is important to note that both methods had consistent detection of most of the mesial temporal lobe structures. For full names of the grey matter regions abbreviated in Figure 4.5 and Appendix B Figure B.2 see Appendix B Table B.2.

4.5 Discussion

This study evaluated DKI added value by implementing the ECOC technique to solve multiclass classification problem. Before training, a classifier wise feature selection approach was performed to detect regional changes related to seizure activity in ITLE and rTLE patient com-
Figure 4.4: Shows the relative frequency of the first five selected white matter features (extracted from MD and MD$_2$MK maps) during the feature selection process (Figure 4.2) for each of the SVM binary classifiers ($h_i$). The yellow and blue bars indicate relative frequency of each feature detected with MD and MD$_2$MK respectively. The features selected more than 50% (above dotted red line) were considered to be more consistent. Names of consistent features: ALIC-Anterior Limb of internal Capsule, BCC-Body of Corpus Callosum, CgC- Cingulum Cingulate, CgH-Cingulum Hippocampus, CP-Cerebral Peduncle, CST- Corticospinal Tract, EC- External Capsule, Fx-Fornix, Fx/ST-Fornix Cres/Stria Terminalis, GCC-Genu of Corpus Callosum, ICP- Inferior Cerebellar Peduncle, MCP-Middle Cerebella Peduncle, ML- Medial Lemniscus, PCR-Posterior Corona Radiata, PCT- Pointing Crossing Tract, PTR- Posterior Thalamic Radiation, SCC-Splenium of Corpus Callosum, SCP-Superior Cerebellar Peduncle, SCR-Superior Corona Radiata, SFO-Superior Fronto occipital Fasciculus, SLF-Superior Longitudinal Fasciculus, SS-Sagittal Stratum, TAP-Tapetum and UNC-Uncinate Fasciculus. See Appendix B Table B.1 for full names of all features or regions.

pared to healthy controls. The results indicated that DKI achieved overall classifier accuracy of 92.1% in both grey and white matter. Although both DTI and DKI had wide spread detection of extra-hippocampal structures, DKI was consistent in detecting few regions of significance to TLE that were undetected with DTI alone.

4.5.1 Analysis of detected white matter

We observed that three of the DTI based classifiers showed the highest overall accuracy (MD = 92.1%, FA = 86.8%, and AD = 92.1%) compared to DKI, with two classifiers showing similar
Figure 4.5: The relative frequency of the first five selected grey matter features (extracted from MD and MD2MK maps) during the feature selection process for each of the SVM binary classifiers ($h_i$). The yellow and blue bars indicate relative frequency of each feature detected with DTI and DKI respectively. The features selected more than 50% (above dotted red line) were considered to be more consistent.

Names of the consistent features: Am-Amygdala, BSTS-Banks Superior Temporal Sulcus, CuC-Cuneus Cortex, EnC- Entorhinal Cortex, FP- Frontal Pole, FuG-Fusiform Gyrus, Hi-Hippocampus, MOFC-Medial Orbital Frontal Cortex, MTG- Middle Temporal Gyrus, Pa-Pallidum, PaCL-Paracentral Lobule, PaHG-Parahippocampal Gyrus, PCG-Posterior Cingulate Gyrus, POOp-Pars Opercularis, POR-Pars Orbitalis, PrCC-Precuneus Cortex, Pu- Putamen, RACC- Rostral Anterior Cingulate Cortex, Th- Thalamus, TP-Temporal Pole and TTC- Transverse Temporal Cortex. See Appendix B Table B.2 for full names of all features or regions.

accuracy to DTI (MD$_2$MK = 92.1% and RD$_2$RK=92.1%). Although most DTI based classifiers scored the highest general accuracy, our findings suggested that the accuracies of both DTI and DKI in detecting white matter microstructural changes are comparable. In contrast to a recent study looking at white matter voxels from the temporal lobe to classifiers iTLE patients [38], our MD observations did not agree with their findings. They found that MK had higher accuracy than MD, while our findings showed both having similar accuracy. This could be due to the difference in the patient cohort and analysis technique. The individual feature selection step was important in this work, since it does not only improve the classifier’s performance but also identify discriminative regions among the class, since distinct TLE types
Figure 4.6: White-matter (blue) and grey matter (red) selected more than 50% of the time by MD classifier (top row) and MD$_2$MK classifier (bottom row). These anatomical regions are overlaid on a registered T1 image in MNI space.

may have inherent pathological effects on the brain tissue [78]. Considering the consistently detected features, our findings generally agree with previous voxel based analysis on DTI and DKI maps to detect microstructural abnormalities [21]. It was observed that both DTI and DKI based classifiers had a broader detection of the WM including most limbic tracts. Multimodal studies have found abnormalities in these structures in TLE patients associating with some form of cognitive deficits [112]. On the other hand, we also observe that DTI was not able to detect changes in the SS$_L$ (which include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) compared to DKI. Abnormalities in these fiber bundles have been related to delayed memory in TLE patients [14]. These discrepancies could be associated with the structural complexity of the sagittal stratum [41]. Detection of subtle changes in fibers with complex architecture has been a challenge for DTI, because of its simplifying assumption of a single fiber direction per voxel, the limitations of which have been widely discussed in the literature [135]. In addition, studies have demonstrated that microstructural changes in the corpus callosum (CC) are related to lateralization in epilepsy patients [114]. Our findings showed that DTI failed to detect changes in the SCC apart from the BCC and GCC compared to DKI. These findings did not agree with a previous analysis which found MD to have significant changes in the SCC in ITLE patients [21]. This again could be due to the difference in the
patient cohort and analysis technique. Nevertheless, both DTI and DKI had comparable detection of abnormalities in extrahippocampal areas, conforming to the idea that TLE is a network disorder [112, 39].

### 4.5.2 Analysis of detected grey matter

The performance of the classifiers based on grey matter features showed that all DKI classifiers had the highest overall accuracy of 92.1% compared to DTI. Looking at the cortical and subcortical discriminative regions between the classes (i.e., the regions selected consistently during the feature selection process), DKI based classifiers generally detected changes mostly in the medial temporal region and frontal lobe regions. These findings again agreed with those observed in a previous voxel based study [21]. We also observed that, in GM DTI was able to detect temporal lobe regions including the amygdala, cingulate cortex, frontal lobe, basal ganglia, and cuneus. Again we note that most of these regions were also detected with DKI in addition to fusiform gyrus and precuneus cortex. The fusiform gyrus (part of the temporal-occipital area) abnormalities associated with TLE had been known to cause deficit in social cognition such as face processing complications [111] and the precuneus (parietooccipital area) changes in its functional connectivity had been related to grey matter atrophy in TLE [95]. Another structure that was identified consistently with DKI and missed by DTI was the right entorhinal cortex (EnC_R). Studies have shown that although the hippocampus is the primary epileptogenic area, seizures can originate in the adjacent structures such as the entorhinal or perirhinal cortices [23]. It was observed that the closer a structure is anatomically to the hippocampus, the higher the degree of atrophy. Hence, the entorhinal cortices tend to display a high degree of atrophy [143]. In addition, DKI detected consistently the left temporal pole (TP_L), a structure that plays potentially underappreciated role in the genesis and propagation of seizures in temporal lobe epilepsy. A recent study [1] looked at the role of temporal pole (TP) in TLE using invasive monitoring with electrocorticography to localize the epileptogenic zone. They found that TP was involved in seizure onset in 70% of their subjects even though these findings did
not necessarily correlate with preoperative neuroimaging abnormalities of the TP. The slight increase in performance of DKI classifiers and the detection of EnC_R, FuG_R, PrCC_R, TP_L could be related to the partial volume effect (i.e., signal mixing of GM, WM and CSF) facilitating non-Gaussian diffusion pattern, reducing the performance of DTI to detect changes in this region [2]. Our observation of DKI performance in the grey matter indicated that DKI is not only sensitive to diffusion abnormalities induced by presence of gliosis, axonal and dendritic reorganization related to TLE, it can also reveal diffusional changes associated with microstructural complexity [112, 145].

### 4.5.3 Limitations

There are several limitations to our work. Firstly the sample size, especially the patient cohort, was small compared to the controls, an investigation with a larger and equal ratio of patient to controls will prove to be more helpful in verifying the reliability of the current findings. Secondly, the sub-grouping of the patient cohort into ITLE and rTLE used the side of resection for surgical patients and seizure onset zones for non-surgical candidates as our gold standard, but there is a possibility that the epileptogenic zone does not always coincide with these regions, therefore this could have led to mislabelling of the sample. Thirdly, although we used the same data to compare DTI since studies have demonstrated that DTI estimation with DKI have better accuracy over traditional DTI fitting and also to avoid biased differences with respect to b-values or number of directions that could affect the fitting, the downside however is that the DTI fitting can become nosier at higher b-values (i.e., due to kurtosis). Finally, it is commonly known that support vector machine performance is highly determined by the quality of the training set. This is typical in dataset like ours (biological data) characterized with large number of features to number of observations. To reduce the effect of this we applied the individual feature selection technique. We suggest that multiclass SVM classification based on multi-parametric MR imaging quantitative features would be an appropriate future research direction.
4.6 Conclusion

In conclusion the study showed that diffusion kurtosis imaging can add value to the traditional diffusion tensor method in characterizing temporal lobe epilepsy patient’s brain microstructure in left and right-TLE. The findings in both grey and white matter suggest that DKI has strong potential in complementing commonly derived DTI metrics in detecting subtle changes in the brain regions with non-Gaussian diffusion pattern induced by complex cytoarchitecture or presence of pathology related to epilepsy.
Chapter 5

Conclusion

Diffusion MRI is more than a non invasive \textit{in vivo} biopsy, it has provided us with ability to probe brain tissue microstructure in regions of interest, or the whole brain, at an unprecedented scale. There have been many diffusion MRI based microstructural quantitative methods developed since the inception of the DTI model, all with the general aim of providing better sensitivity and minimizing acquisition requirements to suit possible clinical applications. There are two general groups of models: one attempts to characterize the microstructure by using prior assumptions, while others aim to represent the raw data. However, they all come with their own challenges. DKI is one of the models that aims to fit the raw data without any prior assumptions. It was developed primarily to address the shortcomings of DTI as discussed in \textbf{Chapter 1}. The overall aim of the studies comprising this thesis was to investigate DKI reliability and its sensitivity in delineating lesions in TLE patients, ultimately leading to accurate diagnosis and improved treatment outcomes. A summary of the methods developed and findings are discussed in the following sections, concluding with future work not explored in this thesis.
5.1 Contributions of this Thesis

Diffusion tensor imaging is a simple way to quantify diffusion properties in brain tissue. However, DTI is inherently based on the assumption of Gaussian free water diffusion and may be suboptimal when diffusion deviates from this diffusion pattern due to the complex intracellular and extracellular in vivo environment. The DTI limitation is particularly apparent in two situations. First, the signal attenuation curve is clearly monoexponential when using a multi-shell DWI sequence and the other is when imaging voxels with crossing fibers (see Figure 1.7). Numerous studies have demonstrated that more than 90% of WM imaging voxels have crossing fibers causing restriction or hindrance to diffusion, in which DTI is inadequate to fully quantify these voxels [135, 107]. To increase sensitivity of DWI acquisition to the diffusion properties in the underlying microstructure, the traditional DTI protocol has been extended to use multi-shell (i.e., more than one b-value) or increase the number of diffusion weighting directions. However, time efficiency is the main challenge, as the number of b-values and/or diffusion weighting directions increase, the acquisition time becomes longer, limiting clinical application. While there are advantages and disadvantages to this type of acquisition, it mostly depends on the target application.

One straightforward extension of standard DTI techniques is the DKI protocol. As discussed in the preceding thesis chapters, DKI aims to provide a more comprehensive characterization of water diffusion properties (i.e., free and non-free diffusion) within the tissue microstructure. In order to capture the non-Gaussian diffusion behaviour of water molecules in biological tissues, larger b-values and/or stronger gradients than those employed in DTI are required. However, higher b-values mean a lower signal-to-noise ratio and a poorer repeatability of the calculated parameters. Therefore, in Chapter 2, the work was aimed to evaluate the reproducibility (test-retest reliability) and quality of fitting for high spatial resolution (1.25mm isotropic) DKI, this includes the DKI-based DTI maps. While high resolution aids better quantification of WM fiber bundles and more isotropic GM, it could also affect
reproducibility if signal-to-noise is low. We examined tissue-specific coefficients of variation and fitting residuals as function of b-values for whole-brain WM, including specific WM fiber bundles, and cortical GM, as well as across lobes. In addition, we verified the in vivo findings using tissue-mimicking phantoms. This work complements the existing literature, as previous studies investigating high resolution DKI reproducibility were limited to 1.75mm isotropic resolution and looked at whole-brain WM only. In addition, the effect of different b-values in different tissue types was not assessed and remained elusive. Furthermore, since DKI has the ability to characterize complex microstructural environments such as GM, it is important to fully investigate DKI reproducibility in these areas which could also aid our understanding of neurodegenerative diseases including aging that are associated with GM abnormalities. The work presented in this chapter identified that the datasets with b-values =1000, 2000, 3000 s/mm², and b-values =1000, 3000 s/mm² have parallel reproducibility compared to the b-value =1000, 2000 s/mm² dataset across all DKI parametric maps (i.e., including DKI-based DTI maps). This demonstrates that high reproducibility can still be achieved within a reasonable scan time, specifically with the sequence with only two b-values (i.e., b-value =1000, 3000 s/mm²), supporting the potential of DKI for aiding clinical tools in detecting microstructural changes.

In Chapter 3 we employed the ability of DKI to quantify complex microstructure in detecting diffusion anomalous in TLE patients. Previous studies have shown that TLE is more of a network disorder and complete delineation of seizure focus can be challenging since seizures are not always exclusive to the hippocampus, but may rather originate from extra-hippocampal structures, which have contributed to long-term recurrence of seizures after selective resections. A number of clinical investigations suggest that, among other extrahippocampal structures possibly involved in seizures, the temporal pole (TP) could play an important and potentially underappreciated role in TLE. Better understanding of the microstructural properties of the TP in TLE patients might improve resective surgery planning. Diffusion kurtosis imaging allows quantification of diffusion in complex tissue environments and potentially more sensitive to
diffusion anomalies compared to the more common DTI in TLE patients. However, the benefit of DKI for detecting subtle alterations in the TP’s microstructure in TLE, particularly in patients with non-lesional MRI (MRI-), has yet to be established. This work sought to evaluate the sensitivity of DKI to detect anomalies at specific regions along the two associated WM fiber bundles (i.e., inferior longitudinal (ILF) and uncinate fasciculus (Unc)) connected to the TP in lesional MRI TLE (‘MRI+’) and MRI- patients. For WM analysis we combined the AFQ tool for sampling the DKI measurements along ILF and Unc generated using the multi-shell CSD anatomically constrained tracking method, which was used to minimize crossing fiber effects. In addition, the connected temporopolar cortex was also investigated using our developed tract-based cortical analysis approach. This study showed that DKI was able to detect possible microstructural changes along the WM tracts segments more towards the TP in both MRI+ and MRI- subjects not clearly visible using DTI metrics. The temporopolar cortex analysis indicated detectable microstructure anomalies in MRI+, and to some extent within the MRI- group too. These findings were verified using a reference cortical region (i.e., RMF). The AWF changes indicate potential neuronal loss possibly due to seizure activities originating either at the temporopolar cortex or the medial temporal lobe structures (e.g. hippocampus). Furthermore, we observed distinct WM-GM boundary differences between controls and the TLE patients (including MRI- patients). This finding could be related to the blurring of this area attributed to various causes (e.g. developmental cortical abnormalities). The current study demonstrated that, the combination of multi-shell ACT tracking, AFQ and DKI could serve as a complementary approach to detect subtle microstructural alterations within the anterior segments of the two associated WM fiber bundles connected to the temporal pole. In addition, our tract-based cortical analysis approach could help to uncover diffusion abnormalities in the temporopolar cortex. Moreover, since we demonstrated that precision of DKI acquisition is clinically feasible (see Chapter 2), the methods developed in this study could be easily implemented in a clinical workflow.

The work reported in Chapter 4 evaluates the added value of a DKI imaging protocol by
assessing how well diffusion metrics (i.e., DTI and DKI metrics, including DKI-based DTI metrics) perform in a machine learning application to classify epilepsy patient groups and controls. DKI provides a more comprehensive characterization of diffusion in the underlying microstructure by measuring both non-Gaussian diffusion (DKI-based quantitative metrics) as well as Gaussian diffusion (DKI-based DTI quantitative metrics). Previous studies have separately looked at the ability of DTI and DKI to identify microstructural alterations in TLE patients, and it was demonstrated that DKI was more sensitive to abnormalities in the microstructure than DTI. However, the value of combining DKI and DKI-based DTI metrics are yet to be explored. Furthermore, left and right TLE patients have possible distinct pathological effects, which could be used to classify different TLE types (i.e., left vs right TLE). Therefore, to investigate the added value of DKI to lateralize mixture of TLE patients, we took a multiclass classification approach, and examined how the regions and metrics chosen by the feature selection algorithm relate to clinical findings. Mean values from region of interest from DTI and DKI derived parametric maps (includes DKI-based DTI maps) were extracted as features, then multiclass classification was performed following classifier-wise feature selection. Trained classifiers were cross-validated and tested using a leave-one-out cross-validation strategy. Overall accuracy, specificity and sensitivity of the classifiers were calculated to find the combination of features with highest prediction accuracy. Features with higher relative frequency were listed as discriminative features. Comparable overall accuracy was observed for both DTI and DKI based classifiers in the WM. On the other hand, all DKI classifiers had slight increase in overall accuracy in the GM. Nevertheless, both DTI and DKI detected anomalies in the mesial temporal lobe and over wide-spread regions, indicative of TLE as a network disorder. DKI demonstrated potential in providing complimentary information to DTI in detecting subtle changes in specific brain regions (e.g., entorhinal cortex), suggesting alteration in water diffusion, possibly induced by cytoarchitectural changes related to TLE. Further research with a larger dataset is required to determine the efficacy of DKI as a potential diagnostic tool in TLE, more specifically, in identifying microstructural alterations relating to different TLE
types (i.e., left vs right TLE).

### 5.2 A Look to the Future

At each chapter, possible future directions were suggested with respect to each method developed. However, an important future research direction is to look at how to underpin the DKI quantitative measurements to the biophysical properties of the brain tissue microstructure, especially in TLE patients. DKI is able to probe the complex microstructure, as we have seen in the results discussed in this thesis and other previous DKI work in TLE. However, the measurements we extract are indirect information of the underlying tissue microstructure. The advantage of DKI over other models is that it aims to provide an empirical description of the diffusion signal behavior in a given voxel without assumptions about the underlying tissue. Thus it is applicable to any tissue type, healthy or diseased, but the estimated parameters lack specificity and remain an indirect characterization of the microstructure. Therefore, validating DKI derived parameters is important to demonstrate accuracy.

Various studies have looked at validating diffusion MRI models using simulation and phantoms. However, although these approaches provide ground truth features, the real tissue properties are likely compromised. In the work described in Chapter 2, we used a simple tissue mimicking 3D phantom to validate our WM results. As shown, DKI had high precision in quantifying diffusion in most of the crossing fibers. The next appropriate step will be to look at validating DKI parameters with true tissue microstructure with biological complexity. One such approach is the use of optical imaging of fixed tissue specimens, since it offers a direct assessment of the physical features of the tissues [25]. The challenge to this validation method is that the histological specimens are limited to 2D samples, however recent work has looked at extending to 3D sections using confocal imaging [82]. As the technological advances in MRI gives us the ability to image the brain with high resolution at ultra-high field MRI systems (i.e., >3T), it opens the door for us to study DKI quantitative measurements and their histological correlates. Future work would focus on developing DKI pipelines incorporating
high resolution post-op images (i.e., resective specimen from TLE patients) for direct validation of DKI \textit{in vivo} measurements. Such DKI validation studies will be key to establish disease and pathology-specific applications, specifically in TLE. Ultimately, the goal of diffusion MRI modeling or in the interest of this thesis, the DKI technique, is to provide a clinically meaningful insight to the complex microstructure for diagnosis and potentially improving treatment outcome of temporal lobe epilepsy patients.
Bibliography


Appendix A

Supplementary data

Figure A.1: WM (top) and GM (bottom) ROIs used for analyses. Color-coded WM structures and GM regions indicate the different WM bundles (CiC-Cingulum Cingulate, CiH-Cingulum Hippocampus, Fx-Fornix, SFOF-Superior Fronto Occipital Fasciculus, SLF-Superior Longitudinal Fasciculus and Unc-Uncinate Fasciculus) as well as GM lobes (FL-Frontal Lobe, PL-Parietal Lobe, LL-Limbic Lobe, TL-Temporal Lobe and OL-Occipital Lobe).
Figure A.2: Pair-wise correlation coefficient (r) for each subject between DKI parametric values from the three datasets: A vs C, A vs B and C vs B (1st row) for MD and A vs C, A vs B and C vs B (2nd row) for MK. Shown are the individual subject voxel-wise values averaged across the whole-brain white matter. There is a consistent high correlation between the three datasets (r~1).

Table A.1: Mean DKI values for each of the phantoms representing different fiber orientations (in degrees), shown for MK and MD only. The Pearson correlation was high between the three datasets (A, B and C, r~1), except for MD from dataset C, where we observed low correlation with the 60° phantom.
Figure A.3: Pair-wise correlation coefficient \( (r) \) for each subject between DKI parametric values from the three datasets: C vs B (1\textsuperscript{st} row), A vs B (2\textsuperscript{nd} row) and A vs C (3\textsuperscript{rd} row) for MD and C vs B (4\textsuperscript{th} row), A vs B (5\textsuperscript{th} row) and A vs C (6\textsuperscript{th} row) for MK. Shown are the individual subject voxel-wise values averaged across the white matter ROIs. There is a consistent high correlation between the three datasets \( (r \sim 1) \).
Figure A.4: Pair-wise correlation coefficient (r) between DKI parametric values from the three datasets: C vs B (1st row), A vs B (2nd row) and A vs C (3rd row) for MD and C vs B (4th row), A vs B (5th row) and A vs C (6th row) for MK. Shown are the individual subject vertex-wise values averaged across each lobe of the left hemisphere (similar results observed in the right hemisphere). For all the lobes there is a consistent high correlation (r~1) between the three datasets.
Figure A.5: Schematic of the fibers crossing angles (0 - 90 degrees) (A). PVA dissolves away when placed in water leaving microporous structure (B). Phantom before dissolving (C) and phantom after dissolving (E). Dissolved phantoms stacked in a test tube with water before imaging (D).
Appendix B

Supplementary data

Figure B.1: (A), (B) and (C) shows the relative frequency of the first five selected white matter features extracted from AD and AD\_2AK, RD and RD\_2RK and FA and FA\_2Kfa maps respectively during the feature selection process for each of the SVM binary classifiers (h\_k). The yellow and blue bars indicate features detected with DTI and DKI respectively. The features selected more than 50% (above dotted red line) were considered to be more consistent. See Appendix Table B.1 for full names of all white matter features or regions.
Figure B.2: (A) and (B) shows the relative frequency of the first five selected grey matter features extracted from AD and AD_{2}AK and RD and RD_{2}RK maps respectively during the feature selection process for each of the SVM binary classifiers (h_{k}). The yellow and blue bars indicate features detected with DTI and DKI respectively. The features selected more than 50% (above dotted red line) were considered to be more consistent. See Appendix Table B.2 for full names of all grey matter features or regions.
Figure B.3: White-matter (blue) and grey matter (red) selected more than 50% of the time by the respective classifiers: (A), FA vs FA$\text{Kfa}$, (B), AD vs AD$\text{AK}$ and (C), RD vs RD$\text{RK}$. These anatomical regions are overlaid on a T1 image in MNI space.
Table B.1: Names and abbreviations of white matter regions

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<th>Abbreviation</th>
<th>Description</th>
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<td>Pointing Crossing Tract part of MCP</td>
<td>PCT</td>
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<td>GCC</td>
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2021

2021
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