Imaging Correlates of the Epileptogenic Zone and Functional

Deficit Zone using

Diffusion Tensor Imaging (DTI)

By

Beate Diehl

Thesis submitted for the degree of Doctor of Philosophy

Department of Clinical and Experimental Epilepsy

Institute of Neurology

University College

London

DECLARATION

I, Beate Diehl, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Beate Diehl   London, October 2010

ABSTRACT

Focal epilepsy is a common serious neurologic disorder. One out of three patients is medication refractory and epilepsy surgery may be the best treatment option. Neuroimaging and electroencephalography (EEG) techniques are critical tools to localise the ictal onset zone and for performing functional mapping to identify the eloquent cortex in order to minimise functional deficits following resection.

Diffusion tensor magnetic resonance imaging (DTI) informs about amplitude (diffusivity) and directionality (anisotropy) of diffusional motion of water molecules in tissue.This allows inferring information of microstructure within the brain and reconstructing major white matter tracts (diffusion tensor tractography, DTT), providing in vivo insights into connectivity.

The contribution of DTI to the evaluation of candidates for epilepsy surgery was examined:

1. **Structure function relationships** were explored particularly correlates of memory and language dysfunction often associated with intractable temporal lobe epilepsy (TLE; chapters 3 and 4). Abnormal diffusion measures were found in both the left and right uncinate fasciculus (UF), correlating in the expected directions in the left UF with auditory memory and in the right UF with delayed visual memory performance. Examining the arcuate fasciculus (AF), bilateral diffusion changes were found with correlations between left AF DTI measures and language scores.

2. The second aim of this thesis was to **validate DTT results** and test the hypothesis that cortical language areas determined by cortical stimulation serve as anchor points for the tractography defined AF (chapter 5). Subdural grid contacts overlying anterior language cortex co-localised in 84.2% with the AF, and in 55.8% in posterior language areas. This provides some validation that the AF

reconstructed using DTT subserves language function, but further study is needed.

3. Lastly, **seizure propagation** was investigated in a case series of patients with cortical dysplasia (chapter 6). Reduced connectivity with reduced arborization and thinning of the fibre bundles between subcortical WM and the dysplastic cortex was demonstrated. Fibre tracts reconstructed from regions underlying the ictal onset zone showed abnormal connectivity.

ACKNOWLEDGEMENTS

This work was conducted part time, initially as a non-resident PhD candidate. The experimental work, data acquisition and main part of the data analysis were performed at the Epilepsy Center, Cleveland Clinic Foundation, Cleveland, USA, where I worked until March 2008. I completed the analysis, resultant publications and the thesis itself following my relocation to the National Hospital for Neurology and Neurosurgery, London, UK, in April 2008.

During the course of the past four and half years, the number of people who have contributed their time, work, advice, knowledge and goodwill is vast.

First and foremost I would like to thank my supervisors. Working with Prof. John Duncan has opened my eyes to applying advanced neuroimaging techniques to epilepsies. His vision and incredible organisational skills remain a great inspiration as he spearheads one of the most successful groups in epilepsy and imaging and I am honoured to work with him now in the Department of Clinical and Experimental Epilepsy and at the National Hospital for Neurology and Neurosurgery. Prof. Hans O. Lüders, my mentor and teacher, has influenced and shaped my way of thinking regarding focal epilepsies in an unprecedented manner. He is a dedicated teacher and an inspiration to countless US and international fellows whom he has taught how to analyse EEGs and localise the focus during the pre-surgical evaluation. His academic rigour, enthusiasm and passion for neurophysiology and epilepsy have left an unforgettable impression on me.

Devising meaningful, translational research requires a solid understanding of the clinical needs; in this context I fondly recall the many discussions I had with Dr Holly Morris. His vast clinical experience has deeply shaped my clinical practice, and inspired inquisitiveness. In addition, his encouragement played a crucial role

am deeply grateful to their generous support for two consecutive years of funding (2006 and 2007).

Lastly I would like to acknowledge my patients, who I had the honour of treating in my first years of independent professional practice. Their unique diseases and the questions they asked, have inspired me to pursue the answers.

STATEMENT OF WORK DONE BY MYSELF AND OTHERS

I performed the following work in all studies underlying this thesis: Study designs and methods, ethics approvals, grant funding, patient selection, a majority of the informed consent procedures (less than 20% patient informed consent was obtained either via a collaborator (Robyn Bush) or a research nurse), data transfers and image analyses including all coregistration procedures, ROI placement and analyses, tractography, all statistical data analyses (in part in consultation with Robyn Busch,PhD), review and collection of clinical data, generation of the first drafts of manuscripts, manuscript submission, and all revisions. Furthermore, I presented all data as either posters or platform presentations in national and international meetings. Some of the patients I personally followed at the Cleveland Clinic and they were also admitted under my care during their presurgical investigation with intracranial EEG. Finally, I performed the cortical stimulation procedures in some patients as part of their clinical care; in other cases, the stimulation data were reviewed retrospectively as part of the research protocol for the study.

As mentioned in the acknowledgements, the following people were instrumental in providing the technical framework and support: Jean Tkach, PhD, Eric LaPresto, MSc, Zhe Piao, MSc. In an advisory function, the Neuroradiologist Dr. Paul Ruggieri participated in study design. Radiographers of the Neuroradiology Department at CCF acquired the clinical MRI scans and the DTI sequence typically as a short additional scan. Robyn Busch, PhD and her team performed the Neuropsychological evaluation of the patients and also advised on statistical

data analysis and the manuscripts concerned with neuropsychological correlations of DTI measures.

DEDICATION

I would like to dedicate this work to my family. My parents, Amalie and Werner Diehl, have kept a watchful and ever supportive eye on my moves and relocations between Germany, France, the USA and the UK. They have enabled me to go to Medical School and embark on the long programme of training to gain all the exceptional experiences I have had.

Most importantly, I have to thank my husband Neill Dunfee, who has been so incredibly understanding, following me to London and continuing to put up with the endless trials and tribulations of balancing a clinical job with research, meeting deadlines and all the other pressures that come with a life devoted to clinical work and scholarship. Without him, this would not be possible.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

GLOSSARY OF ABBREVIATIONS

AF	=	Arcuate fasciculus
ADC	=	Apparent diffusion coefficient
AED	=	Antiepileptic drug
AVM	=	Arteriovenous malformations
BOLD	=	Blood oxygen level dependent
CCEPS	=	Cortico-cortical evoked potentials
CD	=	Cortical dysplasia
CT	=	Computerised tomography
DCM	=	Dynamic causal modelling
DTI	=	Diffusion tensor imaging
DTT	=	Diffusion tensor tractography
DWI	=	Diffusion weighted imaging
EEG	=	Electroencephalography
EPI	=	Echo planar imaging
fMRI	=	Functional Magnetic Resonance Imaging
FA	=	Fractional anisotropy
FACT	=	Fibre assignment by continuous tracking
FLAIR	=	Fluid attenuated inversion recovery
HS	=	Hippocampal sclerosis
IFO	=	inferior fronto occipital
IFOF	=	Inferior fronto occipital fasciculus
MD	=	Mean Diffusivity
MEG	=	Magnetoencephalography
MR	=	Magnetic Resonance
MRI	=	Magnetic Resonance Imaging
MTS	=	Mesial temporal sclerosis
NMR	=	Nuclear magnetic resonance
PET	=	Positron emission tomography
PHG	=	Parahippocampal gyrus

SPECT = Single photon emission computed tomography

SPM = Statistical parametric mapping

TLE = Temporal lobe epilepsy

ROI = Region of interest

SEEG = Stereo EEG

SD = Standard deviation

UF = Uncinate fasciculus

PUBLICATIONS

Parts of this thesis have appeared in the following publications:

Original publications

1. **Diehl B,** Busch RM, Duncan JS, Piao Z, Tkach J, Luders HO. Abnormalities in diffusion tensor imaging of the uncinate fasciculus relate to reduced memory in temporal lobe epilepsy. Epilepsia 2008; 49 (8): 1409-1418.

2. **Diehl B**, Piao Z, Tkach J, Busch RM, Lapresto E, Bingaman W, Duncan J,, Lüders HO. Cortical stimulation for language mapping in focal epilepsy: Correlations with tractography of the arcuate fasciculus. Epilepsia 2010, 51: 639-46.

3. **Diehl B**, Tkach J, Piao Z, Ruggieri P, LaPresto E, Liu P, Fisher E, Bingaman W, Najm I. Diffusion Tensor Imaging in patients with focal epilepsy due to cortical dysplasia in the temporo-occipital region: Electro-clinico-pathological correlations. Epilepsy Research 2010, 90(3):178-87.

Abstracts

Diehl B, Piao Z, Tkach J, LaPresto E, Liu P, Busch R.
Diffusion tensor imaging characteristics of the arcuate fasciculus in patients with temporal lobe epilepsy and correlates with language scores. (Poster, American Epilepsy Society meeting, Seattle, Dec 2008). Abstract 3.123 Epilepsia 2008, 49 (Suppl. 7), 390.

Diehl B, Piao Z, Tkach J, Busch R, Najm I, Bingaman W, Lüders HO.
Extraoperative cortical stimulation for language mapping in intractable focal epilepsy: correlations with tractography of the arcuate fasciculus. (Platform, European Epilepsy meeting, Berlin, September 2008) Abstract 052 Epilepsia 2009, 50(Suppl 4), 59.

Diehl B, Piao Z, LaPresto E, Liu P, Tkach J, Bingaman W, Busch RM.
Diffusion Tensor Imaging characteristics of the Arcuate Fasciculus are not related to a decline in language functioning following temporal lobectomy. (Poster, European Epilepsy meeting. Rhodes, June 2010). Abstract 149 Epilepsia 2010, 51 (Suppl 4), 46.

Book chapters

Vollmar C, **Diehl B.** Tractography in ETLE. Chapter in "Extratemporal Lobe Epilepsy Surgery", as part of the series "Progress in Epileptic Disorders" by John Libbey Eurotext.
Editors: Koubeissi MZ, Maciunas R

Diehl B, Ruggieri P: Chapter 22, History of Neuroimaging as a pre-surgical evaluation tool. Textbook of Epilepsy Surgery. Editor: Lüders HO. Informa healthcare 2008.

Diehl B, Lemieux L: DTI and EEG fMRI. Chapter 77. in Wyllie E , Ed: The Treatment of Epilepsy: Principles & Practice. Wolters Kluwer Health 2010.

CHAPTER 1
INTRODUCTION

1.1. Epilepsy and Epilepsy Surgery

Epilepsy is a chronic disease characterised by recurrent and unprovoked seizures. It is one of the most common serious neurologic disorders, with a lifetime risk of developing epilepsy of 3.2% (Mattson, 1992). Approximately 90% of the incidence of cases in adults have symptomatic partial or localisation-related epilepsy (Camfield and Camfield, 1996; Hauser, 1992). Overall, the mesial temporal lobe is the most epileptogenic region of the brain, and therefore temporal lobe epilepsy (TLE) has remained a focus of attention for many years. With advances in neuroimaging and the introduction of magnetic resonance imaging (MRI) into clinical practice however, extratemporal lobe epilepsies have increasingly become a target for epilepsy surgery, particularly if a structural lesion is detected. Lesions are now identified in about 80% of all refractory focal epilepsies and include mesial temporal sclerosis (MTS), tumor, malformations of cortical development, vascular anomalies and head trauma (Diehl and Luders, 2000; Tassi *et al.*, 2009).

The goal of treatment is to render the individual seizure-free without producing antiepileptic drug (AED) toxicity. Despite the introduction of ''newer'' AEDs, one third of patients with partial epilepsy will not attain a seizure remission with pharmacotherapy (Kwan and Brodie, 2003). A recent randomised, controlled trial of surgery for refractory TLE showed that at 1 year, 58% of all patients were completely seizure free in the surgical group compared to only 8% in the medically treated group (Wiebe *et al.*, 2001).Therefore, a significant number of patients should be evaluated for potential epilepsy surgery. A UK study indicated that 30,000 patients develop epilepsy each year and approximately 6,000 of these have medically refractory seizures (Lhatoo *et al.*, 2003). Figures from this study

suggest the number of "curative" operations for epilepsy would be 422 per year. Although this in line with the number of incident cases being added to the surgical pool (approximately 450 every year, which is 1.5% of 30,000), it does not address the backlog of patients in the prevalent surgical pool, estimated at 4500 patients. In addition it has been noted that only ~1% of the patients undergoing epilepsy surgery in the UK are extratemporal. Recent data from a longitudinal study following a cohort of childhood-onset epilepsy patients suggest that these numbers may be underestimating the need for epilepsy surgery (Berg *et al.*, 2009). Therefore, large numbers of treatment refractory patients, particularly with extratemporal lobe epilepsy, remain untreated.

The objective of epilepsy surgery is the complete resection or at least disconnection of the epileptogenic zone in order to render a patient seizure free. The epileptogenic zone is the area of cortex that is indispensable for the generation of seizures (Diehl and Luders, 2000; Rosenow and Luders, 2001). It must be noted that the epileptogenic zone is a theoretical concept: even if freedom from seizures is accomplished following resection, it is possible that resection of a smaller area of cortex may have resulted in the same outcome. Therefore, we can ascertain that the epileptogenic zone was included in the resection, but do not know its exact extent. Furthermore it is well known that a number of patients will unfortunately relapse even years after initially successful epilepsy surgery. For practical purposes, most centres conclude that the epileptogenic zone was removed if a patient has been seizure free for one to two years, even if they are still on seizure suppressing medications (Janszky *et al.*, 2005; Jeha *et al.*, 2006; Spencer, 2002). This is justified because studies have shown that if a patient remains seizure free for this period, the highest risk of relapsing has passed. It is of note however that a small number of patients can relapse many years later.

The epileptogenic zone cannot be measured with precision using one or even a number or tests and surrogate markers. It was suggested at the Second Palm

Desert Conference on the Surgical Treatment of the Epilepsies (1992), that the epileptogenic tissue could be identified and defined using six different types of abnormalities and these have recently been reviewed by (Rosenow and Luders, (2001):

1. The irritative zone
2. The ictal onset zone
3. The structural epileptogenic lesion
4. The symptomatogenic zone
5. The functional deficit zone.

The irritative zone is the area generating the interictal spikes seen during interictal electroencephalography (EEG) recordings; the ictal onset zone can be recorded and defined using EEG during seizures and the structural epileptogenic lesion is identified on MRI. The area of cortex responsible for the initial ictal symptoms is the symptomatogenic zone, and the functional deficit zone is the area of cortex that is functionally abnormal between seizures. This can be estimated by a number of tests, ranging from physical examination, neuropsychological testing, EEG or Positron Emisson Tomography (PET). The epileptogenic lesion is the radiologically defined lesion likely to be causing the epilepsy.

It is generally believed that all the above markers have a variable relationship with the epileptogenic zone. Complete removal of the ictal onset zone and the epileptogenic lesion is generally considered necessary to achieve a seizure free outcome (Wyllie *et al.*, 1987). In contrary, the irritative zone, symptomatogenic zone and functional deficit zone may be significantly larger or even remote from the ictal onset. Depending on the exact findings, an extensive irritative zone and/or functional deficit zone may raise concerns regarding the seizure outcome following surgery, but does not *per se* have to be included in the resection.

In order to obtain optimised outcomes following epilepsy surgery, preservation of the eloquent cortex is of paramount importance. A variety of diagnostic tools are used to localise the epileptogenic zone, such as detailed analysis of seizure semiology, video EEG recordings (scalp and in selected cases invasive EEG recordings), neuropsychometry and functional and structural neuroimaging methods. Information from all these different modalities is integrated and a hypothesis is formulated regarding the epileptogenic zone. Neuroimaging techniques are an integral part, and have played an increasing role over the years, particularly since the introduction of MRI.

In this thesis, I have examined the contribution of diffusion tensor imaging (DTI) and diffusion tensor tractography (DTT) in the evaluation of candidates for epilepsy surgery.

The overall aims and underlying hypothesis were:

1. To appraise the role of DTI and DTT in the definition of structural abnormalities in the epileptic brain and their functional correlates. Specifically, I explored structure/function relationships, particularly correlates of memory and language dysfunction often associated with intractable temporal lobe epilepsy (TLE; Chapters 3 and 4). It was hypothesised that insights into the microstructure of the brain in patients with TLE could be gained using this technology and there will be a relationship between cognitive performance and potential damage in specific tracts supporting such function.

2. To provide validation of the DTT results by comparing tracts to cortical stimulation results as performed in some patients with focal epilepsy undergoing pre-surgical evaluation. Specifically, the relationship between the results of cortical stimulation for language mapping was compared to results of the DTT of the arcuate fasciculus (AF). It was

hypothesised that cortical language areas serve as anchor points for the tractography defined AF (Chapter 5).

3. To investigate the correlation of the pathway of seizure propagation away from the ictal onset zone as seen during intracranial EEG recordings with connectivity of the ictal onset zone visualised by DTT. Specifically, connectivity of the ictal onset zone was characterised using DTT in a case series of patients with cortical dysplasia (CD). It was hypothesised that the pattern of connectivity would correlate with seizure propagation. The relationship bewteen the resection area with outcome data concerning seizure freedom and functional outcome was also explored (Chapter 6).

1.2 History of neuroimaging in the pre-surgical evaluation

In order to appraise the role of novel neuroimaging techniques during presurgical evaluation, it is useful to understand how such technologies were integrated over time whilst striving to localise the epileptogenic zone.

1.2.1 Historical background

The history of modern pre-surgical evaluation for epilepsy surgery has been shaped by several main influences and approaches in localising the seizure focus: firstly, clinical observation and seizure semiology; secondly the advances in EEG diagnostics; and lastly the advances in our ability to image the brain. Arguably, there is no other technology that compares to modern structural and functional brain imaging in revolutionising our way of thinking regarding epilepsy and the pre-surgical evaluation throughout the last decade of the last century, the decade of the brain.

Therefore, reflecting upon the history of neuroimaging in the context of epilepsy surgery will provide a framework and introduction to the appraisal of the contribution of DTI to the pre-surgical evaluation, the topic of this thesis.

For most of the history of epilepsy surgery, there was no direct way of imaging the brain. In 1896 Sir William Gowers wrote in his famous textbook on Diseases of the Nervous System: "The nervous system is almost entirely inaccessible to direct examination. The exceptions to this are trifling. The termination of one nerve, the optic, can be seen within the eye. Some of the nerve trunks in the limbs can be felt, as the ulnar, in the normal state; others only when enlarged by disease" (Bull, 1982; Gowers, 1886)

Therefore, in the closing decades of the nineteenth century, evidence regarding the presence of pathology could only be gained indirectly, and was mainly based on the careful examination and clinical correlation of the deficit and the pathology later analysed either after surgery or after post-mortem pathological examination. Only in 1895, when Roentgen discovered X-rays, were we able to start to look inside the human body *in vivo*, even though with respect to the brain it remained an indirect window by careful analysis of bony changes, secondary to intracerebral pathology.

1.2.2 The beginnings of imagery of the brain

For many centuries, the role of the brain was unknown. In ancient Egypt for example, the heart was considered the essence of life and the brain discarded in the embalming process. The brain as the seat of the mind was clearly recognised by Alcmaeon of Croton, an early Greek writer and philosopher-scientist. In the years to come this very advanced concept was abandoned and other Greek philosopher physicians such as Hippocrates reverted to more primitive hydraulic theories, postulating that the "essence" of life, a mysterious substance was supposed to be carried by the blood. In the book "on the sacred disease", which is

ascribed to Hippocrates, he recognised however that the brain serves as the controlling center of the body. He also criticised the popular belief that epilepsy was a divine malediction. There is no doubt that Hippocrates recognised that seizures arise in the head (Temkin, 1933). However, for many of the following centuries, scholars, including the natural philosopher Aristotle, would continue to believe in the supremacy of the heart over the brain.

The history of imagery of the brain dates from antiquity, however there is no evidence suggesting that these concepts were used to guide treatment (Engel, Jr., 1993). Surgical interventions for the treatment of seizures were often guided by supernatural concepts concerning the cause of epilepsy.

An important step towards modern medicine was marked by the publication of the first complete textbook of human anatomy in 1543, De Humanis Corporis Fabrica by Andreas Vesalius (1514-1564). It includes sections on the brain, and he disputes the prevailing doctrine that higher functions of the brain are situated in the ventricles.

In 1791, Franz Josef Gall of Vienna may have been the first to propose that different mental faculties and behavioral functions occupied different anatomical locations in the brain (Engel, Jr., 1993). Gall believed that mental function was localised in discrete areas of the brain and called these organs. He located the "organs" serving intellectual function in the cerebral cortex. Although he published these seminal observations, his contributions were overshadowed by his introduction of phrenology, the practice of diagnosis based on palpation of the skull, which evolved increasingly in a pseudoscience. In contrast, Gall and his disciple Spurzheimer, developed a unique system of dissection using alcohol and significantly advanced the knowledge of neuroanatomy (Simpson, 2005) .

It was not until the mid-nineteenth century that neuroscientists began to use clinical pathological correlation and faradic stimulation to prove that cerebral gray

matter indeed comprised functionally discreet regions (Engel, Jr., 1993). In 1861, Broca published his landmark case on M. Leborgne, a patient who had suffered from epilepsy since childhood and had lost the ability to speak. After the patients's death from an unrelated cause, an autopsy showed a chronic progressive softening of the cortex in the third convolution of the frontal lobe. This is considered to be the turning point that persuaded many scientists to believe in cortical localisation of function (Finger, 2000).

Sir Hughlings Jackson, called by many the father of contemporary epileptology, used the information obtained through analysing the clinical manifestations of seizures to localize the ictal onset. In 1861 and 1863 he wrote about the unilateral seizures in cerebral syphilis and commented that "as autopsies of patients who have died after syphilitic epilepsy appear to show, the cause is obvious organic disease on the side of the brain opposite to the side of the body convulsed, frequently on the surface of the hemisphere" (Jackson, 1863). Finally in 1870, Fritsch and Hitzig provided unequivocal experimental confirmation of a "motor cortex" present in the frontal lobes of dogs (Finger, 1994).

Epilepsy surgery in the strict sense of a neurosurgical intervention at an anatomical site that is defined by the seizure semiology, developed from the analytical approach that is closely related to the observations by Jackson. The first epilepsy surgery was performed on May 25, 1886 by Victor Horsley on a 22 year old patient with focal motor seizures, due to a scar that had been caused 15 years earlier by a depressed skull fracture (Horsley, 1886). The surgery was planned purely based on clinical semiology, and performed taking into account the *in situ* appearance of the brain tissue. Krause appears to be the first to utilise intra-operative cortical stimulation to guide surgery (Krause, 1909), particularly to identify the central sulcus in cases of Jacksonian epilepsy. However, until the end of the 19th century, it remained impossible to directly or indirectly image the brain before surgery however this was to change drastically in 1895.

1.2.3 Radiography and the application of X-rays to skull and brain pathology

The history of Neuroimaging arguably starts with a great discovery. On November 8, 1895, Wilhelm Konrad Roentgen, Professor of Physics at the University of Würzburg, discovered X-rays. By the end of December, he published a brief communication "on a new kind of rays", the result of seven weeks of systematic studies and well designed experiments (Roentgen, 1895). Roentgen himself gave the newly discovered phenomenon the name X-rays on account of their unknown character and to distinguish them from other rays. For this discovery he was awarded the first Nobel Prize for Physics in 1901.

Soon after Roentgen's breakthrough, X-rays were applied to examine the neurological system. Arthur Schueller performed systematic studies of the skull and is generally considered the father of Neuroradiology and introduced the term Neuro-Roentgenologie (Eisenberg, 1992). His classic work on the X-ray examination of the skull, carefully correlated autopsy and clinical findings with bony deformations (Schueller, 1912).

The use of skull X-rays in the diagnosis of epilepsy was advocated by a German Neurosurgeon, Fedor Krause. In his "Surgery of the brain and Spinal Cord" (Krause, 1910) he remarks: "Above all other means of diagnosis it furnishes the most useful in tumors with calcareous or bony deposits, as for instance in exostosis and any injury of the skull may bring on epileptic seizures….whenever possible X-ray examination should be made; it is frequently a great aid in clearing up the diagnosis. Even in other forms of epilepsy, roentgenography is of urgent need."

Up to the 1960s and even into the seventies, plain X-rays were recognised as having a valid place in the evaluation of patients with epilepsy, where bony changes and abnormal calcifications were the main findings (Shorvon, 1987).

In 1918 ventriculography, using X-rays to explore the contrast between air and fluid was introduced by Walter Dandy (Dandy, 1918; Dandy, 1919; Eisenberg, 1992). Throughout the first half of the last century, roentgenography was the tool to help localise lesions causing seizures. In conjunction with pneumencephalography, it remained the main imaging technology for more than 50 years.

The extensive documentation of cases undergoing surgery for intractable epilepsy particularly from the Montreal Neurological Institute, illustrates how the new technologies were used to guide the pre-surgical diagnosis.

1.2.4 The use of skull X-rays and pneumencephalogram in the diagnosis of epilepsy in the earlier part of the 20th century

The history of epilepsy surgery in the first half of the last century and the use of imaging techniques to guide epilepsy surgery were dominated by the Montreal Neurological Institute, which was founded by Wilder Penfield in 1934. Penfield had learned the technique of mapping out the sensory and motor cortical areas by cortical stimulation in order to resect "meningocerebral scars" safely (Foerster and Penfield, 1930). Many cases resulted in failure, as there were inadequate means to localise the epileptogenic zone.

The number of surgical epilepsy cases continued to increase every year. Penfield was determined to cure seizures by excision of the "meningocerebral cicatrix". Through careful catalogisation and analysis of seizure type, matched with the type of lesion found during surgery, a wealth of well documented case histories are available from this era.

The causes of epilepsies were inferred from lesions visible by X-ray and pneumencephalography. In Wilder Penfield's book "Epilepsy and the functional

anatomy of the brain" (Penfield and Jasper, 1954) and in a wealth of other books and articles, cases were presented illustrating how indirect roentgenographic evidence was used to infer underlying brain lesions and to guide epilepsy surgery. From the standpoint of diagnosis and treatment, the epilepsies were divided into symptomatic and cryptogenic epilepsies in the first half of the last century. The etiologies were readily recognised or reasonably assumed in the symptomatic cases and when unknown, were classified as cryptogenic ("of obscure origin"). Common causes of epilepsies thought to be amenable to epilepsy surgery were grouped into "expanding lesions" and atrophic lesions" (McRae, 1948). The spectrum of the known causes was remarkably complete for the time (McRae, 1948; Penfield and Erickson, 1941).

Penfield and Flanigan presented their epilepsy surgery results in cases with TLE (Penfield and Flanigan, 1950). The epileptogenic zone was determined using the above described means. Interestingly, the long term seizure outcomes were not so different from the post-MRI era: 52.9% were considered "cured" with no seizures or only one or more attacks before cessation, 29% were felt to have a worthwhile improvement and 14% were surgical failures. The follow up period was between 1 and 11 years.

In 1991, Rasmussen presented another series of results on outcomes after temporal lobe surgery for epilepsy: 63% of 100 patients had complete or marked reduction of seizures after "major hippocampectomy" involved medial removal of the amygdale, the pes and half of the hippocampus (Rasmussen and Feindel, 1991).

1.2.5 Computerised tomography (CT)

In the late 1960s, efforts were directed to perform measurements of X-ray transmissions from all possible directions through the body. The attenuation of the X-ray is measured from hundreds of different angles, the information decoded and

subdivided in a series of "slices" and in 1972, Sir Godfrey Hounsfield introduced CT (Hounsfield, 1980). In the 1970s, CT was introduced into clinical practice. Direct imaging of intraparenchymal abnormalities became possible for the first time. For epilepsy, the scanner was used to detect structural lesions and to determine cerebral atrophy and it was quickly shown that CT was superior to radionuclide scanning (du Boulay and Marshall, 1975).

In 1975 at the 21st European Congress of Electroencephalography and Epilepsy, the results of a total of 1702 patients from seven research groups were published. CT abnormalities were found in 46% of patients with the most common abnormality being atrophy and tumors were detected in 10% of all cases. It is well recognised that CT is quite sensitive to detect cerebral tumors and lesions like gliomas or various developmental tumors. Other pathologies including cerebrovascular disease, both ischemic and hemorrhagic, vascular malformations, post-traumatic changes and infectious disease could be visualised directly for the first time. It was also possible to demonstrate the structural lesions underlying the epilepsy in epilepsy syndromes such as TLE.

The CT scanner therefore replaced plain skull X-rays and pneumencephalography very rapidly during the 1970s. MRI would soon replace CT in its role to evaluate chronic epilepsy, especially as the sensitivity of CT in patients with epilepsy is not higher than 30% in unselected populations.

Today CT is readily available at all times and remains a valuable tool in many emergency situations with potentially the added value for the evaluation of intracranial calcifications (Duncan, 1997). If clinical presentation suggests a serious structural lesion, such as an acute intracranial hemorrhage or larger lesions that require immediate surgical intervention, emergent neuroimaging needs to be performed (Greenberg *et al.*, 1996; Practice Parameter, 1996). For the evaluation of a first seizure, CT is still performed if the patient's history and/or focal neurological signs make an acute symptomatic cause likely.

1.2.6 Positron Emission Tomography (PET) and other Nuclear Medicine applications in the definition of the epileptogenic zone

In February 1896, three months after Roentgen's discovery, Becquerel described natural radioactivity. The rays were being used for medical treatment. However, another 50 years had to pass before spontaneously emitted rays were used for diagnosis. The discovery was made by George Moore, a young surgeon from Minneapolis. He knew that fluorescein was taken up selectively by tumors of the eye. Prior to surgery for suspected gliomas, he injected a small dose intravenously and was able to detect it in the tissue using ultraviolet light. When the brain was exposed during surgery, he would shine the UV light on the brain and be able to identify the glioma and the edges well. The next step was to tag a radioactive substance to fluorescein; Dr. Moore chose radioactive iodine and used a Geiger counter to detect the radioactive emissions. He was immediately successful and localized 12 of 15 brain tumors (Moore G, 1948).

Over the next years this technique was refined and successfully evaluated in the diagnosis of a variety of neurological diseases. The conclusion from a larger study evaluating the utility of the radionuclide brain scan was that it is particularly useful in patients who develop localizing signs, in patents with "focal fits" (eight of 11 such patients had abnormal scans), in patients with vascular disease and gradual onset of localizing signs and in patients with inflammatory conditions of the central nervous system (Nisbet *et al.*, 1983).

To date, functional imaging including PET has remained an important imaging modality to localize the epileptic focus. The evolution of PET began in the early 1960ies. Its initial importance as a diagnostic tool to evaluate the brain for structural abnormalities in the 1960ies paralleled the widespread use of technetium scanning for the evaluation of brain tumors (Eisenberg R, 1992). This method was fast replaced first by CT, then by MRI. Since then the role of PET has shifted to an evaluation of brain function. The first medical cyclotron installation at Washington University in St. Louis and methods were developed to produce

carbon 11 labeled glucose to evaluate glucose metabolism. Subsequently it was shown that fluorodioxyglucose (FDG) had biological properties similar to C11 labeled glucose and the longer lived fluorine 18 labelling procedure could be used.

PET was soon explored in patients with epilepsy undergoing presurgical evaluation (Henry *et al.*, 1993). The first reports of interictal hypometabolism in patients with epilepsy using PET were in the early 1980s (Engel *et al.*, 1982), ictal hypermetabolism was first reported in 1978 (Kuhl *et al.*, 1978; Kuhl *et al.*, 1980). In temporal lobe epilepsy, interictal hypometabolism was described in the mesial temporal structures and has been implemented in the presurgical evaluation in patients with temporal lobe epilepsy (Theodore *et al.*, 1983).

1.2.7 Magnetic resonance Imaging (MRI)

In 1946 the first reports on nuclear magnetic resonance (NMR) were published by Bloch, Hansen and Packard (Bloch *et al.*, 1946) at Stanford and by Purcell, Torrey and Pound (Purcell *et al.*, 1946) at Harvard. The importance of this discovery was recognised and in 1952 the Nobel Prize for Physics was awarded to Bloch and Purcell.

In the 1980's, MRI was introduced in clinical practice. Since then, it has revolutionised the practice of medicine in many areas. The ability to visualise anatomical details and pathologies underlying the focal epilepsy dramatically surpasses all previous technologies. The first publications detailing its usefulness in detecting lesions underlying focal epilepsy date to the mid 1980's (McLachlan *et al.*, 1985; Purcell *et al.*, 1946; Sperling *et al.*, 1986; Theodore *et al.*, 1986). It was soon demonstrated that MRI was more sensitive than CT in detecting structural lesions underlying epilepsy (Theodore *et al.*, 1986).

Currently, approximately 70% of all patients with focal epilepsy referred to a tertiary epilepsy center show structural pathology on MRI (Duncan, 1997; Koepp

and Woermann, 2005). It has become possible to image the temporal lobe and detect hippocampal pathology in a non-invasive way. Several groups have shown conventional MRI studies to be ~90% sensitive and 85% specific in the diagnosis of hippocampal sclerosis (HS) in a series of epilepsy patients undergoing temporal lobectomy (Bronen *et al.*, 1997; Jackson *et al.*, 1993; Watson *et al.*, 1992; Watson *et al.*, 1997).

Over the past two decades, significant strides were made to improve the quality of MRI. The introduction of Fluid-attenuated Inversion Recovery sequences (FLAIR) (Jack, Jr. *et al.*, 1996) for the diagnosis of HS has significantly increased the accuracy of detection of signal abnormalities in the mesial structures, as the CSF is completely suppressed. Assessment of atrophy of the hippocampus can be improved by measuring hippocampal volumes. Visual analysis can detect 85-90% of atrophic hippocampi versus a 90-97% detection rate with quantitative volumetry (Cook, 1994; Jack, Jr. *et al.*, 1990; Kuzniecky *et al.*, 1997). Post-processing methods such as voxel based morphometry and texture analysis have been used to improve the detection rate for CDs (Koepp and Woermann, 2005). Novel MRI sequences such as magnetisation transfer imaging, fast flair T2 imaging and double inversion recovery have enabled identification of abnormalities in about one third of these previously cryptogenic patients (Salmenpera *et al.*, 2007).

In 1995, the relative contributions of MRI, single photon emission computed tomography (SPECT) and PET were summarised in a meta-anlysis (Spencer, 1994). PET had the highest diagnostic sensitivity in TLE (84%) and also had a rather good sensitivity (95%) in mesial temporal sclerosis. In extra TLE, the sensitivity for PET was only considered to be around 33%.

In recent years, receptor imaging using PET, including imaging of benzodiazepine, glutamate, opiate, serotonine and acetylcholine receptors has become feasible and will likely allow further insights into the mechanisms of epileptogenicity (Koepp and Woermann, 2005).

1.2.8 The decade of the brain

During the 1990's, the decade of the brain, functional MRI (fMRI) and Diffusion-weighted imaging (DWI) MRI techniques were introduced.

In 1990, the blood oxygen level dependent (BOLD) effect was first described by Ogawa *et al* . In 1992, within one month of each other, Ogawa *et al.* and Kwong *et al.*, described the BOLD signal change during visual stimulation in humans. Since, mapping of the cortex using fMRI has led to numerous publications within the neurosciences and fMRI of memory and language are important applications in intractable epilepsy patients evaluated for epilepsy surgery (Powell *et al.*, 2004). Imaging of the interictal activity using combined EEG and fMRI has become possible. Initially the MRI scanner was manually triggered to scan following observation of a spike, subsequently EEG fMRI was performed continuously and simultaneously (Allen *et al.*, 1998; Aubert *et al.*, 2009; Diehl *et al.*, 2003; Duchowny *et al.*, 2000; Duchowny, 2009; Rosenkranz and Lemieux, 2010; Salek-Haddadi *et al.*, 2003; Salek-Haddadi *et al.*, 2006; Vulliemoz *et al.*, 2009; Vulliemoz *et al.*, 2010).

Imaging white matter pathways and connectivity became possible with the introduction of DTI and the contribution of DTI to the definition of the epileptogenic zone, its connectivity and the relationship to functional cortex is the topic of this thesis. These technologies are not only capable of highlighting structural abnormalities, but can also provide insights in structural connectivity of areas of the brain. In combination with other techniques such as fMRI, we can now gain insights in brain function in health and disease.

1.3   Diffusion MRI

Diffusion MRI was introduced into clinical practice in the 1990's and rapidly applied to investigate a variety of diseases. The following sections (1.3 and 1.4)

explain why it is of particular interest in the study of epilepsy, and how acute and chronic tissue changes can be shown using diffusion MRI.

1.3.1 Principles of diffusion imaging

The MRI signal is dominated by the signal from water protons. In a medium without any boundaries, the random translational motion or Brownian motion of water molecules results from the thermal energy carried by these molecules. In the brain however, such diffusion is restricted by intra- and extracellular boundaries. Various animal models have been used to assess the most important boundaries affecting diffusion in the brain. Such studies showed that myelin is the main barrier to water diffusion (Beaulieu *et al., 1996;* Song *et al., 2002;* Song *et al.*, 2003; Song *et al.*, 2005) .

The principles of diffusion MRI were first developed *in vivo* in the mid 1980's (Le Bihan *et al.*, 2001; Le Bihan and Van Zijl, 2002). In DWI, images are sensitised to diffusion by using pulsed magnetic field gradients incorporated into a standard spin echo sequence (Le Bihan *et al.*, 2001;Taylor and Bushell, 1985). By taking measurements in at least three directions, it is possible to characterise the mean diffusion properties within a voxel in the image.

By applying diffusion gradients in six or more directions, the diffusion tensor, a mathematical construct, can be calculated. The tensor can be diagonalised to give three eigenvectors, $\varepsilon 1$, $\varepsilon 2$ and $\varepsilon 3$, representing the principal directions of diffusion. Each of these eigenvectors has an eigenvalue, $\lambda 1$, $\lambda 2$ and $\lambda 3$, representing the magnitude of diffusion (or the corresponding apparent diffusion coefficient (ADC) values) along each of these three main directions. Furthermore, a number of diffusion parameters can be derived in each voxel, which are insensitive to subject positioning and fibre tract alignment within the diffusion

gradients of the MRI scanner (Basser and Jones, 2002; Basser and Pierpaoli, 1996; Pierpaoli *et al.*, 1996). Mean diffusivity (MD) is a summary measure of the average diffusion properties of a voxel and is equivalent to the estimated ADC over three orthogonal directions.

It has been noted that the ADC measurements depended on a subject's orientation relative to the magnet (Hajnal *et al.*, 1991). White matter tracts parallel to an applied gradient had the greatest ADC, whereas those at an angle to the gradient had smaller ADC values. Therefore it is important to not only define the mean diffusivity of water molecules within an image voxel, but also their directionality. The fact that diffusion is not the same in the three main spatial directions, but is asymmetric in the brain and restricted in certain directions gave rise to the concept of "anisotropy" (Basser and Pierpaoli, 1996). Diffusion tensor imaging (DTI) has been developed to explore this directional information. When more than five directions are measured, not only the water molecule diffusion can be characterised, but also the degree and direction of anisotropy (Le Bihan *et al.*, 2001).

Exploring the diffusion information in various directions allows the gaining of greater insights into the structural changes, possibly even at a microscopic level. Fractional anisotropy (FA) is a scalar (unitless) index most commonly used to assess the overall degree of directionality; ranging from 0 (full isotropy) to 1 (complete anisotropic diffusion). However this index does not allow for analysis of directional information within the tensor. In order to interrogate diffusion changes in the three main directions, parametric maps for the parallel (main direction of diffusion, $\lambda \parallel$) and radial or perpendicular ($\lambda_T = (\lambda_2 + \lambda_3)/2$) directions to the main fibre tract orientation can be studied. Together, these quantitative measures help to characterise the integrity of the underlying white matter. Such information may allow understanding of the pathophysiologic mechanisms consistent with such diffusion abnormalities. Furthermore, DTI in combination with tractography

has become a powerful opportunity to subdivide compartments of white matter, representing different tracts and study selectively their diffusion properties.

1.3.2 Experimental insights into tissue structure using DTI

Anisotropy of water diffusion is a sensitive indicator of the structural integrity of tissue, particularly white matter. Several animal models of tissue injury and degeneration have been used to measure serial diffusion changes and correlate them carefully with histology. Using an *in vitro* model of Wallerian degeneration in a frog sciatic nerve, axonal and myelin degeneration causes a decrease in diffusion anisotropy due to reduced $\lambda \parallel$ and increased λ_T (Beaulieu *et al.*, 1996). Myelin has been shown to modulate perpendicular diffusivity (Song *et al.*, 2003; Song *et al.*, 2005), although it is not the only factor involved (Beaulieu and Allen, 1994). In order to understand the contributions of axonal versus myelin damage, serial diffusion measurements have been performed on the optic nerve in a mouse model of retinal ischemia (Song *et al.*, 2003). According to this model, parallel diffusivity shows a significant decrease in the first days of degeneration, which corresponds to the disintegration of the axonal microstructure, whereas myelin remains intact. Five days after the initial injury, perpendicular diffusion increased, which corresponds to the degradation of myelin sheaths, showing that $\lambda \parallel$ and λ_T can differentiate axonal from myelin damage during the course of degeneration.

In a mouse model of spinal cord injury, a region of interest analysis was performed and compared to histological markers of axon and myelin integrin. Perpendicular diffusion increased parallel demyelination of the histological marker, and parallel diffusivity decreased in both regions of axonal damage and normal-appearing white matter (Budde *et al.*, 2007).

In humans, reductions in the principal direction and increases in radial diffusivities have been shown in chronically degenerated white matter tracts (Pierpaoli *et al.*,

2001). Serial DTI measurements in three patients who underwent corpus callosotomy to treat medically refractory seizures and drop attacks revealed interesting insights into the diffusion changes in the corpus callosum after the surgery (Concha *et al.*, 2006). After one week, a decrease in parallel diffusivities was seen, evidencing the breakdown of the axons (Concha *et al.*, 2006; Kerschensteiner *et al.*, 2005), creating barriers in the longitudinal displacement of the water molecules. In the chronic stage 2–4 months after corpus callosotomy, an increase of the radial diffusivities was observed. Most likely at this stage, axonal membranes became more degraded and myelin sheaths showed degeneration, allowing water molecules to become more mobile perpendicular to the axons, resulting in an increase in radial diffusivities.

1.3.3 Tractography: technique and limitations

Lastly, anisotropy information forms the basis of reconstructing tracts. Anisotropy in white matter results from the organisation of tissue as bundles of axons and myelin sheaths running in parallel, and the diffusion of water is freer and quicker in the long axis of the fibres, than in the perpendicular direction (Beaulieu, 2001). By assuming that the largest principal axis of the diffusion tensor aligns with the predominant fibre orientation in an MRI voxel, we can obtain vector fields that represent the fibre orientation at each voxel. The three dimensional reconstruction of tract trajectories, or tractography, is an extension of such vector fields (Mori and van Zijl, 2002). However tractography only came into use in the later 1990's and beginning of the new millenium, due to the complexities in developing reliable computer algorithms to reconstruct the tracts. Some of the limitations and technical difficulties of tractography include the spatial resolution of DTI, which is in the order of several mm, as well as noise. Various acquisitions and post-processing analysis techniques have been proposed (Mori and van Zijl, 2002), and methods continue to evolve. Voxel sizes are much larger than the resolution needed to image single axons. Hence, *in vivo* DTI studies can at present only

display an approximation of the main tract direction, and do not have a resolution even close to a cellular level. Furthermore, in every voxel, not only one fibre direction is present. Therefore, different approaches have been taken to delineate major white matter tracts by comparing local main directions of diffusivities measured by DTI.

The algorithms can be broadly classified into two types: deterministic and probabilistic. Initial work in this field focused on deterministic tractography. The implicit underlying assumption is that the principal eigenvector is parallel to the underlying dominant fibre orientation in each voxel and forms a tangent to the space curve traced out by the white matter tract (Basser *et al.*, 1994). The fibre assignment by continuous tracking (FACT) is a commonly used method (Mori and van Zijl, 2002). The path is propagated from a region of interest (seed point) which is manually placed. It propagates from here, parallel to the principal eigenvector until the boundary of the voxel is encountered, at which point the algorithm traverses the next voxel in a direction parallel to the eigenvector at the center of the new voxel (Jones, 2008). Therefore only one main trajectory will be reconstructed per region of interest and branchings of a fasciculus will not be represented. Furthermore there is no indication of confidence for a reconstructed tract (Jones, 2008). In probabilistic tractography, the direction is drawn from a distribution of possible orientations. Instead of reconstructing just a single trajectory in deterministic tractography, probabilistic tractography propagates a large number of pathways from a given seed point. The result of probabilistic tractography is a set of multiple pathways passing through the seed point, and the direction is drawn from a distribution of possible orientations (Jones and Pierpaoli, 2005; Parker *et al.*, 2003; Parker and Alexander, 2003). Conversely, this also means that there is uncertainty in fibre orientation at each stage in the propagation of the tract.

Atlases have been published of the anatomical correlation of the DTI based FA maps and tractography results (Jellison *et al.*, 2004; Mori *et al.*, 2005; Wakana *et*

al., 2004), largely based on comparison to anatomical drawings and dissection maps (Ludwig and Klingler, 1956). However, uncertainty remains regarding the accuracy of the tract representations.

There is no doubt that validation is of central importance for the development of tractography. Identifying the gold standard for *in vivo* validation remains a challenge, and may likely represent a combination of cortical stimulation (both intra- and extraoperatively), direct stimulation of white matter tracts during neurosurgery and cortico-cortical evoked potentials (CCEPS) which will provide proof of structural connectivity between two areas of cortex. Chapter 5 of this thesis will explore tractography of the AF and cortical stimulation in the language system. This study combines a technique for cortical localisation of eloquent language cortex with DTT to underpin the structural connectivity of the language areas. In the next paragraph, different forms of connectivity will be appraised.

1.3.4. Brain connectivity

As described earlier in this chapter on history of Neuroimaging, the advances in nuclear and MR imaging allow the scientific community to investigate brain functions with great spatial resolutionr. When integrating the knowledge gained using fMRI or PET for example and combining this with neurophysiological investigations using EEG or MEG, valuable insights into how our brain works can be gained. EEG or MEG signals can be analysed using a vast number of mathematical toolboxes such as coherence analysis, to allow for insights on brain dynamics over time, with high temporal resolution.

Given the enormous complexity of brain function, the literature is extensive and neuroscientists have used numerous approaches to enhance our understanding on how the brain works. In 2000, Paul Nunez published a target article "Toward a quantitative description of large scale neocortical dynamic function and EEG" (Nunez 2000), which presented a theory describing the dynamic of excitatory and inhibitory synaptic action fields. EEG and MEG provide large scale estimates of

modulation of these synaptic fields around background levels (Nunez 2000). This however also implies that there are connections between them (direct or indirect via several synapses) and in recent years multidisciplinary research in neuroimaging has provided methods capable of exploring in vivo and noninvasively both structural and functional connectivity of these networks at the macroscopic level (Guye *et al.*, 2008).

There is a long tradition to emphasize that brain regions are 'functionally specialized' for certain cognitive operations. This understanding was uniquely shaped by many lesion studies, which clearly demonstrate that damage to specific brain regions is directly associated with impairment of specific abilities. Functional specialization can therefore be defined as the degree of processing specificity of a given brain region for a particular cognitive ability or facet of cognitive operations (Friston, 2002; Stevens, 2005). It is however rather obvious that specialised brain regions function as part of an entity and it is paramount to understand the connectivity amongst them.

There are three main types of brain connectivity: structural (anatomical), functional and effective connectivity (Fingelkurts *et al.*, 2005). They can be measured using different techniques with varied temporal and spatial resolution, such as PET, fMRI or EEG and MEG. Combining them may lead to greater insights into the spatiotemporal characteristics of brain activity.

Functional connectivity is a term often used to refer to statistical associations between remote neurophysiological events (Friston 1993,Friston, 2002). When distributed brain regions display strongly correlated patterns of neural activity change, it is taken as evidence that those regions are functionally connected (Stevens, 2009). Such connections occur via excitatory neurotransmission through white matter pathways (Fingelkurts *et al.*, 2005, Fonteijn *et al.*, 2008). DTT aims at quantifying such **structural (or anatomical) connectivity** by tracking putative bundle pathways of macroscopic white matter fibres linking cortical areas (Guye, 2008).

Cortical brain areas interact to allow for higher order cognitive and motor functions. Such functional integration of the varied specialised brain areas has

been studied with two kinds of analyses: **functional connectivity** analyses and **effective connectivity** analyses. FMRI indirectly reflects neuronal activity and provides whole brain coverage, therefore it is a tool that allows measurement of such temporal correlations between spatially remote neurophysiological events (functional connectivity). Neurophysiological/functional interactions through structural connections can be derived from the temporal correlations of BOLD signals.

However, such analysis methods do not allow making inferences about the directionality of these correlations, and therefore the functional hierarchy of the brain structures under investigation cannot be assessed. **Effective connectivity** has been defined as the influence one neural system or region exerts over another (Friston,1994). In effective connectivity analyses, models are defined a priori, comprising the brain structures of interest and assumptions about the afferent and efferent connections between them (Friston, 2003). These models are then fitted to the activity of these brain areas to obtain the strength of these connections.

Functional and effective connectivity measures in combination with DTT providing qualitative and quantitative information on structural links will shed new insights into brain organization.

1.4 DWI and DTI in epilepsy

DWI was initially introduced into clinical practice for the early detection of strokes. It has proven to be very sensitive to areas affected by ischemia. Subsequently, periictal and postictal changes in diffusivity have been observed in animal models of status epilepticus and in patients, both after status epilepticus and after single short seizures. It therefore appeared to be an interesting technology in order to gain better understanding of periictal changes in animal models and assess if such changes may be useful to delineate the area of ictal onset. In addition, understanding the impact of acute seizures on diffusion imaging may allow insights in development of chronic changes on DWI and DTI.

1.4.1 Peri- and postictal changes in animal models of status epilepticus

Animal models have systematically examined rats with bicuculline, kainic acid and pilocarpine induced status epilepticus and evaluated diffusion changes. Using for example the experimental model of kainic acid-induced status epilepticus in rats, it has been shown that postictal ADC was decreased in the pyriform cortex, hippocampus and amygdala for 24 to 72 hours, indicating areas of decreased mean diffusivity which normalised within seven to nine days (Nakasu *et al.*, 1995a; Nakasu *et al.*, 1995b; Righini *et al.*, 1994; Wang *et al.*, 1996). The ADC changes were closely correlated with the presumed area of seizure onset and the resulting histopathologic changes. Simultaneous measurements of sodium content in the rat brain parenchyma led to the hypothesis that diffusivity is initially reduced in the cortex due to cellular swelling and a reduction of extracellular space, possibly due to a failure of ATPase, that leads to intracellular sodium accumulation followed by influx of water (Righini *et al.*, 1994; Wang *et al.*, 1996).

Several studies investigated a pilocarpine model of status epilepticus (Engelhorn *et al.*, 2007; Wall *et al.*, 2000) and reported on very early increases in ADC (for example 110%–127% of baseline) between 3 and 5 minutes after the onset of seizures in the retrosplenial and pyriform cortex, the amygdala, thalamus, and the hippocampus (Engelhorn *et al.*, 2007). This was followed by a significant continuous decrease in ADC that returned to 52%–60% of baseline in all examined brain regions except the thalamus. ADC changes were a good predictor of cell loss and if a decline in ADC of greater than 60% was seen in the retrosplenial parietal and temporal cortex this was associated with the subsequent death of the animal.

Animal models therefore provided convincing evidence for dynamic changes in diffusion during and after status epilepticus, and that these areas also corresponded with histological changes. Therefore, diffusion imaging may provide

an opportunity to directly image the areas involved in seizure generation and possibly spread.

1.4.2 Periictal DWI and DTI changes in humans

The first report of diffusion changes in a patient with status epilepticus was published in 1997. The status consisted of clonic jerking of the right leg, which continued for 22 days and was followed by transient paresis. DWI during status showed decreased diffusion in the motor cortex of the right leg, and an area of facilitated diffusion in the underlying white matter. This was explained by a shift of water into cortical neurons at the site of the seizure focus, and vasogenic edema, a shift of water in the extracellular space in the underlying white matter (Lux *et al.*, 1986).

Following this case report, multiple investigations explored periictal DWI in an attempt to assess the usefulness of this novel technology to delineate the ictal onset zone. Overall, the presence of dynamic diffusion changes was documented in the majority of cases, but the correlation between the presumed epileptogenic zone and the diffusion changes remained quite variable (Diehl *et al.*, 2001; Diehl *et al.*, 2005; Hufnagel *et al.*, 2003; Oh *et al.*, 2004; Salmenpera *et al.*, 2006). Correlations seemed however closer in patients with longer seizures (or status) and short duration between seizure end and scan (Diehl *et al.*, 2001; Hufnagel *et al.*, 2003). A single case report confirms that indeed an area of restricted diffusion in a patient with repetitive prolonged focal motor seizures originating from a lesion in the right frontal lobe corresponds to the ictal onset zone. An area of restricted diffusion adjacent to the lesion in the right frontal lobe corresponded to the region of focal electrocorticographic seizures that was mapped intra-operatively (Diehl *et al.*, 1999).

Later studies used DTI to study periictal changes. This allowed for comparison of the sensitivity of diffusivity changes versus anisotropy changes, and to assess

whether DTI provides higher sensitivity to seizure induced changes. The results remained rather disappointing, and it became apparent that dynamic changes affected the diffusivity to a much higher degree than the directionality (Diehl *et al.*, 2005). Salmenpera *et al.*(2006) also noted periictal mean diffusivity reductions in about half of the 20 patients scanned, but only about 20% co-localised with the presumed ictal onset zone, even though all were scanned within 45 min after the seizure. In addition, whole brain analysis using statistical parametric mapping (SPM) revealed distant areas of diffusivity change, possibly highlighting the networks involved in ictal spread.

In order to investigate if shorter delays between seizure and scanning would yield better results, a study was conducted using flumazenil to induce seizures and delineate the epileptogenic focus (Konermann *et al.*, 2003). This selective competitive benzodiazepine (BZD)-receptor antagonist was given 10 min prior to scanning. Results on 12 patients assessed for epilepsy surgery showed decreases in the hippocampus on the seizure-onset side (of the order of 15%), decreases in the parahippocampal gyrus (PHG) on both sides and decreases in the cortex on the contralateral side, but to a smaller degree (order of 7-8%). The authors concluded that these changes co-localised with the side of the postulated seizure focus.

Therefore it seems possible that diffusion changes after single seizures appear more transient and require immediate access to scanning. In addition, such techniques are also likely to indicate the networks that may be secondarily affected by a seizure. If in the future such an environment can be provided, in combination with higher resolution scanning and possibly also higher field strengths of magnetic resonance (MR) scanners, the yield may increase.

1.4.3 Interictal DTI and DWI

1.4.3.1. Temporal lobe epilepsy (TLE)

Studies quickly revealed that diffusion abnormalities were present in the interictal state, and diffusion measures were explored as markers of structural integrity in a variety of known pathologies, and also in non-lesional cases. Initially, studies focused on TLE cases with HS, to assess if diffusivity offered lateralising information.

It was shown that mesial TLE with HS revealed increased diffusivity in the ipsilateral hippocampus, indicative of structural disorganisation and expansion of extracellular space, reflecting neuronal loss and other microstructural changes associated with epileptogenesis in the hippocampus (Assaf *et al.*, 2003; Hakyemez *et al.*, 2005; Hugg *et al.*, 1999; Wehner *et al.*, 2007; Wieshmann *et al.*, 1999; Yoo *et al.*, 2002). These changes paralleled the abnormalities noted on conventional MRI scans with atrophy and T2 signal increase.

However, when assessing DWI compared to conventional MR imaging using volumetric T1 acquisitions and FLAIR, it was not more sensitive in detecting HS. In a group of 14 mesial TLE patients with pathology confirmed HS on imaging, ADC was elevated ipsilateral to the ictal onset compared to the contralateral hippocampus. In eight patients with normal imaging, pathology revealed gliosis without neuronal loss in the hippocampus after temporal lobectomy. ADC equally did not allow to lateralise the epilepsy and hence DWI does not appear more sensitive than conventional MRI in detecting possible subtle lesions in the mesial structures (Wehner *et al.*, 2007). In addition it became apparent that in patients without lateralising differences between the hippocampal formations, often both hippocampi showed increased ADC compared to a control population, indicating bilaterality of the disease. Such bilateral abnormalities were documented

throughout the limbic system, including fornix and cingulum in both adults (Concha *et al.*, 2005; Concha *et al.*, 2009) and children (Nilsson *et al.*, 2008).

When evaluating patients with TLE using region of interest (ROI) approaches, including areas outside the mesial structures, there was increasing evidence that diffusion abnormalities in TLE were not confined to areas of seizure onset, but extended into the ipsilateral hemisphere, and even contralateral. (Arfanakis *et al.*, 2002; Concha *et al.*, 2005; Concha *et al.*, 2009; Govindan *et al.*, 2008; Gross *et al.*, 2006). Areas exhibiting lower FA in TLE patients outside the limbic system included the corpus callosum and the external capsule.

In another more recent study, a group of 33 TLE patients (21 left TLE) with HS was evaluated using DTI and two voxel based approaches (Focke *et al.*, 2008). Such approaches compare individual whole brain MRIs to a group of controls (n=37) on a voxel by voxel base, without selection bias to a particular ROI. It was demonstrated that the ipsilateral temporal lobe showed widespread FA reduction of areas directly connected to one another, involving white matter paths in the ipsilateral temporal lobe and the limbic system. Left and right TLE had slightly different patterns of diffusivity and FA changes, with more widespread involvement of the limbic system and the AF in left TLE. Lower statistical power in the right TLE group may have accounted for some of the differences. In addition it was noted that extratemporal areas, particularly the inferior frontal region and the AF, a large white matter bundle connecting into the temporal lobe, was also affected (Focke *et al.*, 2008).

It was shown that such widespread diffusion changes are not reversible after successful temporal lobectomy, suggesting structural abnormalities as opposed to functional changes due to seizures (Concha *et al.*, 2007). In this study by Concha *et al.*, a cohort of eight patients with seizure free outcome at one year underwent DTI before surgery and at 1-year follow-up. Tractography and ROI analyses were performed in the fornix, cingulum, genu, and splenium of the corpus callosum and

external capsules, revealing pre-operative bilateral abnormal diffusion parameters (i.e. decreased diffusion anisotropy and increased mean and perpendicular diffusivities). The fornix and cingulum ipsilateral to the resected mesial temporal structures showed signs of wallerian degeneration at 1-year follow-up. The contralateral tracts of the fornix, cingulum, and external capsules, as well as the genu of the corpus callosum, failed to show normalisation of their diffusion parameters.

One of the earliest reports testing the hypothesis that DTI would identify abnormal areas in temporal and extratemporal cryptogenic focal epilepsy evaluated 30 patients by comparing each individual patient to a group of controls (Rugg-Gunn *et al.*, 2001). Eight patients had areas of increased diffusivity, only two patients had areas of decreased FA. Six of the eight MD alterations were in the presumed epileptogenic zone. 15 patients had TLE (nine left). Group analysis of the left TLE patients revealed increased diffusivity and reduced anisotropy; the right TLE group (six patients) displayed a trend in the same direction (Rugg-Gunn *et al.*, 2001). Although such a group effect is not helpful for an individual patient, it suggests that given greater sensitivity and increased signal to noise ratios, an effect in individual patients may be demonstrated. Overall, such occult lesions are most likely caused by disruption of white matter architecture due to occult dysgenesis, or by seizure related damage. Damage caused by repeated seizures may lead to atrophy, gliosis and expansion of the extracellular space, resulting in increased diffusivity and potentially also decreased anisotropy.

Findings of widespread diffusion abnormalities were not only shown in adults but also in children (Govindan *et al.*, 2008; Meng *et al.*, 2010) . In one study, 13 children aged 11 months to 19 years with non-lesional left TLE were compared to 12 age matched controls (Govindan *et al.*, 2008). The three major tracts from the temporal lobe were analysed: the uncinate fasciculus (UF), AF and inferior longitudinal fasciculus, as well as the corticospinal tract, outside the temporal lobe for reference were examined, and all showed abnormal water diffusion. This

implies that widespread alterations of the white matter are present in patients with focal epilepsy, and this is seen in both adults and children.

1.4.3.2 Extratemporal lobe epilepsy

Extratemporal epilepsies represent a growing group being evaluated for epilepsy surgery, and often are challenging as precise localisation of the epileptogenic zone in relation to cortical function is mandatory. Evidence has rapidly accumulated that diffusion changes can be seen in a variety of lesions associated with focal epilepsy and are often localised outside the temporal lobe, such as CD.

The first report on DTI changes due to various CDs used a voxel based statistical approach to compare objectively tissue organization in 22 patients with various CDs to 30 control subjects (Eriksson *et al.*, 2001). Reductions in anisotropy were noted in 17 patients, and increased diffusivity in ten. Of interest was that changes in FA and diffusivity were also seen outside the MR visible dysplasia (in six patients for FA and ten for diffusivity). In general, diffusivity changes were larger than FA changes. No decreases in diffusivity were seen and increases of FA values were very rare (seen in two patients).

Another study (Dumas *et al.*, 2005) used a region of interest approach and described reductions in FA in 13 out of 15 patients in normal appearing white matter surrounding lesions seen on conventional MRI (five patients with tumors, four with HS, six CD). Detailed microscopic analysis of the tissue surrounding the lesion revealed gliosis, axonal loss, poor myelinisation or increased cell bodies (for example ectopic or abnormal neurons, balloon cells), likely the cause of the diffusion changes noted. In addition, distant anisotropic changes were also observed in 12 of the 15 studied patients, possibly due to Wallerian degeneration of white matter tracts or gliosis resulting from chronic seizures. Diffusion changes in the white matter surrounding CD and the impact on connectivity and adjacent tracts were evaluated in 13 children (Widjaja *et al.*, 2007). Reduced FA was

found to be a sensitive but non-specific marker of alteration in microstructure of white matter. Diffusivity was mainly influenced by increased perpendicular diffusivity, which may reflect a dominant effect of abnormal myelin. Furthermore alteration in white matter tracts was observed in most cases of CD, revealing decreased tract size and displacement of tracts in larger dysplasias.

1.4.3.3 Probing diffusion changes: what can it tell us in human epilepsy?

To date, the pathopysiological mechanism of the diffusion changes measured in focal epilepsy is unknown. As detailed above, these changes may be seen within lesions, but also adjacent and remote to the lesion. Diffusion changes are also present in patients with normal conventional MRI. DTI has been increasingly used to gain insight by probing the diffusion changes in all three main directions. Analysing the pattern of diffusion changes with respect to diffusivities parallel and perpendicular (radial) to the main axonal direction provides *in vivo* insights into the underlying cause of decreased FA.

Several studies have investigated the mechanisms leading to overall increased diffusivity and reduced FA. The most commonly seen pattern of DTI changes associated with focal epilepsy was unchanged parallel diffusivity and increased perpendicular diffusivity (Concha *et al.*, 2009; Diehl *et al.*, 2008; Govindan *et al.*, 2008; Gross *et al.*, 2006; Kim *et al.*, 2008) .   As detailed above, such a pattern of FA changes seen in most studies evaluating DTI in TLE is most consistent with chronic Wallerian degeneration, possibly due to cell loss in the temporal lobe secondary to seizure-induced cell death.

In order to evaluate potential mechanisms for such more widespread diffusion changes in TLE, it was investigated if different underlying pathologies as determined by pre-operative MRI cause differential diffusion changes (Concha *et al.*, 2009). 17 patients with TLE and HS, 13 patients with non-lesional TLE and 25 controls were included in the study. The fornix, cingulum, external capsules and

the corpus callosum were evaluated using DTI. Some interesting differences emerged: while some white matter bundles are affected equally in both forms of TLE, abnormalities of the bundles directly related to the mesial temporal structures (i.e. the fornix and cingulum) appear to be unique to TLE with HS.

Most recently, histological correlation between electron microscopy and DTI of human fimbriae was performed on 11 patients undergoing temporal lobe resections for intractable epilepsy (six with HS, five without). Electron microscopic findings of TLE patients with HS showed increased extra-axonal fraction, and reduced cumulative axonal membrane circumference and myelin area (Concha *et al.*, 2010). Consistent with the animal literature, water diffusion anisotropy over the crus of the fimbria-fornix was strongly correlated with axonal membranes of the surgical specimen (cumulative membrane circumference). This provides validation in humans of in vivo DTI analysis, accurately predicting histological changes from *in vivo* DTI.

In conclusion, interictal DTI highlights areas of abnormal diffusion measures in temporal and extratemporal lobe epilepsies, lesional and non-lesional. Specifically,

1. MD appears more sensitive to changes seen in patients with chronic refractory epilepsy compared to FA. The only exception may be CDs.
2. DTI abnormalities are seen in all areas also indicating pathology on conventional MRI.
3. DTI changes may often be found outside the lesions, both continguous and less frequently also away and non-contiguous to the lesion.
4. Abnormalities mostly with increased MD and reduced FA have also been found in patients with cryptogenic focal epilepsy.
5. Analysis of water diffusivity changes reveals a pattern of increase in perpendicular diffusivity and not of parallel diffusivity. This may indicate Wallerian degeneration as one of the main mechanisms accounting for the

structural changes underlying the DTI abnormalities remote from focus and lesion.

6. Such abnormal areas in patients with intractable epilepsy therefore probably represent structural disruption, possibly reflecting either an underlying pathology or gliosis due to secondary damage. This requires further study with MRI-histology correlation in more patients.

1.4.4 Interictal DTI and the epileptogenic zone

Close correlations between the interictal abnormalities highlighted using DTI, pathology and epileptogenicity are rare. Recently, histopathological correlation of an area of abnormally increased diffusivity was obtained in a patient with cryptogenic intractable focal epilepsy. Intracranial recordings showed seizure onset in the right orbitofrontal region, co-localising with the area of abnormal diffusivity (Rugg-Gunn *et al.*, 2002) and post-resection pathology revealed gliosis. Of note is that this patient is not seizure free (ILAE Grade 4 at 7 years post-operatively; Wieser *et al.*, 2001).

Few papers have evaluated in detail the concordance between diffusion abnormalities and irritative zone and ictal onset zone as evaluated using invasive recordings. The two studies decribed below have used voxel based statistical approaches to highlight areas of abnormal diffusion.

In one study, the correlation of DTI with findings with stereo EEG (SEEG) was evaluated in 16 patients (Thivard *et al.*, 2006). 13 of the 16 patients were found to have DTI abnormalities, consisting mainly of increases in MD. FA abnormalities were present in nine patients, but added little in localisation. Overall, the abnormalities present concurred with the epileptogenic zone in only seven of the 13 patients. Congruence between the area of interictal spiking and ictal onset on SEEG and the diffusion abnormalities was determined. The specificity of DTI abnormalities was better in extratemporal lobe epilepsy than in TLE: only 20% of

TLE had congruent findings, whereas four of five extratemporal epilepsies concurred. In addition, when diffusion abnormalities concurred with some part of the SEEG data, the irritative zone defined by SEEG, representing the area of interictal spikes, was most optimally congruent with the diffusion abnormalities.

Another study investigated 14 patients with frontal lobe epilepsy (9 non-lesional) and assessed only diffusivity (Guye *et al.*, 2007). 13 patients showed areas of increased diffusivity. In this study, the sensitivity of diffusion imaging in defining regions that were the site of electrical abnormalities was about 57% for the area of seizure onset and 65% for the irritative zone. The specificity in that study was low. It is of note however that areas of diffusion abnormalities may not have been sampled, as coverage is necessarily limited with SEEG. An interesting aspect in this study is that lesional epilepsies had very high sensitivity, as the lesion led to diffusion abnormalities, but very low specificity. In non-lesional epilepsies, cases in which epileptologists may particularly turn to novel imaging for additional support of a hypothesis for invasive recordings, three out of the nine patients with negative-MRI had diffusion changes in the seizure onset zone, four in the area of spiking and eight outside.

Overall, the limited data available leads to the conclusion that diffusion changes correlate better with areas of interictal spiking than the ictal onset. Furthermore, the presence of DTI abnormalities certainly does not mean that the seizures are arising in the vicinity. However, DTI changes may provide some additional information to guide placement of invasive electrodes. Correlating electroclinical abnormalities using invasive recordings with diffusion changes may allow for better insights in the future.

1.5 Interictal DTI, tractography and correlations with cognitive function

The white matter architecture in health and disease can be explored using DTI. Sections 1.3 and 1.4 have provided an overview of the investigations of focal epilepsies using DTI and DWI which revealed diffusion abnormalities in areas of seizure onset and spiking, but also in adjacent and remote, and even contralateral areas. In order to understand the meaning of such changes, investigations into structure and function in controls and patients were undertaken. There is mounting evidence that the integrity of white matter tract pathways, as measured by DTI, is systematically related to individual differences in performance across a wide range of cognitive skills. Furthermore, analysis of white matter structure may give insights into the organisation of function in individuals, and possibly into reorganisation in disease. In addition, studies have explored those structure function correlations in disease and a number of publications have addressed cognitive disability in patients with epilepsy, particularly focusing on language and memory.

1.5.1 DTI measures and neuropsychological correlates

1.5.1.1 Language lateralisation and DTI measures in controls and epilepsy

A number of studies explored language lateralisation in healthy controls and patients with epilepsy with a variety of different methods (Buchel *et al*., 2004; Cao *et al*., 2003; Glasser and Rilling, 2008; Nucifora *et al*., 2005; Powell *et al*., 2006; Rodrigo *et al*., 2008; Vernooij *et al*., 2007).

Studies in healthy controls were undertaken to correlate language lateralisation with DTI measures, to gain insights into structure/function relationships. Using voxel-based statistical analyses of DTI in 15 healthy volunteers, an asymmetry of the AF was observed, with higher fractional anisotropy in the left hemisphere (Buchel *et al*., 2004). Leftward structural asymmetries have also been reported in

the subinsular region in right handed volunteers (Cao *et al.*, 2003), and a cohort of 27 right handed healthy volunteers showed a greater relative fibre density in the left AF compared to the right in nearly all participants. This strong degree of asymmetry was specific to the AF, and was not found in the corticospinal tract (Nucifora *et al.*, 2005). These data reflect that in a control population regional brain function indeed corresponds to higher connectivity in those areas.

Patients with left hemisphere focal epilepsy have a larger percentage of atypical language organisation (Adcock *et al.*, 2003; Springer *et al.*, 1999; Thivard *et al.*, 2005). Such changes may be disease related, with epileptogenicity leading to disruption of the language network on the affected side (Janszky *et al.*, 2003; Janszky *et al.*, 2004). Alternatively, it may represent an adaptive process following a brain insult earlier in life, which may also be related to the development of epilepsy. Lateralisation to the right in a percentage exceeding the incidence in controls may hence represent an expression of plasticity. Such changes in function are likely paralleled by changes in structure and connectivity.

The first study evaluating language lateralisation and DTI asymmetry in epilepsy included nine patients with focal epilepsy, eight had left hemispheric focal epilepsy (5 temporal, 3 frontal). In two patients with atypical language lateralisation per fMRI, these findings were paralleled by atypical anisotropy value lateralisation to the right using a ROI approach (Briellmann *et al.*, 2003).

fMRI is the most commonly used non-invasive tool to evaluate language lateralisation. It was used to assess the correlation between language lateralisation, side of epilepsy and DTI measures in 14 patients with TLE (7 left) (Powell *et al.*, 2006). fMRI paradigms used included verb generation and reading comprehension tasks to define starting regions for a probabilistic tractography algorithm. The measures used to assess connectivity were the tract volume and FA connecting the anterior and posterior language areas as delineated by the fMRI activations. It was shown that controls and patients with right TLE had a

more left lateralised pattern of both fMRI activations and connectivity. Patients with left TLE had more symmetrical language activations, which was paralleled by increased right hemispheric connectivity. This was felt to provide 1. evidence of a close structure function relationship with evidence for the language dominant hemisphere showing greater connectivity and 2. evidence of language reorganisation to the right in left TLE, paralleled by plasticity in connectivity.

However, one subsequent study did not reproduce this finding (Rodrigo *et al.*, 2008). In 20 patients with TLE (8 left) fMRI-based lateralisation indices were computed in the inferior frontal gyrus and correlated with probabilistic tractography of the AF and inferior frontooccipital fasciculus (IFOF). fMRI indices were left-lateralised in 16 patients and bilateral or right-lateralised in four. In the AF, FA was higher on the left than on the right side, reaching significance in right but not in left TLE. There was a positive correlation between AF anisotropy and fMRI-based lateralisation indices in right TLE, but not in left TLE patients. No correlation was observed for the IFOF. In left TLE patients, the loss of the significantly greater leftward anisotropy within the AF does indicate damage to that side, although the leftward asymmetry in functional activation was still preserved.

Low numbers and methodological differences account for some of the variability of results, and ultimately many other variables such as age of onset, duration and severity of the epilepsy, likely etiology (if known) and histopathology, exact location of the epileptogenic zone (even within the temporal lobe), and genetic predisposition will all be modifiers of a structure function relationship.

1.5.1.2 DTI correlates of impairment in memory performance in patients with epilepsy

Neuropsychological assessments in patients with TLE have revealed material specific memory impairment (Mayeux *et al.*, 1980), and patients undergoing

temporal lobectomies with removal of the medial temporal structures are at further risk of memory deterioration. Hence, DTI was used to assess white matter and tracts implicated in memory function, such as the UF and PHG to gain insights into material specific memory in patients with TLE. The UF, a frontotemporal connection, is thought to be required for the retrieval of past information, with the right UF implicated in retrieval of episodic-context dependent memory and the left mediating retrieval of semantic-context free memory (general knowledge of concepts and facts) (Aralasmak *et al.*, 2006). Connections implicated in memory function to and from the hippocampus involve the PHG (Rolls, 2000).

In one study, probability maps of connectivity in the PHG were analysed in a group of 18 patients with TLE (8 left) and an asymmetry index calculated between left and right (Yogarajah *et al.*, 2008), revealing smaller tract volume and lower FA ipsilateral to the seizure focus. In that study, correlations with material specific memory was analysed in the 17 patients with left hemisphere language dominance and PHG FA was correlated with pre-surgical verbal learning, and right parahippocampal FA with design learning. Of interest is that there was no correlation between ipsilateral hippocampal volumes and tract volume or FA, whereas there was a correlation between tract volume and FA. This is in keeping with other tractography studies showing that FA is a more sensitive and robust measure for pathology than the volume of white matter tracts (Heiervang *et al.*, 2006).

Evaluating the UF, parahippocampal cingulum and IFOF in 17 patients with TLE (9 left) and 17 controls, increases in MD of the left UF, parahippocampal cingulum, and IFOF were associated with poorer verbal memory in TLE, as were bilateral increases in MD of the AF, and decreases in FA of the right AF. (McDonald *et al.*, 2008). This study again confirmed the strong association between integrity of the UF and memory. The PHG as an important link in the Papez circuit comes as no surprise. The association of DTI abnormalities and memory within the IFOF was however not expected. As it subserves the

semantic system with a putative role in providing a link between phonology and sentence comprehension (Duffau *et al.*, 2008). The authors felt that their verbal memory task may have placed high demands on semantic processing, accounting for the strong association.

In another study, the UF was evaluated using tractography in 10 patients with right TLE and controls. A left-minus-right FA UF asymmetry index was computed to test for intergroup differences. Whereas asymmetries were found in the control group with right-greater-than-left FA, this asymmetrical pattern was lost in the patient group. Right FA values were lower in patients with right HS versus controls (Rodrigo *et al.*, 2007).

Taken together, these results provide additional insights into underlying structure-function relationships in TLE, and demonstrate how DTI can be used to delineate the neurocognitive correlates of localised white matter damage.

In chapter 3, I investigate DTI characteristics of the UF in a larger group of left and right TLE patients and provide systematic correlation with verbal and visual memory performance.

1.5.1.3 DTI correlates of language performance in patients with epilepsy

In an effort to establish relationships between local white matter changes and cognitive impairment in TLE, 17 patients with TLE (nine left) and 17 controls were investigated using fibre tracking to segment out the different tracts (McDonald *et al.*, 2008). In particular, the AF, UF and inferior fronto occipital (IFO) tract were analyzed. It was shown that decreased FA and increased MD in the left and right UF, the left and right AF and the left IFO correlated with the poor performance on the Boston naming test (BNT). Verbal fluency however did not reveal such correlations in this study. The authors therefore confirmed the role of the left AF in naming and also found evidence of a contribution of the right AF, as well as the

UF and IFO. Even though classically the AF is thought to be involved in language processing, other evidence for involvement of UF and IFO has been reported. Intra-operative electrical stimulation of the left inferior frontooccipital tract has been shown to lead to semantic paraphasias, thus confirming this tracts involvement in language processing (Duffau *et al.*, 2005; Duffau *et al.*, 2008). The UF, although mainly associated with episodic memory, has been implicated in lexical semantic retrieval tasks, important for naming performance (Lu *et al.*, 2002).

In chapter 4, systematic correlations of language performance of a larger group of left and right TLE patients with AF DTI measures are presented.

1.5.1.4 DTI to predict post-operative deficits after epilepsy surgery

Studies evaluating the cognitive correlates of DTI may potentially provide information regarding patients being at particular risk for neurocognitive decline after epilepsy surgery. This was explored in a small study on seven patients undergoing dominant temporal lobectomy (6 were left language dominant, one right) (Powell *et al.*, 2008). Tract lateralisation was quantified and correlated to post-operative naming decline. Patients with higher structural connectivity to the side of resection suffered greater post-operative naming deficits.

This is in keeping with results of fMRI studies, showing that in a semantic decision making task fMRI laterality indices were predictive of naming outcome after temporal lobectomy. Greater left lateralised language activiation was correlated with greater post-operative naming decline (Sabsevitz *et al.*, 2003).

Evaluating tractography and DTI based diffusion measures to predict cognitive outcome after epilepsy surgery is of great interest, as it may allow better counseling of patients undergoing such surgery. There are no systematic larger

studies available to date that explore the predictive value of integrity of individual tracts for cognitive outcome following epilepsy surgery.

1.6 Tractography and epilepsy surgery

Aside from structure and function correlations, delineation of white matter tracts may be an important first step to using tractography to inform neurosurgeons. Epilepsy surgery is an option in a subset of patients with intractable focal epilepsy. However, to minimise morbidity of the procedure it is important to identify eloquent cortex. In addition, major white matter tracts connected to these eloquent cortical brain areas, have also to be preserved during surgery. DTI is the first imaging modality that allows direct non-invasive visualisation of white matter tracts.

Several investigations have focused on retrospectively correlating DTI based tractography with post-operative deficits, to assess if the technology could provide predictive information for a deficit and maybe even could aid in preservation of function if such information were integrated in neuronavigation systems.

The most common procedure in epilepsy surgery is a temporal lobectomy. Anterior temporal lobectomies can cause significant visual field defects in up to 10% of patients. In about 5% it can be severe enough to render the patient ineligible for a driving license in the UK, despite being seizure-free (Manji & Plant, 2000). The visual field defects occur in the superior homonymous field contralateral to the resection and are due to disruption of fibres of Meyer's loop. The anterior extent of Meyer's loop has large interindividual variability and cannot be visualised using conventional imaging (Ebeling and Reulen, 1988). Tractography has been used to demonstrate the optic radiation in normal subjects (Yamamoto *et al.*, 2005). Some experience has been gained in patients with arteriovenous malformations (AVM), and has been applied to pre- and post-operative surgical patients with tumors and AVM of the visual pathways. The

magnitude of pre- and post-operative visual field loss after resection of AVM from the geometrical relationship between the optic radiation and the malformation has been successfully predicted in 10 patients (Kikuta *et al.*, 2006) The application to temporal lobe surgery for epilepsy was first described in 2005; the optic radiation was visualised before and after temporal lobectomy using tractography, and disruption of Meyer's loop was demonstrated in a patient who developed a quadrantanopia (Powell *et al.*, 2005). Conversely in another patient, the full course of the left optic radiation was visible on the pre- and post-operative images, and he did not suffer any field cut.

The largest study investigated pre- and intra-operative DTI based fibre tracking in 48 patients undergoing temporal lobectomies to visualise the optic radiation and to predict the post-operative visual field defects (Chen *et al.*, 2008). The course of the optic radiation could be successfully reconstructed by DTI based fibre tracking. There was significant correlation between the fibre tracking estimation and the outcome of visual field deficits after surgery. Yogarajah *et al.* (2009) correlated the size of temporal lobectomy in 21 post-operative patients with tractography of the optic radiation. By applying a linear regression analysis it was shown that the distance from the tip of Meyer's loop to the temporal pole and also the extent of resection predicted the postoperative visual field defects.

These data provide evidence that tractography has the potential to provide informformation about risks of epilepsy surgery procedures. Once successfully implemented into neuronavigation systems, this information may also be used intra-operatively to tailor resections (Nimsky *et al.*, 2007a). However, a great number of difficulties and methodological challenges have yet to be overcome in order to consider using tractography for neuronavigation. Coregistration errors, distortions inherent to echo planar imaging (EPI) sequences represent some technical challenges. In addition, it is unknown how reliable DTT can map the entire tract in health and disease. Intra-operative brain shift after craniotomy is another significant impediment. The availability of intra-operative MRI may

represent one method to correct for this movement and may improve the accuracy of the data to aid surgical planning.

Particularly extratemporal surgeries will also benefit from visualising of the tracts such as the pyramidal tract. Implementation of DTI based tractography has already been shown to be of benefit in brain tumor surgeries and resections of vascular malformations (Chen *et al.*, 2007; Nimsky *et al.*, 2005; Nimsky *et al.*, 2007b; Wu *et al.*, 2007), and will certainly be increasingly used in epilepsy surgery. To what degree they may improve functional outcome following epilepsy surgery is unknown. The potential however appears great and it is therefore crucial to understand strengths and limitations of DTT in human epilepsy. Tractography results require validation; such validation may be obtained by comparing tratography results to other modalities determining connectivity and cortical localisation. The following paragraphs will discuss how pre-surgical evaluation and patricularly patients undergoing invasive investigations can assist in such studies.

1.7 Invasive recordings and cortical stimulation

A number of patients with focal epilepsy will need to undergo invasive EEG recordings using subdural electrodes and depth electrodes for localisation of ictal onset with precision. Such recordings provide great opportunities to validate novel technologies such as DTT. Insights of location of cortical function based on cortical stimulation can be correlated with white matter anatomy as reconstructed using DTT. Furthermore, ictal onset and propagation patterns as seen during such invasive recordings can be correlated with structural connectivity delineated using DTT.

It has been estimated that approximately 25% of patients with intractable focal epilepsy require invasive evaluations to localise the epileptogenic zone (Nair *et al.*, 2008). In addition, proximity to eloquent cortex may require functional

mapping, which can also be performed extraoperatively after implantation of invasive electrodes. The need for such evaluations is generally higher in patients with extratemporal lobe epilepsies. Often, invasive recordings are needed due to absence of a lesion, or a lesion in close proximity to eloquent cortex. In addition, if information obtained from ictal and interictal EEG, neuropsychometry, structural and functional imaging such as PET provides discrepant information, invasive recordings may be necessary to formulate and confirm a hypothesis of the epileptogenic zone.

Subdural grids typically consist of stainless steel or platinum contacts embedded in a thin matrix. Each contact is an individually wired electrode. To delineate epileptogenicity, subdural grids and depths can be used in isolation or combination (Spencer *et al.*, 1990). Invasive recordings are closer to the electrical generators of EEG and therefore have better a signal to noise ratio and signals are larger in amplitude. Comparing scalp and invasive EEG recordings it has been noted that spikes or sharp waves can only be seen on scalp EEG if a larger area of cortex discharges synchronously. Initial studies suggested that $6cm^2$ of gyral cortex needs to be activated simultaneously (Cooper *et al.*, 1965). More recent investigations have suggested that the area of cortex may indeed be in the order of $8cm^2$ (Tao *et al.*, 2005). Invasive studies allow mapping of the area of cortex generating spikes (irritative zone) and the ictal onset zone with greater precision. However, as coverage using subdural grids and depth electrodes is necessarily limited, successful localisation depends on the accuracy of the initial hypothesis for ictal onset. This initial hypothesis will lead to an implantation strategy to localise the epileptogenicity.

Routine extraoperative invasive recordings to delineate the ictal onset zone became possible when van Buren *et al.* (1975) introduced subdural strip electrodes in TLE. Subsequently, such techniques were also used in extratemporal lobe epilepsy (Ludwig *et al.*, 1976). Larger subdural grid electrode arrays allowed extraoperative functional mapping using electrical cortical

stimulation. By applying a small current it is assumed that stimulation produces a temporary, reversible lesion affecting the area of cortex underlying the respective electrodes (Hamberger, 2007; Ranck, Jr., 1975). Outside motor and sensory cortex the effect of stimulation is generally inhibitory. The exact volume of brain that is affected by the stimulation is however unknown. Despite these uncertainties, the gold standard method for localising eloquent cortex such as language, motor and sensory function to guide neurosurgical resections is cortical stimulation, either performed pre-operatively or intra-operatively.

1.7.1 DTI and cortical stimulation

The introduction of DTT has led to an explosion in the literature on the study of structural connectivity. However, as DTT is a relatively new technique, it is important to assess its validity. DTT findings can be compared to anatomical knowledge from human anatomical preparations, or to compare tractography data in primates to tracer studies done *in vivo* in the same species (Croxson *et al.*, 2005). Phantoms can be used in which the fibre architecture is known, however is challenging to produce realistic phantoms (Johansen-Berg and Rushworth, 2009; Perrin *et al.*, 2005). Close correlation between invasive recordings, cortical stimulation findings and tractography results may provide *in vivo* validation in humans. The underlying hypothesis is that the area of cortex that gives rise to a function is also the anchor point of the white matter tract that provides the structural connectivity to other areas of cortex. Such studies could provide some further support that a reconstructed tract indeed represents the known structural connection between two cortical areas.

In chapter 5, correlations between language mapping using cortical stimulation and DTT of the AF are presented.

1.8 DTT and connectivity of the epileptogenic zone

Lastly, DTT can be used to investigate the connectivity of the epileptogenic zone and may contribute in our understanding how seizures propagate. In addition, it may aid in our understanding of alterations in connectivity due to brain plasticity in patients with focal epilepsy. It is likely that several factors have an influence on the connectivity of the ictal onset zone: 1. the underlying pathology (i.e. tumour, HS, CD, non-lesional MRI); 2. the epileptogenic process itself; 3. the location within the brain and its normal anatomical connections. Whether DTT can be useful as a tool to predict seizure propagation has not been systematically assessed before.

In chapter 6, DTT from the ictal onset zone was correlated with ictal propagation patterns as seen during inasive EEG recordings in a small but well characterised case series of patients with CD in the temporo-occipital region. Due to its frequency in temporal and particularly extratemporal lobe epilepsies and its developmental nature, CD is an important pathological entity to investigate.

1.8.1 Cortical dysplasia and connectivity

Focal epilepsy due to CD has been recognised as a common cause of intractable seizures. It represents the second most common identified cause of refractory focal epilepsy in adults after HS (Sisodiya, 2000) and is characterised by a high degree of intrinsic epileptogenicity (Palmini *et al.*, 1995; Palmini *et al.*, 2004).

In recent surgical cohorts, CD has been found in 14% of all resections combining adult and paediatric patients (Mathern, 2009). In children, this percentage is higher and in a recent survey of pediatric epilepsy centers conducted by the International League Against Epilepsy (ILAE) CD was found in 67% of children operated on in the first year of life (Harvey *et al.*, 2008).

There is a spectrum of severity of CD with a variable clinical presentation (Sisodiya, 2000). During human brain development, the interruption of the orderly process of neuroblast proliferation and differentiation, neuroblast migration or cortical organisation may result in disordered neocortical development (Barkovich *et al.*, 2001). Modern neuroimaging has significantly advanced our understanding of these developmental lesions and has allowed for *in vivo* characterisation and *post hoc* correlation with pathology. One widely accepted pathological classification of CD distinguishes the following types of CD using histological criteria: type 1A, isolated architectural abnormalities; type 1B, architectural abnormalities with immature but not dysmorphic neurons; type 2A, architectural abnormalities with dysmorphic neurons; type 2B, architectural abnormalities, dysmorphic neurons and balloon cells (Palmini *et al.*, 2004). Most recently, an ILAE task force has issued a consensus classification on the clinico pathological spectrum of focal cortical dysplasia (Blumcke I *et al.*, 2010). FCD type I will now refer to isolated lesions, which present either as radial (FCD type Ia) or tangential (FCD type Ib) dyslamination of the neocortex, microscopically identified in one or multiple lobes. FCD type II is an isolated lesion characterized by cortical dyslamination and dysmorphic neurons without (type IIa) or with balloon cells (type IIb). The major change since a prior classification represents the introduction of FCD type III. This occurs in combination with other lesions, such as hippocampal sclerosis (FCD type IIIa), with epilepsy-associated tumors (FCD type IIIb), adjacent to vascular malformations (type IIIc) or epileptogenic lesions acquired in early life (FCD type IIId).

Dysplastic lesions may be temporal or extratemporal. Type 1 CDs are more commonly found in the temporal lobe, whereas type 2 CD is more often located outside the temporal lobe; in addition, there may be associated HS (Bautista *et al.*, 2003; Fauser *et al.*, 2004; Fauser *et al.*, 2006; Tassi *et al.*, 2002).

Extratemporal dysplastic lesions often present a challenge for potential resection for several reasons: 1.Proximity to eloquent cortex requires precise delineation of

function in relation to the ictal onset zone, 2. The dysplastic lesion visible on MRI may not represent the entire extent of the lesion. Large areas of dysplastic tissue may not be clearly delineated on MRI, 3. The extent of epileptogenicity cannot be easily delineated. Hence, often invasive recordings are required (Marusic *et al.*, 2002).

Outcome following epilepsy surgery in focal epilepsy due to CD is overall inferior to surgery in TLE due to HS, with a reported average of 62% seizure freedom in a recent meta-analysis (Mathern, 2009).

The surgical treatment of CD may also be challenging as the epileptogenic zone may be organised as a more complex network extending beyond the lesion. When analysing frequency and propagation patterns on invasive EEG recordings in patients with CD it has been noted that distant sites also show early involvement of rapid discharges and rapidly involve widespread, often atypical networks (Aubert *et al.*, 2009; Duchowny *et al.*, 2000; Duchowny, 2009).

Although there is involvement of the dysplastic process in areas of white matter, little attention has focused on characterising the underlying white matter changes and assessing the connectivity of areas of dysplasia and its impact on cortical eloquent function, localisation of ictal onset zone and the corresponding ictal spread patterns.

Abnormalities in diffusivity and anisotropy have been described in patients with CD (Eriksson *et al.*, 2001); more recently, DTI and tractography were performed in patients with CD (Eriksson *et al.*, 2001; Gross *et al.*, 2005; Lee *et al.*, 2004; Lee *et al.*, 2005; Lim *et al.*, 2005; Widjaja *et al.*, 2007). Lee *et al.* observed in 12 patients with focal CD that on DTT, all had a reduction of the subcortical fibres, indicating reduced connectivity between the dysplastic area as seen on conventional MRI and the deep white matter. Using semi-quantitative analysis of the fibre bundles adjacent to the dysplastic cortex, a significant mean reduction of

subcortical fibre bundles showed mean FA reductions compared to the contralateral region.

Improved understanding of how a (dysplastic) lesion is connected and how readily seizures can effectively spread and propagate will provide valuable insights into semiology and possible risk of frequent secondarily generalised seizures. Connectivity information of the ictal onset zone may also add information to devise a surgical strategy.

1.8.2 Delineating propagation of interictal and ictal epileptic activity by DTT

Few studies have investigated DTT as a tool for delineation of pathways for interictal spike propagation. One case report combined EEG fMRI and DTT to understand propagation of interictal activity in a patient with left TLE and left HS. The BOLD activations seen with left temporal spikes were seen in the left temporal, bilateral parietal and left greater than right occipital regions (Hamandi *et al.*, 2008). The relation between interictal spikes and BOLD signal change was investigated using dynamic causal modelling (DCM). DCM is a statistical method for determining the functional interaction between specified brain areas that may be applied to fMRI data, and thus infer whether changes at one region are driving changes at another (Penny *et al.*, 2004).

Recently, in six children with TLE, spread of interictal discharges from temporal to the rolandic region was delineated using magnetoencephalography (MEG). DTT was used to illustrate the connection between the temporal and rolandic region. Two volumes of interest that encompassed the MEG dipoles were placed, one in the temporal lobe, one in the rolandic region. Similar volumes of interest were placed contralaterally and also in control subjects. An aberrant tract was visualised only in patients on the side of the epileptiform discharges, travelling through the external capsule. The authors hypothesise that the reported aberrant

pathway indicates an existing tract which may facilitate the spread of epileptiform activity from the temporal lobe to the rolandic region. Alternatively, it was considered that such connections may form under the condition of intractable epilepsy in children (Bhardwaj *et al.*, 2010).

These reports indicate that DTT may have the potential to assist in understanding ictal propagation patterns, and give insights in connectivity of the epileptogenic zone. Chapter 6 will explore seizure spread and DTT in patients with CD.

CHAPTER 2
EXPERIMENTAL METHODS

This thesis includes original research work on:

1. Correlations of DTI measures in regions of interests and tracts with cognition in the language and memory domain.

2. Correlations of results from language mapping using cortical stimulation and the arcuate fasciculus based on DTT.

3. Analysis on seizure propagation in a case series of patients with cortical dysplasia.

DTI acquisition methods are the same in all studies and therefore are described in this common methods section; methods specific to the individual study are discussed separately in the respective chapters.

2.1 Patient recruitment and pre-surgical evaluation at the Cleveland Clinic Foundation (CCF)

All patients were recruited whilst undergoing pre-surgical evaluation at the Epilepsy Center at the Cleveland Clinic and all had pharmacoresistant focal epilepsy.

CCF is large quaternary centre for epilepsy surgery, with a US national and international referral basis. All patients are initially seen during an outpatient clinic visit with an epileptologist. All faculty staff are trained Neurologists and Clinical Neurophysiologists with considerable experience in pre-surgial evaluation. Following initial consultation, if a patient is felt to be a potential candidate for epilepsy surgery, all evaluations comprising Phase 1 are scheduled. These include video EEG monitoring to capture seizures and to define the irritative zone, ictal onset zone and symptomatogenic zone with the greatest precision possible.

High resolution MRI and Fluoro-deoxyglucosePET imaging are also performed routinely at this stage, together with neuropsychometric assessment and a psychiatric   evaluation. Following this, data will be presented by the staff epileptologist in a multidisciplinary patient management meeting. If a hypothesis of the epileptogenic zone can be formulated, the patient will be invited for epilepsy surgery or for further testing, if required. In further testing is needed, such as ictal SPECT or further imaging, the patient will return. Invasive evaluations are performed in a selected group of focal epilepsies, when a hypothesis regarding the epileptogenic zone can be formulated, but needs confirmation. Often, cortical functional mapping using direct electrical cortical stimulation is also required. There are several clinical scenarios that require delineation of the exact area of ictal onset; for indications for invasive recordings and these are described in table 2.1. It is of note that the presence or absence of a presumed epileptogenic lesion visualised using MRI is a critical factor. However, the information provided by analysis of semiology, interictal and ictal EEG and neuropsychological data is very important too, and should converge and support the hypothesis that the lesion is indeed epileptogenic. In addition, the lesion itself may be very subtle, or very large, or of doubtful relation to the epilepsy.

Ethics approval was obtained for all studies from the Institutional Review Board (Cleveland Clinic IRB 6960; IRB 8062 and IRB06-035). Patients agreed in writing to participate to the respective study.

All DTI took place prior to resection and prior to invasive recordings.

Table 2.1 Indications for invasive recordings in the pre-surgical evaluation of patients with medication refractory focal epilepsy

#	Clinical Scenario	Strategy
1	• Clear lesion • Congruent EEG and semiology • Away from eloquent cortex	(Almost) no invasive recordings needed
2	• Clear lesion • Congruent EEG and semiology • Close to eloquent cortex	May require invasive recordings (SD+/- depths) Extra- or intraoperatively
3	• Clear lesion • Discordant EEG and/or semiology	May require invasive (SD+/- depths)
4a	• No lesion seen on MRI • EEG and semiology concordant Note: additional imaging and electrical source analysis data may be very helpful and can change strategy	Almost always invasive needed (SD+/- depth, or depth alone)
4b	• Two lesions, subtle or large lesions • Concordant EEG and semiology	(Almost) always invasive needed (SD+/- depth, or depth alone)
5	• Two or more lesions, subtle or large lesions • Discordant/confusing EEG and semiology	Likely not surgical candidate

2.2 MRI protocol

MR-images were acquired on a 1.5T whole body MR scanner (Siemens Vision). For the patients, the protocol typically included volumetric T1-weighted gradient echo, coronal FLAIR and axial T2-weighted fast spin echo scans and DTI sequences. The control subjects had volumetric T1 and DTI acquisitions. The DTI acquisition comprised axial 2D echo planar imaging (2D EPI) diffusion weighted sequence with TR/TE = 6000/112msec, FOV = 24 cm, matrix = 128x128, 3mm contiguous slices without gap, resulting in a voxel size of 1.875mm x 1.875mm x 3mm. Furthermore, two b values = 0 and 1000 s/mm^2; 12 directions and 6 averages were utilised. In order to ascertain consistent quality, routine preventative maintenance is performed on the MRI scanner. The measures

always remained well within specifications for main field stability, gradient stability, rf stability, and eddy current compensation performance.

2.3 DTI Quantitation

Data were transferred to a "Leonardo" workstation (Siemens Medizintechnik AG, Erlangen, Germany) from each set of diffusion/orientation weighted images and processed using DTI task card software (Massachusetts General Hospital, https://www.nmr.mgh.harvard.edu). Specifically, multiple linear regression was used to generate the diffusion tensor $\underline{D}$, ($S_b = S_0 * \exp(-b\underline{D})$; $\ln(S_b/S_0) = -\underline{b}(\underline{D})$) from each set of diffusion/orientation-weighted images. S_b, is the MR signal measured for a given b value, S_0 is the MR signal for b=0, $\underline{b}$ = is the b matrix characterizing the diffusion gradient pluses (timing, amplitude; shape) along each direction(s/mm^2); $\underline{D}$ = the diffusion tensor which describes the molecular mobility along each direction and correlation between these directions. The diffusion tensor $\underline{D}$ is then diagonalized to obtain the eigenvectors and eigenvalues (λ_i, i = 1,2,3). The eigenvectors represent the major diffusion directions and the eigenvalues are the associated diffusivities. The ADC (units = mm^2/s) is calculated from the trace of the diagonalised diffusion tensor (($\lambda_1 + \lambda_2 + \lambda_3$)/3). For isotopic diffusion, $\Box \lambda_1 = \lambda_2 = \lambda_3$; for anisotropic diffusion, $\lambda_1 > \lambda_2 \geq \lambda_3$. Parametric maps of the ADC and fractional anisotropy (FA) were generated. FA, a scalar (unitless) quantity, indicates the degree of directionality of the diffusion within a given voxel; it ranges from 0 to 1, with an FA of 0 indicating full isotropy and FA=1 indicating complete anisotropic diffusion. Similarly, parametric maps for the axial or parallel (main direction of diffusion, $E1 = \lambda_1$) and radial (perpendicular to the main axis, $\lambda_T = (\lambda_2 + \lambda_3)/2$) diffusivities were also created. Together, these quantitative measures help to characterise the integrity of the underlying white matter.

2.4 Diffusion tensor tractography (DTT)

Fibre tracking was performed using the FACT algorithm (Mori *et al.*, 1999; Stieltjes *et al.*, 2001) implemented within the DTI task card software. The algorithm developed fibre tracts by following the direction of the principle eigenvector at each step starting from a region of interest (ROI). Tracking propagates on the basis of the orientation of the eigenvector that is associated with the largest eigenvalue. In all studies, tracking is terminated when it reaches a voxel with an FA lower than a threshold of 0.2. The second criterion is the angle between the two principal eigenvectors; to reconstruct the unicinate fasciculus (UF) (chapter 3) and the fibres arising from the ictal onset zone (chapter 6) it was set at greater than 50°. The AF was reconstructed using an angle of 70° or greater. Both of these thresholds are user defined. The software also allows for obtaining mean measures of FA and ADC for ROIs and also for the entire reconstructed tract.

As detailed under "DTI quantitation", measurements in the axial and perpendicular direction allow elucidation of the mechanism producing the observed changes in anisotropy, thus providing insights into the underlying pathology. Due to the non-linear trajectory of the white matter tracts, such estimates of axial and perpendicular diffusivities are only meaningful in one single plane. Consequently, due to the complex geometric shape of the entire fasciculus, we chose to report on these changes only in one ROI, contained within the respective tract.

CHAPTER 3

CORRELATES OF MEMORY FUNCTION, DTI MEASURES AND TRACTOGRAPHY

Diffusion abnormalities have been found in patients with focal epilepsy using DTI and DWI not only in areas of seizure onset and spiking, but also in adjacent, remote and even contralateral areas, as discussed in sections 1.4.2 - 1.4.4. Cognitive dysfunction in memory and language domains is common in patients with temporal lobe epilepsy and DTI could provide insights into mechanisms of such dysfunction.

Chapters 3 and 4 include investigations into correlations of neuropsychological measures of language and memory with DTI measures of regions of interest and tracts in patients with medication refractory TLE. This chapter focuses on memory functions in TLE and the UF (Diehl *et al.*, 2008).

3.1 INTRODUCTION: The uncinate fasciculus in TLE

The UF is a major white matter tract connecting the anterior temporal and frontal lobes (Schmahmann *et al.*, 2007). It has the form of a curved dumbbell and links the anterior three temporal convolutions and the amygdala with the gyrus rectus, medial retro orbital cortex and subcallosal area (Ebeling and von Cramon, 1992). The UF has an important role in the formation and retrieval of episodic memories (Nestor *et al.*, 2004; Squire and Zola-Morgan, 1991) and is a pathway of seizure spread to the frontal lobe in TLE (Mayanagi *et al.*, 1996).

The purpose of this study was to test the hypothesis that DTI would reveal structural abnormalities of the UF ipsilateral to the seizure focus in TLE and that the degree of abnormality would correlate with functional abnormality, as shown by reduced memory scores.

3.2 METHODS

3.2.1 Participants

This study included 28 patients with medically intractable TLE and 10 age- and sex-matched controls. Eighteen patients had left TLE (13 mesial temporal, five lateral temporal) and 10 right TLE (five mesial temporal, five lateral temporal). All patients underwent temporal lobe resection for treatment of epilepsy and all but one patient had good seizure outcome (ILAE class 1, n=25; ILAE class 2, n=2; ILAE class 3, n=1 (Wieser *et al.*, 2001)) at 6 months to 2 years (median 1 year) follow-up. Nine patients had pathologically proven hippocampal sclerosis, 14 non-specific gliosis, and two type 1A cortical dysplasia, characterised by architectural disorganisation (Palmini *et al.*, 2004).

The study was approved by the Institutional Review Board of the Cleveland Clinic Foundation, and all patients gave informed consent prior to enrollment in the study.

3.2.2 Region of interest analysis and tractography

The UF was reconstructed using a two ROI approach to restrict fibre assignment to the UF (Figure 3.1). On the axial colourised FA map, a ROI was placed encompassing the perpendicular fibres passing through the temporal stem in the anterior temporal lobe towards the orbitofrontal cortex (Mori *et al.*, 2005). A second ROI was placed in each patient on an inferior axial slice closer to the inferior and anterior portion of the temporal lobe, encompassing the fibres of the UF, in order to restrict fibre assignment to the UF. Fibres were reconstructed that passed through both ROIs. Fibre tracking was performed using the FACT algorithm (Mori *et al.*, 1999; Stieltjes *et al.*, 2001) implemented within the DTI task card software, as described in chapter 2. In this study, tracking was terminated when it reached a voxel with a FA lower than a threshold of 0.2 and when the

angle between the two principal eigenvectors was greater than 50°. Both of these thresholds were user defined. Measures of FA and ADC were obtained for the entire reconstructed UF.

Figure 3.1 Reconstruction of the UF

A: The figure illustrates placement of the two ROIs to reconstruct the UF.
The white arrow shows the location of the fibres of the right UF in the axial slice of the colourised fibre orientation map. The ROI in orange on the left shows the superior of the two ROIs used to reconstruct the UF.
B: The reconstructed left UF is displayed from a left lateral angle. The two ROIs used for reconstruction are visible in orange and pink colour.
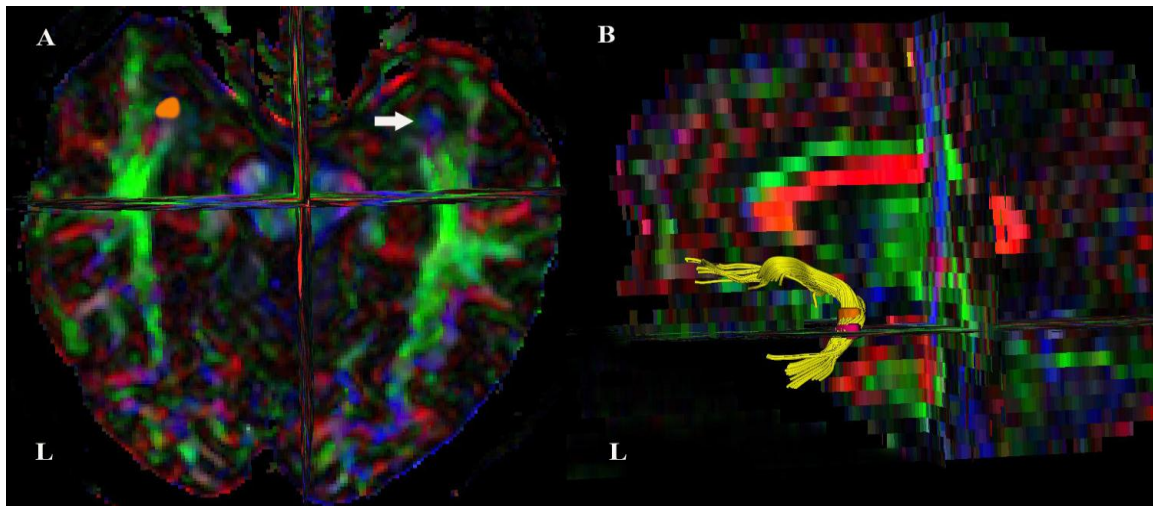
In order to gain insight into the underlying microstructural sources of the observed differences in the FA and ADC values measured for the tracts, the diffusion along each of the main three directions, i.e. eigenvalues ($\lambda1$, $\lambda2$, $\lambda3$) (mean ± SD), was examined along with the FA and ADC, for an ROI contained within the rostro-caudal course of the UF within the temporal stem. This ROI was selected after reconstruction of the UF to include only fibres that followed the course of the UF.

The axial and radial diffusivities were computed for each individual ROI within the UF in order to independently evaluate the degree of diffusion parallel and

perpendicular to the UF tract at that location. Such measurements in the axial and perpendicular direction allow elucidation of the mechanism producing the observed changes in anisotropy, thus providing insights into the underlying pathology. Due to the non-linear trajectory of the white matter tracts, such estimates of axial and perpendicular diffusivities are only meaningful in one single plane and these changes were only reported for one ROI, contained within the UF. This region was located within the temporal stem, where the UF has a rostro caudal orientation and can be easily identified.

Figure 3.2 DTT of the UF

A: Sagittal and axial cuts of colourised fibre orientation map of a 34 years old woman with intractable left temporal neocortical epilepsy. The UF is displayed in yellow (left UF) and red (right UF).
B. The UFs were coregistered and overlaid onto the patient's T1 volumetric study.
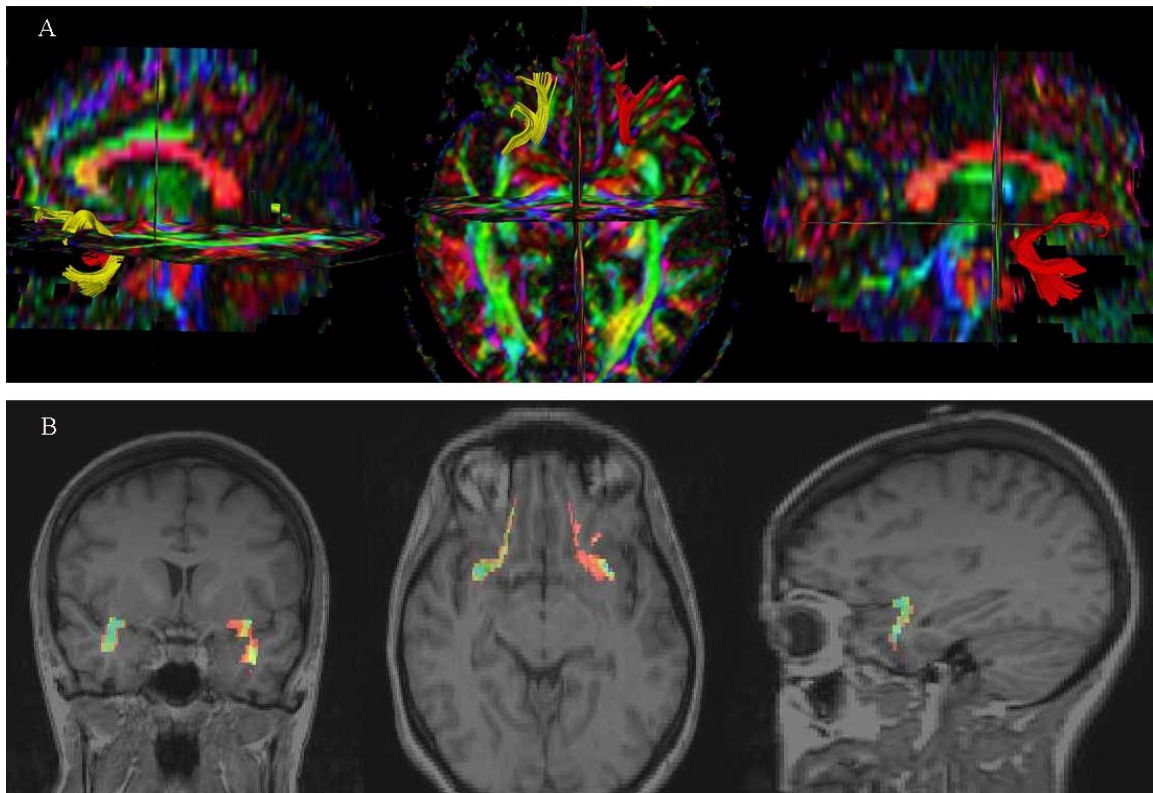
3.2.3 Neuropsychological protocol

All TLE patients underwent a comprehensive neuropsychological evaluation as part of their pre-surgical investigations. The Wechsler Memory Scale – Third Edition (WMS-III) was administered as part of the neuropsychological battery. Four memory indices from the WMS-III were used in the current study to evaluate memory performance. The Auditory Immediate Memory Index and the Auditory Delayed Memory Index were used to assess verbal memory. The Visual Immediate Memory Index and the Visual Delayed Memory Index were used to assess visual memory.

3.2.4 Analyses

In order to compare age at seizure onset and duration of epilepsy in the TLE groups (left, right), U tests were computed.

To evaluate DTI measures, two-tailed t-tests were conducted to examine differences in FA and ADC between left and right UF among the study groups and differences in FA and ADC values between the groups. Then, Spearman correlations between DTI and memory measures in the TLE groups were examined. Given the exploratory nature of this study, no correction for Type I error was made.

To obtain measures of reliability, the UF was reconstructed in ten controls on both sides, on two separate occasions four months apart, by the same rater (BD) and reliability was assessed using Cronbach's alpha values.

In all tests, statistical significance was set to $P<0.05$. All analyses were performed using the SPSS software package (SPSS, Chicago, IL).

3.3 RESULTS

Demographics were comparable between the study groups and are shown in Table 3.1 (controls: age range 26-52, median 37; right TLE: range 28-55, median 39, mean 36.3 ± 6.6 years; left TLE: range 24-47, median 36, mean 41.8 ± 8.2 years). Specifically, no difference was found in age at onset of epilepsy in the left versus right TLE group (right TLE: median age at seizure onset 16.5 years, range 10-42; median duration of epilepsy 23 years, range 2-28; left TLE: median age at onset 23 years, range 5-42; median duration 22.5 years, range 1-41).

All controls and the majority of epilepsy patients were right-handed using the Edinburgh handedness questionnaire. A total of 10 patients were left-handed or ambidextrous. These patients were confirmed to be left hemisphere dominant for speech on Wada testing or functional MRI; therefore all subjects are likely to be left hemisphere dominant for language.

Table 3.1 Demographic and seizure data for study patients

Variable	Left Temporal	Right Temporal
	Median (range)	Median (range)
Age	36.00 (24-47)	39.00 (28-55)
Education	14.00 (12-19)	12.00 (8-17)
Age of seizure onset	23.00 (5-42)	16.50 (10-42)
Duration of Epilepsy	22.50 (1-41)	23.00 (2-28)
Sex	Male = 5 (28%)	Male = 6 (60%)
	Female = 13 (72%)	Female = 4 (40%)
Race	Caucasian = 18 (100%)	Caucasian = 10 (100%)

3.3.1 DTI values of the UF in controls and patients with left and right TLE

3.3.1.1 Controls

Mean FA in the left UF tract was higher than in the right UF (left UF FA $0.3654\pm$ 0.033; right UF FA $0.33\pm$ 0.02; p<0.01). No other differences in DTI values were identified. Tract volume was symmetric bilaterally. The reliability measure (Cronbach's alpha) for reconstruction of the bilateral UF in the 10 controls on two occasions four months apart was excellent (ADC left UF, 0.9920; FA left UF, 0.9950; ADC right UF, 0.9983; FA right UF, 0.9950).

3.3.1.2 Comparison between TLE patients and controls

In the left TLE group (n=18), FA was reduced in the left UF, but not in the right as compared to the controls. ADCs and radial diffusivities were increased bilaterally. (Table 3.2)

In the right TLE group (n=10), the FA was lower in the left UF than the controls. FA in the right UF, although lower than in left TLE and in controls, was not statistically significant. ADCs were increased in both the left and right UF. Subanalysis of the eigenvalues of the diffusivities within the left ROI revealed significant increases in the radial diffusivities. In the right ROI, although nominally higher, this difference failed to reach statistical significance. Volume of the left and right UF was symmetrical in both left and right TLE (Table 3.2).

3.3.1.3 Comparison between TLE patients

There were no differences in DTI measurements between patients with mesial versus lateral temporal lobe epilepsy. Patients with hippocampal sclerosis and patients without any specific pathology within the resected tissue had comparable DTI measurements to those without either pathology.

Table 3.2 DTI values in controls and patients with left and right TLE

	Controls (n=10) Mean (SD)	Left TLE (n=18) Mean (SD)	Right TLE (n=10) Mean (SD)
lt UF tract, FA	0.365 (0.033)	**0.335*** (0.030)	**0.326**** (0.031)
lt UF tract, ADC	8.204 .2995	**8.714**** (0.465)	**8.815**** **(0.597)**
ROI within lt UF, FA	0.506 (0.085)	**0.416**** (0.070)	**0.389**** (0.068)
ROI within lt UF, ADC	7.595 (0.410)	**8.060**** (0.393)	7.899 (0.459)
ROI within lt UF, E1	12.401 (1.189)	12.083 (0.793)	11.603 (0.729)
ROI within lt UF, radial diffusivities	5.192 (0.633)	**6.051**** (0.612)	**6.047**** (0.625)
rt UF tract, FA	0.330 (0.019)	0.324 (0.029)	0.3174 (0.0331)
rt UF tract, ADC	8.338 (0.281)	**8.664*** (0.440)	**8.884*** (0.628)
ROI within rt UF, FA	0.469 (0.042)	0.423 (0.066)	0.400 (0.099)
ROI within rt UF, ADC	7.51780 (0.271)	**7.879*** (0.477)	8.202 (1.043)
ROI within rt UF, E1	11.783 (0.630)	11.854 (0.798)	11.999 (0.735)
ROI within rt UF, radial diffusivities	5.385 (0.620)	**5.896*** (0.599)	6.302 (1.303)

SD= Standard deviation, Lt= left, Rt= right, ROI=Region of Interest
* = $P<0.05$; ** = $P<0.001$ (unpaired t-test).
E1= eigenvalue 1. ADC, E1 and radial diffusivities all in 10^{-4} mm^2/s

3.3.1.4 Correlations between duration of epilepsy and DTI measures

Correlations between age at seizure onset, duration of epilepsy, and DTI measures were examined. These correlations were calculated on all TLE patients as a group as well as separately for those with left TLE and those with right TLE. There were no significant correlations between age at seizure onset or disease duration and DTI measures.

3.3.2 Correlations between DTI measures and memory scores

These results are summarised in table 3.3 and shown graphically in figure 3.2

3.3.2.1 Left temporal lobe epilepsy patients

The following correlations with DTI measures in the left UF were found: The Auditory Immediate Memory Index score was negatively correlated with ADC. Performance on the Auditory Delayed Memory Index score was negatively correlated with ADC and radial diffusivities, and positively correlated with FA in the ROI in the left UF. In summary, evidence of damage to the left UF based on DTI measurements is associated with reduced performance on measures of Auditory Immediate and Delayed Memory in left TLE patients.

The following correlations with DTI measures in the right UF (ROI only) were found: The Visual Delayed Memory Index score was positively correlated with the FA in the ROI and negatively correlated with radial diffusivities. In summary, evidence of damage to the right UF based on DTI measurements is associated with reduced performance on measures of Visual Delayed Memory.

3.3.2. 2 Right temporal lobe epilepsy

No significant correlations between DTI values and memory scores were found in the right TLE group.

Table 3.3 Correlations between DTI measurements and auditory and visual memory scores in all TLE, left TLE, and right TLE

Left TLE

	Auditory Immediate Index Score	Auditory Delayed Index Score	Visual Immediate Index Score	Visual Delayed Index Score
lt UF tract, FA	0.272	0.382	0.109	0.210
lt UF tract, ADC	-0.512*	-0.535**	-0.083	0.126
ROI within lt UF, ADC	-0.304	-0.435	-0.112	0.032
ROI within lt UF, FA	0.412	0.534*	0.258	0.314
ROI within lt UF, E1	0.191	0.197	0.189	0.377
ROI within lt UF, radial diffusivity	-0.437	-0.571*	-0.279	-0.262
rt UF tract, FA	0.057	0.145	0.032	0.090
rt UF tract, ADC	-0.107	-0.286	-0.085	0.139
ROI within rt UF, FA	0.006	0.079	.397	0.547*
ROI within rt UF, ADC	-0.318	-0.369	-0.366	-0.322
ROI within rt UF, E1	-0.160	-0.198	0.055	0.108
ROI within rt UF, radial diffusivity	-0.287	-0.333	-0.376	-0.539*

Spearman's correlation   ** Correlation is significant at the 0.01 level (2-tailed)
                               *   Correlation is significant at the 0.05 level (2-tailed)

Right TLE

	Auditory Immediate Index Score	Auditory Delayed Index Score	Visual Immediate Index Score	Visual Delayed Index Score
lt UF tract, FA	0.483	0.091	0.431	0.254
ADC in lt UF tract	-0.250	-0.006	0.000	0.100
ROI within lt UF, ADC	-0.268	-0.310	-0.311	-0.044
ROI within lt UF, FA	0.128	0.158	0.116	-0.069
ROI within lt UF, E1	0.189	-0.097	-0.140	-0.263
ROI within lt UF, Perpendicular diffusivity	-0.183	-0.219	-0.287	0.088
FA in rt UF tract	0.367	0.390	0.550	0.386
ADC in rt UF	-0.140	0.359	-0.195	0.382
ROI within rt UF, FA	0.238	0.152	-0.024	-0.138
ROI within rt UF, ADC	0.140	0.079	0.146	0.200
ROI within rt UF, E1	0.575	0.335	0.315	0.320
ROI within rt UF Radial diffusivity	-0.152	-0.152	0.018	0.156

Spearman's correlation   ** Correlation is significant at the 0.01 level (2-tailed)
                          *   Correlation is significant at the 0.05 level (2-tailed)

Figure 3.2 Graphs illustrating correlations between memory performance and UF DTI measures in right and left TLE

A: Correlation between Performance on auditory immediate memory measures and ADC in the left UF tract
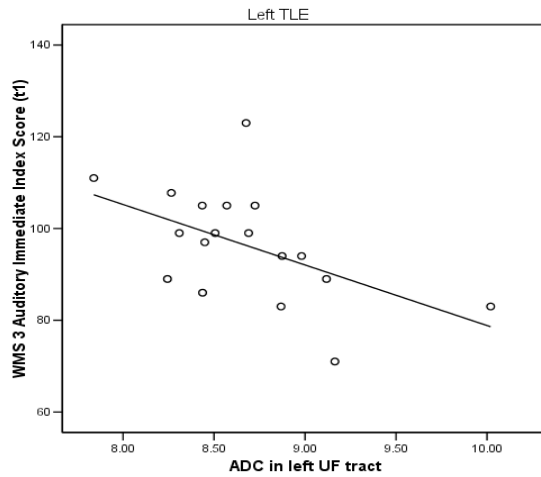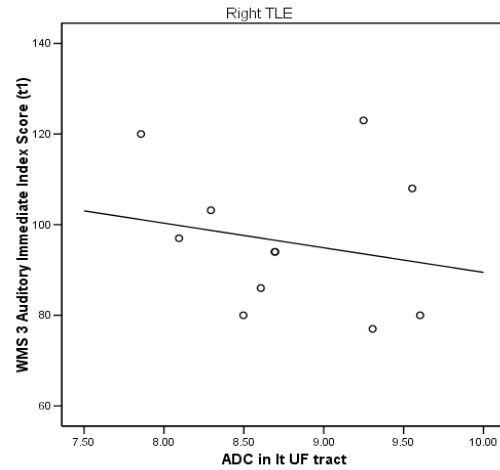
r=-0.512, P<0.05   r=-0.250, not significant (ns)

B: Correlation between performance on auditory delayed memory measures and ADC in the left UF tract
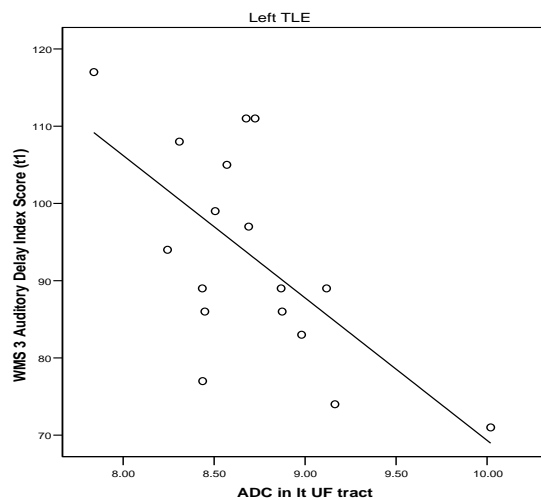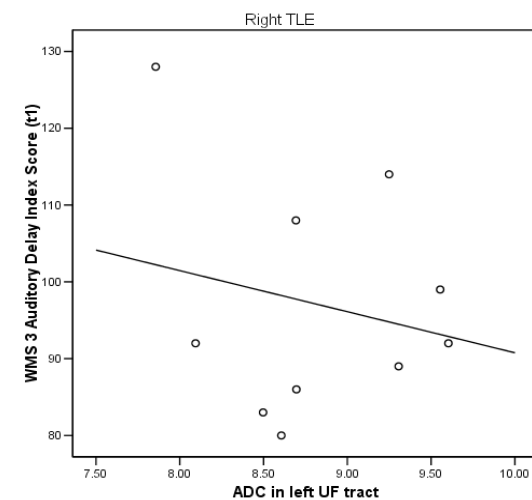
r= -0.535, p<0.01   r=-0.006, ns

C: Correlation between performance on auditory delayed memory measures and FA in the ROI in the left UF tract
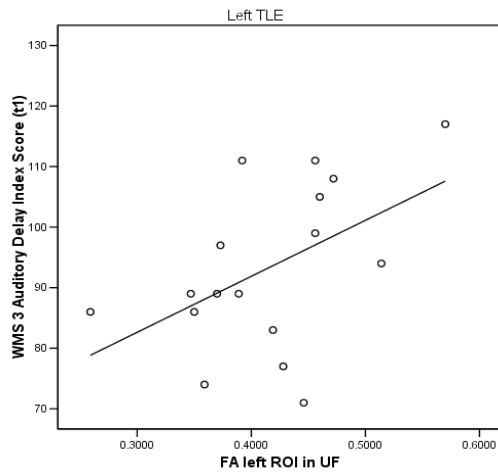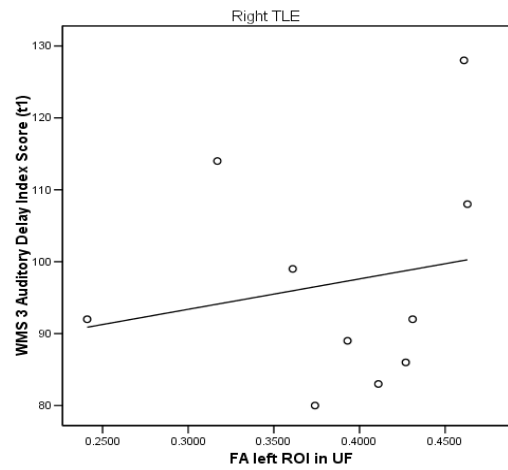
r=0.543, p<0.05   r=0.158, ns

D: Correlation between Performance on auditory delayed memory measures and radial diffusivities in the ROI in the left UF tract
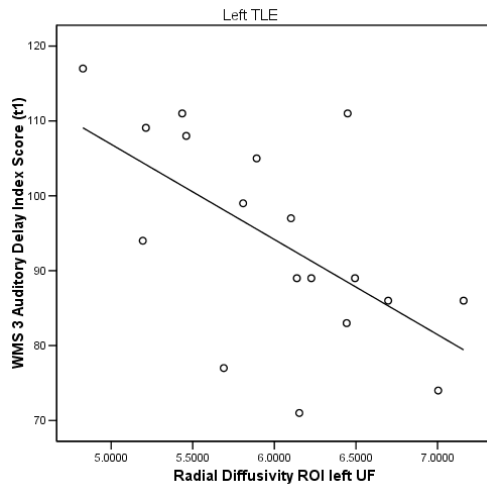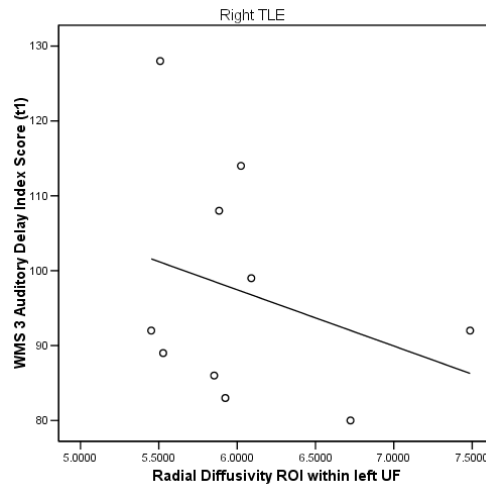
r=-0.571, p<0.05   r=-0.219, ns

E: Correlation between performance on visual delayed memory measures and FA in the ROI in the right UF tract
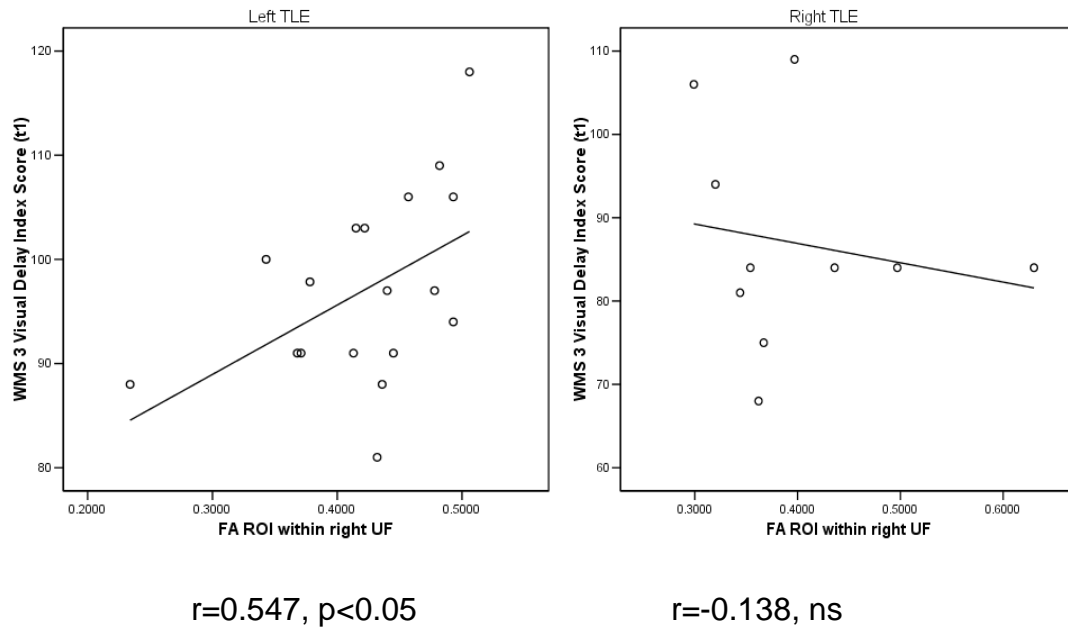
r=0.547, p<0.05   r=-0.138, ns

F: Correlation between performance on visual delayed memory measures and radial diffusivity in the ROI in the right UF tract

r=-0.539, p<0.05   r=0.156, ns
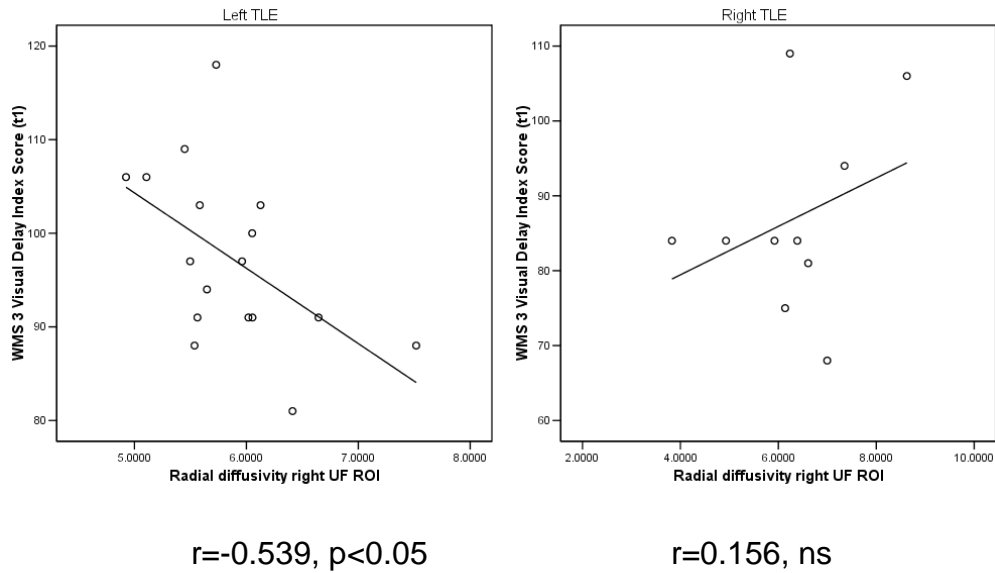
3.4 DISCUSSION

3.4.1 DTI of the UF in controls

In this study the FA in the controls was found to be greater in the left than the right UF with symmetric tract volume. The literature on UF asymmetries in controls remains controversial. Some groups have demonstrated a greater left than right asymmetry in UF FA (Kubicki *et al.*, 2002); others however, found that the right UF had a higher FA (Rodrigo *et al.*, 2007). These differences may in part be due to methodological differences both in image acquisition and analysis. It is likely that there is a variability of diffusion values that can be measured at different locations within the UF; some authors describe a greater right than left asymmetry in the stem and the inferior (temporal) aspect of the UF (Park *et al.*, 2004; Rodrigo *et al.*, 2007), and a greater left than right asymmetry in the frontal aspect of the UF. Detailed analysis in one study showed that greater right than left asymmetry was present in the middle and inferior portion, and greater left than right in the superior portion of the UF (Park *et al.*, 2004). The methodology used in this study did not allow for separation of those two parts of the UF.

3.4.2 DTI of the UF in patients with Epilepsy

This study showed that patients with TLE have abnormal measures of diffusivity and anisotropy in the UF bilaterally. Reduced FA was noted in the left UF as well as the ROI in the left UF in patients with left and right TLE.

The only study reporting DTI of the UF in patients with epilepsy available at the time of conducting the study reported ten patients with right TLE due to right hippocampal sclerosis compared to ten controls (Rodrigo *et al.*, 2007). It showed that the right, but not the left FA was lower in the epilepsy patients as compared to the controls. There was no report on diffusivity measures.

This study showed more bilateral involvement in the UF with significantly increased ADCs in the right UF and decreased FA and increased ADCs in the left UF in both right and left TLE patients. This is in concordance with reports of bilateral diffusion abnormalities in limbic structures in patients with TLE. Also, several groups have demonstrated that diffusion abnormalities in TLE exist in areas remote and even contralateral to the presumed seizure focus (Arfanakis *et al.*, 2002; Concha *et al.*, 2005; Gross *et al.*, 2006).

Preferential pathways for seizure spread in TLE may be the fornix and stria terminalis, amygdalofugal fibres, and UF (Mayanagi *et al.*, 1996). Therefore, it is conceivable that the abnormal DTI values may be related to damage of the axonal pathways that are involved in ictal spread. Alternatively, neuronal damage from seizures may lead to secondary white matter loss in connected areas. Interestingly, the current study failed to demonstrate any difference between mesial versus lateral TLE or between the patients with and without hippocampal sclerosis. It is possible however, that changes may not be apparent because of the small sample size. Studies with larger sample sizes are required to definitively answer this question.

Both epilepsy groups were comparable in age at seizure onset and duration of the epilepsy; hence assuming similar seizure burden, we would expect comparable damage in both the left and right TLE. Indeed, both TLE groups showed evidence of comparable patterns of DTI abnormalities in both UFs. However, as the number of seizures or seizure types was not prospectively investigated, it cannot be determined whether there is a correlation between degree of DTI abnormalities and severity of epilepsy. Other variables such as history of status epilepticus and febrile seizures should also be evaluated in a larger group of patients with epilepsy to understand their impact on DTI abnormalities in patients with epilepsy.

To date, the exact mechanism of such seizure-induced damage is unknown. In this study, the characteristics of the diffusion changes in a ROI within the UF were

examined to gain further insight into the type of changes. Analysing the pattern of diffusion changes with respect to diffusivities parallel and radial to the main axonal direction provides *in vivo* insights into the underlying cause of decreased FA. This study found unchanged parallel diffusivity and increased perpendicular diffusivity. In order to understand the contributions of axonal versus myelin damage, serial diffusion measurements have been performed on the optic nerve in a mouse model of retinal ischemia (Song *et al.*, 2003). According to this model, parallel diffusivity shows a significant decrease in the first days of degeneration, which corresponds to the disintegration of the axonal microstructure, whereas myelin remains intact. Five days after the initial injury perpendicular diffusion increased, which corresponds to the degradation of myelin sheaths. As demonstrated using an *in vitro* model of Wallerian degeneration in frog sciatic nerve, axonal and myelin degeneration causes a decrease in diffusion anisotropy due to reduced parallel and increased radial diffusion (Beaulieu *et al.*, 1996). In humans, reductions in the principal direction and increases in radial diffusivities have been shown in chronically degenerated white matter tracts (Pierpaoli *et al.*, 2001). Serial DTI measurements in three patients who underwent corpus callosotomy to treat medically refractory seizures and drop attacks, revealed interesting insights into the diffusion changes in the corpus callosum after the surgery (Concha *et al.*, 2006). After one week, a decrease in parallel diffusivities was seen, evidencing the breakdown of the axons (Concha *et al.*, 2006; Kerschensteiner *et al.*, 2005), creating barriers in the longitudinal displacement of the water molecules. In the chronic stage, 2-4 months after corpus callosotomy, an increase of the radial diffusivities was observed. Most likely at this stage, axonal membranes became more degraded and myelin sheaths showed degeneration, leading to preferential increase in radial diffusivities. It would appear that the overall pattern of FA changes seen in this study is most consistent with chronic Wallerian degeneration, possibly due to cell loss in the temporal lobe secondary to seizure-induced cell death.

3.4.3 Correlations with neuropsychological dysfunction

3.4.3.1 The role of the uncinate fasciculus in memory

The UF is the major fibre tract connecting the inferior frontal and anterior and mesial temporal lobes (Ebeling and von Cramon, 1992). A multitude of functional neuroimaging data has implicated the temporal lobes, particularly mesial temporal and frontal structures in encoding and retrieval of memories. The anterior temporal area receives information from sensory association areas as well as the limbic nuclei and integrates sensory input (Damasio *et al.*, 1985; Markowitsch *et al.*, 1985). In healthy subjects, fMRI has confirmed that episodic memory is associated with both mesial temporal and frontal lobe activation (Brewer *et al.*, 1998; Kirchhoff *et al.*, 2000; Markowitsch *et al.*, 1985; Wagner *et al.*, 1998). There is material specific lateralisation of memory in both healthy volunteers and patients with unilateral mesial temporal lobe lesions. Encoding of verbal information activates the left medial temporal structures, whilst encoding of less verbalisable stimuli, such as patterns, activates the right mesial temporal structures, with encoding of intermediate verbalisable stimuli, such as faces and scenes, resulting in approximately symmetric activation (Brewer *et al.*, 1998; Golby *et al.*, 2001; Golby *et al.*, 2002; Hwang and Golby, 2006). In general, the lateralisation of memory performance regarding verbal material appears stronger; conversely, there is a less firm association of right TLE with disturbed figural learning (Helmstaedter *et al.*, 1995; Powell *et al.*, 2007b).

The medial temporal lobes have been consistently implicated not only in encoding, but also in retrieval (Schacter and Wagner, 1999; Wagner *et al.*, 1998). Pre-frontal regions in the left hemisphere are differentially activated during episodic encoding and semantic retrieval, whereas right pre-frontal areas are differentially involved during episodic memory retrieval. It therefore seems reasonable to assume that the integrity of the UF linking the frontal and anterior and mesial temporal lobes is important for optimal performance on memory tasks.

3.4.3.2   Correlations of DTI abnormalities in the UF in disease

In line with the above hypothesis, correlations were found between DTI measures suggesting damage to the UF and dysfunction in lateralised memory tasks. Specifically, the current study suggests that in patients with left TLE, left UF diffusivity is related to reduced verbal memory performance, whereas right UF DTI measures are related to reduced visual memory performance. In patients with right TLE, such correlations could not be demonstrated. This may in large part be due to the small sample size in the right TLE group. Although none of the correlations in the right TLE group reached statistical significance, it should be noted that the variance of correlation coefficients observed in this group was large and some of the correlations were in the medium to large range (Table 3.3). This suggests that if the sample sizes had been bigger in the right TLE group, these correlations would likely have reached statistical significance.

In the dominant hemisphere, strong structure and function relationships have been found for both language and memory in a variety of DTI and fMRI studies in temporal lobe epilepsy patients (Focke *et al*., 2008; Powell *et al*., 2007a; Powell *et al*., 2008; Powell *et al*., 2007b). Subjects with more lateralised functional activation had also more highly lateralised DTI values. In left TLE, more symmetrical language activations were seen on fMRI, along with reduced left hemisphere and increased right hemisphere structural connections. fMRI in the patients undergoing non-dominant anterior temporal lobe resection showed no significant correlation between right hippocampal encoding activation for faces or pictures and post-operative change in design learning, suggesting a less strong structure-function relationship in non-dominant TLE. Therefore, lack of correlation between visual memory performance and DTI values in the UF in the smaller right TLE group may not be surprising.

Correlations between lateralised memory performance evaluating both verbal and visual memory paradigms and DTI abnormalities have been shown in other

diseases. Patients with schizophrenia have reduced levels of functioning across all neuropsychological measures and selective relationships between memory performance and DTI measures have been demonstrated. Reduced left UF FA correlated with reduced scores in measures of declarative-episodic memory, and reduced right UF FA correlated with lower scores on measures of working memory, general intelligence, verbal intelligence and verbal comprehension. The authors felt that the latter finding underscored the widely distributed nature of higher cognition in the brain, thus cautioning against simple isomorphic relationships between function and anatomy (Nestor *et al.*, 2004). Another study reported that lower FA in the right UF correlated with reduced performance on measures of visual attention (Kubicki *et al.*, 2002). In five subjects with schizotypal personality disorder, bilateral reductions of FA in the UF were reported. Correlations were found between right UF abnormalities and clinical symptoms such as restricted affect and social anxiety. Left UF measurements indicative of microstructural damage were correlated with lower performance on measures of verbal and visual memory (Nakamura *et al.*, 2005).

In a group of TLE patients suffering from psychosis (Flugel *et al.*, 2006), a positive correlation was found between verbal fluency and DTI measurements in the left frontal, right frontal, and left temporal regions. Prediction of poor fluency could be made using FA of left frontal and bilateral temporal regions. It was felt that the significant association between impairment on particular executive tests and reductions of frontotemporal FA may reflect the contribution of frontotemporal white-matter abnormalities to the cognitive deficits in these patients. This argument is further strengthened by data from diseases mostly affecting white matter, such as multiple sclerosis, where lesion burden and abnormal diffusivity measures correlate with cognitive performance (Rovaris *et al.*, 2002).

Microstructural abnormalities within the UF therefore could contribute to memory dysfunction in patients with TLE. Furthermore, the UF carries cholinergic fibres from the basal nucleus of Meynert, as part of a cholinergic pathway that supplies

frontal, parietal and temporal neocortices and the perisylvian division of the frontotemporal operculum, insula and superior temporal gyrus. Altered cholinergic innervation through the UF may contribute to disturbed memory functions (Selden *et al.*, 1998).

3.4.3.3 Correlations of DTI abnormalities in the UF in epilepsy

Since publication of these results (Diehl *et al.*, 2008), one further study has investigated relationships between memory and DTT and has in part replicated these findings. McDonald *et al.* (2008) found increased diffusivity of numerous fibre tracts associated with poorer verbal, but not nonverbal memory performances in TLE. These associations were strongly left-lateralised for the UF. McDonald *et al.* also investigated the parahippocampal cingulum and the inferior occipitofrontal gyrus, which also showed strong correlations with memory performance. The parahippocampal cingulum, the white matter running along the ventral aspect of the parahippocampal gyrus and connecting medial temporal lobe regions to the posterior cingulate cortex is an important part of the limbic circuit and therefore unsurprisingly related to memory function. The authors felt that the damage in the inferior fronto-occipital fasciculus may have affected memory performance through impaired attention.

In the same study, correlations between visual memory and right UF DTT was examined, but did not yield any systematic relation, contrary to the findings of this study. Aside from methodological reasons the authors also discuss that overall the relation between nonverbal memory and right temporal lobe function is known to be more tenuous than the association between verbal memory and left temporal lobe function (Vaz, 2004).

3.4.3.3 Limitations of the study

One of the shortcomings of the current study is that neuropsychological measures were available only for the patient groups and not for the controls. Therefore, it cannot be determined whether similar correlations exist between memory performance and UF diffusion measures in a healthy control population. The current study is also limited by the rather small sample size, and larger prospective studies will need to be undertaken to confirm the results. Furthermore, due to the exploratory nature of the study, no correction for Type I errors were made. However, the strong correlations in the expected direction despite small sample size are a good indicator that the correlation between memory performance and integrity of the UF is a robust finding, particularly in the dominant hemisphere. Regarding tractography, all limitations mentioned in section1.6 apply.

This chapter has shown that in left TLE, strong structure function relationships exist when investigating visual and verbal memory. In the following chapter, results of similar correlation studies between white matter connections and performance in the language domain are presented.

CHAPTER 4

CORRELATES OF LANGUAGE FUNCTION, DTI MEASURES AND TRACTOGRAPHY

4.1 INTRODUCTION: The arcuate fasciculus in TLE

The dominant temporal lobe is particularly important to language functioning, and confrontation naming tasks have been shown to be sensitive to left temporal lobe dysfunction (Busch *et al.*, 2005; Mayeux *et al.*, 1980). Successful naming performance requires integration of information from a variety of cortical sensory association areas including visual and auditory association cortex and also the basal temporal and occipital areas (Mayeux *et al.*, 1980). Dysfunction in patients with dominant TLE is likely to be related not only to dysfunction in the posterior language area, but may also be related to abnormalities throughout the entire network. As such, the language system in patients with TLE may differ from normal controls as the result of subtle structural damage to the language network, secondary to seizures or as a primary insult that resulted in seizures. We hypothesised that DTI measures are abnormal in patients with temporal lobe epilepsy and that they will correlate with language dysfunction.

4.2 METHODS

4.2.1 Participants

Thirty-six patients with medically intractable TLE (22 left, 14 right) and left hemispheric language dominance, as determined by Wada testing and/or functional MRI, were included in the study. DTI was performed during the patients' clinical imaging studies as part of their pre-surgical investigations. All patients eventually underwent anterior temporal lobectomy and were seizure-free at the

time of their most recent follow-up (range 6 months to 3 years; median 18 months).

Patients ranged in age from 25 to 58 years (M=mean; SD= standard deviation; M = 38.72, SD = 7.96) and in education from 8 to 20 years (M = 13.83, SD = 2.62). Fifty-six percent of the sample was female and 94% were Caucasian. The mean age at seizure onset was 21.03 years (SD = 12.39), and mean duration of epilepsy was 17.69 years (SD = 12.21).

Pathology showed HS in 13 patients (8 left TLE). The other 23 patients (14 left TLE) had non-specific pathology such as gliosis or microscopic cortical dysplasia.

In addition, 10 healthy controls without any history of neurological disease were included. They underwent DTI imaging as well as a volumetric T1 MRI scan. Control participants ranged in age from 26 to 52 years (M = 37.70, SD = 8.46).

4.2.2 Region of interest analysis and tractography of the AF

Fibre tracking was performed to reconstruct the AF using the FACT algorithm (Mori *et al.*, 1999) implemented within the DTI task card software (Wang, 2006), as described in the common methods section and an example in shown in figure 4.1. Tracking was terminated when a voxel with a FA lower than 0.2, or a trajectory angle (i.e. the angle between the principal eigenvectors associated with the current voxels) greater than 70° were encountered. Measures of FA and ADC were obtained for the entire reconstructed tract.

In order to gain insights into the underlying microstructural sources of the observed DTI measures, the diffusion along each of the main three directions, i.e. eigenvalues ($\lambda 1$, $\lambda 2$, $\lambda 3$) (mean ± SD) was examined in a ROI contained within the AF. This ROI was selected after reconstruction of the AF as a 20 voxel subset of the ROI used for reconstructing the AF, to only include fibres that were felt to follow the course of the AF.

Figure 4.1 Illustration of the reconstruction of the AF

Guided by the axial colour fibre orientation maps, a ROI is defined to encompass the horizontal fibres lateral to the corona radiata and medial to the cortex (A and B). C and D show the AF tracked from the ROI.
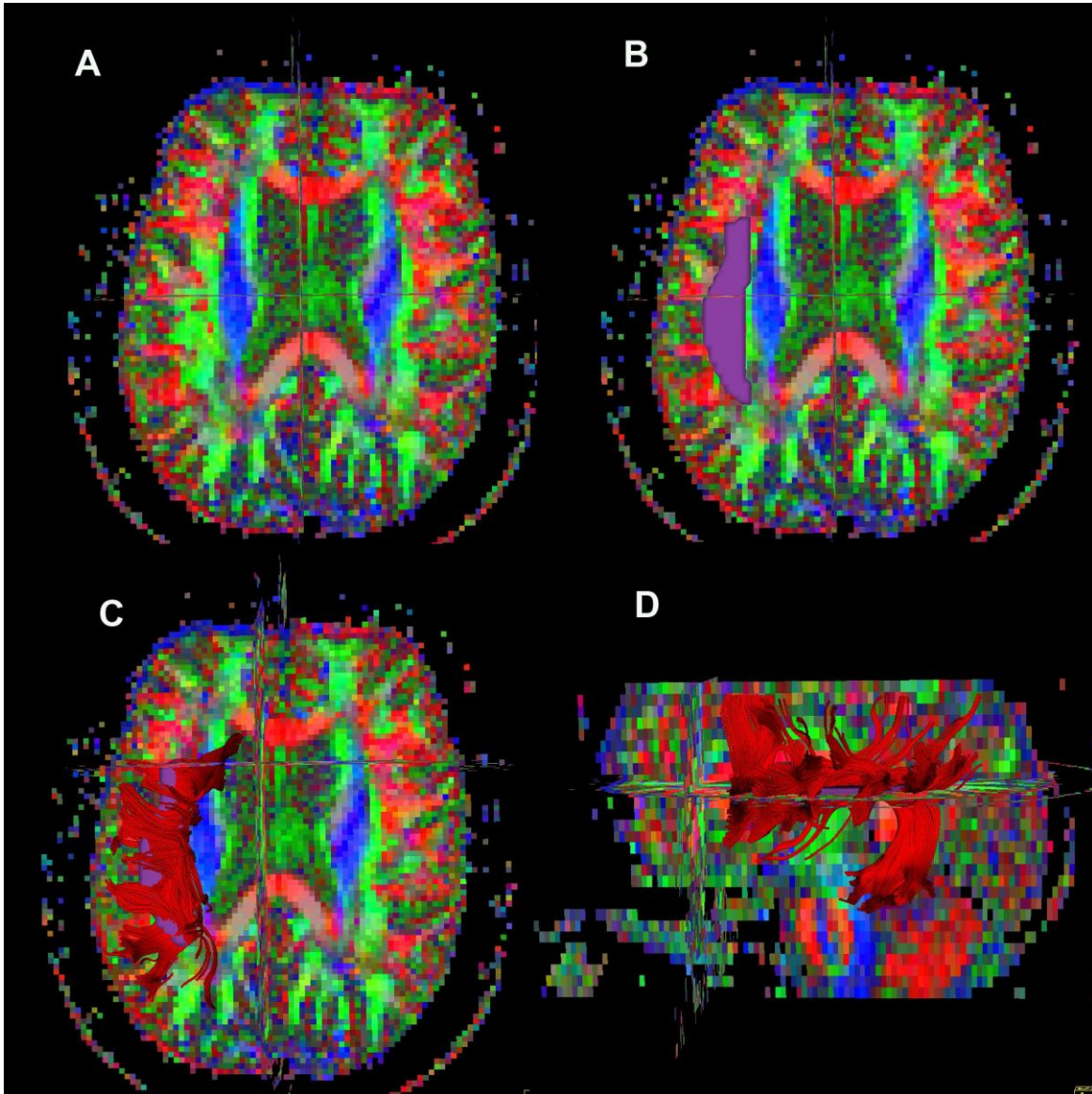
4.2.3 Neuropsychological protocol

All patients with TLE (22 left; 14 right) underwent a comprehensive neuropsychological evaluation as part of their pre-surgical investigations. The Boston Naming Test (BNT; Kaplan, Goodglass & Weintraum, 1983) and a semantic fluency (i.e. animal naming) measure were administered as part of this standard battery of tests. One patient with outlying data on these measures was excluded from the statistical analyses. A subset of patients who consented to participate in this study (10 left; 5 right) also completed selected subtests of the Multilingual Aphasia Examination – Second Edition (MAE; Benton, de Hamsher, & Siven, 1994) including Sentence Repetition and the Token Test, a measure of verbal comprehension.

4.2.4 Analyses

First, the study groups were compared on demographic and seizure variables to ensure there were no pre-existing group differences that may have confounded the results. Second, paired-sample t-tests were conducted to examine differences in FA and ADC between left and right AF among each of the three study groups. Third, an Analysis of Variance (ANOVA) was used to compare DTI values between patients with and without MTS to rule out potential pathology-related differences. Finally, Spearman correlations (two-tailed) between DTI measures (FA and ADC in the left AF tract) and language measures were examined separately for patients with left and right TLE. Only correlations with moderate to large effect sizes (i.e., $r > .30$) were interpreted (Cohen, 1988). All analyses were performed using the SPSS software package (SPSS, Chicago, IL).

4.3 RESULTS

4.3.1 Demographic analyses

There were no differences observed between the three study groups in age or sex, and there were no differences between the two TLE groups on any other demographic or seizure variables.

4.3.2 Comparisons of left and right AF among the three study groups

There were no significant differences observed in FA or ADC values between the left and right AF in any of the three study groups, although the FA was nominally higher in the left AF compared to the right in controls, left and right TLE groups (paired T test).

4.3.3 Comparison of FA and ADC values between the three study groups

Using unpaired t- tests for comparison with the control group, the following differences emerged:

In the left TLE group, FA values in the entire left and right AF tract were comparable; however ADC values were elevated bilaterally. Radial diffusivities were higher in the ROI in the left AF, but only nominally higher in the ROI of the right AF.

In the right TLE group, significantly higher ADC values and lower FA values in both the left and right AF compared to controls were observed. Radial diffusivities were elevated.

Table 4.1. FA and ADC of the AF in left and right TLE

	Controls (n=10) Mean (SD)	Left TLE (n=22) Mean (SD)	Right TLE (n=14) Mean (SD)
Left AF Tract			
FA	0.441 (0.010)	0.433 (0.017)	**0.421** (0.02)**
ADC	7.408 (0.245)	**7.616** (0.199)**	**7.667** (0.23)**
FA ROI	0.647 (0.051)	**0.594** (0.058)**	**0.569** (0.074)**
ADC ROI	6.802 (0.272)	7.026 (0.325)	7.068 (0.398)
AF ROI E1	12.568 (0.923)	12.301 (1.089)	12.032(1.094)
Radial Diffusivities ROI	3.918 (0.406)	**4.385** (0.367)**	**4.582** (0.610)**
Right AF Tract			
FA	.436 (0.010)	0.422 (0.022)	**0.418** (0.083)**
ADC	7.397(0.270)	**7.642** (0.178)*	**7.748** (0.312)*
FA ROI	0.627 (0.047)	0.602 (0.069)	**0.564** (0.061)*
ADC ROI	6.798 (0.269)	**7.076** (0.317)*	7.077 (0.404)
AF ROI E1	12.297(0.956)	12.498 (1.025)	11.995 (0.796)
Radial Diffusivities ROI	4.047 (0.419)	4.436 (0.522)	**4.630** (0.609)*

AF = arcuate fasciculus; FA = fractional anisotropy; ADC = apparent diffusion coefficient; ROI = region of interest; SD = standard deviation; E1= eigenvalue; 1. ADC, E1 and radial diffusivities all in 10^{-4} mm^2/s

$* = P < 0.05; ** = P < 0.001$ (unpaired t-test)

4.3.4 Comparison of DTI variables between TLE patients with and without MTS

Patients with MTS had comparable DTI measurements to those without any specific pathology or microscopic cortical dysplasia within the resected tissue.

4.3.5 Correlations between DTI measures and language scores in patients with epilepsy

In patients with left TLE, FA in the left AF tract was positively correlated with a semantic verbal fluency measure ($r = 0.613$), and ADC in the left AF tract was negatively correlated with measures of sentence repetition ($r = -0.532$) and verbal comprehension ($r = -0.332$, Table 4.2).

In patients with right TLE, FA in the left AF tract was positively correlated with sentence repetition ($r = 0.447$). ADC in the left AF tract was negatively correlated with measures of sentence repetition ($r = -0.671$) and verbal comprehension ($r = -0.527$) and positively correlated with semantic verbal fluency ($r = 0.469$, Table 4.2)
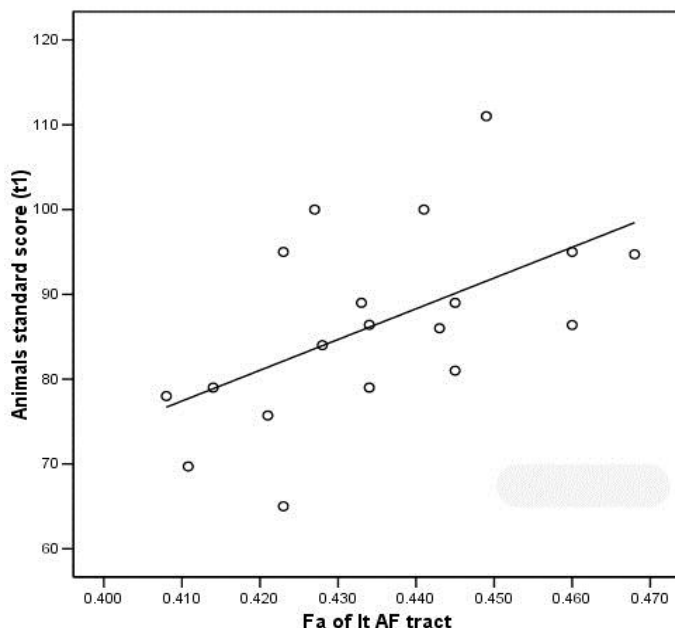
Figure 4.2 Correlation of left AF FA with semantic fluency

Table 4.2 Spearman correlations (two-tailed) between left AF values and language scores in patients with TLE

	N	FA left AF tract	ADC left tract
Left TLE			
Boston Naming Test	22	0.103	-0.188
Semantic Fluency	19	**0.613**	-0.283
Sentence Repetition	10	0.188	**-0.532**
Token Test	10	-0.271	**-0.332**
Right TLE			
Boston Naming Test	14	0.062	-0.153
Semantic Fluency	11	-0.032	**0.469**
Sentence Repetition	5	**0.447**	**-0.671**
Token Test	5	-0.053	**-0.527**

AF = arcuate fasciculus; FA = fractional anisotropy; ADC = apparent diffusion coefficient; Note: Correlations with effect sizes ≥ 0.30 are noted in bold text.

4.4 DISCUSSION

This study shows abnormal DTI measurements not only ipsilateral but also contralateral to the ictal onset in TLE patients, confirming previous observations of more widespread DTI abnormalities in temporal and extratemporal areas (Concha *et al.*, 2005; Concha *et al.*, 2007; Gross *et al.*, 2006; Yogarajah and Duncan, 2008). It has been shown recently that extratemporal changes are similar in TLE patients with and without HS white matter and only abnormalities in the fornix seem to be specific to TLE with HS (Concha *et al.*, 2009). The finding here of similar diffusion changes in the AF in patients with and without HS therefore is not surprising.

There is increasing evidence that DTI measures correlate with performance in both healthy controls and a variety of patient populations. For example, patients with Alzheimers disease show reduced FA and increased diffusivity measures (Minati *et al.*, 2007) and there was a correlation between FA values in a left temporo-parietal white matter region and reading ability and disability in children (Niogi and McCandliss, 2006). Recently we reported a correlation between abnormal DTI measures in the uncinate fasciculus of patients with TLE and memory performance (Diehl *et al.*, 2008). The current study shows that patients with left TLE have a positive correlation between FA of the AF and semantic fluency, confirming such relationships also for the language domain. The absence of such a correlation in right TLE may be due to lower patient numbers in that group.

The score from the Boston Naming Test (BNT) did not show a positive correlation in this study, whereas in another study (McDonald *et al.*, 2008) a significant correlation between BNT scores and the FA value of left AF tract in patients with TLE was demonstrated. This discrepancy may in part be due to methodological differences. The authors used the BNT and a verbal fluency test from a smaller number of left TLE patients (n=9) to correlate with FA and diffusivity based on a probablilistic diffusion tensor atlas. In our study, semantic fluency, which was not assessed by McDonald *et al.* correlated better with DTI values.

The mechanism of interictal language dysfunction in TLE is unknown, but may include seizure related neuronal loss and deafferentation in eloquent language areas. Using fMRI and PET studies, reorganisation of language function has been shown to occur at a distance from the ictal onset zone in patients with mesial TLE. This suggests that the epileptic process itself may affect functions beyond the epileptogenic zone (Thivard *et al.*, 2005). The described changes in DTI measures may be a structural marker of such dysfunction in the language network.

Such changes in diffusivity measures can be examined parallel and radial to the main axonal direction, providing *in vivo* insights into the underlying cause of decreased FA. This study found unchanged parallel diffusivity and increased perpendicular diffusivity, in keeping with findings seen in experimental models of Wallerian degeneration (Beaulieu *et al.*, 1996; Song *et al.*, 2003) and in humans that had undergone corpus callosotomy (Concha *et al.*, 2006).

This preliminary finding may indicate that diffusion measures are related to performance on language measures, and that semantic fluency may be a sensitive marker for damage to the language network, although analyses with larger sample sizes will be required to replicate this finding.

Future studies should include a language test battery more sensitive to numerous aspects of language functioning and in order to examine the relationship between these measures and DTI values. To date it is unknown if such measures may prognosticate in naming decline after temporal lobe resections.

CHAPTER 5

CORTICAL STIMULATION FOR LANGUAGE MAPPING IN FOCAL EPILEPSY: CORRELATIONS WITH TRACTOGRAPHY OF THE ARCUATE FASCICULUS

Close correlation between invasive recordings, cortical stimulation findings and tractography results may provide *in vivo* validation of DTT in humans. In this chapter, I will explore the correlation between language mapping using cortical stimulation and DTT of the AF (Diehl *et al.*, 2010a).

5.1 INTRODUCTION

Although successful mapping of the AF has been accomplished, the accuracy of the tract representation using DTI based tractography remains unknown. Very little information is available comparing such "gold standard" techniques in identifying areas of eloquent cortex with underlying tractography connectivity studies. (Duffau et al., 2003; Duffau, 2008; Duffau *et al.*, 2008;Henry *et al.*, 2004; Powell *et al.*, 2006). The goal of this study was to examine the correlation between language areas identified by pre-operative stimulation and results of tractography of the AF in candidates for epilepsy surgery. The hypothesis was that areas of language cortex identified by cortical stimulation would show strong co-localisation with areas of high subcortical connectivity via the AF, as delineated by tractography.

5.2 METHODS

5.2.1 Patients

Fourteen patients (eight female) with left hemisphere focal epilepsy and left hemisphere language dominance were studied. They all underwent invasive evaluations to localise epileptogenicity to establish surgical candidacy and to perform cortical mapping. Conventional MRI for clinical diagnostic purposes and DTI was performed prior to the invasive evaluation. Clinical information for each patient is detailed in table 5.1.

MRI acquisition and DTI post-processing were performed as described in the common methods section. In addition, the following specific methods applied to this study:

5.2.2 Tractography to reconstruct the AF

Fibre tracking was performed to reconstruct the AF using the FACT algorithm (Mori and van Zijl, 2002) implemented within the DTI task card software (Wang R, 2006).

Identification of the AF was performed using previously established methods (Catani *et al.*, 2005;Mori *et al.*, 2005). Guided by the colour fibre orientation maps, a single ROI was defined on the fractional anisotropy map to encompass the horizontal fibres lateral to the corona radiata. All fibres passing through this ROI were reconstructed in three dimensions and visualised (Figure 4.1). The AF was then saved in the "analyse" format to allow overlay onto the structural imaging and comparison with language cortex as identified by extraoperative cortical stimulation.

Table 5.1 Clinical data for all study patients

Pt #	Age/Gender	Epilepsy Syndrome	Sz semiology	Interictal	Ictal	Surgery	Pathology	MRI
1	24, M	Left neocortical TLE	Aura -> CPS	S: SW, regional left posterior temporal I: Spikes, focal left amygdala Spikes, posterior hippocampus and basal temporal Spikes, left inferior parietal	S: Regional left posterior temporal I: Focal left lateral posterior and basal temporal	Small left inferior temporal gyrus/ fusiform gyrus resection	Inflammatory changes	MRI negative, except for evidence of previous MST
2	38, M	Left mesial TLE	Aura -> CPS	S: Normal I: Spikes, focal left amygdala and anterior hippocampus	S: Regional left temporal I: Focal left amygdala and anterior hippocampus	Left temporal lobectomy	Gliosis	Normal
3	31, F	Left neocortical TLE (temporal pole)	Aura -> CPS ->motor sz	S: SW, regional left temporal I: Spikes, focal left amygdale	S: Regional left temporal I: Focal anterior lateral temporal	Tailored left temporal resection (preservation of hippocampus)	Type 1A CD (architectural disorganisation temporal pole)	MRI negative, except for prior pituitary surgery
4	27, F	Left mesial TLE	Abdominal aura-> CPS	S: Slow, regional left temporal I: Spikes, focal left mesial temporal Paroxysmal fast, focal left basal temporal	S: Regional left temporal I: Focal left mesial temporal	Left temporal lobectomy	Inflammation/ infarct/gliosis likely secondary to depth placement	Normal
5	37, F	Left temporoparietal epilepsy	Aphasic seizure –> CPS	S: SW, regional left frontotemporal I: Spikes, focal left basal temporal, left angular gyrus and anterior superior temporal gyrus	S: Regional left frontotemporal I: Regional left temporoparietal	No resection, onset not covered	None	Normal
6	41, F	Left mesial TLE	Aura -> CPS	S: Spikes, regional left mesial temporal I: Spikes, focal left hippocampus Spikes, focal anterior basal	S: Regional left temporal I: Focal left posterior hippocampus	Selective left amygdala-hippocampectomy	No pathology sent	Normal
7	21, F	Left neocortical TLE (posterior middle temporal gyrus)	Right visual aura -> right face clonic sz -> GTC	S: No abnormalities I: Spikes, left lateral temporal	S: Regional left temporo-occipital I: Focal, left middle temporal gyrus	Corticectomy left lateral temporal	Type 1A CD	Left posterior middle temporal gyrus FLAIR hyperintensity

8	44, M	Left neocortical TLE	CPS -> right face clonic sz -> GTC	S: SW, regional left temporal I: Spikes, focal basal and lateral temporal, 90% Spikes, focal mesial temporal, 10%	S: Regional left temporal I: Focal left lateral temporal	Tailored left temporal resection (preservation of hippocampus)	Inflammatory changes from invasive recordings, otherwise normal	Normal
9	48, F	Left neocortical TLE	CPS -> GTS	S: SW, regional left temporal I: Spikes, focal left superior temporal gyrus Spikes, focal, left lingual gyrus Spikes, focal, left hippocampus	S: Regional left temporal I: Focal left superior temporal gyrus	Lateral temporal resection	Non-specific inflammatory changes	Cystic encephalomalacia left supramarginal gyrus
10	29, F	Left neocortical TLE (middle temporal gyrus)	Abdominal aura -> CPS	S: SW, regional right and left temporal I: Spikes, focal anterior and post hippocampus	S: Regional left temporal I: Regional left hippocampal and lateral neocortical	Small neocortical resection	Type 1 CD	Normal
11	37, M	Left FLE (middle frontal gyrus)	Aura -> CPS	S: Normal I: Spikes, focal left middle frontal gyrus	S: Regional left fronto-central I: Focal left middle frontal gyrus	Frontal lobectomy	Type IIB CD CD with balloon cells	Superior frontal gyrus mild FLAIR signal abnormality
12	18, M	Left centro-parietal epilepsy	Aura -> bilateral asymmetric tonic sz	S: SW, Regional left parietal I : Spike, focal left lateral parietal, left mesial fronto-parietal Left lateral and mesial frontal	S: Regional, left centroparietal I: Regional left centroparietal	No surgey, as precise localisation of the ictal onset zone was not possible	None	Normal
13	22, F	Left FLE (middle frontal gyrus)	Aura -> axial tonic sz	S: Spikes, vertex I: Spikes, focal left middle frontal gyrus Spikes, regional left paracentral lobule and precuneus	S: vertex I: Left middle frontal gyrus clinical, subclinical left paracentral lobule	Resection left middle frontal gyrus	Type 1A CD Architectural disorganization	Middle frontal gyrus hyperintesnity on FLAIR
14	18, M	Left FLE (inferior frontal gyrus)	Aura->CPS	S: Spike, regional left frontal I: Spikes focal left middle frontal gyrus	S: regional left frontotemporal I: focal, inferior frontal gyrus	Resection left superior and middle frontal gyrus	Type IIA CD (dysmorphic neurons, no balloon cells)	Left insular and inferior frontal hyperintensity

S: surface EEG recording result, I: invasive EEG; TLE: temporal lobe epilepsy; FLE: frontal lobe epilepsy, CD: cortical dysplasia; MST: multiple subpial transsections; sz: seizure, CPS: complex partial seizure.

5.2.3 Electrode identification on T1 volume MRI

After implantation of the invasive electrodes, the patients had a high resolution CT scan (1 mm isotropic voxels) to visualise the electrode contacts. Using the artifact caused by the electrode on CT images, each electrode of the individual grid was manually identified, marked, and a file generated containing the coordinates of each electrode position.

The CT scan used to identify the grid position was then coregistered to the pre-operative MRI using maximisation of normalised mutual information methods (Maes F *et al.*, 1997; Studholme *et al.*, 1999). CT voxels were transformed using a linearly interpolated, six degree of freedom rigid-body matrix. The transformation matrix of this coregistration for each patient was retained and used to transform the electrode positions into the MRI space.

5.2.4 Display of the AF on individual volumetric and surface rendered MRIs

To obtain better anatomical information on the AF connectivity, FA maps were coregistered to the structural MRI used for 3D reconstruction and electrode display using the same maximisation of normalised mutual information methods. The transformation matrix of this coregistration for each patient was retained. The AF generated from the respective FA maps in the DTI task card was exported and saved as an "analyse" file, then a linear transformation was implemented to bring the AF into structural space (3D surface rendered MRI volume with electrode display, Figure 5.2). This allowed for assessment of the anatomic relationship of the reconstructed AF and the grid electrode position.

5.2.5 Display of electrode positions in the FA map and reconstruction from ROIs underlying language cortex

The information from the transformation matrix was used to localise electrode positions directly in the colourised fibre orientation map and to compare them to the location of the AF reconstructed by the anatomical ROI method. Furthermore, a ROI comprised of 3x3 voxels was drawn on the area underlying the electrode producing language disturbance on the axial FA map. Fibres arising from the defined regions were reconstructed. The resulting reconstructed fibre tract was compared to the AF tract reconstructed using the anatomical method, and its localisation relative to the electrode positions was evaluated (Figure 5.1).

5.2.6 Rating of electrode positions with respect to AF terminations

Co-localisation between the electrode location producing speech arrest and AF was then assessed using the following criteria:

Good co-localisation (electrode positions marked in green in figure 5.3, see also figures 5.2 and 5.4) was rated if the following conditions were met:

1. Less than 1 cm distance between the AF and the electrode contact that produced language disturbance during cortical stimulation (spatial resolution of the subdural grid coverage: 1cm electrode spacing).

2. Fibres reconstructed from a single ROI underlying the electrode were travelling within the confines of the AF in the perisylvian region (Fig 5.1).

Conversely, poor co-localisation was present if the distance between the electrode and AF was greater than 1 cm and tracking from an underlying ROI did not produce fibres travelling within the AF.

Figure 5.1 Reconstruction of fibre tracts from electrode positions indicating Broca's territory and the correlation with the AF

24 year old right handed patient with non-lesional neocortical left TLE (Patient 1, Table1). Axial and sagittal fractional anisotropy map, displaying markers at electrode positions B29, B30, B24 and B25 and the AF.
B24 and B29 were overlying language cortex, B25 and 30 were overlying primary motor area (face/tongue motor cortex).
Yellow: tracts reconstructed from ROI underlying electrode position B24 and 29.
Red: AF reconstructed using a single ROI as described in Catani (2005).
Fibres reconstructed from the electrode position overlying language cortex were a subset of and within the confines of the AF.
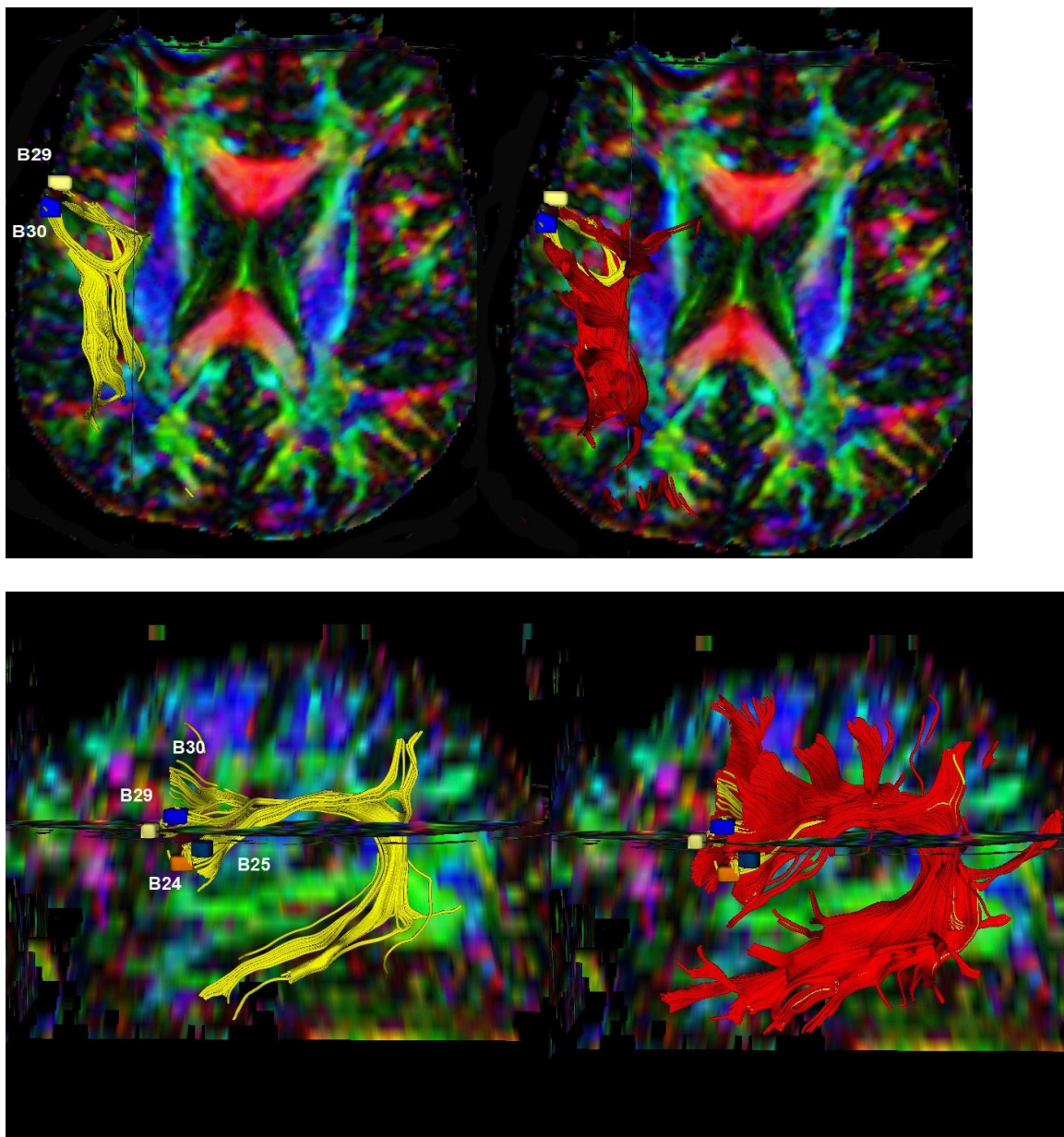
Figure 5.2: Illustration of reconstruction of the AF overlaid on the T1 volumetric scan and assessment of co-localisation between AF and electrode overlying Broca's area.

See case history for figure 5.1 (Patient 1, Table 1). A: Coronal, sagittal and axial T1 weighted image displaying electrode B29 in green in relation to the AF. B29, one of two electrodes that elicited speech arrest when stimulated (see stimulation map below), is located on pars opercularis of the inferior frontal gyrus. There is good co-localisation between subcortical connectivity (AF) with the electrode position. This patient had multiple subpial transsections surrounding the posterior language area in the past; analysis of that region was therefore excluded.
B: On the left, 3D reconstruction based on the T1 volumetric scan. The cross-hairs intersect on electrode location B29. On the right: Schematic representation of a stimulation map. To facilitate illustration, some depth electrodes inserted in the mesial temporal structures have been omitted.
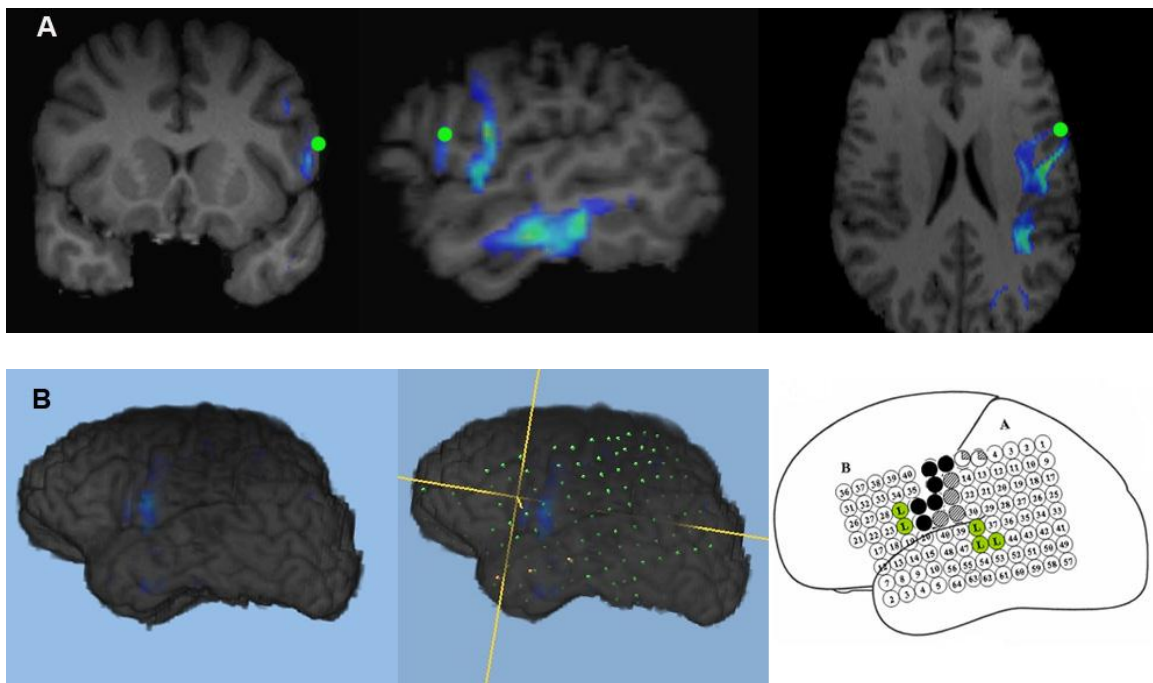
Figure 5.3 Illustration of reconstruction of the AF overlaid on the T1 volumetric scan and assessment of co-localisation between AF and electrode overlying Broca's area.

Patient 2, Table 5.1. 39 year old right handed man with non-lesional intractable left TLE. Left temporal lobe resection after subdural electrode and depth electrode evaluation confirming ictal onset in the left mesial temporal structures resulted in seizure freedom to date (>1 year). The left AF was reconstructed and coregistered with the T1 volumetric scan. The green dots highlighted by the cross-hairs intersection on the T1 image, show electrode **A23** (located on pars opercularis of the left inferior frontal gyrus) overlying language cortex. Strong subcortical connectivity is seen in the pars opercularis in close proximity to electrode A23, hence this electrode was rated as co-localising well with the AF. There is also strong connectivity to the inferior aspect of the precentral gyrus underlying electrodes marking tongue motor function (not illustrated). Electrode A24, 1 cm anterior to A23, also produced speech arrest (at higher stimulation voltage than A24). No increased subcortical connectivity was seen here when mapping the AF, hence this electrode was co-localising poorly with the AF ("blue" electrode).
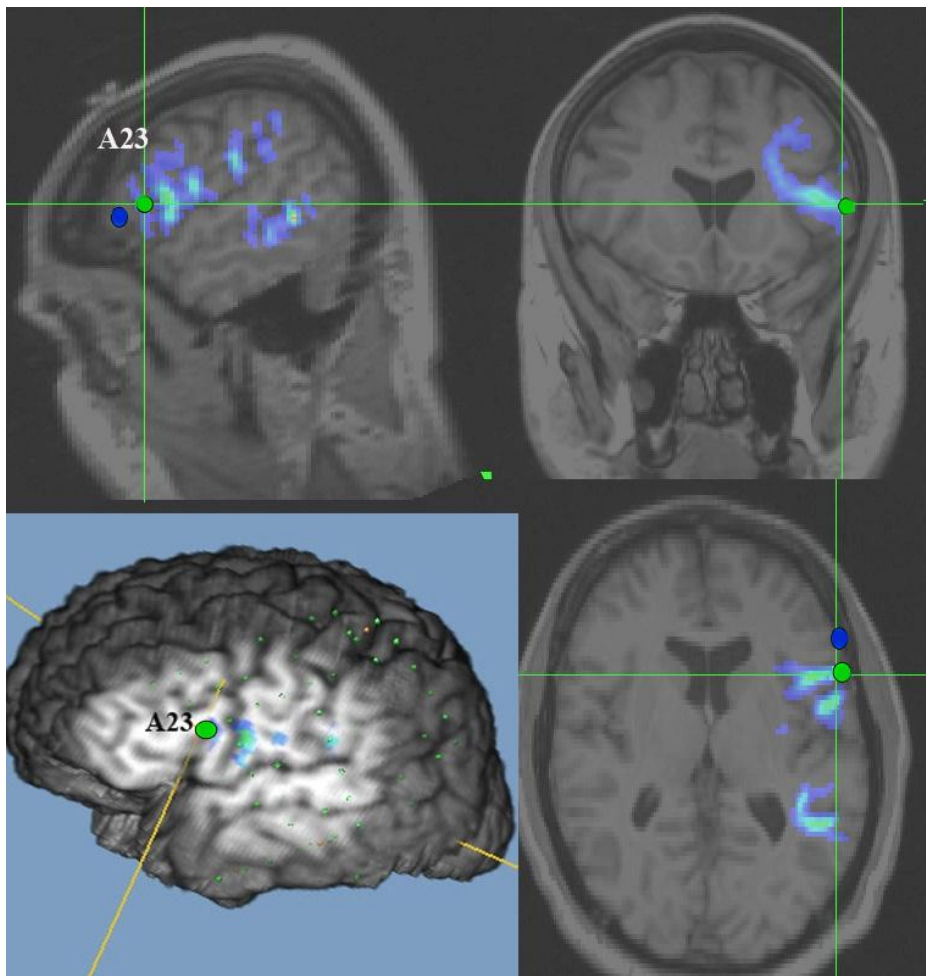
Figure 5.4 Illustration of reconstruction of the AF overlaid on the T1 volumetric scan and assessment of co-localisation between AF and electrode overlying Wernicke's area.

Axial and coronal T1, 3D reconstruction of volumetric T1 scan (Patient 10, Table 5.1): Cross-hairs highlight electrode position A41. There was good co-localisation between this electrode overlying the posterior language cortex.
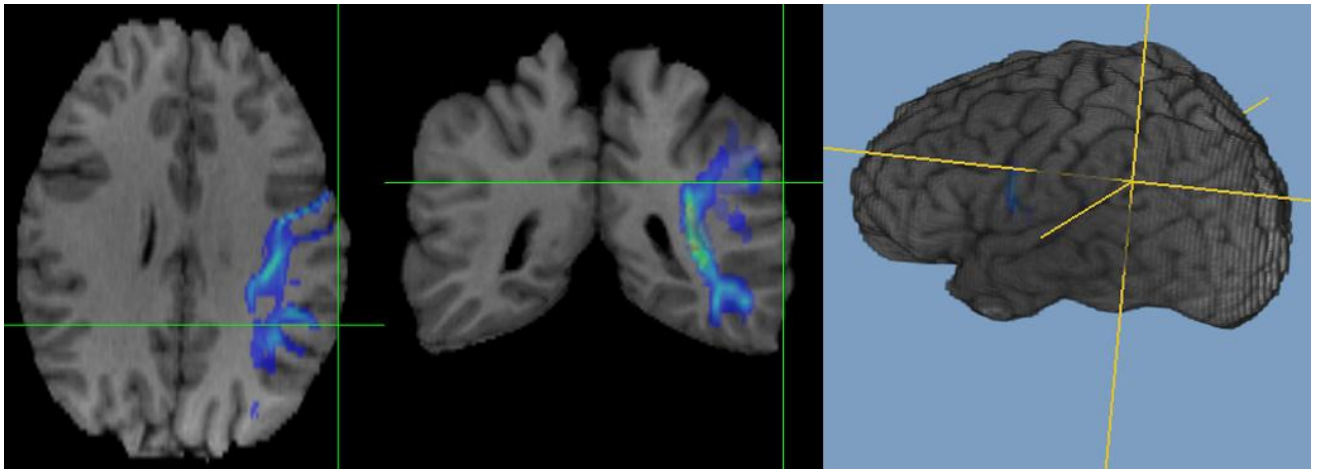
Normalization, transformation into MNI space and display on a single brain image

As all subdural grid contact locations that were overlying language cortex on a single brain were requird to be displayed, each patient's T1 MRI volumetric scan was converted with grid electrode positions into a single space, using the MNI standard brain volume and maximisation of normalised mutual information methods. The transformation matrix of each coregistration was also retained. The electrode positions that produced language dysfunction during cortical stimulation are shown in figure 5.5. They were colour-coded green if there was good co-localisation by the criteria described above. Electrodes were colour-coded blue if they had poor co-localisation with the AF.

5.2.7 Cortical electrical stimulation

Cortical stimulation was performed in all 14 patients according to the clinical question, to delineate anterior or posterior language areas, or both. Stimulation

was typically performed after all antiepileptic medications had been reintroduced. The electrical stimulus consisted of 5 to 10 second trains of 50-Hz unipolar biphasic square wave pulses of 0.3 ms duration. Stimulation was delivered using GRASS S-88 stimulation unit and two GRASS SIU-7 constant-current isolation units, Astromed, (West Warwick, RI), starting at each electrode at 1mA and titrating in increments of 1mA to a maximum stimulus intensity of 15mA, or until desired clinical response or after discharges were noted. Monitored for negative or positive motor symptoms which could interfere with speech production was also performed. The stimulus was applied to an "active" electrode, while a distant "reference electrode" in a non-eloquent region served as a non-active current sink. The active electrode was switched, electrode by electrode throughout the entire grid, thereby testing the function of the cortical region underlying each electrode in turn (Nair *et al.*, 2008). Recording during electrical stimulation was performed using a 192 channel EEG machine, Nihon Kohden (Tokyo, Japan). Spontaneous speech and reading aloud were used as screening tests, and was followed by more detailed language testing if language difficulties were noted during stimulation. In addition, such testing was also systematically performed at the highest stimulus intensity in electrode contacts overlying cortical areas usually implicated as anatomical language areas. More detailed language testing included auditory and visual naming, auditory and written comprehension, repetition and sometimes writing. In all electrodes, rapidly alternating hand and tongue motor movement were tested to exclude confusion with negative motor areas.

As detailed in table 5.2, electrode coverage was determined by the clinical question and hypothesis of the potential epileptogenic zone and presumed proximity to the eloquent cortex. Mapping was performed according to the clinical indication. Therefore, some patients had the anterior language area covered, but if the seizures were proven to arise in the temporal lobe and not frontally, no stimulation of these electrodes was undertaken.

If proximity of the language cortex to the epileptogenic zone was suspected, the respective anatomical area was implanted and covered throughout with grids. Language areas mapped could then be readily compared to the results of the tractography of the AF.

Ratings on colocalisation were only performed in areas that had adequate coverage for mapping and had been mapped.

5.3 RESULTS

AF mapping was successfully performed in all patients. Rating was performed in 10 of the 14 patients six months apart with excellent intra-rater reliability (Cronbach's alpha =0.98).

Whenever there was a less than 1 cm distance between the AF and the electrode contact that produced language disturbance during cortical stimulation, a subset of fibres following the course of the AF could be reconstructed from a ROI underlying the respective electrode location. By visual analysis, length and volume of these fibres however revealed large variability.

Grid coverage and areas stimulated varied based upon the clinical indication. Five patients had both anterior and posterior language areas identified. In one patient (Patient # 1 in Table 1), the posterior language area was excluded from analysis as the patient had previously undergone multiple subpial transsections, which is likely to interfere with the results of the tractography in that area. Only anterior language areas were identified in three patients and only posterior areas in six patients.

A total of 71 grid contacts were overlying language cortex. Nineteen contacts in eight patients were localised over Broca's area, 16 of which (84.2%) co-localised with the AF. Fifty-two contacts in ten patients were on Wernicke's area, 29 of

which (55.8%) co-localised. Co-localisation was significantly greater in anterior regions than in posterior regions [χ^2(1)=4.850, p<.05]. Figure 5.3 shows a composite map of all electrode positions that elicited language dysfunction in the patient group and includes colour-coded rating of whether or not they co-localised with the AF.

The anatomical locations for all electrode contacts eliciting language dysfunction during cortical stimulation were as follows: electrodes in the anterior language area with good co-localisation were on the precentral gyrus (n=9), pars opercularis of the inferior frontal gyrus (n=5) or pars triangularis (n=2). Of the three electrodes without good co-localisation, one was on the precentral gyrus and two on pars triangularis. Those latter two electrodes appeared the furthest anterior in location and closest to pars orbitalis of the inferior frontal gyrus.

Areas in the posterior language region showed a much more complex picture with electrodes that did and did not show co-localisation intermingled. Anatomical areas identified as posterior language areas included the supramarginal and angular gyri as well as the superior and middle temporal gyri. The vast majority of contacts were located in a cluster on the superior temporal gyrus and the supramarginal gyrus. It is of note that the most anterior electrodes on the superior temporal gyrus and the most inferior electrodes did not co-localise well with connectivity through the AF as visualised using tractography.

Figure 5.5 Composite map of all electrode positions in 14 patients overlying the language cortex.

Displayed on an MRI scan of a normal control, in MNI space. The electrode positions overlying language cortex were rated as co-localising well (green colour code) with the AF, or not localising well (blue).
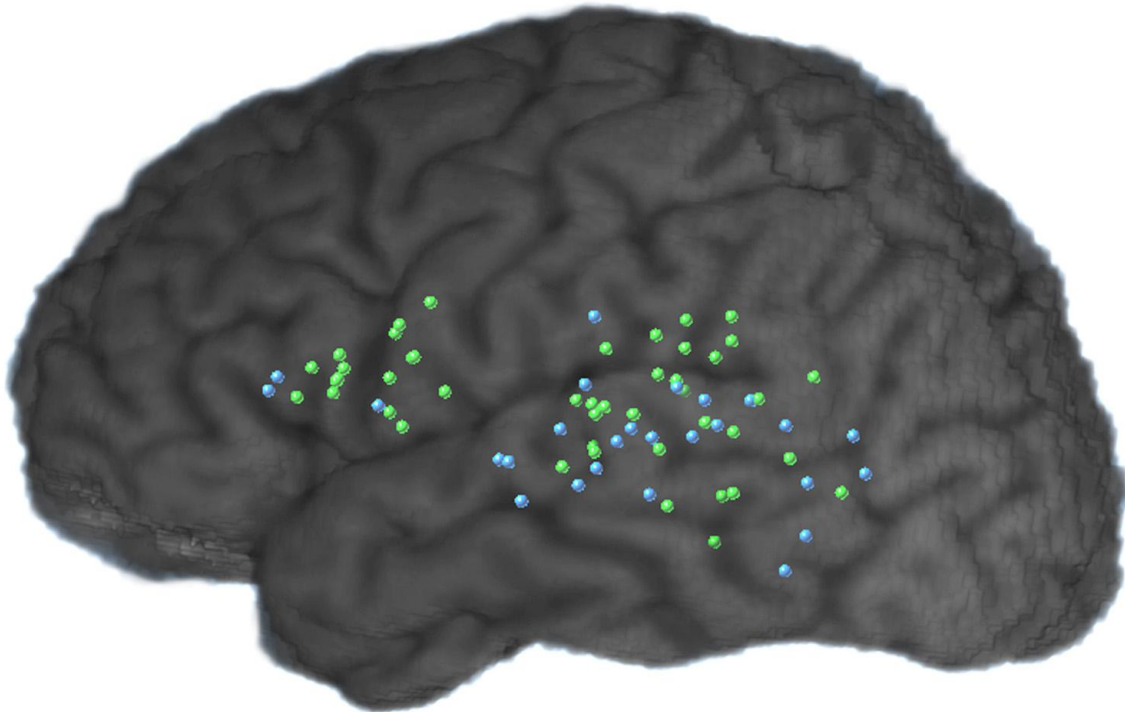
Table 5.2 Results of language mapping and tractography of the AF

Pt #	Age/ Gender	Epilepsy Syndrome	Grid placement	Full coverage of anatomical language areas stimulated (yes/no)	Electrode contact overlying language		Anatomical location	Co-localisation with AF
1*	24, M	Left neocortical TLE	A 8x8 posterior temporo-parietal B 8x5 inferior fronto-temporal C 4x4 orbitofrontal D 2x6 posterior basal temporal E 1x6 temporal pole	Broca yes Wernicke yes	B24 B29	Broca Broca	IFG, Pars opercularis PCG	Good Good
2	38, M	Left mesial TLE	A 8x8 lateral fronto-temporal B 4x4 orbitofrontal C 2x6 mid subtemporal D 2x6 lateral temporo-parietal E 1x6 anterior basal temporal LAM, LAH,LPH	Broca yes Wernicke yes	A23 A24 A33 A34 A41 A42 A50	Broca Broca Wernicke Wernicke Wernicke Wernicke Wernicke	IFG, Pars opercularis IFG, Pars triangularis SMG SMG STG STG MTG	Good Poor Good Good Poor Poor Poor
3	31, F	Left neocortical TLE (temporal pole)	A 4x11 lateral temporal B 4x4 lateral dorsal frontal C 2x4 orbitofrontal D,E,F 1x6 basal temporal LAM, LAH	Broca yes (not stimulated) Wernicke good posterior temporal coverage, no parietal coverage	A6	Wernicke	STG	Good
4	27, F	Left mesial TLE	A 8x8 lateral fronto-temporal B 4x4 orbitofrontal C 2x6 posterior inferior frontal D 1x6 temporo-polar E 1x6 mid temporobasal F 1x6 basal temporo-occipital LAM, LAH, LPH	Broca yes (not stimulated) Wernicke yes	A35 A36 A43 A44	Wernicke Wernicke Wernicke Wernicke	SMG STG STG STG	Good Good Poor Poor
5	37, F	Left temporoparietal epilepsy	A 4x9, lateral temporal B 5x8 lateral fronto-parietal C 4x4 orbitofrontal D 2x6 posterior basal temporal E 1x6 ant basal temporal LAM, LAH, LPH	Broca yes (not stimulated) Wernicke yes	A7 A8 A14 A15 A25 A4 A5	Wernicke Wernicke Wernicke Wernicke Wernicke Wernicke Wernicke	STG STG STG STG MTG STG STG	Poor Poor Good Good Poor Good Good

6	41, F	Left mesial TLE	A 8x8 lateral fronto-temporal B 4x4 orbitofrontal C and D 1x6, basal temporal LAM,LAH,LPH,RAM,RAH,RPH	Broca yes Wernicke yes	A31 Broca A32 Broca A35 Wernicke A36 Wernicke A40 Broca A41 Wernicke A42 Wernicke A43 Wernicke A44 Wenicke A45 Wernicke A49 Wernicke A50 Wernicke	IFG, Pars triangularis, IFG, Pars triangularis STG STG PCG MTG MTG MTG MTG STG ITG MTG	Good Good Good Good Poor Poor Good Poor Poor Poor Poor Good
7	21, F	Left neocortical TLE (posterior middle temporal gyrus)	A 4x11 lateral temporo-occipital B 4x6 lateral frontal C 4x6 lateral parietal D 2x6, basal temporal E 2x6 basal occipital F 1x6 anterior temporal	Broca yes Wernicke yes	B3 Broca A9 Wernicke	PCG STG	Good Good
8	44, M	Left neocortical TLE	A 4x11 lateral temporal B 4x4 orbitofrontal C 2x6 lateral frontal D 2x6 mid basal temporal E 1x6 anterior basal temporal F 1x6 posterior basal temporal LAM, LAH, LPH	Broca yes (not stimulated) Wernicke yes	A6 Wernicke A16 Wernicke A17 Wernicke A18 Wernicke	STG STG STG STG	Good Good Good Poor
9	48, F	Left neocortical TLE	A 8x8 lateral temporo-parietal B 4x6 lateral frontal C 4x4 orbitofrontal D 1x6 temporal pole E 1x6 basal temporal LAM,LAH,LPH	Broca yes (not stimulated) Wernicke yes	A36 Wernicke A37 Wernicke A38 Wernicke A43 Wernicke A44 Wernicke A45 Wernicke A46 Wernicke A50 Wernicke A51 Wernicke A52 Wernicke A53 Wernicke	SMG STG STG STG STG STG STG MTG MTG MTG MTG	Good Good Poor Poor Poor Poor Good Poor Poor Good Good

10	29, F	Left neocortical TLE (middle temporal gyrus)	A 8x8 lateral fronto-parieto-temporal B 4x4 orbitofrontal C 2x6 lateral inferior frontal D,E 2x6 basal temporal	Broca yes (not stimulated) Wernicke yes	A41 A35 A42 A50	Wernicke Wernicke Wernicke Wernicke	STG SMG STG STG	Good Poor Good Poor
11	37, M	Left FLE (middle frontal gyrus)	A 8x8 lateral fronto-parietal B 4x4 lateral frontal C 4x4 orbitofrontal	Broca yes Wernicke no	A47 A55	Broca Broca	IFG, Pars opercularis PCG	Good Good
12	18, M	Left centro-parietal epilepsy	A 8x8 lateral parietal B 5x8 lateral fronto-parietal C 4x6 lateral temporo-occipital D 4x6 mesial fronto-parietal E 2x6 mesial parieto-occipital	Broca yes Wernicke yes	B7 B18 A59 A60 A61 A62 A64 A63	Broca Broca Wernicke Wernicke Wernicke Wernicke Wernicke Wernicke	PCG PCG AG AG STG STG STG STG	Good Good Good Good Good Good Good Poor
13	22, F	Left FLE (middle frontal gyrus)	A 8x8 lateral fronto-parietal B 5x8 lateral frontal C 4x4 orbitofrontal	Broca yes Wernicke no (not stimulated)	B26 B31 B32 B33 B36 B38	Broca Broca Broca Broca Broca Broca	PCG PCG IFG, Pars opercularis IFG, Pars triangularis PCG IFG, Pars opercularis	Good Good Good Poor Good Good
14	18, M	Left FLE (inferior frontal gyrus)	SA 8x8- lateral fronto-parietal SB 4x6- lateral frontal SC 4X4-frontopolar SD 4x4- orbitofrontal SE 2x6- lateral temporal SF 2x6- basal temporal	Broca yes Wernicke no (not stimulated)	A55	Broca	PCG	Good

Grids are named by capital letters; within each grid, the electrodes are numbered (for example from 1-64 in an 8x8 contact grid, from 1-40 in a 5x8 contact grid).
AG: angular gyrus; IFG: inferior frontal gyrus, LAM: left amygdala depth, LAH: left anterior hippocampal depth, LPH: left posterior hippocampal depth, PCG: precentral gyrus;
SMG: supramarginal gyrus; STG: superior temporal gyrus; MTG: middle temporal gyrus. TLE: temporal lobe epilepsy, FLE: frontal lobe epilepsy.
- The posterior language area was mapped but not rated as the patient had multiple subpial transsections in the area.

5.4 DISCUSSION

5.4.1 The AF- from anatomical preparation to *in vivo* imaging

The AF is a large fibre pathway that connects the temporal lobe and the inferior frontal lobe, curving around the sylvian fissure. The role of the AF in connecting Broca's and Wernicke's language areas in the dominant hemisphere has been well recognised. Evidence for the importance of the AF in language processing comes from multiple sources: 1) lesion models, although these are often problematic as lesions may involve more than just the one pathway of interest (Catani and Mesulam, 2008b). 2) Evidence from surgery: It is known from past neurosurgical practice that removal of the insula and its cortico-cortical connections with language areas does not result in speech difficulties. Hence, cortico-subcortical connections need to be involved to cause a language deficit (Rasmussen T and Milner B, 1975), again highlighting the role of the AF in connecting the language areas. 3) Evidence from intra-operative mapping of the subcortical pathways using direct electrical stimulation have produced anomia when the AF has been stimulated (Duffau *et al*., 2002). For the purpose of this study it was felt that evaluating extraoperative cortical localisation of speech areas via cortical stimulation and its correlation with areas highlighted when reconstructing the AF using DTI would provide important validation of tractography results of the AF.

Only recently has it become possible to image white matter tracts *in vivo*. There has been particular interest in visualising the connections serving language function using tractography, leading to a number of important observations in control subjects and patients with epilepsy including evidence for structural asymmetry that underpins functional language hemispheric specialisation. The perisylvian language network is lateralised with greater connectivity in the left hemisphere in individuals with left hemisphere language dominance (Buchel et

al., 2004;Nucifora et al., 2005;Powell et al., 2006). Furthermore, higher fractional anisotropy values have been correlated with better performance on neuropsychological tests (Briellmann et al., 2003;Niogi and McCandliss, 2006). These findings suggest that *in vivo* visualisation of the structural pathways can provide important functional insights. Increasingly, such information on connectivity is explored to improve functional outcomes after surgery, not only by identifying cortical localisation of function but also subcortical connections.

DTI has multiple limitations including poor spatial resolution and difficulties in accurately mapping tracts in areas of the brain where multiple fibrepathways cross. Although tractography results are compared to knowledge from anatomical dissections, the accuracy of tract representation using DTI based tractography remains unknown. Therefore, particularly if tractography information is utilised to guide resective surgery, close correlations between mapping of cortical function as well as subcortical tract delineation are needed. To date very little information is available comparing such "gold standard" techniques to identify areas of eloquent cortex with underlying tractography connectivity studies. (Duffau *et al.,* 2003;Duffau, 2008;Duffau *et al.*, 2008;Henry *et al.*, 2004;Powell *et al.*, 2006).

This study utilised extraoperative cortical mapping of language areas to define the presumed cortical end points of a DT-imaged track, the AF. We found that in the anterior cortical language area as defined by cortical stimulation, there was good concordance between the cortical areas identified and the underlying connectivity via the AF. Only three of the 19 contacts were at a 1 cm or greater distance from the AF as reconstructed based on DTI.

Of those, two were located on pars triangularis of the inferior frontal gyrus. This represents 50% of all language sites stimulated on pars triangularis. Using DTI in healthy controls, it has recently been shown that the pars opercularis (Brodmann area 44) has distinct connections with the rostral inferior parietal lobule via the AF, whereas the pars triangularis (area 45) connects with the superior temporal gyrus (Frey *et al.*, 2008). We could therefore speculate that it may be more challenging

to map all fibres connecting the temporal lobe to the pars triangularis with the methods used in this study.

Such co-localisation was less frequently found in the posterior language areas. In order to assess possible reasons for inconsistent co-localisation between DTI tractography results and cortical stimulation in posterior regions, an appraisal of strengths and limitations of cortical stimulation for essential language areas is important. Furthermore, methodological limitations of tractography and the image analysis presented need to be examined.

5.4.2 Cortical stimulation of language areas

Although a variety of techniques are available to highlight areas of cortex that are involved in language processing, cortical stimulation remains the gold standard to localise essential cortical functions (Hamberger, 2007). Most non-invasive technologies, such as fMRI and PET, will activate a large network of cortical areas involved in a given language task (Vigneau *et al.*, 2006). However, it is known that not all of these areas are essential, and not all will lead to a discernable language problem after removal of the cortical area. Cortical stimulation produces a temporary functional deficit (Hamberger, 2007) and highlights essential functionally active cortex. With the exception of the motor and sensory cortices, it generates an inactivation of the underlying tissue. The precise mechanisms of such inactivation are not known; however, the neurophysiological effects of cortical stimulation have been explored and recently reviewed in detail (Nair *et al.*, 2008). For years prior to the introduction of cortical stimulation, operations in the dominant hemisphere were only carried out if the involved regions were far anterior in the frontal lobe or far posterior in the occipital lobe for fear of causing aphasia (Hamberger, 2007;Penfield W, 1959). With the introduction of cortical stimulation into epilepsy surgery, this practice has changed.

Anterior and posterior language areas as found in this study are well within the range of previously published data. The language areas as defined by cortical stimulation have been summarised in detail by Rasmussen and Milner (Rasmussen T and Milner B, 1975). Dysphasic speech arrest in the frontal lobe of the dominant hemisphere is elicited from one or both of the frontal opercular convolutions. The temporal speech areas are located from the second temporal gyrus behind the level of the postcentral sulcus and extend posteriorly 2-3 cm, behind the transverse gyri of Heschl. Speech arrest is seen in "comparable numbers" with stimulation of the first temporal gyrus extending in the parieto temporo opercular region (Rasmussen T and Milner B, 1975). The "parietal speech zone" resides in the parietal opercular region. The anterior limit is the postcentral sulcus, the superior limit 1-4 cm above the sylvian fissure, the posterior limit from 2-4 cm behind the postcentral sulcus, and the inferior limit is continuous with the posterior portion of the temporal speech area.

Since 1975, multiple studies in various patient populations have described the localisation of language function as elicited by intra-operative cortical stimulation. In a recent large study on patients undergoing glioma resection, all language sites based on intra-operative stimulation were compiled, showing tremendous variability between patients (Sanai *et al.*, 2008). Equally, in patients with TLE, a high degree of variability in language representation as defined by cortical stimulation particularly in the temporal lobe in Wernicke's area was described (Ojemann et al., 2008;Ojemann and Whitaker, 1978;Van Buren et al., 1978). Hence, it is very important to ascertain that no essential language cortex is removed, particularly if larger temporal neocortical resections are planned to optimise chances of seizure freedom.

Stimulation procedures are not well standardised across centres. The stimulation in this study was performed using a single electrode contact as the active electrode, while a distant reference electrode in a non-eloquent region served as a current sink (Nair *et al.*, 2008). Hence, the stimulation was confined to a small

area of cortex, and the adjacent areas were carefully assessed for afterdischarges. These methods have been practiced at our institution for many years and are described elsewhere (Luders et al., 1986;Nair et al., 2008). In brief, a screening task involving higher linguistic functions (reading) was used; if language difficulties were noted at an electrode position, further detailed testing including naming was performed. Negative motor phenomena and interference with consciousness were routinely assessed to ascertain that only language-specific performance was affected by the stimulation. Thus, there is a high certainty that the cortex identified was involved in language processing.

The reading test effectively screens for language sites, also in the posterior language area. Stimulation of the posterior language area is known to not only affect comprehension but to also elicit speech arrest (Lesser *et al.*, 1986). This is in contrast to the fluent aphasia with comprehension problems seen in lesions affecting this cortical area. After prolonged trains of cortical stimulation however, some fluency recurs and comprehension remains problematic. This may in part be due to habituation as the brain begins to utilize alternative language areas and pathways (Lesser *et al.*, 1986). It does highlight that cortical stimulation in an area may not elicit the same symptoms during deactivation procedures than when affected by a lesion. Hence task selection should not have adversely affected the cortical localisation in Wernicke's area in this study.

However, language testing is necessarily basic as it needs to unveil disturbances during a 5s stimulation period, which may make identification of higher cognitive language functions difficult. This represents an obvious limitation of cortical stimulation methods to identify eloquent language cortex.

5.4.3 The AF as delineated using tractography

Detailed studies in healthy controls have shown that it is possible to reconstruct the AF in all individuals (Catani et al., 2005;Catani and Thiebaut, 2008).

However, there is significant variability in the shape and volume of the fasciculus, which has been demonstrated using both a ROI driven deterministic approach, and probabilistic methods (Catani et al., 2005;Powell et al., 2006).

Efforts were made to understand the structure function relationship between DTI and other imaging modalities informative about language function. fMRI has been successfully implemented to lateralise language functions in patients with epilepsy (Adcock et al., 2003;Thivard et al., 2005;Woermann et al., 2003). When fMRI and tractography are combined, it has been shown that a left lateralised pattern with language fMRI was associated with left lateralisation of white matter organisation (Powell *et al.*, 2007). In patients with left temporal lobe epilepsy and language reorganisation with greater right sided activation, loss of structural asymmetry of the white matter was observed.

Tractography studies have shown that the anatomy is more complex than initially assumed. A single ROI approach has been used to delineate the entire extent of the AF. Further dissection of this pathway has highlighted a direct long pathway connecting Broca and Wernicke's areas. In addition, shorter connections are located more laterally: One anterior segment connects Broca's area with the inferior parietal lobule, and a more posterior segment connects the parietal lobule with Wernicke's area (Catani et al., 2005;Catani and Mesulam, 2008a). Furthermore, the extent of connectivity of the AF was documented to involve areas outside the traditional Broca and Wernicke areas. Connections of the AF into the middle frontal gyrus and precentral gyrus, as well as the middle temporal gyrus, have also been documented using DTI. Such areas are in keeping with areas of phonemic and semantic processing demonstrated using fMRI (Demonet et al., 2005;Glasser and Rilling, 2008;Price, 2000;Vigneau et al., 2006).

In this study language sites in the precentral gyrus, premotor areas and the middle temporal gyrus were noted. Most of those co-localised with subcortical

connectivity via the AF. This provides some validation that such areas are also connected via the AF.

5.4.4 The perisylvian language network: white matter connectivity and language processing

Although traditionally the AF has been implicated in connecting the cortical language areas, there is evidence that other areas of cortex must also be connected for successful performance of linguistic tasks.

Much interest has been developed in integrating not only the cortical language sites into a model, but also taking into account its mutual connectivity and possible parallel processing of different streams (Hickok and Poeppel, 2007). An integrated view of the cortical localisation and the subcortical connectivity has been suggested. Such a view based on the interrelationship between parallel distributed networks has been proposed (Catani, 2007;Catani and ffytche, 2005;Duffau, 2008) where hodology refers to the pattern of white matter connections between cortical areas. Language is a complex cognitive task, and some aspects of it include phonemes (the basic sounds that make up words), lexical-semantics (the concepts and meanings of words and the vocabulary of words associated with these meanings), and prosody (the modification of the pronunciation of speech to convey additional meaning). Successful performance for all these tasks requires interplay of several cortical areas. There is evidence that certain cortical areas are more involved in specific aspects of language processing. For example, lexical semantic processing fMRI tasks have highlighted areas in the middle temporal gyrus (Brodmann Area (BA) 21 and 37) in conjunction with Broca's area and frontal areas more anterior and superior to it (BA 44, parts of 6, 9 and 45) (Binder, 1997;Glasser and Rilling, 2008;Hickok and Poeppel, 2004;Price, 2000). Phonologic processing has two aspects: receptive processing of phonemes in Wernicke's area (posterior BA 22) and BA 40 and

expressive production of phonemes during speech in posterior Broca's area (BAs 44 and 6). It is therefore possible that some of these processing streams may be subserved by different white matter bundles.

5.4.5 Technical considerations and methodological limitations

Spatial resolution of DTI and noise are significant problems, and various acquisitions and postprocessing analysis techniques have been proposed (Mori and van Zijl, 2002).

Voxel sizes are much larger than the resolution needed to image single axons. Hence, DTI studies will only be able to display an approximation of the main tract direction, and do not have a resolution even close to a cellular level. In this study, a voxel size of approximately 1.9x1.9x3 mm was used. Such a resolution, although not ideal, allows for total brain coverage in a short scanning period, which is important for patients often unable to lie still for a prolonged period. Our patients had the DTI protocol added to their routine clinical MRI scans; the additional 8 minutes, although acceptable, increased the total scan duration, including positioning, to about 35-40 min. Furthermore, in every voxel the main direction of water diffusion is used for tract reconstruction. Hence, crossing fibres will not be represented, and only the main tracts and its main direction will be displayed.

Deterministic tractography algorithms, such as that used for this study, are particularly prone to this problem, whereas probabilistic approaches are considered more robust in that respect. However, in another study, results of probabilistic and deterministic tractography were compared, and locations of tract terminations were very similar in both (Glasser and Rilling, 2008). We certainly cannot exclude that some of the lack of convergence of tractography and cortical stimulation results is due to methodological shortcomings.

Another source of error lies in the need for coregistration of various imaging modalities and using linear transformations for various registrations. Also, EPI images suffer from some inherent distortions, introducing another source of uncertainty. DTI images are coregistered with the T1-weighted MRI scan, and the AF reconstructed in the DTI space is overlaid on the T1 volume using the same transformation parameters as in the coregistration. Co-localisation of tract and language cortex/electrode positions was assessed both on the T1 volumetric scan and also in the original DTI space with identical results, thus illustrating its robustness, with excellent intra-rater reliability. Ratings were performed in individual patients, thus eliminating the need for normalisation at this stage. Finally, when displaying electrode locations marking language cortex, great care was taken to visually ascertain that anatomical locations of language cortex identified in each individual patient was transposed correctly into the common space.

5.4.6 Outlook

As DTI based tractography is increasingly integrated in pre-operative planning, there is a need for clinicians and neurosurgeons to develop improved understanding of limitations of the technology. It appears that in various areas of the brain, tractography may be more or less reliable in visualising connectivity. Hence, maps of probability for accurate delineation may be helpful, to highlight areas that may be difficult to accurately represent using such technology. Such an approach may be limited by the variability in acquisition and tract reconstruction and analysis between centers, but it can still provide valuable information.

This study has provided some additional validation that the AF, as reconstructed using DTI, connects cortical language areas in individual patients. This study found that there is tighter co-localisation between language sites in the frontal lobe compared to temporoparietal language sites. This may be a combination of

technical limitations and greater anatomical variability in the posterior language area. Future research needs to integrate the DTI based tractography and cortical localisation procedures that define eloquent cortex and dictate extent of resection.

Since this study was conceptualised and published, one other investigation has been published, evaluating AF and intraoperative cortical stimulation for language in a mixed group of 10 patients, the majority suffering from tumours (Ellmore *et al.*, 2009). Nine of the ten patients underwent left hemispheric cortical stimulation intraoperatively. The sites identified were compared to the AF reconstructed using a streamline tractography algorithm and a 2 voxel of interest approach. One voxel was placed in the Broca area and the second in a small area of white matter superior to the insula. Proximity between the tracts and the language site defined by cortical stimulation was assessed visually but also using a statistical bootstrap method. 79% of 102 essential language sites were closely related to the AF. Of all such essential language sites, 59% were located within 7.5 mm of AF fibre pathway terminations, and another 20% contained pathways terminating closer to the AF than would be expected by chance ($P < 0.05$). The authors therefore came to the same conclusion as in this study that the majority of the cortical sites essential for both expressive and receptive aspects of language are closely related to the AF. The authors also highlighted that this finding also implies that DTT could be used to predict language sites based entirely on their close spatial relationship to AF terminations. The authors did not evaluate anterior and posterior language sites separately.

In conclusion, DTT of the AF has great potential to inform neurosurgeons and contribute to preservation of essential language sites and their connections during surgery.

CHAPTER 6

ICTAL ONSET AND PROPAGATION: INSIGHT GAINED USING DTI AND TRACTOGRAPHY ON CASE STUDIES OF CORTICAL DYSPLASIA

6.1 DTI IN PATIENTS WITH FOCAL EPILEPSY DUE TO CORTICAL DYSPLASIA IN THE TEMPORO-OCCIPITAL REGION: Electro-clinico-pathological correlations

6.1.1 INTRODUCTION

Cortical dysplasia is often located in the neocortex and in extratemporal locations or the temporo-occipital junction. The resection of epileptogenic foci in the temporo-occipital junction is complicated by the proximity of the geniculo-calcarine radiations, carrying a risk of visual field deficits. Little data on surgery outcomes involving this brain region are available. The goal of this study was to assess the utility of DTI in describing white matter changes associated with pathology proven CD in the temporo-occipital region and to correlate the findings with ictal onset, seizure propagation and outcome after surgery.

Three patients suffering from focal CD are described together in section 6.1. Section 6.2 is a case report of a patient with polymicrogyria and heterotopic gray matter in the right posterior quadrant.

6.1.2 METHODS

The study was approved by the Institutional Review Board and written informed consent was obtained from all subjects prior to scanning. Three patients (two female) with pathologically proven focal CD in the temporo-occipital region were included in the study and underwent conventional MRI and DTI prior to implantation of subdural grids and epilepsy surgery.

6.1.2.1 Image analysis

Data was transferred to a PC workstation and DTI task card software (Massachusetts General Hospital, https://www.nmr.mgh.harvard.edu) was used to generate parametric maps for FA and apparent diffusion coefficient (ADC, in 10^{-4} mm^2/s). A neuroradiologist (PR) blinded to the clinical data and conventional MRIs reviewed the FA maps and visually assessed symmetry between the hemispheres and location, and relative size and morphology of the individual tracts.

Fibre tracking was performed on patients 2 and 3 using the FACT algorithm (Mori *et al.*, 1999; Stieltjes *et al.*, 2001) implemented within the DTI task card software. The algorithm generates fibre tracts by iteratively following the direction of the principle eigenvector at each adjacent voxel starting from a user defined ROI. Tracking propagates on the basis of the orientation of the eigenvector that is associated with the largest eigenvalue for that voxel. Tracking is terminated when a voxel with a FA lower than or a trajectory angle (i.e. the angle between the principal eigenvectors associated with the current voxels) greater than a user defined threshold is encountered. In this study, a FA and trajectory angle threshold of 0.2 and 50° respectively, were used.

Tractography was performed to improve visualisation of tracts in the vicinity of the lesion. In particular, the superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior and superior frontooccipital fasciculus were reconstructed by placing a ROI on the axial colourised FA map in a location encompassing the respective fibres. Identification of the tracks was guided by published data (Mori *et al.*, 2005). Tracts were visually analysed on the FA maps and the tractography images with particular attention to the subcortical connectivity ipsilateral and contralateral to the ictal onset zone. Additional evaluation criteria included tract volume (number of voxels and fibres per tract) and qualitative visual assessment of tract displacement, relative size and morphology.

6.1.2.2 ROI analysis and tractography from regions of ictal onset

A high resolution CT scan was obtained after the patients were implanted with subdural grid electrodes. DTI images and CT were co-registered with the 3D MP-RAGE MRI images using the Maximization of Mutual Information algorithm (Maes *et al.*, 1999) and were trilinearly resampled to match the MRIs resolution. The coregistration process did not require the use of external fiduciary markers or pre-processing of the image data.

Electrode artifact on CT allowed for the electrode positions to be visually identified. ROIs were placed, and included grey and white matter, in anatomical areas underlying the electrode of ictal onset and in the contralateral homologous anatomical region. The size of the ipsi- and contralateral ROIs selected within each patient was the same. The mean diffusivity and fractional anisotropy was computed for each ROI. The mean of three trials of ROI placement was calculated and compared ipsi and contralateral in each individual using U test statistics. The same ROIs were also used as seed points for the tractography.

Tractography results were analysed visually. Additionally, the numbers of fibres tracked from the ROIs underlying the electrodes of ictal onset including total number of voxels per track were computed and the average of three trials was reported for each measure. A paired U test was used to compare the ROI diffusivity and anisotropy values and the tract metrics reconstructed from the ROI overlying ictal onset and from the contralateral homologous ROI.

6.1.2.3 Pathological characteristics and classification of resected tissue

Tissue resected from all patients was saved in formalin and paraffin fixed before sectioning and pathological examination by a board certified clinical neuropathologist. All patients had pathological changes consistent with focal CD.

For the purpose of this study, I will refer to the classification as proposed by Palmini *et al.*: type 1A : cortical architectural abnormalities; type 1B: architectural abnormalities with giant cells (meganeurons) but no dysmorphic neurons; type 2A: dysmorphic neurons in the setting of architectural disorganization with dysmorphic neurons but without balloon cells and type 2B: architectural abnormalities with dysmorphic neurons, with balloon cells (Najm *et al.*, 2007; Palmini *et al.*, 2004).

6.1.3 RESULTS

6.1.3.1 Case descriptions

Detailed clinical descriptions are shown in table 6.1. All patients had pathology proven CD and typical findings on conventional MRI (Table 6.1 and Figure 6.1 A,B, and Figure 6.2C). Two patients revealed type 2B CD (patients 1 and 2) in the right lateral occipital cortex and one patient had type 1A CD (patient 3) in the left temporooccipital region, however the imaging findings of patient 3 revealed FLAIR hyperintensity in a small area at the bottom of the left MTS indicative of possible focal CD with balloon cells (type 2B).

6.1.3.2 Visual analysis of the FA maps and tractography

In patients 1 and 2, both with type 2B cortical dysplasia, there was a displacement of the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and the optic radiation mesially and thinning compared to the contralateral side. There was also a noticeable reduction of the subcortical fibres in the areas of the cortical thickening (Figure 6.1D and Figure 6.2A and C). These findings are highlighted using tractography in patient 2 (Figure 6.2B).

Table 6.1 Clinical characteristics of study patients

	Patient 1	Patient 2	Patient 3
Age at surgery	42 M	45 F	21 F
Age at onset	13 years	3 years	16 years
Epilepsy risk factors	Closed head trauma age 13 years, loss of awareness for minutes	None	Uncomplicated febrile seizures age 9 months to 4 years
Seizure semiology	Visual aura (illusion) - psychic aura (anxiety)- complex partial seizure Frequency : two per day	Left visual aura (flashing lights)- complex partial seizure. Frequency: several a week	Visual aura (right inferior visual field)- complex partial seizure Psychic aura-aphasic seizure Frequency: 2-3 per week
Scalp EEG	Interictal: spikes, regional right temporo-occipital Ictal: regional right temporooccipital	Interictal: SW, regional right occipital (max O2) Ictal: non-localisable	Interictal: normal Ictal : regional left temporo-parietooccipital
Invasive EEG	Interictal: spikes focal, right lateral occipital. Ictal: focal, lateral and inferior aspects of the right occipital lobe (inferior to lesion)	Interictal: spikes, focal, right lateral occipital and paroxysmal fast Ictal: focal, right lateral occipital (superior to lesion)	Interictal: spikes, focal left posterior middle temporal gyrus Ictal: focal, left posterior temporal
Pathology	Type 2B CD	Type 2B CD	Type 1A CD*
Seizure outcome	Seizure free x 5 years	Seizure free x 4 years	Total of 2 seizures shortly after surgery, thereafter none for over two years
Functional outcome	Pre-operative visual field intact Post-operative visual field intact	Objective visual fields attempted but unable to accomplish. Pre-operative left field defect, post-operative probably left hemianopia	Pre-operative full visual fields. Post-operative no visual field or language deficit.
PET	Right occipital hypometabolism	Right occipital hypometabolism	Left posterior temporal hypometabolism
Ictal SPECT	Not done	Right temporooccipital hyperperfusion, anterior to lesion.	Not done
Language lateralisation	Not done	WADA: Bilateral dependent speech, bilateral memory	FMRI: left hemisphere language dominance
MRI	Thickening right lateral occipital cortex; FLAIR hyperintensity	Thickening right lateral occipital cortex; FLAIR hyperintensity involving the lateral and infracalcarine cortex	FLAIR hyperintensity on the bottom of the left middle temoporal sulcus*

F=female; M=male; WADA: intracarotid amobarbital procedure; CD=cortical dysplasia;
FLAIR = fluid attenuated inversion recovery, SW = sharp wave.
* Pathology compatible with type 1 CD, however imaging findings indicative of the bottom of the sulcus focal cortical dysplasia with balloon cells (type 2 B).

On the normal contralateral side, the fibres reached the gyri with a branching pattern. Patient 3 showed minimally reduced subcortical connectivity in the area underlying the abnormal cortex. Mild thinning of the AF and the IFOF was noted on the colourised fibre orientation map (Figure 6.4C).

6.1.3.3 Pathological, electrocorticographic and tractography correlations

Patient 1: Invasive EEG revealed ictal onset on the lateral and inferior aspects of the right occipital lobe, at the borders of the area of cortical thickening and FLAIR hyperintensity was detected by MRI (sparing the primary visual cortex, figure 6.1). The ictal EEG remained localised for the first 5s to the electrodes that were immediately adjacent and contiguous along the inferior margins of the plate. Spread to the mesial occipital regions was observed within the next 5-10 seconds.

Patient 2: The region of ictal onset was located in the superior margin of the MRI-identified lesion. The ictal spread patterns within the first 5 seconds after onset remained confined to the contiguous electrodes along the superior margins of the dysplasia (Figure 6.3A). Within the next 5-20s, ictal propagation was seen to the basal occipital, mesial parietal and anterior temporal regions. In this patient, reduced subcortical connections were visible at the site of the dysplastic lesion compared to the contralateral side (Figure 6.2); in addition, fewer and shorter fibres were reconstructed from the ictal onset zone compared to the contralateral homologous area (Figure 6.3B and Table 6.2). Measures of diffusivity and anisotropy in the ROIs underlying the electrodes of ictal onset did not show any differences between the area of ictal onset and the contralateral homologous area.

Patient 3: Focal ictal onset was seen in the posterior segment of the middle temporal gyrus, adjacent to the area of signal hyperintensity on FLAIR, which was noted in the depth of the sulcus (Figure 6.4A); spread occurred at about 5s after

ictal onset to the adjacent electrodes superior and inferior to the lesion, as well as to basal temporal electrodes. The *in situ* electrical sampling did not include direct recordings of the depth of the sulcus (where the MRI identified abnormality was mainly localised). However, the fact that the ictal onset region remained localised in a small cortical region could be more consistent with an adjacent more superficial neocortical ictal onset (rather than a spread pattern).

Reconstruction of the tract generated from the ROI underlying the two electrodes of ictal onset revealed fewer fibres (Figure 6.4B). The FA was lower in the ROI underlying the electrode of ictal onset compared to the contralateral homologous area (Table 6.2).

In conclusion, in the three patients with CD, ictal onsets were focal, involving only two grid electrodes at onset that were located over the cortical region bordering the MRI-identified lesion in the lateral occipital or temporooccipital cortex. This focal ictal activity was sustained over an extended period of time (in the order of 5s), without significant spread and involving electrodes adjacent to the ictal onset. This spread pattern was referred to as slow contiguous spread. Reconstructing fibres from a ROI underlying the ictal onset revealed poor subcortical connectivity via large white matter tracts.

Figure 6.1 Patient with a right occipital CD (type 2B). T1 and FLAIR before surgery, T1 post-resection. Colourised fibre anisotropy map

Patient 1, table 6.1
A: Axial T1 weighted and B: FLAIR images illustrating right occipital Type IIB CD with cortical thickening and FLAIR signal increase. C: Post-resection axial T1 image.
D: Axial colourised fibre orientation map showing displacement of the right inferior longitudinal fasciculus, inferior frontooccipital fasciculus and optic radiation (sagittal stratum). There is also reduction of the subcortical connectivity in the right posterior inferior quadrant.
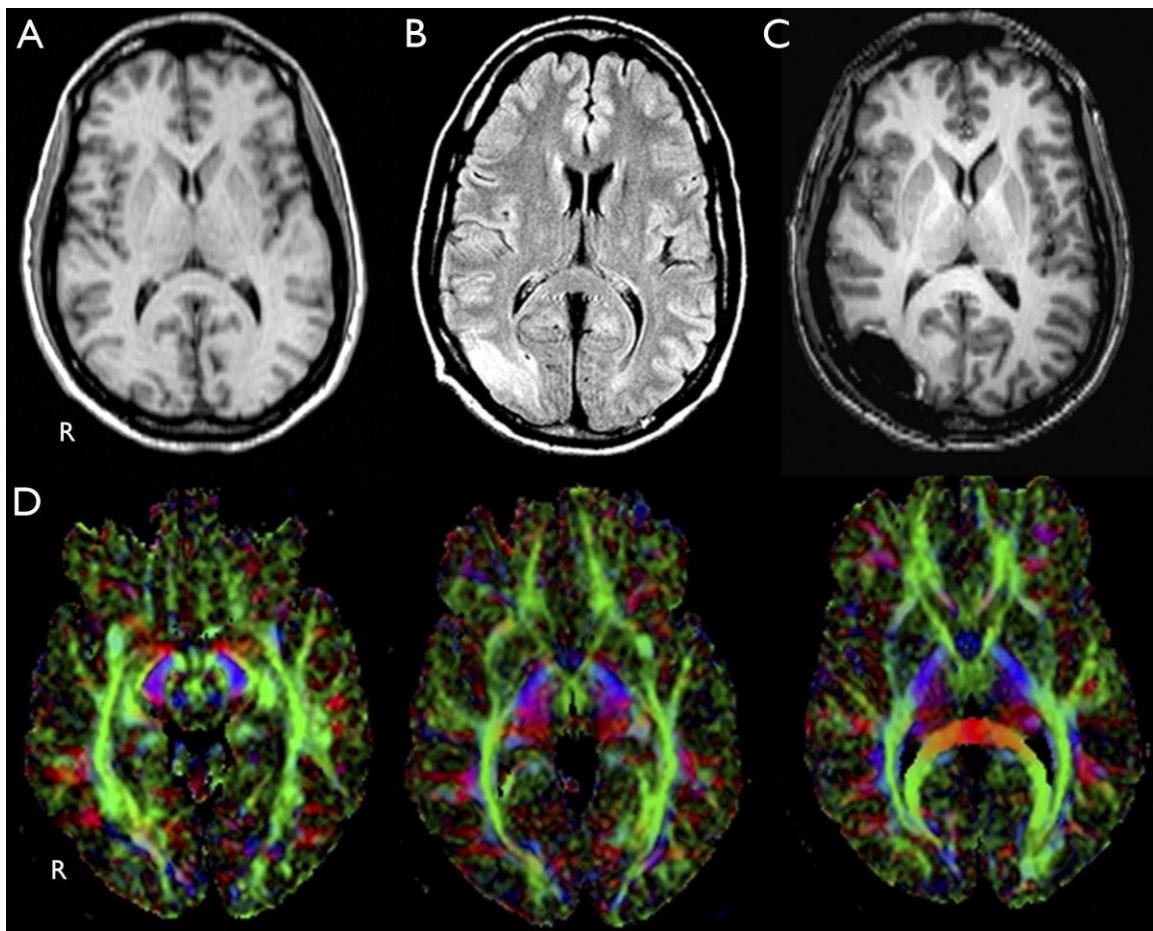
Figure 6.2 Patient with a right occipital CD (type 2B). Reconstruction of tracts surrounding the lesion and contralateral tracts. Overlay with T1 images.

Patient 2,table 6.1

A: Axial colourised fibre orientation map showing displacement of the right inferior longitudinal fasciculus, inferior frontooccipital fasciculus and sagittal stratum. There is also reduction of the subcortical connectivity in the right inferior posterior quadrant.

B: Three dimensional display of tractography ipsilateral to the lesion (red) and contralateral to the lesion (yellow) highlights the reduced subcortical connectivity in the right posterior quadrant.

C: Two dimensional illustrations of the tractography results coregistered with the T1 image. The area demonstrating cortical thickening did not show fibre connections between deep white matter and dysplastic cortex. On the contralateral side, longitudinal fibres reached each gyrus with a branching pattern.
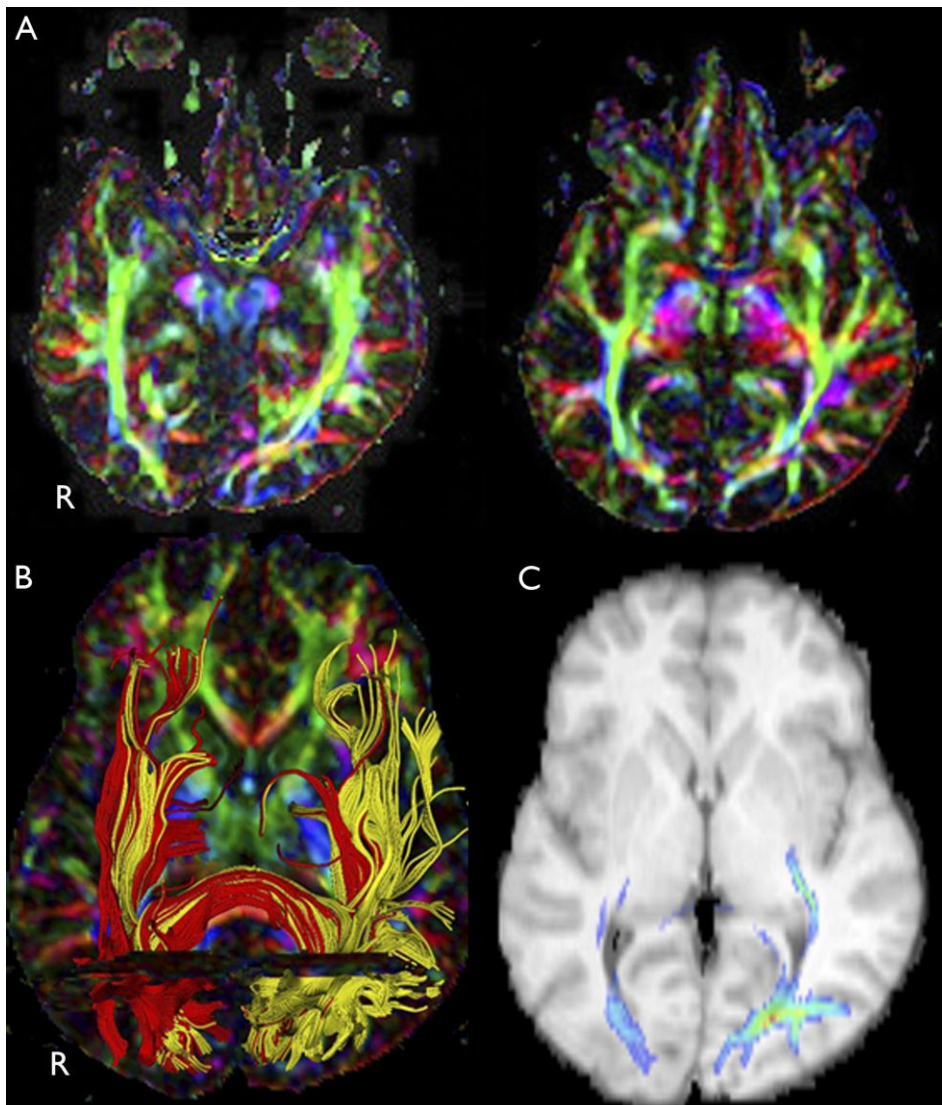
Figure 6.3 Patient with right occipital CD (type 2B) . Ictal onset zone and spread as delineated with invasive recordings and tractography from area of ictal onset.

Patient 2, table 6.1
A: 3 D reconstruction with display of grid electrodes. Area of FLAIR signal change is highlighted in blue. Ictal onset (black solid circle) and spread are highlighted on the respective electrode positions.
B: Axial FA map with display of fibres (in red) reconstructed from a small ROI underlying the electrode A44 (ictal onset; small circle on right image). The yellow fibres were reconstructed from a same size ROI in the contralateral homologous region. Please note that the fibres reconstructed from the ictal onset ROI are shorter compared to the contralateral homologous counterparts.

Figure 6.4 Patient with left temporooccipital CD. Ictal onset zone and spread as delineated with invasive recordings and tractography from area of ictal onset

Patient 3, table 6.1

A: 3 D reconstruction with display of grid electrodes. Area of FLAIR signal change is highlighted in blue. Ictal onset (black solid circle) and spread are highlighted on the respective electrode positions. Invasive EEG recording showed the ictal onset with largest amplitude on contacts A26 and 27 (4x11 subdural grid covering the lateral temporooccipital region, solid black circles). B: Axial FA map with display of fibres (in red) reconstructed from small ROI underlying the electrode A27 (ictal onset; small circle on right image). The yellow fibres were reconstructed from a same size ROI in the contralateral homologous region. Please note that the fibres reconstructed from the ictal onset ROI are much shorter compared to the contralateral homologous counterparts. C: Axial colorized FA map illustrating the displacement of the arcuate (shown in blue) and inferior frontooccipital fasciculi (in green color on this cut; see arrow).
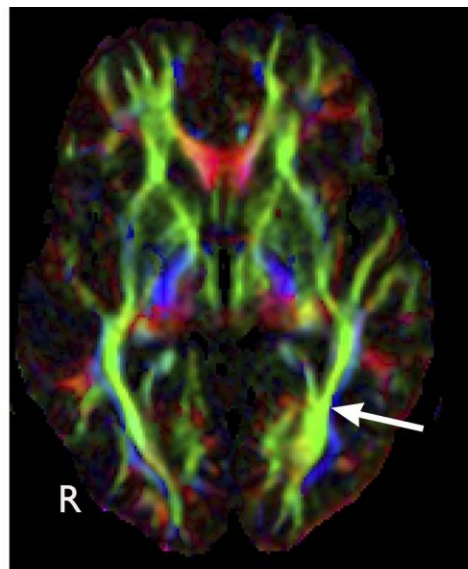
Table 6.2 DTI measures from ROI underlying the ictal onset zone compared to contralateral homologous region

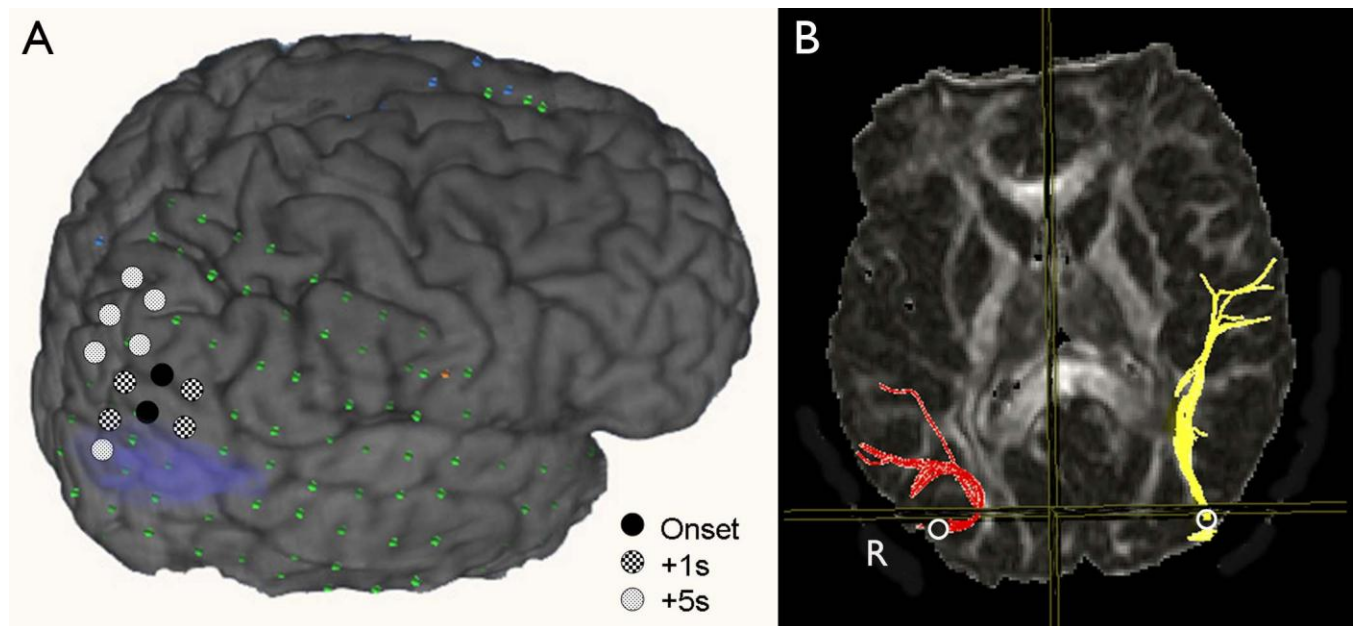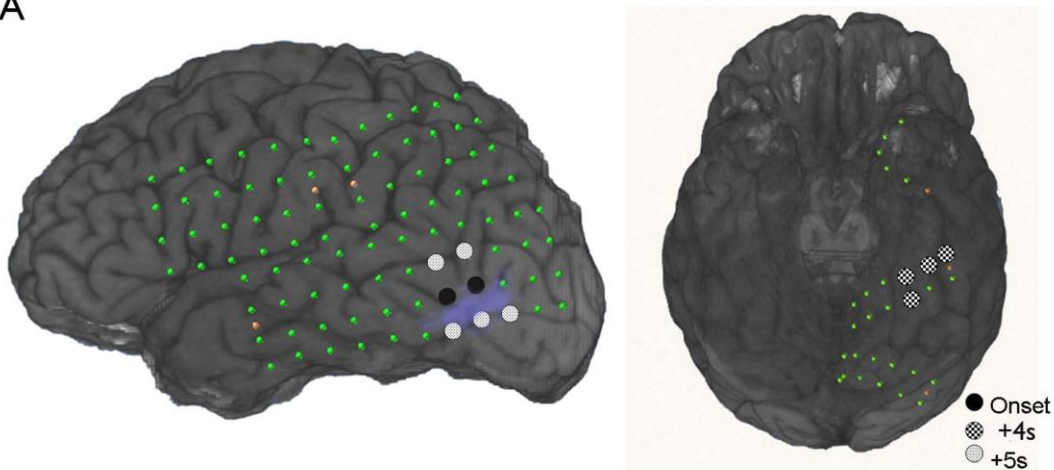|	Patient 2	Patient 3
ROI ADC ipsilateral (10^{-4} mm^2/s)	8.592 (0.963)	9.31 (0.5)
ROI ADC contralateral (10^{-4} mm^2/s)	8.113 (0.538)	8.87 (0.51)
ROI FA ipsilateral	0.206 (0.045)	**0.186 (0.053)**
ROI FA contra	0.235 (0.033)	**0.211 (0.038)**
Number of fibres reconstructed ipsilateral	**32.8 (10.4)**	**24.3 (11.85)**
Number of fibres reconstructed contralateral	**83.8 (46.8)**	**214.5 (87.01)**
Number of voxels per tract reconstructed ipsilateral	40.4 (15.7)	**15.28 (3.64)**
Number of voxels per tract reconstructed contralateral	40.83 (14.38)	**113.83 (17.76)**

In bold: These measures were significantly different ipsilateral and contralateral to the ictal onset ($P<0.05$, paired U test). Reported as mean of three ROI placement trials; standard deviation in parenthesis (see page 118 for details).

6.1.3.4 Imaging and functional outcome correlations following occipital lobe surgery

Two patients remained seizure free after surgery (follow up 4 and 5 years respectively). One patient had a couple of post-operative seizures but then none for the duration of the follow up interval (2 years). In patient 1, who did not have a pre-existing visual field deficit, visual fields were intact after a tailored resection that was guided by ictal recordings and MRI coregistration. Retrospective comparison between the FA map and the post-surgical MRI revealed that the lateral occipital resection had spared the longitudinal white matter fibres lateral to

the ventricle including optic radiations (Figure 6.1). This correlates with preservation of visual fields.

Patient 2 had a pre-existing left upper quadrantanopia prior to surgery and could not cooperate with formal post-operative field testing, but was felt to have a homonymous hemianopia after occipital lobe resection. FLAIR changes in this patient involved the optic radiation and tracked down to the inferior horn of the lateral ventricle, thus accounting for the pre-existing visual field deficit. A larger occipital resection was performed including the entire FLAIR abnormality.

Patient 3 had a small CD in the posterior middle temporal gyrus without visual field deficit. A small resection was performed with preservation of the visual fields.

6.1.4 DISCUSSION

This study highlights that CD is not a disease that exclusively affects cortex and examines the impact of CD in patients with intractable focal epilepsy on the white matter. White matter connectivity and its changes will affect cortical function and ictal propagation.

6.1.4.1 Impact of the CD on local connectivity and underlying white matter tracts

Our study illustrates decreased subcortical connection of the dysplastic cortex in our patients, evidenced by visual analysis of both the FA maps and tractography results. This finding is consistent with recent reports of reductions of fibre connections with the cortex in areas underlying the thickened gray matter of focal CD (Lee *et al.*, 2004). Furthermore, several studies have found altered diffusion values underlying CDs. Specifically, reductions in FA have been described. Further sub-analysis of changes in diffusion values oriented radially and parallel to the axons revealed results suggestive of possible reductions of myelinated fibre

density. One study on five patients with CD could only confirm such changes in three patients who also demonstrated increased white matter T2 signal (Gross *et al.*, 2005), whereas others found such alterations independent of signal changes (Widjaja *et al.*, 2007).

6.1.4.2 CD, ictal onset and seizure propagation

The two patients with pathologically confirmed type 2B CD and the third with pathology proven type 1A but suspected type 2B CD based on imaging characteristics in the depth of the sulcus exhibited very focal and restricted ictal onset, adjacent to (but not overlying), the area of maximum FLAIR signal abnormality. These results are consistent with, and extend our previously published data on patients with mainly frontal and temporal dysplasia (Boonyapisit *et al.*, 2003; Marusic *et al.*, 2002; Najm *et al.*, 2007). Ictal onset was either superior or inferior to the FLAIR abnormality, highlighting that there is a lack of *in situ* epileptogenicity in balloon cells- containing dysplastic lesions (Boonyapisit *et al.*, 2003; Marusic *et al.*, 2002; Najm *et al.*, 2007). The cellular and network mechanisms that underlie the pathology-based differential expression of *in situ* epileptogenicity in CD remain largely unknown. One hypothesis is that balloon cells, though not excitable by themselves, may lead to a modification in the structure of the surrounding cortex thus leading to increased excitability in adjacent tissue (Cepeda *et al.*, 2003).

Although there is significant investigation underway to better understand the mechanisms of ictal onset, little is known about the mechanisms of seizure propagation. In general, direct cortical recordings permit the distinction between fast (early) and slow (late) propagation of the ictal patterns. In addition, the fact that grid electrodes are placed in a contiguous manner (fixed interelectrode distance) allows the study of the propagation pattern: contiguous versus non-contiguous (subcortical or "saltatory"). Propagation speed in human seizures may be quite variable. In one study on frontal lobe epilepsy, the time to initial

propagation was 1-45s, thus suggesting speeds in this first phase of spread of less than 200 micro m/s to greater than 10 mm/s, taking cortical foldings into account (Blume *et al.*, 2001;Trevelyan *et al.*, 2007). In our study, all three patients with pathologically confirmed CD had slow contiguous spread. We assume that this spread mainly occurred via direct horizontal cortical propagation. Such propagation may occur horizontally through cortical layer V (Adrian, 1936; Telfeian and Connors, 1998). If inhibition is impaired, propagation may also occur through other cortical layers (Telfeian and Connors, 1998). Antidromic propagation from the cortex to the thalamic relay neurons has also been described (Gutnick and Prince, 1974). In humans, direct ictal spread to ipsilateral or contralateral homotopic or heterotopic areas has been observed (Baumgartner *et al.*, 1996; Blume *et al.*, 2001; Lieb *et al.*, 1987), suggesting spread via white matter tracts such as connections through corpus callosum and the anterior commissure, or other major white matter tracts. This may also be an explanation for the observed non-contiguous spread patterns in human epilepsy.

In this study, we investigated the connectivity of the cortical region of ictal onset. In two patients this was accomplished by performing tractography from the area underlying the grid electrode contacts exhibiting the ictal change. These areas were adjacent to the observed FLAIR signal increase demarcating the CD. Both patients (2 and 3) had focal onset and slow contiguous spread. Tractography revealed that both the number and length of imaged fibres underlying the area of ictal onset was rather low. This may indicate limited connectivity to larger subcortical white matter tracts from the epileptogenic region, resulting in slower propagation speeds as mainly cortico-cortical propagation takes place, slowly involving adjacent electrodes. However, these results are preliminary results, obtained from a small sample and allow the formulation of a hypothesis rather than providing final proof.

In conclusion, information on the connectivity patterns of the ictal onset zone may provide interesting information to understand and possibly predict ictal spread

patterns. This needs to be reproduced in a larger cohort of patients. In addition, it remains to be shown whether patients with rapid non-contiguous spread have strong subcortical connectivity and how such information relates to outcome. Such knowledge may contribute to further our understanding of brain areas at risk for secondary damage induced by ictal spread. Furthermore, it may provide opportunities to improve surgical outcomes by disconnecting pathways of ictal spread in selected cases.

6.1.4.3 Functional outcome after epilepsy surgery

There is evidence for persistence of eloquent cortex function in areas of CD that are devoid of balloon cells (Leblanc *et al.*, 1995; Preul *et al.*, 1997) whereas dysplastic cortex containing balloon cells is often non-functional cortex (Marusic *et al.*, 2002). Careful correlation of cortical stimulation results, ictal onset zone and imaging findings are important to assess the risk of functional deficit of the surgical procedure.

Larger balloon cell-containing CD as those described in cases 1 and 2 are likely to lead to reduction of subcortical connectivity in the area of thickened cortex. They also result in displacement of underlying white matter tracts, as illustrated in all three cases. In the future, better delineation of these underlying large tracts may allow for more adequate pre-surgical mapping, improved counseling prior to surgery and potentially the preservation of function following epilepsy surgery.

The potential utility of tractography to spare visual fields has been demonstrated in ten patients with AVM surrounding the visual pathway (Kikuta *et al.*, 2006), by performing careful correlation between visual field findings and tractography of the optic radiation. Four of the 10 patients underwent surgical resection of the AVM. The authors were able to predict the amount of pre-and post-operative visual field loss from the geometrical relationship between lesion and optic radiation.

Therefore it can be suggested that DTI in patients with extra-calcarine or temporo-occipital lesions and preserved visual function in the affected hemisphere, may positively impact upon the surgical outcome. Given that a major deterrent for the surgical management of pharmaco-resistant temporo-occipital epilepsy is the high likelihood of visual deficit, localising cortical and subcortical substrates crucial to visual function will help quantify, and perhaps reduce the risk from resections in this region.

6.1.4.4 Technical challenges, limitations and outlook

Limitations of the DTI and tractography performed in this study include those imposed by the relatively large voxel sizes that were necessary to obtain sufficient signal to noise and spatial coverage within a reasonable scan time. Diffusion information carries microscopic anatomical information which is averaged over the large voxel volume. In addition, ROI analysis may introduce some inaccuracies, as both gray and white matter may be included particularly in areas of cortical thickening, potentially lowering FA values even further. For tractography, multiple fibre populations with different fibre orientations are often present within a given voxel and such information will therefore be lost (Mori and Zhang, 2006). Directionality of diffusion is also unknown, hence we cannot comment on anterograde versus retrograde flow. This study was performed on a 1.5T magnet; future investigations will be performed with higher field strengths allowing the use of smaller voxel sizes. In addition, the higher signal to noise in itself will likely allow the impact of CD on the underlying white matter to be elucidated in greater detail. Understanding the connectivity of the lesion and the area of ictal onset may enable us to predict ictal propagation patterns.

6.2 CASE REPORT- Ictal onset and seizure propagation in a case with posterior quadrant polymicrogyria and heterotopias

6.2.1 CASE HISTORY

This patient is a 26 year old right handed man with seizures since age 12 years. Semiology is characterised by a psychic aura with anxiety followed by a focal seizure with mouth and hand automatisms and loss of awareness. Auras occurred up to 10 times a day and complex partial seizures once or twice a day. Physical examination showed a left inferior quadrantanopia.

Scalp interictal EEG showed spikes and polyspikes in the posterior temporal region. Ictal EEG was lateralised to the right hemisphere. In order to delineate ictal onset with the greatest precision, invasive recordings were performed with grid coverage as shown in figure 6.6. Ictal onset was found in the right temporooccipital region, with very rapid spread to the inferior frontal region as seen in figure 6.6A. A large posterior quadrant resection was performed. Post-operatively, the patient has rare complex partial seizures and continues to take two antiepileptic medications. Visual fields revealed an inferior left quadrantanopia (incomplete) prior to surgery. Post-operatively, a left hemianopia was noted on examination.

6.2.2 RESULTS: DTI characteristics and tractography

6.2.2.1 Visual analysis of the FA maps

This patient demonstrated significant abnormalities with displacement and thinning of all major tracts in the right posterior quadrant (Figure 6.5A and B).

Figure 6.5 Axial colourised fibre orientation maps and DTT of the inferior frontooccipital fasciculus in a patient with right temporooccipital polymicrogyria.

A: Axial colourised fibre orientation maps showing displacement of the right superior fronto-occipital fasciculus and superior longitudinal fasciculus.
B: Two dimensional illustration of the tractography results overlaid on to the T1 image demonstrates the spatial relationship between the heteotopic gray matter and the white matter tracts (in blue).
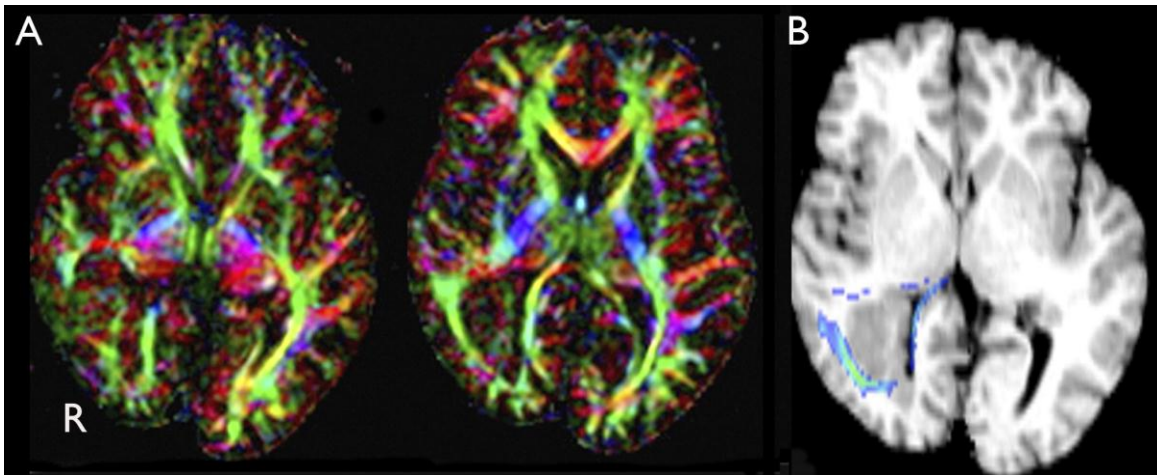
Figure 6.6 Ictal onset and rapid propagation from the right temporooccpiptal region and DTT

A: 3D reconstruction with display of grid electrodes. Ictal onset (black solid circled electrodes) is regional and widespread, suggesting a possible spread pattern. Rapid ictal propagation from this temporo-parieto-occipital area is seen within ms to the inferior lateral frontal lobe. Arrow indicates electrode D16, one of the electrodes involved in the fast propagation, also marked in C.
B: Sagittal colourised fibre orientation map displaying the fibres reconstructed from the region of ictal onset. Connections are seen into the anterior temporal lobe and the frontal lobe.
C: Possible pathway of ictal propagation as reconstructed and displayed in B overlaid on the axial T1 image. The location of electrode D16 is marked with a red circle, one of the electrodes involved in the fast propagation. The direct connectivity between the region of ictal onset as recorded on subdural grids and the area in the ipsilateral frontal lobe may explain the fast and non-contiguous propagation into the lateral frontal lobe.
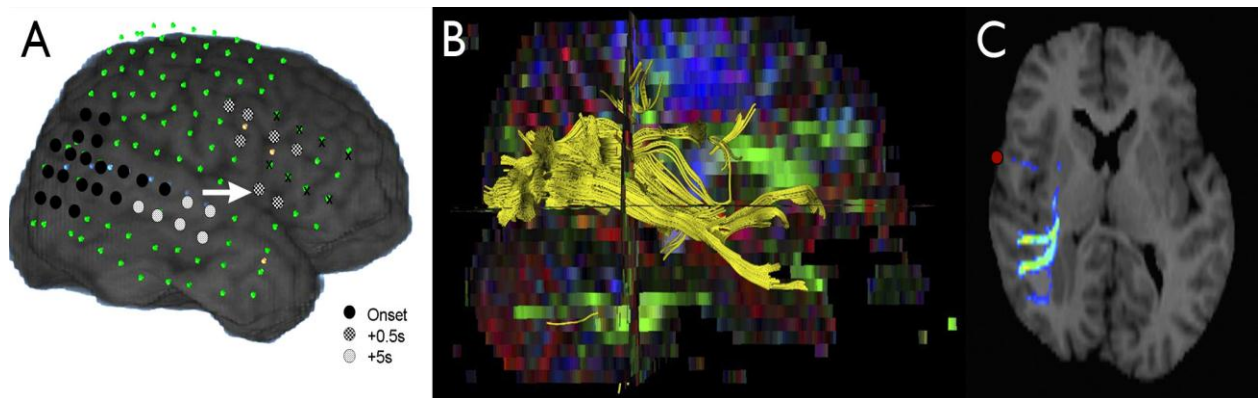
6.2.2.2 Pathological, electrocorticographic and imaging correlations

In contrast to the case series of three patients with more focal CD presented above, this patient (type 1A CD) showed regional ictal onset in the right posterior temporo-occipital region that showed a very rapid spread (within 200 ms, Figure 6.6A) to the dorsolateral parieto-occipital cortex. In addition, rapid anterior non-contiguous spread to the temporal and lateral frontal lobe was observed within 500 msec of ictal onset, and with late involvement of the orbitofrontal region. Visual evaluation of the tractography results revealed proximity of the ictal onset zone to the inferior fronto-occipital fasciculus, and to the inferior longitudinal fasciculus, thus providing a potential pathway of subcortical seizure spread to both anterior temporal and frontal lobes (illustrated in Figure 6.6B and C). DTI measures were comparable between the ipsilateral and contralateral side (ADC right 8.06+/- 0.3; left 8.5+/-0.63; right FA 0.278+/-0.043; left 0.276+/-0.038). Fibres reconstructed from the large area of polymicrogyria and heterotopias were nominally fewer and shorter, but this difference did not reach statistical significance.

6.2.2.3 Imaging and functional outcome correlations following occipital lobe surgery

This patient had a pre-existing inferior quadrantanopia on visual field testing. Given the widespread nature of the imaging abnormality and the presumed large epileptogenic zone, resection of the temporo-parieto-occipital cortex was recommended and performed. The patient clinically had a homonymous hemianopia post-operatively.

6.2.3 DISCUSSION

In polymicrogyria, DTI findings are variable. In one study, no change in diffusion values of the underlying white matter was found (Trivedi *et al.*, 2006), consistent

with the report here. Another case showed reduced FA and increased diffusivity (Isik *et al.*, 2007). In the patient reported here, no significant differences between the FA and ADC values in the left and right temporooccipital regions were found.

The direct cortical recordings permit the distinction between fast (early) and slow (late) propagation of the ictal patterns. In this patient non-contiguous (subcortical or "saltatory") propagation pattern was seen. In the above three patients slow continuous spread was seen, in this patient with type 1 CD very abnormal connectivity in the region of ictal onset as recorded by grids was noted. Due to the large lesion and the lack of additional depth electrode recordings from the deeper parts of the MRI identified dysplastic abnormality, admittedly, it must be assumed that the exact area of ictal onset is not covered; either buried deep in the heterotopic gray matter or on the cortex, adjacent to the grid. Therefore a larger region including the underlying heterotopic gray matter was chosen as a starting point for mapping connectivity, likely encompassing the ictal onset region, but also surrounding regions. Of note was the clear connectivity with the inferior frontal region. Ictal spread showed non-contiguous rapid propagation to this area, thus providing evidence for possible subcortical white matter pathway propagation via the fronto-occipital and inferior longitudinal fasciculi.

A reduced fibre number compared to the contralateral side was reconstructed from the rather large seizure onset area. In this patient we have to assume that the ictal onset zone was not precisely covered and sampled and may represent a spread pattern from an ictal onset in a cortical surface region outside the grid coverage area, or from the deep underling heterotopic gray matter (that was not sampled by depth electrodes).

In conclusion, information on the connectivity patterns of the ictal onset zone may provide interesting information to understand and possibly predict ictal spread patterns. Such knowledge may not only contribute to further our understanding of brain areas at risk for secondary damage induced by ictal spread, but may also

provide opportunities to improve surgical outcomes by disconnecting pathways of ictal spread in selected cases.

CHAPTER 7
SUMMARY, CONCLUSION AND FUTURE PLANS

7.1 Summary and appraisal of the research presented

The introduction of MRI into clinical practice for the diagnosis of the underlying causes of many epilepsies has been an important milestone and arguably represents the greatest advance in diagnostics in epilepsy since the EEG was discovered. The studies underlying this thesis investigated the possible contribution of a novel imaging technology, DTI to the pre-surgical evaluation in medication-refractory focal epilepsy. In particular, DTI provides information on the microstructure of tracts that are crucial to performance in specific cognitive domains. Such information can add to our understanding of normal function, and may add to explain dysfunction. In addition, DTI allows reconstructing major white matter tracts and gives *in vivo* insights into connectivity of the human brain. Once appropriate validation of such tracts is available and the technique is optimised, this will certainly become a valuable tool to inform resection and improve functional outcomes. In addition, understanding the connectivity of the epileptogenic zone may be relevant to seizure propagation patterns.

Today's advances in neuroimaging have only been possible following a long history of improved knowledge of neurological function and dysfunction in the context of brain topography, as detailed in section 1.2. Linking clinical manifestations during seizures to brain localisation allowed for targeted interventions at the site presumed close to the ictal onset zone. At the same time it spurred the need to obtain tools to interrogate the brain non-invasively. Neuroimaging and in particular MRI has held a special role over the past 20 years in optimising pre-surgical evaluation and has hugely improved our ability to gain insights into the structure and function of the epileptic brain. It is hoped that improved imaging techniques will inform on potential structural correlates and in

an increasingly greater percentage of patients an "epileptogenic lesion" can be detected. Due to the increased sensitivity of the technologies, more differences between the brain structure of patients with epilepsy and control groups have emerged. Some of these may be consequences of seizures rather than their cause and may parallel some of the well known comorbidities of focal epilepsy.

The broad aim of this thesis was to examine the contribution of DTI to the evaluation of candidates for epilepsy surgery. Specifically, three areas were addressed:

1. To investigate the correlation of DTI abnormalities and neuropsychological deficits in patients with refractory TLE, specifically in memory and language domains.

2. To provide validation of DTT, specifically of a method of reconstructing the AF using a deterministic tractography algorithm, by comparing it to results of cortical stimulation.

3. To explore DTT as a tool to assess the connectivity of the ictal onset zone and compare it *in vivo* with ictal propagation measured using intracranial EEG.

1. In sections 1.3 and 1.4, I have provided an overview of the imaging investigations of focal epilepsies using DTI and DWI which revealed diffusion abnormalities in areas of seizure onset and spiking, but also in adjacent and remote and even in contralateral areas.

In order to understand the meaning of such changes, investigations into structure and function in controls and patients were undertaken, as summarised in section 1.5. There is mounting evidence that the integrity of white matter tract pathways, as measured by DTI, is systematically related to individual differences in performance across a wide range of cognitive skills.

In chapters 3 and 4 I presented results of correlations between neuropsychological performance measures and DTI.

Patients with TLE often suffer from modality specific memory deficits; therefore the UF was explored to assess whether possible diffusion abnormalities in this important memory network would correlate with performance. In a group of TLE patients, abnormal diffusion measures were found in both the left and right UF. In left TLE, diffusion measures correlated in the expected directions in the left UF with immediate and delayed auditory memory. There was also a relationship between poor delayed visual memory performance and abnormal diffusion measures in the right. No significant correlations were found in right TLE, likely due to small sample size (Diehl *et al.*, 2008).

At the time of the study, the only work reporting on DTI of the UF in patients with epilepsy reported only ten patients with right TLE due to right hippocampal sclerosis compared to ten controls (Rodrigo *et al.*, 2007). It showed that FA was lower in the epilepsy patients as compared to the controls in the right, but not left UF. Furthermore, patients with TLE had abnormal measures of diffusivity and anisotropy in the UF bilaterally. No systematic structure function relationship had been published.

This study showed more bilateral involvement in the UF with significantly increased ADCs in the right UF and decreased FA and increased ADCs in the left UF in both right and left TLE patients (Chapter 3). This is in concordance with reports of bilateral diffusion abnormalities in limbic structures in patients with TLE, as well as remote changes from ictal onset (Arfanakis *et al.*, 2002; Concha *et al.*, 2005; Gross *et al.*, 2006).

Few studies have investigated the link between DTI measures and memory performance. In this group of left TLE patients it was demonstrated that increased diffusivity in the left UF was related to poorer auditory memory, whereas

increased diffusivity and reduced FA in the right UF were related to poorer visual memory. This finding has since in part been replicated in one further study (McDonald *et al.*, 2008).

Language dysfunction is also often present in patients with TLE, particularly in patients with dominant TLE. Therefore, the AF was assessed and correlations with DTI measures and language performance computed (Chapter 4). Results provided evidence bilateral diffusion changes in the AF. Specifically, in the left TLE group, FA values in the entire left and right AF tract were comparable to controls; however ADC values were elevated bilaterally, with higher radial diffusivities in the left AF. The right TLE group had higher ADC values and lower FA values in both the left and right AF compared to controls. Radial diffusivities were elevated.

The correlation data with language performance suggested a relationship between DTI measures in the left AF and language scores in patients with TLE. In particular, semantic fluency may be a sensitive marker for damage to the language network with demonstrated positive correlations of FA in the left AF tract. ADC in the left AF tract was negatively correlated with sentence repetition and verbal comprehension. However analyses with larger sample sizes will be required to replicate this finding.

The relation between language lateralisation and integrity of the AF has been shown in other studies (Ellmore *et al.*, 2010; Powell *et al.*, 2006) and the contribution of the AF to language performance was also recently shown (McDonald *et al.*, 2008), in concordance with the findings presented in this thesis.

It is noted that abnormal DTI measures were found bilaterally in the UF and AF in both studies presented in this thesis. It is conceivable that the abnormal DTI values may be related to damage of the axonal pathways that are involved in ictal

spread, as is the UF in TLE. Alternatively, neuronal damage from seizures may lead to secondary white matter loss in connected areas (Mayanagi *et al.*, 1996).

To date, the exact mechanism of such seizure-induced damage is unknown. In both studies, the characteristics of the diffusion changes in a ROI within the UF and AF were examined and shown to be compatible with chronic Wallerian degeneration, possibly due to cell loss in the temporal lobe secondary to seizure-induced cell death. Microstructural abnormalities within the UF and AF therefore could contribute to memory and language dysfunction in patients with TLE.

2. The second aim of this thesis is to contribute to validation of DTT results. DTT has increasingly been used to delineate major white matter tracts as reviewed in sections 1.6 and 1.7. Several investigations have focused on retrospectively correlating DTI based tractography with postoperative deficits, to assess if the technology could provide predictive information for a deficit and maybe even could aid in preservation of function. The approach taken in this study correlates language sites identified by extraoperative cortical stimulation with the AF, thereby testing the hypothesis that those cortical language areas underpin the tractography defined AF (Chapter 5; Diehl *et al.*, 2010a).

The study showed that 84.2% of all 19 electrode positions in 8 patients overlying the anterior language area co-localised with the AF. Fifty-two contacts in 10 patients were over Wernicke's area, with co-localisation in 29 (55.8%) patients. Co-localisation was significantly greater in anterior regions than in posterior regions.

Therefore, although some validation could be provided, the co-localisation was not perfect which may in part be due to a number of technical issues. Spatial resolution of DTI and noise are significant problems, voxel sizes are much larger than the resolution needed to image single axons. The choice of tractography algorithms does likely have some influence on the reconstructed tract. It is

thought that deterministic tractography algorithms, such as that used for this study, have shortfalls particularly in dealing with crossing fibres (see also 7.1.2). Other approaches such as probabilistic line propagation (Koch *et al.*, 2003; Parker *et al.,* 2003) improve the ability to cope with fibre crossing, however at the expense of increased "fuzziness" of the solution (Hagmann *et al.,* 2010). Coregistration errors across different sequences and uncertainties of brain shift following implantation of the subdural grids add to this.

It was of interest that a tighter co-localisation between language sites in the frontal lobe compared to temporo-parietal language sites was found. This may be a combination of technical limitations and greater anatomical variability in the posterior language area.

One other study has correlated cortical stimulation with DTT. The study explored intra-operative cortical stimulation to identify language functions and compared the language sites to DTT (Ellmore *et al.*, 2009). A deterministic streamline algorithm was used for reconstruction of the AF; in addition, mediolateral frontal pathways the UF and IFOF were reconstructed. The rating of concordance was done using two different methods: 1. visual analysis to assess a direct relationship, as a positive cortical stimulation site with AF pathway terminations located within the immediate region (radius 7.5 mm). 2. By using a bootstrap method indirect sites were determined. These sites were defined as fibre pathways with one end within an immediate region (radius = 7.5 mm) whose other termination points were closer to the terminations of the AF pathways than would be expected by chance.

It was shown that the majority of essential language sites (58.8%) had a direct relationship to the AF. An additional 20.6% of all stimulation sites had an indirect relationship. The authors assume that the neurons at the AF termination sites would be affected via an indirect corticocortical route (U fibres for example). It was noted that although the majority of the language sites per cortical stimulation had

a close relationship (either direct or indirect, as explained above) to the above tracts, 21% of the sites were unrelated.

Other methods of validation in the human have focused on intra-operative stimulation of underlying white matter tracts (Leclercq *et al.*, 2010). In patients with low grade gliomas, intra-operative subcortical stimulation elicited language deficits in 8 of 10. DTT of the AF, occipito-frontal fasciculus and premotor fascicule were reconstructed and correlated with the positions of electrical stimulation. In 17 of 21 positions stimulated, a fibre tract was found within 6 mm of the stimulation induced language deficit; in 4, no fibre tract could be found. This highlights that DTT is not yet reliable enough to base resections on the information presented. In particular, when pathological tissue such as tumors is present, great caution needs to be exerted.

Taken together, all these studies indicate that the correlations with the current "gold standard" of cortical stimulation are still imperfect. It needs to be noted however that cortical stimulation is our best standard, but certainly also has shortcomings (Hamberger M., 2007). Integration into neuronavigation systems to guide resections can only be considered once the technology is robust and has undergone more widespread validation. It is anticipated that in the near future DTT will be more systematically integrated into pre-surgical planning procedures and further validated using intra-operative and extraoperative cortical stimulation and correlated with outcome.

3. Lastly, DTT may be used as a tool to reveal likely paths of seizure propagation. I investigated characteristics of DTT from the ictal onset zone and correlation with spread as shown on invasive recordings in a case series of patients with cortical dysplasia (Chapter 6; Diehl *et al.*, 2010b). Cortical dysplasias are a frequent underlying substrate of medication refractory focal epilepsy and often require invasive EEG investigations (sections 1.7 and 1.8) to delineate the ictal onset zone. Ictal onset is most commonly found in dysplastic areas without balloon

cells, which are often not clearly demarcated on MRI (Boonyapisit *et al.*, 2003). In addition it is well known amongst neurophysiologists that seizure propagation patterns may differ vastly from patient to patient. Some patients have very focal ictal onset and slow propagation across the subdural grids, and other patients show quick propagation to remote areas of cortex, skipping subdural electrodes on the surface of the cortex, hence propagating using subcortical pathways.

In the group of patients in this study, DTI measures and DTT confirmed the presence of reduced connectivity with reduced arborisation and thinning of the fibre bundles between the subcortical white matter and the dysplastic cortex in three patients with presumed type 2B cortical dysplasia. Fibre tracts reconstructed from regions underlying the ictal onset helped explain ictal propagation patterns in this small case series of patients. In the three patients with slow contiguous spread, poor subcortical connectivity of the focal ictal onset zone was seen. In the one patient with polymicrogyria however, rapid non-contiguous spread showed rapid subcortical spread via the fronto-occipital and inferior longitudinal fasciculi. This case however is not ideal, as the ictal onset zone may have been located deep and has not been precisely covered. Future studies need to investigate the relationship between pathology, ictal onset and propagation and connectivity of the ictal onset zone in greater detail.

In the two patients without pre-existing visual field deficit, resections spared the optic radiation visible on the FA map.

Diffusivity measures and visualisation of tracts provides complementary information on white matter changes accompanying CD and may assist to explain ictal spread patterns. Careful correlation with measures of function will allow the assessment of the functional significance of various dysplastic lesions and may help to design resective strategies.

1. 2 Conclusion and Future Plans

It is hoped that improved imaging techniques will allow identification of abnormalities of brain structure and function with ever greater sensitivity. It is crucial, particularly for the third of patients with medication refractory focal epilepsy to detect subtle lesions, as it informs epileptologists and neurosurgeons on potential targets for resective surgery. However, understanding the relevance of a lesion in the context of a patient's epilepsy is of paramount importance. Close correlation between neurophysiology and imaging is required to gain better understanding of the meaning of a lesion.

DTI has shown more widespread changes in areas close to ictal onset but also remote areas. The underlying diffusion changes appear to show the characteristics of Wallerian degeneration, however it is unclear if all those changes occur as a result of seizures or some may be there from onset of the epilepsy and be part of the epileptogenic lesion. To date, one small study in children investigated 11 patients with idiopathic generalised epilepsy, eight with localisation related epilepsy and non-lesional MRI (Hutchinson *et al.*, 2010). DTI showed reduced FA and increased radial diffusivity of the posterior corpus callosum and cingulum. These results provide evidence of microstructural abnormalities in cerebral white matter among children with recent onset idiopathic epilepsies. In the future, it will be crucial to understand the impact of new imaging technologies also on the developing brain, particularly as epilepsy surgery is no longer considered a measure of last resort in the management of children with medication resistant focal epilepsy (Cross JH, 2010). Early referral to a comprehensive epilepsy centre and the integration of the advances in neuroimaging has greatly increased the numbers of possible candidates for epilepsy surgery in children.

Larger prospective studies of newly diagnosed epilepsy may be able to shed some light on the presence of microstructural abnormalities at onset and during

the course of the disease. Important differences regarding seizure control, seizure semiology and comorbidities may emerge. Longitudinal prospective studies to evaluate the time relationship between the overall cognitive decline, and decline in specific neuropsychological areas and DTI alterations are needed to clarify the causes and impact of DTI changes. Such studies may be difficult as they will likely require following a large group of patients for many years in order to detect changes over time and their impact on cognitive function.

Large prospective studies are crucial to understand potential contributions of the technology 1. to develop biomarkers for cognitive difficulties associated with epilepsy and 2. to assess whether DTI can aid in predicting risks of deficit following surgery. Ideally, they should be performed as multicenter studies, using well characterised cohorts of patients investigated using the same methodology. Such studies, although much needed, may however prove challenging for a variety of reasons (Richardson M, 2010). For example, most recently the inter- and intra-site reproducibility of two nominally identical 3 T scanners at different sites was investigated in nine healthy controls using a DTI protocol representative of typical current "best practice". Reproducibility maps of the whole scan volume showed a low variation of less than 5% in the major white matter tracts but higher variations of 10–15% in gray matter regions (Vollmar *et al.*, 2010). Taking into account the variability of different scanners between centres, such multicentre trials will be difficult. However, a recent meta-analysis of predictive accuracy for focus localization and cost effectiveness in epilepsy highlighted a large evidence gap. It was concluded that due to limitations of the studies included, the results do not inform clinical practice usefully (Whiting *et al.,* 2006), again highlighting the great need to work towards multicentre trial designs.

Overall, the extent of DTI changes in the epileptic brain is certainly surprising, and we are in the process of gaining insights in structure function relationships. There clearly seems to be some relationship between language and memory performance and integrity of main tracts, which are structurally supporting such

functions. However it is also clear that damage to a specific tract may also influence other functions via more non-specific mechanisms, such as attention and concentration for example.

In addition, given the complexity of higher cognitive functions and the functioning of the brain in networks, it is very unlikely that correlations between performances in particular tests will be confined to only one major tract. Recent reviews of fMRI studies of the language system provide impressive insights into the large number of cortical areas activated during language tasks (Price, 2000; Price, 2010; Vigneau *et al.*, 2006). Therefore, focusing only on the AF as the work underlying this thesis has done can only be a start. In fact, one study had shown that there is a relationship between naming performance and DTI measures of the AF, UF, and the left IFOF (McDonald *et al.*, 2008). Evidence from cortical stimulation followed by glioma resection in 13 patients however suggests that the UF is not essential for language (Duffau *et al.*, 2009). Intra-operative stimulation studies have however highlighted the importance of the AF, superior frontooccipital fasciculus, the IFOF and the subcallosal fasciculus (Duffau, 2008a). In particular, stimulation of the IFOF elicits semantic paraphasias, suggesting that this tract is essential to the semantic language system (Duffau *et al.*, 2005; Duffau, 2008a). Stimulation of the subcallosal fasciculus, a white matter bundle that surrounds the lateral angle of the frontal horn and connects the cingulum and the supplementary motor area, has induced a transcortical motor aphasia (Duffau *et al.*, 2002).

In addition, it now has been shown that there may be a significant contribution of the right hemisphere to a successful naming performance, particularly in older people (Obler *et al.*, 2010). The older adults with relatively better naming skills relied on right-hemisphere peri-Sylvian and mid-frontal regions and pathways, in conjunction with left-hemisphere peri-Sylvian and mid-frontal regions. Therefore, future studies need to also investigate all tracts potentially involved in a particular network.

Whether the degree of microstructural abnormalities in specific tracts of patients with focal epilepsy will prognosticate the risk of a decline in performance following resection is uncertain at this point. However, some relationship would appear logical. In the case of pre-existing damage of white matter tracts that are connecting cortical areas essential for a certain tasks, risk of further potential damage through surgery should decrease.

Some fMRI studies and combined DTT/fMRI studies linked strong language lateralisation to increased risk for naming decline after left TL resection. In one study, the relationships between the fMRI laterality index, Wada language dominance, and naming outcome were examined in 24 left TLE patients, revealing that fMRI showed 100% sensitivity and 73% specificity in predicting significant naming decline (Sabsevitz *et al.*, 2003). It has also been shown that the degree of lateralisation on fMRI correlates with more highly lateralised connectivity pathways (Powell *et al.*, 2007a). Furthermore, in a small group (seven patients with dominant temporal lobe resections) the degree of tract lateralisation correlated with language decline (Powell *et al.*, 2008). These findings need to be replicated in a larger group of patients. The size, and shape of tracts however has not yet been systematically investigated and not been linked to outcomes following dominant temporal lobe resection.

It would be ideal to characterise an individual patient's language performance via neuropsychological profile, tractography and fMRI and stratify risk of epilepsy surgery procedures accordingly. Aside from integrity of a tract, its particular shape and connectivity to cortical areas in an individual may vary and be important predictors of impact of resection. Stratifying individual patient's risk according to the surgical plan however is still a vision for the future.

As DTI based tractography is increasingly integrated in pre-operative planning, there is a need for clinicians and neurosurgeons to develop improved understanding of limitations of the technology. It is likely that in specific areas of

the brain, tractography may be more or less reliable in visualising connectivity due to varied percentages of crossing fibres and fibre density. Hence, maps of probability for accurate delineation may be helpful, to highlight areas that may be difficult to accurately represent using such technology. Such an approach may be limited by the variability in acquisition and tract reconstruction and analysis between centers, but it can still provide valuable information. Overall, as in many other areas of clinical and translational research, numbers are still limited and the generalisability of data suffers from varied methods in centers.

In order to integrate DTT in a systematic way into pre-surgical workup and neuronavigation systems, the technique needs to be proven to be robust and reproducible. In addition, there are particular challenges in delineating tracts in disease; tumour tissue for example poses particular challenges to visualise tracts that may have decreased FA but be still functional. Clinicians and neurosurgeons will have to be very cautious to not rely on DTT alone and be aware of both false negative and false positive results. However, if the technique is optimised and a better understanding of strengths and limitations is achieved, DTT will likely be an essential tool to plan and perform epilepsy surgery, to minimise functional deficits after resection.

As mentioned previously, advances in both acquisition and postprocessing will likely improve DTT results. DTI cannot measure multiple fibre orientations within one voxel. To address this limitation, Diffusion Spectrum Imaging (DSI) and related methods were developed, allowing the imaging of complex distributions of fibre orientations within a voxel (Wedeen *et al.*, 2005; Wedeen *et al.*, 2008). However, such techniques are far from clinical application as high performance scanners (typically 3T) with very powerful magnetic gradients and multichannel headcoils being required. In addition, long acquisition times are needed (Hagmann *et al.*, 2010). Undoubtedly the near future will bring improved ways of reconstructing tracts, and repeated studies correlating function as localised using cortical stimulation will possibly yield improved correlation.

Lastly, DTT may have a role in the evaluation of the connectivity of the ictal onset zone. Close correlation with ictal propagation patterns as seen on intra-cranial recordings will provide valuable insights into the larger areas of cortex that are recruited. In case very efficient remote connectivity exists, ictal spread may occur very rapidly and some remote cortical areas may get activated. Some may even be able to sustain an independent seizure pattern of distinct morphology, rhythmicity, and evolution and which outlasts the activity from the primary zone of onset. This has been termed an ''intraictally'' activated regions. It was shown in the past that these areas may be capable of self-sustaining epileptogenesis. They may arise at a considerable distance from the primary focus, and contribute to surgical failure if not fully excised (Duchowny, 2009; Jayakar *et al.*, 1994). These connections and propagation patterns are important to identify, as the resective strategy will be affected. In case such intraictal areas are close by the initial ictal onset zone, they should also be resected. However, in case they are more remote, this becomes more difficult to decide and will certainly be a balance of best possible seizure free outcome and avoidance of functional deficits. More research is certainly needed in the area of extent of resection.

In the future, connectivity of a presumed epileptogenic zone/lesion may allow planning implantation better beforehand, to cover adjacent and possibly also some more remote areas of strong connectivity. Information streams such as seizure semiology, scalp interictal and ictal EEG as well as other modalities for example MEG, PET and EEG fMRI can be used to determine which areas of cortex are likely involved in ictal onset and rapid propagation. This information can then used to guide resection or, in complicated cases, the implantation strategy for subdural grids and/or depths. Close correlation with DTT will help explain propagation patterns and additional strategies such as resections in combination with disconnection for example could be guided by utilising a combination of the information.

The contribution of DTI and DTT in the pre-surgical evaluation therefore has great potential to inform resective strategies in epilepsy surgery. Future research needs to integrate the DTI based tractography and cortical localisation procedures that define eloquent cortex, highlight dysfunctional brain areas, and the ictal onset and irritative zones. As efforts are under way to characterize the added contribution of various neuroimaging techniques to clarify their value in the presurgical evaluation (Knowlton *et al*. 2008 a,b), DTI will need to pass rigorous assessments in the future.

Understanding connectivity of the human brain in health and disease will also shed light on the relationship between structure and normal and abnormal function. The many changes in the epileptic brain relating to cortical thickness, gray and white matter volumes, electrophysiology and metabolism are likely reflected in changes in underlying connectivity. If appropriate tools become available to integrate all the information from multimodal structural and functional brain imaging and neurophysiology, crucial insights in focal epilepsy and possibly also epileptogenesis will be gained. To gain such information and then translate these insights into improved outcome for our patients with focal epilepsy, a cure or even intervention during epileptogenesis will be a main focus of many clinician scientists in the future.

CHAPTER 8

REFERENCES

Adcock,J.E., Wise,R.G., Oxbury,J.M., Oxbury,S.M., Matthews,P.M., 2003. Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. Neuroimage 18, 423-438.

Adrian,E.D., 1936. The spread of activity in the cerebral cortex. J Physiol 88, 127-161.

Allen,P.J., Polizzi,G., Krakow,K., Fish,D.R., Lemieux,L., 1998. Identification of EEG events in the MR scanner: the problem of pulse artifact and a method for its subtraction. Neuroimage 8, 229-239.

Aralasmak,A., Ulmer,J.L., Kocak,M., Salvan,C.V., Hillis,A.E., Yousem,D.M., 2006. Association, commissural, and projection pathways and their functional deficit reported in literature. J Comput Assist Tomogr 30, 695-715.

Arfanakis,K., Hermann,B.P., Rogers,B.P., Carew,J.D., Seidenberg,M., Meyerand,M.E., 2002. Diffusion tensor MRI in temporal lobe epilepsy. Magn Reson Imaging 20, 511-519.

Assaf,B.A., Mohamed,F.B., Abou-Khaled,K.J., Williams,J.M., Yazeji,M.S., Haselgrove,J., Faro,S.H., 2003. Diffusion tensor imaging of the hippocampal formation in temporal lobe epilepsy. AJNR Am J Neuroradiol 24, 1857-1862.

Aubert,S., Wendling,F., Regis,J., McGonigal,A., Figarella-Branger,D., Peragut,J.C., Girard,N., Chauvel,P., Bartolomei,F., 2009. Local and remote epileptogenicity in focal cortical dysplasias and neurodevelopmental tumours. Brain 132, 3072-3086.

Barkovich,A.J., Kuzniecky,R.I., Jackson,G.D., Guerrini,R., Dobyns,W.B., 2001. Classification system for malformations of cortical development: update 2001. Neurology 57, 2168-2178.

Basser,P.J., Jones,D.K., 2002. Diffusion-tensor MRI: theory, experimental design and data analysis - a technical review. NMR Biomed 15, 456-467.

Basser,P.J., Mattiello,J., Lebihan,D., 1994. Estimation of the effective self-diffusion tensor from the NMR spin echo. J Magn Reson B 103, 247-254.

Basser,P.J., Pierpaoli,C., 1996. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B 111, 209-219.

Baumgartner,C., Flint,R., Tuxhorn,I., Van Ness,P.C., Kosalko,J., Olbrich,A., Almer,G., Novak,K., Luders,H.O., 1996. Supplementary motor area seizures: propagation pathways as studied with invasive recordings. Neurology 46, 508-514.

Bautista,J.F., Foldvary-Schaefer,N., Bingaman,W.E., Luders,H.O., 2003. Focal cortical dysplasia and intractable epilepsy in adults: clinical, EEG, imaging, and surgical features. Epilepsy Res 55, 131-136.

Beaulieu,C., Allen,P.S., 1994. Determinants of anisotropic water diffusion in nerves. Magn Reson Med 31, 394-400.

Beaulieu,C., Does,M.D., Snyder,R.E., Allen,P.S., 1996. Changes in water diffusion due to Wallerian degeneration in peripheral nerve. Magn Reson Med 36, 627-631.

Berg,A.T., Mathern,G.W., Bronen,R.A., Fulbright,R.K., DiMario,F., Testa,F.M., Levy,S.R., 2009. Frequency, prognosis and surgical treatment of structural abnormalities seen with magnetic resonance imaging in childhood epilepsy. Brain 132, 2785-2797.

Bhardwaj,R.D., Mahmoodabadi,S.Z., Otsubo,H., Snead,O.C., III, Rutka,J.T., Widjaja,E., 2010. Diffusion tensor tractography detection of functional pathway for the spread of epileptiform activity between temporal lobe and Rolandic region. Childs Nerv Syst 26, 185-190.

Binder,J.R., 1997. Neuroanatomy of language processing studied with functional MRI. Clin Neurosci 4, 87-94.

Bloch, F, Hansen, HH, and Packard, ME.,1946. Nuclear induction. Phys Rev 69, 127-129.

Blumcke, I., Tom, M., Aronica, E. et al. 2010. The clinico pathological spectrum of focal cortical dysplasia: a consensus classification propsed by an ad hoc task force of the ILAE Diagnostic Methods Commission. Epilepsia, in print.

Blume,W.T., Ociepa,D., Kander,V., 2001. Frontal lobe seizure propagation: scalp and subdural EEG studies. Epilepsia 42, 491-503.

Boonyapisit,K., Najm,I., Klem,G., Ying,Z., Burrier,C., LaPresto,E., Nair,D., Bingaman,W., Prayson,R., Luders,H., 2003. Epileptogenicity of focal malformations due to abnormal cortical development: direct electrocorticographic-histopathologic correlations. Epilepsia 44, 69-76.

du Boulay,G.H., Marshall,J., 1975. Comparison of E.M.I. and radioisotope imaging in neurological disease. Lancet 2, 1294-1297.

Brewer,J.B., Zhao,Z., Desmond,J.E., Glover,G.H., Gabrieli,J.D., 1998a. Making memories: brain activity that predicts how well visual experience will be remembered. Science 281, 1185-1187.

Briellmann,R.S., Mitchell,L.A., Waites,A.B., Abbott,D.F., Pell,G.S., Saling,M.M., Jackson,G.D., 2003. Correlation between language organization and diffusion tensor abnormalities in refractory partial epilepsy. Epilepsia 44, 1541-1545.

Bronen,R.A., Fulbright,R.K., King,D., Kim,J.H., Spencer,S.S., Spencer,D.D., Lange,R.C., 1997. Qualitative MR imaging of refractory temporal lobe epilepsy requiring surgery: correlation with pathology and seizure outcome after surgery. AJR Am J Roentgenol 169, 875-882.

Buchel,C., Raedler,T., Sommer,M., Sach,M., Weiller,C., Koch,M.A., 2004. White matter asymmetry in the human brain: a diffusion tensor MRI study. Cereb Cortex 14, 945-951.

Budde,M.D., Kim,J.H., Liang,H.F., Schmidt,R.E., Russell,J.H., Cross,A.H., Song,S.K., 2007. Toward accurate diagnosis of white matter pathology using diffusion tensor imaging. Magn Reson Med 57, 688-695.

Bull,J., 1982. The History of Neuroradiology. Rose C, Bynum WF (Eds.) Historical aspects of Neurosciences. Raven Press, New York, pp. 255-264.

Busch,R.M., Frazier,T.W., Haggerty,K.A., Kubu,C.S., 2005. Utility of the Boston naming test in predicting ultimate side of surgery in patients with medically intractable temporal lobe epilepsy. Epilepsia 46, 1773-1779.

Camfield,P.R., Camfield,C.S., 1996. Antiepileptic drug therapy: when is epilepsy truly intractable? Epilepsia 37 Suppl 1, S60-S65.

Cao,Y., Whalen,S., Huang,J., Berger,K.L., DeLano,M.C., 2003. Asymmetry of subinsular anisotropy by in vivo diffusion tensor imaging. Hum Brain Mapp 20, 82-90.

Catani,M., 2007. From hodology to function. Brain 130, 602-605.

Catani,M., Ffytche,D.H., 2005. The rises and falls of disconnection syndromes. Brain 128, 2224-2239.

Catani,M., Jones,D.K., Ffytche,D.H., 2005. Perisylvian language networks of the human brain. Ann Neurol 57, 8-16.

Catani,M., Mesulam,M., 2008. The arcuate fasciculus and the disconnection theme in language and aphasia: History and current state. Cortex 44(8): 953-61.

Catani,M., Thiebaut,d.S., 2008. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. Cortex 44(8): 1105-32.

Cepeda,C., Hurst,R.S., Flores-Hernandez,J., Hernandez-Echeagaray,E., Klapstein,G.J., Boylan,M.K., Calvert,C.R., Jocoy,E.L., Nguyen,O.K., Andre,V.M., Vinters,H.V., Ariano,M.A., Levine,M.S., Mathern,G.W., 2003. Morphological and electrophysiological characterization of abnormal cell types in pediatric cortical dysplasia. J Neurosci Res 72, 472-486.

Chen,X., Weigel,D., Ganslandt,O., Buchfelder,M., Nimsky,C., 2008. Prediction of visual field deficits by diffusion tensor imaging in temporal lobe epilepsy surgery. Neuroimage 45(2):286-97.

Chen,X., Weigel,D., Ganslandt,O., Fahlbusch,R., Buchfelder,M., Nimsky,C., 2007. Diffusion tensor-based fiber tracking and intraoperative neuronavigation for the resection of a brainstem cavernous angioma. Surg Neurol 68, 285-291.

Concha,L., Beaulieu,C., Collins,D.L., Gross,D.W., 2009. White-matter diffusion abnormalities in temporal-lobe epilepsy with and without mesial temporal sclerosis. J Neurol Neurosurg Psychiatry 80, 312-319.

Concha,L., Beaulieu,C., Gross,D.W., 2005. Bilateral limbic diffusion abnormalities in unilateral temporal lobe epilepsy. Ann Neurol 57, 188-196.

Concha,L., Beaulieu,C., Wheatley,B.M., Gross,D.W., 2007. Bilateral white matter diffusion changes persist after epilepsy surgery. Epilepsia 48, 931-940.

Concha,L., Gross,D.W., Wheatley,B.M., Beaulieu,C., 2006. Diffusion tensor imaging of time-dependent axonal and myelin degradation after corpus callosotomy in epilepsy patients. Neuroimage 32, 1090-1099.

Concha,L., Livy,D.J., Beaulieu,C., Wheatley,B.M., Gross,D.W., 2010. In vivo diffusion tensor imaging and histopathology of the fimbria-fornix in temporal lobe epilepsy. J Neurosci 30, 996-1002.

Cook,M.J., 1994. Mesial temporal sclerosis and volumetric investigations. Acta Neurol Scand Suppl 152, 109-14.

Cooper, R., Winter , A. L., Crow, H. J., and Walter, WG., 1965. Comparison of subcortical, cortical and scalp activity using chronic ally indwelling electrodes in man. Electroencephalogr.Clin.Neurophysiol. 18, 217-228.

Cross, JH, 2010. Epilepsy surgery in children – no longer a last resort. Dev Med Child Neurol. 52 (2), 111-12.

Croxson,P.L., Johansen-Berg,H., Behrens,T.E., Robson,M.D., Pinsk,M.A., Gross,C.G., Richter,W., Richter,M.C., Kastner,S., Rushworth,M.F., 2005. Quantitative investigation of connections of the prefrontal cortex in the human and macaque using probabilistic diffusion tractography. J Neurosci 25, 8854-8866.

Damasio,A.R., Eslinger,P.J., Damasio,H., Van Hoesen,G.W., Cornell,S., 1985. Multimodal amnesic syndrome following bilateral temporal and basal forebrain damage. Arch Neurol 42, 252-259.

Dandy, W.E., 1918.Ventriculography folllowing the injection of air in the cerebral ventricles. Ann Surg , 5.

Dandy, W.E., 1919, Roentgenography of the brain after the injection of air in the spinal canal. Ann Surg 70, 397.

Demonet,J.F., Thierry,G., Cardebat,D., 2005. Renewal of the neurophysiology of language: functional neuroimaging. Physiol Rev 85, 49-95.

Diehl,B., Busch,R.M., Duncan,J.S., Piao,Z., Tkach,J., Luders,H.O., 2008. Abnormalities in diffusion tensor imaging of the uncinate fasciculus relate to reduced memory in temporal lobe epilepsy. Epilepsia 49, 1409-1418.

Diehl,B., Luders,H.O., 2000. Temporal lobe epilepsy: when are invasive recordings needed? Epilepsia 41 Suppl 3, S61-S74.

Diehl,B., Najm,I., Ruggieri,P., Foldvary,N., Mohamed,A., Tkach,J., Morris,H., Barnett,G., Fisher,E., Duda,J., Luders,H.O., 1999. Periictal diffusion-weighted imaging in a case of lesional epilepsy. Epilepsia 40, 1667-1671.

Diehl,B., Najm,I., Ruggieri,P., Tkach,J., Mohamed,A., Morris,H., Wyllie,E., Fisher,E., Duda,J., Lieber,M., Bingaman,W., Luders,H.O., 2001. Postictal diffusion-weighted imaging for the localization of focal epileptic areas in temporal lobe epilepsy. Epilepsia 42, 21-28.

Diehl,B., Piao,Z., Tkach,J., Busch,R.M., LaPresto,E., Najm,I., Bingaman,B., Duncan,J., Luders,H., 2010a. Cortical stimulation for language mapping in focal epilepsy: correlations with tractography of the arcuate fasciculus. Epilepsia 51, 639-646.

Diehl,B., Salek-Haddadi,A., Fish,D.R., Lemieux,L., 2003. Mapping of spikes, slow waves, and motor tasks in a patient with malformation of cortical development using simultaneous EEG and fMRI. Magn Reson Imaging 21, 1167-1173.

Diehl,B., Symms,M.R., Boulby,P.A., Salmenpera,T., Wheeler-Kingshott,C.A., Barker,G.J., Duncan,J.S., 2005. Postictal diffusion tensor imaging. Epilepsy Res 65, 137-146.

Diehl,B., Tkach,J., Piao,Z., Ruggieri,P., LaPresto,E., Liu,P., Fisher,E., Bingaman,W., Najm,I., 2010b. Diffusion tensor imaging in patients with focal epilepsy due to cortical dysplasia in the temporo-occipital region: electro-clinico-pathological correlations. Epilepsy Res 90, 178-187.

Duchowny,M., 2009. Clinical, functional, and neurophysiologic assessment of dysplastic cortical networks: Implications for cortical functioning and surgical management. Epilepsia 50 Suppl 9, 19-27.

Duchowny,M., Jayakar,P., Levin,B., 2000. Aberrant neural circuits in malformations of cortical development and focal epilepsy. Neurology 55, 423-428.

Duffau,H., 2008. The anatomo-functional connectivity of language revisited. New insights provided by electrostimulation and tractography. Neuropsychologia 46, 927-934.

Duffau,H., Capelle,L., Sichez,N., Denvil,D., Lopes,M., Sichez,J.P., Bitar,A., Fohanno,D., 2002. Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. Brain 125, 199-214.

Duffau,H., Gatignol,P., Denvil,D., Lopes,M., Capelle,L., 2003. The articulatory loop: study of the subcortical connectivity by electrostimulation. Neuroreport 14, 2005-2008.

Duffau,H., Gatignol,P., Mandonnet,E., Peruzzi,P., Tzourio-Mazoyer,N., Capelle,L., 2005. New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. Brain 128, 797-810.

Duffau,H., Gatignol,P., Moritz-Gasser,S., Mandonnet,E., 2009. Is the left uncinate fasciculus essential for language? A cerebral stimulation study. J Neurol 256, 382-389.

Duffau,H., Gatignol,P., Mandonnet,E., Capelle,L., Taillandier,L., 2008a. Intraoperative subcortical stimulation mapping of language pathways in a consecutive series of 115 patients with Grade II glioma in the left dominant hemisphere. J Neurosurg 109, 461-471.

Duffau,H., Thiebaut,deSchotten, M., Mandonnet,E., 2008b. White matter functional connectivity as an additional landmark for dominant temporal lobectomy. J Neurol Neurosurg Psychiatry 79, 492-495.

Dumas,de le.Roque. A., Oppenheim,C., Chassoux,F., Rodrigo,S., Beuvon,F., Daumas-Duport,C., Devaux,B., Meder,J.F., 2005. Diffusion tensor imaging of partial intractable epilepsy. Eur Radiol 15, 279-285.

Duncan,J.S., 1997. Imaging and epilepsy. Brain 120 (Pt 2), 339-377.

Ebeling,U., Reulen,H.J., 1988. Neurosurgical topography of the optic radiation in the temporal lobe. Acta Neurochir (Wien) 92, 29-36.

Ebeling,U., von Cramon,D., 1992. Topography of the uncinate fascicle and adjacent temporal fiber tracts. Acta Neurochir (Wien) 115, 143-148.

Eisenberg,R., 1992. Neuroradiology. Eisenberg,R. (Ed.) Radiology: an illustrated history. Mosby, St. Louis, pp. 323-346.

Eisenberg R.,1992. Nuclear Medicine. In: Eisenberg R, editor. Radiology: an illustrated history. St. Louis: Mosby, pp 409-429.

Ellmore,T.M., Beauchamp,M.S., Breier,J.I., Slater,J.D., Kalamangalam,G.P., O'Neill,T.J., Disano,M.A., Tandon,N., 2010. Temporal lobe white matter asymmetry and language laterality in epilepsy patients. Neuroimage 49, 2033-2044.

Ellmore,T.M., Beauchamp,M.S., O'Neill,T.J., Dreyer,S., Tandon,N., 2009. Relationships between essential cortical language sites and subcortical pathways. J Neurosurg 111, 755-766.

Engel, J., Jr., Brown, W.J., Kuhl, D.E., Phelps, M.E., Mazziotta, J.C., Crandall, P.H. 1982. Pathological findings underlying focal temporal lobe hypometabolism in partial epilepsy. Ann Neurol 12(6), 518-528.

Engel,J., Jr., 1993. Appendix I: Historical Perspectives. Engel,J., Jr. (Ed.) Surgical Treatment of the Epilepsies, Second Edition Ed. Raven Press, New York, pp. 695-705.

Engelhorn,T., Hufnagel,A., Weise,J., Baehr,M., Doerfler,A., 2007. Monitoring of acute generalized status epilepticus using multilocal diffusion MR imaging: early prediction of regional neuronal damage. AJNR Am J Neuroradiol 28, 321-327.

Eriksson,S.H., Rugg-Gunn,F.J., Symms,M.R., Barker,G.J., Duncan,J.S., 2001. Diffusion tensor imaging in patients with epilepsy and malformations of cortical development. Brain 124, 617-626.

Fauser,S., Huppertz,H.J., Bast,T., Strobl,K., Pantazis,G., Altenmueller,D.M., Feil,B., Rona,S., Kurth,C., Rating,D., Korinthenberg,R., Steinhoff,B.J., Volk,B., Schulze-Bonhage,A., 2006. Clinical characteristics in focal cortical dysplasia: a retrospective evaluation in a series of 120 patients. Brain 129, 1907-1916.

Fauser,S., Schulze-Bonhage,A., Honegger,J., Carmona,H., Huppertz,H.J., Pantazis,G., Rona,S., Bast,T., Strobl,K., Steinhoff,B.J., Korinthenberg,R., Rating,D., Volk,B., Zentner,J., 2004. Focal cortical dysplasias: surgical outcome in 67 patients in relation to histological subtypes and dual pathology. Brain 127, 2406-2418.

Fingelkurts, A.A., Fingelkurts, A.A., Kahkonen, S. 2005. Functional connectivity in the brain – is it an elusive concept? Neuroscience and Biobehavioral Reviews 28, 827-836.

Finger,S., 1994. The pyramidal system and the motor cortex. Finger,S. (Ed.) Origins of neuroscience. pp. 193-207.

Finger,S., 2000. Paul Broca: Cortical Localization and cerebral dominance. Finger,S. (Ed.) Minds behind the brain: A history of the pioneers and their discoveries. Oxford University Press, New York, pp. 137-154.

Flugel,D., Cercignani,M., Symms,M.R., O'Toole,A., Thompson,P.J., Koepp,M.J., Foong,J., 2006. Diffusion tensor imaging findings and their correlation with neuropsychological deficits in patients with temporal lobe epilepsy and interictal psychosis. Epilepsia 47, 941-944.

Focke,N.K., Yogarajah,M., Bonelli,S.B., Bartlett,P.A., Symms,M.R., Duncan,J.S., 2008a. Voxel-based diffusion tensor imaging in patients with mesial temporal lobe epilepsy and hippocampal sclerosis. Neuroimage 40, 728-737.

Foerster, O and Penfield, W., 1930. Der Narbenzug am und im Gehirn bei traumatischer Epilepsie in seiner Bedeutung fuer das Zustandekommen der Anfaelle und fuer die therapeutische Bekaempfung derselben. Z Gesamte Neurol Psychiatry 125, 475-572.

Fonteijn, H.M.J., Norris, D.G., Verstraten, F.A.J. 2008. Exploring the Anatomical Basis of Effective Connectivity Models with DTI-Based Fiber Tractography. International Journal of Biomedical Imaging, 2008, article ID 423192,

Frey,S., Campbell,J.S., Pike,G.B., Petrides,M., 2008. Dissociating the human language pathways with high angular resolution diffusion fiber tractography. J Neurosci 28, 11435-11444.

Friston, K.J., Frith, C.D., Liddle, P.F., Frackowiak, R.S., 1993. Functional connectivity: the principal-component analysis of large (PET) data sets. J Cereb Blood Flow Metab 13, 5–14.

Friston, K.J.1994. Functional and effective connectivity in neuroimaging:a synthesis. Human Brain Mapping 2, 56–78.

Friston, K., 2002. Beyond phrenology: What can neuroimaging tell us about distributed circuitry? Annual Review of Neuroscience 25, 221–250.

Friston, K.J., Harrison,L., Penny, W. 2003. Dynamic causal modelling. NeuroImage 19 (4), 1273–1302.

Glasser,M.F., Rilling,J.K., 2008. DTI Tractography of the Human Brain's Language Pathways. Cereb Cortex 18(11):2471-82.

Golby,A.J., Poldrack,R.A., Brewer,J.B., Spencer,D., Desmond,J.E., Aron,A.P., Gabrieli,J.D., 2001. Material-specific lateralization in the medial temporal lobe and prefrontal cortex during memory encoding. Brain 124, 1841-1854.

Golby,A.J., Poldrack,R.A., Illes,J., Chen,D., Desmond,J.E., Gabrieli,J.D., 2002. Memory lateralization in medial temporal lobe epilepsy assessed by functional MRI. Epilepsia 43, 855-863.

Govindan,R.M., Makki,M.I., Sundaram,S.K., Juhasz,C., Chugani,H.T., 2008. Diffusion tensor analysis of temporal and extra-temporal lobe tracts in temporal lobe epilepsy. Epilepsy Res 80, 30-41.

Gowers,W., 1886. Diseases of the Nervous System. J.& A. Churchill, London.

Greenberg, M.K., Barsan W.G., Starkman S., 1996. Neuroimaging in the emergency patient presenting with seizure. Neurology 47, 26-32.

Gross,D.W., Bastos,A., Beaulieu,C., 2005. Diffusion tensor imaging abnormalities in focal cortical dysplasia. Can J Neurol Sci 32, 477-482.

Gross,D.W., Concha,L., Beaulieu,C., 2006. Extratemporal white matter abnormalities in mesial temporal lobe epilepsy demonstrated with diffusion tensor imaging. Epilepsia 47, 1360-1363.

Gutnick,M.J., Prince,D.A., 1974. Effects of projected cortical epileptiform discharges on neuronal activities in cat VPL. I. Interictal discharge. J Neurophysiol 37, 1310-1327.

Guye,M., Ranjeva,J.P., Bartolomei,F., Confort-Gouny,S., McGonigal,A., Regis,J., Chauvel,P., Cozzone,P.J., 2007. What is the significance of interictal water diffusion changes in frontal lobe epilepsies? Neuroimage 35, 28-37.

Guye, M., Bartolomei, F., Ranjevaa, J.P., 2008. Imaging structural and functional connectivity: towards a unified definition of human brain organization? Current Opinion in Neurology 21, 393–403.

Hagmann,P., Cammoun,L., Gigandet,X., Gerhard,S., Ellen,G.P., Wedeen,V., Meuli,R., Thiran,J.P., Honey,C.J., Sporns,O., 2010. MR connectomics: Principles and challenges. J Neurosci Methods ,doi:10.1016/j.jneumeth.2010.01.014.

Hajnal,J.V., Doran,M., Hall,A.S., Collins,A.G., Oatridge,A., Pennock,J.M., Young,I.R., Bydder,G.M., 1991. MR imaging of anisotropically restricted diffusion of water in the nervous system: technical, anatomic, and pathologic considerations. J Comput Assist Tomogr 15, 1-18.

Hakyemez,B., Erdogan,C., Yildiz,H., Ercan,I., Parlak,M., 2005. Apparent diffusion coefficient measurements in the hippocampus and amygdala of patients with temporal lobe seizures and in healthy volunteers. Epilepsy Behav 6, 250-256.

Hamandi,K., Powell,H.W., Laufs,H., Symms,M.R., Barker,G.J., Parker,G.J., Lemieux,L., Duncan,J.S., 2008. Combined EEG-fMRI and tractography to

visualise propagation of epileptic activity. J Neurol Neurosurg Psychiatry 79, 594-597.

Hamberger,M.J., 2007. Cortical language mapping in epilepsy: a critical review. Neuropsychol Rev 17, 477-489.

Harvey,A.S., Cross,J.H., Shinnar,S., Mathern,B.W., 2008. Defining the spectrum of international practice in pediatric epilepsy surgery patients. Epilepsia 49, 146-155.

Hauser,W.A., 1992. The natural history of drug resistant epilepsy: epidemiologic considerations. Epilepsy Res Suppl 5, 25-28.

Heiervang,E., Behrens,T.E., Mackay,C.E., Robson,M.D., Johansen-Berg,H., 2006. Between session reproducibility and between subject variability of diffusion MR and tractography measures. Neuroimage 33, 867-877.

Helmstaedter,C., Pohl,C., Elger,C.E., 1995. Relations between verbal and nonverbal memory performance: evidence of confounding effects particularly in patients with right temporal lobe epilepsy. Cortex 31, 345-355.

Henry, T., Chugani, H., Abou-Khalid, B., Theodore, W.H., Swartz, B.E.,1993. Positron Emission Tomography. In: Engel J, Jr., editor. Surgical treatment of the epilepsies. New York: Raven Press, pp 211-232.

Henry,R.G., Berman,J.I., Nagarajan,S.S., Mukherjee,P., Berger,M.S., 2004. Subcortical pathways serving cortical language sites: initial experience with diffusion tensor imaging fiber tracking combined with intraoperative language mapping. Neuroimage 21, 616-622.

Hickok,G., Poeppel,D., 2004. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. Cognition 92, 67-99.

Hickok,G., Poeppel,D., 2007. The cortical organization of speech processing. Nat Rev Neurosci 8, 393-402.

Horsley,V., 1886. Brain-Surgery. Br Med J 2, 670-674.

Hounsfield,G.N., 1980. Computed medical imaging. Science 210, 22-28.

Hufnagel,A., Weber,J., Marks,S., Ludwig,T., de Greiff,A., Leonhardt,G., Widmann,G., Stolke,D., Forsting,M., 2003. Brain diffusion after single seizures. Epilepsia 44, 54-63.

Hugg,J.W., Butterworth,E.J., Kuzniecky,R.I., 1999. Diffusion mapping applied to mesial temporal lobe epilepsy: preliminary observations. Neurology 53, 173-176.

Hutchinson,E., Pulsipher,D., Dabbs,K., Gutierrez,A., Sheth,R., Jones,J., Seidenberg,M., Meyerand,E., Hermann,B., 2010. Children with new-onset epilepsy exhibit diffusion abnormalities in cerebral white matter in the absence of volumetric differences. Epilepsy Res 88, 208-214.

Hwang,D.Y., Golby,A.J., 2006. The brain basis for episodic memory: insights from functional MRI, intracranial EEG, and patients with epilepsy. Epilepsy Behav 8, 115-126.

Isik,U., Dincer,A., Ozek,M.M., 2007. Surgical treatment of polymicrogyria with advanced radiologic and neurophysiologic techniques. Childs Nerv Syst 23, 443-448.

Jack,C.R., Jr., Bentley,M.D., Twomey,C.K., Zinsmeister,A.R., 1990. MR imaging-based volume measurements of the hippocampal formation and anterior temporal lobe: validation studies. Radiology 176, 205-209.

Jack,C.R., Jr., Rydberg,C.H., Krecke,K.N., Trenerry,M.R., Parisi,J.E., Rydberg,J.N., Cascino,G.D., Riederer,S.J., 1996. Mesial temporal sclerosis: diagnosis with fluid-attenuated inversion-recovery versus spin-echo MR imaging. Radiology 199, 367-373.

Jackson,G.D., Connelly,A., Duncan,J.S., Grunewald,R.A., Gadian,D.G., 1993. Detection of hippocampal pathology in intractable partial epilepsy: increased sensitivity with quantitative magnetic resonance T2 relaxometry. Neurology 43, 1793-1799.

Jackson,J., 1863. Convulsive spasms of the right hand and arm preceding epileptic seizures. Medical Times and Gazette 1, 110-111.

Janszky,J., Janszky,I., Schulz,R., Hoppe,M., Behne,F., Pannek,H.W., Ebner,A., 2005. Temporal lobe epilepsy with hippocampal sclerosis: predictors for long-term surgical outcome. Brain 128, 395-404.

Janszky,J., Jokeit,H., Heinemann,D., Schulz,R., Woermann,F.G., Ebner,A., 2003. Epileptic activity influences the speech organization in medial temporal lobe epilepsy. Brain 126, 2043-2051.

Janszky,J., Ollech,I., Jokeit,H., Kontopoulou,K., Mertens,M., Pohlmann-Eden,B., Ebner,A., Woermann,F.G., 2004. Epileptic activity influences the lateralization of mesiotemporal fMRI activity. Neurology 63, 1813-1817.

Jayakar,P., Duchowny,M., Alvarez,L., Resnick,T., 1994. Intraictal activation in the neocortex: a marker of the epileptogenic region. Epilepsia 35, 489-494.

Jeha,L.E., Najm,I.M., Bingaman,W.E., Khandwala,F., Widdess-Walsh,P., Morris,H.H., Dinner,D.S., Nair,D., Foldvary-Schaeffer,N., Prayson,R.A., Comair,Y., O'Brien,R., Bulacio,J., Gupta,A., Luders,H.O., 2006. Predictors of

outcome after temporal lobectomy for the treatment of intractable epilepsy. Neurology 66, 1938-1940.

Jellison,B.J., Field,A.S., Medow,J., Lazar,M., Salamat,M.S., Alexander,A.L., 2004. Diffusion tensor imaging of cerebral white matter: a pictorial review of physics, fiber tract anatomy, and tumor imaging patterns. AJNR Am J Neuroradiol 25, 356-369.

Johansen-Berg,H., Rushworth,M.F., 2009. Using diffusion imaging to study human connectional anatomy. Annu Rev Neurosci 32, 75-94.

Jones,D.K., 2008. Studying connections in the living human brain with diffusion MRI. Cortex 44, 936-952.

Jones,D.K., Pierpaoli,C., 2005. Confidence mapping in diffusion tensor magnetic resonance imaging tractography using a bootstrap approach. Magn Reson Med 53, 1143-1149.

Kerschensteiner,M., Schwab,M.E., Lichtman,J.W., Misgeld,T., 2005. In vivo imaging of axonal degeneration and regeneration in the injured spinal cord. Nat Med 11, 572-577.

Kikuta,K., Takagi,Y., Nozaki,K., Hanakawa,T., Okada,T., Miki,Y., Fushimi,Y., Fukuyama,H., Hashimoto,N., 2006. Early experience with 3-T magnetic resonance tractography in the surgery of cerebral arteriovenous malformations in and around the visual pathway. Neurosurgery 58, 331-337.

Kim,H., Piao,Z., Liu,P., Bingaman,W., Diehl,B., 2008. Secondary white matter degeneration of the corpus callosum in patients with intractable temporal lobe epilepsy: a diffusion tensor imaging study. Epilepsy Res 81, 136-142.

Kirchhoff,B.A., Wagner,A.D., Maril,A., Stern,C.E., 2000. Prefrontal-temporal circuitry for episodic encoding and subsequent memory. J Neurosci 20, 6173-6180.

Knowlton, R.C., Elgavish, R.A., Limdi, N., Bartolucci, A., Ojha, B., Blount, J., Burneo, J.G. Ver Hoef, L., Paige, L., Faught, E., Kankirawatana, P., Riley, K., Kuzniecky, R., 2008a. Functional imaging: I. Relative predictive value of intracranial electroencephalography. Ann Neurol. 64, 25–34.

Knowlton, R.C., Elgavish, R.A., Bartolucci A., Ojha, B., Limdi, N., Blount, J., Burneo, J.G., Ver Hoef, L., Paige, L., Faught, E., Kankirawatana, P., Riley, K., Kuzniecky, R., 2008b. Functional imaging II. Prediction of epilepsy surgery outcome. Ann Neurol. 64, 35–41.

Koch M.A., Norris D.G., Hund-Georgiadis M. 2002. An investigation of functional and anatomical connectivity using magnetic resonance imaging. Neuroimage16,241–50.

Koepp,M.J., Woermann,F.G., 2005. Imaging structure and function in refractory focal epilepsy. Lancet Neurol 4, 42-53.

Konermann,S., Marks,S., Ludwig,T., Weber,J., de Greiff,A., Dorfler,A., Leonhardt,G., Wiedemayer,H., Diener,H.C., Hufnagel,A., 2003. Presurgical evaluation of epilepsy by brain diffusion: MR-detected effects of flumazenil on the epileptogenic focus. Epilepsia 44, 399-407.

Krause, F. Die operative Behandlung der Epilepsie. 1909. Med Klin Berlin , 1418-11422.

Krause, F. Surgery of the Brain and Spinal Cord. 1910. London, HK Lewis.

Kuhl, D.E., Engel, J., Jr., Phelps, M.E., Kowell, A.P. 1978. Epileptic patterns of local cerebral metabolism and perfusion in man: investigation by emission computed tomography of 18F-fluorodeoxyglucose and 13N-ammonia. Trans Am Neurol Assoc 103,52-53.

Kuhl, D.E., Engel, J. Jr., Phelps, M.E., Selin, C. 1980. Epileptic patterns of local cerebral metabolism and perfusion in humans determined by emission computed tomography of 18FDG and 13NH3. Ann Neurol 8(4), 348-360.

Kubicki,M., Westin,C.F., Maier,S.E., Frumin,M., Nestor,P.G., Salisbury,D.F., Kikinis,R., Jolesz,F.A., McCarley,R.W., Shenton,M.E., 2002. Uncinate fasciculus findings in schizophrenia: a magnetic resonance diffusion tensor imaging study. Am J Psychiatry 159, 813-820.

Kuzniecky,R.I., Bilir,E., Gilliam,F., Faught,E., Palmer,C., Morawetz,R., Jackson,G., 1997. Multimodality MRI in mesial temporal sclerosis: relative sensitivity and specificity. Neurology 49, 774-778.

Kwan,P., Brodie,M.J., 2003. Clinical trials of antiepileptic medications in newly diagnosed patients with epilepsy. Neurology 60, S2-12.

Kwong,K.K., Belliveau,J.W., Chesler,D.A., Goldberg,I.E., Weisskoff,R.M., Poncelet,B.P., Kennedy,D.N., Hoppel,B.E., Cohen,M.S., Turner,R., ., 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci U S A 89, 5675-5679.

Le Bihan,D., Mangin,J.F., Poupon,C., Clark,C.A., Pappata,S., Molko,N., Chabriat,H., 2001. Diffusion tensor imaging: concepts and applications. J Magn Reson Imaging 13, 534-546.

Le Bihan,D., Van Zijl,P., 2002. From the diffusion coefficient to the diffusion tensor. NMR Biomed 15, 431-434.

Leblanc,R., Robitaille,Y., Andermann,F., Ptito,A., 1995. Retained language in dysgenic cortex: case report. Neurosurgery 37, 992-997.

Leclercq,D., Duffau,H., Delmaire,C., Capelle,L., Gatignol,P., Ducros,M., Chiras,J., Lehericy,S., 2010. Comparison of diffusion tensor imaging tractography of language tracts and intraoperative subcortical stimulations. J Neurosurg 112, 503-511.

Lee,S.K., Kim,D.I., Kim,J., Kim,D.J., Kim,H.D., Kim,D.S., Mori,S., 2005. Diffusion-tensor MR imaging and fiber tractography: a new method of describing aberrant fiber connections in developmental CNS anomalies. Radiographics 25, 53-65.

Lee,S.K., Kim,D.I., Mori,S., Kim,J., Kim,H.D., Heo,K., Lee,B.I., 2004. Diffusion tensor MRI visualizes decreased subcortical fiber connectivity in focal cortical dysplasia. Neuroimage 22, 1826-1829.

Lesser,R.P., Luders,H., Morris,H.H., Dinner,D.S., Klem,G., Hahn,J., Harrison,M., 1986. Electrical stimulation of Wernicke's area interferes with comprehension. Neurology 36, 658-663.

Lhatoo,S.D., Solomon,J.K., McEvoy,A.W., Kitchen,N.D., Shorvon,S.D., Sander,J.W., 2003. A prospective study of the requirement for and the provision of epilepsy surgery in the United Kingdom. Epilepsia 44, 673-676.

Lieb,J.P., Hoque,K., Skomer,C.E., Song,X.W., 1987. Inter-hemispheric propagation of human mesial temporal lobe seizures: a coherence/phase analysis. Electroencephalogr Clin Neurophysiol 67, 101-119.

Lim,C.C., Yin,H., Loh,N.K., Chua,V.G., Hui,F., Barkovich,A.J., 2005. Malformations of cortical development: high-resolution MR and diffusion tensor imaging of fiber tracts at 3T. AJNR Am J Neuroradiol 26, 61-64.

Lu,L.H., Crosson,B., Nadeau,S.E., Heilman,K.M., Gonzalez-Rothi,L.J., Raymer,A., Gilmore,R.L., Bauer,R.M., Roper,S.N., 2002. Category-specific naming deficits for objects and actions: semantic attribute and grammatical role hypotheses. Neuropsychologia 40, 1608-1621.

Luders,H., Lesser,R.P., Hahn,J., Dinner,D.S., Morris,H., Resor,S., Harrison,M., 1986. Basal temporal language area demonstrated by electrical stimulation. Neurology 36, 505-510.

Ludwig,B.I., Marsan,C.A., Van Buren,J., 1976. Depth and direct cortical recording in seizure disorders of extratemporal origin. Neurology 26, 1085-1099.

Lux,H.D., Heinemann,U., Dietzel,I., 1986. Ionic changes and alterations in the size of the extracellular space during epileptic activity. Adv Neurol 44, 619-639.

Maes F, Collignon A, Vandermeulen D, Marchal G, Suetens P, 1997. Multimodality image registration by maximation of mutual information. IEEE Trans Med Imaging 16, 187-198.

Maes,F., Vandermeulen,D., Suetens,P., 1999. Comparative evaluation of multiresolution optimization strategies for multimodality image registration by maximization of mutual information. Med Image Anal 3, 373-386.

Markowitsch,H.J., Emmans,D., Irle,E., Streicher,M., Preilowski,B., 1985. Cortical and subcortical afferent connections of the primate's temporal pole: a study of rhesus monkeys, squirrel monkeys, and marmosets. J Comp Neurol 242, 425-458.

Marusic,P., Najm,I.M., Ying,Z., Prayson,R., Rona,S., Nair,D., Hadar,E., Kotagal,P., Bej,M.D., Wyllie,E., Bingaman,W., Luders,H., 2002. Focal cortical dysplasias in eloquent cortex: functional characteristics and correlation with MRI and histopathologic changes. Epilepsia 43, 27-32.

Mathern,G.W., 2009. Challenges in the surgical treatment of epilepsy patients with cortical dysplasia. Epilepsia 50 Suppl 9, 45-50.

Mattson,R.H., 1992. Drug treatment of uncontrolled seizures. Epilepsy Res Suppl 5, 29-35.

Mayanagi,Y., Watanabe,E., Kaneko,Y., 1996. Mesial temporal lobe epilepsy: clinical features and seizure mechanism. Epilepsia 37 Suppl 3, 57-60.

Mayeux,R., Brandt,J., Rosen,J., Benson,D.F., 1980. Interictal memory and language impairment in temporal lobe epilepsy. Neurology 30, 120-125.

McDonald,C.R., Ahmadi,M.E., Hagler,D.J., Tecoma,E.S., Iragui,V.J., Gharapetian,L., Dale,A.M., Halgren,E., 2008. Diffusion tensor imaging correlates of memory and language impairments in temporal lobe epilepsy. Neurology 71, 1869-1876.

McLachlan,R.S., Nicholson,R.L., Black,S., Carr,T., Blume,W.T., 1985. Nuclear magnetic resonance imaging, a new approach to the investigation of refractory temporal lobe epilepsy. Epilepsia 26, 555-562.

McRae, DL., 1948.Focal Epilepsy: Correlation of the pathological and radiological findings. Radiology 50, 439-457..

Meng,L., Xiang,J., Kotecha,R., Rose,D., Zhao,H., Zhao,D., Yang,J., Degrauw,T., 2010. White matter abnormalities in children and adolescents with temporal lobe epilepsy. Magn Reson Imaging doi:10.1016/j.mri.2010.03.046.

Minati,L., Grisoli,M., Bruzzone,M.G., 2007. MR spectroscopy, functional MRI, and diffusion-tensor imaging in the aging brain: a conceptual review. J Geriatr Psychiatry Neurol 20, 3-21.

Moore, G. 1948. Use of radioactive diiodofluorescein in the diagnosis and localization of brain tumors. Science 107, 56-57.

Mori,S., Crain,B.J., Chacko,V.P., van Zijl,P.C., 1999. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol 45, 265-269.

Mori,S., van Zijl,P.C., 2002. Fiber tracking: principles and strategies - a technical review. NMR Biomed 15, 468-480.

Mori, S., Wakana, S, Nagae-Poetscher, LM, and Zijl, PCM. MRI Atlas of Human White Matter. First edition, 2005. Amsterdam, Elsevier p.61.

Mori,S., Zhang,J., 2006. Principles of diffusion tensor imaging and its applications to basic neuroscience research. Neuron 51, 527-539.

Nair,D.R., Burgess,R., McIntyre,C.C., Luders,H., 2008. Chronic subdural electrodes in the management of epilepsy. Clin Neurophysiol 119, 11-28.

Najm,I.M., Tilelli,C.Q., Oghlakian,R., 2007. Pathophysiological mechanisms of focal cortical dysplasia: a critical review of human tissue studies and animal models. Epilepsia 48 Suppl 2, 21-32.

Nakamura,M., McCarley,R.W., Kubicki,M., Dickey,C.C., Niznikiewicz,M.A., Voglmaier,M.M., Seidman,L.J., Maier,S.E., Westin,C.F., Kikinis,R., Shenton,M.E., 2005. Fronto-temporal disconnectivity in schizotypal personality disorder: a diffusion tensor imaging study. Biol Psychiatry 58, 468-478.

Nakasu,Y., Nakasu,S., Kizuki,H., Uemura,S., Morikawa,S., Inubushi,T., Handa,J., 1995a. Changes in water diffusion of rat limbic system during status epilepticus elicited by kainate. Psychiatry Clin Neurosci 49, S228-S230.

Nakasu,Y., Nakasu,S., Morikawa,S., Uemura,S., Inubushi,T., Handa,J., 1995b. Diffusion-weighted MR in experimental sustained seizures elicited with kainic acid. AJNR Am J Neuroradiol 16, 1185-1192.

Nestor,P.G., Kubicki,M., Gurrera,R.J., Niznikiewicz,M., Frumin,M., McCarley,R.W., Shenton,M.E., 2004. Neuropsychological correlates of diffusion tensor imaging in schizophrenia. Neuropsychology 18, 629-637.

Nilsson,D., Go,C., Rutka,J.T., Rydenhag,B., Mabbott,D.J., Snead,O.C., III, Raybaud,C.R., Widjaja,E., 2008. Bilateral diffusion tensor abnormalities of temporal lobe and cingulate gyrus white matter in children with temporal lobe epilepsy. Epilepsy Res 81, 128-135.

Nimsky,C., Ganslandt,O., Fahlbusch,R., 2007a. Implementation of fiber tract navigation. Neurosurgery 61, 306-317.

Nimsky,C., Ganslandt,O., Hastreiter,P., Wang,R., Benner,T., Sorensen,A.G., Fahlbusch,R., 2007b. Preoperative and intraoperative diffusion tensor imaging-based fiber tracking in glioma surgery. Neurosurgery 61, 178-185.

Nimsky,C., Grummich,P., Sorensen,A.G., Fahlbusch,R., Ganslandt,O., 2005. Visualization of the pyramidal tract in glioma surgery by integrating diffusion tensor imaging in functional neuronavigation. Zentralbl Neurochir 66, 133-141.

Niogi,S.N., McCandliss,B.D., 2006. Left lateralized white matter microstructure accounts for individual differences in reading ability and disability. Neuropsychologia 44, 2178-2188.

Nisbet, A., Ratcliffe, G., Ellam, S., Rankin, S., Maisey, M. 1983. Clinical indications for optimal use of radionuclide brain scan. Br.J.Radiol. 56, 377-381.

Nucifora,P.G., Verma,R., Melhem,E.R., Gur,R.E., Gur,R.C., 2005. Leftward asymmetry in relative fiber density of the arcuate fasciculus. Neuroreport 16, 791-794.

Nunez, P.L. 2000. Toward a quantitative description of large scale neocortical dynamic function and EEG. Behavioral and Brain Sciences 23, 371-437.

Obler,L.K., Rykhlevskaia,E., Schnyer,D., Clark-Cotton,M.R., Spiro,A., III, Hyun,J., Kim,D.S., Goral,M., Albert,M.L., 2010. Bilateral brain regions associated with naming in older adults. Brain Lang 113, 113-123.

Ogawa,S., Lee,T.M., Kay,A.R., Tank,D.W., 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A 87, 9868-9872.

Ogawa,S., Tank,D.W., Menon,R., Ellermann,J.M., Kim,S.G., Merkle,H., Ugurbil,K., 1992. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci U S A 89, 5951-5955.

Oh,J.B., Lee,S.K., Kim,K.K., Song,I.C., Chang,K.H., 2004. Role of immediate postictal diffusion-weighted MRI in localizing epileptogenic foci of mesial temporal lobe epilepsy and non-lesional neocortical epilepsy. Seizure 13, 509-516.

Ojemann,G., Ojemann,J., Lettich,E., Berger,M., 2008. Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. 1989. J Neurosurg 108, 411-421.

Ojemann,G.A., Whitaker,H.A., 1978. Language localization and variability. Brain Lang 6, 239-260.

Palmini,A., Gambardella,A., Andermann,F., Dubeau,F., da Costa,J.C., Olivier,A., Tampieri,D., Gloor,P., Quesney,F., Andermann,E., 1995. Intrinsic epileptogenicity of human dysplastic cortex as suggested by corticography and surgical results. Ann Neurol 37, 476-487.

Palmini,A., Najm,I., Avanzini,G., Babb,T., Guerrini,R., Foldvary-Schaefer,N., Jackson,G., Luders,H.O., Prayson,R., Spreafico,R., Vinters,H.V., 2004. Terminology and classification of the cortical dysplasias. Neurology 62, S2-S8.

Park,H.J., Westin,C.F., Kubicki,M., Maier,S.E., Niznikiewicz,M., Baer,A., Frumin,M., Kikinis,R., Jolesz,F.A., McCarley,R.W., Shenton,M.E., 2004. White matter hemisphere asymmetries in healthy subjects and in schizophrenia: a diffusion tensor MRI study. Neuroimage 23, 213-223.

Parker,G.J., Alexander,D.C., 2003. Probabilistic Monte Carlo based mapping of cerebral connections utilising whole-brain crossing fibre information. Inf Process Med Imaging 18, 684-695.

Parker,G.J., Haroon,H.A., Wheeler-Kingshott,C.A., 2003. A framework for a streamline-based probabilistic index of connectivity (PICo) using a structural interpretation of MRI diffusion measurements. J Magn Reson Imaging 18, 242-254.

Penfield W, 1959. Evidence from Cortical Mapping. Princeton University Press, Princeton NJ.

Penfield, W and Erickson TC. 1941.Epilepsy and cerebral localization. Springfield, IL, Charles C. Thomas.

Penfield,W., Jasper,H., 1954. Epilepsy and the functional anatomy of the human brain. Cranial Roentgenography. Little, Brown and Company, Boston, pp. 667-691.

Penfield,W., Flanigan,H., 1950. The surgical therapy of temporal lobe seizures. Trans Am Neurol Assoc 51, 146-149.

Penny,W.D., Stephan,K.E., Mechelli,A., Friston,K.J., 2004. Modelling functional integration: a comparison of structural equation and dynamic causal models. Neuroimage 23 Suppl 1, S264-S274.

Perrin,M., Poupon,C., Rieul,B., Leroux,P., Constantinesco,A., Mangin,J.F., Lebihan,D., 2005. Validation of q-ball imaging with a diffusion fibre-crossing phantom on a clinical scanner. Philos Trans R Soc Lond B Biol Sci 360, 881-891.

Pierpaoli,C., Barnett,A., Pajevic,S., Chen,R., Penix,L.R., Virta,A., Basser,P., 2001. Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. Neuroimage 13, 1174-1185.

Pierpaoli,C., Jezzard,P., Basser,P.J., Barnett,A., Di Chiro,G., 1996. Diffusion tensor MR imaging of the human brain. Radiology 201, 637-648.

Powell,H.W., Koepp,M.J., Richardson,M.P., Symms,M.R., Thompson,P.J., Duncan,J.S., 2004. The application of functional MRI of memory in temporal lobe epilepsy: a clinical review. Epilepsia 45, 855-863.

Powell,H.W., Parker,G.J., Alexander,D.C., Symms,M.R., Boulby,P.A., Barker,G.J., Thompson,P.J., Koepp,M.J., Duncan,J.S., 2008. Imaging language pathways predicts postoperative naming deficits. J Neurol Neurosurg Psychiatry 79, 327-330.

Powell,H.W., Parker,G.J., Alexander,D.C., Symms,M.R., Boulby,P.A., Wheeler-Kingshott,C.A., Barker,G.J., Koepp,M.J., Duncan,J.S., 2005. MR tractography predicts visual field defects following temporal lobe resection. Neurology 65, 596-599.

Powell,H.W., Parker,G.J., Alexander,D.C., Symms,M.R., Boulby,P.A., Wheeler-Kingshott,C.A., Barker,G.J., Koepp,M.J., Duncan,J.S., 2007a. Abnormalities of language networks in temporal lobe epilepsy. Neuroimage 36, 209-221.

Powell,H.W., Parker,G.J., Alexander,D.C., Symms,M.R., Boulby,P.A., Wheeler-Kingshott,C.A., Barker,G.J., Noppeney,U., Koepp,M.J., Duncan,J.S., 2006. Hemispheric asymmetries in language-related pathways: a combined functional MRI and tractography study. Neuroimage 32, 388-399.

Powell,H.W., Richardson,M.P., Symms,M.R., Boulby,P.A., Thompson,P.J., Duncan,J.S., Koepp,M.J., 2007b. Reorganization of verbal and nonverbal memory in temporal lobe epilepsy due to unilateral hippocampal sclerosis. Epilepsia 48, 1512-1525.

Practice parameter: 1996. Neuroimaging in the emergency patient presenting with seizure--summary statement. Quality Standards Subcommittee of the American Academy of Neurology in cooperation with American College of Emergency Physicians, American Association of Neurological Surgeons, and American Society of Neuroradiology. Neurology 47, 288-291.

Preul,M.C., Leblanc,R., Cendes,F., Dubeau,F., Reutens,D., Spreafico,R., Battaglia,G., Avoli,M., Langevin,P., Arnold,D.L., Villemure,J.G., 1997. Function and organization in dysgenic cortex. Case report. J Neurosurg 87, 113-121.

Price,C.J., 2000. The anatomy of language: contributions from functional neuroimaging. J Anat 197 Pt 3, 335-359.

Price,C.J., 2010. The anatomy of language: a review of 100 fMRI studies published in 2009. Ann N Y Acad Sci 1191, 62-88.

Purcell, EM, Torrey, HC, and Pound, RV., 1946. Resonance adsorption by nuclear magnetic moments in a solid. Phys Rev 69, 37-38..

Ranck,J.B., Jr., 1975. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res 98, 417-440.

Rasmussen T and Milner B. Clinical and surgical studies of cerebral speech areas in men. 1975. Berlin, New York, Springer. Cerebral Localization: an Ottfried Foerster Smposium, pp.238-257.

Rasmussen,T., Feindel,W., 1991. Temporal lobectomy: review of 100 cases with major hippocampectomy. Can J Neurol Sci 18, 601-602.

Richardson, M. 2010. Current themes in neuroimaging of epilepsy: Brain networks, dynamic phenomena, and clinical relevance. Clinical Neurophysiology 121, 1153-1175.

Righini,A., Pierpaoli,C., Alger,J.R., Di Chiro,G., 1994. Brain parenchyma apparent diffusion coefficient alterations associated with experimental complex partial status epilepticus. Magn Reson Imaging 12, 865-871.

Rodrigo,S., Oppenheim,C., Chassoux,F., Golestani,N., Cointepas,Y., Poupon,C., Semah,F., Mangin,J.F., Le Bihan,D., Meder,J.F., 2007. Uncinate fasciculus fiber tracking in mesial temporal lobe epilepsy. Initial findings. Eur Radiol 17, 1663-1668.

Rodrigo,S., Oppenheim,C., Chassoux,F., Hodel,J., de Vanssay,A., Baudoin-Chial,S., Devaux,B., Meder,J.F., 2008. Language lateralization in temporal lobe epilepsy using functional MRI and probabilistic tractography. Epilepsia 49, 1367-1376.

Roentgen, WC. 1895. Ueber eine neue Art von Strahlen (vorlaeufige Mitteilung). Sitzungsberichte der Physikalischen Medizingesellschaft zu Wuerzburg , pp.132-141.

Rolls,E.T., 2000. Hippocampo-cortical and cortico-cortical backprojections. Hippocampus 10, 380-388.

Rosenkranz,K., Lemieux,L., 2010. Present and future of simultaneous EEG-fMRI. MAGMA PMID: 20101434.

Rosenow,F., Luders,H., 2001. Presurgical evaluation of epilepsy. Brain 124, 1683-1700.

Rovaris,M., Iannucci,G., Falautano,M., Possa,F., Martinelli,V., Comi,G., Filippi,M., 2002. Cognitive dysfunction in patients with mildly disabling relapsing-remitting multiple sclerosis: an exploratory study with diffusion tensor MR imaging. J Neurol Sci 195, 103-109.

Rugg-Gunn,F.J., Eriksson,S.H., Symms,M.R., Barker,G.J., Duncan,J.S., 2001. Diffusion tensor imaging of cryptogenic and acquired partial epilepsies. Brain 124, 627-636.

Rugg-Gunn,F.J., Eriksson,S.H., Symms,M.R., Barker,G.J., Thom,M., Harkness,W., Duncan,J.S., 2002. Diffusion tensor imaging in refractory epilepsy. Lancet 359, 1748-1751.

Sabsevitz,D.S., Swanson,S.J., Hammeke,T.A., Spanaki,M.V., Possing,E.T., Morris,G.L., III, Mueller,W.M., Binder,J.R., 2003. Use of preoperative functional neuroimaging to predict language deficits from epilepsy surgery. Neurology 60, 1788-1792.

Salek-Haddadi,A., Diehl,B., Hamandi,K., Merschhemke,M., Liston,A., Friston,K., Duncan,J.S., Fish,D.R., Lemieux,L., 2006. Hemodynamic correlates of epileptiform discharges: an EEG-fMRI study of 63 patients with focal epilepsy. Brain Res 1088, 148-166.

Salek-Haddadi,A., Friston,K.J., Lemieux,L., Fish,D.R., 2003. Studying spontaneous EEG activity with fMRI. Brain Res Brain Res Rev 43, 110-133.

Salmenpera,T.M., Symms,M.R., Boulby,P.A., Barker,G.J., Duncan,J.S., 2006. Postictal diffusion weighted imaging. Epilepsy Res 70, 133-143.

Salmenpera,T.M., Symms,M.R., Rugg-Gunn,F.J., Boulby,P.A., Free,S.L., Barker,G.J., Yousry,T.A., Duncan,J.S., 2007. Evaluation of quantitative magnetic resonance imaging contrasts in MRI-negative refractory focal epilepsy. Epilepsia 48, 229-237.

Sanai,N., Mirzadeh,Z., Berger,M.S., 2008. Functional outcome after language mapping for glioma resection. N Engl J Med 358, 18-27.

Schacter,D.L., Wagner,A.D., 1999. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus 9, 7-24.

Schmahmann,J.D., Pandya,D.N., Wang,R., Dai,G., D'Arceuil,H.E., de Crespigny,A.J., Wedeen,V.J., 2007. Association fibre pathways of the brain:

parallel observations from diffusion spectrum imaging and autoradiography. Brain 130, 630-653.

Schueller, A. Roentgendiagnostik der Erkrankungen des Kopfes. 1912. Vienna, Leipzig, Hoelder.

Selden,N.R., Gitelman,D.R., Salamon-Murayama,N., Parrish,T.B., Mesulam,M.M., 1998. Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. Brain 121 (Pt 12), 2249-2257.

Shorvon,S., 1987. Imaging in the Investigation of Epilepsy. Epilepsy. University Press, Cambridge, pp. 201-228.

Simpson,D., 2005. Phrenology and the neurosciences: contributions of F. J. Gall and J. G. Spurzheim. ANZ J Surg 75, 475-482.

Sisodiya,S.M., 2000. Surgery for malformations of cortical development causing epilepsy. Brain 123 (Pt 6), 1075-1091.

Song,S.K., Sun,S.W., Ju,W.K., Lin,S.J., Cross,A.H., Neufeld,A.H., 2003. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage 20, 1714-1722.

Song,S.K., Sun,S.W., Ramsbottom,M.J., Chang,C., Russell,J., Cross,A.H., 2002. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage 17, 1429-1436.

Song,S.K., Yoshino,J., Le,T.Q., Lin,S.J., Sun,S.W., Cross,A.H., Armstrong,R.C., 2005. Demyelination increases radial diffusivity in corpus callosum of mouse brain. Neuroimage 26, 132-140.

Spencer,S.S., 1994. The relative contributions of MRI, SPECT, and PET imaging in epilepsy. Epilepsia 35 Suppl 6, S72-S89.

Spencer,S.S., 2002. Neural networks in human epilepsy: evidence of and implications for treatment. Epilepsia 43, 219-227.

Spencer,S.S., Spencer,D.D., Williamson,P.D., Mattson,R., 1990. Combined depth and subdural electrode investigation in uncontrolled epilepsy. Neurology 40, 74-79.

Sperling,M.R., Wilson,G., Engel,J., Jr., Babb,T.L., Phelps,M., Bradley,W., 1986. Magnetic resonance imaging in intractable partial epilepsy: correlative studies. Ann Neurol 20, 57-62.

Springer,J.A., Binder,J.R., Hammeke,T.A., Swanson,S.J., Frost,J.A., Bellgowan,P.S., Brewer,C.C., Perry,H.M., Morris,G.L., Mueller,W.M., 1999.

Language dominance in neurologically normal and epilepsy subjects: a functional MRI study. Brain 122 (Pt 11), 2033-2046.

Squire,L.R., Zola-Morgan,S., 1991. The medial temporal lobe memory system. Science 253, 1380-1386.

Stieltjes,B., Kaufmann,W.E., van Zijl,P.C., Fredericksen,K., Pearlson,G.D., Solaiyappan,M., Mori,S., 2001. Diffusion tensor imaging and axonal tracking in the human brainstem. Neuroimage 14, 723-735.

Studholme,C., Hill,D.L., Hawkes,D.J., 1999. An overlap invariant entropy measure of 3D medical image alignment. Pattern Recognition 32, 71-86.

Tao,J.X., Ray,A., Hawes-Ebersole,S., Ebersole,J.S., 2005. Intracranial EEG substrates of scalp EEG interictal spikes. Epilepsia 46, 669-676.

Tassi,L., Colombo,N., Garbelli,R., Francione,S., Lo,R.G., Mai,R., Cardinale,F., Cossu,M., Ferrario,A., Galli,C., Bramerio,M., Citterio,A., Spreafico,R., 2002. Focal cortical dysplasia: neuropathological subtypes, EEG, neuroimaging and surgical outcome. Brain 125, 1719-1732.

Tassi,L., Meroni,A., Deleo,F., Villani,F., Mai,R., Russo,G.L., Colombo,N., Avanzini,G., Falcone,C., Bramerio,M., Citterio,A., Garbelli,R., Spreafico,R., 2009. Temporal lobe epilepsy: neuropathological and clinical correlations in 243 surgically treated patients. Epileptic Disord 11, 281-292.

Taylor,D.G., Bushell,M.C., 1985. The spatial mapping of translational diffusion coefficients by the NMR imaging technique. Phys Med Biol 30, 345-349.

Telfeian,A.E., Connors,B.W., 1998. Layer-specific pathways for the horizontal propagation of epileptiform discharges in neocortex. Epilepsia 39, 700-708.

Temkin, O., 1933.The doctrine of epilepsy in hippocratic writings. Bull.Inst.Hist.Med. I, 277-322.

Theodore, W.H., Newmark, M.E., Sato, S., Brooks, R., Patronas, N., De La PR et al. 1983. [18F]fluorodeoxyglucose positron emission tomography in refractory complex partial seizures. Ann Neurol 14(4),429-437.

Theodore,W.H., Dorwart,R., Holmes,M., Porter,R.J., DiChiro,G., 1986. Neuroimaging in refractory partial seizures: comparison of PET, CT, and MRI. Neurology 36, 750-759.

Thivard,L., Adam,C., Hasboun,D., Clemenceau,S., Dezamis,E., Lehericy,S., Dormont,D., Chiras,J., Baulac,M., Dupont,S., 2006. Interictal diffusion MRI in partial epilepsies explored with intracerebral electrodes. Brain 129, 375-385.

Thivard,L., Hombrouck,J., du Montcel,S.T., Delmaire,C., Cohen,L., Samson,S., Dupont,S., Chiras,J., Baulac,M., Lehericy,S., 2005. Productive and perceptive language reorganization in temporal lobe epilepsy. Neuroimage 24, 841-851.

Trevelyan,A.J., Sussillo,D., Yuste,R., 2007. Feedforward inhibition contributes to the control of epileptiform propagation speed. J Neurosci 27, 3383-3387.

Trivedi,R., Gupta,R.K., Hasan,K.M., Hou,P., Prasad,K.N., Narayana,P.A., 2006. Diffusion tensor imaging in polymicrogyria: a report of three cases. Neuroradiology 48, 422-427.

van Buren,J.M., Ajmone-Marsan,C., Mutsuga,N., Sadowsky,D., 1975. Surgery of temporal lobe epilepsy. Adv Neurol 8, 155-196.

van Buren,J.M., Fedio,P., Frederick,G.C., 1978. Mechanism and localization of speech in the parietotemporal cortex. Neurosurgery 2, 233-239.

Vaz,S.A., 2004. Nonverbal memory functioning following right anterior temporal lobectomy: a meta-analytic review. Seizure 13, 446-452.

Vernooij,M.W., Smits,M., Wielopolski,P.A., Houston,G.C., Krestin,G.P., van der,L.A., 2007. Fiber density asymmetry of the arcuate fasciculus in relation to functional hemispheric language lateralization in both right- and left-handed healthy subjects: a combined fMRI and DTI study. Neuroimage 35, 1064-1076.

Vigneau,M., Beaucousin,V., Herve,P.Y., Duffau,H., Crivello,F., Houde,O., Mazoyer,B., Tzourio-Mazoyer,N., 2006. Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing. Neuroimage 30, 1414-1432.

Vollmar C., O'Muircheartaigh, J., Barker, G.J., Symms, M.R., Thompson, P., Kumari, V., Duncan, J.S., Richardson M.P., Koepp M.J. 2010. Identical, but not the same: Intra-site and inter-site reproducibility of fractional anisotropy measures on two 3.0 T scanners. NeuroImage 51: 1384–1394.

Vulliemoz,S., Lemieux,L., Daunizeau,J., Michel,C.M., Duncan,J.S., 2009. The combination of EEG Source Imaging and EEG-correlated functional MRI to map epileptic networks. Epilepsia 51(4):491-505.

Vulliemoz,S., Rodionov,R., Carmichael,D.W., Thornton,R., Guye,M., Lhatoo,S.D., Michel,C.M., Duncan,J.S., Lemieux,L., 2010. Continuous EEG source imaging enhances analysis of EEG-fMRI in focal epilepsy. Neuroimage 49, 3219-3229.

Wagner,A.D., Schacter,D.L., Rotte,M., Koutstaal,W., Maril,A., Dale,A.M., Rosen,B.R., Buckner,R.L., 1998. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science 281, 1188-1191.

Wakana,S., Jiang,H., Nagae-Poetscher,L.M., van Zijl,P.C., Mori,S., 2004. Fiber tract-based atlas of human white matter anatomy. Radiology 230, 77-87.

Wall,C.J., Kendall,E.J., Obenaus,A., 2000. Rapid alterations in diffusion-weighted images with anatomic correlates in a rodent model of status epilepticus. AJNR Am J Neuroradiol 21, 1841-1852.

Wang R. DTI task card. [1.7]. 2006. Martinos Center for Biomedical Imaging, MGH. http://www.nmr.mgh.harvard.edu/~rpwang/siemens/dti_taskcard/new/

Wang,Y., Majors,A., Najm,I., Xue,M., Comair,Y., Modic,M., Ng,T.C., 1996. Postictal alteration of sodium content and apparent diffusion coefficient in epileptic rat brain induced by kainic acid. Epilepsia 37, 1000-1006.

Watson,C., Andermann,F., Gloor,P., Jones-Gotman,M., Peters,T., Evans,A., Olivier,A., Melanson,D., Leroux,G., 1992. Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. Neurology 42, 1743-1750.

Watson,C., Jack,C.R., Jr., Cendes,F., 1997. Volumetric magnetic resonance imaging. Clinical applications and contributions to the understanding of temporal lobe epilepsy. Arch Neurol 54, 1521-1531.

Wedeen,V.J., Hagmann,P., Tseng,W.Y., Reese,T.G., Weisskoff,R.M., 2005. Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. Magn Reson Med 54, 1377-1386.

Wedeen,V.J., Wang,R.P., Schmahmann,J.D., Benner,T., Tseng,W.Y., Dai,G., Pandya,D.N., Hagmann,P., D'Arceuil,H., de Crespigny,A.J., 2008. Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. Neuroimage 41, 1267-1277.

Wehner,T., LaPresto,E., Tkach,J., Liu,P., Bingaman,W., Prayson,R.A., Ruggieri,P., Diehl,B., 2007. The value of interictal diffusion-weighted imaging in lateralizing temporal lobe epilepsy. Neurology 68, 122-127.

Whiting, P., Gupta, R., Burch, J., Mota, R.E., Wright , K., Marson, A., Wieshman U., Haycox, A., Kleijnen, J., Forbes, C. A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery. Health Technol Assess 10 (4), 1-250.

Widjaja,E., Blaser,S., Miller,E., Kassner,A., Shannon,P., Chuang,S.H., Snead,O.C., III, Raybaud,C.R., 2007. Evaluation of subcortical white matter and deep white matter tracts in malformations of cortical development. Epilepsia 48, 1460-1469.

Wiebe,S., Blume,W.T., Girvin,J.P., Eliasziw,M., 2001. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 345, 311-318.

Wieser,H.G., Blume,W.T., Fish,D., Goldensohn,E., Hufnagel,A., King,D., Sperling,M.R., Luders,H., Pedley,T.A., 2001. ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. Epilepsia 42, 282-286.

Wieshmann,U.C., Clark,C.A., Symms,M.R., Barker,G.J., Birnie,K.D., Shorvon,S.D., 1999. Water diffusion in the human hippocampus in epilepsy. Magn Reson Imaging 17, 29-36.

Woermann,F.G., Jokeit,H., Luerding,R., Freitag,H., Schulz,R., Guertler,S., Okujava,M., Wolf,P., Tuxhorn,I., Ebner,A., 2003. Language lateralization by Wada test and fMRI in 100 patients with epilepsy. Neurology 61, 699-701.

Wu,J.S., Zhou,L.F., Tang,W.J., Mao,Y., Hu,J., Song,Y.Y., Hong,X.N., Du,G.H., 2007. Clinical evaluation and follow-up outcome of diffusion tensor imaging-based functional neuronavigation: a prospective, controlled study in patients with gliomas involving pyramidal tracts. Neurosurgery 61, 935-948.

Wyllie,E., Luders,H., Morris,H.H., III, Lesser,R.P., Dinner,D.S., Hahn,J., Estes,M.L., Rothner,A.D., Erenberg,G., Cruse,R., ., 1987. Clinical outcome after complete or partial cortical resection for intractable epilepsy. Neurology 37, 1634-1641.

Yamamoto,T., Yamada,K., Nishimura,T., Kinoshita,S., 2005. Tractography to depict three layers of visual field trajectories to the calcarine gyri. Am J Ophthalmol 140, 781-785.

Yogarajah,M., Duncan,J.S., 2008. Diffusion-based magnetic resonance imaging and tractography in epilepsy. Epilepsia 49, 189-200.

Yogarajah,M., Focke,N.K., Bonelli,S., Cercignani,M., Acheson,J., Parker,G.J., Alexander,D.C., McEvoy,A.W., Symms,M.R., Koepp,M.J., Duncan,J.S., 2009. Defining Meyer's loop-temporal lobe resections, visual field deficits and diffusion tensor tractography. Brain 132, 1656-1668.

Yogarajah,M., Powell,H.W., Parker,G.J., Alexander,D.C., Thompson,P.J., Symms,M.R., Boulby,P., Wheeler-Kingshott,C.A., Barker,G.J., Koepp,M.J., Duncan,J.S., 2008. Tractography of the parahippocampal gyrus and material specific memory impairment in unilateral temporal lobe epilepsy. Neuroimage 40, 1755-1764.

Yoo,S.Y., Chang,K.H., Song,I.C., Han,M.H., Kwon,B.J., Lee,S.H., Yu,I.K., Chun,C.K., 2002. Apparent diffusion coefficient value of the hippocampus in patients with hippocampal sclerosis and in healthy volunteers. AJNR Am J Neuroradiol 23, 809-812.