# The role of $^{18}$FDG-PET in predicting seizure outcomes and memory deficits following an anterior temporal lobe resection for drug resistant epilepsy

Varduhi Cahill
MD MRCP (London) MRCP (Neurology)

Faculty of Medicine, Dentistry and Health Sciences
The University of Melbourne

Melbourne Brain Centre, Royal Melbourne Hospital

ORCID iD: 0000-0003-2994-071X

Submitted in total fulfilment of the requirements for the degree of

Doctor of Philosophy

April 2020

# Abstract

Epilepsy surgery is the treatment of choice for suitable patients with drug resistant temporal lobe epilepsy (TLE), however a significant proportion of patients experience seizure recurrence following surgery. Seizure freedom is the primary goal of epilepsy surgery, yet postoperative memory deficits can significantly impact on patients' quality of life, which calls for better predictors of seizure and memory outcomes.

$^{18}$FDG-PET is a commonly utilised tool for localising the epileptogenic zone in the presurgical evaluation. Recent studies demonstrated an association between interictal high frequency oscillations and $^{18}$FDG-PET hypometabolism in patients with TLE, opening up new prospects to explore its role as a metabolic biomarker of epileptogenicity, which, along with previous reports of neurocognitive deficits being associated with reduced $^{18}$FDG-PET uptake gave rise to the current inquiry. This study explored the yield of $^{18}$FDG-PET in predicting seizure and memory outcomes, lateralising value of material-based neurocognitive tests and the role of postoperative gliosis in seizure recurrence using real world clinical data in a well characterised patient cohort and rendered the following findings:

1. $^{18}$FDG-PET hypometabolism patterns differed significantly between patients with left versus right MTLE. The extent of the ipsilateral hypometabolism was significantly greater in left MTLE patients. Right MTLE patients had significantly higher rates of bitemporal hypometabolism, which was a strong predictor of poor seizure outcomes associated with a 5-fold increase in seizure recurrence rates. In left MTLE patients, a more extensive ipsilateral temporal lobe hypometabolism resection was associated with lower rates of seizure recurrence, however without reaching statistical significance.

2. The clinical utility of $^{18}$FDG-PET in predicting memory deficits was of limited clinical value in the real world setting, with preoperative verbal memory scores and the ATLR laterality being strongest predictors of postoperative memory deficits.

3. Low arbitrary learning scores in right MTLE patients with bitemporal hypometabolism were comparable to left MTLE patients. In contrast, right MTLE patients without evidence of bitemporal hypometabolism performed

significantly better compared to left MTLE patients. Between-group comparisons showed no statistical difference in arbitrary relational learning in right MTLE patients, however bitemporal hypometabolism was associated with lower arbitrary learning scores in this cohort.

4. Material-based neurocognitive tests were of limited lateralising value, whereas task-specific tests were of higher yield.

5. The extent of the postoperative gliosis correlated, albeit weakly, with the interval to postoperative scanning, however no association with seizure outcomes was observed.

The laterality-specific differential $^{18}$FDG-PET findings converge with the findings of connectomic studies and support the notion of right versus left MTLE syndromes being distinct clinical entities. $^{18}$FDG-PET could serve as a metabolic biomarker for predicting surgical outcomes, while its real world clinical utility in predicting memory outcomes is limited. The role of arbitrary learning as a candidate biomarker of left mesial temporal lobe dysfunction in patients with right MTLE and bitemporal hypometabolism warrants exploration in a larger patient cohort, whereas the limited lateralising value of material-based neurocognitive tools calls for the wider use of task-specific memory tests. Lastly, a larger cohort study of postoperative gliogenesis could illuminate our understanding of epileptogenic versus neuroprotective properties of astroglia in focal epilepsy syndromes.

*To my Parents*

# Acknowledgements

This thesis is a tribute to Melbourne, which not only became my alma mater for epileptology but also shaped my way of thinking more than I ever thought. I thank my Melbourne family for their unfading support, enduring friendship and for making our AES meetings the highlight of every year.

I am indebted to Professor Terry O'Brien and Professor Patrick Kwan for this exceptional opportunity, for welcoming me to Australia for the first time, for their mentorship and for always being there for me. Terry's leadership, collegiate sprit and mind-blowing levels of energy have been the source of inspiration and strength for me. It has been my great privilege to work with Patrick whose scholarly works have influenced the care pathways for patients with drug resistant epilepsy.

I am grateful to Dr Anne McIntosh for her expert guidance, her mentorship and her wisdom. I thank Dr Charles Malpas for introducing me to the works of Professor Saling, for his expert guidance and erudite discussions. I am indebted to Professor Samuel Berkovic, Professor Sarah Wilson and Dr Marie O'Shea for their expert input.

I am grateful to Dr Benjamin Sinclair for his expert guidance, for being the source of light in the radiology dungeon and for all the support and expert knowledge he shared with me. I thank Dr Zhibin Chen for his expert guidance, I would have never thought that statistics could be fun if not for Ben. I am grateful to Dr Lucy Vivash, Nerissa Cordy, Dr Chris Stewart and Dr Simon Salinas for their support and technical guidance.

I am grateful for the camaraderie of Dr Andrew Neal, Dr Pierro Perucca, Dr Ofer Gonen, Dr Tomas Kalincik, Dr Neil Wareing, Dr Vilija Jokubaitis, Benjamin Siveges, Dr Gagan Sharma, Dr Neha Kaul, Jack Germain, Dr Meaghan Clough, Dr Jillian Naylor and Maddie Reagan. Without your support and sharing a good laugh it would have been hard to endure the ups and downs of imaging postprocessing and navigate the deep waters of neurocognition.

I thank Susan Belbin for her support, for being a guardian of the Epilepsy Unit, the mother to all the fellows and scientists and for those signature Epilepsy MDT special biscuits. I thank all my colleagues from Neurology and Clinical Neurophysiology Departments Dr Meng Tan, Dr Raju Yerra, Dr Chris French, Elise White, Callum Hollis, Andrew Strawhorn and John Carino who made my Clinical Epilepsy Fellowship at the Royal Melbourne a time to cherish and remember.

I am grateful Dr Shobi Sivathamboo, Dr Gita Soraya and Dr Mastura Monif for all their support and enduring friendship.

I thank my son Robert for his unconditional love and understanding, for being the source of joy and pride for me and for his inspirational creative works.

I thank Julian Cahill for being my bedrock. Always.

# Declaration

I, **Varduhi Cahill**, hereby confirm that:

I The work presented in this thesis is my own

II The information derived from other sources has been indicated and referenced throughout the thesis

III The thesis is fewer than 100,000 words in length, exclusive of tables, bibliographies and appendices.

Varduhi Cahill

Manchester, UK
April 2020

# Preface

This work, including the data acquisition and data analyses, was conducted during my tenure as a PhD candidate at the University of Melbourne and a Clinical Epilepsy Fellow at the Royal Melbourne Hospital, Melbourne, Australia. The composition was completed following my relocation to the Manchester Centre for Clinical Neurosciences, UK.

All the data used in this study was acquired as part of the standard clinical care at the Royal Melbourne, Austin Hospital and Peter McCallum Cancer Centre, Melbourne, Australia. Some of the patients I personally followed at the Royal Melbourne Hospital, Melbourne, Australia.

I carried out the following work in all studies underlying this thesis: study designs and methods, review and curation of clinical data, data transfers, raw image analyses, interpretation of the results, data presentation in this thesis and archiving of the data.

All statistical data analyses were carried out in consultation with Dr Zhibin Chen and Dr Charles Malpas.

Post-acquisition image processing was carried out in consultation with Dr Benjamin Sinclair who helped to provide the technical framework pertaining to developing the image processing pipeline. Dr Yong Hao was a collaborator on the project entailing manual segmentation by two independent operators for quality assurance purposes.

All results and interpretations were presented by myself and discussed at regular supervision meetings with Professor Terence O'Brien, Professor Patrick Kwan, Dr Anne McIntosh and Dr Charles Malpas.

Professor Sarah Wilson, Dr Marie O'Shea and Dr Charles Malpas provided expert guidance and advisory support pertaining to neuropsychological data curation and analyses.

Chapter 3 is the reproduction of a paper published in the Annals of Neurology, 2019. I was the primary author and was responsible for writing the first draft, submission and revisions of the manuscript. Contributions of my fellow researchers at the University of Melbourne, my colleagues and collaborators at the Royal Melbourne Hospital, Austin Hospital and Peter McCallum Centre are acknowledged and reflected in the co-authorship.

All the data from this thesis was presented as either oral or poster presentations at national and international meetings.

No work was carried out prior to my enrolment as a PhD candidate and no third party editorial assistance was used for the formatting of this thesis.

# Publications and awards

Parts of this thesis have appeared in the following publications and presentations:

Cahill V, Sinclair B, Malpas CB, McIntosh AM, Chen Z, et al. Metabolic patterns and seizure outcomes following anterior temporal lobectomy. *Annals of Neurology, 2019; 85*(2), 241-250. doi: 10.1002/ana.25405

Cahill V, Sinclair B, Malpas CB, Chen Z, McIntosh AM, et al. Exploring the real-world clinical utility of $^{18}$FDG-PET in predicting verbal memory deficits in patients with drug-resistant mesial temporal lobe epilepsy, Abstract 2.284, 2019, American Epilepsy Society Annual Meeting, www.aesnet.org

Cahill V, Sinclair B, Malpas CB, McIntosh AM, Chen Z, et al. The extent of resection of pre-operative $^{18}$F-FDG-PET hypometabolism and contralateral temporal lobe hypometabolism predict seizure control following anterior temporal lobectomy, Abstract 1.238, 2017, American Epilepsy Society Annual Meeting, www.aesnet.org

Cahill V, Sinclair B, Malpas CB, Chen Z, McIntosh AM, et al. Predictive value of $^{18}$F-FDG-PET in verbal memory outcomes: myths and reality of clinical practice, Abstract 39, 2017, ILAE British Branch Annual Scientific Meeting, www.ilaebritish.org.uk

Cahill V, Chen Z, Sinclair B, McIntosh A, Malpas CB, et al. Arbitrary relational learning as a neurocognitive marker of left mesial temporal lobe dysfunction in patients with right mesial temporal lobe epilepsy, Abstract 513, 2017, Epilepsy Society of Australia Annual Scientific Meeting, www.epilepsy-society.org.au

Cahill V, Hao Y, Sinclair B, McIntosh A, Chen Z et al. The role of postoperative gliosis in surgical outcomes following ATLR in patients with drug resistant MTLE: a pilot study, Abstract 556, 2017, Epilepsy Society of Australia Annual Scientific Meeting, www.epilepsy-society.org.au

Cahill V, Malpas CB, Cordy NJ, McIntosh AM, Kwan P, et al. In the precision medicine era, the material-specific memory concept is of limited value in epilepsy surgery evaluation, Abstract 271, 2016, Epilepsy Society of Australia Annual Scientific Meeting, www.epilepsy-society.org.au

## Awards

Melbourne International Research Scholarship
Melbourne International Fee Remission Scholarship

# Glossary of Abbreviations

| | |
|---|---|
| $^{18}$FDG-PET | $^{18}$Fluorodeoxyglucose Positron Emission Tomography |
| AAL | Automated Anatomic Labelling |
| AEDs | Anti Epileptic Drugs |
| ATLR | Anterior Temporal Lobe Resection |
| BNT | Boston Naming Test |
| BTH | Bitemporal $^{18}$FDG-PET Hypometabolism |
| CEP | Comprehensive Epilepsy Programme |
| CSF | Cerebral Spinal Fluid |
| CTE | Chronic Traumatic Encephalopathy |
| CTL | Contralateral Temporal Lobe |
| DAN | Dorsal Attention Network |
| DMN | Default Mode Network |
| DREZ | Drug Resistant Epileptogenic Zone |
| DTI | Diffusion Tensor Imaging |
| EEG | Electroencephalogram |
| ETH | Extratemporal Hypometabolism |
| FCD | Focal Cortical Dysplasia |
| FDA | Food and Drug Administration |
| FLAIR | Fluid Attenuated Inversion Recovery |
| fMRI | Functional Magnetic Resonance Imaging |
| FSIQ | Full Scale Intelligence Quotient |
| fTDS | Functional Transcranial Doppler Sonography |
| FWHM | Full Width at Half-Maximum |
| GLM | General Linear Model |
| GLM | General Linear Model |
| GM | Grey Matter |
| HFO's | High Frequency Oscillations |
| HS | Hippocampal Sclerosis |
| iEEG | Intracranial EEG |
| IQ | Intelligence Quotient |
| LITT | Laser Interstitial Thermal Therapy |
| LVFA | Low Voltage Fast Activity |
| MATLAB | Matrix Laboratory |
| MBq | Megabecquerel |
| mCi | Millicurie |
| MDT | Multidisciplinary Team |
| MEG | Magnetoencephalography |
| MPRAGE | Magnetisation Prepared Rapid Acquisition Gradient Echo |
| MRgFUS | Magnetic resonance-guided focused ultrasound |
| MRS | Magnetic Resonance Spectroscopy |
| MTLE | Mesial Temporal Lobe Epilepsy |
| MTLE-HS | Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis |
| PAL | Paired Associate Learning |
| PIQ | Performance Intelligence Quotient |
| QoL | Quality of Life |
| RAVLT | Rey Auditory Verbal Learning Test |
| RCFT | Rey-Osterrieth Complex Figure and Recognition Trial |
| RFTC | Radiofrequency Thermocoagulation |
| SAH | Selective Amygdalohippocampectomy |
| SEEG | Stereoelectroencephalography |

| | |
|---|---|
| SPECT | Single Photon Emission Computed Tomography |
| SPM | Statistical Parametric Mapping |
| SPSS | Statistical Package for the Social Sciences |
| SUDEP | Sudden Unexpected Death in Epilepsy |
| T | Tesla |
| TCH | Total Cerebral Hypometabolism |
| TLE | Temporal Lobe Epilepsy |
| TLH | Temporal Lobe Hypometabolism |
| TPE | Temporal Plus Epilepsy Syndrome |
| WAIS | Wechsler Adult Intelligence Scale |
| WFU | Wake Forest University |
| WM | White Matter |
| WMS | Wechsler Memory Scale |
| WTAR | Wechsler Test of Adult Reading |

# Table of Contents

# List of figures

# List of Tables

Chapter 1

# Introduction

## 1. 1 MTLE: scope and definitions

### 1.1.1 MTLE: place in the world of drug resistant epilepsy

Epilepsy, being one of the most common chronic neurological disorders globally, remains a major public health concern as over 70 million people worldwide suffer with this condition (Ngugi et al., 2010; Weaver & Pohlmann-Eden, 2013; WHO, 2019). In one third of patients, epilepsy runs a drug resistant course, which is defined as the failure of adequate trials of two appropriately chosen and tolerated antiepileptic agents to render the patient seizure free (Kwan et al., 2010). Despite the expanding list of antiepileptic agents, the introduction of novel antiepileptic drugs (AEDs) does not appear to have significantly influenced the rates of drug resistant epilepsy, which remain comparable to those three decades ago, with up to a third of epilepsy patients continuing to experience unremitting seizures (Chen et al., 2018; Kwan & Brodie, 2006).

The importance of drug resistant epilepsy is hard to underestimate, as the increased morbidity and mortality rates speak for themselves. Mortality rates in patients with drug resistant epilepsy are five times higher than in the general population (Bell et al., 2010), with rates of Sudden Unexpected Death in Epilepsy (SUDEP) being 1.2/1000 adults (Devinsky et al., 2016; Harden et al., 2017). Needless to say, that the psychosocial impact of drug resistant epilepsy on the patient's quality of life (QoL) and that of their families is substantial and has long been recognised (French, 2007; Löscher & Potschka, 2005; Siddiqui et al., 2003). The socioeconomic burden of drug resistant epilepsy remains high (Begley et al., 2000; Kwan et al., 2011), while the pool of surgical candidates has been growing year by year (Burneo et al., 2016; Lhatoo et al., 2003).

There has been significant progress made in epilepsy research and the conceptualisation of the epileptogenic networks, including the potential aetiologies behind these, which have signalled a new era in experimental and clinical epilepsy, from the connectome based modelling of the epileptogenic networks (Besson et al., 2017; Gleichgerrcht et al., 2018) to the autoregulatory antiepileptic gene therapies (Lieb et al., 2018). However,

the lack of disease modifying AEDs, poor tolerability of pharmacological treatments, including the novel antiepileptic agents (Alsfouk et al., 2020) and the constantly expanding pool of potential surgical candidates (Lhatoo et al., 2003), calls for alternative treatment strategies to the standard pharmacological interventions. With advanced multimodal imaging technologies and the increased accessibility of intracranial exploration techniques, the surgical treatment options continue to be of immediate relevance.

The findings of the landmark randomised controlled trial by Wiebe *et al* (Wiebe et al., 2001) revolutionised the care of patients with drug resistant epilepsy, providing Class I evidence for epilepsy surgery being an unsurpassed treatment option for patients with drug resistant temporal lobe epilepsy (TLE). These findings have been replicated by subsequent studies rendering confirmatory results with the drug resistant mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) patients benefitting from early surgical intervention the most (Engel et al., 2012; Gomez-Alonso & Bellas-Lamas, 2015). A common myth of epilepsy surgery as being a costly undertaking has been repeatedly dispelled by cost-effectiveness studies (Jetté & Wiebe, 2015; Picot et al., 2016). Choi *et al* demonstrated that epilepsy surgery resulted in an increase of 7.5 quality adjusted life years compared to the pharmacological treatment options (Choi et al., 2008). The majority of patients following epilepsy surgery found their lives transformed, including gaining social independence (Hamiwka et al., 2011) and a marked improvement of psychiatric comorbidities (Macrodimitris et al., 2011).

A worldwide census of 107 epilepsy surgery programmes identified TLE as being the most prevalent type of focal drug resistant epilepsy in the epilepsy surgery patient cohort (Wiebe, 2000). MTLE has been shown to be the commonest type of focal epilepsy in adults (Boon et al., 1991). While the original studies of epilepsy surgery outcomes have traditionally focused on seizure freedom rates in patients with MTLE-HS, it has been repeatedly demonstrated that favourable seizure outcomes have also been reliably achieved in MRI negative MTLE patients with $^{18}$Fluorodeoxyglucose Positron Emission Tomography ($^{18}$FDG-PET) hypometabolic findings identified in the ipsilateral temporal lobe region. Both groups of patients have been shown to enjoy favourable seizure outcomes with comparable rates of seizure freedom (Carne et al., 2004; Muhlhofer et al., 2017a). The wider use of stereoelectroencephalography (SEEG)

techniques enables us to now devise successful surgical treatment strategies for patients with extratemporal epilepsies (Vakharia et al., 2018).

### 1.1.2 MTLE: nosology and definitions

The terminology surrounding the MTLE syndrome could at first appear confusing. It is, however, a mere reflection of the reconceptualisation of our understanding of the epilepsy syndromes, as the field of epilepsy evolves driven by the technological advancements in intracranial electroencephalography (iEEG), multimodal neuroimaging techniques and reflective conceptual thinking. We have now lived through the "epileptogenic lesion" era followed by the "epileptogenic zone" and entered by far the most exciting era for surgical epilepsy, the "network'" epilepsy era (Jehi, 2018). The changes in the epilepsy classification have traditionally been the subject of fervent debates by clinicians and researchers alike, however the ultimate goal has always been the same, regardless of the classification used, which is to improve the standards of care for people with epilepsy (Scheffer et al., 2017). It is not inconceivable that in the future several operational classifications would be required, with the advancements of non-invasive computer assisted epileptic network modelling resulting in a "network" classification of drug resistant epilepsies to enable the further precision required for advancing patients' care and also for the generation of high fidelity data so that the specific determinants of the drug resistant epileptogenic zone (DREZ) could be understood and targeted accordingly (Zhang & Kwan, 2019).

Hughlings Jackson was the first to describe the "uncinate fit" manifesting with a "dreamy state" (Jackson & Stewart, 1899), which would now be categorised as a focal impaired awareness seizure typically observed in patients with MTLE. French *et al* first coined the term MTLE in 1993 (French et al., 1993). Following that, in 2004 the role of HS in the aetiology of MTLE was acknowledged and MTLE-HS made its entry into the International League Against Epilepsy (ILAE) classification as a distinct anatomo-electro-clinical syndrome (Wieser, 2004). It was a major milestone, considering that HS has long been recognised to be a hallmark of drug resistant TLE, thus there was a pressing need for MTLE-HS, being a surgically remediable epilepsy syndrome, to be acknowledged as an independent entity. Classically, the hippocampal formation was specified to be the anatomical substrate for MTLE (Wieser, 2004). Ryan *et al* have elegantly addressed the challenges stemming from the intricacies surrounding the hippocampus related terminology (Ryan et al., 2001). However, it is not uncommon for

the terms pertaining to the hippocampus and its surrounding structures to be used interchangeably. The “hippocampus proper” refers to the *Cornu ammonis* (CA) fields and the dentate gyrus, the “hippocampal formation” refers to the hippocampus proper and the subiculum and lastly, the “hippocampal complex”, is comprised of the hippocampal formation, entorhinal, perirhinal and parahippocampal gyri. The use of iEEG has enhanced our understanding of the MTLE-HS syndrome. It has been duly recognised that apart from the hippocampus, other structures of the limbic system, with the amygdala being a major player, are commonly implicated in the development of MTLE and therefore the overarching term of “limbic epilepsy” was agreed upon (Engel, 2001).

Historically, the MTLE syndrome has been contrasted with the syndrome of neocortical TLE. However, it has now been demonstrated that the epileptic networks implicated in MTLE are heterogeneous and depending on the extent of the epileptic network as well as the seizure propagation pathways, the seizures originating in the mesial temporal structures could leave their “footprint” outside the limbic system (Bartolomei et al., 2008; Chassoux, 2017). The findings of a recent study by Blümcke *et al* looking at over 9500 brain specimens demonstrated that to this day HS remains the most common finding amongst the histopathology samples obtained as a result of epilepsy surgery (Blümcke et al., 2017). However, while HS has long been considered to be a hallmark of drug resistant MTLE (Labate et al., 2016), the iEEG studies confirmed the hippocampal seizure onset in only 20-60% of the patients (King et al., 1997; Munari et al., 2007). In many patients, however, the seizures were observed to arise from the amygdala or the brain regions adjacent to the hippocampus proper, i.e. perirhinal, entorhinal and parahippocampal cortex (Bertram, 2003; Munari et al., 2007; Spanedda et al., 1997; Vossler et al., 2004) without necessarily influencing the seizure semiology (Kahane & Bartolomei, 2010). Thus, it is not uncommon for the umbrella term of TLE to be used instead as an acknowledgement of our understanding of the complexity and heterogeneity of epileptic networks implicated in the development of this focal epilepsy syndrome.

## 1. 2 MTLE: from hodology to semiology

### 1.2.1 Temporal lobe: hodological properties

The advances in iEEG recordings have enhanced our understanding of the focal epilepsies and of MTLE in particular. The works of Bartolomei and colleagues have consistently demonstrated evidence of aberrant connectivity patterns implicated in the temporal lobe epilepsies, whereby seizure generation and propagation alike, has been shown to extend beyond the boundaries of the structural findings, including the well established radiological findings of HS, providing support that MTLE is a network disorder (Akanuma et al., 2003; Bartolomei et al., 2017; Mueller et al., 2009; Vermathen et al., 2003). The findings of Margerison and Corsellis suggested that the hippocampal involvement in patients with unilateral MTLE was in fact bilateral, however asymmetrical, based on the evidence of widespread histopathological changes extending beyond the ipsilateral hippocampal formation, thus providing early insights of a wider epileptic network implicated in the development of MTLE, contrary to the long held belief that MTLE was a well circumscribed and confined "focal" disease (Margerison & Corsellis, 1966).

In light of Brodmann's "in all domains, physiology has its firmest foundations in anatomy", there has been renewed interest in the temporal lobe's hodological properties, beyond the well-studied *arcuate fasciculus* connecting Broca's and Wernicke's areas, which is one of the most influential hodological pathways bridging between the caudal temporal cortex and the inferior frontal lobe region (Dick & Tremblay, 2012), in an attempt to conceptualise potential seizure propagation pathways with a view of tracking the seizure footprints. The interconnections between the ipsilateral amygdala and the hippocampus as well as their widespread extra-limbic projections into the ipsilateral temporal neocortex, including the temporal pole, the superior temporal gyrus and the extratemporal projections to the frontal lobe have long been documented (Alarcón et al., 1994). While the presence of the ventral hippocampal commissure in humans is unmistakable, its role in subserving interhemispheric connections was found to be largely rudimentary (Alarcón et al., 1994; Catani et al., 2002). The dorsal hippocampal commissure fibres, however, have been shown to project towards the contralateral parahippocampal region including the presubilucum, entorhinal cortex and the neocortical subsets of the posterior parahippocampal gyrus (Demeter et al., 1985). Thus, it was postulated that in patients with unilateral MTLE the seizures, after originating in

the ipsilateral hippocampus, follow a multisynaptic propagation pathway and spread to the contralateral parahippocampal cortical regions first, followed by the involvement of the contralateral hippocampus (Wilson, 1995). It has also been demonstrated that the homologous contralateral inferotemporal cortices are connected via the anterior commissure and the corpus callosum. All areas of the temporal lobe project to the frontal lobe in a topographically organised and reciprocal manner with the vast majority of the connections involving the prefrontal brain regions (Streitfeld, 1980).

In addition, the findings arising from the studies of the temporal lobe structures as well as the advances in structural diffusion tensor imaging (DTI) and functional (fMRI) connectivity techniques have been converging in uncovering the laterality-specific differential temporal lobe characteristics in patients with TLE. Riederer *et al* demonstrated preferential temporal lobe grey matter volume changes depending on the seizure onset laterality. For example, in patients with left MTLE, more widespread changes were observed within the ipsilateral parahippocampal region, superior temporal gyrus, frontal regions, cerebellum and right cingulum (Riederer et al., 2008) thus giving rise to inferences that left MTLE patients are likely to exhibit more prominent epileptic network changes within the ipsilateral left temporal region. Patients with right MTLE exhibited widespread changes in connectivity patterns involving the contralateral temporal and parietal brain regions as opposed to patients with left MTLE (Coito et al., 2015; Haneef et al., 2013; Vanicek et al., 2016). Importantly, it has been observed that the seizure spread in MTLE patients follows preferential propagation pathways determined by the specifics of the temporal lobe functional connectivity properties. These entail the spread of ictal activity with the involvement of the ipsilateral neocortex, orbitofrontal regions and posterior cingulate as well as the contralateral mesial temporal lobe structures (Berg et al., 2010; Meldrum, 1990). A thorough understanding of the aberrant networks implicated in the development of MTLE is necessary to deliver high standards of clinical care, from the evaluation of epilepsy surgery candidates to patient centred surgical planning strategies.

Conceptualising TLE from the network perspective, notwithstanding the hodological temporal lobe properties, allows for precision in the diagnostic evaluation of patients with focal epilepsies. The extent of the epileptic network could be underestimated unless a high index of suspicion is exercised during the routine anatomo-electro-clinical evaluation of epilepsy surgery candidates. For example, it has now been recognised that

TLE-plus syndrome, relatively recently outlined as a separate electro-clinical entity by Kahane and Ryvlin (Kahane et al., 2015), is responsible for a significant proportion of surgical failures in patients with TLE (Barba et al., 2016) and reflects the complexity of neural circuitry implicated in focal epilepsy involving the temporal lobe.

### 1.2.2 Epileptic networks and seizure semiology

The seizure semiology in patients with MTLE is determined by the involvement of specific symptomatogenic zones activated as a result of preferential seizure propagation pathways. The study by Bartolomei *et al* identified several iEEG signatures in patients with TLE (Bartolomei et al., 2005). The epileptic networks have been shown to be more widespread than originally thought and heterogeneous, with epileptogenicity index characteristics suggestive of epileptic network progression over time (Bartolomei et al., 2005). The iEEG signatures, characteristic of the ictal generators within the mesial temporal lobe structures are specific and allow for the differentiation between hippocampal and extra-hippocampal seizure onset within the MTLE syndrome (Bartolomei et al., 2005). The seizures originating within the mesial temporal lobe structures were found to be the most common and were typically associated with HS or normal MRI findings (Bartolomei et al., 2010).

In light of the hodological properties of the temporal lobe and the heterogeneity of the epileptic networks implicated in TLE, the clinical manifestations differ, depending on the preferential seizure propagation pathway. The seizures in MTLE manifest with focal awareness or focal impaired awareness events typically associated with oral, vocal, manual automatisms and contralateral tonic upper limb posturing, whereas bilateral generalised convulsions are rare. The advances in SEEG enhanced our understanding of the symptomatogenic cortical areas. For example, ictal déjà vu was observed to originate within the rhinal cortices (Bartolomei et al., 2004), while the symptoms of a rising epigastric sensation have been associated with seizure spread to the insular cortex (Isnard et al., 2004). Vignal *et al* observed ictal activity to originate within the amygdala, hippocampus, parahippocampal gyrus and rhinal cortices in a group of MTLE patients experiencing a feeling of déjà vu in association with a highly intrusive feeling of strangeness (Vignal et al., 2006).

It has been widely documented that seizure activity arising from the amygdala itself produces a feeling of fear in patients. However, Biraben *et al* suggested that ictal fear

resulting from amygdala involvement is nonintrusive, whereas it is the frontal lobe seizures that tend to manifest with an intense feeling of fear, often reported by patients as a feeling that resembles a "panic attack" (Biraben et al., 2001). Chabardes *et al* described another important epileptic network within TLE syndrome, mesiotemporopolar, involving both, the mesial temporal lobe structures and the temporal pole (Chabardes et al., 2005). Clinical manifestations in this group of patients are similar to those in patients with MTLE. However, the latency between iEEG onset and the first clinical sign, including altered awareness, was much shorter in patients with temporopolar network involvement. Importantly, in up to 35% of patients with radiological evidence of HS the seizure onset on iEEG was localised to the temporal pole (Chabardes et al., 2005). This is of particular clinical significance in selective amygdalohippocampectomy (SAH) candidates and iEEG evaluation would be required to minimise the likelihood of surgical failures in this particular patient cohort.

One might argue that knowledge of the exact site of the ictal generator within the temporal lobe structures is less critical in patients undergoing an anterior temporal lobe resection (ATLR), as long as the seizures arise from somewhere within the resection margins. In ATLR candidates, with a radiological finding of HS, the importance of looking for "red flags" has now been recognised. Symptoms like head and eye versions, gustatory, auditory hallucinations, ipsilateral tonic arm posturing, piloerection and postictal psychiatric manifestations often raise suspicions of a wider epileptic network involvement as part of the TLE-plus syndrome (Kahane et al., 2015). In TLE-plus syndrome the extension of the epileptic networks to the orbito-frontal, temporo-occipital or perisylvian cortex has been observed (Bartolomei et al., 2010). The recent study by Barba *et al* demonstrated that TLE-plus syndromes constitute a substantial proportion of surgical failures following an ATLR (Barba et al., 2016). Therefore, a thorough evaluation of the clinical semiology is warranted to minimise the likelihood of unfavourable surgical outcomes.

Importantly, scalp EEG recordings could also be helpful in picking up the electrical signatures suggestive of an extensive epileptic network involvement. In patients with temporal lobe seizures, the EEG changes are seen predominantly in the derivations topographically representing the anterior and basal temporal lobe regions (Kahane & Bartolomei, 2010), whereas the patients with TLE-plus syndrome have been shown to exhibit bilateral or precentral interictal findings and anterior frontal, temporo-parietal and precentral ictal EEG changes (Barba et al., 2007), which along with less typical

seizure semiology should raise a suspicion of a TLE-plus syndrome. The heterogeneity of the epileptic networks in patients with TLE is a major determinant of surgical failures, aggravated by the lean approach to the presurgical evaluation whereby reliance on the concordant radiological finding of HS along with concordant electro-clinical evaluation data has been traditionally viewed as sufficient in order to proceed to surgery (Jones & Cascino, 2016; Quarato et al., 2005).

Having a network-oriented approach to devising the surgical strategies would be particularly important in patients considering minimally invasive epilepsy surgery procedures, therefore it would be absolutely critical to localise the ictal onset by employing an iEEG prior to any minimally invasive intervention. In addition, by viewing both, ictal and cognitive manifestations as part of one epilepsy continuum, one could be alerted to the potential concomitant neurocognitive deficits at the time of analysing the ictal semiology. For example, while the feeling of ictal déjà vu has been observed to originate within the rhinal cortices (Bartolomei et al., 2004), it has been demonstrated, within the limitations of the heuristics underlying the intratemporal memory organisation model, that the rhinal cortices play a key role in arbitrary learning (Saling, 2009) and rhinal pathology has been shown to manifest with episodic memory impairment (Desgranges et al., 2002). Therefore, maintaining the network approach to the diagnosis and management of epilepsy patients is necessary in order to deliver a comprehensive patient care. For example, it would be important to understand the neurocognitive sequelae in patients with an ictal generator localised to the rhinal cortices and as to whether or not the neurocognitive deficits would differ depending on the rhinal cortices being the seizure onset zone versus the zone of seizure spread. This prompts us to explore the role of arbitrary learning as a candidate neurocognitive marker in this patient cohort and to deploy neurocognitive measures in a timely manner should the clinical need arise.

## 1.3 MRI findings in MTLE

The association between MTLE and HS has been recognised for decades. The MRI features of HS are characterised by reduced hippocampal volume on T1 and the increased signal intensity of T2-weighted and T2 fluid attenuated inversion recovery (FLAIR) imaging in association with the loss of the internal hippocampal architecture (Malmgren & Thom, 2012). Current MRI protocols for patients with MTLE include the use of coronal slices perpendicular to the hippocampal axis. The accuracy of hippocampal imaging has been significantly improved since the introduction of the FLAIR sequence. The use of the FLAIR sequence in the TLE setting was first suggested by Jack *et al*. (Jack et al., 1996) and its accuracy in identifying HS corroborated by the histopathological findings which is reported to be as high as 97% (Kuzniecky et al., 1997). Kreilcamp *et al* have shown that dedicated MRI protocols and expert re-evaluation of the images could result in the identification of epileptogenic lesions in up to 30% of patients previously deemed to be "non-lesional". It was found that HS was still amongst the most common pathologies picked up after the re-evaluation of the scans in the setting of a multidisciplinary discussion (Kreilkamp et al., 2019).

Camacho *et al* described that in 3-10% of patients with unilateral drug resistant MTLE, bilateral MRI findings of HS have been reported (Camacho & Castillo, 2007), however this should not prevent the patients from being considered for epilepsy surgery and the clinical significance of a bilateral radiological finding of HS needs to be determined. Salanova *et al* have shown that in up to 15% of patients the finding of HS on the MRI scan could constitute part of a dual pathology, e.g. focal cortical dysplasia (FCD), vascular malformation, evidence of old ischemia or cerebral contusions sustained in childhood. It has originally been suggested that the dual pathology was observed exclusively in association with congenital or pre-existing lesions and it was therefore inferred that HS as part of a dual pathology tends to develop in childhood due to the increased vulnerability of the mesial temporal lobe structures, which was believed to be age related. This is controversial however, as Diaz-Arrastia *et al* subsequently observed the presence of HS in adolescents with new onset post-traumatic epilepsy, with unequivocal evidence that the culprit was the neocortical frontal lobe thus raising the possibility that HS could develop later on in life, as a sequelae of the extratemporal epilepsy syndrome (Diaz-Arrastia et al., 2000). Importantly, while the radiological finding of HS and FCD is not uncommon in patients with TLE (Kim et al., 2010),

Srikijvilaikul *et al* reported no differences in seizure outcome in patients with FCD and FCD-HS following temporal lobe resection (Srikijvilaikul et al., 2003). In up to 30% of patients with MTLE a preoperative MRI scan does not identify any obvious structural abnormality (Muhlhofer et al., 2017a). In such cases, histopathological examination demonstrates either absent or mild neuronal loss (Aaron et al., 2005; Cascino et al., 1992). From a clinical prospective, the patients with MTLE-HS and MRI-negative PET-positive MTLE patients have been shown to have comparable seizure freedom rates following epilepsy surgery (Carne et al., 2004; Muhlhofer et al., 2017a).

Some epilepsy surgery programmes now have access to ultrahigh field strength MRI. Henry *et al* also demonstrated the role of 7T MRI in the detection of hippocampal atrophy (Henry et al., 2011). It has been reported that 7T MRI could be of added value in detecting subtle FCD in patients with drug resistant epilepsy (De Ciantis et al., 2016; Veersema et al., 2017). However, one has to be mindful, that not unexpectedly, the introduction of the ultrahigh field strength MRI into routine clinical care could result in higher rates of incidental findings, including anatomical variants of no clinical significance. For example, Tsai *et al* demonstrated that hippocampal malrotation not infrequently detected on 7T MRI in the MRI-negative patient cohort with drug resistant epilepsy was an incidental finding and had no bearing on surgical decision making (Tsai et al., 2016).

Apart from the radiological finding of HS, the loss of the anterior temporal lobe grey-white matter differentiation has also been observed in the MRI scans of patients with MTLE. Mitchell *et al* suggested that such appearances of the temporal pole are likely to be the sequelae of an impaired maturation process as a sequel of recurrent seizures (Mitchell et al., 2003). Coan *et al* however, found that abnormal changes of the white and grey matter differentiation in patients with drug resistant MTLE tend to be progressive and correlated with both, the epilepsy duration and the seizure burden (Coan et al., 2009). Over and above however, it has long been recognised that epilepsy surgery as opposed to a "lesionectomy" approach to the evaluation of surgical candidates with positive radiological findings is warranted with a view of establishing the culprit epileptic network part of the presurgical evaluation (Weber et al., 1993). The seizure onset is likely to overlap with the epileptogenic lesion (Rosenow & Lüders, 2001), however the patient may still require a phase 2 presurgical evaluation, which would be particularly critical in patients with an extratemporal seizure onset zone so

that the resection margins could be ascertained, including electrocortical stimulation in patients where the seizure onset zone lies within close proximity to the eloquent cortex.

## 1.4 MTLE: histopathological substrate

Ammon's horn sclerosis, commonly referred to as HS, is the main histopathological substrate in patients with MTLE. The association between HS and complex febrile seizures, including status epilepticus is well established (Lewis et al., 2014), notwithstanding the association described between HS and an early perinatal insult, head injury or neuroinfection (Cendes et al., 2014). However, the causative relationship is not fully understood (Cendes, 2004). In the presence of dual pathology findings, including the radiological finding of HS in patients with post-traumatic epilepsy (Diaz-Arrastia et al., 2000; Salanova et al., 2004), it is conceivable that the causes for HS are likely to be heterogeneous, resulting from a complex interplay between genetic and environmental factors (Cendes et al., 2014).

The main histopathological characteristics of HS, such as segmental loss of pyramidal neurons, granule cell dispersion and reactive gliosis, have been well documented (Blümcke et al., 2002). Considering the marked variations in the qualitative interpretation of the histopathological findings observed across epilepsy centres, a system based on the semi-quantitative evaluation of epilepsy surgery samples has been proposed by the ILAE taskforce. It has been agreed to classify the patterns of neuronal loss into three categories, ILAE HS 1-3, based on the extent of the neuronal loss observed. It was also acknowledged that some surgical specimens will not have histopathological evidence of HS and may show evidence of reactive gliosis while the neuron count remains within the normal range (Blümcke et al., 2013). There have been reports of clinical phenotypes associated with heterogeneous HS patterns, for example HS ILAE type 1 was reported to be commonly seen in patients with a history of febrile convulsions and early epilepsy onset. This HS category is often observed in patients with excellent surgical outcomes, whereas the rates of seizure freedom in patients with HS ILAE type 2 and type 3 have been shown to be considerably less successful by Blümcke *et al* (Blümcke et al., 2013). Deleo *et al* however, found that patients with HS type 1 had a higher seizure recurrence rate in the long term. In addition, the authors reported that the presence of concomitant FCD was associated with worse seizure outcomes following an ATLR (Deleo et al., 2015).

As well as applying the ILAE HS classification to characterising the histopathology samples it has also been agreed to employ a standardised surgical sample procurement protocol to enable adequate future histopathology studies in epilepsy patients. This

recommendation is particularly timely, considering that the wider use of minimally invasive epilepsy surgery techniques is likely to reduce the availability of high quality histopathology samples, thus there is a pressing need for improved sampling in the appropriate clinical setting (Blümcke et al., 2016). HS has been studied in detail in association with MTLE and has been seen as a hallmark of drug resistant epilepsy. In the meantime, HS can also be found on post mortem examinations in the elderly with no previous history of epilepsy or reported cognitive decline. Intriguingly, however, the HS identified in the elderly differs from the HS seen in patients with epilepsy, where the HS phenotypes reflect changes in neuronal circuitry. In the elderly however, the finding of HS was associated with the presence of Hirono bodies, which were not seen in patients with epilepsy (Bandopadhyay et al., 2013). The role of Hirono bodies is not fully understood however recent studies have suggested that Hirono bodies may play a protective role in neurodegeneration (Furgerson et al., 2012).

Traditionally, histopathology studies in patients with TLE have been rather HS-/lesion-centric. However, the last decade, following the reconceptualisation of epilepsy as a network disorder, saw us expand our horizons and see beyond the obvious. It has now been confirmed that histopathology findings in TLE extend beyond the mesial temporal lobe structures, similar to the radiological findings of temporal pole changes with the loss of grey white matter differentiation observed in patients with drug resistant TLE. Evidence of widespread amygdala as well as neocortical pathology has been reported in association with MTLE, and it is not uncommon for the pathological findings to involve not only temporal but also extratemporal lobe structures, such as the frontal poles and the orbito-frontal cortex in patients with epilepsy (Aroniadou-Anderjaska et al., 2008; Blanc et al., 2011).

There have been consistent reports of phosphorylated tau deposits being identified in patients with epilepsy (Thom et al., 2011). These findings were originally believed to be associated with chronic traumatic encephalopathy (CTE), whereby CTE was seen as a common denominator for both epilepsy and the cause of phosphorylated tau deposits, however the findings of a recent study by Smith *et al* suggest otherwise (Smith et al., 2019). The authors identified tau deposits in the surgical specimens of patients undergoing resective procedures for drug resistant epilepsy and in whom there was no clinical history of brain trauma or CTE. The relationship between drug resistant epilepsy, premature brain aging and associated cognitive decline has been observed

previously (Tai et al., 2016). The causative relationship between the tau deposits and the epileptogenic process however remains currently unknown. It has been suggested that the tau load may be the sequelae of seizures, whereas another hypothesis entertains the possibility of epilepsy being a neuro-degenerative disease. The interplay between epilepsy and Alzheimer's disease has been a topic of enduring interest and extensive studies over the last few years. It is inherent to the concept of neuro-degeneration however for structural changes to precede the loss of function, whereas in epilepsy the tau deposits could be the sequelae of neuronal dysfunction. These discoveries signal a new exciting era in epilepsy neuropathology research, with the opportunity to understand not only the neurobiological foundations of epilepsy but to also explore potential therapeutic targets and genetic determinants of tau formation in patients with TLE.

## 1.5 Memory constructs in patients with MTLE: from material- to task-specificity and beyond

### 1.5.1 Hemispheric and language lateralisation conceptualised

The concept of hemispheric specialisation, with the language handedness function being lateralised to the left hemisphere, stems from the pioneering observations of Marc Dax and Paul Broca, followed by corroborative findings resulting from the split brain studies indicative of both, speech and right hand function lateralisation to the left hemisphere in the vast majority of adults, thus resulting in the left hemisphere being christened the dominant hemisphere (Gazzaniga, 2000). The anatomical differences between the left and right hemispheres, with the Yakovlevian torque being the most prominent feature discriminating between the two, have long been established (Josse et al., 2008). The findings of subsequent structural neuroimaging studies, with the focus on the cortical thickness measurements have been consistent with the previous observations of anatomical and functional asymmetry resulting in differences between the two hemispheres at both a global and regional level. For example, the thickness of the grey matter in the precentral gyrus, as well as the middle frontal, anterior temporal, superior parietal regions and the anterior medial brain regions was found to be greater in the left hemisphere while the right hemisphere was described to exhibit preferential thickness in the inferior posterior temporal lobe, inferior frontal lobes and posterior mesial brain regions ( Lüders et al., 2005).

Considering the observations of hemispheric and regional structural asymmetries there has been an ongoing debate as to whether or not the link between structure and function is causative or merely statistical. Ezzati *et al* suggested that structural asymmetry is likely to be driven by functional performance, based on the observation that the volume of the left hippocampus correlated with the level of performance on the episodic memory tasks and the right hippocampal volume was associated with spatial task performance scores (Ezzati et al., 2016). This view has been corroborated by Maguire *et al* who studied the relationship between hippocampal volumes and functional performance of navigating within a busy city in London taxi versus bus drivers (Maguire et al., 2006). It has been shown that London taxi drivers have significantly greater grey matter volume in their mid-posterior hippocampi, which correlated with their ability to use already acquired spatial knowledge. At the same time, there was less grey matter volume observed in the anterior hippocampi of the same cohort, which in

turn impacted on their ability to acquire new visuospatial tasks. It was therefore proposed that the differences in the intra-hippocampal volume changes were the sequelae of environmental plasticity, whereby preferential engagement of the mid-posterior hippocampi came at a cost to the anterior hippocampal regions and impacted on their functional performance. This finding, suggestive of neuronal plasticity, resonates with the findings of Sidhu *et al* who observed the finding of memory network plasticity following an ATLR in both, the residual posterior hippocampus and the contralateral hippocampus (Sidhu et al., 2016). These findings could influence neurocognitive pre and rehabilitation in patients undergoing epilepsy surgery.

Apart from morphological differences between the two hemispheres, which have been the subject of extensive studies, the two hemispheres have also been shown to exhibit different functional connectivity patterns whereby linguistic task processing resulted in activation confined to the left hemisphere whereas visuospatial and attention processing was associated with bilateral fMRI activation in healthy adults (Gotts et al., 2013; Vigneau et al., 2011). This finding challenges the concept of the material-specific memory organisation model, which posits that verbal and visuospatial memory functions are two unitary constructs within the left, presumed dominant, hemisphere being responsible for verbal memory processing and the right hemisphere, for non-verbal memory function (Milner & Penfield, 1955). Brenda Milner first proposed the concept of interhemispheric memory specialisation during her doctorate research while studying severe memory deficits observed in patients following a left temporal lobectomy for drug resistant epilepsy (Penfield & Milner, 1958). While verbal memory deficits are consistently observed in patients with left dominant MTLE, the association between the right temporal dysfunction and the visuospatial memory performance in right MTLE patients appears to be weak. It has been suggested that visuospatial memory processing relies on the use of verbalisation techniques thus suggestive of bi-hemispheric participation in non-verbal memory processing (Helmstaedter et al., 1995).

The association between verbal memory and language lateralisation has been documented previously (Kim et al., 2003). Kovac *et al* documented such a relationship in a cohort of drug resistant epilepsy patients undergoing a Wada test as part of their presurgical workup (Kovac et al., 2009). This observation was corroborated by the findings of the fMRI studies in a cohort of patients with drug resistant epilepsy by Everts *et al* (Everts et al., 2009). The language fMRI studies showed the evidence of

bilateral hemispheric activation with the continuum of activation asymmetry observed. The majority of individuals showed some degree of right hemispheric activation, whereas categorical left hemispheric language dominance has been seen in up to 95% of right-handers. In 6% of subjects bilateral and fairly symmetrical language representation was observed. There was no exclusive rightward dominance observed in healthy subjects (Benjamin et al., 2018). These findings have been consistently corroborated by earlier studies (Knecht et al., 2000; Springer et al., 1999).

Atypical language lateralisation however is not uncommon in patients with epilepsy. The left hemispheric dominance is found in up to 80% of patients, bilateral language representation - in 16% and right hemispheric dominance in up to 6% of epilepsy patients (Gaillard et al., 2007; Risse et al., 1997; Springer et al., 1999). The atypical language lateralisation is often observed in association with left handedness, familial sinistrality, early onset of epilepsy, before the age of 6, with seizures originating in the left hemisphere and cerebral insults and structural changes affecting the left hemisphere (Satz et al., 1988; Stewart et al., 2014; Strauss & Wada, 1983). These observations highlight the importance of a laterality-specific approach to understanding structural, hodological and functional brain properties, serving as a canvas to further our understanding of aberrant epileptic networks and influencing the choice of pharmacological and surgical strategies on a journey to seizure freedom.

### 1.5.2 MTLE: memory constructs

Clinical neuropsychology, as an independent discipline, originated at the Montreal Neurological Institute with Penfield's observations of pre and postoperative neurocognitive deficits in patients undergoing epilepsy surgery and the enduring enthusiasm of his colleagues taking part in the evaluation of epilepsy surgery patients being instrumental in giving rise to the discipline which has been an integral part of the evaluation of epilepsy surgery candidates ever since (Loring, 2010). Brenda Milner, often credited as the founder of neuropsychology for her pioneering and extensive work dedicated to epilepsy neurocognition, made a monumental contribution conceptualising the material-specific model of memory organisation (Milner & Penfield, 1955).

With the limbic structures being at the heart of memory processing, the studies of memory deficits in epilepsy patients, including pre and postoperative characterisation of memory decline in patients with MTLE gave rise to a lasting alliance between

epileptology, epilepsy surgery and neuropsychology resulting in a further understanding of the neurocognitive phenotypes (Loring, 2010). It has long been postulated that patients with left hemisphere dominant MTLE exhibit verbal memory deficits (Berg et al., 2010), whereas the memory impairment in right MTLE patients has traditionally been perceived to be associated with visuospatial deficits, although less consistently (Gleissner et al., 1998; Saling, 2009).

The apparently straightforward concept of material-specificity, is overall consistent with the concept of hemispheric lateralisation of cortical functions, including the interplay between the language and verbal memory lateralisation, has been dominating the field of neuropsychology for decades. However, the reconceptualisation of epilepsy as a network disorder placed new demands on the standards of epilepsy surgery care as a whole. The network driven hypothesis as a prerequisite for devising the SEEG implantation scheme, places new demands on the precision of electro-clinical, neuroimaging and increased expectations of the comprehensive neuropsychological assessment pertaining to seizure onset localisation, language lateralisation and intraoperative language mapping, notwithstanding the estimation of the neurocognitive costs of epilepsy surgery and the arrangements of neurocognitive pre and rehabilitation measures tailored to the individual patient needs (Baxendale et al., 2019).

It soon become obvious that the material-specific approach to memory organisation, although elegant in its simplicity, could no longer explain the full range of heterogeneous neurocognitive deficits observed in epilepsy surgery candidates nor assist with surgical decision making. Based on the findings of earlier studies into the pathological substrate for specific memory deficits and observations of neurocognitive deficits resulting from various neurosurgical interventions, it has been proposed that impaired arbitrary, i.e. protosemantic, and semantic memory components were consistently localisable to specific intratemporal structures of the dominant hemisphere (Lillywhite et al., 2007; Saling et al., 1993; Weintrob et al., 2002). To this effect, Saling, in his seminal paper scrupulously outlined the concept of intratemporal verbal memory specialisation (Saling, 2009) advancing our understanding of a differential verbal memory impairment in patients with MTLE and allowing for clinically relevant inferences (Saling, 2009).

Importantly, significant functional dissociability between the mesial, i.e. rhinal-hippocampal complex, and lateral, i.e. the temporal neocortex, of the temporal lobe, results in a preferential memory impairment in patients with left MTLE, depending on the exact localisation of the pathological process within the temporal lobe (Saling, 2009; Weintrob et al., 2002). For example, mesial temporal pathology, confined to the hippocampal and rhinal cortices, was observed to result in the impairment of the arbitrary memory component, i.e. concerned with the learning of unrelated word pairs, e.g. “book-water”, “car-flower”, whereas pathological processes affecting the lateral neocortical temporal lobe structures tends to manifest with the impairment of semantic memory, whereby related, i.e. semantically linked, paired associates learning, e.g. “apple-tree”, “daisy-flower”, becomes impaired. Remarkably, the rhinal cortices, electrical stimulation of which produced a feeling of familiarity, i.e. déjà vu, have been shown to be indispensable for facilitating arbitrary learning serving as a relay between the hippocampus, phylogenetically tasked with information encoding, and the temporal neocortex, tasked with the processing of semantic memory components.

In brief, the role of the rhinal cortex is to enable the efficient encoding of novel information by the hippocampus. Therefore, the rhinal cortex is tasked with sieving the information stream through the “filter of familiarity” so that only semantically unrelated word pairs are being relayed to the hippocampus for encoding with a view of facilitating arbitrary learning, whereas related word pairs are not relayed to the hippocampus for encoding. In the meantime, the temporal neocortex continues to support semantic memory components, without burdening the hippocampus where encoding is not warranted (Saling, 2009).

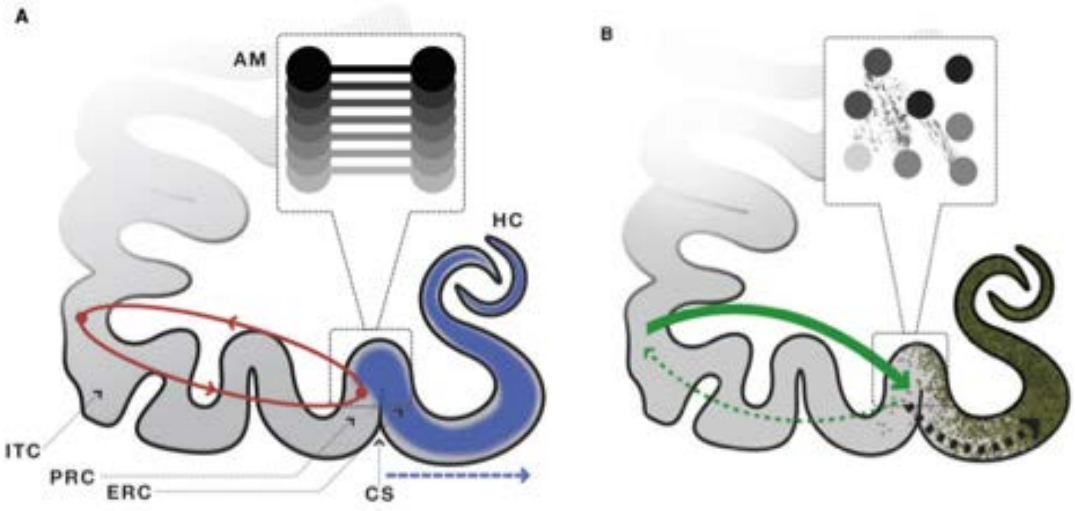



**Figure 1.1: The role of the left mesial temporal lobe structures in protosemantic memory encoding**

Incoming information is sieved through by the rhinal cortices (PRC, ERC, CS), compared to pre-established semantic representations in the neocortex (ITC) and only unfamiliar, semantically unrepresented associations are then relayed to the hippocampus (HC) for encoding. Healthy hippocampus (A) forms new associations (AM); mesial temporal structures affected by epileptic process (B) fail to form new memories. ITC – inferior temporal cortex; PRC – perirhinal cortex; ERC – entorhinal cortex; CS – collateral sulcus; AM – association module. Taken from Sailing (2009) as sited in "Verbal memory in mesial TLE: beyond material specificity" (Saling, 2009).

Therefore, the intratemporal model of memory specialisation rests upon not only intratemporal but also intra-mesial differential verbal memory encoding. It has therefore been proposed that the patients, in whom the limbic structures are implicated as a pathological substrate for ictus generation, may not exhibit semantic memory deficits but are likely to manifest with arbitrary learning impairment instead. Therefore, in this patient cohort the nature of the postoperative neurocognitive deficit would depend on the type of surgical intervention. For example, minimally invasive epilepsy surgery procedures, such as laser interstitial thermal therapy (LiTT) or SAH, would be unlikely to result in a perceivable neurocognitive deficit, providing that arbitrary learning impairment was already discernible at the preoperative assessment.

In the meantime, an ATLR is likely to result in semantic memory impairment powered by the lateral neocortex, which would inevitably be included in the resection during an ATLR. The intratemporal memory specialisation model, with arbitrary learning being a

hallmark of left mesial temporal lobe dysfunction, exercises a more granular approach to understanding the neurobiological basis of neurocognitive memory deficits observed in patients with MTLE and is better placed to address the queries arising during the process of the presurgical evaluation of patients with drug resistant MTLE. In the meantime, considering the hodological affiliations of the temporal lobe, heterogeneity of the epileptic networks and laterality-specific differential connectivity patterns observed in patients with MTLE, one would expect the large-scale network dysfunction to be implicated in the neurocognitive deficits in this patient cohort. There has been a move to investigate memory networks throughout the entire brain, with the Default Mode Network (DMN) being in the spotlight of current neurocognitive exploits. Interestingly, the DMN which is comprised of the precuneus, angular gyrus, mesial temporal lobes, posterior cingulate and prefrontal cortex, was first discovered by Railchle using PET studies (Raichle et al., 2001), following which the role of the DMN in neurocognition has been examined using resting state functional MRI (rs-fMRI).

It has been suggested that the frontal and parietal lobes play a more substantial role in subserving episodic memory function, including arbitrary learning, familiarity and recollection than previously thought (Dickerson & Eichenbaum, 2010). While intratemporal memory specialisation is regarded as plausible however not exhaustive (Saling, 2009), Bettus *et al* posited the concept of the anterior temporal network being another player in subserving verbal memory processing and therefore exhibiting abnormal connectivity patterns in patients with MTLE (Bettus et al., 2010). Intriguingly, the anterior temporal network is comprised of mesiotemporopolar structures and it would therefore be interesting to understand its role as a candidate biomarker of mesiotemporopolar epileptic network dysfunction implicated in the TLE subtype, where the seizure onset zone is localised to the temporal pole (Chabardes et al., 2005). The field of epilepsy neurocognition has seen an explosion of interest in the role of DMN and other candidate large-scale networks in predicting memory deficits in patients with TLE with multiple studies underway.

This brings us to conclude that we have entered the era of neurocognitive networks, which holds the distinct promise of being able to identifying specific neurocognitive biomarkers characteristic of underlying epileptic network dysfunction in patients with TLE (Rayner et al., 2019; Wilson & Baxendale, 2014).

### 1.5.3 MTLE: hodological model of memory function

There has been growing interest in the hodological aetiology of cognitive dysfunction (Roger et al., 2018). The developments in the field of structural neuroimaging, such as DTI and diffusion MRI has illuminated our understanding of the role of white matter tracts in human cognition. Unlike previous approaches to memory conceptualisation, based on rather unitary constructs, for example material-specific memory organisation (Milner & Penfield, 1955) followed by the intratemporal compartmentalisation of memory constructs with a particular focus on task-specific memory dysfunction in patients with MTLE (Saling, 2009), the hodological approach to cognitive function aims to embrace the complexity of the cerebral pathways as one of the major determinants of normal cognition. Entering the era of epilepsy networks has given rise to the rapidly expanding field of structural and functional connectivity studies, whereby epileptic networks in patients with drug resistant epilepsy are now being thoroughly explored preoperatively (Morgan et al., 2017) with a view of identifying a computer-assisted network-targeted presurgical planning algorithm to increase the yield of epilepsy surgery procedures and minimise its neurocognitive costs and to assist with the prediction of surgical outcomes. In addition, there have been an increasing number of studies looking into epileptic network behaviour, e.g. reorganisation, following epilepsy surgery and correlating the network changes with surgical outcomes (Maccotta et al., 2017; Victoria et al., 2019).

Similarly, in the field of epilepsy neurocognition there has been a move to explore the role of the white matter tracts in memory and language dysfunction (Kaestner et al., 2020a). The findings of a recent study by Reyes *et al* suggested that at least four cognitive phenotypes could be identified in patients with TLE, based on the patterns of white matter alterations. Interestingly, in patients with both language and memory involvement, the superficial white matter connectivity appeared to be altered globally, whereas in patients manifesting with isolated language dysfunction the aberrant connectivity changes were confined to the perisylvian region. In one out of four groups studied, the connectivity patterns were comparable to those in healthy controls (Reyes et al., 2019). These findings are indicative of the heterogeneity of the neurocognitive phenotypes in TLE syndrome which although seemingly unitary on the surface, are characterised by the heterogeneity of epileptic network dysfunction. Admittedly, the role of white matter tracts in subserving memory and language processing is not

unexpected, e.g. Lüders *et al* elegantly demonstrated that basal temporal language areas implicated in language deficits in patients with drug resistant focal epilepsy, which was regarded to be a sequela of the discharge propagation to the perisylvian regions (Lüders et al., 1991). The hodological model of language connectivity proposed by Duffau *et al* reflects the complexity of the underlying large-scale networks. The data derived from the cortical stimulation of anatomical constructs has unequivocally demonstrated the role that ventral semantic and the dorsal phonological pathways play in memory and language processing (Duffau et al., 2013). It has been demonstrated by Catani *et al* that the lack of hodological synergy between the mesial temporal lobe structures and the lateral temporal neocortex is implicated in episodic memory impairment in patients with epilepsy (Catani et al., 2013).

The role of the large-scale networks in neurocognition has been the subject of ongoing research in patients with epilepsy (Bettus et al., 2010) and the role of DMN in sub-serving normal memory functions has long been recognised (Raichle, 2015). There has been a growing number of studies exploring the role of DMN in predicting memory deficits in patients with epilepsy with the suggestion that reduced $^{18}$FDG uptake in the extra-temporal mesial fronto-parietal regions were associated with memory deficits in patients with MTLE (Guedj et al., 2010; Laurent et al., 2020) and the search for specific neurocognitive biomarkers continues. Importantly, it has been shown by Warren *et al* that following the successful outcome of epilepsy surgery in a patient with Lennox-Gastaut syndrome, there was a significant improvement in neurocognitive function, which was correlated with substantial changes in cerebral connectivity patterns, including DMN and the dorsal attention network (DAN), which the authors studied before and after the neurosurgical intervention (Warren et al., 2017). It has been demonstrated that in cats the large-scale network plasticity allowed, within the limitations of the structural brain architecture, for cross modal functional colonisation as part of the adaptive changes following the loss of function in one of the sensory modalities (Roger et al., 2018). It would therefore be important to understand the role of cross modal functional colonisation in humans as this would open up new avenues in the field of neurocognitive rehabilitation. Considering that seizures have been shown to follow preferential propagation pathways in patients with both, temporal and extratemporal epilepsies (Bartolomei et al., 2010; Chabardes et al., 2005) and with the brain's hodological properties being the anatomical substrate enabling this seizure propagation in a preferential manner, it is plausible that aberrant networks implicated in

the development of epilepsy and the large-scale networks implicated in memory dysfunction in patients with epilepsy share common neurobiological aetiologies. It would therefore be interesting to understand if the identification of neurocognitive phenotypes could assist with a non-invasive epileptic network mapping in patients with drug resistant epilepsy.

The evaluation of surgical candidates is a complex process of assimilation of the anatomo-electro-clinical data in conjunction with multimodal imaging findings and iEEG results. It is not inconceivable that in the future an integrated epilepsy surgery model could also be populated with the data derived from neurocognitive phenotyping with a view of visualising the continuum of aberrant pathways implicated in an individual patient's drug resistant epilepsy thus allowing for precision in surgical decision making, estimation of neurocognitive costs and devising effective and efficient therapeutic interventions, notwithstanding individualised neurorehabilitation strategies.

## 1.6 Memory deficits in patients with MTLE

It has been documented previously that verbal memory performance in patients with MTLE is influenced by both, patient specific and epilepsy specific factors, including the age of the epilepsy onset, the level of educational attainment, seizure burden and the nature of the underlying epileptogenic substrate. Interestingly, the study of verbal memory performance in patients with newly diagnosed versus chronic left TLE by Aikiä *et al* (Äikiä et al., 2001) demonstrated that verbal memory impairment was evident in both patient cohorts, regardless of the epilepsy duration. These findings were replicated by Taylor *et al* who demonstrated that verbal memory performance was affected early on in the disease (Taylor et al., 2010), thus calling for wider recognition of the bidirectional relationship between epilepsy and cognition, similar to that established between epilepsy and depression (Kanner & Balabanov, 2002), and highlighting the need for early neurocognitive intervention in patients with epilepsy (Helmstaedter & Witt, 2017).

It has been observed that the younger the age of the epilepsy onset, the more impaired the preoperative neurocognitive functioning was found to be (Black et al., 2010; O'Leary et al., 1981), whereas the patients with an older age of epilepsy onset suffered more significant memory decline following the epilepsy surgery (Bell & Davies, 1998). In addition, the greater the chronological age at the time of the ATLR was independently associated with more prominent postoperative memory deficits (Bell & Davies, 1998), which could be explained by a reduced cognitive reserve (Chelune, 1995). Higher educational attainment at the time of the epilepsy onset was found to be associated with less extensive verbal memory impairment which suggests that seizures have a significant deleterious effect on neurocognitive development and learning often putting the patients with epilepsy at a heightened risk of suboptimal educational attainments resulting in socioeconomic disadvantages (Baxendale et al., 2006; Pai & Tsai, 2005; Piazzini et al., 2006). High convulsive seizure burden rates and status epilepticus have been shown to exert detrimental effects on patients' cognitive function with verbal memory performance being affected the most (Äikiä et al., 2001; Dodrill, 2002; Thompson et al., 2015).

In relation to the underlying epileptogenic lesion, it has been observed that both, the lesions topography as well as its nature could give rise to specific memory deficits. The

findings of previous research suggest that hemispheric dominant mesial temporal lobe structures and rhinal cortices in particular, are instrumental in verbal memory encoding, a prerequisite for arbitrary learning (Lillywhite et al., 2007; Saling et al., 1993; Weintrob et al., 2002). Therefore, the epileptogenic lesion, e.g. HS, localised to the mesial temporal lobe structures would result in arbitrary learning impairment, whereas the lesions in the lateral neocortex are likely to result in predominantly impaired semantic memory components (Maizuliana et al., 2020). Mueller *et al* observed a differential influence of the underlying histopathology findings on verbal memory performance in patients with MTLE-HS. Interestingly, neuronal loss in the dentate gyrus and the CA3 hippocampal subfields was associated with significantly impaired verbal memory performance in this patient cohort, whereas histopathology findings identified in other hippocampal subfields had no bearing on the verbal memory performance in patients with MTLE-HS, in whom verbal memory scores were comparable to those in patients with MRI-negative MTLE (Mueller et al., 2012).

The impact of antiepileptic treatment on neurocognitive function in patients with MTLE has been the subject of debate and controversy for many years with the findings of early studies implying a deleterious effect of AED therapy on memory performance (Mula & Trimble, 2009). However, the latest studies have not demonstrated an independent association between AED exposure and neurocognitive function thus advocating optimisation of pharmacological treatment in order to achieve better rates of seizure control, which in turn would have a favourable bearing on the patient's cognitive function (Foster et al., 2020; Meador, 2006). The relationship between depression and neurocognitive function in patients with epilepsy and TLE in particular, has been another topic of fervent debate. Galioto *et al*, for example, observed that the patients with TLE and comorbid depression exhibited higher rates of executive dysfunction, corroborated by self-reports of impaired cognitive performance in this patient cohort, whereas otherwise healthy controls with depression demonstrated no evidence of cognitive impairment (Galioto et al., 2016). On the other hand, Demin *et al* found no association between depression and cognitive impairment in patients with TLE (Demin et al., 2018). One could argue that it is the extra-temporal large-scale network dysfunction, corroborated by the findings of predominantly frontal hypometabolic changes (Takaya et al., 2006) and the changes observed within the DMN in patients with TLE (Laurent et al., 2020), that accounts for the impaired executive functioning in patients with TLE rather than depression itself. However, considering the high

prevalence of depression in patients with epilepsy, approximately 25-55% (Mendez et al., 1986) and the suggestion of a bidirectional relationship between the two conditions (Harden, 2002; Kanner & Balabanov, 2002), it is plausible that epilepsy, neurocognitive deficits and mood disorders are all part of a large-scale network dysfunction in patients with TLE.

## 1.7 Epileptogenic zones conceptualised

Needless to say, that regardless of the surgical technique, the success of epilepsy surgery rests on securing a complete resection of the epileptogenic zone, which is the cortical region responsible for the generation of the seizures (Rosenow & Lüders, 2001). It is presumed that in patients who are rendered seizure free following epilepsy surgery, the epileptogenic zone, or at least the drug resistant epileptogenic zone (Zhang & Kwan, 2019), has been removed in its entirety. The "reflection-on-action" approach to localising the epileptogenic zone does not allow for prospective determination of its extent. Therefore, the distinct possibility remains that patients with excellent seizure outcomes could have been rendered seizure free with a more sparing surgical resection. The epileptogenic zone is essentially a core part of a "syndicate" known as the epileptogenic tissue, this concept was first outlined by Lüders and Awad at the 2nd Palm Desert Conference on the Surgical Treatment of the Epilepsies in 1992. Further elaborations offered a heuristic approach to the conceptualisation of epileptogenic tissue by subdividing it into tiered entities (Table 1.1) (Rosenow & Lüders, 2001). This is to facilitate our understanding of the complex task at hand when it comes to interpreting the presurgical evaluation data through the lens of a tiered yield attached to each non-invasive or invasive investigatory technique, depending on their proximity to the epileptogenic zone.

**Table 1.1: Epileptic zone conceptualised**

| | |
|---|---|
| **Seizure onset zone** | The area of cortex generating the seizures, used as proxy for epileptogenic zone |
| **Epileptogenic lesion** | The lesion casually related to the ictal generator |
| **Ictal symptomatogenic zone** | The area of cortex generating initial seizure semiology |
| **Irritative zone** | Refers to the region of cortex generating inter-ictal epileptiform discharges |
| **Functional deficit zone** | The area of cortex interictally exhibiting evidence of abnormal cerebral function |

Adapted from Rosenow (2001) "Presurgical evaluation of epilepsy" (Rosenow & Lüders, 2001)

This core conceptual framework has been at the heart of a multifaceted approach to the presurgical evaluation (Höller et al., 2015; Jehi, 2018; Rosenow & Lüders, 2001). A thorough evaluation of the seizure semiology continues to be of immediate relevance and offers a unique opportunity to deduce the potential epileptogenic zone through the dissection of the seizure semiology and making inferences based on hodological brain properties, thus video-EEG-telemetry assessment continues to remain a critical part of the presurgical evaluation (Elwan et al., 2018).

The aim of the current multimodal investigatory tools is to assist with the lateralisation and localisation of the seizure onset zone and to help plan SEEG implantation strategies, including the MRI-negative patient cohorts (McGonigal et al., 2008). It has been proposed that while EEG, EEG-fMRI and MEG studies are best placed to determine the extent of both, the irritative and the seizure onset zones, ictal SPECT is required to determine the epileptogenic zone with a higher degree of precision while iEEG currently remains the gold standard for identifying the seizure onset zone (Jehi, 2018). Despite the enduring appeal of the elegantly simple heuristic approach to defining the epileptogenic zone (Rosenow & Lüders, 2001), the intricate interplay between its components and their respective roles in the epileptogenesis, do not remain unchallenged by the advancements in epilepsy research. The findings of pathological High Frequency Oscillations (HFO's) arising from the $^{18}$FDG-PET hypometabolic tissue studies by Lamarche *et al*., suggest that the role of $^{18}$FDG-PET extends beyond reflecting the extent of the functional deficit zone (Lamarche et al., 2016).

Considering the compelling evidence that the epileptogenic zone is a dynamic as opposed to a static entity (Bartolomei et al., 2017; Jehi, 2018), electrophysiological techniques and functional imaging modalities are best placed to reflect the evolution and heterogeneity associated with this complex entity. The recent findings by Grinenko *et al* hold the promise of a potential electrical biomarker of epileptogenicity, i.e. a "fingerprint" of the epileptogenic zone discriminating between the electrical signature inherent to the ictal generator itself and the electrographic changes resulting from the seizure propagation using a time frequency specific pattern (Grinenko et al., 2017). Furthermore, as a result of the extensive study by Lagarde *et al* at least eight distinct seizure onset patterns have now been identified with the low voltage fast activity (LVFA) being a predictor of favourable seizure outcomes, even so 21% of seizure onset patterns did not include LVFA (Lagarde et al., 2019). Importantly, compelling evidence

produced by Lagarde *et al* highlighted the notion that the spatial organisation of the epileptogenic zone was the most important determinant of the seizure outcomes.

These findings resonate with the nascent concept of DREZ, substantiated by clinical observations stemming from postoperative seizure recurrence patterns (Zhang & Kwan, 2019). Conceptual framework behind DREZ offers fresh perspectives on potential management strategies in patients with drug resistant epilepsy. It would be crucial to understand what exactly sets apart the drug resistant and the drug responsive epileptogenic zones and how one could gauge the critical resection volume in order to render the patients free from DREZ. This challenge places new demands on identifying the biomarkers, which would enable differential stratification of the epileptogenic zone and guide our surgical and pharmacological treatment strategies. The computational network approach to devising simulation models of the epileptogenic networks with a view of assisting with surgical decision making has rendered some promising findings (Morgan et al., 2017; Sinha et al., 2019).

In the meantime, there has been a move to revisit the role of already established neuroimaging modalities as new and improved technologies become available, e.g. PET/MRI techniques draw on the strengths of structural imaging and the unique features of $^{18}$FDG-PET enabling *in vivo* visualisation of the cerebral metabolic activity, which is inherently linked to its function. The finding of pathological HFO's in association with reduced $^{18}$FDG uptake suggests that $^{18}$FDG-PET could no longer be seen as a mere bystander of the epileptogenic process (Lamarche et al., 2016). While the "PET-ectomy" approach to the surgical resection has been criticised (Paesschen et al., 2007), the findings of Vinton *et al* (Vinton et al., 2007) suggest that $^{18}$FDG-PET could shed further light on the relationship between the hypometabolic regions and DREZ. This study set out to evaluate the role of $^{18}$FDG-PET in predicting seizure outcomes in patients undergoing an ATLR, with the network epilepsy approach being at the core of this inquiry.

## 1.8 Presurgical evaluation in MTLE: general principles

### 1.8.1 The role of neuroimaging modalities

MTLE syndrome, being the commonest form of drug resistant focal epilepsy (Boon et al., 1991) has been the subject of multiple studies. There is compelling evidence pointing towards a wider and more heterogeneous epileptogenic network implicated in seizure generation in MTLE (Bartolomei et al., 2008; Kahane & Bartolomei, 2010), resulting in the reconceptualisation of MTLE as a network disorder (Bartolomei et al., 2008; Kahane & Bartolomei, 2010). Considering the Class I evidence for epilepsy surgery as being the most efficacious treatment option in patients with TLE (Wiebe et al., 2001), the aim of the presurgical evaluation in patients with MTLE is to confirm the surgical candidacy, to provide the patient and their families with presurgical counselling and identify the need for cognitive prehabiliation (Baxendale, 2020a). The evaluation of epilepsy surgery candidates entails a multidisciplinary approach whereby the data derived from non-invasive, i.e. a phase 1, presurgical evaluation such as the outcome of the video-EEG-telemetry admission, comprehensive neuropsychological and psychiatric evaluation, structural MRI, $^{18}$FDG-PET, SPECT and language fMRI is amalgamated and scrutinised with the purpose of arriving at a decision as to whether or not the patient can proceed to epilepsy surgery or a phase 2, invasive evaluation is warranted.

The core conceptual framework behind the multifaceted approach to the presurgical evaluation revolves around the identification of the epileptogenic zone (Höller et al., 2015; Jehi, 2018; Rosenow & Lüders, 2001). Despite the fact that TLE is the most studied surgically remediable focal epilepsy syndrome, it is imperative, as part of the presurgical evaluation, including in patients with radiological evidence of HS, to gain a detailed understanding of the potential extent of the epileptogenic zone involved. With shared decision making being at the heart of patient centred care and the increasing availability of minimally invasive surgical techniques, it is the estimation of the extent of the epileptogenic network that can influence the type of epilepsy surgery that could be offered to the patient. This notion has been substantiated by the recent findings of Lagarde *et al* which confirmed the paramount importance of the extent of the epileptogenic zone as a strong predictor of the seizure outcomes (Lagarde et al., 2019).

Patients with bilateral TLE, for example, would not be suitable candidates for resective surgery however responsive neuro-modulation based treatment options could be

considered in this patient cohort. For patients with an electroclinical suggestion of the temporal pole being implicated as part of the epileptogenic network, a selective amygdalohippocampectomy procedure or a minimally invasive surgical procedure would not be recommended as extensive networks implicated in this TLE subtype are likely to result in surgical failures hence an ATLR would be the treatment of choice here (Chabardes et al., 2005). Importantly, TLE-plus has been shown to be the culprit in a significant proportion of epilepsy surgery failures in patients undergoing TLE surgery and therefore the patients in whom the seizure semiology or scalp EEG signatures are indicative of more extensive epileptic network involvement, phase 2 evaluation would be warranted (Barba et al., 2016).

The presurgical evaluation of patients with drug resistant MTLE commences with the characterisation of the electro-clinical syndrome, starting at the point of the neurological consultation and followed by further electro-clinical evaluation in the video-EEG-telemetry unit so that all the habitual seizure types are captured and confirmed. Most epilepsy surgery programmes aim to capture at least three habitual seizures of the same seizure type (Shih et al., 2018). Scalp video-EEG-telemetry in MTLE patients typically renders the inter-ictal findings of spike-and-wave discharges with phase reversal in basal derivations. These interictal changes could be seen to arise independently from both hemispheres in patients with unilateral MTLE and do not portend unfavourable seizure outcomes if observed in isolation (Hamer et al., 1999; Vakharia et al., 2018). Ictal scalp EEG onset typically manifests with 5-8Hz rhythmic discharges preceded by the clinical seizure onset in the form of an aura followed by impaired awareness as the seizure propagates beyond the mesial temporal structures. A thorough evaluation of the seizure semiology offers a unique opportunity to enhance our understanding of the symptomatogenic zone with the inference to a potential ictal generator based on the hodological properties of the underlying brain structures, thus video-EEG-telemetry assessment continues to be the cornerstone of the presurgical evaluation, the results of which, play an important role in the lateralisation and localisation of the seizure onset zone and assist with the choice of neuroimaging modalities employed in the presurgical evaluation (Elwan et al., 2018).

The MRI findings characteristic of MTLE have been addressed in detail in Chapter 3. Radiological evidence of HS is seen in the vast majority of patients, however up to 30% of patients are MRI-negative. Unequivocal and concordant structural pathology

identified on the preoperative MRI has been strongly associated with favourable seizure outcomes in patients with MTLE (Berkovic et al., 1995; Cascino et al., 1992). However, the seizure outcomes in MRI-negative PET-positive patients have been reported to be comparable (Carne et al., 2007; Muhlhofer et al., 2017b). Traditionally, a phase 1, i.e. non-invasive presurgical evaluation has been deemed sufficient in the majority of epilepsy surgery candidates with MTLE where the electro-clinical evaluation results, structural MRI and neuropsychological assessment outcomes rendered concordant findings (Knowlton et al., 1997; Kuzniecky & Devinsky, 2007). While the core aspects of the presurgical evaluation in this patient group are comparable across all the epilepsy surgery programmes worldwide, which entails a period of video-EEG-telemetry on admission and a structural MRI scan as a minimum requirement, the availability and access to functional neuro-imaging modalities varies amongst the epilepsy surgery centres depending on the healthcare commissioning arrangements and local specifics of the epilepsy surgery programmes.

It has been suggested that $^{18}$FDG-PET be reserved for either MRI-negative patients or those with discordant findings following video-EEG-telemetry, MRI and neuropsychological assessment (Duncan et al., 2000; Jones & Cascino, 2016). However, the results of the survey carried out by Mouthaan *et al* (Mouthaan et al., 2016) looking into the accessibility of the neuro-imaging modalities and the use of post-acquisition processing techniques in 25 European epilepsy surgery centres demonstrated that most of the surveyed centres had consistent access to $^{18}$FDG-PET and SPECT and utilised the post-acquisition processing techniques, which were shown to increase the diagnostic yield of MRI and $^{18}$FDG-PET, in particular, during the presurgical evaluation (Bernasconi & Bernasconi, 2011; van't Klooster et al., 2014). Considering the complexity of the epileptic networks implicated in TLE (Bartolomei et al., 2017; Chassoux, 2017), notwithstanding the clinical scenarios associated with dual pathologies (Lopez-Gonzalez et al., 2011), $^{18}$FDG-PET and SPECT are commonly employed in the evaluation of TLE patients (O'Brien et al., 2008; Ryvlin & Rheims, 2008). The diagnostic yield of SISCOM has long been recognised (Brien et al., 1998), however the technical challenges associated with the timely administration of the radiotracer has been one of the arguments for reserving its use for MRI-negative patients (Kuzniecky & Devinsky, 2007).

Multimodal neuroimaging techniques and computer assisted technologies play a key part in surgical planning (Elwan et al., 2018; Vakharia et al., 2019). These are used not only for surgical decision making but also for preoperative counselling. The use of fMRI in language lateralisation has been widely employed already (Bargalló et al., 2020), whereas the use of memory fMRI for predicting cognitive risks associated with epilepsy surgery has been gradually transitioning from a research setting into clinical care (Sidhu et al., 2016). The increased yield of using multimodal imaging techniques in the evaluation of surgical candidates has long been recognised (Murphy et al., 2001), especially after using co-registration (Varrone et al., 2009). The epileptogenic lesions, which could be easily overlooked on structural MRI are detected after co-registration with $^{18}$FDG-PET resulting in improved surgical outcomes (Chassoux et al., 2010). Current technologies allow for the incorporation of DTI data outlining the topography of Meyer's loop in an individual patient thereby allowing for increased intraoperative precision and reduced surgical morbidity rates (Vakharia et al., 2019). Importantly, there have been an increasing number of studies utilising computer assisted technologies for seizure prediction and preoperative mapping of the epileptogenic zone based on the analysis of aberrant connectivity patterns representative of the epileptogenic networks implicated in patients with drug resistant TLE (Sinha et al., 2019; Victoria et al., 2019). The connectomic research opens up new avenues for developing non-invasive tools for the preoperative mapping of the epileptogenic zone and adding extra precision to the evaluation of surgical candidates.

### 1.8.2 The role of iEEG in patients with TLE

Despite the long held belief that epilepsy surgery candidates evaluated for drug resistant MTLE require only a "lean" phase 1 presurgical workup, the complexity of the underlying epileptic networks observed in patients with TLE (Bartolomei et al., 2008; Bartolomei et al., 2010), their heterogeneous and progressive nature not uncommonly calls for a phase 2 evaluation. Therefore, on some occasions contrasting MTLE with neocortical TLE is more a matter of heuristics rather than a true reflection of reality. A recent study by Herskovitz *et al* demonstrated that intracranial evaluation was warranted in up to one third of patients with TLE following a phase 1 presurgical evaluation (Herskovitz & Schiller, 2016). The use of grid and depth electrodes in patients with TLE is gradually being replaced by the use of SEEG. The last decade has seen these phase 2 evaluation techniques gain further popularity and wider implementation by the

epilepsy surgery centres due to the low morbidity rates associated with its use and the high diagnostic yield that SEEG has to offer.

While it is not uncommon for patients with unilateral MTLE and radiological evidence of unilateral HS to exhibit bitemporal independent inter-ictal spikes with no significant bearing on the postoperative seizure freedom rates (Hamer et al., 1999), the finding of bilateral ictal changes under the same circumstances calls for an iEEG evaluation before the patient's surgical candidacy could be confirmed. Hirsch *et al* found that *circa* 20% of referrals for iEEG exploration were made with a view of excluding bitemporal epilepsy syndrome (Hirsch et al., 1991). In the meantime, Aghakhani *et al* demonstrated that in up to 70% of these patients a unilateral seizure onset was confirmed on iEEG with at least 50% of patients standing a good chance of achieving seizure freedom following epilepsy surgery (Aghakhani et al., 2014). On the other hand, the patients with no discernible structural or functional neuroimaging findings were thought to be less suitable surgical candidates thus iEEG was carried out only in a carefully selected minority of patients (Diehl & Lüders, 2000). On the contrary, the patients with radiological evidence of bilateral hippocampal atrophy and unilateral iEEG seizure onset were found to benefit from epilepsy surgery (King et al, 1995), providing the adequacy of the contralateral temporal lobe is confirmed prior to the surgical intervention.

MRI-negative patients with inconsistent seizure semiology and widespread scalp EEG changes call for further clarification of the seizure onset zone, considering the complex interplay between the seizure generators identified within the extensive epileptic networks implicated in TLE (Bartolomei et al., 2010; Chabardes et al., 2005). In addition, TLE-plus being yet another well recognised culprit for epilepsy surgery failures is found in up to 30% of patients referred for iEEG with perisylvian network involvement being confirmed in the majority of patients (Barba et al., 2016; Kahane et al., 2015). TLE mimics result from a silent extratemporal ictal generator typically found within close proximity to the temporal lobe structures (Andermann, 2003; Richard et al., 1965), often in the orbito-frontal cortical regions (Smith et al., 2004). In this patient group temporal lobe seizure semiology is the result of ictal propagation from an otherwise silent seizure onset zone. A high index of suspicion is warranted for identifying indistinct extratemporal changes on $^{18}$FDG-PET or SPECT in conjunction with the subtle inconsistencies in seizure semiology that could be observed in this

particular patient cohort. The electro-clinical intricacies reflect the heterogeneous properties of the epileptic networks in patients with TLE thus highlighting the importance of employing multimodal neuroimaging techniques in the presurgical evaluation of patients with TLE.

The use of iEEG is necessary in patients undergoing minimally invasive epilepsy surgery procedures. Within the limitations of spatial sampling, iEEG in this patient cohort could influence surgical decision making and the choice of the surgical procedure depending on the extent of the epileptogenic zone identified by iEEG. This would also hold true in selective amygdalohippocampectomy candidates should there be any doubt about the wider network involvement with the epileptogenic zone extending to the temporal lobe, in which case an ATLR would be the treatment of choice in this patient cohort.

## 1.9 The role of Neuropsychology in epilepsy surgery candidates

### 1.9.1 General principles of neuropsychological assessment

A comprehensive neuropsychological assessment constitutes an integral and mandatory part of the presurgical evaluation. There has been an ongoing quest for improved neuropsychological input and the role it plays in epilepsy care, including its contribution to the evaluation of epilepsy surgery candidates in particular. It has been the ambition of the ILAE Neuropsychology Task Force to deliver high standards of care for patients with epilepsy and epilepsy surgery candidates in particular (Sallie et al., 2019; Wilson et al., 2015). The role of neuropsychological assessment in epilepsy surgery care is multifaceted, which includes a significant contribution to seizure onset lateralisation and localisation. The prediction of postoperative memory decline pertaining to particular type of epilepsy surgery is another key area where our neuropsychology colleagues play a critical role in presurgical planning and preoperative counselling (Sallie et al., 2019).

In the postoperative period, the neuropsychology input is concerned not only with the quantification of the memory decline following epilepsy surgery but also with exploring and addressing the patients' perceptions of cognitive and mood outcomes following the neurosurgical procedure, notwithstanding their impact on patients' health related QoL and devising long term management plans focusing on neurocognitive rehabilitation (Coleman et al., 2020; Wilson et al., 2015). The findings of Sherman *et al*, suggest that 44% of patients undergoing a dominant hemispheric ATLR develop postoperative verbal memory deficits. The rate of cognitive decline following a non-dominant ATLR is 20%, which is not trivial either (Sherman et al., 2011). These figures are comparable with the neurocognitive outcomes reported across comprehensive epilepsy surgery programmes. Epilepsy surgery has long been recognised as the treatment of choice for patients with drug resistant MTLE (Wiebe et al., 2001), and yet it remains highly underutilised (Benbadis et al., 2003; Wiebe, 2016). The reasons for the suboptimal uptake of epilepsy surgery interventions are multifactorial including apprehension regarding potential postoperative memory decline and the unfading legacy of severe memory loss in patient H.M., being amongst the factors which could influence a patients decision not to proceed to epilepsy surgery (Anderson et al., 2013; Dewar & Pieters, 2015).

From a practical standpoint, neurocognitive assessment with the use of task-specific neurocognitive markers could highlight preoperative memory deficits pertaining to impaired arbitrary learning in patients with hemispheric dominant TLE. The task-specific memory deficits stemming from left mesial temporal lobe dysfunction in patients with MTLE are unlikely to worsen following neurosurgical intervention. However, preserved semantic memory, broadly localised to the temporal neocortex, could decline following an ATLR and therefore neurocognitive prehabilitation arrangements could mitigate the effects of epilepsy surgery. The role of neurocognitive prehabilitation has been recognised and specifically highlighted in the recent recommendations by the ILAE Neuropsychology Task Force, which is a major step towards delivering improved standards of epilepsy surgery care (Sallie et al., 2019). This could also enhance patient engagement and assist with shared decision making, which is not infrequently influenced by the fear of postoperative memory loss (Dewar & Pieters, 2015).

In the past, the Wada test, commonly known as the intra-carotid amobarbital procedure, was widely employed to assess language cortex lateralisation and the risk of postoperative amnesia following an anterior temporal lobectomy. With the advancement of non-invasive memory assessment techniques, the Wada test has been gradually replaced by fMRI (Baxendale et al, 2008b). While memory fMRI has been widely used in the research setting (Bonelli et al., 2010; Sidhu et al., 2016) with promising results, memory fMRI is yet to be implemented as a standard part of routine clinical care. This long overdue preoperative investigation modality would enable us to ascertain both, the adequacy of the to be removed hippocampus and to characterise cognitive reserve in order to assist with preoperative estimation of potential postoperative neurocognitive decline (Bonelli et al., 2010; Sidhu et al., 2016).

The estimation of the neurocognitive risks associated with epilepsy surgery is not straightforward. Multiple factors, such as the patients' baseline cognitive performance, the laterality and type of epilepsy surgery proposed, the aetiology of the drug resistant epilepsy, notwithstanding the patient's age and co-existing psychiatric comorbidities are being factored in, thus a modelling approach to the risk stratification has been proposed (Baxendale et al., 2006). At this stage, however, the modelling-based prediction of cognitive decline is limited by hard to predict temporal tissue resection volumes, which constitutes a postoperative variable. In the meantime, the clinical interview and the

paper-and-pencil based neurocognitive testing continue to be the starting point of the neuropsychological evaluation. It has been proposed that using the task-specific as opposed to the material-specific orientated neurocognitive tests could yield better outcomes in terms of eliciting neurocognitive deficits characteristic of memory impairment associated with particular neuroanatomical constructs affected by the epileptic networks in patients with MTLE (Lillywhite et al., 2007; Saling, 2009; Weintrob et al., 2002). The concept of intratemporal compartmentalisation of verbal memory organisation, not entirely devoid of heuristics, rests on the principles of task- as opposed to material-specificity. This begs the question are the current, predominantly material-based neuropsychological tests, contained within the neuropsychology armamentarium and routinely used in the evaluation of epilepsy surgery candidates, accurate enough to elicit the neurocognitive deficits resulting from hemispheric dominant mesial temporal lobe dysfunction in patients with MTLE.

In addition, the baseline neurocognitive scores obtained during the preoperative neuropsychological assessment are in turn influenced by multiple factors, such as the current seizure burden, active psychiatric comorbidities and the contributory effects of AEDs on neurocognitive performance. Considering the complex interplay between an individual and the epilepsy specific factors influencing neurocognitive deficits, notwithstanding the impact of the repeat neurocognitive testing itself, the memory scores obtained during a neuropsychological assessment are always interpreted within the clinical context rather than in isolation. There is however an ongoing demand for neurospecific cognitive markers which would facilitate the detection of task-specific memory deficits as part of the presurgical evaluation, including the neurocognitive marker for eliciting memory deficits resulting from non-hemispheric dominant temporal lobe dysfunction (Saling, 2009). Vogt *et al* surveyed the European epilepsy surgery centres to explore the range of neurocognitive tools routinely used in the evaluation of surgical candidates (Vogt et al., 2017). Evidently, the neuropsychological assessment tests currently employed by the epilepsy surgery programmes across the world have, by and large, been influenced by the material-specific approach to memory testing (Vogt et al., 2017). This is understandable, as the material-specificity based conceptualisation of the memory constructs has been dominating the field of neuropsychology for decades.

The neurocognitive assessment scores, similar to the neurological examination findings, are always interpreted within the clinical context. On the other hand, it might be helpful

to illustrate the need for more specific neurocognitive markers by comparing the interpretation of the findings of neuropsychological testing with the findings resulting from a neurological assessment. The diagnostic value of the neurological signs elicited during the neurological examination varies. For example, slight asymmetry of deep tendon reflexes is duly noted however the finding of sustained ankle clonus, indicative of a pyramidal deficit, is considered a hard sign when assessing cortico-spinal tract integrity (Araújo et al., 2015; O'Brien, 2014). Similarly, the move towards task-specific neurocognitive markers could increase the independent yield of the neurocognitive tests used in the presurgical evaluation in order to improve the lateralisation and localisation of the seizure onset zone, crucial for presurgical planning. Considering the network-driven approach to the evaluation of epilepsy surgery candidates, it would be important, along with the detailed characterisation of the epileptic networks to also identify neurocognitive phenotypes specific to the epileptic network dysfunction (Englot et al., 2016; Reyes et al., 2019; Roger et al., 2018).

As part of this study I set out to explore the lateralising value of the most commonly used neuropsychological tests presently employed in the evaluation of surgical candidates. The research findings are outlined in Chapter 6.

### 1.9.2 Language function lateralisation

Language impairment has been described in up to 50% of patients with epilepsy (Balter et al., 2019). Considering the inherent relationship between language processing and verbal memory performance and the higher rates of atypical language lateralisation in patients with epilepsy, it is recommended that language lateralisation should be carried out routinely as part of the presurgical evaluation in epilepsy surgery candidates, with particular focus on those considered for hemispheric dominant surgical interventions (Duncan et al., 2016). Prior to the wider use of fMRI techniques, a Wada test, based on the deactivation of cortical language areas achieved through an intra-carotid amobarbital injection was considered to be the gold standard for assessing language lateralisation (Baxendale et al., 2008b). The Wada test was originally developed for language lateralisation only (Juhn & Theodore, 1960) and was subsequently repurposed to assess the risk of postoperative amnesia (Rausch et al., 1989).

The Wada test however has been gradually replaced by non-invasive techniques aiming at both, language lateralisation and the prediction of memory outcomes in epilepsy

surgery candidates. Both, fMRI and functional transcranial doppler sonography (fTDS) techniques are currently employed for language lateralisation. These have been firmly embedded in the evaluation of surgical candidates across epilepsy surgery programmes worldwide (Abou-Khalil, 2007; Binder, 2011; Knake et al., 2003; Schmidt & Sillanpää, 2017). In the meantime, the findings of a systematic review by Schmid *et al* looking at the comparative diagnostic accuracy of the Wada test, fMRI and fTDS with the view of developing clinical guidelines and recommendations for the preoperative evaluation of surgical candidates demonstrated a lack of consistency in the current clinical practices resulting in low quality heterogeneous data (Schmidt & Sillanpää, 2017).

The findings of a recent survey on the clinical use of language fMRI across 49 European epilepsy surgery centres by Bargalló *et al* confirmed the widespread use of fMRI in the evaluation of surgical candidates, however, again, the distinct lack of reference standards highlighted the pressing need for a uniform approach to the use of language and memory fMRI in epilepsy surgery centres (Bargalló et al., 2020). Apart from the non-invasive techniques, in epilepsy surgery candidates where phase I presurgical evaluation data suggests the possibility of close proximity of the epileptogenic zone to the eloquent cortex, electrical cortical stimulation or an awake craniotomy, or a combination of both, is employed for language mapping to ascertain the operability of the surgical candidate and to guide the surgical resection margins (Szelényi et al., 2010). Importantly, Lüders *et al* demonstrated that electrical stimulation of the dominant basal temporal region, mainly fusiform gyrus produced significant language disturbance manifesting with global, i.e. receptive and expressive aphasia. It was therefore suggested that the dominant basal temporal region is involved in language processing. Moreover, it has been shown that aphasia produced by the stimulation of the basal temporal language area was clinically indistinguishable from that produced by stimulation of Wernicke's area. Therefore, it was inferred that language dysfunction resulting from the stimulation of the basal temporal language area occurred due to disruption of the hodological links between the basal language region and Wernicke's area (Lüders et al., 1991). This is of particular clinical significance in patients undergoing SAH procedures via the inferior temporal approach. It has been shown by Lüders *et al* however that intra-operative damage to the basal language area is unlikely to result in permanent disturbance of language function and that a gradual recovery ensues within the first 12 months postoperatively.

From an epilepsy surgery prospective, it has been postulated that the language areas instrumental in language production are localised to Broca's and Wernicke's, supplementary motor area and the basal temporal language areas. While these heuristics are comforting indeed, it does not account for the complexity of large-scale neuronal networks involved in language processing, whereby language network disruptions account for a variety of language deficits observed in patients with TLE. Previous studies by Crinion *et al*, for example, showed that implicit comprehension of narrative speech, free of task demands, heavily relies on normal functioning of the antero-lateral and the ventral temporal lobe regions with the dominant temporal lobe exhibiting predominant involvement in comprehension of simple speech (Crinion et al., 2003). Despite the long held belief that speech recognition, dependent on auditory analysis and processing of spoken speech, was subserved by the dominant temporal lobe (Shtyrov et al., 1998), the findings of Boatman *et al* demonstrated marked impairment of speech recognition in patients with drug resistant right TLE (Boatman et al., 2006).

Furthermore, it has been proposed that the dominant perisylvian cortex mediates auditory naming, thus there has been ongoing concern that the patients undergoing hemispheric dominant ATLR are at heightened risk of developing auditory naming deficits. Hamberger *et al* however showed that following a left ATLR, auditory naming function was relatively preserved in patients with radiological evidence of HS, whereas MRI-negative patients suffered significantly higher rates of postoperative decline in language performance (Hamberger et al., 2007). In addition, the authors demonstrated that in patients with HS the auditory naming function was localised to the posterior temporal region, as a result of intra-hemispheric reorganisation, whereas in MRI-negative patients the auditory naming was subserved by the anterior temporal regions thus resulting in a postoperative language deficit. Chelune proposed over a decade ago that the functional adequacy of the temporal lobe ipsilateral to the side of the ATLR and the cognitive reserve of the contralateral temporal lobe structures were the main determinants of the magnitude of the postoperative deficits (Chelune, 1995) thus suggesting the possibility of postoperative functional reorganisation, depending on the availability of the postoperative cognitive reserve.

The concept of inter- and intra-hemispheric reorganisation resonates with the findings of the postoperative memory reorganisation described by Sidhu *et al* (Sidhu et al., 2016), illustrative of the compensatory mechanisms aiming at the reorganisation of

verbal memory processing observed in ATLR patients. Importantly, it has been observed that the language processing and memory functions are closely associated (Everts et al., 2009; Willment & Golby, 2013). This is not entirely unexpected and over the last few years there has been a move towards the reconceptualisation of our understanding of language and memory dysfunction in patients with TLE. There has been a growing body of evidence pointing towards the extension of aberrant connectivity patterns beyond the anatomical boundaries of the mesial temporal lobe structures (Bartolomei et al., 2017; Englot et al., 2016). It has now been shown that the language processing in normal subjects relies on the integrity of the perisylvian network as a whole as opposed to being localised to the cytoarchitectonic areas of Broca's or Wernicke's taken in isolation (Catani et al., 2005). The findings of recent connectomics studies challenged our localisationist approach to attributing the patient's neurological symptoms to a single brain lesion while failing to also consider the underlying network dysfunction stemming from a single lesion (Boes et al., 2015; Fox, 2018).

Similarly, the epileptic networks implicated in the development of MTLE have the distinct potential to cause language dysfunction in this patient group (Helmstaedter et al., 2004; Hermann et al., 1992; Powell et al., 2004). The findings of a recent study by Kaestner *et al* demonstrated evidence of wide bilateral and inter-hemispheric aberrant white matter connectivity changes being implicated in language impairment in patients with TLE (Kaestner et al., 2020b). The authors suggested that the abnormal connectivity patterns identified by diffusion MRI as opposed to DTI studies could serve as a potential biomarker of language impairment in patients with TLE. This approach to exploring the neurocognitive dysfunction patterns in patients with epilepsy has been corroborated by Roger *et al* looking into the role of diffusion MRI in defining the neurocognitive networks underlying memory deficits in patients with TLE (Roger et al., 2018). The complexity of language and memory deficits in patients with TLE stimulated further exploits in an attempt to understand as to how exactly the large-scale network dysfunction translates into neurocognitive deficits in patients with TLE. Several DTI studies focusing on structural connectivity patterns identified the main white matter tracts subserving language processing in normal subjects, with commissural, projection and association fibres being the key players (Dick & Tremblay, 2012). The findings of subsequent fMRI studies identified the key cortical regions, including the parietal cortex, insula, posterior cingulate, primary sensorimotor cortex as well as the supplementary motor area as being the main players in cortical language

representation (Binder et al., 2009). The findings of Geranmayeh *et al* demonstrated the role of the fronto-temporo-parietal system and the DMN in language processing (Geranmayeh et al., 2014), uncovering the neurobiological reasons for overlapping deficits in memory and language processing observed in patients with TLE.

## 1.10 MTLE: surgical treatment options

### 1.10.1 Anterior temporal lobe resection

The ATLR was first proposed by Penfield in 1950 as a surgical treatment option for patients with drug resistant TLE (Penfield & Flanigin, 1950) and has since become the gold standard as well as the most employed type of epilepsy surgery in patients with MTLE, offering a high rate of seizure freedom in carefully selected surgical candidates (Gomez-Alonso & Bellas-Lamas, 2015; Wiebe et al., 2001). Clusmann and Schramm have elegantly outlined the most commonly used types of ATLR in their comprehensive review of surgical procedures proposed for patients with drug resistant TLE (Clusmann & Schramm, 2012).

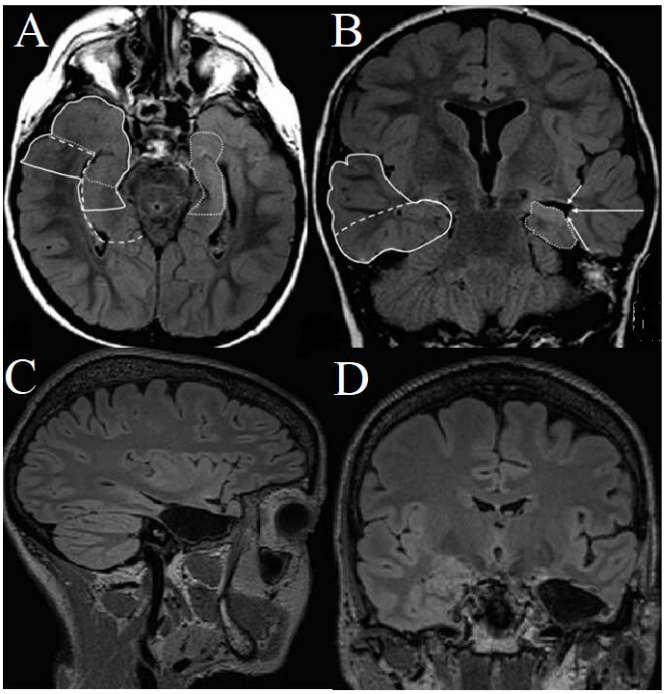



**Figure 1.2: Types of temporal lobe resections and surgical approaches**

A –axial view, right TP resection and anterior amygdalohippocampectomy (dotted line); standard ATLR (solid line); TP resection and radical hippocampectomy (dashed line) in an axial view; left – SAH ; B – coronal view, right - standard ATLR (solid line); TP resection and radical hippocampectomy (dashed line); left – SAH approaches: transsylvian (short arrow), transcortical (long arrow) and sub temporal; C – sagittal view, left Spencer's resection; D – coronal view, left Spencer's resection

Adapted from Clusmann (2012) (Clusmann & Schramm, 2012)

The resective technique developed by Spencer *et al* where the limited cortical excision is coupled with an extended posterior hippocampal resection, otherwise known as an anteromedial temporal lobectomy or a radical hippocampectomy, has gained its popularity amongst epileptologists owing to its less extensive surgical resection volume, which would be particularly advantageous in patients with left hemispheric dominant MTLE and would allow for the preservation of the superior temporal gyrus (Fried, 1993; Spencer et al, 1984). It is not uncommon however for the residual posterior hippocampus to be identified on postoperative scans. Sidhu *et al* described posterior hippocampal memory organisation following an ATLR, however ipsilateral posterior hippocampal memory encoding proved to be transient and inefficient (Sidhu et al., 2016). Therefore, the ATLR has been traditionally associated with postoperative verbal memory deficits in at least 40% of patients undergoing an ATLR (Baxendale et al., 2013).

As pointed out by Fried *et al* the ATLR is a rather ambiguous term encompassing a range of surgical procedures (Fried, 1993). This surgical procedure ranges from substantial temporal lobe resections, i.e. a standard ATLR to more tailored and less extensive surgical techniques. This reflects the ongoing quest for the optimal resection volume in patients with TLE (Schramm, 2008). This is complicated by the heterogeneity of the epileptic networks implicated in the development of MTLE (Bartolomei et al., 2010) (Kahane & Bartolomei, 2010). While in some patients with less extensive epileptic network involvement, such as mesial or anterior mesial (Chassoux et al., 2016), tailored temporal lobe resections could be sufficient for securing seizure freedom. On the other hand, with more widespread epileptic network involvement, e.g. mesial lateral, wider resections are often required. While the extent of the temporal lobe resection varies, it has been consistently observed that the resection of the entorhinal region is a common denominator associated with higher rates of seizure freedom (Fried, 1993). The recent findings by Galovic *et al* suggest that the resection of the piriform cortex in patients undergoing an ATLR was associated with favourable surgical outcomes (Galovic et al., 2019). It is likely that both regions play a crucial role in the viability of epileptic networks in MTLE, thus the resection of these areas renders higher rates of seizure freedom in patients with MTLE.

There has been a proposal, with a view of cost-effective epilepsy surgery service delivery across the world, to rationalise the investigatory pathway and surgical

procedures in MTLE patients (Quarato et al., 2005). This approach however could prove counterproductive in light of the complexity of the epileptogenic networks in MTLE. One could propose wider as opposed to tailored temporal lobe resections, which are likely to cast a wider net, thus capturing wider epileptic networks and ultimately leading to a better chance of seizure freedom for patients. However, considering that the ATLR is associated with considerable neurocognitive costs, a one size fits all approach may not be the best therapeutic strategy. Moreover, in light of the nascent concept of the drug resistant epileptogenic zone (Zhang & Kwan, 2019), it would be warranted to determine the critical resection volume, which would render the patient seizure free yet at minimal functional costs, including memory deficits. ATLR typically results in deafferentation of the ipsilateral extratemporal and contralateral temporal lobe structures. It has been described that following an ATLR the contralateral hippocampus undergoes a volume reduction (Elliott et al., 2016; Fernandes et al., 2014). A longitudinal study by Fernandes *et al* found no evidence of neurocognitive decline in association with volume loss in the contralateral hippocampus, whereas seizure control was a strong determinant of postoperative seizure control (Fernandes et al., 2014).

The findings of Winston *et al* showed evidence of the widespread Wallerian degeneration following an ATLR and further study into the cognitive sequelae of the postoperative white matter changes is underway (Winston et al., 2014). Previous reports emphasised the role of the fusiform gyrus and the inferotemporal regions in language processing (Lüders et al., 1991), which could confer a risk of anomia in patients undergoing a left ATLR thus emphasising the need for individualised patient centred network guided resection plans to offer patients the maximum chance of being free from seizures at no extra cost to function.

### 1.10.2 Selective amygdalohippocampectomy

For decades the epileptology community has been faced with a continuous balancing act searching for surgical solutions, which would enable patients to achieve the highest rates of seizure freedom and yet minimise neurocognitive deficits resulting from neurosurgical intervention. There have been multiple studies aiming to identify the optimal surgical resection volume, which would offer maximal therapeutic benefits without increasing the rates of surgical morbidity however the quest is yet to be fulfilled (Schramm, 2008)

The SAH procedure was proposed as an alternative to the ATLR in patients with drug resistant MTLE under the premise that the removal of the limbic structures, while sparing the temporal neocortex, would result in improved neurocognitive outcomes. This approach aligns with the concept of intratemporal memory specialisation, whereby the preservation of the temporal neocortex could mitigate semantic memory deficits (Saling, 2009). In reality, however, the neurocognitive deficits resulting from SAH are not trivial (Helmstaedter, 2013). In light of the hodological properties of the limbic system, including ample extratemporal hippocampal connections projecting to the frontal regions (Stretton et al., 2012), hippocampal removal inevitably results in a wider range of neurocognitive deficits, including executive functions and working memory impairments (Stretton et al., 2012).

It has long been recognised that the surgical access to the mesial temporal structures could be challenging and varies depending on local neurosurgical expertise. The trans-sylvian approach, popularised by Yaşargil, has the advantage of sparing the temporal neocortex with minimal impact on the underlying white matter tracts. On the other hand, this approach is far more challenging considering the complexity of the venous vasculature overlying the sylvian fissure, including a potential increase in the surgical morbidity rates stemming from the minimal surgical exposure during the en-bloc removal of the mesial temporal lobe structures (Yaşargil et al., 1993). Therefore, the transcortical approach, whereby access to the limbic structures is achieved by traversing through the middle temporal gyrus, is not uncommonly used, with another option being the sub temporal approach (Wheatley, 2008). While both, the transcortical and the sub temporal approaches entail cortical incisions of the temporal neocortex and the white matter tracts, traction and microdissection techniques inevitably impact on the neurocognitive outcomes. The trans-sylvian approach is also not devoid of the sequelae pertinent to white matter damage occurring as part of the surgical procedure. In addition, a sub temporal approach could potentially require substantial retraction of the temporal lobe and carries a heightened risk of injury to the vein of Labbe.

The intricacies surrounding the surgical approaches during a SAH explain why the neurocognitive outcomes of SAH are not always superior to those following an ATLR procedure (Lutz et al., 2004). The seizure control rates after a SAH are inferior to those following an ATLR, which boasts significantly higher rates of Engel Class I outcomes (Josephson et al., 2013; Wen-Han et al., 2013). Considering the heterogeneous involvement of the epileptic networks implicated in patients with TLE and in the

absence of preceding phase 2 evaluations, the lower seizure freedom rates following the wider excisions could be explained by a higher likelihood of having encompassed a critical cortical region associated with seizure generation. This is of particular importance in patients with temporopolar cortex involvement (Chabardes et al., 2005). In this patient cohort SAH would inevitably result in surgical failure. Therefore, should SAH be contemplated, a phase 2 presurgical evaluation would need to be employed as appropriate. Considering the inconsistent reports of the neurocognitive benefits of SAH, thorough presurgical counselling is paramount to assure informed patient choice in accordance with the patient's expectations.

### 1.10.3 Minimally invasive surgery in patients with MTLE

Over the last few years there has been a considerable paradigm shift with the patient reported outcomes focusing on QoL following epilepsy surgery being the focal point of patient centred care. The health related QoL outcome measures enhance our understanding as to what influences the patient's perception of surgical success versus surgical failure the most (Coleman et al., 2020). Shared decision making has resulted in patients taking an active role in their care, at times opting for "memory sparing" surgical procedures at the cost of not achieving complete seizure freedom and accepting the freedom from disabling seizures to be the optimal outcome. The patient centred healthcare systems have given rise to several minimally invasive surgical interventions, which are currently paving their way to becoming widely established epilepsy surgery treatment options (Grewal et al., 2018; Kang & Sperling, 2017; Waseem et al., 2015). The nascent minimally invasive neurosurgical procedures are reported to be well tolerated and efficacious however the lack of randomised controlled trials and long term outcome studies makes it highly challenging when it comes to informing patient decision making in routine clinical practice.

**MR guided laser interstitial thermal therapy**

The MR guided laser interstitial thermal therapy (MRgLiTT) ablation procedure was first approved by the Food and Drug Administration (FDA) for soft tissue ablation in neurosurgery in 2007 and as a treatment option in patients with drug resistant epilepsies in 2012 (Shimamoto et al, 2019). The LiTT procedure entails focused delivery of laser energy under real time MRI guidance and MR thermography. This technique allows for several lesions to be created along the trajectory of the intracranial electrode during a single pass through the axis of the hippocampus. A steep temperature drop off allows

for a gauged process so that the brain tissues surrounding the target lesion can be maximally spared. The probe used by LiTT creates an ablation volume of between 4-10 mm in diameter and is repeated during the procedure. As a result, a cylinder shaped lesion is produced along the axis of the hippocampus in patients with MTLE (Shimamoto et al., 2019). Jermakowicz *et al* explored the relationship between the seizure outcomes and preferential LiTT trajectories employed in patients with MTLE (Jermakowicz et al., 2017). The authors reported that 15 out of 23 patients were free from disabling seizures within 12 months following the laser ablation. The volume of ablated tissue or LiTT trajectory did not appear to influence the rates of seizure freedom and showed no association with memory outcomes. However, it has been confirmed that sparing the hippocampal head significantly correlated with surgical failures. This finding has been corroborated by Rolston *et al* who found that complete ablation of hippocampal head was necessary in order to achieve seizure freedom (Rolston & Chang, 2016).

While amygdalohippocampal ablation procedures have shown some promising results in relation to reduced lengths of stay, improved rates of surgical morbidity and favourable neurocognitive outcomes (Grewal et al., 2018; Willie et al., 2014), the studies exploring the role of LiTT in patients with drug resistant MTLE have been disadvantaged by the small number of study participants and the lack of long term postoperative follow up thus making it hard at this stage to arrive at meaningful inferences regarding the surgical success of these endeavours. Interestingly, the LiTT ablation volume does not appear to have any bearing on favourable seizure outcomes in patients with MTLE (Grewal et al., 2018; Kang & Sperling, 2017; Willie et al., 2014). Kang *et al* reported that 3 out of 4 patients with unfavourable seizure outcomes were rendered seizure free following an ATLR (Kang & Sperling, 2017), which could be explained by the heterogeneous and rather extensive epileptogenic networks in patients with MTLE resulting in the failure of the “selective” surgical procedures to render the patients seizure free (Kahane & Bartolomei, 2010). The promise of a neurocognitive panacea and minimally invasive neurosurgical approach generated a steadfast interest in LiTT. There is a pressing need for a multicentre prospective study of LiTT therapy, including the role of stage 2 presurgical evaluation in achieving high seizure freedom rates following minimally invasive intervention.

**SEEG guided radiofrequency thermocoagulation**

SEEG guided radiofrequency thermocoagulation (RFTC) is another minimally invasive epilepsy surgery procedure, which was first proposed for treatment of drug resistant TLE over 30 years ago. The recent study by Catenoix *et al* reported favourable seizure outcomes in 41% of patients within the first 12 months in a small and heterogeneous cohort of patients. The lesions during RFTC are produced using a radiofrequency generator connected to the SEEG electrodes. This technique enables the delivery of small cortical lesions and is widely used in patients with extratemporal epilepsies, especially where the ictal generators are not easily accessible using resective surgical techniques, e.g. insular epilepsies (Mullatti et al., 2019) (Catenoix et al., 2018). The procedure again is well tolerated and carries minimal risks associated with its use considering that the same SEEG electrodes used for diagnostic intracranial explorations are also used to deliver RFTC. The lack of thermal control however is the main limitation of this technique (Cossu et al., 2017).

In the future RFTC could prove to be an efficacious stand-alone treatment option in patients where a wide epileptic network involvement has been confirmed by SEEG once the biomarkers for the DREZ are identified. At this stage however, some surgical programs make wider use of RFTC compared to others however, there is a trend of using RFTC as a bridging procedure prior to resective epilepsy surgery (Catenoix et al., 2018). The recent findings by Chipaux *et al* suggests that even a temporary reduction in the seizure burden as a result of RFTC in patients with malformations of cortical development undergoing SEEG as part 2 of their standard presurgical evaluation, could predict favourable seizure outcomes following subsequent resective surgery. RFTC proved to deliver palliative effects in those patients where resective surgery was not feasible due to the overlap between the epileptogenic zone and eloquent cortex confirmed during stimulation procedures as part of the SEEG exploration (Chipaux et al., 2019). Lee *et al* found that limited RFTC in patients with MTLE resulted in a worthwhile reduction in the seizure burden demonstrated by a small case series with a short term follow up of six months (Lee et al., 2018).

**Stereotactic radiosurgery**

Stereotactic radiosurgery (SRS) using Gamma Knife as a treatment option in MTLE was first introduced in 1995 with a small case series of studies reporting mixed results and the uptake of the SRS approach to epilepsy treatment has been rather controversial

(Quigg et al., 2012). The findings of a randomised controlled study looking into the comparative benefits of ATLR versus SRS in patients with MTLE have shown that seizure freedom rates in the SRS cohort were 15% lower than in patients undergoing an ATLR. However, the longitudinal data suggested that favourable seizure outcome rates in the SRS cohort were not inferior to those following an ATLR. The neurocognitive deficits resulting from both procedures appeared to be comparable. Considering that health reported quality of life has been correlated closely with the seizure freedom rates, the authors concluded that the ATLR should therefore be the treatment of choice in this patient cohort, while SRS could provide an alternative option in patients where medical comorbidities may prevent the patients from having an ATLR or in those reluctant to consider resective epilepsy surgery options (Barbaro et al., 2018).

**Magnetic resonance-guided focused ultrasound**

Magnetic resonance-guided focused ultrasound (MRgFUS) is a rapidly evolving area of neurosurgery mainly focusing on the treatment of movement disorders and neuro-oncological pathologies (Elias et al., 2013; Wintermark et al., 2014). However, there has been a distinct interest amongst the epilepsy surgery community and a call for a clinical trial looking into the use of MRgFUS for patients with drug resistant epilepsies. MRgFUS is an MR guided minimally invasive technique using the energy of ultrasound for tissue targeted ablation. The sequelae of MRgFUS treatments have been studied in the animal epilepsy model looking for evidence of disrupted neural circuitries. The findings of Parker *et al* demonstrated that the DTI evidence of disrupted white matter tracts, which would assist with ascertaining the therapeutic yield and the role of MRgFUS as an epilepsy surgery technique is yet to be determined (Whitney et al., 2019). The findings of the recent feasibility study exploring the use of MRgFUS in patients with epilepsy by Monteith *et al* confirmed that the mesial temporal lobe structures could be reached adequately and rendered promising findings (Stephen et al., 2016). While the heating temperatures required for cerebral tissue ablation were achievable, longer sonications were necessary thus warranting further optimisation of this technique before it could be utilised in a clinical setting as a treatment option for drug resistant epilepsy.

While there is little doubt that these techniques do not have the same efficacy for seizure freedom as open surgery in patients with TLE, considering the much wider epileptic network involvement than was previously thought (Bartolomei et al., 2010), their use is justified in many circumstances, including in patients with significant

comorbidities making them unsuitable for an ATLR. However, in patients with extratemporal epilepsies, especially those not amenable to resective surgical techniques, e.g. where seizures originate in the posterior insula (Mullatti et al., 2019), minimally invasive techniques could prove to be indispensable. While MR guidance may not be the best strategy when it comes to treating epilepsy thus explaining the sub-optimal efficacy of minimally invasive techniques, these have the distinct potential to succeed as "network guided" procedures, whereby DREZ biomarkers could guide the network targeted ablations with good effect and yet allow for the maximal preservation of cerebral tissue and minimal neurocognitive deficits.

## 1.11 Predicting surgical outcomes

### 1.11.1 Predictors of seizure freedom in resective surgery

Randomised controlled trials have provided Class I evidence that epilepsy surgery is an unsurpassed treatment option in patients with TLE (Engel et al., 2012; Wiebe et al., 2011). Seizure freedom rates within the first anniversary after an ATLR have been reported to be as high as 90% in patients with TLE (Spencer et al., 2003), whereas the long term outcome studies have demonstrated a decrease in the seizure freedom rates of up to 60% (McIntosh et al., 2004). It has been consistently shown that 80-86% of patients who remain seizure free for at least two years are likely to enjoy seizure freedom in the long term (de Tisi et al., 2011; McIntosh et al., 2012).

There are two main modifiable factors, which have been described that can influence the surgical outcomes. The patients' age at the time of the surgery had a small but significant effect, whereas older patients had a significantly higher risk of surgical failure (de Tisi et al., 2011). As a result, appeals for earlier referrals of surgical candidates have been launched repeatedly (Dario et al., 2013; Engel et al., 2012). Secondly the extent of the temporal lobe resection has been shown to correlate with higher rates of seizure freedom in patients with unilateral TLE (McIntosh et al., 2001; Wyler et al., 1995) however, what constitutes the optimal extent of the surgical resection remains a highly debated topic (Schramm, 2008). The seizure outcomes following SAH were found to be less favourable when compared to those following an ATLR (Josephson et al., 2013). This could be explained by the wider epileptic network involving the temporal lobe (Chabardes et al., 2005).

The findings of the recent meta-analysis by Bjellvi *et al* demonstrated that a shorter epilepsy duration was associated with favourable seizure outcomes (Bjellvi et al., 2019) corroborating the previous findings by Salanova *et al* (Salanova et al., 2005), which could be explained by the progressive recruitment of epilepsy networks over time observed by iEEG studies (Bartolomei et al., 2008). Kahane and Bartolomei described a statistically significant correlation between the number of limbic structures exhibiting a high epileptogenicity index and the duration of the MTLE, thus emphasising the evolving nature of the epileptogenic process (Bartolomei et al., 2008; Kahane & Bartolomei, 2010). Epilepsy syndromes associated with extensive epileptogenic zone involvement, such as TLE-plus or TLE mimics, constitute yet another reason for

surgical failures in a minority of patients following ATLR (Barba et al., 2016; Kahane et al., 2015). Focal to bilateral convulsions in patients with TLE portended poor seizure outcomes following epilepsy surgery (McIntosh et al., 2004). These were often seen in patients with TLE-plus or TLE mimics, which could explain the association (Barba et al., 2016; Kahane et al., 2015). By the same token, the patients who proceeded to phase 2 of the presurgical evaluation workup were more likely to suffer seizure recurrence following epilepsy surgery (Schwartz et al., 2006). On the contrary, a history of febrile convulsions, traditionally associated with the finding of HS on preoperative MRI scans (Cendes et al., 2016), reliably predicted higher rates of postoperative seizure freedom (Salanova et al., 2005). The indications for iEEG have been discussed in earlier chapters.

The multimodal neuroimaging findings enhanced our ability to stratify the risks for postoperative seizure recurrence (Knowlton, 2006; Paesschen et al., 2007). The unequivocal radiological finding of HS in patients with unilateral MTLE has been associated with higher rates of postoperative seizure freedom (Berkovic et al., 1995). The lack of an identifiable lesion on the preoperative MRI in the absence of a discernible area of ipsilateral temporal lobe hypometabolism on the $^{18}$FDG-PET heralds early postoperative seizure recurrence and are considered to be independent predictors of poor seizure outcomes (Carne et al., 2004; Goellner et al., 2013; McIntosh et al., 2005). These findings are consistent with the growing body of evidence that the epileptogenic networks in patients with MTLE-HS differ from the aberrant connectivity patterns observed in MRI-negative MTLE patients (Mueller et al.). However, it has been consistently shown that seizure freedom rates in the MRI-negative PET-positive patients are comparable to those in patients with MTLE-HS (Carne et al., 2004; Muhlhofer et al., 2017a).

On the contrary, bitemporal $^{18}$FDG-PET hypometabolism in TLE patients portends unfavourable seizure outcomes. The role of $^{18}$FDG-PET in the presurgical evaluation will be discussed in depth in Chapter 1.12. This study explored the role of $^{18}$FDG-PET in predicting seizure outcomes in patients with drug resistant MTLE following an ATLR. The findings of this inquiry are outlined in Chapter 3. There have been an increasing number of studies looking at the outcomes of relatively novel minimally invasive surgical interventions. It has been observed that the laser ablation volume had no bearing on seizure outcomes in patients undergoing LiTT (Grewal et al., 2018; Kang

& Sperling, 2017; Willie et al., 2014). However, Kang *et al* found that the majority of patients with LiTT failures were rendered seizure free following an ATLR procedure (Kang & Sperling, 2017). This is consistent with the conceptual framework of the epileptic network heterogeneity in patients with MTLE (Bartolomei et al., 2008; Kahane & Bartolomei, 2010) and emphasises the need for iEEG so that informed decisions regarding the epilepsy surgery options can be made.

In relation to the histopathology findings, the efforts made by Blumcke *et al* in introducing the ILAE recommendations in the systematic reporting of the histopathology findings have been unsurpassed (Blumcke et al., 2016). The histopathology findings consistent with classical HS have been consistently associated with excellent seizure outcomes, whereas atypical HS portended postoperative seizure recurrence (Thom et al., 2010). Interestingly, while the number of studies exploring the role of reactive astrocytes in epileptogenesis has markedly soared over the last few years (Robel & Sontheimer, 2016; Xu et al., 2019), the studies into the role of postoperative gliogenesis in *de novo* epileptogenesis have been sparse (Alsaadi et al., 2001). The findings of the current inquiry into the relationship between the extent of the postoperative gliosis and the seizure recurrence rates are outlined in Chapter 7.

Seizure freedom is the ultimate goal of epilepsy surgery in patients with MTLE. Considering the complicated interplay between patient specific factors, epilepsy neurobiology and epilepsy surgery itself, it is not entirely unexpected that seizure freedom rates of 100% are challenging to achieve at this stage. The heterogeneity of surgical outcomes illustrates the current challenges and inspires further research in pursuit of therapeutic strategies, which would enable us to achieve a sustainable seizure freedom for our patients. Postoperative seizure outcomes have been traditionally categorised using the Engel Surgical Outcome Scale (Engel et al., 1993), which requires a substantive period of postoperative follow up of at least 2 years in order to categorise Engel's I-III seizure outcomes (Blume, 2011). ILAE seizure outcome classification is characterised by a more granular approach to quantifying the absolute seizure count on an annual basis following the epilepsy surgery (Wieser et al., 2001). Both approaches however were found to be comparable (Durnford et al., 2011).

Engel's surgical outcomes scale, despite being criticised for relying on the patient's account of what the "worthwhile" seizure burden may constitute, continues to be used

widely owing to its pragmatic and patient centred approach. From a clinical standpoint, one could argue that Engel's outcome scale reflects a much bigger picture, whereby the "running down" phenomenon is being accounted for, which in turn allows for meaningful long term management strategies to be put in place, tailored to an individual patient and the epilepsy surgery outcome from early recurrence to the "running down" postoperative seizure course (Goellner et al., 2013).

### 1.11.2 Memory outcome predictors

To this day, despite the advances in iEEG and multimodal imaging techniques, prospective identification of the exact margins of the epileptogenic zone remains a challenge therefore the distinct possibility remains that the resection margins in patients with excellent seizure outcomes could have been less extensive however, in the absence of precise guidance, it is hard to be certain about the minimal volume of the resection needed to achieve seizure freedom (Rosenow & Lüders, 2001; Schramm, 2008). Pragmatically, considering the heterogeneity of the MTLE-HS syndrome (Kahane & Bartolomei, 2010) and in light of the high epileptogenic indices exhibited by the limbic structures (Bartolomei et al., 2008) it has been customary for resective surgery to incorporate the removal of the amygdala, hippocampus, parahippocampal and rhinal cortices to maximise the likelihood of postoperative seizure freedom.

On the other hand, however, the cognitive costs of epilepsy surgery are hard to overestimate, with significant verbal memory decline being observed in at least 40% of patients following an ATLR (Baxendale & Thompson, 2017) and the impact of the postoperative memory deficits on the patient's quality of life is far from trivial (Giovagnoli et al., 2014). It has been proposed that selective amygdalectomy could offer a cognitive panacea. The "memory-sparing" effect of a selective amygdalohippocampectomy has been demonstrated previously (Josephson et al., 2013), however inconsistently.

While minimally invasive neurosurgical techniques may prove themselves useful in delivering higher rates of seizure freedom at minimal cognitive costs, the quest for identifying the optimal resection volume remains an ongoing ambition. This however is not straightforward. Preoperative neurocognitive deficits in patients with TLE have traditionally been viewed as a mere reflection of a functional deficit zone (Rosenow & Lüders, 2001), which would imply that neurocognitive deficits result from ipsilateral

temporal lobe dysfunction and have a good chance to recover following the surgery. With epilepsy being a network disorder, our understanding of the neurocognitive deficits as the sequelae of a network dysfunction, extending beyond the anatomical boundaries of the temporal lobe, is likely to influence our future approach to the clinical assessment of cognition (Wilson & Baxendale, 2014). While the immediate neurocognitive outcomes of SAH and LiTT have been promising, the seizure outcomes were found to be inferior to those following an ATLR (Grewal et al., 2018; Kang et al., 2016; Willie et al., 2014). In patients with a shorter duration of epilepsy and favourable seizure outcomes, memory improvements were reported by Baxendale *et al*. (Baxendale et al., 2008a), which emphasises the need for early intervention in patients with drug resistant epilepsy. Executive function was also shown to improve in patients with TLE following successful epilepsy surgery (Jokeit et al., 1997).

On the contrary, the findings of the longitudinal study by Dodrill *et al* suggested that epilepsy surgery failure and ongoing seizure activity aggravated postoperative memory decline which has been shown to be progressive (Dodrill, 2002). Therefore, the balancing act of achieving seizure freedom at no cost to verbal memory performance continues. In the meantime, it has been proposed that tailored surgical resections could mitigate the neurocognitive sequelae of surgical interventions (Clusmann & Schramm, 2012) (Schramm, 2008). To this effect, Bonelli *et al* suggested that sparing the posterior hippocampus, which has been shown to play a role in verbal memory encoding, could result in improved postoperative memory outcomes following an ATLR (Bonelli et al., 2013). The findings of a subsequent study by Sidhu *et al* however demonstrated that memory reorganisation in the residual hippocampus is inefficient and it is the ability and efficiency of the contralateral hippocampus to take over the role of memory encoding which could buffer the cognitive hit following the ATLR (Sidhu et al., 2016). This brings us to Chelune's postulates of cognitive adequacy versus cognitive reserve, whereby the extent of the neurocognitive deficits following an ATLR would depend on the adequacy of the resected mesial temporal lobe structures and the cognitive reserve of the contralateral hippocampus (Chelune, 1995).

The material-specific approach to memory organisation would assume that the patients undergoing a hemispheric dominant temporal lobe resection are at risk of verbal memory deficits, whereas following a right ATLR, one would expect to observe visuospatial deficits. While a reliable biomarker of right temporal lobe dysfunction is

yet to be identified (Saling, 2009), verbal memory decline has been consistently observed in patients with both, left and right TLE following an ATLR (Baxendale et al., 2013). Stroup *et al* found that the patients undergoing left hemispheric dominant epilepsy surgery were at heightened risk of verbal memory deficits (Stroup et al., 2003), whereas the findings of Baxendale *et al* suggest that patients undergoing an ATLE were at risk of verbal memory decline irrespective of the ATLR laterality (Baxendale et al., 2013).

The patient's preoperative verbal memory performance has been consistently associated with a heightened risk of postoperative memory decline or it is likely to be readily noticeable in this patient group (Baxendale et al., 2013), which is an expected sequela of resecting the "adequate" tissue and is not surgical morbidity as such. While a younger age at the time of the epilepsy surgery in association with a higher IQ resulted in less extensive postoperative memory deficits (Baxendale et al., 2013), in the elderly, the evidence of an accelerated cognitive decline following an ATLR was demonstrated by Rausch *et al* (Rausch et al., 2003).

The findings of Baxendale *et al* challenged the long held belief that radiological evidence of HS was associated with better neurocognitive outcomes thus influencing patient counseling (Baxendale et al., 2013). While the patients with HS stand a substantial chance of achieving seizure freedom following an ATLR, a significant minority of patients, *circa* 1 in 10, with preoperative findings other than HS, would suffer a double hit resulting from both, postoperative memory deficits and the failure to achieve seizure freedom (Baxendale & Thompson, 2017).

Much progress has been made in the research setting with fMRI showing promise in predicting memory deficits in patients undergoing an ATLR (Bonelli et al., 2010; Sidhu et al., 2013), however these are yet to transition into real world clinical practice. In the meantime, this study explored the yield of $^{18}$FDG-PET in predicting memory outcomes in patients undergoing an ATLR. The results of this study are presented in Chapter 4. On a positive note, neuropsychological input in the field of epilepsy surgery has now extended beyond assisting with the seizure onset lateralisation/localisation and estimating the cognitive risks associated with epilepsy surgery (Baxendale, 2020a). The current ambition of moving towards identifying practical solutions tailored to the needs of epilepsy surgery candidates and employing prehabilitation strategies could offer

patients the best of both worlds in the form of seizure freedom at minimal neurocognitive costs (Baxendale, 2020b).

## 1.12 The role of $^{18}$FDG-PET in the presurgical evaluation

### 1.12.1 $^{18}$FDG-PET potential neurobiological foundations

$^{18}$FDG-PET is a well-established functional neuroimaging modality which has been employed in the evaluation of epilepsy surgery candidates for over four decades (Engel et al., 1990; Henry et al., 1990; O'Brien et al., 2008; Theodore et al., 1997) and provides a unique opportunity for the quantitative assessment of cerebral glucose metabolism. The rates of $^{18}$FDG uptake reflect the metabolic demands of cerebral tissue. $^{18}$FDG molecules after entering the cell undergo, unlike glucose, only the first step of glycolysis, following which $^{18}$FDG-6-phosphate remains within the intracellular space and starts emitting protons. Each time a proton collides with the cerebral tissue electron, two photons are born. Subsequently, the photons detected by the PET camera undergo computational quantification resulting in the ultimate image of the three-dimensional radioactivity distribution commonly referred to as $^{18}$FDG-PET (Boellaard et al., 2009).

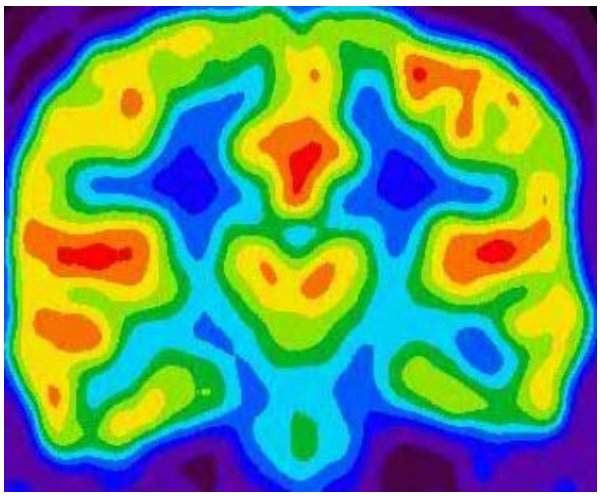


**Figure 1.3: $^{18}$FDG-PET (coronal view) in a patient with drug resistant left MTLE**

Example of $^{18}$FDG-PET hypometabolism in patient with drug resistant left MTLE

Interictal $^{18}$FDG-PET continues to play a major role in the evaluation of surgical candidates and has stood the test of time as being a cost efficient nuclear imaging modality (O'Brien et al., 2008). The feasibility of using ictal $^{18}$FDG-PET in the presurgical evaluation however is limited due to a relatively long period of $^{18}$FDG uptake of *circa* 30 mins resulting in a non-differential continuum of interictal, ictal and postictal changes (Siclari et al., 2013). $^{18}$Fluoro-2-deoxyglucose is the most widely used radiotracer in the evaluation of surgical candidates (Murphy et al., 2001; O'Brien et al., 2008), however the use of radio ligands targeting specific receptors, e.g. $^{11}$C-flumazenil delivers even higher sensitivity rates in detecting the epileptogenic cortical regions (Koepp et al., 2000; Ryvlin & Rheims, 2008; Vivash et al., 2013). The current literature suggests a range of potential reasons behind the reduced $^{18}$FDG uptake resulting in $^{18}$FDG-PET hypometabolic appearances in patients with epilepsy, which remain the subject of ongoing debates.

The neuronal death theory was proposed as a potential determinant of the $^{18}$FDG-PET changes in the past (Gaillard et al., 1995; Hajek et al., 1993). The posit of reduced $^{18}$FDG uptake being the result of synaptic dysfunction, where impaired synaptic inhibition manifests in reduced glucose uptake has been consistently outlined in the literature (Bruehl & Witte, 1995; Knowlton et al., 2001; Koutroumanidis et al., 1998). The reversibility of $^{18}$FDG-PET hypometabolism observed following successful epilepsy surgery (Spanaki et al., 2000; Takaya et al., 2009) supports the notion of the $^{18}$FDG-PET changes being illustrative of neuronal dysfunction rather than irreversible cell death. The lack of correlation between the structural temporal lobe changes, e.g. HS, and hypometabolic compromise reported by previous studies (O'Brien et al., 1997; Tasch et al., 1999; Theodore et al., 1999) do not support the cell death hypothesis either.

Jupp *et al* demonstrated that detectable hypometabolic changes within the limbic system become apparent early in the development of epilepsy. These were shown to be the result of progressive neuronal dysfunction caused by epileptic activity in the absence of discernible structural pathology (Jupp et al., 2012). It has also been demonstrated that a higher seizure burden and longer epilepsy duration was associated with progressive hypometabolic changes (Govil-Dalela et al, 2018). Contrary to the findings of the previous, albeit rather small sample studies (Akman et al., 2010; Jokeit et al., 1999), the presence or frequency of generalised convulsive seizures had no bearing on the extent

of the hypometabolic changes seen within the ipsilateral temporal lobe or the rates of bitemporal hypometabolism (Theodore et al, 2004).

The findings of early $^{18}$FDG-PET studies in patients with TLE suggested that metabolic changes were confined to the ipsilateral temporal lobe cortex only (Abou-Khalil et al., 1987; Henry et al., 1990). Subsequent research, however, demonstrated hypometabolic changes in remote brain regions consistent with the hodological brain properties and reflecting the seizure propagation pathways (Chassoux 2017; Chassoux et al., 2004). The extratemporal, mostly frontal, hypometabolic changes identified by the $^{18}$FDG-PET in patients with TLE are thought to be diaschisis related, resulting from seizure propagation. The areas of extratemporal hypometabolism have been commonly observed in patients with TLE, especially those with MRI-negative TLE (Jokeit, et al., 1997; Morgan et al., 2007; Savic et al., 1997). This could be explained by the preferential properties of the epileptogenic network implicated in the MRI-negative patient cohort.

The heterogeneity of the findings resulting from the $^{18}$FDG-PET studies in patients with drug resistant epilepsy reflects not only the differences in research methodology, including the heterogeneity of the epilepsy syndromes studied, but also the properties of the epileptogenic networks implicated in the different epilepsy syndromes. There have been four different patterns of $^{18}$FDG-PET hypometabolism described in patients with TLE (Chassoux et al., 2016). Interestingly, while $^{18}$FDG uptake has been traditionally seen to reflect the health of the neurons, Zimmer *et al* call for a re-evaluation of the role of astroglia in the $^{18}$FDG uptake and for further studies looking into the differential contributions of neurons and astroglia to the neurometabolic compromise visualised by $^{18}$FDG-PET (Volterra & Meldolesi, 2005; Zimmer et al., 2017).

The findings of Smith *et al* demonstrated the finding of phosphorylated tau in a cohort of patients with drug resistant TLE (Smith et al., 2019). This nascent finding suggestive of a possible neurodegenerative process being part of TLE continuum, could potentially contribute to the hypometabolic changes seen on $^{18}$FDG-PET. Future studies are warranted to determine the exact neurobiological aetiologies of $^{18}$FDG-PET hypometabolism.

### 1.12.2 $^{18}$FDG-PET in predicting seizure outcomes

$^{18}$FDG-PET has been shown to lateralise the seizure focus in 87-90% of patients with TLE and in up to 55% of patients with extratemporal epilepsies, respectively (Drzezga et al., 1999; Gaillard et al., 2011; Knowlton, 2006). The increasing use of the post-acquisition processing techniques in clinical epileptology enhances the diagnostic yield of $^{18}$FDG-PET with its specificity reaching 90% in patients with drug resistant TLE (Kumar et al., 2010; Mendes Coelho et al., 2017; van't Klooster et al., 2014). In extratemporal epilepsies, Da Silva *et al* reported the sensitivity of $^{18}$FDG-PET as being up to 60% in a paediatric patient cohort (da Silva et al., 1997). The role of $^{18}$FDG-PET is particularly critical in the evaluation of MRI-negative TLE patients. In patients with radiologically identifiable candidate epileptogenic lesions $^{18}$FDG-PET renders lateralising findings in up to 95% of cases. Importantly, its lateralising yield in patients with equivocal or normal MRI scans is not trivial either and approaches 70-85% (Gok et al., 2013; Komoto et al., 2015). MRI-negative PET-positive patients with drug resistant MTLE have been consistently shown to enjoy excellent rates of postoperative seizure freedom, comparable to those observed in patients with a detectable epileptogenic lesion on the preoperative MRI (Carne et al., 2007; Muhlhofer et al., 2017a; Yıldırım Capraz et al., 2015).

The use of $^{18}$FDG-PET in patients with drug resistant TLE has been traditionally reserved only for patients with discordant electro-clinical and MRI findings or those without a radiological finding of a candidate epileptogenic lesion (Duncan et al., 2000; Pittau et al., 2014). In this category the use of $^{18}$FDG-PET influenced surgical decision-making in over 70% of patients (Rathore et al., 2014; Uijl et al., 2007). Menon *et al* found that the use of $^{18}$FDG-PET influenced surgical decision making in up to 70% of patients with TLE and it was also instrumental in influencing surgical planning in MTLE-HS (Menon et al., 2015). Compelling evidence of the heterogeneity of the large-scale networks implicated in TLE (Bartolomei et al., 2017; Kahane & Bartolomei, 2010) resulted in the wider use of $^{18}$FDG-PET in the evaluation of surgical candidates with TLE (Verger et al., 2018; von Oertzen, 2018). Importantly, the wider use of iEEG highlighted the fact that TLE-plus is one of the major determinants of surgical failures in patients undergoing an ATLR (Barba et al., 2016), notwithstanding TLE mimics, thus the presurgical workup of TLE candidates requires the amount of consideration

comparable to that employed in the presurgical evaluation of patients with extratemporal lobe epilepsies.

The findings of the previous studies demonstrated the heterogeneity of the metabolic patterns observed in patients with MTLE, thus reflecting the preferential involvement of the epileptogenic networks in this patient cohort (Bartolomei et al., 2008; Chassoux et al., 2004). Chassoux *et al* described four distinct $^{18}$FDG-PET patterns in patients with TLE: mesial, anterior mesial lateral, widespread mesial lateral and bitemporal associated with their respective semiological characteristics (Chassoux et al., 2016). The mesial $^{18}$FDG-PET hypometabolic pattern was associated with the highest rates of postoperative seizure freedom, whereas bitemporal hypometabolism heralded poor seizure outcome in patients with unilateral MTLE (Chassoux et al., 2016). Joo *et al* reported similar findings in relation to unfavourable seizure outcomes in patients with MTLE and bitemporal $^{18}$FDG-PET hypometabolism (Joo et al, 2004). It has also been suggested that the use of image post-processing techniques resulted in better precision in detecting bitemporal $^{18}$FDG-PET hypometabolic changes (Kim et al., 2006).

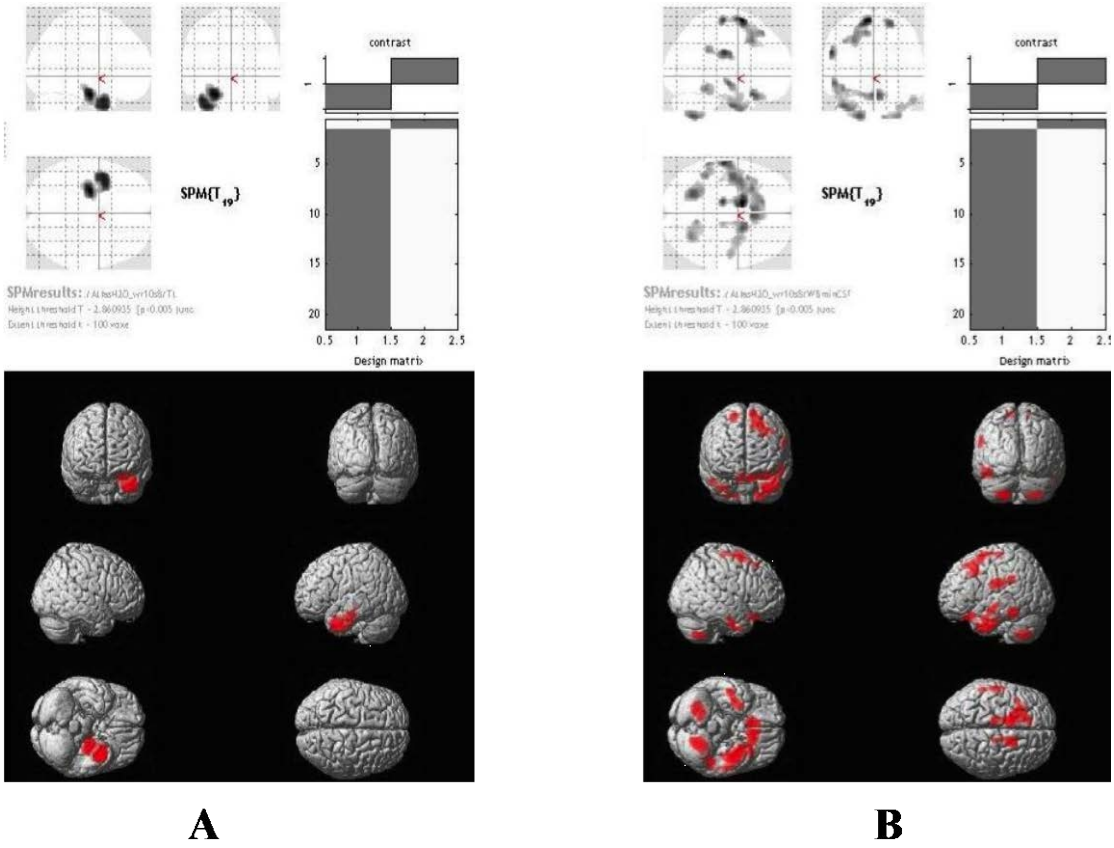



**Figure 1.4**: **$^{18}$FDG-PET hypometabolism patterns in patients with temporal lobe epilepsy**

Example of SPM output images of significant $^{18}$FDG-PET hypometabolism in patient with favourable seizure outcome (A) and poor seizure outcome (B). In patient A hypometabolic changes are confined to the ipsilateral TL region, whereas in patient (B) – hypometabolism is widespread involving both TL and extra-temporal regions

The diagnostic accuracy of $^{18}$FDG-PET has been shown to increase through its co-registration with the preoperative MRI (Varrone et al., 2009). As a result, both, the identification of small obscure lesions causative of drug resistant epilepsy and commonly missed on structural MRI scans, such as areas of focal cortical dysplasia, and also enhanced precision of the anatomical constructs underlying the $^{18}$FDG-PET changes, becomes a reality (Chassoux et al., 2010). This principle of using the best of both worlds with simultaneous acquisition of both molecular and structural neuroimaging, gave rise to a hybrid $^{18}$FDG-PET modality, which has been confidently paving its way into epilepsy research and clinical care (Shin et al., 2015). PET/MRI opens up unprecedented diagnostic and research opportunities, which is bound to take the epilepsy surgery service provision to the next level (Chen et al., 2018).

While the lateralising properties of $^{18}$FDG-PET have long been recognised, its localising role remains the topic of ongoing debate. Despite the long-held belief that

$^{18}$FDG-PET changes represented the functional deficit zone (Rosenow & Lüders, 2001) thus the extent of the identifiable $^{18}$FDG-PET hypometabolism was of no immediate relevance to the seizure onset zone, the emerging evidence suggests otherwise. The findings of recent studies suggest that $^{18}$FDG-PET changes are likely to represent a metabolic continuum closely associated with the underlying epileptogenic zone and reflecting its heterogeneity (Lamarche et al., 2016; Montaz-Rosset et al., 2019). Guej *et al* demonstrated that $^{18}$FDG-PET hypometabolic patterns significantly differed, depending on their proximity to the epileptogenic zone (Guedj et al., 2015).

The role of $^{18}$FDG-PET in epileptogenicity mapping was further explored by Lamarche *et al* who demonstrated the presence of pathological HFO's in association with the areas of metabolically compromised cerebral cortex (Lamarche et al., 2016). Both groups demonstrated that at least some of the hypometabolic tissue fell within the epileptogenic zone. Further, the findings of a recent study suggested that $^{18}$FDG-PET changes bear heterogeneous characteristics and differ depending on their association with the seizure onset zone versus the irritative zone (Montaz-Rosset et al., 2019). A previous study by Vinton *et al* demonstrated that the greater the extent of the resection of the $^{18}$FDG-PET hypometabolic tissue resulted in significantly higher rates of postoperative seizure freedom (Vinton et al., 2007). This was consistent with the findings of an earlier study by Juhasz *et al* who demonstrated that $^{11}$C-flumazenil-PET guided resections resulted in higher seizure freedom rates (Juhász et al., 2001).

"PET-ectomy" approach however attracted numerous criticisms (Paesschen et al., 2007), based predominantly on the previous postulates of $^{18}$FDG-PET changes being a mere reflection of the functional deficit zone rather than anything else. In light of the findings of recent studies, however, it is entirely conceivable that the heterogeneous $^{18}$FDG-PET findings reflect the range of hypometabolic compromise associated with the ictogenicity continuum, from the seizure onset zone to the functional deficit zone. This could explain the higher rates of favourable seizure outcomes in patients from Vinton's and Juhász's cohorts, respectively. Savic *et al* did not replicate these findings. Their study found that the extent of $^{18}$FDG-PET resection had no bearing on seizure outcomes (Savic et al., 1997). This study further explored the role of $^{18}$FDG-PET in predicting seizure outcomes following an ATLR and as to whether or not more extensive resections of the ipsilateral temporal lobe $^{18}$FDG-PET hypometabolic tissue was associated with higher rates of postoperative seizure freedom. The study findings are

outlined in Chapter 3, which is the exact reproduction of the publication resulting from this research.

### 1.12.3 $^{18}$FDG-PET in predicting memory outcomes

$^{18}$FDG-PET offers unique insights into neuronal metabolism at a synaptic level (Knowlton et al., 2001). It has retained its relevance in the evaluation of epilepsy surgery candidates for over three decades owing to its well established role in seizure onset lateralisation and localisation as well as its cost efficacy (O'Brien et al., 2008). The latest advent of hybrid MRI/PET scanning technologies, with improved spatial resolution and image quality, opens up new avenues for its use in epilepsy research and presurgical evaluation (Shin et al., 2015). In light of the long held postulates of cerebral $^{18}$FDG-PET hypometabolism and neurocognitive deficits in patients with drug resistant TLE reflecting the extent of the functional deficit zone (Rosenow & Lüders, 2001), the interest in understanding the exact association between reduced $^{18}$FDG uptake in the ipsilateral temporal lobe region and neurocognitive deficits in patients with drug resistant TLE has been ongoing.

Previous studies have reported that reduced $^{18}$FDG-PET hypometabolism was associated with impaired verbal memory scores in patients with left TLE (Knopman et al., 2015; Rausch et al., 1994). Griffith *et al* (Griffith et al., 2000) found that MTLE patients with mild or no identifiable preoperative $^{18}$FDG-PET hypometabolism suffered a significantly greater verbal memory decline following a left ATLR (Griffith et al., 2000). Furthermore, there have been reports of task-specific memory deficits, such as impaired arbitrary learning (Weintrob et al., 2007) or recognition memory impairment, respectively, identified in association with reduced $^{18}$FDG uptake in the perirhinal region of patients with left TLE (Guedj et al., 2010). On the other hand, Griffith *et al* observed no correlation between the $^{18}$FDG-PET hypometabolic changes in the parahippocampal gyrus and verbal memory scores in patients with TLE, however the authors suggested that the extent of the resected hippocampal volume was a strong predictor of verbal memory performance (Griffith et al., 2004). The relationship between HS and verbal memory performance has been a long-standing topic of fervent debates with the findings of the histopathology studies being rather controversial (Jardim et al., 2018; Saghafi et al., 2018).

Previous studies found that the radiological evidence of unilateral HS was predictive of less prominent postoperative memory decline (Trenerry et al., 1995), whereas Baxendale *et al* showed that patients with HS and preserved preoperative verbal memory performance were not "immune" to postoperative memory deficits and suffered significant postoperative verbal memory decline (Baxendale et al., 2013). It has been previously demonstrated that HS was not a major determinant of the extent of the temporal lobe $^{18}$FDG-PET hypometabolism in patients with TLE (O'Brien et al., 1997; Semah et al., 1995). It was therefore suggested that the $^{18}$FDG-PET changes in TLE patients could be a reflection of aberrant neural connectivity as opposed to neuronal loss (Semah et al., 1995). Collectively, the above observations and the findings of Griffith *et al* in particular, whereby left ATLR patients with moderate/severe ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism experienced significantly fewer rates of postoperative memory decline than those with no or mild metabolic compromise (Griffith et al., 2000), suggest that $^{18}$FDG-PET may have a role in predicting postoperative memory deficits in this patient cohort.

The recent study by Kamm *et al* suggested that in patients with drug resistant MTLE, reduced $^{18}$FDG uptake was associated with impaired preoperative verbal memory scores and had less of an impact following the temporal lobe resection on the postoperative verbal memory performance, whereas the radiological presence of HS was of no predictive value (Kamm et al., 2018). Leeman *et al* however found no significant correlation between the extent of the preoperative ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism and preoperative verbal memory scores or the role of $^{18}$FDG-PET in predicting postoperative memory decline (Leeman et al., 2009). Neither group pursued the quantification of the extent of the resection of the ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism as a potential predictor of postoperative memory decline. Interestingly, Osorio *et al* examined the relationship between the preoperative verbal memory performance and the level of mitochondrial enzyme activity in the histopathology samples obtained from MTLE patients undergoing epilepsy surgery. While the authors found no correlation between the measures of the respiratory chain enzyme activity and the neurocognitive scores attained on preoperative testing, it would however have been challenging to account for the levels of mitochondrial enzyme activity across the resected tissue sample due to the inherent limitations of the study design pertaining to the integrity of the surgical specimen being a prerequisite for answering this query (Osório et al., 2017).

In light of the findings by Kamm *et al* (Kamm et al., 2018), corroborated by the findings of a previous study by Griffith *et al* (Griffith et al., 2000), one could hypothesise that reduced $^{18}$FDG uptake reflects reduced functional adequacy of the ipsilateral temporal lobe thus its resection is unlikely to result in significant memory deficits following an ATLR. This conclusion however would be rather premature for several reasons. Changes in $^{18}$FDG uptake have been traditionally seen to reflect the functional state of neurons. There have been emerging reports however suggestive of a contributory role of astroglia, the extent of which has not been explored at this stage. Joo *et al* demonstrated the dynamic nature of $^{18}$FDG-PET changes (Joo et al., 2005), therefore one could not reliably conclude that the hypometabolic temporal lobe tissue is of no cognitive value. In other words, it has not been explored as to what extent the $^{18}$FDG-PET hypometabolism impacts on the adequacy of the resected temporal lobe, over and above the ATLR laterality and the preoperative verbal memory performance in patients with TLE. In light of the extratemporal large-scale networks being implicated in the neurocognitive deficits observed in patients with TLE, one could hypothesise that the level of the neurocognitive performance would rest on the differential contribution of both temporal and extra-temporal large-scale networks to memory performance.

The advances in connectomic studies enhanced our understanding of the potential neurobiological foundations of neurocognitive deficits in patients with TLE. It has been suggested that memory dysfunction in this patient cohort results from a wider network dysfunction, extending beyond the anatomical boundaries of the ipsilateral temporal lobe (Bell et al, 2011). On the other hand, the findings of the fMRI studies demonstrated the role of the mesial temporal lobe structures, including the contralateral hippocampus which play a key part in the postoperative memory reorganisation process (Bonelli et al., 2010). Sidhu *et al* demonstrated that while the residual ipsilateral hippocampal activations reflected its important role in verbal memory performance early on in the postoperative period, it was the contralateral hippocampus, which contributed significantly to the level of verbal memory performance following an ATLR (Sidhu et al., 2016). These findings are consistent with the previous notion by Chelune suggesting that in patients with TLE both, the adequacy of the resected tissue as well as the cognitive reserve of the contralateral hippocampus affect the extent of the memory decline following an ATLR (Chelune, 1995).

Bitemporal $^{18}$FDG-PET hypometabolism has been associated with unfavourable seizure outcomes in patients with drug resistant unilateral MTLE (Chassoux et al., 2016; Koutroumanidis et al., 2000). Considering the key role that the contralateral hippocampus plays in memory reorganisation following an ATLR it would be prudent to know whether or not bitemporal reduction in $^{18}$FDG uptake could indicate a reduced cognitive reserve in the contralateral hippocampus, which would influence the selection of surgical candidates and the need for cognitive prehabilitation. With $^{18}$FDG-PET being firmly embedded into the evaluation of epilepsy surgery candidates and in light of the previous findings suggestive of metabolic correlates of verbal memory impairment in patients with drug resistant MTLE, however ambivalent, this study set out to explore the role of $^{18}$FDG-PET in predicting memory deficits in patients with drug resistant TLE. The findings of this inquiry are presented in Chapters 4 and 5.

## 1.13 Postoperative seizure recurrence

The findings of previous studies converge in reporting excellent seizure outcomes following an ATLR in as many as 80% of patients within the first year (Jeha et al., 2007; Ramesha et al., 2011; Spencer et al., 2003). The findings of the long-term outcome studies however have been less favourable. Seizure recurrence has been observed in up to 50% of patients (Goellner et al., 2013; McIntosh et al., 2005; McIntosh et al., 2004; Najm et al., 2013; Tellez-Zenteno et al., 2005). Goellner *et al* demonstrated that most surgical failures tend to manifest relatively early, with 60-80% of patients exhibiting seizure recurrence within the first 6-12 months following epilepsy surgery (Goellner et al., 2013; Najm et al., 2013). In this group of patients', failure to localise the epileptogenic zone during the preoperative evaluation results in ongoing seizures with unchanged seizure semiology. TLE-plus syndrome has been described as one of the reasons for surgical failures observed in a minority of patients following an ATLR (Barba et al., 2016). In the majority of cases however, incomplete resection of the epileptogenic zone was found to be the main reason for the early surgical failures (Najm et al., 2013).

Evidently, the success of epilepsy surgery is determined by the reliable identification of the epileptogenic zone, which is indispensable for seizure generation (Rosenow & Lüders, 2001). The challenges surrounding the identification of the epileptogenic zone are related to the lack of reliable preoperative epileptogenicity biomarkers perpetuated by the lack of optical technologies allowing for intra-operative differentiation between normal and epileptogenic brain tissue, which, unlike the use of 5-aminolevulinic acid fluorescence guided high grade glioma surgery (Müther et al., 2019), would not be easily achievable in epilepsy surgery due to the very nature of the epileptogenic zone, which is considerably more complex and unpredictable. Moreover, the recent posit of DREZ could transform our approach to the presurgical evaluation, being a game changer in delivering epilepsy surgery in a more refined and targeted fashion, offering hope of a life changing experience to those patients where the traditional "all-or-none" approach to the surgical resection is not an option.

The wider utilisation of SEEG in epilepsy research and clinical care has been instrumental in the reconceptualisation of epilepsy as a network disorder (Bartolomei et al., 2017; Englot et al., 2016). It has been elegantly demonstrated that the epileptogenic zone tends to evolve over time (Bartolomei et al., 2008) and is therefore, in principle,

dynamic as opposed to static in its very nature (Jehi, 2018). Hippocampal dysfunction in patients with unilateral MTLE has long been seen as a bilateral condition, however the epileptogenic potential of bilateral hippocampal dysfunction is likely to be heterogeneous. While some patients with bilateral interictal spikes enjoy seizure freedom following an ATLR, others suffer the sequelae of a mirror epileptogenic focus, which could declare itself as an independent ictal generator after a few years following the ATLR (Hennessy et al, 2000).

SEEG is considered to be the gold standard in outlining the epileptogenic zone and it certainly plays a critical role in differentiating between temporal and extra-temporal epilepsies, it assists in surgical planning and offers an excellent opportunity to carry out electrical stimulation. By ensuring that the ictal generator is reliably identified and that it does not clash with an eloquent area, SEEG facilitates safe surgical resection with the distinct possibility of achieving high rates of seizure freedom. However, while focusing and zooming in on the immediate task at hand of localising the ictal generator one could miss out on the much bigger picture, which iEEG could not possibly embrace, limited by spatial sampling and the number of intracranial electrodes, notwithstanding the fact that human made implantation schemes are not fail proof and are heavily reliant on the strength of the hypothesis.

There have been an increasing number of connectomics and iEEG studies aiming at identifying the fingerprint of the epileptogenic zone (Grinenko et al., 2017) and to employ computer-assisted modelling of the epileptogenic zone, which could potentially guide network-targeted interventions and assist with predicting seizure outcomes (Sinha et al., 2019). In light of the dynamic nature of the epileptogenic zone it is not entirely unexpected that mirror epileptogenic foci could establish themselves following the original neurosurgical intervention. Now that the concept of DREZ (Zhang & Kwan, 2019) has been clearly outlined, one has to stand up to the challenge of understanding the exact aetiology of DREZ and to come up with a new term, which would allow for differentiating between the two types of DREZ, i.e. the drug resistant epileptogenic zone and the drug responsive epileptogenic zone. Considering the complexity and heterogeneity of the epileptogenic networks, the identification of epileptogenic biomarkers and predictors of seizure outcomes, or rather predictors of the extent of the epileptogenic networks and the differential properties within the network itself whereby the DREZ itself is also likely to sport heterogeneous properties, calls for the use of

multimodal imaging looking at the behaviour of the epileptic networks in their natural habitat. $^{18}$FDG-PET offers a unique opportunity to study the bigger picture of the metabolic reflection of the epileptogenic network, which was the main focus of this study and the results are outlined in Chapters 3-5.

While we accept that re-kindling of old flames within the preexistent epileptogenic zone, or the development of the *de novo* ictal generators are the main reasons for late seizure recurrence the role of postoperative gliogenesis has received little attention. The possibility of postoperative gliogenesis being implicated in the generation of late onset seizures was first postulated by Wilder Penfield almost a century ago (Penfield, 1929) and despite renewed interest in the role of reactive astrocytes in epileptogenesis (Robel & Sontheimer, 2016; Wetherington et al., 2008), there have been hardly any studies looking into the role of postoperative astrogliosis in late seizure recurrence (Alsaadi et al., 2001). In light of the heterogeneous characteristics of the astrocyte populations and their tendency to undergo molecular, cellular and functional transformations, whereby the process of reactive astrogliosis is to be viewed as a continuum rather than an all in one glial response to CNS injury (Sofroniew, 2009), the neurobiological properties of postoperative astrogliosis deserve further attention.

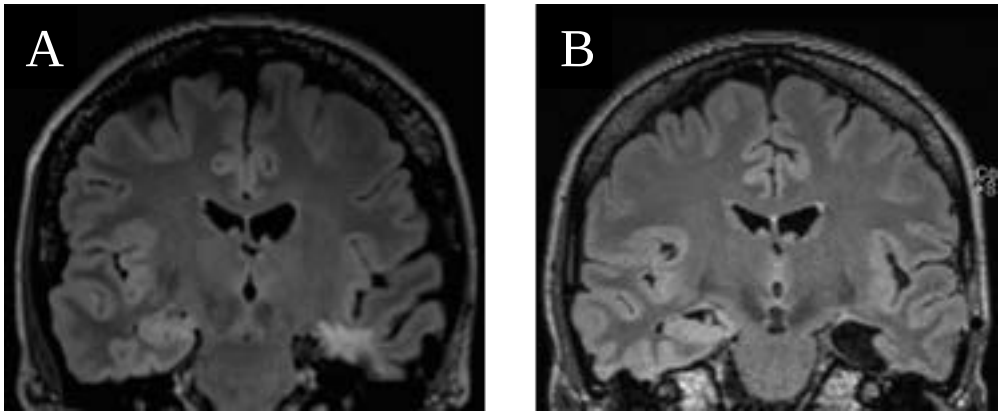



**Figure 1.5: Postoperative gliosis in patients with MTLE following an ATLR.**

Example of the extent of postoperative gliosis in two patients following a left ATLR: extensive (A) versus minimal (B)

Considering that reactive astrocytes are versatile and are capable of exhibiting both, neuroprotective as well as neurotoxic properties, and the range of appearances of the astroglial scars observed on postoperative scans, one inevitably queries as to whether or not there is any relationship between the extent of the gliosis and postoperative seizure recurrence. Moreover, it would be particularly interesting to know what the role of the reactive astrocytes is in the "running down phenomenon" (Geller et al., 2018; Salanova et al., 1996; Zhang & Kwan, 2019). It is not inconceivable that in some patients' reactive astrocytes execute their neuroprotective effects hence making the seizures run down, while in others the epileptogenic properties contribute to the revival of the DREZ following epilepsy surgery. As part of an encompassing inquiry into the understanding of the potential reasons for postoperative seizure recurrence, this study explored the relationship between the extent of the postoperative gliosis and its bearing on late seizure recurrence following an ATLR. The results of this inquiry are outlined in Chapter 7.

**Objectives and Scope**

The overall focus of this study is to enhance our understanding of the potential predictors of surgical outcomes in patients with unilateral drug resistant MTLE using real-world clinical data.

Chapter 3 addresses the role of $^{18}$FDG-PET as a metabolic biomarker in predicting surgical outcomes following an ATLR. This study focuses on the laterality-specific patterns of the $^{18}$FDG-PET hypometabolism and their role in predicting seizure

outcomes in patients with left and right MTLE, respectively. In addition, the relationship between the extent of the resection of the $^{18}$FDG-PET hypometabolism and the rates of postoperative seizure freedom was examined in the context of laterality-specific differentiality of the preoperative $^{18}$FDG-PET hypometabolism findings.

Chapter 4 focuses on examining the real-world clinical utility of $^{18}$FDG-PET and the potential challenges surrounding its use for predicting preoperative verbal memory performance in epilepsy surgery candidates and postoperative memory outcomes following an ATLR.

Chapter 5 builds upon the findings of the laterality-specific differentiality of $^{18}$FDG-PET hypometabolic patterns and proceeds to explore the role of arbitrary learning as a candidate neurocognitive marker of left mesial temporal lobe dysfunction in patients with right MTLE and bitemporal $^{18}$FDG-PET hypometabolism.

Chapter 6 examines the lateralising value of neuropsychological tests routinely administered in the evaluation of epilepsy surgery candidates undergoing an ATLR. This study highlights the challenges behind using a material-specific as opposed to a task-specific approach to neurocognitive testing in the context of intra-temporal memory organisation.

Chapter 7 evaluates the association between the extent of the postoperative gliosis and seizure recurrence following an ATLR within the context of the renewed interest in the role of astrogliosis in epileptogenesis.

Chapter 8 integrates the findings of the above studies, elaborates on their potential mechanisms and examines their clinical utility in advancing the care of patients with drug resistant epilepsy. It offers further insights into the methodological challenges and informs future research strategies aimed at advancing the care of patients with drug resistant epilepsy.

# CHAPTER 2

# COMMON METHODOLOGY

This chapter outlines the core methodology common to the studies described in Chapters 3-7, including details pertaining to patient recruitment and neuroimaging acquisition, as well as post-processing techniques. Methods specific to the individual studies are outlined separately in their respective results chapters.

## 2.1 Study Subjects

The patients included in this retrospective two-centre study were identified from the prospective Epilepsy Surgery databases at the Comprehensive Epilepsy Programmes (CEPs) based at the Royal Melbourne Hospital and the Austin Hospital, Melbourne, Australia, respectively. Both centres serve as quaternary centres receiving local, national and international referrals, and have comparable epilepsy surgery pathways as described previously (Berkovic et al., 1995; Carne et al., 2004). Approval from the Research Ethics Committee has been obtained for both sites: Melbourne Health (HREC 2012.044) and Austin Health (HREC/14/Austin/603).

### 2.1.1 Presurgical evaluation

All the patients included in this study, as part of their standard phase 1 presurgical evaluation, underwent a 5-day period of scalp video-EEG-telemetry which included a neurological examination and a detailed electroclinical evaluation of their epilepsy syndrome including the seizure semiology and epilepsy risk factors, an expert review of their high resolution MRI brain scans and comprehensive neuropsychological and neuropsychiatric assessments. The language fMRI studies were carried out in all manifest left handers, patients with familial sinistrality and in patients undergoing a left ATLR procedure. All the patients underwent interictal $^{18}$FDG-PET and SPECT studies followed by co-registration of both nuclear imaging modalities with structural MRI whereby an increased diagnostic yield of the $^{18}$FDG-PET and SPECT studies was achieved (Brien et al., 1998; Vinton et al., 2007). The patient data derived from phase 1 of the presurgical evaluation was subsequently discussed in the Epilepsy Surgery Multidisciplinary Team (MDT) meeting, in case conference format where, upon the confirmation of the patient's surgical candidacy, further decisions to either proceed directly to epilepsy surgery or to progress to phase 2 of the presurgical evaluation was

made. Based on the outcome of the MDT discussion none of the patients included in this study were deemed to warrant phase 2, i.e. invasive presurgical evaluation.

### 2.1.2 Postoperative follow up

All the patients included in this study underwent an ATLR after satisfying the electroclinical criteria for unilateral drug resistant MTLE (Wieser, 2004) and had no clinical indication for phase 2 presurgical evaluation. All patients included in this study underwent an ATLR between 1998 and 2014 and were at least 16 years old at the time of the surgery. All the patients included in this study had radiological evidence of ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism and either unequivocal concordant HS or no obvious epileptogenic lesion identified on their preoperative MRI scans. In the postoperative period, follow up of at least 2 years was achieved in all patients. Patients with a history of previous neurosurgery, perioperative vascular morbidity, bilateral HS or dual pathology on the preoperative MRI, incomplete neuropsychological assessment records or the patients in whom pre/postoperative MRI/$^{18}$FDG-PET scans or the neuropsychological assessment records were irretrievably lost to archives were excluded.

### 2.1.3 Neuropsychological Assessment

All the patients included in this study had a Full Scale IQ $\geq$ 70, were fluent English speakers and underwent a comprehensive neuropsychological assessment by the specialist neuropsychologists as part of their standard clinical care within the presurgical evaluation. Neuropsychological assessments took place approximately 4 months prior (t1) and 6 months following the ATLR (t2). Further neuropsychological follow ups were arranged as clinically indicated at the Royal Melbourne Hospital site and span at least 2 years at the Austin Hospital site at regular intervals of approximately 3 months (Wilson et al., 1998). The measure of the preoperative Full Scale Intelligence Quotient (FSIQ) or Performance Intelligence Quotient (PIQ) was estimated based on the Wechsler Test of Adult Reading (WTAR) (Carter, 2013) or the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1999). Three versions of WAIS were used: WAIS-R, WAIS III and WAIS IV, respectively, depending on the timing of the assessment.

PIQ was estimated based on the scaled scores of WAIS measures used in order of relevance to the measure of general fluid intelligence: matrix reasoning, similarities,

information, vocabulary and block design. This approach was favoured over the "best performance" one, as it was less likely to result in "inflated" estimates (Mortensen et al., 1991). The Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1941; Taylor et al., 2010) and WAIS were consistently administered in all patients across both CEPs whereas Paired Associate Learning (PAL) and the Wechsler Memory Scale (WMS) (Form 1) (Wechsler, 1945) was consistently employed as part of the comprehensive neuropsychological evaluation at the CEP based at the Austin Hospital (Saling et al., 1993). RAVLT and PAL were administered for verbal memory assessment with RAVLT focusing predominantly on the testing of the semantic memory component while PAL testing addressed both, arbitrary and semantic memory constructs.

The RAVLT entailed the following steps: a patient was read a list of 15 words unchanged over the course of 5 trials. The total number of words recalled in each trial was scored individually and recorded against each trial (Trial 1, Trial 2 etc.). The total number of words recalled over all 5 trials represented the RAVLT total score with 75 being the highest score achievable. Following that, a so-called "interference list" consisting of 15 words, different to those used in trials 1-5, was read to the patient with the intention of "interfering" with the immediate recall of the words learnt over the course of the previous 5 trials. The total number of words recalled by the patient immediately after the "interference" was scored and recorded as the result of Trial 6, commonly known as the "post-interference" recall. Finally, after a delay of 20 to 30 minutes, the patient was asked to recall as many words learnt during the first 5 trials and the result was recorded as Trial 7, commonly known as the delayed recall.

The PAL test was used to assess both, arbitrary and semantic associative learning. Patients were presented with pairs of words that were either semantically related (easy pairs) or unrelated (hard pairs) and the total number of word pairs learnt over 3 trials was recorded as immediate recall. Within 20-30 minutes patients were asked to recall the word pairs learnt earlier and the results were recorded as the delayed recall. The Rey-Osterrieth Complex Figure and Recognition Trial (RCFT) (Rey, 1941) was used for the assessment of non-verbal memory performance. During this test, which uses a complex geometric figure as a stimulus, the patients were asked to draw a copy of the figure as precisely as possible. Following that, after a period of 30 minutes the patients were asked to reproduce the drawing from memory and the delayed recall performance was assessed accordingly. The Boston Naming Test (BNT) was used for the assessment

of the language ability by means of confrontational testing. The patients were given credit for each correctly named item within 20 seconds, with the total score derived from the sum of the number of spontaneous correct responses and also the correct responses after a stimulus cue, whereas the correct answers given after a phonemic cue were not counted towards the total score (Kaplan et al., 1983).

### 2.1.4 Epilepsy surgery

The preoperative seizure burden was categorised using the seizure frequency scoring system suggested by So *et al* (So et al., 1997). All patients underwent a Spencer type procedure, otherwise known as a radical anteromesial temporal lobe resection. This is a type of ATLR typically carried out in a step wise manner and entails the resection of the middle and inferior temporal gyrus 3-3.5 cm from the temporal tip, followed by an en bloc excision of the amygdala, hippocampal complex, uncus and fusiform gyrus (Clusmann & Schramm, 2012; Spencer et al., 1984). The left hemispheric dominant patients, had less extensive resections of the temporal lobe tissue, similar to the left hemispheric ATLR's performed in other epilepsy surgery centres (Bonelli et al., 2010; Yogarajah et al., 2010). The postoperative appearances and the adequacy of the hippocampal resection were assessed on the postoperative MRI scans carried out at least 3 months following the ATLR.

**Table 2.1 Postoperative seizure outcomes categories**

Adapted from Engel et al (Engel et al. , 1993)

| | | |
|---|---|---|
| **Class I** – seizure free | **A** | Completely seizure free since surgery |
| | **B** | Aura only since surgery |
| | **C** | Some seizures after surgery, but seizure free for at least 2 years |
| | **D** | Atypical generalised convulsion with antiepileptic drug withdrawal only |
| **Class II** – rare seizures | **A** | Initially seizure free but has rare seizures now |
| | **B** | Rare seizures since surgery |
| | **C** | More than rare seizures after surgery, but rare seizures for at least 2 years |
| | **D** | Nocturnal seizures only, which cause no disability |
| **Class III** – worthwhile improvement | **A** | Worthwhile seizures reduction (≥75% seizure reduction) |
| | **B** | Prolonged seizure free interval amounting to greater than half the follow up period, but not less than 2 years |
| **Class IV** – no worthwhile improvement | **A** | Significant seizure reduction |
| | **B** | No appreciable change |
| | **C** | Seizures worse |

### 2.1.5 Surgical outcomes

Seizure outcomes were determined at the time of the last follow up appointment and classified using the Engel' Epilepsy Surgery Outcome Scale (Blume, 2011; Engel et al., 1993). The duration of follow up of at least 2 years was achieved for all patients. The patients with Engel class I outcomes were categorised as seizure free and the patients with Engel class II-IV as not seizure free (Barba et al., 2016). The "worthwhile improvement" was defined as ≥ 75% reduction in seizure frequency compared to the preoperative seizure burden (Table 2.1).

Acute seizures within the first week following an ATLR were discounted (Bhaskara Rao et al., 1998). Postoperatively, the seizures manifesting with impaired awareness were counted towards seizure recurrence (McIntosh et al., 2005). Following the ATLR, antiepileptic treatment was rationalised within the first 6-12 months, depending on the seizure outcome and decided upon jointly with the patients.

## 2.2 Neuroimaging acquisition and processing steps

All processing was carried out using Statistical Parametric Mapping (SPM) software, version 12 (Wellcome Department of Cognitive Neurology, University College London, London, UK) run within an interactive Matrix Laboratory (MATLAB) environment, version R2012-A (MathWorks, Natick, MA).

### 2.2.1 MRI acquisition and processing

All patients had their MRI and $^{18}$FDG-PET scans carried out as part of their standard clinical care. Before 2005, MRI examinations were performed on a Genesis Signa 1.5 T (GE Medical Systems); from 2005 onwards, the patients were scanned using a Magnetom Avanto 1.5 T and a Magnetom Trio Tim 3T (Siemens Medical Solutions, Erlangen, Germany). Three-dimensional, T1-weighted, magnetisation prepared rapid acquisition gradient echo (MPRAGE) sequences were subsequently used for post acquisition processing.

Pre and postoperative MRI images were segmented into grey matter (GM), white matter (WM) and cerebral spinal fluid (CSF). The GM and WM partitions were added and thresholded at 0.1, to produce an image of the brain tissue. A total cerebral volume image was constructed by taking the union of brain segmentations derived from pre and postoperative MRI scans. The estimation of the resected brain tissue was carried out by matching pre and postoperative MRIs and deriving the difference between the two. Pre and postoperative MRIs were non-linearly registered using SPMs longitudinal registration toolbox (Ashburner & Ridgway, 2013). A non-linear registration was performed as the outcome of linear registration but was considered to be suboptimal due to an inaccurate reflection of the postoperative brain shift, thus the collapse of the brain tissue into the resection cavity had to be factored in accordingly.

The resection volume was measured as the difference between the preoperative and postoperative MRIs. To minimise the contribution of the pre and postoperative image registration errors including those resulting from segmentation related imprecisions, the largest cluster of the difference image was identified, invariably constituting the resected tissue, following which, in a stepwise manner, the resected tissue was separated from the registration error by eroding the image by two voxels. Subsequently, the now outlined resected tissue was selected, and dilated by two voxels to restore it to its original size. Subsequently, all the resected tissue images were inspected by two

independent operators to ensure that the selected region on the postoperative MRI image was filled accurately, with no filling defects. The volumes of the resected tissue and of the total cerebral volume were calculated by summing the non-zero voxels and multiplying by the voxel size.

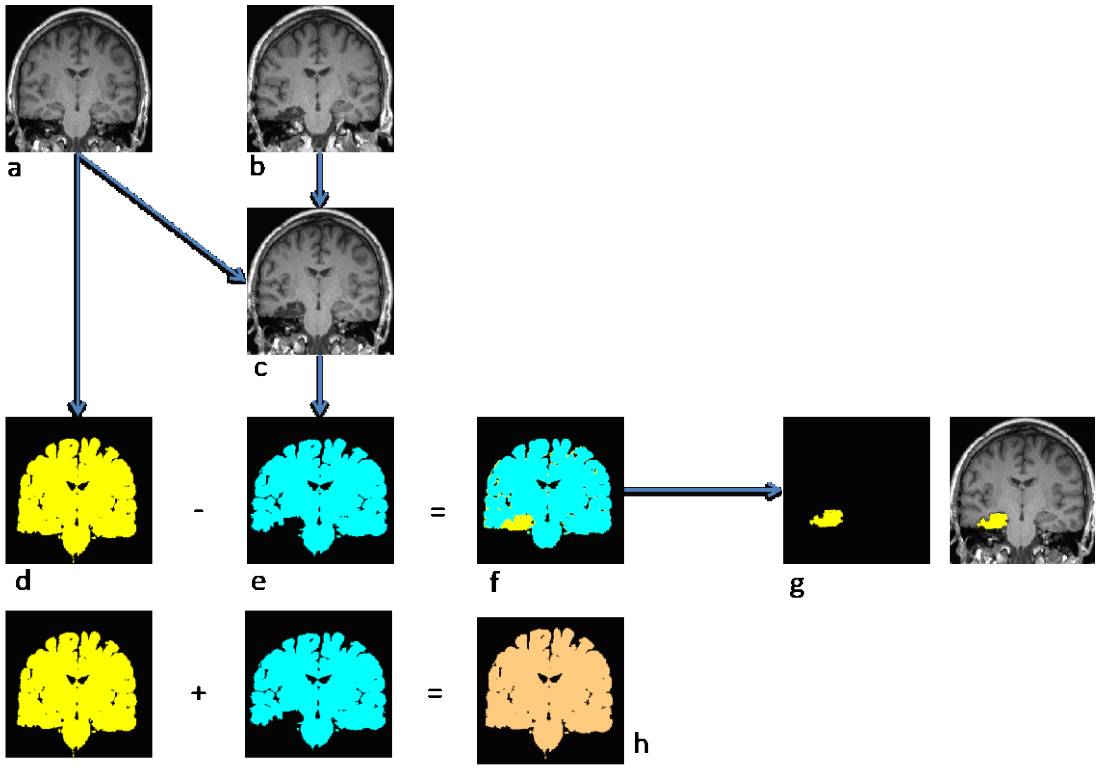



**Figure 2.1: Key steps outlining MRI postprocessing**

Flowchart outlining the key steps in deriving the resected temporal lobe tissue volume from pre and postoperative MRI scans: a – preoperative MRI; b – postoperative MRI; c – preoperative MRI non-linearly registered to postoperative MRI; d – preoperative MRI mask; c – postoperative MRI mask; f – largest cluster selection; g – resected tissue; h – total cerebral volume

### 2.2.2 $^{18}$FDG-PET acquisition and processing

The interictal $^{18}$FDG-PET scans of the patients undergoing their presurgical evaluation at the Austin Hospital based CEP were acquired on a Phillips Allegro (Phillips Medical Systems, Best, the Netherlands) with a voxel size of 2 × 2 × 2 mm. The patients treated within the CEP based at the Royal Melbourne Hospital had their scans carried out on a GE Discovery 690 (GE Medical Systems, Milwaukee, WI) at the Peter MacCallum Cancer Centre with a voxel size of 1.82 × 1.82 × 3.27 mm as described previously (Vinton et al., 2007). A three-dimensional whole head acquisition was carried out with a 250 mm field of view. All patients were fasted for 4-6 hours prior to scanning with no caffeine or alcohol intake. The patients were interviewed to confirm they were not using therapeutic or recreational agents, which could influence cerebral metabolism. The patients had blood glucose measured to ensure they were not hyperglycaemic. The intravenous cannula was placed in advance. The patients were rested in a quiet, dimly lit room, with eyes open, for at least 30 minutes prior to $^{18}$FDG administration, following which a bolus injection of $^{18}$FDG was administered at the dose of 150-327 megabecquerel (MBq), which is equivalent to 4-9 millicurie (mCi). The scanning began within 30-60 minutes. Routine EEG monitoring was not carried out during the scan. The patients underwent clinical interview prior to scanning to ensure that they were seizure free within the preceding at least 24 hours.

The images of the patients and 20 healthy age matched controls (10 males, aged 16-65) were first reoriented and non-linearly normalised to the PET template available within SPM using the default parameters associated with the Old Normalise algorithm including grand mean scaling of 50 and a relative threshold of 0.8. Normalisation parameters were saved for later use. Normalised images were smoothed with an 8 mm full width at half maximum Gaussian kernel. Hypometabolic regions of the brain were identified with reference to 20 controls. For each patient, a general linear model was composed to enable a comparison of the patient's $^{18}$FDG-PET to the 20 normal controls at each voxel, with a 2-sample t-test carried out for each subject. To optimise the detection of the total cerebral $^{18}$FDG-PET hypometabolism (TCH), the modelling was carried out at every voxel within the whole brain mask, excluding the cerebellum, and a temporal lobe mask obtained from the Automated Anatomic Labeling atlas using the Wake Forest University (WFU) Pick Atlas toolbox (Functional MRI Laboratory, Wake Forest University School of Medicine, Winston-Salem, NC) (Tzourio-Mazoyer et al., 2002) so that a t-statistic image for each subject could be produced. T-statistic images

were transformed from the space of the PET atlas, in which inter subject comparisons were made, back to the native space of each patient's $^{18}$FDG-PET using the inverse of the normalisation parameters.

### 2.2.3 Combined MRI and $^{18}$FDG-PET post-acquisition processing

To ascertain the extent of the resection of the $^{18}$FDG-PET hypometabolism, linear co-registration of the patient's $^{18}$FDG-PET image to their preoperative MRI scan was carried out using SPM's co-registration algorithm, which utilises normalised mutual information to discern and quantify the similarities between the two images of different modalities. The co-registered $^{18}$FDG-PET/MRI images were again inspected by two independent operators for quality assurance of the co-registration accuracy. This co-registration was used to transform the t-statistic images from the patient's native $^{18}$FDG-PET space to their respective native preoperative MRI space. Following that, the t-statistic images were transformed to the preoperative MRI space and thresholded (uncorrected $p = 0.005$, cluster extent >100 voxels) to delineate the region of hypometabolism, followed by binarisation. The level of optimal SPM thresholding was achieved through the identification of parameters whereby the ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism was identifiable in all patients. Thresholding was undertaken in the high-resolution MRI space, as opposed to the low-resolution PET template space, to increase the accuracy of interpolation to a continuous, i.e. the t-statistic image, rather than to a discontinuous, i.e. a thresholded t-statistic image to enable smoother appearances of the hypometabolism boundaries.

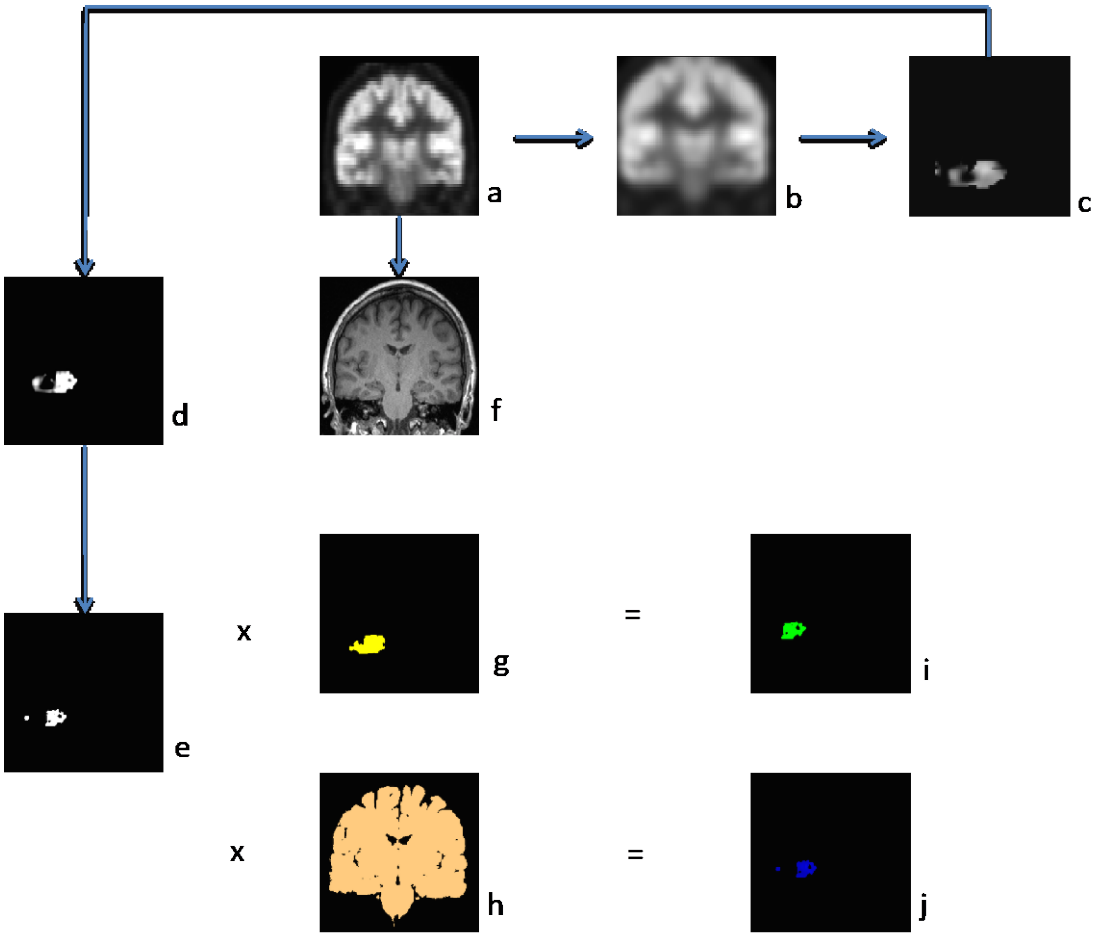



**Figure 2.2: Key steps in combined $^{18}$FDG-PET and MRI postprocessing**

Flowchart outlining the key steps of combined $^{18}$FDG-PET and MRI postprocessing and deriving the resected temporal lobe hypometabolic tissue volume: a – raw $^{18}$FDG-PET image; b – $^{18}$FDG-PET normalised to MNI space and smoothened at 8mm FWHM Gaussian kernel; c – SPM output outlining significant hypometabolism; d – SPM output co-registered to preoperative MRI; e – thresholded SPM output; f – preoperative MRI; g – resected tissue; h – total cerebral volume; i – resected hypometabolism; j – total hypometabolism

The calculation of the amount of hypometabolism resected was carried out by masking the hypometabolism image in the MRI space by the resected tissue image. The total amount of hypometabolism was calculated by masking the hypometabolism image by the total cerebral volume image. The number of voxels in these masked images were summed and then multiplied by the voxels size to produce the volume of the resected temporal lobe PET hypometabolism (TLH) and the volume of the TCH. The proportion of the TLH resected was derived as follows: % TLH resected = (volume of TLH resected x100)/volume of TLH. The proportion of the resected TCH was calculated using the following formula: % TCH resected = (volume of TLH resected x 100)/volume of TCH. The proportion that extratemporal hypometabolism (ETH) within

TCH was derived by first estimating the volume of ETH through subtracting the TLH volume from the TCH volume, followed by the estimation of its proportion: % ETH = (ETH volume x 100)/TCH volume. In addition, the SPM thresholded images were also inspected for the topographic boundaries of the ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism and the presence of ETH, including the pattern of its distribution.

## 2.3 Statistical Analyses

All statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) 21.0 (IBM, Armonk, NY). Statistical analyses specific to the individual studies are outlined in detail in the respective results chapters.

# Chapter 3

# Metabolic patterns and seizure outcomes following anterior temporal lobectomy

## 3.1 Introduction

Epilepsy surgery remains the treatment option of choice in patients with drug resistant MTLE. However, despite a thorough multimodal presurgical evaluation, a significant proportion of patients continue to have seizures following surgery (McIntosh et al., 2001; Tellez-Zenteno et al., 2010). Accordingly, the need for reliable predictors of treatment outcomes in this era of personalised medicine remains ongoing. $^{18}$FDG-PET is one of the most established functional imaging modalities employed in the evaluation of epilepsy surgery candidates and offers unique insights into cerebral glucose metabolism at the synaptic level (Duncan et al., 2016; Gaillard et al., 2011; Knowlton, 2006; Willmann et al., 2007). The cost-efficiency of $^{18}$FDG-PET has long been recognised and the wider availability of post-acquisition processing techniques has increased its yield in surgical planning (Murphy et al., 2001; O'Brien et al., 2008; Rathore et al., 2014; Whiting, 2006; Zhang et al., 2014).

With the advances in EEG and imaging technologies, including multimodal co-registration techniques, the role of $^{18}$FDG-PET in the presurgical evaluation has been enhanced beyond being a useful diagnostic tool reserved for the “MRI-negative” cases or clinical scenarios with discordant electroclinical and structural imaging findings (Carne et al., 2004; Knowlton et al., 2008; LoPinto-Khoury et al., 2012; Pittau et al., 2014). There is a growing body of evidence suggesting that the extent of the metabolic compromise correlates with the distribution of the ictal EEG discharges (Guedj et al., 2015; Lamarche et al., 2016). Furthermore, the findings of recent $^{18}$FDG-PET and functional connectivity studies have been convergent in demonstrating the role of $^{18}$FDG-PET as a metabolic biomarker of the extent of the epileptic network dysfunction (Chassoux et al., 2016; Vanicek et al., 2016). It has also been suggested that hypometabolic changes affecting the contralateral temporal lobe may impact on seizure outcomes in patients with drug resistant MTLE (Blum et al., 1998; Choi et al., 2003; Joo et al., 2004; Kim et al., 2006; Wong et al., 2010). While stereoelectroencephalography (SEEG) and intraoperative imaging co-registration

technologies open up new avenues for the use of $^{18}$FDG-PET in surgical planning (Murphy et al., 2001; Zhang et al., 2014), the studies on how the extent of the resection of $^{18}$FDG-PET hypometabolism affects long-term surgical outcomes have been rather sparse and somewhat contradictory, which could be explained by a modest patient cohort size and methodological differences (Stanisic et al., 2015; Vinton et al., 2007).

Furthermore, the results of functional and metabolic connectivity studies have been suggestive of distinct functional connectivity patterns depending on the laterality of the MTLE, including higher rates of contralateral temporal lobe involvement in patients with right MTLE (Coito et al., 2016; Dupont et al., 2002; Englot et al., 2016; Haneef et al., 2014; Vanicek et al., 2016). Higher rates of bitemporal hypometabolism have been observed in patients with unilateral right MTLE (Chassoux et al., 2016), however the effect of this distinct metabolic pattern on seizure outcomes following an ATLR has not been demonstrated. This study investigated the role of $^{18}$FDG-PET in predicting surgical outcomes in a large, well characterised cohort of patients with drug resistant unilateral MTLE. The predictive value of the extent of the resection of $^{18}$FDG-PET hypometabolism and the influence of contralateral temporal lobe $^{18}$FDG-PET changes on surgical outcomes in patients with right and left MTLE were evaluated.

## 3.2 Methods

**Study subjects**

This was a retrospective two-centre study. A total of 82 patients with drug resistant unilateral MTLE who underwent an ATLR between 2001 and 2014 were included. Patients were identified from the prospectively administered Comprehensive Epilepsy Program databases at the Royal Melbourne and the Austin Hospitals in Melbourne, Australia. The inclusion criteria were: (1) age $\geq$ 16 years at the time of surgery, (2) preoperative MRI findings consistent with unilateral hippocampal sclerosis (HS) or no identifiable lesion ("MRI negative"), (3) concordant results of presurgical investigations and seizure semiology, (4) the presence of concordant ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism on visual inspection of interictal $^{18}$FDG-PET and (5) at least 2 years of follow up following the ATLR.

The two centres utilised a similar presurgical evaluation protocol, which has been described previously (Berkovic et al., 1995; Carne et al., 2004; Vinton et al., 2007). Briefly, this was comprised of at least one five-day period of video-EEG-telemetry

including a neurological examination, re-evaluation of the clinical presentation and seizure semiology, an expert neuroradiology review, as well as neuropsychiatric and neuropsychological assessments. Postoperatively, antiepileptic therapy was commonly rationalised within the first 6-12 months, depending on the seizure outcome. The study was approved by the Melbourne Health and the Austin Health Human Research Ethics Committees.

**Seizure variables and outcomes**

Seizure outcomes were assessed at the time of the last follow-up and categorised using Engel's classification of postoperative outcomes as seizure free (Engel's class I) or not seizure free (Engel's class II-IV) (Engel et al., 1993). The duration of follow-up varied between the patients (Table 1) however a minimum of 2 years of postoperative follow-up was achieved for all patients, consistent with the previous published work from our group evaluating predictors of surgical outcomes (Berkovic et al., 1995). The "worthwhile improvement" was set at a $\geq$ 75% reduction in seizure frequency compared to the preoperative seizure burden. Acute seizures occurring within the first week following surgery were discounted (Bhaskara Rao et al., 1998). Postoperatively, only seizures manifesting with impaired awareness were counted towards seizure recurrence (McIntosh et al., 2005).

**Neurosurgical Procedure**

All patients underwent a Spencer-type resection, which is a type of ATLR also known as an anteromedial temporal lobectomy or a radical hippocampectomy (Fried, 1993). In brief, it is a two-step procedure involving the resection of the middle temporal gyrus and the inferior temporal gyrus 3-3.5 cm from the tip of the temporal pole, followed by resection of the mesial temporal lobe structures including the amygdala, hippocampus and the parahippocampal gyrus. It was the policy of our surgeons to perform a less extensive cortical resection, sparing the superior temporal gyrus, in patients with left (i.e. language dominant) MTLE. This is consistent with the results of previous studies that have reported smaller volume temporal lobe resections in patients undergoing a left ATLR (Bonelli et al., 2010; Yogarajah et al., 2010). The adequacy of the hippocampal resection was determined based on a postoperative MRI performed at least three months following surgery.

### $^{18}$FDG-PET and MRI acquisition and post-processing

Preoperative $^{18}$FDG-PET and MRI examinations were carried out as part of the presurgical evaluation. $^{18}$FDG-PET scans were acquired on a Phillips Allegro (Phillips Medical Systems, Best, The Netherlands) at the Austin Hospital with a voxel size of 2 x 2 x 2mm or a GE Discovery 690 (GE Medical Systems Milwaukee, WI) at the Peter MacCallum Cancer Centre with a voxel size of 1.82 x 1.82 x 3.27mm as described previously (Vinton et al., 2007). The median timing of the $^{18}$FDG-PET scan was 5 months preceding surgery (interquartile range [IQR]: 3-10.25; range 1-23 months). Until 2005 the MRI examinations were carried out on a Genesis Signa 1.5T (GE Medical Systems Milwaukee, WI), thereafter the scans were performed on a Magnetom Avanto 1.5T and a Magnetom Trio Tim 3T (Siemens Medical Solutions, Erlangen, Germany). Three-dimensional, T1-weighted, magnetisation prepared rapid acquisition gradient echo sequences were used for post-acquisition processing. All processing was conducted using Statistical Parametric Mapping (SPM) software, version 12 (Wellcome Department of Cognitive Neurology, University College London, London, UK) mounted on a MATLAB R2012-A (MathWorks, Natick, MA, U.S.A.).

### $^{18}$FDG-PET post-processing.

The images of the patients and 20 healthy controls were reoriented and non-linearly normalised to SPM's built-in PET template using the default parameters within SPM's Old Normalise algorithm including a grand mean scaling of 50 and a relative threshold of 0.8. Normalisation parameters were saved for later use. Normalised images were smoothed with an 8 mm full width at half-maximum Gaussian kernel. Hypometabolic regions of the brain were determined with reference to 20 healthy controls of an equivalent age range (16-65). For each patient, a General Linear Model (GLM) was constructed to compare the patient to the 20 controls at each voxel, with a two-sample t-test carried out for each subject. To optimise the detection of the total cerebral $^{18}$FDG-PET SPM hypometabolism (TCH) the modelling was conducted at every voxel within the whole brain mask (excluding the cerebellum) and a temporal lobe mask obtained from the Automated Anatomic Labeling atlas using WFU Pick Atlas toolbox (The Functional MRI Laboratory Wake Forest University School of Medicine) (Tzourio-Mazoyer et al., 2002). This yielded a t-statistic image for each subject. T-statistic images were first transformed from the space of the PET atlas in which inter-subject comparisons were made and then back to the native space of each patient's $^{18}$FDG-PET using the inverse of the normalisation parameters.

**MRI post-processing**

The resected tissue volume was estimated by deriving the difference through matching preoperative and postoperative MRI's. Preoperative and postoperative MRI's were non-linearly registered using SPM's longitudinal registration toolbox with default parameters (Ashburner & Ridgway, 2013). We opted for non-linear registration, since linear registration was not sufficient due to an inaccurate account of the postoperative brain changes, in particular the collapse of the brain tissue into the resection cavity. Preoperative and postoperative images were segmented into grey matter (GM), white matter (WM) and cerebral spinal fluid. The GM and WM partitions were added and thresholded at 0.1, resulting in an image of the brain tissue.

A total cerebral volume image was constructed by taking the union of the preoperative and registered postoperative brain segmentations. The resection volume was measured as the difference between the preoperative and postoperative scans. To minimise the contribution of the pre and postoperative image registration and segmentation errors, the largest cluster of the difference image was selected, which was invariably the resected tissue. To make this selection, the resected tissue was separated from the registration error by eroding the image by two voxels. Subsequently, the now separate resected tissue was selected, and dilated by two voxels to restore it to its original size. All resected tissue images were inspected by two independent operators to ensure the resected region on the postoperative MRI image was filled accurately. The volumes of resected tissue and of the total cerebral volume were calculated by summing the non-zero voxels and multiplying by the voxel size.

**Combined MRI and PET post-processing**

To ascertain the extent of the $^{18}$FDG-PET hypometabolism resected, the patient's $^{18}$FDG-PET images were matched to their preoperative MRI. The $^{18}$FDG-PET images were linearly co-registered to the preoperative MRI scans using SPM's co-registration algorithm, which utilises normalised mutual information to quantify similarity between two images of different modalities. The co-registered $^{18}$FDG-PET/MRI images were inspected by two independent operators to ensure the adequacy of the co-registration. This co-registration was used to transform the t-statistic images from the native $^{18}$FDG-PET space to the native preoperative MRI space. The t-statistic images were transformed to the preoperative MRI space, were then thresholded (uncorrected $p$=0.005, cluster extent >100 voxels) to elicit the region of hypometabolism and

binarised. The optimal level of SPM thresholding was achieved through the identification of parameters whereby the $^{18}$FDG-PET hypometabolism was identifiable in the ipsilateral temporal lobe in all patients. Thresholding was undertaken in the MRI space, rather than the PET template space to allow for the application of more accurate interpolation to a continuous image, i.e. the t-statistic image, as opposed to a discontinuous image, i.e. a thresholded t-statistic image. This resulted in a smoother hypometabolism boundary when applying the threshold in the higher resolution MRI space, rather than the low resolution PET template space.

The amount of hypometabolism resected was calculated by masking the hypometabolism image in the MRI space by the resected tissue image. The total amount of hypometabolism was calculated by masking the hypometabolism image by the total cerebral volume image. The number of voxels in these masked images were summed and multiplied by the voxel size to derive the volume of resected temporal lobe PET hypometabolism (TLH) and the volume of the TCH. The proportion of the TLH resected was derived as follows: % TLH resected = (volume of TLH resected x100)/volume of TLH. The proportion of the resected TCH was calculated as follows: % TCH resected = (volume of TLH resected x 100)/volume of TCH. The proportion that extra-temporal hypometabolism (ETH) constituted within the TCH was derived by first estimating the volume of the ETH by subtracting the TLH volume from the TCH volume, followed by: % ETH = (ETH volume x 100)/TCH volume. The SPM thresholded images were also inspected for the boundaries of the ipsilateral $^{18}$FDG-PET hypometabolism and the presence of ETH, including its distribution pattern. In all patients the $^{18}$FDG-PET SPM hypometabolism identifiable in the ipsilateral temporal lobe was confined to the temporal lobe region without extension into the neighbouring regions (i.e. fronto-orbital, opercular or the temporo-parieto-occipital junction). The ETH areas were identified in the frontal regions (ipsilateral, contralateral and bilateral) and contralateral temporal lobe region.

**Statistical Analysis**

Univariable analyses using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables were performed to first explore the differences in pertinent demographic, seizure, pre and postoperative neuroimaging variables in patients with right versus left MTLE, and subsequently, to explore the differences within the subgroups, depending on the seizure outcomes. Pertinent

neuroimaging variables with univariable *p*-value <0.1 were included in multivariable logistic regression to explore the predictive value of neuroimaging variables on seizure outcomes in patients with right and left MTLE, respectively. A two-tailed *p* value of <0.05 was considered statistically significant for all tests performed unless otherwise specified. All statistical analyses were performed using IBM SPSS 21.0 (IBM Corp., Armonk, NY).

## 3.3 Results

**Patients' characteristics and seizure outcomes**

There were 43 patients with right MTLE and 39 patients with left MTLE with comparable gender composition, the age of epilepsy onset, the epilepsy duration, age at surgery and the duration of postoperative follow up (Table 3.1).

**Table 3.1.** Patients' characteristics.

| *Variables* | Right MTLE | Left MTLE | *p* value[#] |
|---|---|---|---|
| Gender, male – n (%) | 21/43 (48.8) | 20/39 (51.3) | 1.00 |
| Age of epilepsy onset, years – median (IQR) | 17.0 (7.0 – 27.0) | 16.0 (4.0 – 26.0) | 0.50 |
| Duration of epilepsy, years – median (IQR) | 19.0 (11.0 – 31.0) | 19.0 (9.0 – 30.0) | 0.91 |
| Age at operation, years – median (IQR) | 40.0 (29.0 – 46.0) | 34.0 (29.0 – 47.0) | 0.58 |
| Duration of follow up, years – median (IQR) | 4.0 (3.0 – 8.0) | 5.0 (2.0 – 8.0) | 0.60 |

# Fisher's exact test was used for categorical variables and Mann-Whitney U test was performed for continuous variables.

The median postoperative follow up period in patients with right MTLE was 4 years, ranging from 2 to 10 years, and 5 years in patients with left MTLE, ranging from 2 to 14 years. The preoperative seizure burden did not differ in patients with right and left MTLE ($p$=0.98) (Table 3.3). The seizure outcomes, excellent (Engel's class I) versus unfavourable (Engel's class II-IV), did not differ in patients with right and left MTLE ($p$=1.00) with excellent outcomes observed in 30 patients (68.9%) with right MTLE and 28 patients (71.8%) with left MTLE. The striking differences in the interictal metabolic patterns observed in patients with right and left MTLE are outlined in Table 3.2.

**Table 3.2.** Summary of pre and postoperative imaging variables in patients with left versus right MTLE/ATLR.

| *Variables* | *Right MTLE/ATLR* n=43 (52.4%) | *Left MTLE/ATLR* n=39 (47.6%) | *p* value[#] |
|---|---|---|---|
| HS on preoperative MRI – n (%) | 34/43 (79.1) | 36/39 (92.3) | 0.12 |
| Volume of preop ipsilateral TL SPM hypometabolism, $mm^3$ – median (IQR) | $3.79 \times 10^3$ ($1.67 \times 10^3 – 6.85 \times 10^3$) | $9.28 \times 10^3$ ($3.57 \times 10^3 – 14.58 \times 10^3$) | **<0.001** |
| % of TCH confined to ipsilateral TL – median (IQR) | 29.9 (20.7 – 41.0) | 63.0 (49.8 – 73.5) | **<0.001** |
| % TCH SPM hypo distributed extra-temporally – median (IQR) | 70.1 (59.0 – 79.3) | 37.0 (26.4 – 50.2) | **<0.001** |
| Presence of contralateral TLH – n (%) | 17/43 (39.5) | 4/39 (10.3) | **0.003** |
| Volume of TL tissue resected, $mm^3$ – median (IQR) | $21.9 \times 10^3$ ($17.7 \times 10^3 – 28.0 \times 10^3$) | $15.4 \times 10^3$ ($11.8 \times 10^3 – 21.3 \times 10^3$) | **<0.001** |
| % TLH resected – median (IQR) | 59.1 (35.9 – 70.9) | 36.4 (23.6 – 58.3) | **0.008** |

# Fisher's exact test was used for categorical variables and Mann-Whitney U test was performed for continuous variables.

**Table 3.3.** Preoperative seizure burden in patients with right (n=43) and left (n=39) MTLE.

| Seizure frequency | Right MTLE<br>n (%) | Left MTLE<br>n (%) |
|---|---|---|
| 4-10/day | 2 (4.7) | 1 (2.6) |
| 1-3/day | 5 (11.6) | 3 (7.7) |
| 1-6/week | 17 (39.5) | 15 (38.5) |
| 1-3/month | 16 (37.2) | 16 (40.9) |
| 4-11/year | 1 (2.3) | 3 (7.7) |
| 1-3/year | 2 (4.7) | 1 (2.6) |

Importantly, the left MTLE patients were observed to have significantly higher rates in the extent of the ipsilateral TLH ($p<0.001$), with a markedly higher proportion of the TCH being confined to the ipsilateral temporal lobe ($p<0.001$). The right MTLE patients had a significantly higher proportion of the TCH falling extra-temporally ($p<0.001$), with the preferential CTL TLH occurrence in right MTLE patients ($p=0.003$). The estimated volumes of the resected temporal lobe tissue in patients with right MTLE significantly exceeded those in patients with left MTLE ($p<0.001$), in keeping with the commonly employed more sparing approach to an ATLR in patients with left MTLE (Shamim et al., 2009; Yogarajah et al., 2010).

**Pre and postoperative imaging variables in relation to seizure outcomes**

Interestingly, the presence of SPM hypometabolism detected outside the ipsilateral temporal lobe was common 54/82 (65.9%), however significantly more prevalent in right MTLE patients (33/43, 76.7%, $p=0.037$). The most commonly sighted distributions of hypometabolism outside the ipsilateral temporal lobe in patients with right and left MTLE are outlined in Table 3.4.

**Table 3.4.** Distribution of ET hypometabolism and its association with seizure outcomes.

| | Right MTLE cohort | | | Left MTLE cohort | | |
|---|---|---|---|---|---|---|
| ET distribution n (%) | Engel's I 30/43 (69.8) | Engel's II-IV 13/43 (30.2) | *p* value[#] | Engel's I 28/39 (71.8) | Engel's II-IV 11/39 (28.2) | *p* value[#] |
| Ipsilateral frontal | 13/30 (43.3) | 8/13 (61.5) | 0.33 | 8/28 (28.6) | 4/11 (36.4) | 0.71 |
| Contralateral frontal | 14/30 (46.7) | 5/13 (38.5) | 0.74 | 8/28 (28.6) | 5/11 (45.5) | 0.45 |
| Bilateral frontal | 9/30 (30.0) | 4/13 (30.8) | 1.00 | 5/28 (17.9) | 3/11 (27.3) | 0.66 |
| Contralateral TL | 8/30 (26.7) | 9/13 (69.2) | **0.016** | 2/28 (7.1) | 2/11 (18.2) | 0.56 |

# Fisher's exact test was used.

Hypometabolic changes in the frontal regions were common and comparable in patients with right and left MTLE and were not associated with worse outcomes. The presence of CTL TLH in patients with left MTLE did not influence the rates of seizure freedom, however in the right MTLE cohort, it was associated with unfavourable seizure outcomes ($p$=0.016) (Table 3.5). In the left MTLE cohort the excellent seizure outcomes were associated with a larger volume of resected temporal lobe tissue ($p$=0.005) as well as a greater extent of resection of the ipsilateral temporal lobe hypometabolism ($p$=0.004) (Table 3.6), which resonates with the findings of previous studies (Thom et al., 2010; Vinton et al., 2007).

**Table 3.5.** Pre and postoperative seizure variables pertinent to seizure outcomes in patients with right MTLE *(univariable analyses).*

| | Engel's I | Engel's II-IV | |
|---|---|---|---|
| | 30/43 (69.8%) | 13/43 (30.2%) | *p* value |
| HS on MRI – n (%) | 26/30 (86.7) | 8/13 (61.5) | 0.10 |
| Estimated MRI volume of resected TL tissue, $mm^3$ – median (IQR) | 22.17 x $10^3$ (18.22 x $10^3$ – 28.03 x $10^3$) | 21.08 x$10^3$ (14.99 x $10^3$ – 26.52 x $10^3$) | 0.58 |
| Volume of preoperative TLH, $mm^3$ – median (IQR) | 3.62 x $10^3$ (1.70 x $10^3$ – 7.47 x $10^3$) | 3.94 x $10^3$ (1.40 x $10^3$ – 6.16 x $10^3$) | 0.94 |
| % TLH resected – median (IQR) | 58.67 (35.92 – 73.01) | 60.26 (45.98 – 65.27) | 0.63 |
| % of TCH confined to ipsilateral TL – median (IQR) | 30.72 (22.92 – 42.09) | 24.81 (14.55 – 36.35) | 0.17 |
| % TCH distributed in ET regions – median (IQR) | 69.28 (57.91 – 77.08) | 75.19 (63.65 – 85.45) | 0.17 |
| Patients with contralateral TLH – n (%) | 8/30 (26.7) | 9/13 (69.2) | **0.016** |

**Table 3.6.** Pre and postoperative seizure variables pertinent to seizure outcomes in patients with left MTLE *(univariable analyses).*

| | Engel's I<br><br>28/39<br>(71.8%) | Engel's II-IV<br><br>11/39<br>(28.2%) | *p* value |
|---|---|---|---|
| HS on MRI – n (%) | 27/28 (96.4) | 9/11 (81.8) | 0.19 |
| Estimated MRI volume of resected TL tissue, $mm^3$ – median (IQR) | 17.78 $x10^3$ ($12.89 \times 10^3 – 22.95 \times 10^3$) | 11.78 $x10^3$ ($8.84 \times 10^3 – 14.56 \times 10^3$) | **0.005** |
| Volume of preoperative TLH, $mm^3$ – median (IQR) | 9.75 $x10^3$ ($4.60 \times 10^3 – 14.73 \times 10^3$) | 8.33 $x10^3$ ($3.57 \times 10^3 – 11.42 \times 10^3$) | 0.83 |
| % TLH resected – median (IQR) | 46.22 (31.29 – 60.30) | 24.06 (18.01 – 29.42) | **0.004** |
| % of TCH confined to ipsilateral TL – median (IQR) | 63.31 (51.03 – 74.15) | 62.06 (49.82 – 69.77) | 0.62 |
| % TCH distributed in ET regions – median (IQR) | 36.69 (25.85 – 48.97) | 37.94 (30.23 – 50.18) | 0.62 |
| Patients with contralateral TLH – n (%) | 2/28 (7.1) | 2/11 (18.2) | 0.56 |

While the higher rates of HS on preoperative MRI (86.7% in right MTLE and 96.4% in left MTLE patients) in patients with excellent seizure outcomes were in keeping with previous studies (Berkovic et al., 1995), they did not reach statistical significance in influencing seizure outcomes ($p$=0.10 and $p$=0.19 in patients with right and left MTLE, respectively).

**Predictors of seizure outcomes**

The results of the multivariable logistical regression exploring the predictive value of pertinent pre and postoperative neuroimaging features, focusing on preoperative MRI findings and $^{18}$FDG-PET patterns in right MTLE patients and the extent of both, the temporal lobe tissue resection and the ipsilateral temporal lobe hypometabolism in the left MTLE group, are shown in Tables 3.7 and 3.8, respectively.

**Table 3.7.** Predictors of postoperative seizure recurrence in right MTLE patients.

| *Variables* | *OR* | *95% CI* | *p value* |
|---|---|---|---|
| MRI findings (HS vs HS-negative) | 2.13 | 0.39-11.73 | 0.38 |
| Presence of CTL hypometabolism | 4.90 | 1.07-22.39 | **0.04** |

**Table 3.8.** Predictors of postoperative seizure recurrence in left MTLE patients.

| *Variables* | *OR* | *95% CI* | *p value* |
|---|---|---|---|
| Estimated MRI volume of resected TL tissue, $mm^3$ | 1.00 | 1.00-1.00 | 0.14 |
| % TLH resected | 0.96 | 0.90-1.02 | 0.19 |

In the right MTLE patients, the presence of contralateral TLH was the strongest predictor of a heightened risk of unfavourable seizure outcomes and was associated with a nearly five-fold increase in the risk of postoperative seizure recurrence (OR 4.90, 95% confidence interval [CI]: 1.07-22.39, $p$=0.04). In the left MTLE group, the predictive value of both, the temporal lobe resection volume and the extent of the ipsilateral temporal lobe hypometabolism resection was explored however neither of the above predictors reached statistical significance ($p$=0.14 and $p$=0.19, respectively). The presence of HS on the preoperative MRI has long been shown to be an independent predictor of favourable seizure outcomes in patients with drug resistant MTLE (Berkovic et al., 1995). Our results corroborate with the above findings in that 76% of patients with HS on the preoperative MRI achieved seizure freedom and only 42% of patients with normal MRI brain findings had a favourable outcome. The subgroup analysis of the seizure outcome predictors is summarised in Table 3.9. The presence of CTL hypometabolism predicted an unfavourable seizure outcome ($p$=0.018).

**Table 3.9.** Predictors of postoperative seizure recurrence in a subgroup of patients with HS on preoperative MRI.

| *Variables* | *OR* | *95% CI* | *p value* |
|---|---|---|---|
| ATLR side | 1.17 | 0.29-4.78 | 0.83 |
| Volume of resected TL tissue, $mm^3$ | 1.00 | 1.00-1.00 | 0.39 |
| % TLH resected | 0.98 | 0.95-1.02 | 0.28 |
| Presence of CTL hypometabolism | 5.45 | 1.34-22.17 | **0.018** |

## 3.4 Discussion

The results of our study demonstrated striking differences in metabolic patterns in patients with right and left MTLE, with significantly greater rates of bitemporal hypometabolic changes observed in patients with right MTLE, whereas the patients with left MTLE had more extensive ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism. The studies examining the evolution of the $^{18}$FDG-PET hypometabolism over time have been sparse and mostly focused on paediatric populations. Gaillard *et al* studied the temporal evolution of the $^{18}$FDG-PET changes in a mixed paediatric patient cohort, including a sub-group with drug resistant epilepsy who were evaluated for epilepsy surgery, over a mean interval of 3.0 years (Gaillard et al., 2007). They demonstrated no evidence of hypometabolic progression, with seizure frequency and time since the last seizure being the most important determinants of the differences in regional hypometabolism over the serial scans. In contrast a recent study evaluating the interval changes in $^{18}$FDG-PET hypometabolism in a heterogenous group of paediatric patients with drug resistant epilepsy did find progression in the PET hypometabolism over time, with the median interval between the scans being over 4 years, in particular in patients with ongoing drug resistant seizures (Govil-Dalela et al., 2018). In some of these cases unilateral hypometabolism evolved into bilateral hypometabolism on the subsequent scans. In our study, the homogeneity of our cohort and the timing of the $^{18}$FDG-PET scans, with the median being 5 months preceding surgery, substantially diminishes the possibility of dynamic changes influencing the findings. However, the possibility of interval changes cannot be excluded completely.

Remarkably, our findings resonate with the results of functional and metabolic connectivity studies (Coito et al., 2015; Dupont et al., 2002; Englot et al., 2016; Haneef et al., 2014; Vanicek et al., 2016), demonstrating evidence of altered connectivity

patterns in patients with MTLE, depending on the laterality. In addition, while it remains unknown whether or not metabolic and functional asymmetry share the same underlying mechanisms our findings corroborate with the results of Magnetic Resonance Spectroscopy (MRS) studies by Zubler *et al*. (Zubler et al., 2003), who demonstrated widespread abnormalities, with the involvement of the CTL temporal lobe, in patients with right MTLE. It is not inconceivable, in light of the growing body of evidence demonstrating distinct aberrant metabolic and connectivity patterns, depending on the MTLE laterality, that the right and left MTLE may represent two different entities where further research may not only advance our understanding of epileptogenesis but also influence patient management. Our findings have shown that the overall extent of the ETH and the hypometabolic changes in the frontal regions was not associated with adverse seizure outcomes, regardless of the MTLE laterality and may represent changes associated with the seizure propagation pathways (Paesschen et al., 2007).

Conversely, in right MTLE patients the presence of contralateral TLH heralded unfavourable seizure outcomes, heightening the risk of postoperative seizure recurrence five-fold. While the association of poor seizure outcomes in patients with unilateral MTLE and bitemporal hypometabolism has been reported previously (Blum et al., 1998; Choi et al., 2003; Joo et al., 2004; Kim et al., 2006; Wong et al., 2010), with Joo *et al*. reporting higher rates of non-lateralising EEG patterns in patients with bitemporal hypometabolism (Joo et al., 2004), we found that patients with right MTLE had higher rates of contralateral temporal lobe hypometabolism and to our knowledge, it has not been described previously in conjunction with the laterality of MTLE.

Within the limitations of the current study, we therefore propose that it is not the extent but the location of the ETH, which is the ultimate determinant of unfavourable seizure outcomes. Interestingly, in the left MTLE cohort, the greater temporal lobe resection volume was associated with excellent seizure outcomes and so was the greater the extent of the resected ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism, in keeping with previous studies (Thom et al., 2010; Vinton et al., 2007), albeit none of these potential predictors reached statistical significance. It has been proposed that the extent of $^{18}$FDG-PET hypometabolism is a metabolic biomarker of the extent of neural network dysfunction in patients with MTLE (Chassoux, 2017; Chassoux et al., 2016; Chassoux et al., 2004; Vinton et al., 2007). It might be, in light of potentially distinct

networks implicated in right versus left MTLE, that neuronal dysfunction in left MTLE patients tends to be more confined within the ipsilateral temporal lobe and further studies looking into the influence of the extent of resection of the ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism would be warranted with the focus on the left MTLE cohort.

It has been shown that larger temporal lobe resection volumes were associated with favourable seizure outcomes on several occasions (Joo et al., 2005; Thom et al., 2010), and yet, the quest for the optimal volume of temporal lobe resection remains ongoing to this day (Schramm, 2008). In reality, the left ATLR procedures tend to be more sparing with the left superior temporal gyrus being commonly preserved, resulting in a less extensive temporal lobe resection in left MTLE patients (Shamim et al., 2009; Yogarajah et al., 2010). Our findings demonstrate distinct metabolic patterns with more extensive ipsilateral temporal lobe involvement in left MTLE patients and preferential CTL involvement in patients with right MTLE, which may help to explain the disparity between the extent of the temporal lobe resection volume and the seizure freedom rates. Further studies are warranted to explore the potential value of $^{18}$FDG-PET tailored resections in patients with left MTLE.

**Conclusions**

Our findings, demonstrate striking differences in the metabolic patterns in patients with right versus left MTLE and offer further insights into potentially distinct epileptogenic network dysfunction, depending on the laterality of the MTLE. From a practical standpoint, our findings call for the extended role of $^{18}$FDG-PET in presurgical planning. Current guidelines reserve the use of $^{18}$FDG-PET for “MRI-negative” cases and for the patients with discordant MRI and electro-clinical findings. With the results of our study demonstrating CTL TH being a strong predictor of unfavourable seizure outcomes heralding a five-fold increase in seizure recurrence in patients with right MTLE, the wider use of $^{18}$FDG-PET can influence the stratification of surgical candidates and improve presurgical counselling, in line with the expectations of personalised patient care.

# Chapter 4

# The real world clinical utility of $^{18}$FDG-PET in predicting memory deficits in patients with MTLE

## 4.1 Introduction

Predicting memory outcomes in patients undergoing epilepsy surgery remains an ongoing challenge despite the advances in multimodal imaging technologies and the progress made in predicting seizure outcomes. There has been a paradigm shift, whereby a shared decision making approach to patient centred care, highlighted by patients perspectives of a desirable outcome of surgical intervention with health related QoL being the main priority, where favourable seizure outcomes are inseparable from the optimal neurocognitive, neuropsychiatric and social outcomes (Coleman et al., 2020; Perry & Duchowny, 2013).

$^{18}$FDG-PET is one of the most commonly utilised functional neuroimaging modalities employed in the evaluation of epilepsy surgery candidates (Duncan et al., 2016; Gaillard et al., 2011; Theodore et al., 1997). This readily accessible and well-established diagnostic tool has been assisting with the lateralisation and localisation of the seizure onset zone for over 30 years (Chassoux, 2017; O'Brien et al., 2008). An association between temporal lobe $^{18}$FDG-PET hypometabolism and impaired verbal memory performance has been repeatedly described in patients with MTLE (Arnold et al., 1996; Jokeit et al., 1997; Knopman et al., 2015; Rausch et al., 1994). The findings of the most recent study by Kamm *et al* suggest that preoperative changes in $^{18}$FDG uptake predicted postoperative memory deficits in patients undergoing temporal lobe resection (Kamm et al., 2018). Leeman *et al* however did not observe this relationship (Leeman et al., 2009). Previous studies focused on separate aspects pertaining to memory deficits in patients with TLE, however without addressing the impact of the overall temporal lobe resection volume and the differential role that the extent of the resection of the $^{18}$FDG-PET hypometabolic and metabolically intact temporal lobe tissue plays in postoperative verbal memory outcomes. While more extensive surgical resections of $^{18}$FDG-PET hypometabolism has been shown to improve the seizure outcomes (Vinton et al., 2007), to our knowledge there have been no prior studies addressing the relationship between the extent of the resection of the temporal lobe hypometabolism and its bearing on memory outcomes. This study aimed to investigate the role of $^{18}$FDG-PET as a potential

metabolic biomarker in predicting pre and postoperative verbal memory deficits in patients with drug resistant unilateral MTLE. The added value of the $^{18}$FDG-PET in predicting postoperative verbal memory performance following an ATLR over and above the long established predictors of postoperative verbal memory decline, such as the ATLR laterality and preoperative verbal memory performance (Baxendale et al., 2013; Lee et al., 2002) was also examined in this study.

## 4.2 Methods

**Research participants**

A total of 71 patients with unilateral drug resistant MTLE who underwent an ATLR between 2001 and 2014 at two Comprehensive Epilepsy Programmes in Melbourne, Australia were included in this study. Data curation was carried out using prospectively maintained CEP databases. Inclusion criteria were: (1) hippocampal sclerosis or no epileptogenic lesion identified on the preoperative MRI; (2) preoperative Full Scale Intelligence Quotient (FSIQ) $\geq$ 70; (3) fluent English; (4) no previous neurosurgical intervention and (5) no symptoms of an active psychiatric illness at the time of the neuropsychological assessment. The patients where the $^{18}$FDG-PET imaging or the pre and postoperative MRI scans were irretrievable, lost to archives or not performed were excluded from this study. This study was approved by the Melbourne Health and Austin Health Human Research Ethics Committees.

**Neurosurgical Procedure**

All patients underwent a Spencer's type resection (Fried, 1993), which is a type of ATLR, performed in a twostep fashion and entails the resection of the middle temporal gyrus and the inferior temporal gyrus 3-3.5 cm from the temporal tip, followed by resection of the mesial temporal lobe structures including the amygdala, hippocampal complex, uncus and fusiform gyrus. The adequacy of the hippocampal resection was determined based on the postoperative MRI scan carried out at least 3 months following the procedure.

**Neuropsychological evaluation**

A comprehensive neurocognitive evaluation was carried out by the clinical neuropsychologists as part of the patient's standard clinical care on average four months prior to the ATLR and at least six months following the ATLR (Wilson et al., 1998).

The selection of the neurocognitive tests performed on an individual patient in the pre and postoperative period was guided by the outcome of the clinical interview and therefore slightly differed between patients, however the verbal memory performance was consistently assessed using the RAVLT (Rey, 1941) and the verbal PAL test (Wechsler, 1945). The difference between the memory scores attained before (t1) and after the ATLR (t2) served as a measure of the postoperative memory change (Jokeit et al., 1997). All patients underwent a pre and postoperative neuropsychiatric evaluation.

### $^{18}$FDG-PET and MRI acquisition and post-processing

$^{18}$FDG-PET and MRI scans were carried out as part of the routine clinical care. $^{18}$FDG-PET scans were acquired on a Phillips Allegro (Phillips Medical Systems, Best, The Netherlands) with voxel size 2 x 2 x 2 mm and a GE Discovery 690 (GE Medical Systems Milwaukee, WI) with voxel size 1.82 x 1.82 x 3.27 mm as described in Chapter 2. Routine EEG monitoring was not performed during the scan however, the patients were observed for clinical signs of ictal activity and were seizure free within the preceding 24 hours. Until 2005 MRI examinations were acquired on a Genesis Signa 1.5T (GE Medical Systems Milwaukee, WI), from 2006 onwards the scans were carried out on a Magnetom Avanto 1.5T and a Magnetom Trio Tim 3T (Siemens Medical Solutions, Erlangen, Germany). Three-dimensional, T1-weighted magnetisation prepared rapid acquisition gradient echo (MPRAGE) sequences were used for post-acquisition processing. Post-acquisition processing was conducted using Statistical Parametric Mapping software (SPM version 12, Wellcome Trust Centre for Neuroimaging, University College London, UK) mounted on a MATLAB R2012-A (MathWorks, Natick, MA, U.S.A.) (Penny, 2006).

### $^{18}$FDG-PET image post-processing

The images of the patients and 20 age matched healthy controls were reoriented and non-linearly normalised to a built in PET template using the default parameters within the SPM's Old Normalise algorithm including grand mean scaling to 50 with a relative threshold of 0.8. Normalisation parameters were saved for later use. The normalised images were smoothed with an 8 mm full width at half maximum (FWHM) Gaussian kernel. Hypometabolic regions of the brain were determined with reference to 20 healthy age matched controls. For each patient, a General Linear Model (GLM) was constructed to compare the patient to the 20 controls at each voxel, using a two-sample t-test. Modelling was conducted at every voxel within a temporal lobe mask, obtained

from the Automated Anatomic Labeling (AAL) atlas using the WFU Pick Atlas toolbox (The Functional MRI Laboratory Wake Forest University School of Medicine) (Tzourio-Mazoyer et al., 2002). This yielded a t-statistic image for each subject. T-statistic images were first transformed from the space of the PET atlas in which inter subject comparisons were made and then back to the native space of each patient's $^{18}$FDG-PET using the inverse of the normalisation parameters.

**MRI post-processing**

Resected tissue was derived from the difference between pre and postoperative MRIs. Preoperative and postoperative MRIs were non-linearly registered using SPM's longitudinal registration toolbox with default parameters (Ashburner & Ridgway, 2013). The non-linear registration was carried out since linear registration was considered insufficient due to an inaccurate account of the postoperative brain changes, in particular the collapse of the brain tissue into the resection cavity. Preoperative and postoperative images were segmented into grey matter (GM) and white matter (WM). The GM and WM partitions were added and thresholded at 0.1, resulting in an image of the brain tissue. A total cerebral volume image was constructed by taking the union of the preoperative and registered postoperative brain segmentations. The resection volume was measured as the difference between the preoperative and postoperative scans. To minimise the contribution of the pre and postoperative image registration and segmentation errors, the largest cluster of the difference image was selected, which was invariably the resected tissue. To make this selection, the resected tissue was separated from the registration error by eroding the image by two voxels. Subsequently, the now separate resected tissue was selected, and dilated by two voxels to restore it to its original size. All resected tissue images were visually inspected by two independent operators to ensure the resected region on the postoperative MRI image was filled accurately. The volumes of resected tissue and of the total cerebral volume were calculated by summing the non-zero voxels and multiplying by the voxel size. The percentage of tissue resected was calculated as: % tissue resected = (volume tissue resected / total cerebral volume) x 100.

**Combined MRI and $^{18}$FDG-PET post-processing**

To ascertain the extent of the $^{18}$FDG-PET hypometabolism resected, the patient's $^{18}$FDG-PET images were matched to their preoperative MRI. $^{18}$FDG-PET images were linearly co-registered to the preoperative MRI using SPM's co-registration algorithm,

which utilises normalised mutual information to quantify the similarity between two images of different modalities. The co-registered $^{18}$FDG-PET and MRI images were inspected by two independent operators to ensure the adequacy of the co-registration. This co-registration was used to transform the t-statistic images from the native $^{18}$FDG-PET space to the native preoperative MRI space. The t-statistic images were transformed to the preoperative MRI space, were thresholded at an uncorrected $p$=0.005, and binarised to elicit the region of hypometabolism. Thresholding was undertaken in the MRI space, rather than the PET template space, as is conventional, to allow for the application of more accurate interpolation to a continuous image (i.e. the t-statistic image), as opposed to a discontinuous image (i.e. a thresholded t-statistic image). This resulted in a smoother hypometabolism boundary when applying the threshold in the higher resolution MRI space, rather than the low-resolution PET template space.

The amount of hypometabolism resected was calculated by masking the hypometabolism image in the MRI space by the resected tissue image. The total amount of hypometabolism was calculated by masking the hypometabolism image by the total cerebral volume image. The number of voxels in these masked images was summed and multiplied by the voxel size to derive the volume of resected hypometabolism and the volume of total hypometabolism. The percentage of the temporal lobe hypometabolism resected was calculated as: % temporal lobe hypometabolism resected = (volume of temporal lobe hypometabolism resected/total volume of preoperative hypometabolism) x 100. The proportion of temporal lobe tissue affected by hypometabolism was derived first: (volume of SPM temporal lobe hypometabolism resected x 100%)/total volume of MRI tissue resected, followed by the calculation of the proportion of "metabolically intact" temporal lobe tissue.

**Statistical Analysis**

Statistical analyses were performed using IBM SPSS 21.0 (IBM Corp., Armonk, NY). Univariable analyses (independent sample t-test, Mann-Whitney U and Fisher's exact tests) were performed to determine any differences in the verbal memory performance at a group level in patients with right and left MTLE and to explore the clinical and demographic characteristics of the patient cohort as well as the differences between the pre and postoperative neuroimaging variables. Raw scores for verbal memory tests attained before (at t1) and after the ATLR (at t2) were analysed. Partial correlation was

used to explore the relationship between the extent of the $^{18}$FDG-PET SPM hypometabolism and preoperative memory performance. Hierarchical linear regression was performed to examine the added value of pre and postoperative imaging variables in predicting postoperative memory deficits over and above the ATLR laterality and preoperative memory scores.

## 4.3 Results

The clinical and demographic characteristics of the patient cohort are summarised in Table 4.2. The details of the preoperative verbal memory performance relative to the MTLE laterality are featured in Table 4.1. The patients with right MTLE had significantly higher verbal memory scores attained on the subsets of RAVLT and PAL Hard pairs tests. The results of PAL Easy pairs did not differ between the two groups, regardless of the MTLE laterality ($p$=0.5).

**Table 4.1.** Preoperative verbal memory performance relative to mTLE laterality

| Test | Left mTLE N=33 | | Right mTLE N=38 | | *p* value |
|---|---|---|---|---|---|
| | *n* | *Mean (SD)* | *n* | *Mean (SD)* | |
| PAL Easy pairs | 31 | 14.5 (3.7) | 37 | 15.1 (3.6) | 0.5 |
| PAL Hard pairs | 31 | 4.4 (3.1) | 37 | 6.8 (2.9) | **0.002** |
| RAVLT list 5 | 25 | 10.6 (2.5) | 34 | 13.2 (1.8) | **<0.005** |
| RAVLT post-interference | 26 | 7.3 (3.8) | 34 | 10.8 (2.8) | **<0.005** |
| RAVLT 20-minute recall | 25 | 6.8 (3.7) | 33 | 10.6 (2.8) | **<0.005** |
| RAVLT total learning score | 29 | 42.7 (9.9) | 35 | 52.7 (7.7) | **<0.005** |

PAL – paired associated learning test, RAVLT – Ray Auditory Learning Test

**Table 4.2.** Clinical and demographic characteristics of the patient cohort.

| | Left mTLE N=33 | Right mTLE N=38 | *p value* |
|---|---|---|---|
| Females, n (%) | 15 (44.5) | 19 (51.4) | 0.8 |
| MRI findings HS n (%) | 30 (90.9) | 29 (76.3) | 0.1 |
| non-lesional | 3 (9.1) | 9 (23.7) | |
| Age of epilepsy onset – Median (IQR) | 19 (19.5) | 17 (18.8) | 0.8 |
| Duration of epilepsy- Median (IQR) | 19 (21) | 19.9 (23.5) | 0.9 |
| Age at neuropsychological assessment –Median (IQR) | 34 (17.5) | 41 (17.5) | 0.5 |
| FSIQ – Median (IQR) | 95 (20) | 100 (18) | 0.3 |
| Years of education –Median (IQR) | 10 (2) | 11(2) | 0.6 |

FSIQ – Full Scale Intelligence Quotient

The relationship between the extent of the $^{18}$FDG-PET SPM hypometabolism and the preoperative verbal memory scores was explored using partial correlation, controlled for the MTLE laterality, age at t1 and years of education (Table 4.3). There was no significant correlation observed between the memory scores obtained at t1 and the

extent of the ipsilateral temporal lobe hypometabolism except for a positive albeit weak correlation between the RAVLT post-interference scores ($r$=0.29, $p$=0.031) and RAVLT 20-minute delayed recall score ($r$=0.31, $p$=0.016).

**Table 4.3.** The relationship between temporal lobe hypometabolism and preoperative memory scores.

| *Test* | *n* | *r* | *p value* |
|---|---|---|---|
| PAL Easy pairs | 68 | 0.21 | 0.1 |
| PAL Hard pairs | 68 | 0.08 | 0.5 |
| RAVLT list A5 | 59 | 0.19 | 0.2 |
| RAVLT post-interference | 60 | 0.29 | **0.031** |
| RAVLT 20-minute recall | 58 | 0.31 | **0.016** |
| RAVLT total learning score | 64 | 0.17 | 0.2 |

PAL – paired associated learning test, RAVLT – Ray Auditory Learning Test

The extent of the ipsilateral temporal lobe hypometabolism was significantly greater in patients with the left MTLE ($p$<0.005). The patients with right MTLE had a significantly greater volume of temporal lobe tissue resected during the ATLR ($p$<0.005), including a significantly greater proportion of temporal lobe hypometabolism included in the resection ($p$=0.004), along with the amount of "metabolically intact" temporal lobe tissue removed, which again was significantly greater in the right MTLE patient cohort ($p$=0.001) (Table 4.4).

**Table 4.4.** The relationship between pre and postoperative imaging variables relative to MTLE/ATLR laterality.

| | *Left MTLE* *Median (IQR)* | *Right MTLE* *Median (IQR)* | *p values* |
|---|---|---|---|
| Volume of interictal $^{18}$FDG-PET TL SPM hypometabolism, $mm^3$ | $7.1 \times 10^3$ ($9.03 \times 10^3$) | $3.3 \times 10^3$ ($4.48 \times 10^3$) | **<0.005** |
| Volume of TL tissue resected, $mm^3$ | $16.4 \times 10^3$ ($9.53 \times 10^3$) | $21.9 \times 10^3$ ($9.4 \times 10^3$) | **<0.005** |
| % of TL hypometabolism included in the resection | 34.8 (31.1) | 63 (31.12) | **0.004** |
| % of non-hypometabolic resected TL tissue | 83.4 (12.41) | 93.1 (13.03) | **0.001** |

TL – temporal lobe

The ATLR laterality ($p$=0.007) and the preoperative verbal memory scores ($p$=0.01) were found to be the only predictors of postoperative decline in verbal memory performance. There was no relationship observed between the age at the operation and postoperative memory outcome ($p$=0.9). The patients with higher educational attainment were found to have significantly higher postoperative memory scores on RAVLT 20-minute delayed recall ($p$=0.037) and the RAVLT total subsets ($p$=0.038).

**Table 4.5.** Potential predictors of postoperative verbal memory deficits. *The results summary of hierarchical linear regression (p values obtained from final model).*

| Variables | PAL Easy pairs (n=50) | PAL Hard pairs (n=50) | RAVLT A5 list (n=44) | RAVLT post-interference (n=47) | RAVLT 20-minute recall (n=40) | RAVLT total learning score (n=49) |
|---|---|---|---|---|---|---|
| ATLR side | **0.005** | **<0.005** | **0.009** | **<0.005** | **0.007** | **0.007** |
| Neuropsychological testing scores preoperatively. | **<0.005** | **<0.005** | **0.014** | **<0.005** | **0.001** | **0.010** |
| Age at operation | 0.1 | 0.2 | 0.6 | 0.2 | 0.8 | 0.9 |
| Years of education | 0.8 | 0.1 | 0.4 | 0.3 | **0.037** | **0.038** |
| Volume of $^{18}$FGD-PET TL SPM hypometabolism, mm | 0.2 | 0.3 | 0.9 | 0.7 | 0.6 | 0.9 |

ATLR- anterior temporal lobe resection; TL – temporal lobe; PAL-paired associate learning; RAVLT – Rey Auditory Learning Test

The extent of the preoperative ipsilateral temporal lobe hypometabolism changes did not appear to influence the postoperative verbal memory performance ($p$=0.9) (Table 4.5). Similarly, there was no relationship seen between the extent of the resection of the ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism and postoperative memory decline ($p$=0.9). The verbal memory decline on RAVLT performance was associated with the ATLR laterality and the preoperative verbal memory scores (Table 4.6), except for PAL Hard pairs ($p$=0.2).

**Table 4.6.** Potential predictors of postoperative verbal memory decline following an ATLR. *The results summary of hierarchical linear regression (p values obtained from final model).*

| Variables | PAL Easy pairs (n=50) | PAL Hard pairs (n=50) | RAVLT A5 list (n=44) | RAVLT post-interference (n=47) | RAVLT 20-minute recall (n=40) | RAVLT total learning score (n=49) |
|---|---|---|---|---|---|---|
| ATLR side | **0.038** | **0.001** | **0.011** | **<0.005** | **0.009** | **0.005** |
| Scores at t1 | **0.001** | 0.2 | **0.015** | **<0.005** | **0.001** | **0.007** |
| Age at operation | 0.3 | 0.1 | 0.6 | 0.2 | 0.8 | 0.9 |
| Years of education | 0.9 | 0.1 | 0.4 | 0.3 | **0.041** | **0.034** |
| % of $^{18}$FGD-PET TL hypometabolism resected | 0.4 | 0.2 | 0.6 | 0.9 | 0.9 | 0.9 |

ATLR- anterior temporal lobe resection; TL – temporal lobe; PAL-paired associate learning; RAVLT – Rey Auditory Learning Test

The estimated temporal lobe tissue resection volume and the amount of cerebral tissue with no apparent evidence of $^{18}$FDG-PET hypometabolism included in the temporal lobe resection did not predict postoperative verbal memory decline over and above the ATLR laterality and preoperative verbal memory scores (Table 4.7 & 4.8).

**Table 4.7.** Predictive value of the extent of MRI tissue resection on postoperative verbal l performance. *The results summary of hierarchical linear regression (p values obtained from final model).*

| Variables | PAL Easy pairs (n=50) | PAL Hard pairs (n=50) | RAVLT A5 list (n=44) | RAVLT post-interference (n=47) | RAVLT 20-minute recall (n=40) | RAVLT total learning score (n=49) |
|---|---|---|---|---|---|---|
| ATLR side | **0.049** | **<0.005** | **0.019** | **0.001** | **0.011** | **0.027** |
| Scores at t1 | **0.001** | **<0.005** | **0.015** | **<0.005** | **0.001** | **0.011** |
| Age at operation | 0.2 | 0.1 | 0.5 | 0.1 | 0.8 | 0.9 |
| Years of education | 0.8 | 0.7 | 0.4 | 0.3 | **0.043** | **0.040** |
| Volume of MRI tissue resection, mm$^3$ | 0.6 | 0.1 | 0.7 | 0.4 | 0.9 | 0.5 |

ATLR- anterior temporal lobe resection; PAL-paired associate learning; RAVLT – Rey Auditory Learning Test

**Table 4.8.** Predictive value of the extent of non-hypometabolic brain included in the resection on post-operative verbal memory performance. *The results summary of hierarchical linear regression (p values obtained from final model).*

| Variables | PAL Easy pairs (n=50) | PAL Hard pairs (n=50) | RAVLT A5 list (n=44) | RAVLT post-interference (n=47) | RAVLT 20-minute recall (n=40) | RAVLT total learning score (n=49) |
|---|---|---|---|---|---|---|
| ATLR side | **0.008** | **<0.005** | **0.008** | **<0.005** | **0.006** | **0.010** |
| Scores at t1 | **<0.005** | **<0.005** | **0.015** | **<0.005** | **0.001** | **0.015** |
| Age at operation | 0.2 | 0.1 | 0.6 | 0.2 | 0.8 | 0.9 |
| Years of education | 0.8 | 0.1 | 0.4 | 0.3 | **0.041** | **0.043** |
| Proportion of non-hypometabolic brain included in the resection | 0.4 | 0.1 | 0.9 | 0.6 | 0.8 | 0.6 |

ATLR- anterior temporal lobe resection; PAL-paired associate learning; RAVLT – Rey Auditory Learning Test

## 4.4 Discussion

This study identified significant differences in $^{18}$FDG-PET hypometabolism patterns in patients with left versus right MTLE, whereby the patients with left MTLE had a significantly greater extent of ipsilateral temporal lobe hypometabolism detected preoperatively (Table 4.4). The finding of differential metabolic asymmetry in left versus right MTLE patients was consistent with the findings of previous functional and metabolic connectivity studies reporting laterality specific differentiality in aberrant patterns in patients with left versus right MTLE (Besson et al., 2014; Haneef et al., 2014). Convergent with the previous research was the finding of significantly impaired verbal memory performance observed in patients with left MTLE (Berg et al., 2010). However, contrary to the previous reports of ipsilateral $^{18}$FDG-PET hypometabolism being associated with impaired memory scores in MTLE patients (Arnold et al., 1996; Knopman et al., 2015; Rausch et al., 1994), this study overall did not demonstrate a correlation between the extent of the ipsilateral temporal hypometabolism and the preoperative verbal memory scores in this patient cohort. The latter could be due to methodological differences and the heterogeneity of TLE cohorts studied previously. The temporal lobe parcellation was carried out by some research groups looking into the association of task-specific memory performance in relation to the topography of the $^{18}$FDG-PET hypometabolism (Weintrob et al., 2002), whereas no temporal lobe parcellation was carried out in this study to allow for a higher fidelity to the real world

clinical setting and the temporal lobe was considered as a whole in light of previous reports of both, mesial and lateral temporal lobe structures exhibiting reduced $^{18}$FDG uptake in patients with MTLE (Henry et al., 1993).

It is not inconceivable that the intriguing finding of a weak positive correlation between the extent of the ipsilateral temporal lobe hypometabolism and the RAVLT post-interference ($r$=0.29, $p$=0.031) as well as the RAVLT 20-minute delayed recall total score ($r$=0.31, $p$=0.016) could be associated with the reorganisation of memory function previously described by Hillary *et al* who suggested a compensatory shift of neurocognitive processing as a result of adaptation mechanisms supporting the resilience of the large scale networks (Hillary & Grafman, 2017). Hamberger *et al*, for example, previously reported language function reorganisation in patients with hemispheric dominant TLE (Hamberger et al., 2007).

This study demonstrated that the extent of the resection of the $^{18}$FDG-PET hypometabolism did not predict postoperative verbal memory deficits over and above long-established predictors such as ATLR laterality and preoperative verbal memory performance. It has been postulated that postoperative memory deficits would largely depend on the adequacy of the removed temporal lobe and on the cognitive reserve of the contralateral hippocampus (Chelune et al., 1991). $^{18}$FDG-PET hypometabolism in patients with epilepsy reflects the large-scale network dysfunction, which in this patient cohort tends to extend beyond the actual boundaries of the ipsilateral temporal lobe, including bitemporal lobe involvement (Chassoux et al., 2016).

There has been growing evidence of extratemporal, including default mode networks being implicated in neurocognitive impairment in patients with epilepsy (Laurent et al., 2020), notwithstanding previous reports by Jokeit *et al* of bifrontal $^{18}$FDG-PET hypometabolism being associated with neurocognitive impairment in a TLE patient cohort (Jokeit et al., 1997). It would therefore have been challenging to ascertain as to exactly what extent the temporal lobe $^{18}$FDG-PET hypometabolism may have influenced the verbal memory encoding without a granular account of $^{18}$FDG uptake within the temporal lobe itself. In addition, $^{18}$FDG-PET hypometabolism being the sequelae of an epileptic network disorder in patients with MTLE and while it offers valuable insights into the epileptogenicity process and the distribution of aberrant epileptic networks, it may not reflect to the same degree the neurobiological basis for neurocognitive deficits in this patient cohort. Considering that $^{18}$FDG uptake tends to

improve following successful epilepsy surgery (Takaya et al., 2009), one could expect that the bearing of reduced $^{18}$FDG uptake on preoperative cognition would also be reversible to some extent. This makes it challenging to infer the likelihood of postoperative memory deficits with a high degree of precision befitting the needs of preoperative patient counseling.

Furthermore, considering the previous reports of reduced temporal lobe resections being associated with preserved memory function and in light of the functional adequacy of the removed tissue influencing postoperative neurocognitive deficits (Chelune, 1995; Helmstaedter et al., 2011), one would expect that the less extensive the resection of the metabolically intact tissue would result in less postoperative memory decline. This prediction however could only be possible if one could account with precision, as to what extent the hypometabolic tissue contributes to the overall memory performance so that the true functional adequacy could be ascertained to begin with. This study demonstrated no association between the extent of the resected temporal lobe volume, both total and metabolically intact, and the postoperative verbal memory deficits, thus adding yet another layer of uncertainty as to what might constitute the optimal temporal lobe resection volume in patients undergoing MTLE surgery, from a neurocognitive rather than a seizure control point of view.

Considering that the $^{18}$FDG-PET hypometabolic changes, by and large, reflect the complexity of the epileptogenic networks implicated in the drug resistant MTLE those are therefore unlikely to assist with the prognostication of postoperative memory deficits over and above the long established predictors, such as the laterality of the ATLR and the preoperative verbal memory performance scores (Baxendale et al., 2006; Stroup et al., 2003). The suggestion of a wider, extratemporal network involvement on memory function in patients with epilepsy, could potentially limit the yield of the studies focusing exclusively on the ipsilateral lobe changes to identify reliable predictors of postoperative memory decline in patients with TLE. The findings of Sidhu *et al* demonstrating the role of the contralateral hippocampus in postoperative memory organisation and absorbing the cognitive hit following an ATLR, regardless of hemispheric dominance (Sidhu et al., 2016), could not be accounted for on this occasion.

In light of the findings outlined in Chapter 3, whereby the laterality specific differential

$^{18}$FDG-PET hypometabolism patterns were strong predictors of postoperative seizure recurrence, with heightened risk of postoperative seizure recurrence seen in right MTLE patients with bitemporal $^{18}$FDG-hypometabolism, I set out to explore the potential neurocognitive value of this observation. The findings of the study exploring the role of arbitrary learning as a neurocognitive biomarker of bitemporal dysfunction with the involvement of the left temporal lobe in patients with right MTLE and evidence of bitemporal $^{18}$FDG-PET hypometabolism are outlined in Chapter 5.

Chapter 5

# Arbitrary relational learning as a candidate neurocognitive marker of left mesial temporal lobe dysfunction in right MTLE

## 5.1 Introduction

$^{18}$FDG-PET is the most established nuclear imaging modality widely utilised in the evaluation of surgical candidates, serving as a metabolic biomarker of neural network dysfunction in patients with MTLE (Chassoux et al., 2004; Guedj et al., 2015; Knowlton, 2006; Lamarche et al., 2016). Furthermore, the presence of bitemporal $^{18}$FDG-PET hypometabolism (BTH) in patients with unilateral drug resistant MTLE was found to indicate a wider neural network dysfunction implicated in MTLE epileptogenesis, thus heralding a heightened risk of seizure recurrence following an ATLR (Choi et al., 2003; Joo et al., 2004; Kim et al., 2006; Wong et al., 2010).

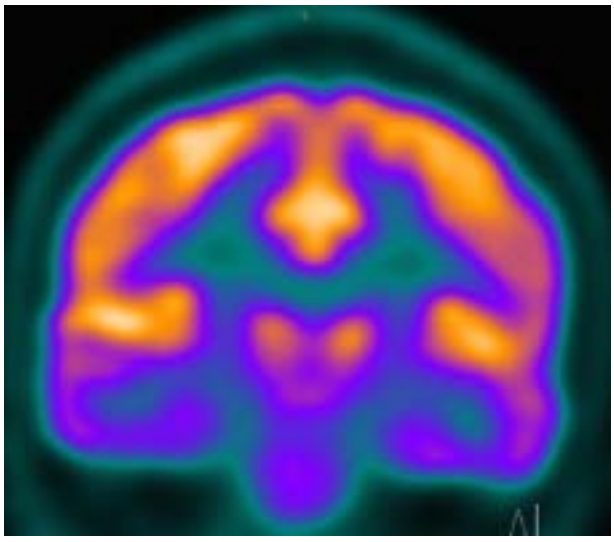


**Figure 5.1: Bitemporal $^{18}$FDG-PET hypometabolism in a patient with unilateral right MTLE.**

Example of bitemporal $^{18}$FDG-PET hypometabolism in a patient with unilateral right MTLE.

Furthermore, based on converging findings of multimodal neuroimaging studies, it has become apparent that right and left MTLE appear to represent two distinct neurobiological entities. In patients with left MTLE, the ipsilateral epileptogenic networks tend to exhibit a more extensive, largely confined to the ipsilateral temporal lobe, pattern of epileptic network dysfunction, which in turn results in neurometabolic manifestations detected by $^{18}$FDG-PET (Vanicek et al., 2016). In right MTLE patients, a pattern of wider epileptogenic network involvement, including bitemporal functional connectivity changes has been commonly observed (Englot et al., 2016; Vanicek et al., 2016). This has been corroborated by the findings of previous molecular imaging studies, e.g. $^{18}$FDG-PET and SPECT (Chassoux et al., 2016; Hogan et al., 2006), which lend further weight to the observations resulting from the nascent connectomics based research exploits (Coito et al., 2015; Haneef et al., 2013).

From a practical standpoint, further attempts have been made to understand the clinical implications of this observation. The findings of this study outlined in Chapter 3 suggest that right MTLE patients with evidence of bitemporal $^{18}$FDG-PET hypometabolism are at a 5-fold heightened risk of seizure recurrence following an ATLR. Considering the previous reports of interconnections between the mesial temporal regions, it is possible that bitemporal epileptic networks could influence verbal memory performance or affect the functional reserve of the contralateral hippocampus (Chelune, 1995) in patient cohorts with bitemporal $^{18}$FDG-PET hypometabolism. Dupont *et al* have previously described an association between bitemporal aberrant connectivity patterns and impaired verbal memory performance in patients with right MTLE (Dupont et al., 2002). There have been numerous reports of ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism being associated with memory deficits in patients with left MTLE (Griffith et al., 2004; Knopman et al., 2015; Rausch et al., 1994; Weintrob et al., 2002), however the neurocognitive sequelae of bitemporal $^{18}$FDG-PET hypometabolism has not been examined. Considering that arbitrary relational learning impairment is a hallmark of mesial temporal lobe dysfunction in patients with left MTLE (Kennepohl et al., 2007; Lillywhite et al., 2007; Saling et al., 1993; Weintrob et al., 2002) this study set out to explore the relationship between bitemporal hypometabolism and arbitrary learning performance in patients with right unilateral drug resistant MTLE.

## 5.2 Methods

### Study participants

A total of 71 patients who underwent an ATLR for drug resistant MTLE between 2001 and 2014 were included in this two-center study. All patients were prospectively identified from the Comprehensive Epilepsy Programmes at the Royal Melbourne and Austin Hospitals as previously described (Berkovic et al., 1995; Carne et al., 2007). The patients included in this study were: (1) aged 16 and above, (2) fluent English speakers, (3) had the FSIQ ≥70 and (4) had no symptoms of an active psychiatric disorder at the time of the preoperative neuropsychological assessment. All patients had evidence of at least ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism and the radiological finding of unequivocal concordant hippocampal sclerosis or no obvious epileptogenic lesion identified on preoperative MRI. The study was approved by the Human Research Ethics Committees at both sites.

### Neuropsychological evaluation

All patients underwent a comprehensive preoperative neuropsychological assessment performed by specialist clinical neuropsychologists as part of their presurgical evaluation. Verbal memory performance was assessed using the RAVLT (Rey, 1941) and the verbal PAL tests (Wechsler, 1945) as described previously (Saling et al., 1993) (Weintrob et al., 2002) and outlined in Chapter 2.

### $^{18}$FDG-PET acquisition and post-processing

Interictal $^{18}$FDG-PET scans were acquired as part of the routine presurgical evaluation on a Phillips Allegro (Phillips Medical Systems, Best, The Netherlands) with voxel size 2x2x2mm and a GE Discovery 690 (GE Medical Systems Milwaukee, WI) with voxel size 1.82x1.82x3.27mm. Post-acquisition processing was conducted using Statistical Parametric Mapping software (Penny, 2006) (SPM version 12, Wellcome Trust Centre for Neuroimaging, University College London, UK) mounted on a MATLAB R2012-A (MathWorks, Natick, MA, U.S.A.).

The images of the patients and that of 20 healthy matched controls were reoriented and non-linearly normalised to a built-in SPM PET template using the default parameters within SPM Old Normalise algorithm. Normalised images were smoothed with a 8mm full-width at half-maximum (FWHM) Gaussian kernel. For each patient, a General Linear Model (GLM) was constructed that compared the patient to the 20 controls at

each voxel. Modelling was conducted at every voxel within a whole brain mask (excluding CSF and the cerebellum), obtained from the Automated Anatomic Labeling atlas using WFU Pick Atlas toolbox (The Functional MRI Laboratory, Wake Forest University School of Medicine) (Tzourio-Mazoyer et al., 2002). The SPM thresholded images were inspected for the presence of BTH by an operator blinded to the outcome of the neuropsychological assessment. The right MTLE patients with BTH were categorised as BTH-"+ ".

**Statistical Analysis**

Statistical analysis was performed using IBM SPSS 21.0 (IBM Corp., Armonk, NY). Univariable analyses (independent sample t-tests, Mann-Whitney U and Fisher's exact tests) were performed to characterise verbal memory performance at a group level in patients with right and left MTLE using the raw scores resulting from the neuropsychological assessment. The comparative analysis of the differences in verbal memory performance was carried out using GLM, controlling for patient age at the time of the neuropsychological evaluation and years of formal education. The patients were assigned into three categories:

Group 1 – patients with left MTLE, regardless of BTH; Group 2 – patients with right MTLE and no evidence of BTH and Group 3, the reference group – the patients with right MTLE-BTH-"+".

## 5.3 Results

As outlined in Table 5.1, patient demographic and clinical characteristics did not differ between the left and right MTLE cohorts. The scores of RAVLT and PAL Hard pairs testing performed as part of the verbal memory assessment were significantly higher in patients with right MTLE, whereas the outcome of the PAL Easy pairs testing did not discriminate between the left and right MTLE groups (Table 5.2).

**Table 5.1.** Demographic and clinical characteristics of the three patient groups

| | Left MTLE N=33 | Right MTLE N=38 | *p value* |
|---|---|---|---|
| Females, n (%) | 15 (44.5) | 19 (51.4) | 0.8 |
| MRI findings HS n (%) | 30 (90.9) | 29 (76.3) | 0.1 |
| non-lesional | 3 (9.1) | 9 (23.7) | |
| Age of epilepsy onset – Median (IQR) | 19 (19.5) | 17 (18.8) | 0.8 |
| Duration of epilepsy- Median (IQR) | 19 (21) | 19.9 (23.5) | 0.9 |
| Age at neuropsychological assessment –Median (IQR) | 34 (17.5) | 41 (17.5) | 0.5 |
| FSIQ – Median (IQR) | 95 (20) | 100 (18) | 0.3 |
| Years of education –Median (IQR) | 10 (2) | 11(2) | 0.6 |

FSIQ – full scale intelligence quotient

**Table 5.2.** Verbal memory performance depending on MTLE laterality

| Test | Left MTLE | | Right MTLE | | *p* value |
|---|---|---|---|---|---|
| | *n* | *Mean (SD)* | *n* | *Mean (SD)* | |
| PAL Easy pairs | 31 | 14.5 (3.7) | 37 | 15.1 (3.6) | 0.5 |
| Hard pairs | 31 | 4.4 (3.1) | 37 | 6.8 (2.9) | 0.002 |
| RAVLT (Trial 5) | 25 | 10.6 (2.5) | 34 | 13.2 (1.8) | <0.001 |
| RAVLT post-interference | 26 | 7.3 (3.8) | 34 | 10.8 (2.8) | <0.001 |
| RAVLT 20-minute recall | 25 | 6.8 (3.7) | 33 | 10.6 (2.8) | <0.001 |
| RAVLT total learning score | 29 | 42.7 (9.9) | 35 | 52.7 (7.7) | <0.001 |

PAL Easy pairs – paired associates learning easy pairs test, PAL Hard pairs – paired associates learning hard pairs test, RAVLT – Rey Auditory Verbal Learning Test

The patient categories depending on the presence/absence of bitemporal hypometabolism are outlined in Table 5.3.

**Table 5.3.** The distribution of patient categories depending on the presence/absence of BTH $^{18}$FDG-PET hypometabolism.

| *Laterality of MTLE +/-BTH* | *n (%)* |
|---|---|
| Left (group 1) | 33 (46.5) |
| Right (group 2) | 22 (31) |
| Right-BTH-"+" (group 3) | 16 (22.5) |

BTH– bitemporal hypometabolism

The between-groups comparison results of verbal memory performance in reference to the right MTLE-BTH-"+" group and the right MTLE with no evidence of BTH, are shown in Tables 5.4 and 5.5, respectively. The verbal memory scores resulting from RAVLT and PAL Easy pairs assessments were significantly higher in patients with right MTLE, irrespective of BTH, compared to those in left MTLE patients ($p$=0.001). In relation to the outcome of the PAL Hard pairs assessment, the scores obtained by right MTLE patients without evidence of BTH were significantly higher (M=7.32, SD=2.8) than those in patients with left MTLE (M=4.4, SD=3.1) ($p$<0.001), whereas the scores obtained by right MTLE-BTH-"+" patient cohort (M=5.9, SD=3.0) did not differ from those obtained in left MTLE patients (M=4.4, SD=3.1)($p$=0.1). There was a trend for right MTLE patients to attain higher scores on PAL Hard pairs testing than their counterparts with right MTLE-BHT-"+", albeit not reaching statistical significance ($p$=0.1).

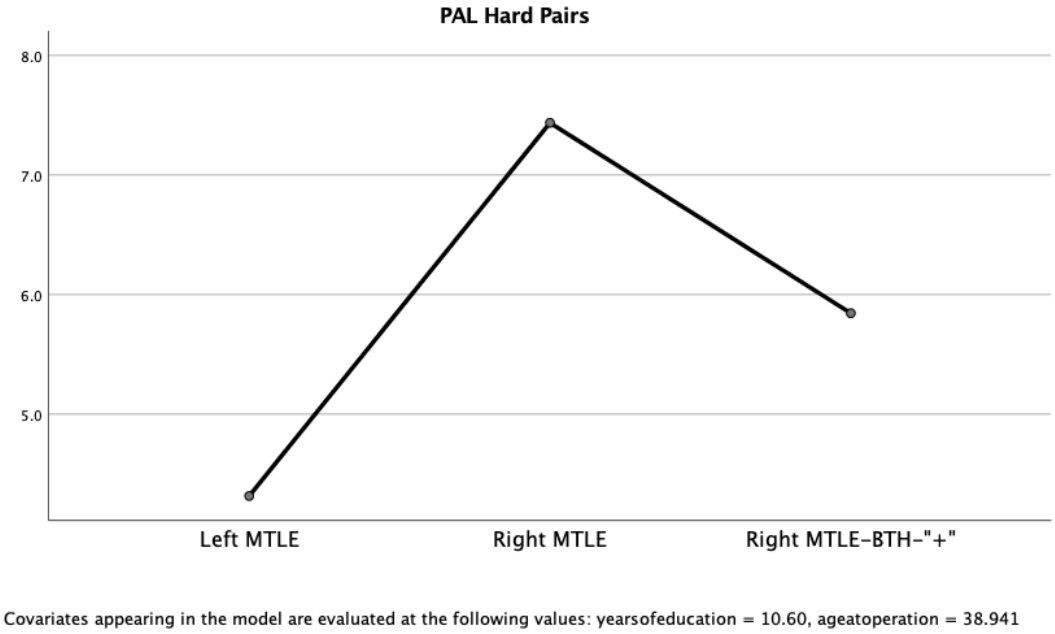



**Figure 5.2: Arbitrary learning as a candidate neurocognitive biomarker of left mesial temporal lobe dysfunction in patients with right MTLE and bitemporal $^{18}$FDG-PET hypometabolism**

Example of PAL Hard pairs performance in patients with right MTLE depending on presence/absence of bitemporal $^{18}$FDG-PET hypometabolism

**Table 5.4.** Between-group comparison of verbal memory performance. *(Ref: right MTLE-BTH-"+").*

***PAL Hard pairs***

| *category* | *n* | *Mean (SD)* | *Difference* | *95% CI* | *p* |
|---|---|---|---|---|---|
| 1 | 31 | 4.4 (3.1) | -1.53 | -3.40 to 0.34 | 0.1 |
| 2 | 22 | 7.3 (2.8) | 1.59 | -0.43 to 3.60 | 0.1 |
| Ref: 3 | 15 | 5.9 (3.0) | | | |

***RAVLT list 5***

| *category* | *n* | *Mean (SD)* | *Difference* | *95% CI* | *p* |
|---|---|---|---|---|---|
| 1 | 25 | 10.6 (2.5) | -2.56 | -4.07 to -1.06 | 0.001 |
| 2 | 21 | 13.3 (1.6) | 0.16 | -1.41to1.72 | 0.8 |
| Ref: 3 | 13 | 13.2 (2.0) | | | |

***RAVLT post-interference***

| *category* | *n* | *Mean (SD)* | *Difference* | *95% CI* | *p* |
|---|---|---|---|---|---|
| 1 | 26 | 7.3 (3.8) | -4.16 | -6.43 to -1.89 | 0.001 |
| 2 | 21 | 10.6 (2.8) | -0.67 | -3.02 to 1.7 | 0.6 |
| Ref: 3 | 13 | 11.2 (2.9) | | | |

***RAVLT 20-minute recall***

| *category* | *n* | *Mean (SD)* | *Difference* | *95% CI* | *p* |
|---|---|---|---|---|---|
| 1 | 25 | 6.8 (3.7) | -4.06 | -6.31to -1.80 | 0.001 |
| 2 | 20 | 10.5 (2.9) | -0.33 | -2.67 to 2.02 | 0.8 |
| Ref: 3 | 13 | 10.7 (2.7) | | | |

***RAVLT total learning score***

| *category* | *n* | *Mean (SD)* | *Difference* | *95% CI* | *p* |
|---|---|---|---|---|---|
| 1 | 29 | 42.7 (9.9) | -12.1 | -18.03 to -6.22 | <0.001 |
| 2 | 22 | 51.7 (7.1) | -2.69 | -8.89 to 3.52 | 0.4 |
| Ref: 3 | 13 | 54.4 (8.7) | | | |

PAL Easy pairs – paired associates learning easy pairs test, PAL Hard pairs – paired associates learning hard pairs test, RAVLT – Rey Auditory Verbal Learning Test; BTH – bitemporal hypometabolism

*category 1 – patients with **left MTLE** (irrespective of BTH)*
*category 2 - patients with **right MTLE** with no evidence of BTH*
*category 3 - patients with **right MTLE-BTH-"+"***

**Table 5.5.** Between-group comparison of verbal memory performance *(Ref: right MTLE with no evidence of BTH).*

***PAL Hard pairs***

| *category* | *n* | *Mean (SD)* | *Difference* | *95% CI* | *p* |
|---|---|---|---|---|---|
| 1 | 31 | 4.36 (3.1) | -3.12 | -4.79 to -1.45 | <0.001 |
| 2 | 15 | 5.93 (3.0) | -1.59 | -3.60 to 0.43 | 0.1 |
| Ref: 3 | 22 | 7.32 (2.8) | | | |

***RAVLT list 5***

| *category* | *n* | *Mean (SD)* | *Difference* | *95% CI* | *p* |
|---|---|---|---|---|---|
| 1 | 25 | 10.64 (2.5) | -2.72 | -4.04 to -1.40 | <0.001 |
| 2 | 13 | 13.15 (2) | -0.16 | -1.72 to 1.41 | 0.8 |
| Ref: 3 | 21 | 13.29 (1.6) | | | |

***RAVLT post-interference***

| *category* | *n* | *Mean (SD)* | *Difference* | *95% CI* | *p* |
|---|---|---|---|---|---|
| 1 | 26 | 7.31 (3.8) | -3.49 | -5.46 to -1.52 | 0.001 |
| 2 | 13 | 11.15 (2.9) | 0.67 | -1.68 to 3.02 | 0.6 |
| Ref: 3 | 21 | 10.62 (2.8) | | | |

***RAVLT 20-minute recall***

| *category* | *n* | *Mean (SD)* | *Difference* | *95% CI* | *p* |
|---|---|---|---|---|---|
| 1 | 25 | 6.84 (3.7) | -3.73 | -5.70 to -1.76 | <0.001 |
| 2 | 13 | 10.69 (2.7) | 0.33 | -2.02 to 2.67 | 0.8 |
| Ref: 3 | 20 | 10.50 (2.9) | | | |

***RAVLT total learning score***

| *category* | *n* | *Mean (SD)* | *Difference* | *95% CI* | *p* |
|---|---|---|---|---|---|
| 1 | 29 | 42.72 (9.9) | -9.44 | -14.46 to -4.42 | <0.001 |
| 2 | 13 | 54.39 (8.7) | 2.69 | -3.52 to 8.89 | 0.4 |
| Ref: 3 | 22 | 51.68 (7.1) | | | |

PAL Easy pairs – paired associates learning easy pairs test, PAL Hard pairs – paired associates learning hard pairs test, RAVLT – Rey Auditory Verbal Learning Test; BTH – bitemporal hypometabolism

*category 1 – patients with **left MTLE** (irrespective of BTH)*
*category 2 - patients with **right MTLE-BTH-"+"***
*category 3 - patients with **right MTLE** with no evidence of BTH*

## 5.4 Discussion

The aim of this study was to investigate the neurocognitive correlates of BTH, arbitrary learning in particular and in patients with drug resistant right MTLE. There has been mounting evidence in support of the laterality-specific differential epileptogenic networks being implicated in the development of right versus left MTLE (Chassoux et al., 2016; Englot et al., 2016; Hogan et al., 2006). The findings of this study demonstrated significantly higher rates of verbal memory impairment in patients with left MTLE on a list learning task (RAVLT) and arbitrary relational learning (PAL Hard pairs), consistent with previous research (Jeyaraj et al., 2013; Kneebone et al., 1997). On the other hand, the non-discriminatory performance of PAL Easy pairs is not entirely unexpected and further emphasises the need for task-specific rather than the "global" approach to memory testing in patients with MTLE (Loring et al., 2008; Raspall et al., 2005; Saling, 2009).

By the same token, with arbitrary relational learning being the hallmark of left mesial temporal lobe dysfunction impaired performance on PAL Hard pairs testing is a common finding in patients with left MTLE (Saling et al., 1993; Weintrob et al., 2002), however to our knowledge, protosemantic learning impairment has not been previously demonstrated in patients with right MTLE. There has been growing evidence of the differential hippocampal network involvement depending on the MTLE laterality. Li *et al* found that left MTLE patients had significantly higher rates of functional connectivity aberrances seen within the anterior hippocampal networks, whereas right MTLE patients were observed to have wider changes, involving both anterior and posterior hippocampal networks, notwithstanding the evidence of altered connectivity in the contralateral hippocampal formation (Chiang et al., 2014; Li et al., 2017).

In addition, impaired verbal memory performance observed by Dupont *et al* in right MTLE patients in association with differentially altered connectivity patterns, prompted further inquiry into the potential neurocognitive correlates of bitemporal neuronal dysfunction in patients with right MTLE. Remarkably, the finding of impaired PAL Hard pairs learning in right MTLE-BTH-"+" patients could indicate a functional inadequacy of the metabolically compromised left temporal lobe in this patient group. It has been proposed that epileptic discharges propagating between homotopic mesial temporal lobe structures in patients with drug resistant focal epilepsy may alter the neuronal circuitry of these structures without impacting on the neocortical temporal lobe structures (Lacuey et al., 2015; Pereira et al., 2010), which could explain the unaffected right MTLE patient performance on semantically loaded tasks, yet again highlighting the need for the use of specific neurocognitive markers, reflecting an intratemporal memory specialisation and task-specific deficits in patients with MTLE (Saling, 2009; Yoon et al., 2003).

In this study, PAL Hard pairs scores attained by the patients with right MTLE-BTH-"+" were overall lower than those in patients with right MTLE without evidence of BTH, however the difference in PAL Hard pairs scores between the two groups did not reach statistical significance. The findings of this study could potentially influence the selection of surgical candidates and identify those at risk of significant postoperative memory decline early on into the presurgical evaluation. It has long been recognised that the extent of the postoperative memory decline would largely depend on the functional adequacy of the to-be-removed temporal lobe structures responsible for the preoperative memory performance and on the functional reserve of the contralateral

hippocampus (Chelune, 1995). Sidhu *et al* demonstrated the importance of postoperative memory reorganisation, whereby the extent of the postoperative memory decline relies on the functional capacity of the contralateral hippocampus to take on the memory encoding function following the ATLR (Sidhu et al., 2013). Therefore, further large cohort studies are warranted to explore the use of an arbitrary relational learning test as a candidate biomarker of the mesial left temporal lobe dysfunction in patients with right MTLE and bitemporal $^{18}$FDG-PET hypometabolism. Should the study render confirmatory findings, the finding of bitemporal hypometabolism in patients with right MTLE could prompt further evaluation of the left hippocampus cognitive reserve. This in turn would improve the identification of epilepsy surgery candidates at a heightened risk of postoperative cognitive decline and trigger the prehabilitation measures in preparation for epilepsy surgery.

Furthermore, it would also be important to ascertain the reversibility of the protosemantic memory deficits in right MTLE patients following an ATLR, which would further emphasise the need for timely epilepsy surgery intervention as one could be oblivious to the soaring interest rates of neurocognitive costs while trying to save on the neurocognitive bill of epilepsy surgery by delaying the only evidence based treatment option for patients with drug resistant epilepsy.

# Chapter 6

# The lateralising value of neurocognitive tests in epilepsy surgery candidates: from material to task-specificity

## 6.1 Introduction

A comprehensive neuropsychological assessment constitutes an integral part of the presurgical evaluation and plays a major role in assisting with seizure onset lateralisation and localisation as well predicting postoperative memory deficits (Jones-Gotman et al., 2014; Jones-Gotman et al., 2010; Wilson et al., 2015). It has been previously shown that not an insignificant proportion of neurocognitive assessments routinely used in the evaluation of epilepsy surgery candidates have been of rather limited lateralising value (Barr, 1997; Jeyaraj et al., 2013; Kneebone et al., 1997; Ogden-Epker & Cullum, 2001; Raspall et al., 2005). The field of epileptology underwent a major transformation benefitting from the advances in SEEG and novel neuroimaging techniques allowing for the reconceptualisation of epilepsy as being a large scale network disorder (Bartolomei et al., 2017; Englot et al., 2016). Furthermore, it has been shown that in MTLE, including MTLE-HS, the epileptogenic networks extend beyond the boundaries of the structural abnormalities visualised on preoperative neuroimaging (Bartolomei et al., 2008). The heterogeneity of epileptogenic networks implicated in the development of MTLE has been consistently demonstrated by the findings of SEEG and neuroimaging studies (Chassoux et al., 2016; Kahane & Bartolomei, 2010). In addition, the differential aberrancies of the altered connectivity patterns depending on the laterality of the MTLE have also been observed (Dupont et al., 2002; Englot et al., 2016).

Furthermore, previous findings suggestive of intratemporal memory specialisation in patients with left MTLE (Saling et al., 1993; Weintrob et al., 2002; Weintrob et al., 2007) have been replicated by subsequent DTI and fMRI studies (Voets et al., 2009; Li et al., 2017; Voets et al., 2012). Considering the neuroanatomical and functional evidence of differential hemispheric lateralisation properties as well as the established interplay between the language lateralisation and verbal memory constructs, the concept of material-specific memory organisation has been dominating the field of neuropsychology for decades (Scoville, 1957). With the majority of neuropsychological

tests currently employed in the presurgical evaluation (Vogt et al., 2017) originating in the era of material-specificity, their discriminatory value in disentangling task-specific deficits resulting from the intricate involvement of the heterogeneous epileptogenic MTLE networks has been rather limited (Barr, 1997; Jeyaraj et al., 2013; Kneebone et al., 1997; Raspall et al., 2005).

A recent survey of 25 European epilepsy centres demonstrated that the RAVLT was one of the commonest neuropsychological assessment tools used for the evaluation of verbal memory performance, while the Boston Naming Test (BNT) and the Rey-Ostherrieth Complex Figure Test (RCFT) were widely employed for the evaluation of language and visuospatial abilities, respectively (Vogt et al., 2017). In this two centre study, we aimed to explore the discriminative properties and lateralising yield of the individual neurocognitive tests most commonly administered in the evaluation of surgical candidates.

## 6.2 Methods

**Participants**

A total of 119 patients with favourable seizure outcomes following an anterior temporal lobe resection for drug resistant MTLE between 1998 and 2014 were included in this study. Only the patients who were rendered seizure free following the ATLR (Engel's class I) were included to assure the accuracy of assessing the role of the neurocognitive tests in seizure onset lateralisation (Kneebone et al., 1997). Patients were identified from prospectively administered databases based on the following inclusion criteria: (1) age at the time of epilepsy surgery ≥ 16 years; (2) fluent English speaker; (3) estimated IQ ≥ 70; (4) HS or no epileptogenic lesion identified on preoperative MRI; (5) no previous neurosurgery; (6) no symptoms of active psychiatric illness at the time of neuropsychological testing; (7) at least 2 years of postoperative follow up. Presurgical evaluation protocols employed at both centres have been described elsewhere (Berkovic et al., 1995; Carne et al., 2004). The study was approved by the Human Research Ethics Committees as described in the Common Methodology section of this thesis.

**Neuropsychological evaluation**

A Comprehensive neuropsychological assessment was carried out as part of the patients' presurgical evaluation. The RAVLT (Rey, 1941), PAL Hard and Easy pairs (Wechsler, 1945), the RCFT (the copy trial and delayed recall) (Rey, 1941) and the BNT (Kaplan et al., 1983) were the most commonly administered tests for verbal,

visuospatial memory assessment and the evaluation of language ability, respectively. The patients' handedness was ascertained on the basis of a clinical interview. Language fMRI was carried out in patients undergoing a left ATLR, manifest left handers and the patients with familial sinistrality.

**Statistical Analysis**

Statistical analysis was performed using IBM SPSS 21.0 (IBM Corp., Armonk, NY). Univariable analyses (independent-samples t-test, Mann-Whitney U and Fisher's exact test) were employed to explore patient sample characteristics and group differences on neurocognitive testing in patients with left and right mTLE, using the raw scores. The univariable (unadjusted) receiver operating characteristic (ROC) curve analysis was carried out to explore the lateralising properties of an individual's neuropsychological tests (Metz, 1978; Zweig & Campbell, 1993), followed by a second model (adjusted), controlling for age and the years of education. Cut-offs, sensitivity and specify metrics were determined using Youden's Index (YI) (Youden, 1950). Positive and negative predictive values (PPV, NPV) were computed.

## 6.3 Results

There were 63 patients (52.9%) with left and 56 patients (47.1%) with right MTLE, of whom 55 (46.2%) were males and 64 (53.8%) were females. Six patients (5%) were manifest left-handers. Preoperative MRI findings were consistent with HS in 115 (96.6%) and in 4 patients (3.4%) there was no identifiable MRI lesion detected. The mean sample age was 38 years (SD=12.1). The left MTLE patients had a significantly earlier age of epilepsy onset ($p$=0.015). The years of postoperative follow-up ranged from 2 to 18 years (Mean=6.6, SD=4.1). The patient characteristics in the left and right MTLE cohorts are outlined in Table 6.1.

**Table 6.1.** Patients' characteristics depending on the MTLE laterality. *The results of univariable analyses.*

| Variable | Left mTLE n=63 | Right mTLE n=56 | *p* value |
|---|---|---|---|
| Age at epilepsy onset, years – Mean (SD) | 16.3 (7.9) | 20.7 (11.0) | **0.015** |
| Age at presurgical evaluation, years – Mean (SD) | 37.4 (12.2) | 38.7(12.0) | 0.6 |
| Epilepsy duration, years – Mean (SD) | 21.1 (12.6) | 18.0 (12.2) | 0.2 |
| Years of education – Mean (SD) | 10.9 (2.1) | 11.0 (1.9) | 0.7 |
| MRI hs | 62 | 53 | |
| no lesion | 1 | 3 | 0.3 |
| Years of follow-up – Mean (SD) | 7.3 (4.4) | 5.9 (3.8) | 0.1 |

Verbal memory performance scores on PAL Hard and RAVLT sub-tests were significantly lower in left MTLE patients, whereas the results of PAL Easy pairs testing did not differ between the two groups ($p$=0.9). In relation to the non-verbal memory measures, there was a tendency observed for the patients with right MTLE to attain lower visual reproduction (RCFT copy trial) and visuospatial memory (RCFT delayed recall) scores however the difference between the right and left MTLE patients did not achieve statistical significance.

**Table 6.2.** Cognitive tests performance in patients with left and right MTLE. *The results of Mann-Whitney U test.*

| Test | Left MTLE n=63 | | Right MTLE n=56 | | *p* value |
|---|---|---|---|---|---|
| | n | Median (IQR) | n | Median (IQR) | |
| PAL Easy | 56 | 13 (7) | 48 | 15 (7.5) | 0.9 |
| PAL Hard | 56 | 3 (4) | 48 | 6 (4.8) | **<0.001** |
| RAVLT list 5 | 46 | 10 (5) | 44 | 13 (3) | **<0.001** |
| RAVLT post-interference | 44 | 8 (5.8) | 44 | 11 (4) | **0.001** |
| RAVLT 20-minute recall | 38 | 7.5 (5.3) | 43 | 11 (7) | **0.003** |
| RAVLT Total learning score | 52 | 43.5 (16.5) | 46 | 50.5 (14) | **0.003** |
| RCFT copy | 58 | 35 (4.5) | 52 | 33 (6) | 0.08 |
| RCFT delayed recall | 59 | 14 (9) | 51 | 12 (7.5) | 0.1 |
| BNT | 43 | 49 (9) | 25 | 51 (8.5) | 0.2 |

PAL Easy–paired associated learning Easy pairs; PAL Hard–paired associated learning Hard pairs; RAVLT–Rey Auditory Verbal Learning Test; RCFT–Rey-Osterrieth Complex Figure Test; BNT–Boston Naming Test

The results of the ROC analysis of the individual neurocognitive tests are outlined in Table 6.3. The discriminatory performance of the RAVLT list 5 (AUC=0.724, 95% CI 0.619-0.828, $p<0.001$) and PAL Hard pairs (AUC=0.701, 95% CI 0.602-0.800, $p<0.001$) was satisfactory, whereas the discriminatory performance of other RAVLT subtests was highly limited, similarly to the BNT (AUC=0.605, 95% CI 0.465-0.744, $p=0.2$). The findings of the PAL Easy pairs did not discriminate between the left and right MTLE patient cohorts (AUC=0.507, 95% CI 0.395-0.619, $p=0.9$). The findings of the visuospatial measures were also non-discriminatory.

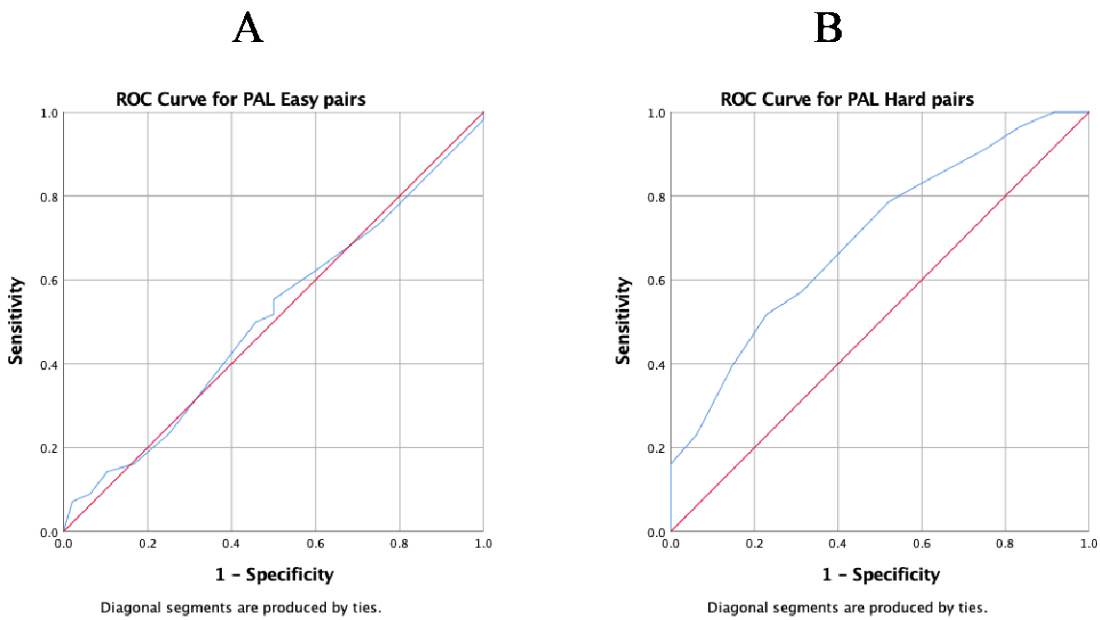



**Figure 6.1: ROC curve demonstrating the lateralising value of PAL Easy and Hard pairs**

(A) Receiver operating characteristic curve for PAL Easy pairs and (B) receiver operating characteristic curve for PAL Hard pairs.

**Table 6.3.** Lateralising performance of individual neurocognitive markers. *The results of univariable ROC analyses (unadjusted).*

| Test | n | AUC | *p* value | 95% CI |
|---|---|---|---|---|
| PAL Easy | 104 | 0.507 | 0.9 | 0.395-0.619 |
| PAL Hard | 104 | **0.701** | <**0.001** | 0.602-0.800 |
| RAVLT list 5 | 90 | **0.724** | <**0.001** | 0.619-0.828 |
| RAVLT post-interference | 88 | 0.698 | **0.001** | 0.589-0.807 |
| RAVLT 20-minute recall | 81 | 0.693 | **0.003** | 0.579-0.806 |
| RAVLT total learning score | 98 | 0.675 | **0.003** | 0.569-0.781 |
| RCFT copy | 110 | 0.407 | 0.1 | 0.300-0.513 |
| RCFT delayed recall | 110 | 0.415 | 0.1 | 0.308-0.523 |
| BNT | 68 | 0.605 | 0.2 | 0.465-0.744 |

PAL Easy–paired associated learning Easy pairs; PAL Hard–paired associated learning Hard pairs; RAVLT–Rey Auditory Verbal Learning Test; RCFT–Rey-Osterrieth Complex Figure Test; BNT–Boston Naming Test; AUC–area under the curve

The results of ROC sensitivity, specificity, positive and negative predictive values analyses of the individual neurocognitive tests are outlined in Table 6.4. The findings demonstrated that the RAVLT post-interference trial appeared to have sufficient sensitivity and specificity of 73%. PAL Hard pairs learning and RAVLT 20-minute recall tests demonstrated relatively low sensitivity of 58% and 51%, respectively, however the estimated specificity of PAL Hard pairs was adequate at 89%, followed by RAVLT 20-minute recall at 79%. In relation to the RCFT, the copy trial and delayed recall were of low sensitivity and specificity in differentiating amongst the patients with left and right MTLE. The estimated sensitivity of the BNT was also low at 40% however the specificity of the BNT was estimated as 77%. To assess an individual discriminatory performance of the neurocognitive tests in lateralising the seizure onset zone the PPV and NPV values were subsequently estimated (Table 6.4). The findings of PPV/NPV testing suggested that the RAVLT post-interference trial (PPV, NPV at 73%)

and PAL Hard pairs learning tests (PPV=70%, NPV=69%) demonstrated superior performance compared to their verbal memory counterparts explored in this study. On the other hand, PPV of PAL Easy pairs, RCFT and BNT in discriminating between the MTLE laterality was near random (52-55%).

**Table 6.4.** Cut-offs, Sensitivity, Specificity, PPV and NPV (adjusted).

| Test | Cut off | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|
| PAL Easy | 0.46 | 67 | 48 | 52 | 63 |
| PAL Hard | 0.51 | 58 | 79 | 70 | 69 |
| RAVLT list 5 | 0.45 | 80 | 61 | 66 | 76 |
| RAVLT post-interference | 0.49 | 73 | 73 | 73 | 73 |
| RAVLT 20-minute recall | 0.66 | 51 | 89 | 85 | 62 |
| RAVLT total learning score | 0.47 | 70 | 63 | 63 | 70 |
| RCFT copy | 0.44 | 79 | 43 | 55 | 69 |
| RCFT delayed recall | 0.43 | 80 | 42 | 55 | 71 |
| BNT | 0.41 | 48 | 77 | 55 | 72 |

PAL Easy–paired associated learning Easy pairs; PAL Hard–paired associated learning Hard pairs; RAVLT–Rey Auditory Verbal Learning Test; RCFT–Rey-Osterrieth Complex Figure Test; BNT–Boston Naming Test; PPV–positive predictive value; NPV–negative predictive value

## 6.4 Discussion

This study explored the lateralising properties of neurocognitive tests most widely used in the neuropsychological assessment of epilepsy patients, including the evaluation of surgical candidates. The statistical analyses employed in this study allowed for the lateralising properties of verbal, visuospatial and language assessment measures to be evaluated at both, group level using ROC analysis and also at an individual level using PPV and NPV. The findings were consistent with the results of previous studies, whereby only some neurocognitive measures, i.e. RAVLT and PAL Hard pairs learning

tests were found to be of lateralising value in patients with MTLE. The PAL Easy pairs, RCFT and BNT appeared to have rather limited if any discriminatory properties in this patient cohort. (Loring et al., 2008; McConley et al., 2008; Soble et al., 2014). The age of epilepsy onset however was significantly younger in the left MTLE patient cohort, which may have influenced the language lateralisation in some patients (Stewart et al., 2014). However, no atypical language lateralisation was identified in this patient cohort.

It has been recognised that the majority of RAVLT subsets and PAL Easy pairs tests make substantial demands on the semantic memory component (Saling et al., 1993). In keeping with intratemporal memory specialisation however, it is the arbitrary learning that suffers most in left MTLE patients whereas semantic memory remains relatively preserved (Saling, 2009). This could explain the non-lateralising findings of the PAL Easy pairs testing observed in this study. PAL Hard pairs, on the contrary, devised to tap into the protosemantic, i.e. arbitrary memory component thus serving as a task-specific marker of the medial temporal lobe dysfunction in patients with left MTLE (Saling, 2009; Weintrob et al., 2002). The findings of this study, demonstrating superior specificity of the PAL Hard pairs compared to other verbal memory tests explored in this study, are in keeping with the results of previous research.

The finding of a non-discriminatory performance of RCFT demonstrated in this research has been consistent with results of previous studies (McConley et al., 2008; Jeyaraj et al., 2013). The search for a reliable neurocognitive marker of right temporal lobe dysfunction in patients with MTLE continues to this day (Saling, 2009). While the findings of a recent survey of neuropsychological practices across European epilepsy centres have been encouraging and the trend of moving away from predetermined extensive test batteries towards the selective use of neurocognitive markers has been observed, the overall choice of the neuropsychological tests appears to be driven by material rather than a task-specific approach to neurocognitive testing (Vogt et al., 2017).

The majority of tests in the neuropsychological armamentarium were not “purpose-built” for the assessment of epilepsy patients. Our findings emphasise the need for task-specific cognitive markers in the evaluation of epilepsy patients and in surgical candidates in particular. Admittedly, the use of neuropsychological verbal and non-verbal memory measures constitutes only one part of the comprehensive

neuropsychological evaluation. However, there has been a pressing need for identification of specific neurocognitive markers, which would assist with the delineation of dysfunctional neurocognitive networks, similarly to the SEEG, the advances of which illuminated our understanding of the epileptogenic networks (Englot et al., 2016).

The identification and wider implementation of current task-specific tests not only would assist with seizure onset lateralisation but could potentially help define specific neurocognitive phenotypes reflective of the heterogeneity observed within focal epilepsy syndromes (Chassoux, 2017; Wilson & Baxendale, 2014). It would be particularly timely considering the rapidly evolving field of neuroimaging modalities and techniques, which have been making the gradual transition from epilepsy research to the clinical care setting (Bonelli et al., 2013; Sidhu et al., 2016). From a practical standpoint, it has been recognised that access to neuropsychological input in patients with epilepsy had been limited across the world thus the need for optimisation of our current approach to neuropsychological testing has been on-going (Baxendale, 2020b; Wilson et al., 2015). In addition, to meet the progressively expanding demands on healthcare provision, computerised neuropsychology assessments may become an integral part of the comprehensive neuropsychological evaluation in the future (Witt et al., 2013). Therefore, moving towards a task-specific approach to neurocognitive testing and the development of purpose-built tests would result not only in optimisation of neuropsychological service provision across epilepsy centres and ultimately improve the selection of surgical candidates but would also open up new avenues for collaborative clinical and research initiatives between the epilepsy programmes across the world.

# Chapter 7

# The association of postoperative gliosis with surgical outcomes following an ATLR in patients with drug resistant MTLE

## 7.1 Introduction

Following the seminal research paper by Wiebe *et al* providing Class I evidence in support of epilepsy surgery being the superior treatment option in patients with drug resistant TLE, the ATLR has established itself as the gold standard surgical treatment for these patients (Wiebe et al., 2001). The long-term outcome studies however have demonstrated that seizure recurrence occurs in up to 60% of patients following an ATLE (de Tisi et al., 2011; Hennessy et al., 2000; McIntosh et al., 2004). Furthermore, in patients with drug resistant TLE two distinct temporal patterns of postoperative seizure recurrence, i.e. early versus late, have been observed. Goellner *et al* demonstrated that the vast majority of epilepsy surgery failures tend to declare themselves relatively early, i.e. within the first 6 months following an ATLR (Goellner et al., 2013) and on most occasions result from either a failure to localise the seizure onset zone or suboptimal resection of the epileptogenic tissue (Najm et al., 2013). Therefore, not unexpectedly, the seizures associated with early surgical failures tend to be drug resistant and herald a poor long-term prognosis (Goellner et al., 2013; McIntosh et al., 2004; Schwartz et al., 2006). On the other hand, the clinical course of seizures recurring late after an ATLR appears to be more favourable (Buckingham et al., 2010; Foldvary et al., 2000). The findings of a recent study reporting seizure reversal to a "nocturnal seizures only" pattern observed in a small however significant proportion of patients with late seizure recurrence following an ATLR (Samarasekera et al., 2019), suggested the heterogeneous basis for late seizure recurrence in this patient cohort.

Despite the suggestions of previous research that neurosurgical intervention disrupting the integrity of the blood brain barrier may give rise to an epileptogenic process, not dissimilar to the sequelae of traumatic brain injuries (Girvin, 2014; Orbach et al., 2001; Penfield, 1929), the role of postoperative gliogenesis in late seizure recurrence has received hardly any attention in the research community (Alsaadi et al., 2001). There has been renewed interest in the epileptogenic properties of reactive astrocytes, with the

converging reports that the aberrant membrane excitability plays a role in the process of epileptogenesis (Orkand, 1966; Pollen, 1970; Tian et al., 2005). The role of reactive astrocytes in *de novo* epileptogenesis resulting in late seizure recurrence is yet to be determined (Najm et al., 2013; Ying et al., 2014). This study aimed to investigate the association between the extent of the postoperative gliosis, as measured by the pre-resection T2 signal change, and seizure outcomes in patients with MTLE following ATLR.

## 7.2 Methods

**Study subjects**

A total of 50 patients with drug resistant unilateral MTLE (Wieser, 2004) who underwent an ATLR between 1998 and 2015 at two Comprehensive Epilepsy Programmes based at the Royal Melbourne Hospital and the Austin Hospital, Melbourne, Australia were included in this retrospective study. The inclusion criteria were: (1) age ≥ 16 years at the time of surgery, (2) preoperative MRI findings consistent with unilateral unequivocal concordant HS with no evidence of dual pathology or showing no obvious epileptogenic lesion, i.e. MRI-negative patients, (3) no previous neurosurgical interventions or perioperative vascular morbidity resulting from the ATLR, (4) at least 2 years of postoperative follow up (5) availability of postoperative volumetric fluid attenuated inversion recovery (FLAIR) images with an MRI performed ≥ 3 months postoperatively. All patients included in this study had evidence of ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism confirmed. The patients with MRI FLAIR thickness slices of >1 mm were excluded from this study. All patients underwent a comprehensive presurgical evaluation as described previously (Berkovic et al., 1995; Carne et al., 2004; Vinton et al., 2007).

**Seizure variables and outcomes**

Seizure outcomes were categorised using Engel's seizure outcomes scale (Engel et al., 1993) as seizure free (Engel's class I, except for IC) or not seizure free (Engel's class II-IV) (Engel et al., 1993). The preoperative seizure burden was quantified using the seizure frequency scoring system by So *et al* (So et al., 1997) and a "worthwhile improvement" was defined as a ≥75% reduction in the seizure burden following epilepsy surgery. Acute postoperative seizures occurring within the first week following an ATLR were discounted (Bhaskara Rao et al., 1998). Postoperative seizure recurrence was formulated based on the recurrence of seizures associated with altered awareness,

as described previously (McIntosh et al., 2005). Seizure recurrence was categorised as early, i.e. within ≤ 6 months following an ATLR, or late, if the seizures recurred after 6 months postoperatively, irrespective of the seizure outcome at the time of the patients last follow up.

**Neurosurgical Procedure**

All patients underwent a Spencer type resection described previously (Fried, 1993). In brief, this entailed the resection of the middle temporal gyrus and the inferior temporal gyrus 3-3.5cm from the temporal tip, followed by resection of the mesial temporal lobe structures including the amygdala, hippocampal complex, uncus and fusiform gyrus. The adequacy of the hippocampal resection was determined based on a postoperative MRI performed at least three months following surgery.

**MRI acquisition and post-processing**

Sagittal 3-D FLAIR sequences were obtained as part of the patients' routine postoperative clinical care with MRI examinations performed on a Magnetom Avanto 1.5T (i) or a Magnetom Trio Tim 3T (ii) (Siemens Medical Solutions, Erlangen, Germany) with a 12-channel phased array coil, isotropic 1mm voxel and comparable acquisition characteristics: (i) flip angle (FA) 120, inversion time (TI) 1800, repetition time (TR) 5000, echo time (TE) 333, matrix 218 x 256 and (ii) FA 120, TI 1800, TR 5000, TE 388, matrix 258 x 256, with 176 and 160 slices, respectively. Post-acquisition processing was conducted using Analyze 12.0 software (Mayo Clinic, Rochester, MN). Postoperative gliotic changes adjacent to the resection cavity margins were manually segmented by two independent operators in the coronal plane. Tracking was guided by the FLAIR signal changes identified and verified in all three reconstruction planes and assisted by the launch of a seed voxel. The inhomogeneity correction was applied to the FLAIR weighted images prior to the tracing as described previously (Brinkmann et al., 1998). Two independent operators blinded to seizure outcomes carried out manual segmentation of postoperative gliosis. The inter-rater reliability was assessed by estimating the intra-class correlation coefficient value (Koo & Li, 2016).

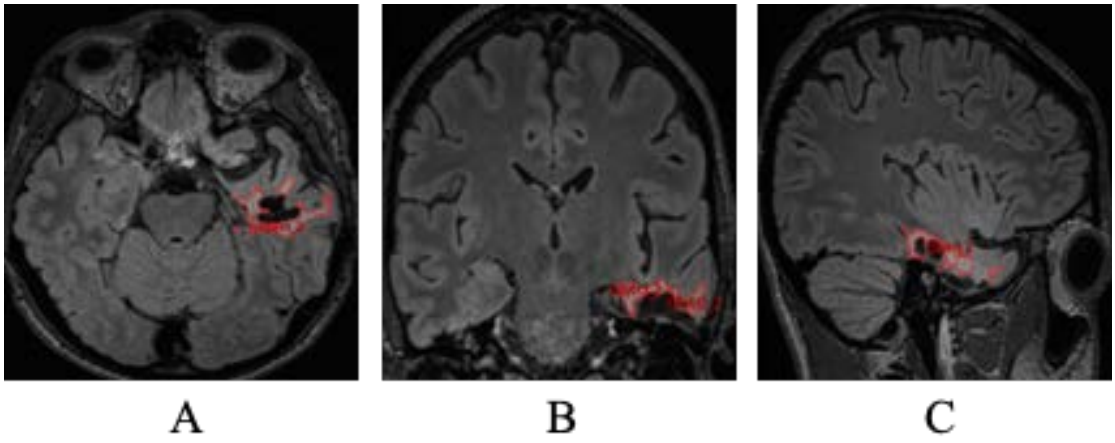



**Figure 7.1: Measuring the extent of postoperative gliosis in patient following ATLR**

Example of manually segmented postoperative gliosis in axial (A), coronal (B) and sagittal (C) view.

**Statistical Analysis**

Statistical analyses were performed using IBM SPSS 21.0 (IBM Corp., Armonk, NY). Univariable statistical analyses (Mann-Whitney U, Fisher's exact test and Kruskal-Wallis test) were employed to explore the differences pertaining to specific patient demographic groups and for exploring the relationship between pre and postoperative imaging variables in relation to the seizure outcomes or seizure recurrence status. Spearman's correlation analysis was performed to explore the association between the extent of postoperative gliosis and the patient age at the time of the ATLR and also the postoperative MRI timing. ICC was performed using a two-way mixed model with an absolute agreement option.

## 7.3 Results

There were 24 (48%) males included in this study with no difference in seizure outcome observed ($p$=0.3). Half of the patients (n=25, 50%) underwent a left ATLR and the other half a right ATLR, respectively. Preoperatively, in 46 patients (92%) the MRI findings were consistent with unilateral hippocampal sclerosis and in 4 patients (8%) there was no obvious epileptogenic lesion identified. At the time of the patients' last follow up 38 patients (76%) remained seizure free (Engel's class I) and 12 patients (24%) continued to experience seizures (Engel's class II-IV) where early seizure recurrence was observed in 7 patients (Mean=2 months, SD 1.2) and late seizure recurrence was seen in 5 patients (Mean=24.4 months, SD 9.9). Postoperative MRI was performed at a median of 10.5 months following ATLR (range 3 – 219 months). The

median duration of the postoperative follow up was 4 years (range 2 –18 years). The patients' demographic characteristics pertinent to their seizure outcomes are summarised in Table 7.1

**Table 7.1.** Patients' characteristics in relation to seizure outcomes.

| *Variables* | Engel's I (n=38) *Median (IQR)* | Engel's II-IV (n=12) *Median (IQR)* |
|---|---|---|
| Age at operation (years) | 34 (16.5) | 37.5 (24) |
| Duration of follow up (years) | 5 (6.5) | 3.5 (3) |
| Side of MTLE/ATLR | 19L/19R | 6L/6R |
| HS on preoperative MRI (n; %) | 35/38 (92.1%) | 11/12 (91.7%) |
| Histopathology findings: | | |
| HS | 37/38 (97.4%) | 11/12 (91.7%) |
| 'normal' findings | 1/38 (2.6%) | 1/12 (8.3%) |
| Time to FLAIR (months) | 10.5 (119.5) | 14 (55.3) |

A high degree of reliability was found between the measurements of the extent of the gliosis (ICC average measure 0.85, 95% CI 0.74-0.92, $p<0.001$). The extent of the postoperative gliosis varied markedly amongst the patients from 1.37 x $10^3$ $mm^3$ to 10.99 x $10^3$ $mm^3$ (Median=3.77 x $10^3$ $mm^3$). The results of the Mann-Whitney U test demonstrated no association between the extent of the postoperative gliosis and seizure outcomes ($p=0.5$) at the last follow up with the median volume of gliosis being 3.89 x $10^3$ $mm^3$ (IQR 2.2 x $10^3$) in patients with excellent seizure outcomes and 3.35 x $10^3$ $mm^3$ (IQR 2.3 x $10^3$) in patients with unfavourable seizure outcomes. No association was found ($p=0.3$) between the volume of gliosis in patients with late seizure recurrence (Median=4.4 x $10^3$ $mm^3$; IQR 6.0 x $10^3$) as opposed to those with no postoperative seizure recurrence (Median=3.88 x $10^3$ $mm^3$; IQR 2.17 x $10^3$), with no significant difference in the timing of the FLAIR sequences obtained ($p=0.8$). The age of the patient at the time of the ATLR had no influence on the extent of the post-operative gliosis ($p=0.7$).

There was a positive, albeit weak, correlation between the extent of the postoperative gliosis and the timing of the postoperative MRI, with the patients scanned later into their postoperative course exhibiting a greater extent of gliotic change ($r=0.4$, $p=0.012$), which could indicate progressive changes, i.e. gliogenesis over time.

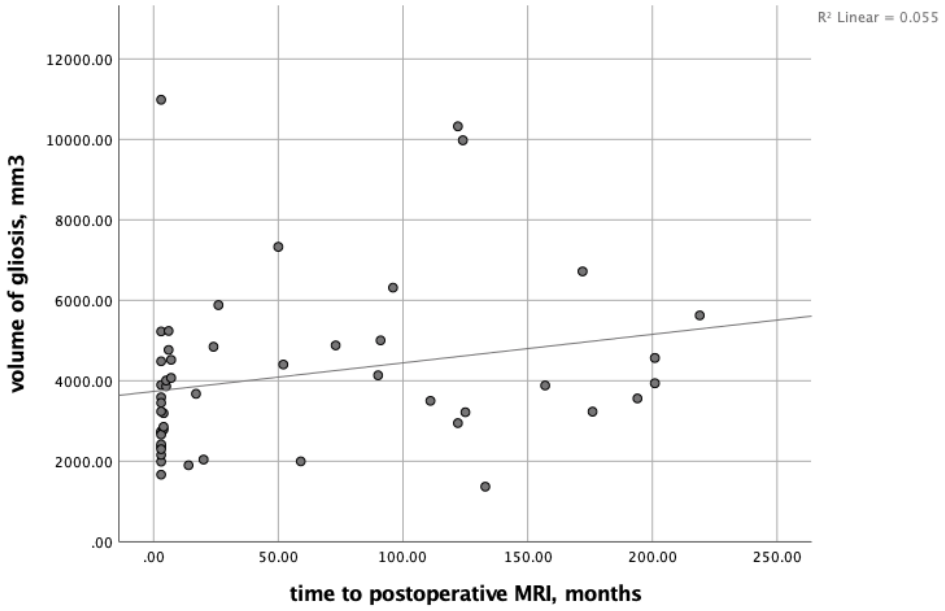



**Figure 7.2: Relationship between the extent of postoperative gliosis and time to scanning.**

Correlation between the extent of hippocampal sclerosis and time to scanning ($r$=0.4, $p$=0.012)

## 7.4 Discussion

To our knowledge, this study is the first to explore the relationship between the extent of the postoperative gliosis and long-term seizure outcomes in a well characterised cohort of patients using volumetric FLAIR, which allows for a more accurate quantification of the gliotic changes. There was no association found between the extent of gliosis and late seizure recurrence rates. Our findings are consistent with the results of a previous study by Alsaadi *et al* who used fast spin echo proton density weighted images, much thicker slices of 5 mm and a single, i.e. axial, plane only for determining the volume of postoperative gliosis in a smaller cohort of patients (Alsaadi et al., 2001). The results of both studies however could be equally limited by the small sample size. The recent success of the ENIGMA consortium project (Thompson et al., 2017) illustrates the strength of multicentre collaborative research initiatives and therefore a large-scale study may be feasible to further explore the role of postoperative gliogenesis in late seizure recurrence more robustly.

Our finding of a positive correlation between the extent of the gliosis and the timing of the MRI scanning, whereby the patients scanned in the early postoperative period showed less prominent gliotic changes as opposed to those scanned a year later, raises the possibility of the progressive nature of postoperative astrogliosis. This finding may encourage further research into the neurobiology underlying the neural tissue regeneration process. From a secondary epileptogenesis perspective, it is not inconceivable that the extent of the gliotic changes *per se* has no bearing on *de novo* epileptogenesis. In the meantime, considering that the populations of reactive astrocytes and their molecular properties significantly vary depending on the type of the CNS insult and its site (Sofroniew, 2014), it is plausible that reactive astrocytes could exercise both neuroprotective and maladaptive behaviour in the process of postoperative gliogenesis. It has been suggested by Waltz *et al* that PRNP variant allele Asn171Ser could influence the surgical outcome in patients with MTLE-HS (Walz et al., 2003). The findings of Waltz *et al* could be of particular interest in light of the recent study by Bradford *et al* who demonstrated the relationship between PRNP genotype and the upregulation of CD44 in the hippocampus (Bradford et al., 2019). CD44 is a trans-membrane glycoprotein highly expressed in the subset of reactive astrocytes thus might explain the differential reactive astrocytes properties in patients with PRNP variant allele, which was found to be highly prevalent in patients with drug resistant MTLE-HS and to influence their surgical outcomes (Walz et al., 2003).

Furthermore, it is not inconceivable that a combination of factors, surrounding surgical intervention, as opposed to postoperative gliotic changes alone could influence the process of secondary epileptogenesis. The epileptogenic properties of cortical haemosiderin deposits have long been described in heterogenous patient cohorts (Roelcke et al., 2013; Ruan et al., 2015; Silverman et al., 2002). The study by Messori *et al* offers further insights into the role of gliosis and hemosiderin deposits in the development of post traumatic epilepsy (Messori et al., 2005), notwithstanding the recent findings by Thevathasan *et al* suggestive of an association between poststroke seizures and haemorrhagic transformation, including petechial, in patients receiving endovascular therapy (Thevathasan et al., 2017). The role of haemosiderin in epileptogenesis has been the subject of continuous debate. Intriguingly, the study by Raabe *et al* identified no relationship between hemosiderin deposits and a heightened risk of seizures in patients with cerebrovascular pathologies (Raabe et al., 2012),

whereas Messori *et al* demonstrated that it was the combination of gliotic changes and haemosiderin deposits that was associated not only with increased rates of post-traumatic epilepsy but also with drug resistance, whereas gliosis alone had no bearing on the rates of post traumatic epilepsy (Messori et al., 2005).

From a practical standpoint, further studies into the role of postoperative gliogenesis in late seizure recurrence may not only shed light into the neurobiological mechanisms underlying secondary epileptogenesis, but could also influence our approach to the rationalisation of antiepileptic therapy following an ATLR. Moreover, with the increasing role of SEEG in the evaluation of surgical candidates and with the minimally invasive epilepsy surgery procedures, e.g. LiTT, increasingly influencing the current landscape of epilepsy surgery (LaRiviere & Gross, 2016; von Lehe & Parpaley, 2017; Willie et al., 2014) it would also be essential to understand the effects of specific surgical techniques on the extent of the postoperative gliogenesis and its relationship with late seizure recurrence in this patient cohort.

# Chapter 8

# General discussion and future directions

## 8.1 General discussion

The reconceptualisation of epilepsy as a network disorder (Bartolomei et al., 2017) (Bernhardt et al., 2016; Engel et al., 2013) has transformed the approach to the epilepsy surgery evaluation. The "one size fits all" strategy is destined to fail in a proportion of patients if we do not take into consideration the multitude of intertwined factors influencing the heterogeneity and the extent of the epileptogenic zone, often beyond the structural pathology, notwithstanding the connectome properties, neurometabolic and genetic determinants implicated in the process of epileptogenicity. MTLE, being the most studied surgical epilepsy entity has now been shown to be a heterogeneous epilepsy syndrome with differential epileptogenic networks identified within what was originally regarded as a uniform electro-clinical MTLE syndrome (Bartolomei et al., 2008; Bonilha et al., 2007; Kahane & Bartolomei, 2010). The findings of a recent study by Galovic *et al* demonstrated the pivotal role of the piriform cortex in seizure generation, whereby the removal of at least 50% of the piriform cortex in patients undergoing an ATLR was associated with a favourable epilepsy surgery outcome in this patient cohort thus inferring its role as a key node within the heterogeneous epileptic networks implicated in MTLE (Galovic et al., 2019). Furthermore, there has been growing evidence of the laterality-specific differentiality of the epileptic networks, including their topography, observed in patients with MTLE (Chassoux et al., 2016; Coito et al., 2015; Dupont et al., 2002; Haneef et al., 2013; Hogan et al., 2006).

The fundamental aim of the present inquiry is to contribute to our understanding of the factors influencing the selection of surgical candidates, surgical decision making and counselling using real world clinical data, stemming from presurgical evaluation tools currently employed as part of the standard clinical care of epilepsy surgery candidates. Discussed are the findings of the studies underlying this thesis, focusing on the following aspects pertaining to the presurgical evaluation, surgical decision making and counselling in patients with drug resistant MTLE: the role of $^{18}$FDG-PET in predicting seizure outcomes, memory deficits following ATLR, the role of neurocognitive

biomarkers in presurgical evaluations and the role of postoperative gliogenesis in seizure recurrence following ATLR.

**The role of $^{18}$FDG-PET in the presurgical evaluation of epilepsy surgery candidates**

The findings of this study contributed further evidence of the differential laterality-specific neurometabolic patterns observed in patients with drug resistant MTLE, with the rates of bitemporal $^{18}$FDG-PET hypometabolic changes being significantly greater in patients with right MTLE, whereas left MTLE patients were found to have significantly greater ipsilateral temporal lobe hypometabolism identified on interictal $^{18}$FDG-PET. It has been previously shown that the unequivocal concordant unilateral hippocampal sclerosis on preoperative MRI scans (Berkovic et al., 1995) and the larger volume of temporal lobe resections were associated with higher rates of postoperative seizure freedom (Arruda et al., 1996; Nayel et al., 1991). However, admittedly the latter point has been the subject of ongoing debate for many years (Schramm, 2008).

This study demonstrated that the finding of bitemporal $^{18}$FDG-PET hypometabolism in right MTLE patients is an independent predictor of seizure outcomes following an ATLR, over and above the preoperative finding of hippocampal sclerosis and the volume of the ATLR resection. The risk of postoperative seizure recurrence was heightened 5-fold in this patient cohort. These findings corroborate the results of previous research reporting laterality-specific altered connectivity patterns in patients with drug resistant MTLE (Coito et al., 2015; Haneef et al., 2014) and the previous observations of bitemporal hypometabolism being associated with poor seizure outcomes (Chassoux et al., 2016; Joo et al., 2004; Koutroumanidis et al., 2000).

The significance of this finding pertains to several aspects of clinical care. First and foremost, it would influence patient selection and counselling thereby setting realistic expectations and facilitating patient-centred decision-making. The laterality-specific finding of bilateral $^{18}$FDG-PET, which in turn has been shown to portend poor seizure outcomes, could challenge our long-established approach to right ATLR's, targeted by larger resection volumes. These do not appear to have influenced seizure outcome in this cohort of patients with right MTLE and therefore tailored and more sparing resections could be considered. While the radiological finding of HS would not inform our understanding of the extent and topography of the underlying epileptic networks,

the $^{18}$FDG-PET is well placed to assist with the visualisation of any abnormal metabolic architecture, especially that it has been shown to identify the laterality-specific metabolic findings, consistent with laterality-specific findings of both, structural and functional imaging modalities (Blumenfeld, 2012; Englot et al., 2010). Interestingly, Spencer *et al* demonstrated evidence of disproportionate seizure onset lateralisation in a significant proportion of patients with bitemporal epilepsy receiving responsive neuro-stimulation (Spencer et al., 2011). My findings which are suggestive of wider epileptogenic network involvement in patients with right MTLE could potentially be indicative of an independent bitemporal seizure generator in this patient cohort, which did not become apparent during video-EEG-telemetry due to potential sampling bias stemming from a relatively short duration of video-EEG-telemetry admissions routinely employed in the evaluation of surgical candidates. This is turn, calls for reconsideration of the current presurgical evaluation strategies and the wider use of iEEG in the evaluation of patients with drug-resistant TLE, especially in those with bitemporal $^{18}$FDG-PET hypometabolism. This aligns with the current concept of epilepsy being a network disorder, thus network driven surgical planning enabled by the contributory findings of $^{18}$FDG-PET stands a good chance of improving surgical outcomes.

It has been previously shown by Lieb *et al* that a rapid, less than five second, inter-hemispheric seizure propagation was associated with greater damage to the contralateral hippocampal formation and unfavourable epilepsy surgery outcomes (Lieb et al.,1987). This has not been studied in relation to the hemispheric specific laterality of the seizure onset. From a semiological prospective, the MTLE patients with an ictal generator localised to the hemispheric dominant mesial temporal lobe, typically left, are more likely to exhibit impaired awareness early on into the seizure. Therefore, it would be interesting to explore as to whether or not bilateral $^{18}$FDG-PET hypometabolism in patients with right MTLE is indicative of fast seizure propagation to the left temporal lobe and if this is reflected in the seizure semiology. The finding of a distinct laterality-specific abnormal metabolic architecture observed in MTLE patients and corroborative of the findings resulting from structural and functional connectivity research, calls for a further inquiry into laterality-specific clinical and neurocognitive phenotypes characteristic of these patient cohorts to understand further as to whether or not right and left MTLE are two distinct clinical entities with their respective neurobiological foundations and response to treatment, both pharmacological and surgical.

While the previous findings of Vinton *et al* regarding the greater extent of the $^{18}$FDG-PET hypometabolism resection being associated with higher rates of postoperative seizure freedom following an ATLR (Vinton et al., 2007), has not been replicated in a right MTLE patient cohort, the trend of the greater extent of the resection of the ipsilateral $^{18}$FDG-PET temporal lobe hypometabolism being associated with favourable seizure outcomes was observed in the left MTLE group, albeit not reaching statistical significance. This could be of further clinical significance considering the association between $^{18}$FDG-PET hypometabolism and pathological HFO's activity reported by Lamarche *et al* (Lamarche et al., 2016), which has challenged the long held belief that $^{18}$FDG-PET changes were a mere reflection of the functional deficit zone (Rosenow & Lüders, 2001). Thus, it is conceivable that a wider excision of the ipsilateral temporal lobe hypometabolic tissue may result in improved seizure outcomes. In other words, it is conceivable that not "all hypometabolic changes are equal" with some being "more equal than others". Similar to Newton's disk, the non-differential approach to hypometabolic findings identified using current post-acquisition processing techniques, would not allow for granular differentiation between the $^{18}$FDG-PET changes representative of the "functional deficit", "irritative" or "epileptogenic" zones. Therefore, optimisation of the post-acquisition processing techniques could allow for more precision in determining the "epileptogenic yield" of the preoperative $^{18}$FDG-PET changes so that one could differentiate between the "core" and the "ripple effects" associated with the indices of epileptogenicity.

By the same token, the advances in $^{18}$FDG-PET techniques, such as hybrid PET/MRI scanning modalities paving its way into both, epilepsy research and clinical care, and the wider use of multicontact micro-electrodes during SEEG implantations open up new avenues for granular research into the neurometabolic foundations of the heterogeneous epileptic networks implicated in the development of drug resistant MTLE (Cash et al., 2009; Halgren et al., 2015; Herff et al., 2020; Martini et al., 2019; Wehrl et al., 2013). This would facilitate the surgical planning of tailored resections or a combination of both, resective and minimally invasive techniques, in patients where the feasibility of a complete resection of the seizure onset zone is constrained by its proximity to the eloquent cortex. Considering the findings of a recent study by Morgan *et al* of altered preoperative connectivity patterns being associated with postoperative seizure outcomes (Victoria et al., 2019) and in light of the emerging research into the feasibility of prospective visualisation of the seizure onset zone being achieved using computational

modelling techniques based on the Brain Network Ictogenecity estimates (Goodfellow et al., 2016) (Sinha et al., 2017), it would be interesting to explore the relationship between the functional connectivity patterns and the metabolic changes, with a view of advancing surgical planning and informing presurgical counselling.

$^{18}$FDG-PET has been firmly imbedded in surgical planning, whereby apart from assisting with the seizure lateralisation and localisation, the metabolic patterns of $^{18}$FDG-PET could also serve as an independent predictor of seizure outcomes, over and above the structural radiological findings identified on preoperative MRI in patients with MTLE. Therefore, further consideration is warranted for expanding the use of $^{18}$FDG-PET in the presurgical evaluation of patients with MTLE. Mouthaan *et al* reported that $^{18}$FDG-PET already forms an integral part of the evaluation of surgical candidates in epilepsy surgery centres across Europe (Mouthaan et al., 2016). However, access to $^{18}$FDG-PET may pose a challenge in other, commissioning reliant, healthcare settings where the use of $^{18}$FDG-PET in patients with drug resistant MTLE is reserved for selected clinical scenarios with discordant findings of electro-clinical, radiological and neuropsychological evaluation (Duncan et al., 2000). In addition, there has been a trend to rationalise the use of $^{18}$FDG-PET based on single reports resulting from the amalgamation of historical data (Jones & Cascino, 2016). The move to identify more cost-efficient ways of delivering epilepsy surgery care is understandable (Quarato et al., 2005), however it would be important to acknowledge that the rates of favourable outcomes following seemingly "straightforward" epilepsy surgery in patients with MTLE remain rather consistently suboptimal. It is plausible that the data derived from routine phase 1 presurgical evaluation may not reflect the complexity of heterogeneous and potentially evolving epileptic networks implicated in the development of MTLE thus there is a need for the current "lean" approach in the evaluation of MTLE candidates to be studied through multicentre research initiatives in order to achieve an expert consensus with the view of advancing the care of patients with drug resistant TLE.

**The role of $^{18}$FDG-PET in predicting memory deficits**

The unique characteristics of $^{18}$FDG-PET imaging with it being an integral part of the non-invasive phase of the presurgical evaluation and often a prerequisite for invasive evaluation, on one hand, as well as being the only functional imaging modality allowing for the visualisation of *in vivo* cerebral glucose metabolism on the other hand, opens up

potential avenues for extending its role in the presurgical evaluation beyond its lateralising and localising value in the identification of the seizure onset zone. The findings of previous, predominantly small cohort studies, suggested an association between $^{18}$FDG-PET hypometabolism and impaired neurocognitive performance in patients with TLE (Knopman et al., 2015; Rausch et al., 1994; Weintrob et al., 2002) thus giving rise to the current inquiry into the role of $^{18}$FDG-PET as an independent predictor of neurocognitive deficits in patients with MTLE. One of the aims of this study was to explore the relationship between verbal memory performance and ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism in a well characterised cohort of patients with unilateral drug resistant MTLE. There was an intriguing finding of a weakly positive correlation between the extent of the $^{18}$FDG-PET hypometabolism and verbal memory scores in two subsets of semantically loaded verbal memory tests. This could be explained by the adaptive mechanisms of neuronal plasticity (Hillary & Grafman, 2017) and would require further evaluation in larger patient cohorts. However, overall, there was no association observed between the extent of the ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism and verbal memory performance in this patient cohort. This could be due to methodological differences including the approach to post-acquisition $^{18}$FDG-PET processing. For example, Weintrobe *et al* found an association between impaired arbitrary learning and reduced $^{18}$FDG uptake within the left rhinal cortex, which was identified a priori as a region of interest in patients with left TLE (Weintrob et al., 2002), whereas the region of interest in the present study was the temporal lobe as a whole to allow for maximal fidelity to the real world clinical setting.

The finding of laterality-specific metabolic patterns in patients with right and left MTLE, whereby the presence of bitemporal $^{18}$FDG-PET hypometabolism in the right MTLE patient cohort heightened the risk of seizure recurrence 5-fold following an ATLR, prompted further inquiry into its neurocognitive sequelae. On the premise of bitemporal hypometabolism being a neurometabolic marker of wider, bitemporal neuronal network dysfunction implicated in patients with right MTLE (Dupont et al., 2002; Joo et al., 2004; Vanicek et al., 2016) and with the arbitrary learning impairment being an established hallmark of the left mesial temporal dysfunction (Saling, 2009) the role of arbitrary learning as a candidate neurocognitive biomarker of left temporal dysfunction in patients with right MTLE was explored. The findings of this study demonstrated that the patients with right MTLE in whom there was no evidence of

bitemporal hypometabolism, had significantly higher arbitrary learning scores than the left MTLE patients. Comparing the arbitrary learning performance in right MTLE patients with and without evidence of bitemporal, in other words concomitant left temporal lobe hypometabolism, the trend for right MTLE patients with bitemporal hypometabolism to attain lower arbitrary learning scores was observed however the difference in arbitrary learning scores did not reach statistical significance to differentiate between the right MTLE patients with and without bitemporal hypometabolic changes, which could be explained by the small sample size.

Interestingly, while right MTLE patients without evidence of bitemporal hypometabolism had significantly higher arbitrary learning performance scores compared to the left MTLE patients, there was no difference in the arbitrary learning performance observed in patients with left MTLE and right MTLE patients with bitemporal $^{18}$FDG-PET hypometabolism. Therefore, a large cohort study is warranted to determine the role of arbitrary learning as a candidate neurocognitive biomarker of left temporal lobe dysfunction in right MTLE patients with bitemporal $^{18}$FDG-PET hypometabolism. The clinical significance of this notion is supported by the findings of a recent study by Aikiä *et al* suggesting that verbal memory impairment could be identified early on into the epilepsy onset in patients with TLE (Äikiä et al., 2001), which in turn could be explained by a common neurobiological basis of neurocognitive dysfunction and seizure generating aberrant networks implicated in the development of epilepsy. It is therefore conceivable that in patients with epilepsy, neurocognitive sequelae of neural network dysfunction could precede the development of actual seizures, i.e. being inter-related parts of one overarching epilepsy continuum, similar to non-motor symptoms being the only clinical manifestation for years before the typical motor deficits become apparent in patients with Parkinson's Disease (Park & Stacy, 2009). Thus, further study is warranted in order to understand if the epileptic network disorder could be identified before the seizures declare themselves.

The role of hippocampal adequacy and hippocampal reserve in predicting memory outcomes following an ATLR was first outlined by Chelune more than a decade ago (Chelune, 1995). He postulated that the risk of postoperative cognitive decline was inversely related to the adequacy of the tissue to be resected and directly correlated with the reserve of the contralateral hippocampus. Sidhu *et al* subsequently demonstrated evidence of neuronal plasticity changes taking place in the memory-encoding network

in both hippocampi (Sidhu et al., 2016). However, posterior hippocampal reorganisation following an ATLR was inefficient and had no long-term bearing on verbal memory performance. On the other hand, the contralateral hippocampus was shown to play a key role in the postoperative recovery of cognitive function, regardless of the ATLR side. Therefore, the current finding of bitemporal $^{18}$FDG-PET hypometabolism in patients with right MTLE being potentially the left temporal lobe dysfunction manifesting with impaired arbitrary learning warrants further investigation. This would enable to further our understanding of postoperative cognitive deficits associated with the potentially depleted functional reserve of the left hippocampus in right MTLE patients. In turn, prehabilitation measures could be considered earlier on in order to mitigate the neurocognitive costs of epilepsy surgery in this patient cohort.

Furthermore, this study examined the role of $^{18}$FDG-PET in predicting postoperative memory decline following an ATLR, over and above the long-established predictors, such as ATLR laterality and the preoperative verbal memory performance (Baxendale et al., 2006). The rates of postoperative verbal memory decline were significantly greater following a left ATLR and in those patients in whom a higher level of verbal memory performance was observed preoperatively. These findings are consistent with the outcomes of previous research by Baxendale *et al* (Baxendale et al., 2006). The extent of the preoperative $^{18}$FDG-PET hypometabolism had no added value in predicting postoperative verbal memory decline. Similarly, there was no association between the extent of the resection of the $^{18}$FDG-PET hypometabolic tissue and a postoperative verbal memory deficit observed in this study. The total volume of the temporal lobe resection did not correlate with postoperative verbal memory scores either. The findings of this inquiry, focusing on the effect of the extent of the ipsilateral temporal lobe $^{18}$FDG-PET hypometabolism and subsequently the extent of its resection on predicting memory deficits in a MTLE cohort has been shown to be of limited added value in the real-world clinical setting. However, renewed interest in the default mode network (DMN), originally discovered by Raichle *et al* as a result of PET-based studies (Raichle et al., 2001), and its role in cognition (Viard et al., 2007) gave rise to a promising new direction in the field of epilepsy cognition (Viard et al., 2007). This is particularly timely, considering that hybrid MRI/PET shows great promise to advance both, epilepsy research and clinical care, with ample opportunity for integrating multimodal imaging techniques to study the metabolic, structural and functional properties of the epileptic networks now with an even higher degree of precision.

**The use of neurocognitive biomarkers in patients with MTLE: from material- to task specificity**

The complexity of the heterogeneous epileptic networks, including their laterality specific differential distribution, notwithstanding the potentially intricate seizure propagation pathways resulting in misleading electro-clinical manifestations, from TLE mimics to TLE plus syndromes, the role of the presurgical evaluation in surgical planning is hard to underestimate. The key role that comprehensive neuropsychological evaluation plays in the presurgical evaluation, including its contribution towards seizure onset lateralisation and localisation has long been recognised (Baxendale, 2018). The choice of neurocognitive tests used in preoperative neuropsychological evaluation is tailored to the individual patient's needs and is decided upon by a clinical neuropsychologist based on the information derived during the clinical interview of the epilepsy surgery candidates. While comprehensive neurocognitive evaluation entails the assimilation of anatomo-electro-clinical data as well as the multimodal neuroimaging findings within the clinical context, the current armamentarium of task-specific neuropsychological tests used in routine clinical practice is limited.

The findings of a recent survey looking into the neuropsychological assessment standards across European epilepsy surgery centres by Vogt *et al* demonstrated that the majority of the neurocognitive tests currently in use are based on a material-specific approach to memory testing (Vogt et al., 2017). Previous studies have shown that material-specificity based neurocognitive tools are of limited value in assisting with seizure onset lateralisation (Jeyaraj et al., 2013; McConley et al., 2008; Raspall et al., 2005). On the other hand, there is growing evidence suggesting that the use of task-specific neurocognitive markers accounts for more accurate seizure lateralisation and localisation (Saling et al., 1993; Weintrob et al., 2002). Furthermore, impaired arbitrary learning has been shown to be a hallmark of left mesial temporal dysfunction in patients with MTLE, however a specific neurocognitive marker for right temporal lobe dysfunction is yet to be determined (Saling, 2009). This study examined the "nett" lateralising value of the neuropsychological tests commonly used in the evaluation of surgical candidates.

The findings of this study, using ROC, PPV and NPV analyses, were consistent with previous research and demonstrated the limited lateralising properties of semantically

loaded neurocognitive tests in patients with MTLE. On the other hand, this study found, consistent with the findings of Saling's research group (Saling et al., 1993) (Lillywhite et al., 2007; Weintrob et al., 2002) that the protosemantically oriented neurocognitive tests, e.g. PAL Hard pairs, devised to examine the arbitrary learning skills, were shown to be more specific in eliciting neurocognitive deficits stemming from left mesial temporal lobe dysfunction thus supporting the concept of intratemporal memory specialisation (Saling, 2009). Considering the complexity of the epileptic networks implicated in MTLE, including distinct anatomo-electro-clinical phenotypes previously described within the TLE syndrome (Bartolomei et al., 2008) (Chassoux, 2017; Kahane & Bartolomei, 2010), it is not entirely unexpected that the material-specificity based test batteries, tapping into semantic, i.e. neocortical memory components only, would struggle to identify isolated left mesial temporal lobe dysfunction (Lillywhite et al., 2007; Weintrob et al., 2002) thus highlighting the pressing need for more precise neuropsychological tools.

Furthermore, in light of the increasing demands for a personalised patient-centred approach to surgical decision-making and neurocognitive pre/rehabilitation planning alike, the number of studies looking to identify specific neurocognitive phenotypes associated with preferential epileptic network involvement in patients with TLE has been steadily increasing. The recent structural connectivity study by Reyes *et al* identified four distinct cognitive phenotypes associated with specific white matter aberrant connectivity patterns (Reyes et al., 2019). These findings converge with the findings of current and previous studies calling for the wider use of task-specific tests in routine clinical practice. The task-specific approach to neurocognitive testing would also be applicable not only to patients with MTLE but also to the evaluation of surgical candidates with extra-temporal epilepsy syndromes. The wider use of task-specific neurocognitive biomarkers in epilepsy care would advance surgical planning and counselling.

**The role of gliogenesis in late seizure recurrence following an ATLR**

There has been a considerable knowledge gap in relation to the potential causes for late seizure recurrence following epilepsy surgery. Goellner *et al* demonstrated that the vast majority of epilepsy surgery failures tend to manifest within the first 6 months following the surgery (Goellner et al., 2013). The incomplete resection of the epileptogenic zone has been traditionally regarded as the culprit for these early surgical

failures (Jeha et al., 2006; Najm et al., 2013). The exact reasons behind the late seizure recurrence however are yet to be determined. The findings of Boshuisen *et al* demonstrated that seizure recurrence occurred in up to 50% of patients following antiepileptic drug withdrawal in patients who were originally rendered seizure free following epilepsy surgery. Furthermore, only two thirds of patients were shown to achieve seizure freedom after their AED therapy was reinstated (Boshuisen et al., 2012). These findings, subsequently corroborated by Schmidt *et al* (Schmidt & Sillanpää, 2017) indicated that as far as postoperative seizure freedom is concerned, a significant proportion of patients fail to achieve "unconditional" seizure freedom, with the majority of these patients being in need of long term antiepileptic pharmacotherapy thus emphasising the neurobiological heterogeneity of surgical outcomes and giving rise to the nascent concept of a drug resistant epileptogenic zone (Zhang & Kwan, 2019), which is likely to influence the field of epileptology for years to come. In the same vein, while the resurrection of the drug resistant epileptogenic zone over time, following the original excision of the drug resistant "culprit nodes" has been proposed as a potential cause for late seizure recurrence, the role of post-operative gliogenesis as another contributory mechanism to late seizure recurrence has not been explored. The findings of earlier research demonstrating the epileptogenic properties of reactive astrocytes resulted in a renewed interest in the role of astrocytes in the epileptic process, including postoperative gliogenesis and its contribution to late seizure recurrence (Goc et al., 2014; Liu et al., 2018; Steinhäuser et al., 2012).

This study investigated the relationship between the extent of the postoperative gliosis and the rates of seizure recurrence following an ATLR using quantitative techniques in determining the volume of gliosis identifiable on postoperative MRI scans. The findings of this small cohort study showed no association between the rates of postoperative seizure recurrence and the extent of gliotic changes following an ATLR, which could be explained by an insufficient sample size. However, the longer the time between the ATLE and the postoperative scanning the greater the extent of the postoperative gliosis was observed. The large cohort longitudinal studies could enhance our understanding of not only the contribution of postoperative gliogenesis to the late seizure recurrence rate but also uncover the neurobiological basis of the neuroregeneration process, including the association between preoperative neurometabolic compromise and the extent of the postoperative gliosis which could be the subject of future studies. The type of the neurosurgical procedure, i.e. resective versus minimally invasive neurosurgical

techniques, could potentially affect the formation of glial scarring in a procedure specific way, thereby influencing the rates of postoperative seizure recurrence, depending of the surgical techniques employed. On the other hand however, there have been multiple reports of seizure remission following SEEG exploration (Katariwala et al., 2001; Kaur et al., 2019; Roth et al., 2012) which begs the question as to whether or not the site, the extent and the type of injury would account for such an effective disruption of an established drug resistant epileptic network. Fong *et al* studied the surgical specimens resulting from resective surgeries preceded by SEEG exploration (Fong et al., 2012). The findings were consistent with chronic inflammation. It would however be more informative to study the properties of glial scarring in a longitudinal fashion, looking for differential astroglial characteristics with the view of distinguishing between neuroprotective and maladaptive gliogenesis.

Importantly, further larger cohort studies would be warranted to look into the long-term outcomes in this patient cohort to explore the relationship between the precision of a preoperative SEEG implantation scheme and the duration of the "SEEG-induced" seizure remission. This may uncover the relationship between high precision SEEG-implantations and successful rates of "SEEG-induced" epileptic network disruptions, potentially also identifying the critical "key nodes" pertaining to specific epilepsy networks and their electrical signatures, which could be successfully disrupted. This study has the distinct potential to transform the care of patients with drug resistant epilepsy, including those previously found to be unsuitable surgical candidates and those typically considered for palliative procedures, for example a hemispherectomy or TPO-disconnection procedures not uncommonly associated with neurological sequelae impacting on the health-related quality of life, which is not insignificant for this particularly vulnerable patient cohort.

## 8.2 Future directions

We have come a long way since the first epilepsy surgery performed by Victor Horsley in 1886. The outstanding achievements of Bancaud and Talairach in the field of SEEG gave rise to further landmark discoveries of epileptogenic networks supported by exploding research in the field of connectomics and microelectrode recording studies in search for the "fingerprints" of the epileptogenic zone (Rosenow & Lüders, 2001), which would allow for a precise surgical intervention culminating in seizure freedom (Besson et al., 2017; Gleichgerrcht et al., 2018; Grinenko et al., 2017; Victoria et al., 2019). The findings of the long-term seizure outcome studies however (Boshuisen et al., 2012; McIntosh et al., 2012; Schmidt & Sillanpää, 2017), demonstrated not only the heterogeneity of surgical gains but also cast new light on the running down phenomenon (Geller et al., 2018; Salanova et al., 1996) whereby it has become obvious that, the "one size fits all" approach, including epilepsy surgery and surgical outcomes, would not account for the complexity of the heterogeneous epileptogenic networks being implicated in drug resistant epilepsy syndromes.

In the network-targeted epilepsy surgery era our approach to what the epileptogenic zone might actually constitute has been undergoing reconsideration and the concept of a "drug resistant epileptogenic zone" was born (Zhang & Kwan, 2019), calling for further precision in identifying the "culprit nodes" within the large-scale epileptic network so that we could do more with less, i.e. to deliver more targeted interventions, including in those patients previously rejected from epilepsy surgery programmes, due to a lack of "concordant findings" thus left with little choice in an "all or none" situation, with a smaller impact on the patient's neurocognition and quality of life. The drug resistant epileptogenic zone concept may potentially open up new avenues for surgical and pharmacological synergy, from clinical trials of novel therapeutic agents to advances in autoregulatory antiepileptic gene therapies (Lieb et al., 2018) ultimately translating into high standards of clinical care for people with epilepsy. The DREZ driven approach, if verified, could transform presurgical evaluation strategies highlighting the need for stratified precision in the identification of the epileptogenic zone thus influencing the development of new epilepsy imaging techniques and revisiting new properties of already well-established imaging modalities.

The findings of the current study demonstrated the role of $^{18}$FDG-PET in the selection of surgical candidates and presurgical planning with $^{18}$FDG-PET being a promising neurometabolic biomarker for the evaluation of epileptic networks implicated in the

development of drug resistant epilepsy. The laterality-specific finding of bitemporal $^{18}$FDG-PET hypometabolism being associated with a heightened risk of seizure recurrence in right MTLE patients warrants further studies into the exact neurobiological meaning of this finding. It would be critical to investigate as to whether or not bitemporal hypometabolism is indicative of a hub and spoke type of neuronal dysfunction in this patient group, whereby a new, mirroring epileptic hub is formed over time in the contralateral temporal lobe following the original epilepsy surgery intervention. This could be achieved by a larger cohort study of surgical failures in a right MTLE patient cohort.

The trend for impaired arbitrary learning associated with bitemporal $^{18}$FDG-PET hypometabolism in the right MTLE cohort could be indicative of left temporal lobe dysfunction in this patient group. Therefore, further larger cohort studies are warranted to evaluate the role of arbitrary learning as a candidate neurocognitive biomarker of left temporal lobe dysfunction in patients with right MTLE. It would be important to understand as to whether or not and as to how soon into the epilepsy onset the deleterious effects of bitemporal dysfunction in this patient cohort are likely to become apparent and what their impact on the patients' quality of life would be. The findings would inform us of the need for timely neurocognitive interventions which could be implemented earlier on. It would also be crucial for presurgical planning whereby the functional reserve of the contralateral, i.e. left, hippocampus would need to be assessed in detail in order to determine the potential neurocognitive costs of surgical intervention, refine surgical strategy and deploy neurocognitive prehabilitation measures in order to provide the patients with the optimal surgical outcomes. From a practical point of view, further study is warranted to determine if right MTLE patients with unfavourable seizure outcomes had unexpected non-lateralising findings of a comprehensive neuropsychological assessment stemming from verbal memory impairment to which these group of patients were not "entitled" to. The use of task-specific neurocognitive tests could flag up protosemantic memory deficits indicative of bitemporal dysfunction in patients with right MTLE. This, in turn, would prompt further evaluation to inform surgical decision-making and preoperative counselling.

The findings of the study looking into the lateralising value of largely material-specificity based neuropsychological tests currently employed in the presurgical evaluation highlighted the need to identify task-specific neurocognitive tools befitting the complexity and heterogeneity of the epileptic networks (Wilson & Baxendale, 2014;

Saling, 2009). Considering specific anatomo-electro-clinical subtypes identified within the MTLE syndrome (Bartolomei et al., 2008; Kahane & Bartolomei, 2010) their neurometabolic correlates deserve further attention. In the SEEG era this could be pursued using a novel hybrid MRI/PET neuroimaging modality allowing for higher precision and integration of the data derived from functional and structural connectivity studies (Aiello et al., 2016; Watabe & Hatazawa, 2019). This would be particularly timely in light of the recent findings by Reyes *et al* who described four distinct neurocognitive phenotypes in patients with TLE based on the outcome of structural connectivity studies (Reyes et al., 2019). Approaching this task in a patient-driven fashion would open up new opportunities for identifying neurocognitive markers thereby increasing the lateralising and also the localising value of the neuropsychological tests employed in the presurgical evaluation. The use of neurospecific cognitive markers could potentially assist with ascertaining the extent of the epileptic network involvement through the identification of neurocognitive phenotypes, manifesting with either mesial or lateral versus widespread temporal lobe dysfunction and highlighting the unexpected neurocognitive deficits, which could influence surgical planning. For example, the identification of neurocognitive phenotypes characteristic of the TLE-plus patient cohort and those presenting with TLE-mimics would enable us to tailor the presurgical evaluation strategies and minimise the likelihood of surgical failures (Barba et al., 2016).

Refining our approach to identifying specific neurocognitive biomarkers befitting not only the immediate needs of the presurgical evaluation, but also translating into ecologically valid neurocognitive measures would influence the long term patient-centred care with improved quality of life being the ultimate goal of our therapeutic interventions, be that surgical or pharmacological epilepsy treatments. The current study demonstrated the limited real world clinical utility of CT/PET in predicting memory deficits in patients with drug resistant MTLE focusing on the temporal lobe as a region of interest, the wider use of MRI/PET in epilepsy research and clinical settings offers new exciting opportunities for neurocognitive studies including the future exploits of the role of DMN in epilepsy cognition. It would be important to explore the extra-temporal sequelae of focal epilepsies, including MTLE. In light of the complex functional neuro-anatomical properties of mesial temporal structures, including the extra-hippocampal and extra-temporal seizure propagation pathways it would be important to study the neurocognitive sequelae of bitemporal and frontal lobe

dysfunction resulting from the involvement of hodological projections in the epileptogenic process and the impact of these neurocognitive deficits on the patients quality of life. The findings of white matter connectivity studies highlight the importance of extra-temporal outlets of the temporal lobe reflected by Wallerian degeneration patterns following an ATLR (Winston et al., 2014). In addition, the latest evidence of tau pathology seen outside the boundaries of the temporal lobe in patients with drug resistant MTLE, irrespective of concomitant CTE (Smith et al., 2019), broadens our understanding of the far reaching sequelae of focal epilepsies and their clinical implications.

It is critical to study the reasons for our surgical failures as well as identifying their predictors. Focusing solely on the predictors of surgical failure may divert our attention away from what could be learnt from the surgical successes and be potentially helpful to our patients, therefore the studies of favourable surgical outcomes are of no less importance. Despite the fact that the use of the ILAE seizure outcome classification was proposed almost a decade ago (Commission on Neurosurgery of the International League Against Epilepsy et al., 2001), the Engel Surgical Outcome Scale has not lost its relevance and popularity and continues to be widely used by researchers and clinicians alike. While the category of "worthwhile improvement" surgical outcome has been repeatedly criticised as imprecise, it, however, reflects the goal of our therapeutic undertakings. In other words, it rests with the patient to decide on whether or not the epilepsy surgery transformed or significantly improved his/her quality of life, which counts over and above the absolute seizure count. This approach would continue to influence how we care for our patients, especially in light of the nascent concept of DREZ. This is likely to influence our surgical strategies for years to come. Having a realistic approach to epilepsy surgery gains and costs to the patients would enable us to refine and combine surgical interventions and devise a DREZ specific treatment strategy that would appeal to our patients thus assuring the patients engagement in the fight against epilepsy. One must not forget that epilepsy surgery remains a highly underutilised treatment option and so a fresh approach to its delivery is warranted.

The granular approach to studying favourable surgical outcomes has the potential to inform our understanding of epilepsy neurobiology similarly to what we gain from dissecting the surgical failures. Tolstoy's "happy families are all alike; every unhappy family is unhappy in its own way" would not necessarily apply when it comes to

favourable surgical outcome categories, which are more heterogeneous than surgical failures. The patients who no longer experience impaired awareness seizures or those free from disabling seizures even if it comes at the cost of continuing on lifelong AED treatment could feel that their lives have been transformed compared to those patients where a IA outcome was achieved. This could prove particularly rewarding, if we could learn early on what DREZ may constitute so that long-term management strategies could be devised, especially considering the findings of recent studies focusing on postoperative connectivity patterns and their relationship with the seizure outcome (Maccotta et al., 2017; Victoria et al., 2019). For example, Maccotta *et al* has shown that aberrant connectivity changes appeared to persist despite favourable surgery outcomes (Maccotta et al., 2017). It would be important to understand if the patients with persistent connectivity changes following an ATLR would be at heightened risk of seizure recurrence following AED withdrawal and whether or not sustained connectivity changes are representative of DREZ. Also, in light of the wider SEEG use and the range of multimodal imaging modalities available to us today it would be crucial to understand the exact mechanisms behind DREZ within the framework of the epileptic networks, which clearly have far reaching consequences in patients with TLE, and what neuroprotective mechanisms keep those "auras only" clinical manifestations "in check", gating and shielding the patients from seizure progression to impaired awareness and focal-to-bilateral generalised convulsions following epilepsy surgery. It would also be important to study the small print and hidden costs associated with this particular surgical outcome category, including the influence of on-going auras on postoperative connectivity patterns and their clinical significance.

The findings of the study looking into the relationship between postoperative gliosis and late seizure recurrence suggest a progressive nature of postoperative gliogenesis. These, along with the wide range of the extent of postoperative gliosis observed in the postoperative period, notwithstanding the case reports of "SEEG-induced" seizure freedom, albeit temporarily, begs more than a single question. To begin with, the epileptogenic properties of reactive astrocytes have now been recognised. However, astrogliosis, also known as reactive astrocytosis, was originally programmed to execute neuroprotective effects in the face of neuronal injury. In the meantime, there are different populations of astrocytes with their respective roles within the CNS and their functional properties, notwithstanding the molecular markers thereby allowing for differentiating one subset from another (Bush et al., 1999; Sofroniew, 2014). Thus, it

would be important to study the relationship not only between the extent of the gliogenesis but also the molecular properties of the reactive astrocytes in association with all categories of seizure outcomes in a larger patient cohort, which could be feasible considering the success of the large-scale collaborative efforts such as the ENIGMA project (Thompson et al., 2017). It is clear that reactive astrocytes could display both, neuroprotective properties, including the sequestration of excessive glutamate on one hand (Boghdadi et al., 2020), while taking part in epileptogenesis on the other hand (Degen et al., 2012; Murphy et al., 2017). Once the markers of the different characteristics of both neuroprotective and epileptogenic astrocytes are fully understood, astrocyte phenotyping could help us distinguish between the two populations, which in turn could inform our therapeutic strategies (Shinozaki et al., 2017).

It would also be warranted to explore as to whether or not the concomitant presence of haemosiderin, including its extent, influences the process of gliogenesis and the properties of reactive astrocytes. Further, with the wider use of SEEG and LiTT/RFTC, one could study not only the longitudinal changes occurring in the glial scar in patients undergoing resective surgery following SEEG or failed LiTT/RFTC, but also the characteristics of the astroglial formation depending on the type of intervention and the techniques used, i.e. resective surgery, thermal ablation, which in turn could then be modified accordingly and potentially enhanced using alternative surgical techniques or local administration of gliosis-modulating agents intra-operatively. Importantly, it has been shown that the process of astrocyte signalling could vary, depending on both, the type of the CNS insult and also on its intensity (Sofroniew, 2014). It would therefore be important to study the properties of different populations of astrocytes exercising either neuroprotective or neurotoxic effects in a particular clinical setting (Liddelow et al., 2017). This could enhance our understanding of the neurobiological basis of reactive astrocytosis following traumatic brain injury or stroke, and potentially influence therapeutic strategies in patients with post-traumatic and stroke-related epilepsy.

It would be interesting to explore as to whether or not the extent of the preoperative $^{18}$FDG-PET hypometabolism has any bearing on the extent of the postoperative gliogenesis and the properties of reactive astrocytes. This could offer additional insights into the neurobiology of CNS regeneration. Importantly, the long-term follow-up studies of patients with “SEEG-induced” seizure remission and the study of the

pathological changes in patients undergoing subsequent resective surgery would inform further understanding of DREZ and the role of DREZ specific reactive astrocytosis in disrupting the epileptogenic networks, albeit temporarily. Should that prove to be the case, one could consider "weaponising" the antiepileptic population of astrocytes applying molecular engineering techniques and down-regulating the populations of astrocytes with maladaptive properties (Leonard et al, 2019).

Following on from the study by Vinton *et al* (Vinton et al., 2007), the findings of current research, showing a trend for larger $^{18}$FDG-PET resections being associated with a favourable outcome in left MTLE patients, could be of clinical significance in light of a nascent posit of DREZ. It has long been proposed that the critical mass of epileptogenic tissue had to be removed in order to render the patient seizure free. The findings of Galovic *et al*, for example, not only suggest that the piriform cortex plays a crucial role in seizure generation in patients with drug-resistant TLE but also that the volume of its excision, i.e. at least 50%, proves to be critical to achieving seizure freedom following an ATLR (Galovic et al., 2019). These findings beget further inferences in relation to DREZ, the mere concept of which opens up new avenues into future research involving larger prospective studies substantiated by the use of preoperative SEEG so that the neurometabolic biomarkers of DREZ could be identified. The challenge lies in identifying this critical mass, while being essentially blindfolded to the exact location and also the extent of the epileptogenic tissue, something that faces the Epilepsy Surgery MTD on a regular basis despite the recent advances in neuroimaging modalities and computer-assisted software. Considering the findings of Lamarche *et al*, demonstrating an association between $^{18}$FDG-PET hypometabolism and pathologic HFO's (Lamarche et al., 2016), it is plausible that the greater the extent of the $^{18}$FDG-PET hypometabolism could result in merely a wider excision of DREZ. The advances in hybrid, i.e. PET/MRI scanning modalities, benefitting from high spatial resolution, have the distinct potential for unravelling neurometabolic biomarkers of potential DREZ, including that imbedded within the piriform cortex, which appears to be a pivotal node within the epileptogenic networks implicated in drug resistant TLE.

Previous studies have demonstrated the role of P-glycoprotein as a marker of drug resistance (Feldmann et al., 2013; Kwan et al., 2010). It has subsequently been shown that seizure control results in the down-regulation of P-glycoprotein expression (Bauer et al., 2014). It would be therefore essential to explore the role of P-glycoprotein

specific radiotracers in circumscribing the DREZ with a view of pursuing DREZ targeted interventions so that a comprehensive surgical strategy could be devised, utilising all the means we currently have in our armamentarium, from resective and minimally invasive neurosurgical interventions to opto- and chemogenetic techniques (Walker & Kullmann, 2020).

Importantly, studies of P-glycoprotein expression have been traditionally focused on the components of the blood brain barrier (BBB) with evidence of P-glycoprotein expression found in the endothelial cells, astrocytes and subsequently in hippocampal neurons, to a lesser extent (Volk et al., 2004). Considering that the BBB has been reconceptualised as a dynamic as opposed to static neurovascular unit characterised by an interaction between all three key players, i.e. endothelial cells, astrocytes and neurons, with the astrocytes playing a major role in modulating the permeability of the BBB through up-regulating the expression of P-glycoprotein and GLUT1 (Abbott et al., 2006), further inquiry into the interplay between astrocyte populations and P-glycoprotein expression not only within DREZ but within the global context of drug resistance is warranted. Given the fact that there are least 11 known distinct types of astrocyte phenotypes and with 8 of them being associated with supporting the BBB function, it is not inconceivable that astrocyte related aberrances play an important role in multidrug resistance. Moreover, it has been shown that the sub-populations of intra-cortical astrocytes, with their characteristic functional properties, specific not only to particular brain regions but also cortical layers, are involved in synaptic transmission (Morel et al., 2019). Understanding the characteristics of neurotoxic astrocytes could potentially influence the development of gene silencing technologies, whereby the relevant therapeutics could be introduced intrathecally (Alterman et al., 2019).

While the extent of the $^{18}$FDG uptake has been traditionally seen as a proxy marker of neuronal function, recent evidence suggests that astrocytes play a more substantial role in cerebral glucose metabolism than previously thought (Volterra & Meldolesi, 2005). GLUT1 expressed in the bodies and end-feet of astrocytes is instrumental in transporting glucose to astrocytes, which is then metabolised into lactate and subsequently utilised by the neurons as a source of energy. Zimmer *et al* have shown that astrocytes play a significant role in the $^{18}$FDG uptake thus suggesting that the granular approach to the $^{18}$FDG-PET evaluation data was warranted, whereby one should attempt and distinguish between a neuronal and astrocytic contribution towards

$^{18}$FDG uptake and its respective changes resulting from neuronal or astrocyte dysfunction (Zimmer et al., 2017). It has also been suggested that reduced $^{18}$FDG uptake could be a biomarker of BBB dysfunction (Sweeney et al., 2019) and it would be interesting to see as to whether or not there is an association with drug resistance. With $^{18}$FDG-PET being a recognised biomarker of neurodegeneration (Jack et al., 2018), its use in epilepsy research could shed more light not only on neurodegenerative changes observed in patients with drug resistant TLE but also allow us to explore as to whether or not DREZ tissue could be differentiated from the rest of the brain by accelerated rates of neurodegenerative processes within it, notwithstanding the interplay between phosphorylated tau deposits and P-glycoprotein expression in patients with drug resistant epilepsy, which might be different from that observed in AD patients. Future $^{18}$FDG-PET studies focusing on DREZ properties and also longitudinal $^{18}$FDG-PET studies in patients with epilepsy show the distinct potential for enhancing our understanding of epilepsy neurobiology and transforming the care of patients with drug resistant epilepsy through exploring potential targets for therapeutic interventions. This brings us to conclude that the role of $^{18}$FDG-PET in predicting seizure and memory deficits in patients with drug resistant epilepsy extends beyond what has been studied and calls for further exciting studies exploring the role of $^{18}$FDG-PET as an independent biomarker of both neuronal and astrocyte dysfunction informing novel therapeutic strategies in the field of epilepsy surgery and pharmacological treatment of patients with epilepsy.

## 8.3 Conclusions

The results of this study confirm the findings of previous research pertaining to laterality-specific differential epileptic network involvement in patients with drug resistant TLE and extend them in several ways. The discovery of significantly greater rates of bitemporal $^{18}$FDG-PET hypometabolism in patients with right MTLE and its association with a heightened risk of postoperative seizure recurrence can influence the selection of surgical candidates and patient counseling.

Furthermore, the role of arbitrary learning, a potential candidate biomarker of left mesial temporal lobe dysfunction in patients with right MTLE, warrants further research with the prospect of identifying surgical candidates who are at greater risk of postoperative memory decline as a result of limited left hippocampal reserve. This could influence not only epilepsy surgery counseling but highlight the need for timely prehabilitation measures. In addition, the patients with right MTLE and neurocognitive deficits could be identified and supported early on thus mitigating the impact of the neurocognitive deficits on their quality of life.

The results of the study examining the lateralising value of the neurocognitive tests routinely used in clinical care extended the findings of previous research and highlighted the need for task-specific neurocognitive markers purpose built for epilepsy care. The study of the role of postoperative astrogliosis in late seizure recurrence triggered fresh thoughts on the potential role of reactive astrocytes following epilepsy surgery, which could potentially be either neuroprotective or maladaptive and therefore deserves further investigation.

The role of $^{18}$FDG-PET in predicting seizure and memory deficits in patients with drug resistant epilepsy extends far beyond what has been studied. The nascent introduction of hybrid PET/MRI into research and clinical practice holds the distinct promise to enhance our understanding of the neurobiology of the DREZ and neurodegenerative process in epilepsy using the synergy of unique molecular imaging in the setting of high spatial resolution. Further understanding of the role of $^{18}$FDG-PET as an independent biomarker of neuronal and astrocyte dysfunction opens up new avenues for developing therapeutic strategies with a view of advancing the care of people with epilepsy.

# References


Aaron, A. C.-G., Christopher, C. B., Anne, W., Jung, H. K., Michael, W., Robert, B. D., & Dennis, D. S. (2005). Normal magnetic resonance imaging and medial temporal lobe epilepsy: the clinical syndrome of paradoxical temporal lobe epilepsy. *Journal of Neurosurgery, 102*(5), 902-909. doi:10.3171/jns.2005.102.5.0902

Abbott, N. J., Rönnbäck, L., & Hansson, E. (2006). Astrocyte–endothelial interactions at the blood–brain barrier. *Nature Reviews Neuroscience, 7*(1), 41-53. doi:10.1038/nrn1824

Abou-Khalil, B. (2007). An update on determination of language dominance in screening for epilepsy surgery: the Wada test and newer noninvasive alternatives. *Epilepsia, 48*(3), 442-455. doi:10.1111/j.1528-1167.2007.01012.x

Abou-Khalil, B. W., Siegel, G. J., Sackellares, J. C., Gilman, S., Hichwa, R., & Marshall, R. (1987). Positron emission tomography studies of cerebral glucose metabolism in chronic partial epilepsy. *Annals of Neurology, 22*(4), 480-486. doi:10.1002/ana.410220407

Aghakhani, Y., Liu, X., Jette, N., & Wiebe, S. (2014). Epilepsy surgery in patients with bilateral temporal lobe seizures: a systematic review. *Epilepsia, 55*(12), 1892-1901. doi:10.1111/epi.12856

Aiello, M., Cavaliere, C., & Salvatore, M. (2016). Hybrid PET/MR Imaging and Brain Connectivity. *Frontiers in neuroscience, 10*, 64-64. doi:10.3389/fnins.2016.00064

Äikiä, M., Salmenperä, T., Partanen, K., & Kälviäinen, R. (2001). Verbal Memory in Newly Diagnosed Patients and Patients with Chronic Left Temporal Lobe Epilepsy. *Epilepsy & Behavior, 2*(1), 20-27. doi:10.1006/ebeh.2000.0140

Akanuma, N., Koutroumanidis, M., Adachi, N., AlarcÓN, G., & Binnie, C. D. (2003). Presurgical assessment of memory-related brain structures: the Wada test and functional neuroimaging. *Seizure, 12*(6), 346-358. doi:10.1016/s1059-1311(02)00323-0

Akman, C. I., Ichise, M., Olsavsky, A., Tikofsky, R. S., Van Heertum, R. L., & Gilliam, F. (2010). Epilepsy duration impacts on brain glucose metabolism in temporal lobe epilepsy: results of voxel-based mapping. *Epilepsy & behavior : E&B, 17*(3), 373-380. doi:10.1016/j.yebeh.2009.12.007

Alarcón, G., Guy, C., Binnie, C. D., Walker, S. R., Elwes, R., & Polkey, C. E. (1994). Intracerebral propagation of interictal activity in partial epilepsy: Implications for source localisation. *Journal of neurology, neurosurgery, and psychiatry, 57*, 435-449. doi:10.1136/jnnp.57.4.435

Alsaadi, T. M., Ulmer, J. L., Mitchell, M. J., Morris, G. L., Swanson, S. J., & Mueller, W. M. (2001). Magnetic resonance analysis of postsurgical temporal lobectomy. *J Neuroimaging, 11*(3), 243-247.

Alsfouk, B. A. A., Brodie, M. J., Walters, M., Kwan, P., & Chen, Z. (2020). Tolerability of Antiseizure Medications in Individuals With Newly Diagnosed Epilepsy. *JAMA Neurology*, e200032. doi:10.1001/jamaneurol.2020.0032

Alterman, J. F., Godinho, B. M. D. C., Hassler, M. R., et al. (2019). A divalent siRNA chemical scaffold for potent and sustained modulation of gene expression throughout the central nervous system. *Nature Biotechnology, 37*(8), 884-894. doi:10.1038/s41587-019-0205-0

Andermann, F. (2003). Pseudotemporal vs neocortical temporal epilepsy: Things aren't always where they seem to be. *Neurology, 61*, 732-733. doi:10.1212/WNL.61.6.732

Anderson, C. T., Noble, E., Mani, R., Lawler, K., & Pollard, J. R. (2013). Epilepsy surgery: factors that affect patient decision-making in choosing or deferring a procedure. *Epilepsy research and treatment, 2013*, 309284-309284. doi:10.1155/2013/309284

Araújo, R., Firmino-Machado, J., Correia, P., et al. (2015). The plantar reflex: A study of observer agreement, sensitivity, and observer bias. *Neurology. Clinical practice, 5*(4), 309-316. doi:10.1212/CPJ.0000000000000155

Arnold, S., Schlaug, G., Niemann, H., Ebner, A., Lüders, H., Witte, O. W., & Seitz, R. J. (1996). Topography of interictal glucose hypometabolism in unilateral mesiotemporal epilepsy. *Neurology, 46*(5), 1422-1430.

Aroniadou-Anderjaska, V., Fritsch, B., Qashu, F., & Braga, M. F. M. (2008). Pathology and pathophysiology of the amygdala in epileptogenesis and epilepsy. *Epilepsy Research, 78*(2-3), 102-116. doi:10.1016/j.eplepsyres.2007.11.011

Arruda, F., Cendes, F., Andermann, F., et al. (1996). Mesial atrophy and outcome after amygdalohippocampectomy or temporal lobe removal. *Annals of Neurology, 40*(3), 446-450. doi:10.1002/ana.410400314

Ashburner, J., & Ridgway, G. (2013). Symmetric Diffeomorphic Modeling of Longitudinal Structural MRI. *Frontiers in neuroscience, 6*, 197.

Balter, S., Lin, G., Leyden, K. M., Paul, B. M., & McDonald, C. R. (2019). Neuroimaging correlates of language network impairment and reorganization in temporal lobe epilepsy. *Brain Lang, 193*, 31-44. doi:10.1016/j.bandl.2016.06.002

Bandopadhyay, R., Liu, J., Sisodiya, S., & Thom, M. (2013). A Comparative Study of the Dentate Gyrus in Hippocampal Sclerosis in Epilepsy and Dementia. *Neuropathology and applied neurobiology, 40*. doi:10.1111/nan.12087

Barba, C., Barbati, G., Minotti, L., Hoffmann, D., & Kahane, P. (2007). Ictal clinical and scalp-EEG findings differentiating temporal lobe epilepsies from temporal 'plus' epilepsies. *Brain, 130*(Pt 7), 1957-1967. doi:10.1093/brain/awm108

Barba, C., Rheims, S., Minotti, L., et al. (2016). Temporal plus epilepsy is a major determinant of temporal lobe surgery failures. *Brain, 139*(Pt 2), 444-451. doi:10.1093/brain/awv372

Barbaro, N. M., Quigg, M., Ward, M. M., et al. (2018). Radiosurgery versus open surgery for mesial temporal lobe epilepsy: The randomized, controlled ROSE trial. *Epilepsia, 59*(6), 1198-1207. doi:10.1111/epi.14045

Bargalló, N., Cano-López, I., Rosazza, C., et al. (2020). Clinical practice of language fMRI in epilepsy centers: a European survey and conclusions by the ESNR Epilepsy Working Group. *Neuroradiology*. doi:10.1007/s00234-020-02397-w

Barr, W. (1997). Receiver Operating Characteristic Curve Analysis of Wechsler Memory Scale - Revised Scores in Epilepsy Surgery Candidates. *Epilepsia, 38*, 171-176.

Bartolomei, F., Barbeau, E., Gavaret, M., Guye, M., McGonigal, A., Régis, J., & Chauvel, P. (2004). Cortical stimulation study of the role of rhinal cortex in déjà vu and reminiscence of memories. *Neurology, 63*(5), 858. doi:10.1212/01.WNL.0000137037.56916.3F

Bartolomei, F., Chauvel, P., & Wendling, F. (2008). Epileptogenicity of brain structures in human temporal lobe epilepsy: a quantified study from intracerebral EEG. *Brain, 131*(Pt 7), 1818-1830. doi:10.1093/brain/awn111

Bartolomei, F., Cosandier-Rimele, D., McGonigal, A., et al. (2010). From mesial temporal lobe to temporoperisylvian seizures: A quantified study of temporal

lobe seizure networks. *Epilepsia, 51*(10), 2147-2158. doi:10.1111/j.1528-1167.2010.02690.x

Bartolomei, F., Khalil, M., Wendling, F., et al. (2005). Entorhinal Cortex Involvement in Human Mesial Temporal Lobe Epilepsy: An Electrophysiologic and Volumetric Study. *Epilepsia, 46*(5), 677-687. doi:10.1111/j.1528-1167.2005.43804.x

Bartolomei, F., Lagarde, S., Wendling, F., McGonigal, A., Jirsa, V., Guye, M., & Bénar, C. (2017). Defining epileptogenic networks: Contribution of SEEG and signal analysis. *Epilepsia, 58*(7), 1131-1147. doi:10.1111/epi.13791

Bauer, M., Karch, R., Zeitlinger, M., et al. (2014). In vivo P-glycoprotein function before and after epilepsy surgery. *Neurology, 83*(15), 1326-1331. doi:10.1212/WNL.0000000000000858

Baxendale, S. (2018). Neuropsychological assessment in epilepsy. *Practical Neurology, 18*, practneurol-2017. doi:10.1136/practneurol-2017-001827

Baxendale, S. (2020a). The cognitive costs, contraindications and complications of epilepsy surgery in adults. *Curr Opin Neurol, 33*(2).

Baxendale, S. (2020b). Cognitive rehabilitation and prehabilitation in people with epilepsy. *Epilepsy & Behavior, 106*, 107027. doi:10.1016/j.yebeh.2020.107027

Baxendale, S., & Thompson, P. (2017). Red flags in epilepsy surgery: Identifying the patients who pay a high cognitive price for an unsuccessful surgical outcome. *Epilepsy & behavior : E&B, 78*. doi:10.1016/j.yebeh.2017.08.003

Baxendale, S., Thompson, P., Harkness, W., & Duncan, J. (2006). Predicting memory decline following epilepsy surgery: a multivariate approach. *Epilepsia, 47*(11), 1887-1894. doi:10.1111/j.1528-1167.2006.00810.x

Baxendale, S., Thompson, P., & Sander, L. (2013). Neuropsychological outcomes in epilepsy surgery patients with unilateral hippocampal sclerosis and good preoperative memory function. *Epilepsia, 54*. doi:10.1111/epi.12319

Baxendale, S., Thompson, P. J., & Duncan, J. S. (2008a). Improvements in memory function following anterior temporal lobe resection for epilepsy. *Neurology, 71*(17), 1319. doi:10.1212/01.wnl.0000319699.04265.fd

Baxendale, S., Thompson, P. J., & Duncan, J. S. (2008b). The role of the Wada test in the surgical treatment of temporal lobe epilepsy: An international survey. *Epilepsia, 49*(4), 715-720. doi:10.1111/j.1528-1167.2007.01515_1.x

Baxendale, S., Thompson, P. J., & Sander, J. W. (2013). Neuropsychological outcomes in epilepsy surgery patients with unilateral hippocampal sclerosis and good preoperative memory function. *Epilepsia, 54*(9), e131-134. doi:10.1111/epi.12319

Baxendale, S., Wilson, S. J., Baker, G. A., et al. (2019). Indications and expectations for neuropsychological assessment in epilepsy surgery in children and adults: Executive summary of the report of the ILAE Neuropsychology Task Force Diagnostic Methods Commission: 2017-2021. *Epilepsia, 60*(9), 1794-1796. doi:10.1111/epi.16309

Begley, C. E., Famulari, M., Annegers, J. F., et al. (2000). The Cost of Epilepsy in the United States: An Estimate from Population-Based Clinical and Survey Data. *Epilepsia, 41*(3), 342-351. doi:10.1111/j.1528-1157.2000.tb00166.x

Bell, B., Lin, J., Seidenberg, M., & Hermann, B. (2011). The neurobiology of cognitive disorders in temporal lobe epilepsy. *Nature reviews. Neurology, 7*, 154-164. doi:10.1038/nrneurol.2011.3

Bell, B. D., & Davies, K. G. (1998). Anterior temporal lobectomy, hippocampal sclerosis, and memory: recent neuropsychological findings. *Neuropsychol Rev, 8*(1), 25-41.

Bell, G. S., Sinha, S., Tisi, J., et al. (2010). Premature mortality in refractory partial epilepsy: Does surgical treatment make a difference? *Journal of neurology, neurosurgery, and psychiatry, 81*, 716-718. doi:10.1136/jnnp.2008.170837

Benbadis, S. R., Heriaud, L., Tatum, W. O., & Vale, F. L. (2003). Epilepsy surgery, delays and referral patterns—are all your epilepsy patients controlled? *Seizure, 12*(3), 167-170. doi:10.1016/s1059-1311(02)00320-5

Benjamin, C. F. A., Li, A. X., Blumenfeld, H., et al. (2018). Presurgical language fMRI: Clinical practices and patient outcomes in epilepsy surgical planning. *Human brain mapping, 39*(7), 2777-2785. doi:10.1002/hbm.24039

Berg, A. T., Berkovic, S. F., Brodie, et al. (2010). Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia, 51*(4), 676-685. doi:10.1111/j.1528-1167.2010.02522.x

Berkovic, S. F., McIntosh, A., Kalnins, R. M., et al. (1995). Preoperative MRI predicts outcome of temporal lobectomy: An actuarial analysis. *Neurology, 45*, 1358-1363. doi:10.1212/WNL.45.7.1358

Bernasconi, A., & Bernasconi, N. (2011). Unveiling epileptogenic lesions: The contribution of image processing. *Epilepsia, 52*(s4), 20-24. doi:10.1111/j.1528-1167.2011.03146.x

Bernhardt, B. C., Bernasconi, A., Liu, M., et al. (2016). The spectrum of structural and functional imaging abnormalities in temporal lobe epilepsy. *Ann Neurol, 80*(1), 142-153. doi:10.1002/ana.24691

Bertram, E. H. (2003). Why does surgery fail to cure limbic epilepsy?: Seizure functional anatomy may hold the answer. *Epilepsy Research, 56*(2), 93-99. doi:10.1016/j.eplepsyres.2003.10.003

Besson, P., Bandt, S. K., Proix, T., et al. (2017). Anatomic consistencies across epilepsies: a stereotactic-EEG informed high-resolution structural connectivity study. *Brain : a journal of neurology, 140*(10), 2639-2652. doi:10.1093/brain/awx181

Besson, P., Dinkelacker, V., Valabregue, R., et al. (2014). Structural connectivity differences in left and right temporal lobe epilepsy. *Neuroimage, 100*, 135-144. doi:10.1016/j.neuroimage.2014.04.071

Bettus, G., Bartolomei, F., Confort-Gouny, S., et al. (2010). Role of resting state functional connectivity MRI in presurgical investigation of mesial temporal lobe epilepsy. *Journal of neurology, neurosurgery, and psychiatry, 81*(10), 1147-1154. doi:10.1136/jnnp.2009.191460

Bhaskara Rao, M., Terence, J. O. B., Gregory, D. C., Elson, L. S., Kurupath, R., Peter, S., & Marsh, W. R. (1998). Acute postoperative seizures following anterior temporal lobectomy for intractable partial epilepsy. *Journal of Neurosurgery, 89*(2), 177-182. doi:10.3171/jns.1998.89.2.0177

Binder, J. R. (2011). Preoperative prediction of verbal episodic memory outcome using FMRI. *Neurosurg Clin N Am, 22*(2), 219-232, ix. doi:10.1016/j.nec.2010.12.002

Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where Is the Semantic System? A Critical Review and Meta-Analysis of 120 Functional Neuroimaging Studies. *Cerebral Cortex, 19*(12), 2767-2796. doi:10.1093/cercor/bhp055

Biraben, A., Taussig, D., Thomas, P., Even, C., Vignal, J. P., Scarabin, J. M., & Chauvel, P. (2001). Fear as the main feature of epileptic seizures. *Journal of neurology, neurosurgery, and psychiatry, 70*, 186-191. doi:10.1136/jnnp.70.2.186

Bjellvi, J., Olsson, I., Malmgren, K., & Wilbe Ramsay, K. (2019). Epilepsy duration and seizure outcome in epilepsy surgery. *Neurology, 93*(2), e159. doi:10.1212/WNL.0000000000007753

Black, L. C., Schefft, B. K., Howe, S. R., Szaflarski, J. P., Yeh, H.-s., & Privitera, M. D. (2010). The effect of seizures on working memory and executive functioning performance. *Epilepsy & Behavior, 17*(3), 412-419. doi:10.1016/j.yebeh.2010.01.006

Blanc, F., Martinian, L., Liagkouras, I., Catarino, C., Sisodiya, S. M., & Thom, M. (2011). Investigation of widespread neocortical pathology associated with hippocampal sclerosis in epilepsy: A postmortem study. *Epilepsia, 52*(1), 10-21. doi:10.1111/j.1528-1167.2010.02773.x

Blum, D. E., Ehsan, T., Dungan, D., Karis, J. P., & Fisher, R. S. (1998). Bilateral temporal hypometabolism in epilepsy. *Epilepsia, 39*(6), 651-659.

Blümcke, I., Aronica, E., Miyata, H., et al. (2016). International recommendation for a comprehensive neuropathologic workup of epilepsy surgery brain tissue: A consensus Task Force report from the ILAE Commission on Diagnostic Methods. *Epilepsia, 57*. doi:10.1111/epi.13319

Blümcke, I., Aronica, E., Miyata, H., et al. (2016). International recommendation for a comprehensive neuropathologic workup of epilepsy surgery brain tissue: A consensus Task Force report from the ILAE Commission on Diagnostic Methods. *Epilepsia, 57*(3), 348-358. doi:10.1111/epi.13319

Blümcke, I., Spreafico, R., Haaker, G., et al. (2017). Histopathological Findings in Brain Tissue Obtained during Epilepsy Surgery. *New England Journal of Medicine, 377*, 1648-1656. doi:10.1056/NEJMoa1703784

Blümcke, I., Thom, M., Aronica, E., et al. (2013). International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: a Task Force report from the ILAE Commission on Diagnostic Methods. *Epilepsia, 54*(7), 1315-1329. doi:10.1111/epi.12220

Blümcke, I., Thom M., & Wiestler, O. D. (2002). Ammon's Horn Sclerosis: A Maldevelopmental Disorder Associated with Temporal Lobe Epilepsy. *Brain Pathology, 12*(2), 199-211. doi:10.1111/j.1750-3639.2002.tb00436.x

Blume, W. T. (2011). Interpreting Seizure Counts after Temporal Lobectomy: Not Just One-Two-Three: Interpreting Seizure Counts. *Epilepsy Currents, 11*(2), 52-53. doi:10.5698/1535-7511-11.2.52

Blumenfeld, H. (2012). Impaired consciousness in epilepsy. *The Lancet Neurology, 11*(9), 814-826. doi:10.1016/S1474-4422(12)70188-6

Boatman, D. F., Lesser, R. P., Crone, N. E., Krauss, G., Lenz, F. A., & Miglioretti, D. L. (2006). Speech Recognition Impairments in Patients with Intractable Right Temporal Lobe Epilepsy. *Epilepsia, 47*(8), 1397-1401. doi:10.1111/j.1528-1167.2006.00562.x

Boellaard, R., O'Doherty, M. J., Weber, W. A., et al. (2009). FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. *Eur J Nucl Med Mol Imaging, 37*(1), 181. doi:10.1007/s00259-009-1297-4

Boes, A. D., Prasad, S., Liu, H., Liu, Q., Pascual-Leone, A., Caviness, V. S., Jr., & Fox, M. D. (2015). Network localization of neurological symptoms from focal brain lesions. *Brain, 138*(10), 3061-3075. doi:10.1093/brain/awv228

Boghdadi, A. G., Teo, L., & Bourne, J. A. (2020). The Neuroprotective Role of Reactive Astrocytes after Central Nervous System Injury. *Journal of Neurotrauma, 37*(5), 681-691. doi:10.1089/neu.2019.6938

Bonelli, S. B., Powell, R. H., Yogarajah, M., et al. (2010). Imaging memory in temporal lobe epilepsy: predicting the effects of temporal lobe resection. *Brain, 133*(Pt 4), 1186-1199. doi:10.1093/brain/awq006

Bonelli, S. B., Thompson, P. J., Yogarajah, M., et al. (2013). Memory reorganization following anterior temporal lobe resection: a longitudinal functional MRI study. *Brain, 136*(Pt 6), 1889-1900. doi:10.1093/brain/awt105

Bonilha, L., Yasuda, C. L., Rorden, C., Li, L. M., Tedeschi, H., de Oliveira, E., & Cendes, F. (2007). Does resection of the medial temporal lobe improve the outcome of temporal lobe epilepsy surgery? *Epilepsia, 48*(3), 571-578. doi:10.1111/j.1528-1167.2006.00958.x

Boon, P. A., Williamson, P. D., Fried, I., Spencer, D. D., Novelly, R. A., Spencer, S. S., & Mattson, R. H. (1991). Intracranial, intraaxial, space-occupying lesions in patients with intractable partial seizures: an anatomoclinical, neuropsychological, and surgical correlation. *Epilepsia, 32*(4), 467-476.

Boshuisen, K., Arzimanoglou, A., Cross, J., Uiterwaal, C., Polster, T., Nieuwenhuizen, O., & Braun, K. (2012). Timing of antiepileptic drug withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): A retrospective observational study. *Lancet neurology, 11*, 784-791. doi:10.1016/S1474-4422(12)70165-5

Bradford, B. M., Wijaya, C. A. W., & Mabbott, N. A. (2019). Discrimination of Prion Strain Targeting in the Central Nervous System via Reactive Astrocyte Heterogeneity in CD44 Expression. *Frontiers in Cellular Neuroscience, 13*, 411.

Brien, T. J., So, E. L., Mullan, B. P., et al. (1998). Subtraction ictal SPECT co - registered to MRI improves clinical usefulness of SPECT in localizing the surgical seizure focus. *Neurology, 50*(2), 445. doi:10.1212/WNL.50.2.445

Brinkmann, B. H., Manduca, A., & Robb, R. A. (1998). Optimized homomorphic unsharp masking for MR grayscale inhomogeneity correction. *IEEE Transactions on Medical Imaging, 17*(2), 161-171. doi:10.1109/42.700729

Bruehl, C., & Witte, O. W. (1995). Cellular activity underlying altered brain metabolism during focal epileptic activity. *Annals of Neurology, 38*(3), 414-420. doi:10.1002/ana.410380311

Buckingham, S. E., Chervoneva, I., Sharan, A., et al. (2010). Latency to first seizure after temporal lobectomy predicts long-term outcome. *Epilepsia, 51*(10), 1987-1993. doi:10.1111/j.1528-1167.2010.02721.x

Burneo, J. G., Shariff, S. Z., Liu, K., Leonard, S., Saposnik, G., & Garg, A. X. (2016). Disparities in surgery among patients with intractable epilepsy in a universal health system. *Neurology, 86*(1), 72-78. doi:10.1212/WNL.0000000000002249

Burneo, J. G., Villanueva, V., Knowlton, R. C., Faught, R. E., & Kuzniecky, R. I. (2008). Kaplan-Meier analysis on seizure outcome after epilepsy surgery: do gender and race influence it? *Seizure, 17*(4), 314-319. doi:10.1016/j.seizure.2007.10.002

Bush, T. G., Puvanachandra, N., Horner, C. H., et al. (1999). Leukocyte Infiltration, Neuronal Degeneration, and Neurite Outgrowth after Ablation of Scar-Forming, Reactive Astrocytes in Adult Transgenic Mice. *Neuron, 23*(2), 297-308. doi:10.1016/S0896-6273(00)80781-3

Camacho, D. L. A., & Castillo, M. (2007). MR Imaging of Temporal Lobe Epilepsy. *Seminars in Ultrasound, CT and MRI, 28*(6), 424-436. doi:10.1053/j.sult.2007.09.005

Carne, R. P., Cook, M. J., MacGregor, L. R., Kilpatrick, C. J., Hicks, R. J., & O'Brien, T. J. (2007). "Magnetic resonance imaging negative positron emission tomography positive" temporal lobe epilepsy: FDG-PET pattern differs from mesial temporal lobe epilepsy. *Mol Imaging Biol, 9*(1), 32-42. doi:10.1007/s11307-006-0073-0

Carne, R. P., O'Brien, T. J., Kilpatrick, C. J., et al. (2004). MRI-negative PET-positive temporal lobe epilepsy: a distinct surgically remediable syndrome. *Brain, 127*(Pt 10), 2276-2285. doi:10.1093/brain/awh257

Carne, R. P., O'Brien, T. J., Kilpatrick, C. J., Macgregor, L. R., Litewka, L., Hicks, R. J., & Cook, M. J. (2007). 'MRI-negative PET-positive' temporal lobe epilepsy (TLE) and mesial TLE differ with quantitative MRI and PET: a case control study. *BMC Neurol, 7*, 16. doi:10.1186/1471-2377-7-16

Carter, A. S. (2013). Wechsler Test of Adult Reading. In F. R. Volkmar (Ed.), *Encyclopedia of Autism Spectrum Disorders* (pp. 3364-3365). New York, NY: Springer New York.

Cascino, G., Jack, C., Parisi, J., et al. (1992). MRI in the presurgical evaluation of patients with frontal lobe epilepsy and children with temporal lobe epilepsy: pathologic correlation and prognostic importance. *Epilepsy Research, 11*, 51-59. doi:10.1016/0920-1211(92)90021-K

Cash, S. S., Halgren, E., Dehghani, N., et al. (2009). The Human K-Complex Represents an Isolated Cortical Down-State. *Science, 324*(5930), 1084. doi:10.1126/science.1169626

Catani, M., Dell'Acqua, F., & Thiebaut de Schotten, M. (2013). A revised limbic system model for memory, emotion and behaviour. *Neuroscience & Biobehavioral Reviews, 37*(8), 1724-1737. doi:10.1016/j.neubiorev.2013.07.001

Catani, M., Howard, R. J., Pajevic, S., & Jones, D. K. (2002). Virtual in Vivo Interactive Dissection of White Matter Fasciculi in the Human Brain. *Neuroimage, 17*(1), 77-94. doi:10.1006/nimg.2002.1136

Catani, M., Jones, D. K., & ffytche, D. H. (2005). Perisylvian language networks of the human brain. *Annals of Neurology, 57*(1), 8-16. doi:10.1002/ana.20319

Catenoix, H., Bourdillon, P., Guénot, M., & Isnard, J. (2018). The combination of stereo-EEG and radiofrequency ablation. *Epilepsy Research, 142*, 117-120. doi:10.1016/j.eplepsyres.2018.01.012

Cendes, F. (2004). Febrile seizures and mesial temporal sclerosis. *Curr Opin Neurol, 17*(2).

Cendes, F., Sakamoto, A., Spreafico, R., Bingaman, W., & Becker, A. (2014). Epilepsies associated with hippocampal sclerosis. *Acta neuropathologica, 128*. doi:10.1007/s00401-014-1292-0

Cendes, F., Theodore, W. H., Brinkmann, B. H., Sulc, V., & Cascino, G. D. (2016). Chapter 51 - Neuroimaging of epilepsy. In J. C. Masdeu & R. G. González (Eds.), *Handb Clin Neurol* (Vol. 136, pp. 985-1014): Elsevier.

Chabardes, S., Kahane, P., Minotti, L., Tassi, L., Grand, S., Hoffmann, D., & Benabid, A. L. (2005). The temporopolar cortex plays a pivotal role in temporal lobe seizures. *Brain, 128*(Pt 8), 1818-1831. doi:10.1093/brain/awh512

Chassoux F, A. E., Semah F, Laurent A, Landré E, Turak B, Gervais P, Helal BO, Devaux B. (2017). 18F-FDG-PET patterns of surgical success and failure in mesial temporal lobe epilepsy. *Neurology, 88*(11).

Chassoux, F., Artiges, E., Semah, F., et al. (2016). Determinants of brain metabolism changes in mesial temporal lobe epilepsy. *Epilepsia, 57*(6), 907-919. doi:10.1111/epi.13377

Chassoux, F., Rodrigo, S., Semah, F., et al. (2010). FDG-PET improves surgical outcome in negative MRI Taylor-type focal cortical dysplasias. *Neurology, 75*(24), 2168. doi:10.1212/WNL.0b013e31820203a9

Chassoux, F., Semah, F., Bouilleret, V., et al. (2004). Metabolic changes and electro-clinical patterns in mesio-temporal lobe epilepsy: a correlative study. *Brain, 127*(Pt 1), 164-174. doi:10.1093/brain/awh014

Chelune, G. J. (1995). Hippocampal adequacy versus functional reserve: predicting memory functions following temporal lobectomy. *Arch Clin Neuropsychol, 10*(5), 413-432.

Chelune, G. J., Naugle, R. I., Lüders, H., & Awad, I. A. (1991). Prediction of cognitive change as a function of preoperative ability status among temporal lobectomy patients seen at 6-month follow-up. *Neurology, 41*(3), 399-404.

Chen, Z., Brodie, M. J., Liew, D., & Kwan, P. (2018). Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. *JAMA Neurology, 75*(3), 279-286. doi:10.1001/jamaneurol.2017.3949

Chen, Z., Jamadar, S. D., Li, S., et al. (2018). From simultaneous to synergistic MR-PET brain imaging: A review of hybrid MR-PET imaging methodologies. *Human brain mapping, 39*(12), 5126-5144. doi:10.1002/hbm.24314

Chiang, S., Stern, J. M., Engel, J., Levin, H. S., & Haneef, Z. (2014). Differences in graph theory functional connectivity in left and right temporal lobe epilepsy. *Epilepsy Research, 108*(10), 1770-1781. doi:10.1016/j.eplepsyres.2014.09.023

Chipaux, M., Taussig, D., Dorfmuller, G., et al. (2019). SEEG-guided radiofrequency thermocoagulation of epileptic foci in the paediatric population: Feasibility, safety and efficacy. *Seizure - European Journal of Epilepsy, 70*, 63-70. doi:10.1016/j.seizure.2019.07.004

Choi, H., Sell, R. L., Lenert, L., Muennig, P., Goodman, R. R., Gilliam, F. G., & Wong, J. B. (2008). Epilepsy Surgery for Pharmacoresistant Temporal Lobe Epilepsy: A Decision Analysis. *Jama, 300*(21), 2497-2505. doi:10.1001/jama.2008.771

Choi, J. Y., Kim, S. J., Hong, S. B., Seo, D. W., Hong, S. C., Kim, B. T., & Kim, S. E. (2003). Extratemporal hypometabolism on FDG PET in temporal lobe epilepsy as a predictor of seizure outcome after temporal lobectomy. *Eur J Nucl Med Mol Imaging, 30*(4), 581-587. doi:10.1007/s00259-002-1079-8

Clusmann, H., & Schramm, J. (2012). Surgery in adults: temporal resections. *Handb Clin Neurol, 108*, 897-913. doi:10.1016/B978-0-444-52899-5.00035-6

Coan, A. C., Appenzeller, S., Bonilha, L., Li, L. M., & Cendes, F. (2009). Seizure frequency and lateralization affect progression of atrophy in temporal lobe epilepsy. *Neurology, 73*(11), 834-842. doi:10.1212/WNL.0b013e3181b783dd

Coito, A., Genetti, M., Pittau, F., et al. (2016). Altered directed functional connectivity in temporal lobe epilepsy in the absence of interictal spikes: A high density EEG study. *Epilepsia, 57*(3), 402-411. doi:10.1111/epi.13308

Coito, A., Plomp, G., Genetti, M., et al. (2015). Dynamic directed interictal connectivity in left and right temporal lobe epilepsy. *Epilepsia, 56*(2), 207-217. doi:10.1111/epi.12904

Coleman, H., McIntosh, A., & Wilson, S. J. (2020). A patient-centered approach to understanding long-term psychosocial adjustment and meaning-making, 15 to 20 years after epilepsy surgery. *Epilepsy & Behavior, 102*. doi:10.1016/j.yebeh.2019.106656

Commission on Neurosurgery of the International League Against Epilepsy, Wieser, H. G., Blume, W. T., Fish, D., et al. (2001). Proposal for a New Classification of Outcome with Respect to Epileptic Seizures Following Epilepsy Surgery. *Epilepsia, 42*(2), 282-286. doi:10.1046/j.1528-1157.2001.35100.x

Cossu, M., Cardinale, F., Casaceli, G., Castana, L., Consales, A., D'Orio, P., & Lo Russo, G. (2017). Stereo-EEG–guided radiofrequency thermocoagulations. *Epilepsia, 58*(S1), 66-72. doi:10.1111/epi.13687

Crinion, J. T., Lambon - Ralph, M. A., Warburton, E. A., Howard, D., & Wise, R. J. S. (2003). Temporal lobe regions engaged during normal speech comprehension. *Brain, 126*(5), 1193-1201. doi:10.1093/brain/awg104

da Silva, E. A., Chugani, D. C., Muzik, O., & Chugani, H. T. (1997). Identification of Frontal Lobe Epileptic Foci in Children Using Positron Emission Tomography. *Epilepsia, 38*(11), 1198-1208. doi:10.1111/j.1528-1157.1997.tb01217.x

Dario, J. E., John, D. R., Doris, D. W., Peter, P. S., Edward, F. C., & Kurtis, I. A. (2013). Seizure outcomes after temporal lobectomy in pediatric patients. *Journal of Neurosurgery: Pediatrics PED, 12*(2), 134-141. doi:10.3171/2013.5.PEDS12526

De Ciantis, A., Barba, C., Tassi, L., et al. (2016). 7T MRI in focal epilepsy with unrevealing conventional field strength imaging. *Epilepsia, 57*. doi:10.1111/epi.13313

de Tisi, J., Bell, G. S., Peacock, J. L., McEvoy, A. W., Harkness, W. F. J., Sander, J. W., & Duncan, J. S. (2011). The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *The Lancet, 378*(9800), 1388-1395. doi:10.1016/S0140-6736(11)60890-8

Degen, J., Dublin, P., Zhang, J., et al. (2012). Dual reporter approaches for identification of Cre efficacy and astrocyte heterogeneity. *The FASEB Journal, 26*(11), 4576-4583. doi:10.1096/fj.12-207183

Deleo, F., Garbelli, R., Milesi, G., et al. (2015). Short- and long-term surgical outcomes of temporal lobe epilepsy associated with hippocampal sclerosis: Relationships with neuropathology. *Epilepsia, 57*. doi:10.1111/epi.13277

Demeter, S., Rosene, D. L., & Van Hoesen, G. W. (1985). Interhemispheric pathways of the hippocampal formation, presubiculum, and entorhinal and posterior parahippocampal cortices in the rhesus monkey: the structure and organization of the hippocampal commissures. *J Comp Neurol, 233*(1), 30-47. doi:10.1002/cne.902330104

Demin, K., Berger, J., Holtkamp, M., & Bengner, T. (2018). Are mental distress and cognitive impairment related in temporal lobe epilepsy? *Epilepsy Research, 146*, 126-131. doi:10.1016/j.eplepsyres.2018.07.020

Desgranges, B., Baron, J. C., Lalevée, C., Giffard, B., Viader, F., de la Sayette, V., & Eustache, F. (2002). The neural substrates of episodic memory impairment in Alzheimer's disease as revealed by FDG–PET: relationship to degree of deterioration. *Brain, 125*(5), 1116-1124. doi:10.1093/brain/awf097

Devinsky, O., Spruill, T., Thurman, D., & Friedman, D. (2016). Recognizing and preventing epilepsy-related mortality. *Neurology, 86*(8), 779. doi:10.1212/WNL.0000000000002253

Dewar, S. R., & Pieters, H. C. (2015). Perceptions of epilepsy surgery: A systematic review and an explanatory model of decision-making. *Epilepsy & Behavior, 44*, 171-178. doi:10.1016/j.yebeh.2014.12.027

Diaz-Arrastia, R., Agostini, M. A., Frol, A. B., Mickey, B., Fleckenstein, J., Bigio, E., & Van Ness, P. C. (2000). Neurophysiologic and Neuroradiologic Features of Intractable Epilepsy After Traumatic Brain Injury in Adults. *Arch Neurol, 57*(11), 1611-1616. doi:10.1001/archneur.57.11.1611

Dick, A. S., & Tremblay, P. (2012). Beyond the arcuate fasciculus: consensus and controversy in the connectional anatomy of language. *Brain, 135*(12), 3529-3550. doi:10.1093/brain/aws222

Dickerson, B. C., & Eichenbaum, H. (2010). The episodic memory system: neurocircuitry and disorders. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 35*(1), 86-104. doi:10.1038/npp.2009.126

Diehl, B., & Lüders, H. (2000). Temporal Lobe Epilepsy: When Are Invasive Recordings Needed? *Epilepsia, 41 Suppl 3*, S61-74. doi:10.1111/j.1528-1157.2000.tb01536.x

Dodrill, C. B. (2002). Progressive cognitive decline in adolescents and adults with epilepsy *Progress in Brain Research* (Vol. 135, pp. 399-407): Elsevier.
Drzezga, A., Arnold S., Minoshima, S., et al. (1999). 18F-FDG PET studies in patients with extratemporal and temporal epilepsy: evaluation of an observer-independent analysis. (0161-5505 (Print)).
Duffau, H., Herbet, G., & Moritz-Gasser, S. (2013). Toward a pluri-component, multimodal, and dynamic organization of the ventral semantic stream in humans: Lessons from stimulation mapping in awake patients. *Frontiers in systems neuroscience, 7*, 44. doi:10.3389/fnsys.2013.00044
Duncan, J. S., Ali, R., Barkovich, J., et al. (2000). Commission on Diagnostic Strategies: recommendations for functional neuroimaging of persons with epilepsy. *Epilepsia, 41*, 1350-1356. doi:10.1111/j.1528-1157.2000.tb04617.x
Duncan, J. S., Winston, G. P., Koepp, M. J., & Ourselin, S. (2016). Brain imaging in the assessment for epilepsy surgery. *The Lancet Neurology, 15*(4), 420-433. doi:10.1016/s1474-4422(15)00383-x
Dupont, S., Samson, Y., Van de Moortele, P. F., et al. (2002). Bilateral hemispheric alteration of memory processes in right medial temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry, 73*(5), 478-485.
Durnford, A. J., Rodgers, W., Kirkham, F. J., et al. (2011). Very good inter-rater reliability of Engel and ILAE epilepsy surgery outcome classifications in a series of 76 patients. *Seizure, 20*(10), 809-812. doi:10.1016/j.seizure.2011.08.004
Elias, W. J., Huss, D., Voss, T., et al. (2013). A Pilot Study of Focused Ultrasound Thalamotomy for Essential Tremor. *New England Journal of Medicine, 369*(7), 640-648. doi:10.1056/NEJMoa1300962
Elliott, C. A., Gross, D. W., Wheatley, B. M., Beaulieu, C., & Sankar, T. (2016). Progressive contralateral hippocampal atrophy following surgery for medically refractory temporal lobe epilepsy. *Epilepsy Research, 125*, 62-71. doi:10.1016/j.eplepsyres.2016.06.007
Elwan, S., Alexopoulos, A., Silveira, D. C., & Kotagal, P. (2018). Lateralizing and localizing value of seizure semiology: Comparison with scalp EEG, MRI and PET in patients successfully treated with resective epilepsy surgery. *Seizure - European Journal of Epilepsy, 61*, 203-208. doi:10.1016/j.seizure.2018.08.026
Engel J Jr, V. N. P., Rasmussen TB, Ojemann LM. (1993). Outcome with respect to epileptic seizures. In J. J. Engel (Ed.), *Surgical Treatment of the Epilepsies.* (pp. 609-621): New York: Raven Press.
Engel J Jr, V. N. P., Rasmussen TB, Ojemann LM. (1993). Outcome with respect to epileptic seizures. *Surgical Treatment of the Epilepsies*, 609–621.
Engel, J., Jr., Henry, T. R., Risinger, M. W., Mazziotta, J. C., Sutherling, W. W., Levesque, M. F., & Phelps, M. E. (1990). Presurgical evaluation for partial epilepsy: relative contributions of chronic depth-electrode recordings versus FDG-PET and scalp-sphenoidal ictal EEG. *Neurology, 40*(11), 1670-1677.
Engel, J., Jr., McDermott, M. P., Wiebe, S., et al. (2012). Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *Jama, 307*(9), 922-930. doi:10.1001/jama.2012.220
Engel, J., Jr., Thompson, P. M., Stern, J. M., Staba, R. J., Bragin, A., & Mody, I. (2013). Connectomics and epilepsy. *Curr Opin Neurol, 26*(2), 186-194. doi:10.1097/WCO.0b013e32835ee5b8
Engel Jr, J. (2001). A Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy: Report of the ILAE Task Force on Classification and Terminology. *Epilepsia, 42*(6), 796-803. doi:10.1046/j.1528-1157.2001.10401.x

Englot, D. J., Konrad, P. E., & Morgan, V. L. (2016). Regional and global connectivity disturbances in focal epilepsy, related neurocognitive sequelae, and potential mechanistic underpinnings. *Epilepsia, 57*(10), 1546-1557. doi:10.1111/epi.13510

Englot, D. J., Yang, L., Hamid, H., et al. (2010). Impaired consciousness in temporal lobe seizures: role of cortical slow activity. *Brain, 133*(12), 3764-3777. doi:10.1093/brain/awq316

Everts, R., Harvey, A., Lillywhite, L., et al. (2009). Language lateralization correlates with verbal memory performance in children with focal epilepsy. *Epilepsia, 51*, 627-638. doi:10.1111/j.1528-1167.2009.02406.x

Ezzati, A., Katz, M. J., Zammit, A. R., Lipton, M. L., Zimmerman, M. E., Sliwinski, M. J., & Lipton, R. B. (2016). Differential association of left and right hippocampal volumes with verbal episodic and spatial memory in older adults. *Neuropsychologia, 93*, 380-385. doi:10.1016/j.neuropsychologia.2016.08.016

Feldmann, M., Asselin, M.-C., Liu, J., et al. (2013). P-glycoprotein expression and function in patients with temporal lobe epilepsy: a case-control study. *The Lancet Neurology, 12*(8), 777-785. doi:10.1016/s1474-4422(13)70109-1

Fernandes, D. A., Yasuda, C. L., Lopes, T. M., et al. (2014). Long-term postoperative atrophy of contralateral hippocampus and cognitive function in unilateral refractory MTLE with unilateral hippocampal sclerosis. *Epilepsy & Behavior, 36*, 108-114. doi:10.1016/j.yebeh.2014.04.028

Foldvary, N., Nashold, B., Mascha, E., et al. (2000). Seizure outcome after temporal lobectomy for temporal lobe epilepsy. *Neurology, 54*(3), 630. doi:10.1212/WNL.54.3.630

Fong, J. S., Alexopoulos, A. V., Bingaman, W. E., Gonzalez-Martinez, J., & Prayson, R. A. (2012). Pathologic Findings Associated With Invasive EEG Monitoring for Medically Intractable Epilepsy. *American Journal of Clinical Pathology, 138*(4), 506-510. doi:10.1309/AJCPGSNL9VDVNJMX

Foster, E., Malpas, C. B., Ye, K., et al. (2020). Antiepileptic drugs are not independently associated with cognitive dysfunction. *Neurology, 94*(10), e1051. doi:10.1212/WNL.0000000000009061

Fox, M. D. (2018). Mapping Symptoms to Brain Networks with the Human Connectome. *New England Journal of Medicine, 379*(23), 2237-2245. doi:10.1056/NEJMra1706158

French, J. A. (2007). Refractory epilepsy: clinical overview. *Epilepsia, 48 Suppl 1*, 3-7. doi:10.1111/j.1528-1167.2007.00992.x

French, J. A., Williamson, P. D., Thadani, V. M., Darcey, T. M., Mattson, R. H., Spencer, S. S., & Spencer, D. D. (1993). Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. *Annals of Neurology, 34*(6), 774-780. doi:10.1002/ana.410340604

Fried, I. (1993). Anatomic Temporal Lobe Resections for Temporal Lobe Epilepsy. *Neurosurgery Clinics of North America, 4*(2), 233-242. doi:10.1016/S1042-3680(18)30590-4

Furgerson, M., Fechheimer, M., & Furukawa, R. (2012). Model Hirano Bodies Protect against Tau-Independent and Tau-Dependent Cell Death Initiated by the Amyloid Precursor Protein Intracellular Domain. *PLoS One, 7*, e44996. doi:10.1371/journal.pone.0044996

Gaillard, W. D., Berl, M. M., Moore, E. N., et al. (2007). Atypical language in lesional and nonlesional complex partial epilepsy. *Neurology, 69*(18), 1761. doi:10.1212/01.wnl.0000289650.48830.1a

Gaillard, W. D., Bhatia, S., Bookheimer, S. Y., Fazilat, S., Sato, S., & Theodore, W. H. (1995). FDG-PET and volumetric MRI in the evaluation of patients with partial epilepsy. *Neurology, 45*(1), 123. doi:10.1212/WNL.45.1.123

Gaillard, W. D., Cross, J. H., Duncan, J. S., Stefan, H., Theodore, W. H., & Task Force on Practice Parameter Imaging Guidelines for International League Against Epilepsy, C. f. D. (2011). Epilepsy imaging study guideline criteria: commentary on diagnostic testing study guidelines and practice parameters. *Epilepsia, 52*(9), 1750-1756. doi:10.1111/j.1528-1167.2011.03155.x

Gaillard, W. D., Weinstein, S., Conry, J., et al. (2007). Prognosis of children with partial epilepsy. *Neurology, 68*(9), 655. doi:10.1212/01.wnl.0000255942.25101.8d

Galioto, R., Tremont, G., Blum, A. S., LaFrance, W. C., Crook, C. L., & Davis, J. D. (2016). Depressive Symptoms Contribute to Executive Deficits in Temporal Lobe Epilepsy. *J Neuropsychiatry Clin Neurosci, 29*(2), 135-141. doi:10.1176/appi.neuropsych.16040064

Galovic, M., Baudracco, I., Wright-Goff, E., et al. (2019). Association of Piriform Cortex Resection With Surgical Outcomes in Patients With Temporal Lobe Epilepsy. *JAMA Neurology, 76*(6), 690-700. doi:10.1001/jamaneurol.2019.0204

Gazzaniga, M. S. (2000). Cerebral specialization and interhemispheric communication: Does the corpus callosum enable the human condition? *Brain, 123*(7), 1293-1326. doi:10.1093/brain/123.7.1293

Geller, A. S., Friedman, D., Fang, M., Doyle, W. K., Devinsky, O., & Dugan, P. (2018). Running-down phenomenon captured with chronic electrocorticography. *Epilepsia open, 3*(4), 528-534. doi:10.1002/epi4.12265

Geranmayeh, F., Wise, R. J. S., Mehta, A., & Leech, R. (2014). Overlapping Networks Engaged during Spoken Language Production and Its Cognitive Control. *The Journal of Neuroscience, 34*(26), 8728. doi:10.1523/JNEUROSCI.0428-14.2014

Giovagnoli, A. R., Parente, A., Tarallo, A., Casazza, M., Franceschetti, S., & Avanzini, G. (2014). Self-rated and assessed cognitive functions in epilepsy: Impact on quality of life. *Epilepsy Research, 108*(8), 1461-1468. doi:10.1016/j.eplepsyres.2014.06.002

Girvin, J. P. (2014). *Operative Techniques in Epilepsy.*: Springer.

Gleichgerrcht, E., Munsell, B., Bhatia, S., et al. (2018). Deep learning applied to whole-brain connectome to determine seizure control after epilepsy surgery. *Epilepsia, 59*(9), 1643-1654. doi:10.1111/epi.14528

Gleissner, U., Helmstaedter, C., & Elger, C. E. (1998). Right hippocampal contribution to visual memory: a presurgical and postsurgical study in patients with temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry, 65*(5), 665-669.

Goc, J., Liu, J. Y. W., Sisodiya, S. M., & Thom, M. (2014). A spatiotemporal study of gliosis in relation to depth electrode tracks in drug-resistant epilepsy. *The European journal of neuroscience, 39*(12), 2151-2162. doi:10.1111/ejn.12548

Goellner, E., Bianchin, M. M., Burneo, J. G., Parrent, A. G., & Steven, D. A. (2013). Timing of early and late seizure recurrence after temporal lobe epilepsy surgery. *Epilepsia, 54*(11), 1933-1941. doi:10.1111/epi.12389

Gok, B., Jallo, G., Hayeri, R., Wahl, R., & Aygun, N. (2013). The evaluation of FDG-PET imaging for epileptogenic focus localization in patients with MRI positive and MRI negative temporal lobe epilepsy. *Neuroradiology, 55*(5), 541-550. doi:10.1007/s00234-012-1121-x

Gomez-Alonso, J., & Bellas-Lamas, P. (2015). Surgical treatment for drug-resistant epilepsy. *Jama, 313*(15), 1572. doi:10.1001/jama.2015.2883

Goodfellow, M., Rummel, C., Abela, E., Richardson, M. P., Schindler, K., & Terry, J. R. (2016). Estimation of brain network ictogenicity predicts outcome from epilepsy surgery. *Scientific Reports, 6*, 29215-29215. doi:10.1038/srep29215

Gotts, S. J., Jo, H. J., Wallace, G. L., Saad, Z. S., Cox, R. W., & Martin, A. (2013). Two distinct forms of functional lateralization in the human brain. *Proceedings of the National Academy of Sciences, 110*(36), E3435. doi:10.1073/pnas.1302581110

Govil-Dalela, T., Kumar, A., Behen, M. E., Chugani, H. T., & Juhász, C. (2018). Evolution of lobar abnormalities of cerebral glucose metabolism in 41 children with drug-resistant epilepsy. *Epilepsia, 59*(7), 1307-1315. doi:10.1111/epi.14404

Grewal, S., Zimmerman, R., Worrell, G., et al. (2018). Laser ablation for mesial temporal epilepsy: a multi-site, single institutional series. *Journal of Neurosurgery, 130*, 1-8. doi:10.3171/2018.2.JNS171873

Griffith, H. R., Perlman, S. B., Woodard, A. R., et al. (2000). Preoperative FDG-PET temporal lobe hypometabolism and verbal memory after temporal lobectomy. *Neurology, 54*(5), 1161-1165.

Griffith, H. R., Pyzalski, R. W., Seidenberg, M., & Hermann, B. P. (2004). Memory relationships between MRI volumes and resting PET metabolism of medial temporal lobe structures. *Epilepsy Behav, 5*(5), 669-676. doi:10.1016/j.yebeh.2004.06.020

Grinenko, O., Li, J., Mosher, J. C., et al. (2017). A fingerprint of the epileptogenic zone in human epilepsies. *Brain, 141*(1), 117-131. doi:10.1093/brain/awx306

Guedj, E., Barbeau, E. J., Liégeois-Chauvel, C., et al. (2010). Performance in recognition memory is correlated with entorhinal/perirhinal interictal metabolism in temporal lobe epilepsy. *Epilepsy & Behavior, 19*(4), 612-617. doi:10.1016/j.yebeh.2010.09.027

Guedj, E., Bonini, F., Gavaret, M., et al. (2015). 18FDG-PET in different subtypes of temporal lobe epilepsy: SEEG validation and predictive value. *Epilepsia, 56*(3), 414-421. doi:10.1111/epi.12917

Hajek, M., Antonini, A., Leenders, K. L., & Wieser, H. G. (1993). Mesiobasal versus lateral temporal lobe epilepsy: metabolic differences in the temporal lobe shown by interictal 18F-FDG positron emission tomography. *Neurology, 43*(1), 79-86. doi:10.1212/wnl.43.1_part_1.79

Halgren, E., Kaestner, E., Marinkovic, K., et al. (2015). Laminar Profile of Spontaneous and Evoked Theta: Rhythmic Modulation of Cortical Processing During Word Integration. *Neuropsychologia, 76*. doi:10.1016/j.neuropsychologia.2015.03.021

Hamberger, M. J., Seidel, W. T., Goodman, R. R., Williams, A., Perrine, K., Devinsky, O., & McKhann, G. M., 2nd. (2007). Evidence for cortical reorganization of language in patients with hippocampal sclerosis. *Brain, 130*(Pt 11), 2942-2950. doi:10.1093/brain/awm187

Hamer, H. M., Najm, I., Mohamed, A., & Wyllie, E. (1999). Interictal Epileptiform Discharges in Temporal Lobe Epilepsy Due to Hippocampal Sclerosis Versus Medial Temporal Lobe Tumors. *Epilepsia, 40*(9), 1261-1268. doi:10.1111/j.1528-1157.1999.tb00856.x

Hamiwka, L., Macrodimitris, S., Tellez-Zenteno, J. F., et al. (2011). Social outcomes after temporal or extratemporal epilepsy surgery: A systematic review. *Epilepsia, 52*(5), 870-879. doi:10.1111/j.1528-1167.2011.03074.x

Haneef, Z., Lenartowicz, A., Yeh, H., Levin, H., Engel, J., & Stern, J. (2013). Functional connectivity of hippocampal networks in temporal lobe epilepsy. *Epilepsia, 55*. doi:10.1111/epi.12476

Haneef, Z., Lenartowicz, A., Yeh, H. J., Levin, H. S., Engel, J., Jr., & Stern, J. M. (2014). Functional connectivity of hippocampal networks in temporal lobe epilepsy. *Epilepsia, 55*(1), 137-145. doi:10.1111/epi.12476

Harden, C., Tomson, T., Gloss, D., et al. (2017). Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors. *Neurology, 88*(17), 1674. doi:10.1212/WNL.0000000000003685

Harden, C. L. (2002). The co-morbidity of depression and epilepsy. *Neurology, 59*(6 suppl 4), S48. doi:10.1212/WNL.59.6_suppl_4.S48

Helmstaedter, C. (2013). Cognitive outcomes of different surgical approaches in temporal lobe epilepsy. *Epileptic Disord, 15*(3), 221-239. doi:10.1684/epd.2013.0587

Helmstaedter, C., Brosch, T., Kurthen, M., & Elger, C. (2004). The impact of sex and language dominance on material-specific memory before and after left temporal lobe surgery. *Brain : a journal of neurology, 127*, 1518-1525. doi:10.1093/brain/awh174

Helmstaedter, C., Petzold, I., & Bien, C. G. (2011). The cognitive consequence of resecting nonlesional tissues in epilepsy surgery--results from MRI- and histopathology-negative patients with temporal lobe epilepsy. *Epilepsia, 52*(8), 1402-1408. doi:10.1111/j.1528-1167.2011.03157.x

Helmstaedter, C., Pohl, C., & Elger, C. E. (1995). Relations Between Verbal and Nonverbal Memory Performance: Evidence of Confounding Effects Particulary in Patients with Right Temporal Lobe Epilepsy. *Cortex, 31*(2), 345-355. doi:10.1016/S0010-9452(13)80367-X

Helmstaedter, C., & Witt, J. A. (2017). How neuropsychology can improve the care of individual patients with epilepsy. Looking back and into the future. *Seizure, 44*, 113-120. doi:10.1016/j.seizure.2016.09.010

Hennessy, M. J., Elwes, R. D. C., Binnie, C. D., & Polkey, C. E. (2000). Failed surgery for epilepsy: A study of persistence and recurrence of seizures following temporal resection. *Brain, 123*(12), 2445-2466. doi:10.1093/brain/123.12.2445

Henry, T. R., Chupin, M., Lehéricy, S., et al. (2011). Hippocampal Sclerosis in Temporal Lobe Epilepsy: Findings at 7 T. *Radiology, 261*(1), 199-209. doi:10.1148/radiol.11101651

Henry, T. R., Engel, J., Jr., & Mazziotta, J. C. (1993). Clinical evaluation of interictal fluorine-18-fluorodeoxyglucose PET in partial epilepsy. *J Nucl Med, 34*(11), 1892-1898.

Henry, T. R., Mazziotta, J. C., Engel, J., Jr., Christenson, P. D., Zhang, J. X., Phelps, M. E., & Kuhl, D. E. (1990). Quantifying interictal metabolic activity in human temporal lobe epilepsy. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism, 10*(5), 748-757. doi:10.1038/jcbfm.1990.128

Herff, C., Krusienski, D. J., & Kubben, P. (2020). The Potential of Stereotactic-EEG for Brain-Computer Interfaces: Current Progress and Future Directions. *Frontiers in neuroscience, 14*, 123.

Hermann, B. P., Seidenberg, M., Haltiner, A., & Wyler, A. R. (1992). Adequacy of language function and verbal memory performance in unilateral temporal lobe epilepsy. *Cortex, 28*(3), 423-433.

Herskovitz, M., & Schiller, Y. (2016). Yield of non-invasive phase 1 presurgical evaluation in drug-resistant epilepsy patients. *18*, 76-79.

Hillary, F. G., & Grafman, J. H. (2017). Injured Brains and Adaptive Networks: The Benefits and Costs of Hyperconnectivity. *Trends in Cognitive Sciences, 21*(5), 385-401. doi:10.1016/j.tics.2017.03.003

Hirsch, L., Spencer, S., Williamson, P., Spencer, D., & Mattson, R. (1991). Comparison of bitemporal and unitemporal epilepsy defined by depth EEG. *Annals of Neurology, 30*, 340-346. doi:10.1002/ana.410300305

Hogan, R. E., Kaiboriboon, K., Bertrand, M. E., Rao, V., & Acharya, J. (2006). Composite SISCOM Perfusion Patterns in Right and Left Temporal Seizures. *Arch Neurol, 63*(10), 1419-1426. doi:10.1001/archneur.63.10.1419

Höller, Y., Kutil, R., Klaffenböck, L., et al. (2015). High-frequency oscillations in epilepsy and surgical outcome. A meta-analysis. *Frontiers in Human Neuroscience, 9*, 574.

Isnard, J., Guénot, M., Sindou, M., & Mauguière, F. (2004). Clinical Manifestations of Insular Lobe Seizures: A Stereo-electroencephalographic Study. *Epilepsia, 45*(9), 1079-1090. doi:10.1111/j.0013-9580.2004.68903.x

Jack, C. R., Bennett, D. A., Blennow, K., et al. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia, 14*(4), 535-562. doi:10.1016/j.jalz.2018.02.018

Jack, C. R., Rydberg, C. H., Krecke, K. N., et al. (1996). Mesial temporal sclerosis: diagnosis with fluid-attenuated inversion-recovery versus spin-echo MR imaging. *Radiology, 199*(2), 367-373. doi:10.1148/radiology.199.2.8668780

Jackson, J. H., & Stewart, P. (1899). Epileptic attacks with a warning of a crude sensation of smell and with the intellectual aura (dreamy state) in a patient who had symptoms pointing to gross organic disease of the right temporo-sphenoidal lobe. *Brain, 22*(4), 534-549. doi:10.1093/brain/22.4.534

Jeha, L. E., Najm, I., Bingaman, W., Dinner, D., Widdess-Walsh, P., & Lüders, H. (2007). Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. *Brain, 130*(Pt 2), 574-584. doi:10.1093/brain/awl364

Jeha, L. E., Najm, I. M., Bingaman, W. E., et al. (2006). Predictors of outcome after temporal lobectomy for the treatment of intractable epilepsy. *Neurology, 66*(12), 1938. doi:10.1212/01.wnl.0000219810.71010.9b

Jehi, L. (2018). The Epileptogenic Zone: Concept and Definition. *Epilepsy Currents, 18*(1), 12-16. doi:10.5698/1535-7597.18.1.12

Jermakowicz, W., Kanner, A., Sur, S., et al. (2017). Laser thermal ablation for mesiotemporal epilepsy: Analysis of ablation volumes and trajectories. *Epilepsia, 58*. doi:10.1111/epi.13715

Jetté, N., & Wiebe, S. (2015). Health Economic Analyses of Epilepsy Surgery. In K. Malmgren, S. Baxendale, & J. H. Cross (Eds.), *Long-Term Outcomes of Epilepsy Surgery in Adults and Children* (pp. 255-267). Cham: Springer International Publishing.

Jeyaraj, M. K., Menon, R. N., Justus, S., Alexander, A., Sarma, P. S., & Radhakrishnan, K. (2013). A critical evaluation of the lateralizing significance of material-specific memory deficits in patients with mesial temporal lobe epilepsy with hippocampal sclerosis. *Epilepsy Behav, 28*(3), 460-466. doi:10.1016/j.yebeh.2013.06.011

Jokeit, H., Ebner, A., Arnold, S., et al. (1999). Bilateral reductions of hippocampal volume, glucose metabolism, and wada hemispheric memory performance are related to the duration of mesial temporal lobe epilepsy. *Journal of Neurology, 246*(10), 926-933. doi:10.1007/s004150050484

Jokeit, H., Ebner, A., Holthausen, H., et al. (1997). Individual prediction of change in delayed recall of prose passages after left-sided anterior temporal lobectomy. *Neurology, 49*(2), 481. doi:10.1212/WNL.49.2.481

Jokeit, H., Seitz, R. J., Markowitsch, H. J., Neumann, N., Witte, O. W., & Ebner, A. (1997). Prefrontal asymmetric interictal glucose hypometabolism and cognitive

impairment in patients with temporal lobe epilepsy. *Brain, 120 ( Pt 12)*, 2283-2294.
Jones, A. L., & Cascino, G. D. (2016). Evidence on Use of Neuroimaging for Surgical Treatment of Temporal Lobe Epilepsy: A Systematic Review. *JAMA Neurology, 73*(4), 464-470. doi:10.1001/jamaneurol.2015.4996
Jones-Gotman, M., Harnadek, M. C. S., & Kubu, C. S. (2014). Neuropsychological Assessment for Temporal Lobe Epilepsy Surgery. *The Canadian Journal of Neurological Sciences, 27*(01), S39-S43. doi:10.1017/s0317167100000639
Jones-Gotman, M., Smith, M. L., Risse, G. L., et al. (2010). The contribution of neuropsychology to diagnostic assessment in epilepsy. *Epilepsy Behav, 18*(1-2), 3-12. doi:10.1016/j.yebeh.2010.02.019
Joo, E. Y., Han, H. J., Lee, E. K., et al. (2005). Resection extent versus postoperative outcomes of seizure and memory in mesial temporal lobe epilepsy. *Seizure, 14*(8), 541-551. doi:10.1016/j.seizure.2005.08.011
Joo, E. Y., Hong, S. B., Han, H. J., et al. (2005). Postoperative alteration of cerebral glucose metabolism in mesial temporal lobe epilepsy. *Brain, 128*(Pt 8), 1802-1810. doi:10.1093/brain/awh534
Joo, E. Y., Lee, E. K., Tae, W. S., & Hong, S. B. (2004). Unitemporal vs bitemporal hypometabolism in mesial temporal lobe epilepsy. *Arch Neurol, 61*(7), 1074-1078. doi:10.1001/archneur.61.7.1074
Josephson, C. B., Dykeman, J., Fiest, K. M., Liu, X., Sadler, R. M., Jette, N., & Wiebe, S. (2013). Systematic review and meta-analysis of standard vs selective temporal lobe epilepsy surgery. *Neurology, 80*(18), 1669-1676. doi:10.1212/WNL.0b013e3182904f82
Josse, G., Seghier, M. L., Kherif, F., & Price, C. J. (2008). Explaining Function with Anatomy: Language Lateralization and Corpus Callosum Size. *The Journal of Neuroscience, 28*(52), 14132. doi:10.1523/JNEUROSCI.4383-08.2008
Juhász, C., Chugani, D. C., Muzik, O., et al. (2001). Relationship of flumazenil and glucose PET abnormalities to neocortical epilepsy surgery outcome. *Neurology, 56*(12), 1650. doi:10.1212/WNL.56.12.1650
Juhn, W., & Theodore, R. (1960). Intracarotid Injection of Sodium Amytal for the Lateralization of Cerebral Speech Dominance. *Journal of Neurosurgery, 17*(2), 266-282. doi:10.3171/jns.1960.17.2.0266
Jupp, B., Williams, J., Binns, D., et al. (2012). Hypometabolism precedes limbic atrophy and spontaneous recurrent seizures in a rat model of TLE. *Epilepsia, 53*(7), 1233-1244. doi:10.1111/j.1528-1167.2012.03525.x
Kaestner, E., Balachandra, A., Bahrami, N., et al. (2020a). The white matter connectome as an individualized biomarker of language impairment in temporal lobe epilepsy. *NeuroImage: Clinical, 25*. doi:10.1016/j.nicl.2019.102125
Kaestner, E., Balachandra, A. R., Bahrami, N., et al. (2020b). The white matter connectome as an individualized biomarker of language impairment in temporal lobe epilepsy. *NeuroImage: Clinical, 25*, 102125. doi:10.1016/j.nicl.2019.102125
Kahane, P., Barba, C., Rheims, S., Job-Chapron, A. S., Minotti, L., & Ryvlin, P. (2015). The concept of temporal 'plus' epilepsy. *Revue neurologique, 171*(3), 267-272. doi:10.1016/j.neurol.2015.01.562
Kahane, P., & Bartolomei, F. (2010). Temporal lobe epilepsy and hippocampal sclerosis: lessons from depth EEG recordings. *Epilepsia, 51 Suppl 1*, 59-62. doi:10.1111/j.1528-1167.2009.02448.x
Kamm, J., Boles Ponto, L. L., Manzel, K., Gaasedelen, O. J., Nagahama, Y., Abel, T., & Tranel, D. (2018). Temporal lobe asymmetry in FDG-PET uptake predicts

neuropsychological and seizure outcomes after temporal lobectomy. *Epilepsy & Behavior, 78*, 62-67. doi:10.1016/j.yebeh.2017.10.006
Kang, J. Y., & Sperling, M. R. (2017). Magnetic Resonance Imaging-Guided Laser Interstitial Thermal Therapy for Treatment of Drug-Resistant Epilepsy. *Neurotherapeutics, 14*(1), 176-181. doi:10.1007/s13311-016-0498-3
Kang, J. Y., Wu, C., Tracy, J., et al. (2016). Laser interstitial thermal therapy for medically intractable mesial temporal lobe epilepsy. *Epilepsia, 57*(2), 325-334. doi:10.1111/epi.13284
Kanner, A. M., & Balabanov, A. (2002). Depression and epilepsy. *Neurology, 58*(8 suppl 5), S27. doi:10.1212/WNL.58.8_suppl_5.S27
Kaplan, E., Goodglass, H., Weintraub, S., & Goodglass, H. (1983). *Boston naming test*. Philadelphia: Lea & Febiger.
Katariwala, N. M., Bakay, R. A. E., Pennell, P. B., Olson, L. D., Henry, T. R., & Epstein, C. M. (2001). Remission of intractable partial epilepsy following implantation of intracranial electrodes. *Neurology, 57*(8), 1505. doi:10.1212/WNL.57.8.1505
Kaur, M., Szaflarski, J. P., Ver Hoef, L., Pati, S., Riley, K. O., & Jaisani, Z. (2019). Long-term seizure freedom following intracranial sEEG monitoring: Therapeutic benefit of a diagnostic technique. *Epilepsy & Behavior Reports, 12*, 100345. doi:10.1016/j.ebr.2019.100345
Kennepohl, S., Sziklas, V., Garver, K. E., Wagner, D. D., & Jones-Gotman, M. (2007). Memory and the medial temporal lobe: hemispheric specialization reconsidered. *Neuroimage, 36*(3), 969-978. doi:10.1016/j.neuroimage.2007.03.049
Kim, D. W., Lee, S. K., Nam, H., et al. (2010). Epilepsy with dual pathology: Surgical treatment of cortical dysplasia accompanied by hippocampal sclerosis. *Epilepsia, 51*(8), 1429-1435. doi:10.1111/j.1528-1167.2009.02403.x
Kim, H., Yi, S., Son, E. I., & Kim, J. (2003). Material-specific memory in temporal lobe epilepsy: Effects of seizure laterality and language dominance. *Neuropsychology, 17*(1), 59-68. doi:10.1037/0894-4105.17.1.59
Kim, M. A., Heo, K., Choo, M. K., et al. (2006). Relationship between bilateral temporal hypometabolism and EEG findings for mesial temporal lobe epilepsy: analysis of 18F-FDG PET using SPM. *Seizure, 15*(1), 56-63. doi:10.1016/j.seizure.2005.11.007
King, D., Spencer, S. S., McCarthy, G., Luby, M., & Spencer, D. D. (1995). Bilateral Hippocampal Atrophy in Medial Temporal Lobe Epilepsy. *Epilepsia, 36*(9), 905-910. doi:10.1111/j.1528-1157.1995.tb01634.x
King, D., Spencer, S. S., McCarthy, G., & Spencer, D. D. (1997). Surface and depth EEG findings in patients with hippocampal atrophy. *Neurology, 48*(5), 1363. doi:10.1212/WNL.48.5.1363
Knake, S., Haag, A., Hamer, H. M., Dittmer, C., Bien, S., Oertel, W. H., & Rosenow, F. (2003). Language lateralization in patients with temporal lobe epilepsy: a comparison of functional transcranial Doppler sonography and the Wada test. *Neuroimage, 19*(3), 1228-1232. doi:10.1016/S1053-8119(03)00174-5
Knecht, S., Deppe, M., Dräger, B., Bobe, L., Lohmann, H., Ringelstein, E. B., & Henningsen, H. (2000). Language lateralization in healthy right-handers. *Brain, 123*(1), 74-81. doi:10.1093/brain/123.1.74
Kneebone, A. C., Chelune, G. J., & Lüders, H. O. (1997). Individual patient prediction of seizure lateralization in temporal lobe epilepsy: a comparison between neuropsychological memory measures and the Intracarotid Amobarbital Procedure. *J Int Neuropsychol Soc, 3*(2), 159-168.
Knopman, A. A., Wong, C. H., Stevenson, R. J., et al. (2015). The relationship between neuropsychological functioning and FDG-PET hypometabolism in intractable

mesial temporal lobe epilepsy. *Epilepsy Behav, 44*, 136-142. doi:10.1016/j.yebeh.2015.01.023
Knowlton, R., Md, K., Ende, G., Md, P., Wong, S., PhD, G., et al. (1997). Presurgical Multimodality Neuroimaging in Electroencephalographic Lateralized Temporal Lobe Epilepsy. *Annals of Neurology, 42*, 829-837. doi:10.1002/ana.410420603
Knowlton, R. C. (2006). The role of FDG-PET, ictal SPECT, and MEG in the epilepsy surgery evaluation. *Epilepsy Behav, 8*(1), 91-101. doi:10.1016/j.yebeh.2005.10.015
Knowlton, R. C., Elgavish, R. A., Limdi, N., et al. (2008). Functional imaging: I. Relative predictive value of intracranial electroencephalography. *Ann Neurol, 64*(1), 25-34. doi:10.1002/ana.21389
Knowlton, R. C., Laxer, K. D., Klein, G., et al. (2001). In vivo hippocampal glucose metabolism in mesial temporal lobe epilepsy. *Neurology, 57*(7), 1184-1190. doi:10.1212/wnl.57.7.1184
Koepp, M., Hammers, A., Labbe, C., Woermann, F., Brooks, D., & Duncan, J. (2000). 11C-Flumazenil PET in patients with refractory temporal lobe epilepsy and normal MRI. *Neurology, 54*, 332-339. doi:10.1212/WNL.54.2.332
Komoto, D., Iida, K., Higaki, T., et al. (2015). Diagnostic Performance of Positron Emission Tomography for the Presurgical Evaluation of Patients with Non-lesional Intractable Partial Epilepsy: Comparison among 18F-FDG, 11C-Flumazenil, and 11C-Flumazenil Binding Potential Imaging Using Statistical Imaging Analysis. *Hiroshima journal of medical sciences, 64*(4), 51-57.
Koo, T. K., & Li, M. Y. (2016). A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *Journal of Chiropractic Medicine, 15*(2), 155-163. doi:10.1016/j.jcm.2016.02.012
Koutroumanidis, M., Binnie, C. D., Elwes, R. D., et al. (1998). Interictal regional slow activity in temporal lobe epilepsy correlates with lateral temporal hypometabolism as imaged with 18FDG PET: neurophysiological and metabolic implications. *Journal of neurology, neurosurgery, and psychiatry, 65*(2), 170-176. doi:10.1136/jnnp.65.2.170
Koutroumanidis, M., Hennessy, M. J., Seed, P. T., et al. (2000). Significance of interictal bilateral temporal hypometabolism in temporal lobe epilepsy. *Neurology, 54*(9), 1811. doi:10.1212/WNL.54.9.1811
Kovac, S., Möddel, G., Reinholz, J., et al. (2009). Memory performance is related to language dominance as determined by the intracarotid amobarbital procedure. *Epilepsy & Behavior, 16*(1), 145-149. doi:10.1016/j.yebeh.2009.07.020
Kreilkamp, B. A. K., Das, K., Wieshmann, U. C., Biswas, S., Marson, A. G., & Keller, S. S. (2019). Neuroradiological findings in patients with "non-lesional" focal epilepsy revealed by research protocol. *Clinical Radiology, 74*(1), 78.e71-78.e11. doi:10.1016/j.crad.2018.08.013
Kumar, A., Juhász, C., Asano, E., Sood, S., Muzik, O., & Chugani, H. T. (2010). Objective detection of epileptic foci by 18F-FDG PET in children undergoing epilepsy surgery. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 51*(12), 1901-1907. doi:10.2967/jnumed.110.075390
Kuzniecky, R., 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. doi:10.1212/WNL.49.3.774
Kuzniecky, R., & Devinsky, O. (2007). Surgery Insight: surgical management of epilepsy. *Nature Clinical Practice Neurology, 3*(12), 673-681. doi:10.1038/ncpneuro0663
Kwan, P., Arzimanoglou, A., Berg, A. T., et al. (2010). Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE

Commission on Therapeutic Strategies. *Epilepsia, 51*(6), 1069-1077. doi:10.1111/j.1528-1167.2009.02397.x
Kwan, P., & Brodie, M. J. (2006). Refractory epilepsy: mechanisms and solutions. *Expert review of neurotherapeutics, 6*(3), 397-406. doi:10.1586/14737175.6.3.397
Kwan, P., Li, H. M., Al-Jufairi, E., et al. (2010). Association between temporal lobe P-glycoprotein expression and seizure recurrence after surgery for pharmacoresistant temporal lobe epilepsy. *Neurobiol Dis, 39*(2), 192-197. doi:10.1016/j.nbd.2010.04.006
Kwan, P., Schachter, S. C., & Brodie, M. J. (2011). Drug-resistant epilepsy. *N Engl J Med, 365*(10), 919-926. doi:10.1056/NEJMra1004418
Labate, A., Aguglia, U., Tripepi, G., et al. (2016). Long-term outcome of mild mesial temporal lobe epilepsy: A prospective longitudinal cohort study. *Neurology, 86*(20), 1904-1910. doi:10.1212/WNL.0000000000002674
Lacuey, N., Zonjy, B., Kahriman, E. S., Kaffashi, F., Miller, J., & Lüders, H. O. (2015). Functional connectivity between right and left mesial temporal structures. *Brain Struct Funct, 220*(5), 2617-2623. doi:10.1007/s00429-014-0810-0
Lagarde, S., Buzori, S., Trebuchon, A., et al. (2019). The repertoire of seizure onset patterns in human focal epilepsies: Determinants and prognostic values. *Epilepsia, 60*(1), 85-95. doi:10.1111/epi.14604
Lamarche, F., Job, A. S., Deman, P., et al. (2016). Correlation of FDG-PET hypometabolism and SEEG epileptogenicity mapping in patients with drug-resistant focal epilepsy. *Epilepsia, 57*(12), 2045-2055. doi:10.1111/epi.13592
LaRiviere, M. J., & Gross, R. E. (2016). Stereotactic Laser Ablation for Medically Intractable Epilepsy: The Next Generation of Minimally Invasive Epilepsy Surgery. *Frontiers in surgery, 3*, 64-64. doi:10.3389/fsurg.2016.00064
Laurent, A., Artiges, E., Mellerio, C., Boutin-Watine, M., Landré, E., Semah, F., & Chassoux, F. (2020). Metabolic correlates of cognitive impairment in mesial temporal lobe epilepsy. *Epilepsy & Behavior, 105*, 106948. doi:10.1016/j.yebeh.2020.106948
Lee, C.-Y., Li, H.-T., Wu, T., Cheng, M.-Y., Lim, S.-N., & Lee, S.-T. (2018). Efficacy of limited hippocampal radiofrequency thermocoagulation for mesial temporal lobe epilepsy. *Journal of Neurosurgery, 131*, 1-9. doi:10.3171/2018.4.JNS184
Lee, T. M., Yip, J. T., & Jones-Gotman, M. (2002). Memory deficits after resection from left or right anterior temporal lobe in humans: a meta-analytic review. *Epilepsia, 43*(3), 283-291.
Leeman, B. A., Leveroni, C. L., & Johnson, K. A. (2009). Does hippocampal FDG-PET asymmetry predict verbal memory dysfunction after left temporal lobectomy? *Epilepsy Behav, 16*(2), 274-280. doi:10.1016/j.yebeh.2009.07.035
Leonard, E., Leff, M., & Spangler, J. (2019). Weaponizing T-cell receptors through molecular engineering. *Journal of Biological Chemistry, 294*, 5805-5806. doi:10.1074/jbc.H119.008479
Lewis, D. V., Shinnar, S., Hesdorffer, D. C., et al. (2014). Hippocampal sclerosis after febrile status epilepticus: The FEBSTAT study. *Annals of Neurology, 75*(2), 178-185. doi:10.1002/ana.24081
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*(5), 673-676. doi:10.1046/j.1528-1157.2003.46002.x
Li, H., Ji, C., Zhu, L., et al. (2017). Reorganization of Anterior and Posterior Hippocampal Networks Associated with Memory Performance in Mesial

Temporal Lobe Epilepsy. *Clinical Neurophysiology, 128*. doi:10.1016/j.clinph.2017.02.018
Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., et al. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. *Nature, 541*(7638), 481-487. doi:10.1038/nature21029
Lieb, A., Qiu, Y., Dixon, C. L., Heller, J. P., Walker, M. C., Schorge, S., & Kullmann, D. M. (2018). Biochemical autoregulatory gene therapy for focal epilepsy. *Nature medicine, 24*(9), 1324-1329. doi:10.1038/s41591-018-0103-x
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. *Electroencephalography and clinical neurophysiology, 67*(2), 101-119. doi:10.1016/0013-4694(87)90033-2
Lillywhite, L. M., Saling, M. M., Briellmann, R. S., Weintrob, D. L., Pell, G. S., & Jackson, G. D. (2007). Differential contributions of the hippocampus and rhinal cortices to verbal memory in epilepsy. *Epilepsy Behav, 10*(4), 553-559. doi:10.1016/j.yebeh.2007.03.002
Liu, J., Reeves, C., Jacques, T., et al. (2018). Nestin-expressing cell types in the temporal lobe and hippocampus: Morphology, differentiation, and proliferative capacity. *Glia, 66*(1), 62-77. doi:10.1002/glia.23211
Lopez-Gonzalez, M. A., Gonzalez-Martinez, J. A., Jehi, L., Kotagal, P., Warbel, A., & Bingaman, W. (2011). Epilepsy Surgery of the Temporal Lobe in Pediatric Population: A Retrospective Analysis. *Neurosurgery, 70*(3), 684-692. doi:10.1227/NEU.0b013e318235183d
LoPinto-Khoury, C., Sperling, M. R., Skidmore, C., Nei, M., Evans, J., Sharan, A., & Mintzer, S. (2012). Surgical outcome in PET-positive, MRI-negative patients with temporal lobe epilepsy. *Epilepsia, 53*(2), 342-348. doi:10.1111/j.1528-1167.2011.03359.x
Loring, D. W. (2010). History of neuropsychology through epilepsy eyes. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists, 25*(4), 259-273. doi:10.1093/arclin/acq024
Loring, D. W., Strauss, E., Hermann, B. P., et al. (2008). Differential neuropsychological test sensitivity to left temporal lobe epilepsy. *J Int Neuropsychol Soc, 14*(3), 394-400. doi:10.1017/s1355617708080582
Löscher, W., & Potschka, H. (2005). Drug resistance in brain diseases and the role of drug efflux transporters. *Nature reviews. Neuroscience, 6*(8), 591-602. doi:10.1038/nrn1728
Lüders, E., Narr, K. L., Thompson, P. M., Rex, D. E., Jancke, L., & Toga, A. W. (2005). Hemispheric Asymmetries in Cortical Thickness. *Cerebral Cortex, 16*(8), 1232-1238. doi:10.1093/cercor/bhj064
Lüders, H., Lesser, R. P., Hahn, J., Dinner, D. S., Morris, H. H., Wyllie, E., & Godoy, J. (1991). Basal Temporal Language Area. *Brain, 114*(2), 743-754. doi:10.1093/brain/114.2.743
Lutz, M. T., Clusmann, H., Elger, C. E., Schramm, J., & Helmstaedter, C. (2004). Neuropsychological Outcome after Selective Amygdalohippocampectomy with Transsylvian versus Transcortical Approach: A Randomized Prospective Clinical Trial of Surgery for Temporal Lobe Epilepsy. *Epilepsia, 45*(7), 809-816. doi:10.1111/j.0013-9580.2004.54003.x
Maccotta, L., Lopez, M., Adeyemo, B., et al. (2017). Postoperative seizure freedom does not normalize altered connectivity in temporal lobe epilepsy. *Epilepsia, 58*. doi:10.1111/epi.13867

Macrodimitris, S., Sherman, E. M., Forde, S., et al. (2011). Psychiatric outcomes of epilepsy surgery: a systematic review. *Epilepsia, 52*(5), 880-890. doi:10.1111/j.1528-1167.2011.03014.x

Maguire, E. A., Woollett, K., & Spiers, H. J. (2006). London taxi drivers and bus drivers: A structural MRI and neuropsychological analysis. *Hippocampus, 16*(12), 1091-1101. doi:10.1002/hipo.20233

Maizuliana, H., Usui, N., Terada, K., Kondo, A., & Inoue, Y. (2020). Clinical, semiological, electroencephalographic, and neuropsychological features of "pure" neocortical temporal lobe epilepsy. *Epileptic Disorders, 22*(1), 55-65. doi:10.1684/epd.2020.1132

Malmgren, K., & Thom, M. (2012). Hippocampal sclerosis--origins and imaging. *Epilepsia, 53 Suppl 4*, 19-33. doi:10.1111/j.1528-1167.2012.03610.x

Margerison, J. H., & Corsellis, J. A. (1966). Epilepsy and the temporal lobes. A clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes. *Brain : a journal of neurology, 89*(3), 499-530. doi:10.1093/brain/89.3.499

Martini, M. L., Oermann, E. K., Opie, N. L., Panov, F., Oxley, T., & Yaeger, K. (2019). Sensor Modalities for Brain-Computer Interface Technology: A Comprehensive Literature Review. *Neurosurgery, 86*(2), E108-E117. doi:10.1093/neuros/nyz286

McConley, R., Martin, R., Palmer, C. A., Kuzniecky, R., Knowlton, R., & Faught, E. (2008). Rey Osterrieth complex figure test spatial and figural scoring: relations to seizure focus and hippocampal pathology in patients with temporal lobe epilepsy. *Epilepsy Behav, 13*(1), 174-177. doi:10.1016/j.yebeh.2008.03.003

McGonigal, A., Bartolomei, F., Régis, J., et al. (2008). Stereoelectroencephalography in presurgical assessment of MRI-negative epilepsy. *Brain : a journal of neurology, 130*, 3169-3183. doi:10.1093/brain/awm218

McIntosh, A. M., Averill, C. A., Kalnins, R. M., Mitchell, L. A., Fabinyi, G. C., Jackson, G. D., & Berkovic, S. F. (2012). Long-term seizure outcome and risk factors for recurrence after extratemporal epilepsy surgery. *Epilepsia, 53*(6), 970-978. doi:10.1111/j.1528-1167.2012.03430.x

McIntosh, A. M., Kalnins, R. M., Mitchell, L. A., & Berkovic, S. F. (2005). Early seizures after temporal lobectomy predict subsequent seizure recurrence. *Ann Neurol, 57*(2), 283-288. doi:10.1002/ana.20372

McIntosh, A. M., Kalnins, R. M., Mitchell, L. A., Fabinyi, G. C., Briellmann, R. S., & Berkovic, S. F. (2004). Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. *Brain, 127*(Pt 9), 2018-2030. doi:10.1093/brain/awh221

McIntosh, A. M., Wilson, S. J., & Berkovic, S. F. (2001). Seizure outcome after temporal lobectomy: current research practice and findings. *Epilepsia, 42*(10), 1288-1307. doi:10.1046/j.1528-1157.2001.02001.x

Meador, K. J. (2006). Cognitive and memory effects of the new antiepileptic drugs. *Epilepsy Research, 68*(1), 63-67. doi:10.1016/j.eplepsyres.2005.09.023

Meldrum, B. S. (1990). Anatomy, physiology, and pathology of epilepsy. *The Lancet, 336*(8709), 231-234. doi:10.1016/0140-6736(90)91747-X

Mendes Coelho, V. C., Morita, M. E., Amorim, B. J., et al. (2017). Automated Online Quantification Method for 18F-FDG Positron Emission Tomography/CT Improves Detection of the Epileptogenic Zone in Patients with Pharmacoresistant Epilepsy. *Frontiers in Neurology, 8*, 453.

Mendez, M. F., Cummings, J. L., & Benson, D. F. (1986). Depression in Epilepsy: Significance and Phenomenology. *Arch Neurol, 43*(8), 766-770. doi:10.1001/archneur.1986.00520080014012

Menon, R. N., Radhakrishnan, A., Parameswaran, R., et al. (2015). Does F-18 FDG-PET substantially alter the surgical decision-making in drug-resistant partial epilepsy? *Epilepsy & Behavior, 51*, 133-139. doi:10.1016/j.yebeh.2015.07.004

Messori, A., Polonara, G., Carle, F., Gesuita, R., & Salvolini, U. (2005). Predicting Posttraumatic Epilepsy with MRI: Prospective Longitudinal Morphologic Study in Adults. *Epilepsia, 46*(9), 1472-1481. doi:10.1111/j.1528-1167.2005.34004.x

Metz, C. E. (1978). Basic principles of ROC analysis. *Seminars in Nuclear Medicine, 8*(4), 283-298. doi:10.1016/S0001-2998(78)80014-2

Milner, B., & Penfield, W. (1955). The effect of hippocampal lesions on recent memory. *Transactions of the American Neurological Association*(80th Meeting), 42-48.

Mitchell, L., Harvey, A., Coleman, L., Mandelstam, S., & Jackson, G. (2003). Anterior Temporal Changes on MR Images of Children with Hippocampal Sclerosis: An Effect of Seizures on the Immature Brain? *AJNR. American journal of neuroradiology, 24*, 1670-1677.

Montaz-Rosset, M.-S., Scholly, J., Voulleminot, P., Severac, F., Hirsch, E., Valenti-Hirsch, M. P., & Namer, I. J. (2019). Comparison of Functional Deficit Zone Defined by FDG PET to the Epileptogenic Zones Described in Stereo-Electroencephalograph in Drug-Resistant Epileptic Patients Treated by Surgery. *Clinical Nuclear Medicine, 44*(7).

Morel, L., Men, Y., Chiang, M. S. R., et al. (2019). Intracortical astrocyte subpopulations defined by astrocyte reporter Mice in the adult brain. *Glia, 67*(1), 171-181. doi:10.1002/glia.23545

Morgan, V. L., Englot, D. J., Rogers, B. P., Landman, B. A., Cakir, A., Abou-Khalil, B. W., & Anderson, A. W. (2017). Magnetic resonance imaging connectivity for the prediction of seizure outcome in temporal lobe epilepsy. *Epilepsia, 58*(7), 1251-1260. doi:10.1111/epi.13762

Morgan, V. L., Gore, J. C., & Abou-Khalil, B. (2007). Cluster analysis detection of functional MRI activity in temporal lobe epilepsy. *Epilepsy Research, 76*(1), 22-33. doi:10.1016/j.eplepsyres.2007.06.008

Mortensen, E., Gade, A., & Reinisch, J. (1991). A critical note on Lezak's 'Best Performance Method' in clinical neuropsychology. *Journal of clinical and experimental neuropsychology, 13*, 361-371. doi:10.1080/01688639108401050

Mouthaan, B. E., Rados, M., Barsi, P., et al. (2016). Current use of imaging and electromagnetic source localization procedures in epilepsy surgery centers across Europe. *Epilepsia, 57*(5), 770-776. doi:10.1111/epi.13347

Mueller, S. G., Laxer, K. D., Barakos, J., Cheong, I., Garcia, P., & Weiner, M. W. (2009). Widespread neocortical abnormalities in temporal lobe epilepsy with and without mesial sclerosis. *Neuroimage, 46*(2), 353-359. doi:10.1016/j.neuroimage.2009.02.020

Mueller, S. G., Laxer Kd., Barakos J., Cheong I., Garcia P., & Weiner, M. W. Widespread neocortical abnormalities in temporal lobe epilepsy with and without mesial sclerosis. (1095-9572 (Electronic)).

Mueller, S. G., Laxer, K. D., Scanlon, C., et al. (2012). Different structural correlates for verbal memory impairment in temporal lobe epilepsy with and without mesial temporal lobe sclerosis. *Human brain mapping, 33*(2), 489-499. doi:10.1002/hbm.21226

Muhlhofer, W., Tan, Y.-L., Mueller, S. G., & Knowlton, R. (2017a). MRI-negative temporal lobe epilepsy-What do we know? *Epilepsia, 58*(5), 727-742. doi:10.1111/epi.13699

Muhlhofer, W., Tan, Y.-L., Mueller, S. G., & Knowlton, R. (2017b). MRI-negative temporal lobe epilepsy—What do we know? *Epilepsia, 58*(5), 727-742. doi:10.1111/epi.13699

Mula, M., & Trimble, M. R. (2009). Antiepileptic Drug-Induced Cognitive Adverse Effects. *CNS Drugs, 23*(2), 121-137. doi:10.2165/00023210-200923020-00003

Mullatti, N., Landre, E., Mellerio, C., et al. (2019). Stereotactic thermocoagulation for insular epilepsy: Lessons from successes and failures. *Epilepsia, 60*. doi:10.1111/epi.16092

Munari, C., E., Francione, S., Tassi, L., et al. (2007). Clinical Ictal Symptomatology and Anatomical Lesions: Their Relationships in Severe Partial Epilepsy. *Epilepsia, 41*, S18-S36. doi:10.1111/j.1528-1157.2000.tb06043.x

Murphy, M., O'Brien, T. J., Morris, K., & Cook, M. J. (2001). Multimodality image-guided epilepsy surgery. *J Clin Neurosci, 8*(6), 534-538. doi:10.1054/jocn.2001.0921

Murphy, T. R., Binder, D. K., & Fiacco, T. A. (2017). Turning down the volume: Astrocyte volume change in the generation and termination of epileptic seizures. *Neurobiology of disease, 104*, 24-32. doi:10.1016/j.nbd.2017.04.016

Müther, M., Koch, R., Weckesser, M., Sporns, P., Schwindt, W., & Stummer, W. (2019). 5-Aminolevulinic Acid Fluorescence-Guided Resection of 18F-FET-PET Positive Tumor Beyond Gadolinium Enhancing Tumor Improves Survival in Glioblastoma. *Neurosurgery, 85*(6), E1020-E1029. doi:10.1093/neuros/nyz199

Najm, I., Jehi, L., Palmini, A., Gonzalez-Martinez, J., Paglioli, E., & Bingaman, W. (2013). Temporal patterns and mechanisms of epilepsy surgery failure. *Epilepsia, 54*(5), 772-782. doi:10.1111/epi.12152

Nayel, M. H., Awad, I. A., & Lüders, H. (1991). Extent of Mesiobasal Resection Determines Outcome after Temporal Lobectomy for Intractable Complex Partial Seizures. *Neurosurgery, 29*(1), 55-61. doi:10.1227/00006123-199107000-00009

Ngugi, A. K., Bottomley, C., Kleinschmidt, I., Sander, J. W., & Newton, C. R. (2010). Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. *Epilepsia, 51*(5), 883-890. doi:10.1111/j.1528-1167.2009.02481.x

O'Brien, M. D. (2014). Use and abuse of physical signs in neurology. *Journal of the Royal Society of Medicine, 107*(10), 416-421. doi:10.1177/0141076814538785

O'Brien, T. J., Miles, K., Ware, R., Cook, M. J., Binns, D. S., & Hicks, R. J. (2008). The cost-effective use of 18F-FDG PET in the presurgical evaluation of medically refractory focal epilepsy. *J Nucl Med, 49*(6), 931-937. doi:10.2967/jnumed.107.048207

O'Brien, T. J., Newton, M. R., Cook, M. J., Berlangieri, S. U., Kilpatrick, C., Morris, K., & Berkovic, S. F. (1997). Hippocampal atrophy is not a major determinant of regional hypometabolism in temporal lobe epilepsy. *Epilepsia, 38*(1), 74-80.

O'Leary, D. S., Seidenberg, M., Berent, S., & Boll, T. J. (1981). Effects of Age of Onset of Tonic-Clonic Seizures on Neuropsychological Performance in Children. *Epilepsia, 22*(2), 197-204. doi:10.1111/j.1528-1157.1981.tb04102.x

Ogden-Epker, M., & Cullum, C. M. (2001). Quantitative and qualitative interpretation of neuropsychological data in the assessment of temporal lobectomy candidates. *Clin Neuropsychol, 15*(2), 183-195. doi:10.1076/clin.15.2.183.1900

Orbach, D., Romanelli, P., Devinsky, O., & Doyle, W. (2001). Late Seizure Recurrence after Multiple Subpial Transections. *Epilepsia, 42*(10), 1316-1319. doi:10.1111/j.1528-1167.2001.45300.x

Orkand, R. K., Nicholls, J. G., & Kuffler, S. W . (1966). Effect of nerve impulses on the membrane potential of glial cells in the CNS of amphibia. *J Neurophysiol, 29*, 788–806.

Osório, C. M., Latini, A., Leal, R. B., et al. (2017). Neuropsychological functioning and brain energetics of drug resistant mesial temporal lobe epilepsy patients. *Epilepsy Research, 138*, 26-31. doi:10.1016/j.eplepsyres.2017.10.009

Paesschen, W., Dupont, P., Sunaert, S., Goffin, K., & Laere, K. (2007). The use of SPECT and PET in routine clinical practice in epilepsy. *Curr Opin Neurol, 20*, 194-202. doi:10.1097/WCO.0b013e328042baf6

Pai, M.-C., & Tsai, J.-J. (2005). Is Cognitive Reserve Applicable to Epilepsy? The Effect of Educational Level on the Cognitive Decline After Onset of Epilepsy. *Epilepsia, 46*(s1), 7-10. doi:10.1111/j.0013-9580.2005.461003.x

Park, A., & Stacy, M. (2009). Non-motor symptoms in Parkinson's disease. *Journal of Neurology, 256*(3), 293-298. doi:10.1007/s00415-009-5240-1

Penfield, W. (1929). The mechanisms of cicatricial contraction in the brain. *Brain, 50*, 499-517.

Penfield, W., & Flanigin, H. (1950). Surgical Therapy of Temporal Lobe Seizures. *A.M.A. Archives of Neurology & Psychiatry, 64*(4), 491-500. doi:10.1001/archneurpsyc.1950.02310280003001

Penfield, W., & Milner, B. (1958). Memory Deficit Produced by Bilateral Lesions in the Hippocampal Zone. *A.M.A. Archives of Neurology & Psychiatry, 79*(5), 475-497. doi:10.1001/archneurpsyc.1958.02340050003001

Penny, W. F., K.; Ashburner, J.; Kiebel, S; Thomas, N. (2006). *Statistical Parametric Mapping: The Analysis of Functional Brain Images.* (1st Edition. ed.): Academic Press.

Pereira, F. R., Alessio, A., Sercheli, M. S., et al. (2010). Asymmetrical hippocampal connectivity in mesial temporal lobe epilepsy: evidence from resting state fMRI. *BMC Neurosci, 11*, 66. doi:10.1186/1471-2202-11-66

Perry, M. S., & Duchowny, M. (2013). Surgical versus medical treatment for refractory epilepsy: Outcomes beyond seizure control. *Epilepsia, 54*(12), 2060-2070. doi:10.1111/epi.12427

Piazzini, A., Turner, K., Chifari, R., Morabito, A., Canger, R., & Canevini, M. P. (2006). Attention and psychomotor speed decline in patients with temporal lobe epilepsy: A longitudinal study. *Epilepsy Research, 72*(2), 89-96. doi:10.1016/j.eplepsyres.2006.04.004

Picot, M.-C., Jaussent, A., Neveu, D., et al. (2016). Cost-effectiveness analysis of epilepsy surgery in a controlled cohort of adult patients with intractable partial epilepsy: A 5-year follow-up study. *Epilepsia, 57*(10), 1669-1679. doi:10.1111/epi.13492

Pittau, F., Grouiller, F., Spinelli, L., Seeck, M., Michel, C. M., & Vulliemoz, S. (2014). The role of functional neuroimaging in pre-surgical epilepsy evaluation. *Front Neurol, 5*, 31. doi:10.3389/fneur.2014.00031

Pollen, D. A., & Trachtenberg, M. C. . (1970). Neuroglia: gliosis and focal epilepsy. *Science*(167), 1252– 1253.

Prada Jardim, A., Liu, J., Baber, J., et al. (2018). Characterising subtypes of hippocampal sclerosis and reorganization: correlation with pre and postoperative memory deficit. *Brain Pathology, 28*(2), 143-154. doi:10.1111/bpa.12514

Quarato, P. P., Di Gennaro, G., Mascia, A., et al. (2005). Temporal lobe epilepsy surgery: different surgical strategies after a non-invasive diagnostic protocol. *Journal of neurology, neurosurgery, and psychiatry, 76*(6), 815-824. doi:10.1136/jnnp.2004.044016

Quigg, M., Rolston, J., & Barbaro, N. M. (2012). Radiosurgery for epilepsy: clinical experience and potential antiepileptic mechanisms. *Epilepsia, 53*(1), 7-15. doi:10.1111/j.1528-1167.2011.03339.x

Raabe, A., Schmitz, A., Pernhorst, K., et al. (2012). Cliniconeuropathologic correlations show astroglial albumin storage as a common factor in epileptogenic vascular lesions. *Epilepsia, 53,* 539-548. doi:10.1111/j.1528-1167.2012.03405.x

Raichle, M. E. (2015). The brain's default mode network. *Annu Rev Neurosci, 38,* 433-447. doi:10.1146/annurev-neuro-071013-014030

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America, 98*(2), 676-682. doi:10.1073/pnas.98.2.676

Ramesha, K. N., Mooney, T., Sarma, P. S., & Radhakrishnan, K. (2011). Long-term seizure outcome and its predictors in patients with recurrent seizures during the first year aftertemporal lobe resective epilepsy surgery. *Epilepsia, 52*(5), 917-924. doi:10.1111/j.1528-1167.2010.02891.x

Raspall, T., Donate, M., Boget, T., et al. (2005). Neuropsychological tests with lateralizing value in patients with temporal lobe epilepsy: reconsidering material-specific theory. *Seizure, 14*(8), 569-576. doi:10.1016/j.seizure.2005.09.007

Rathore, C., Dickson, J. C., Teotonio, R., Ell, P., & Duncan, J. S. (2014). The utility of 18F-fluorodeoxyglucose PET (FDG PET) in epilepsy surgery. *Epilepsy Res, 108*(8), 1306-1314. doi:10.1016/j.eplepsyres.2014.06.012

Rausch, R., Babb, T. L., Engel, J., Jr., & Crandall, P. H. (1989). Memory Following Intracarotid Amobarbital Injection Contralateral to Hippocampal Damage. *Arch Neurol, 46*(7), 783-788. doi:10.1001/archneur.1989.00520430077022

Rausch, R., Henry, T. R., Ary, C. M., Engel, J., Jr., & Mazziotta, J. (1994). Asymmetric interictal glucose hypometabolism and cognitive performance in epileptic patients. *Arch Neurol, 51*(2), 139-144.

Rausch, R., Kraemer, S., Pietras, C. J., Le, M., Vickrey, B. G., & Passaro, E. A. (2003). Early and late cognitive changes following temporal lobe surgery for epilepsy. *Neurology, 60*(6), 951. doi:10.1212/01.WNL.0000048203.23766.A1

Rayner, G., Tailby, C., Jackson, G., & Wilson, S. (2019). Looking beyond lesions for causes of neuropsychological impairment in epilepsy. *Neurology, 92*(7), e680. doi:10.1212/WNL.0000000000006905

Rey, A. (1941). L'examen psychologique dans les cas d'enc´ephalopathie traumatique. *Archives de Psychologie., 28*(21).

Reyes, A., Kaestner, E., Bahrami, N., et al. (2019). Cognitive phenotypes in temporal lobe epilepsy are associated with distinct patterns of white matter network abnormalities. *Neurology, 92*(17), e1957. doi:10.1212/WNL.0000000000007370

Richard, C. S., Elizabeth, C. C., & Saeed, M. F. (1965). Extratemporal Lesions Triggering the Temporal-Lobe Syndrome. *Journal of Neurosurgery, 22*(3), 246-263. doi:10.3171/jns.1965.22.3.0246

Riederer, F., Lanzenberger, R., Kaya, M., Prayer, D., Serles, W., & Baumgartner, C. (2008). Network atrophy in temporal lobe epilepsy. *Neurology, 71*(6), 419. doi:10.1212/01.wnl.0000324264.96100.e0

Risse, G. L., Gates, J. R., & Fangman, M. C. (1997). A Reconsideration of Bilateral Language Representation Based on the Intracarotid Amobarbital Procedure. *Brain Cogn, 33*(1), 118-132. doi:10.1006/brcg.1997.0887

Robel, S., & Sontheimer, H. (2016). Glia as drivers of abnormal neuronal activity. *Nature neuroscience, 19*(1), 28-33. doi:10.1038/nn.4184

Robert Powell, H. W., J. Koepp, M., 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*(7), 855-863. doi:10.1111/j.0013-9580.2004.41603.x

Roelcke, U., Boxheimer, L., Fathi, A. R., Schwyzer, L., Ortega, M., Berberat, J., & Remonda, L. (2013). Cortical hemosiderin is associated with seizures in patients with newly diagnosed malignant brain tumors. *Journal of Neuro-Oncology, 115*(3), 463-468. doi:10.1007/s11060-013-1247-7

Roger, E., Petit, L., Perrone-Bertolotti, M., Job-Chapron, A.-S., Minotti, L., Kahane, P., & Baciu, M. (2018). The link between structural connectivity and neurocognition illustrated by focal epilepsy. *Epileptic disorders: international epilepsy journal with videotape, 20*. doi:10.1684/epd.2018.0958

Rolston, J. D., & Chang, E. F. (2016). Stereotactic Laser Ablation for Hypothalamic Hamartoma. *Neurosurgery Clinics of North America, 27*(1), 59-67. doi:10.1016/j.nec.2015.08.007

Rosenow, F., & Lüders, H. (2001). Presurgical evaluation of epilepsy. *Brain : a journal of neurology, 124*(Pt 9), 1683-1700. doi:10.1093/brain/124.9.1683

Roth, J., Olasunkanmi, A., Ma, T. S., Carlson, C., Devinsky, O., Harter, D. H., & Weiner, H. L. (2012). Epilepsy control following intracranial monitoring without resection in young children. *Epilepsia, 53*(2), 334-341. doi:10.1111/j.1528-1167.2011.03380.x

Ruan, D., Yu, X.-B., Shrestha, S., Wang, L., & Chen, G. (2015). The Role of Hemosiderin Excision in Seizure Outcome in Cerebral Cavernous Malformation Surgery: A Systematic Review and Meta-Analysis. *PLoS One, 10*(8), e0136619-e0136619. doi:10.1371/journal.pone.0136619

Ryan, L., Nadel, L., Keil, K., Putnam, K., Schnyer, D., Trouard, T., & Moscovitch, M. (2001). Hippocampal complex and retrieval of recent and very remote autobiographical memories: Evidence from functional magnetic resonance imaging in neurologically intact people. *Hippocampus, 11*, 707-714. doi:10.1002/hipo.1086

Ryvlin, P., & Rheims, S. (2008). Epilepsy surgery: eligibility criteria and presurgical evaluation. *Dialogues in clinical neuroscience, 10*(1), 91-103.

Saghafi, S., Ferguson, L., Hogue, O., Gales, J. M., Prayson, R., & Busch, R. M. (2018). Histopathologic subtype of hippocampal sclerosis and episodic memory performance before and after temporal lobectomy for epilepsy. *Epilepsia, 59*(4), 825-833. doi:10.1111/epi.14036

Salanova, V., Andermann, F., Rasmussen, T., Olivier, A., & Quesney, L. (1996). The running down phenomenon in temporal lobe epilepsy. *Brain, 119*(3), 989-996. doi:10.1093/brain/119.3.989

Salanova, V., Markand, O., & Worth, R. (2004). Temporal lobe epilepsy: analysis of patients with dual pathology. *Acta Neurol Scand, 109*(2), 126-131. doi:10.1034/j.1600-0404.2003.00183.x

Salanova, V., Markand, O., & Worth, R. (2005). Temporal lobe epilepsy: analysis of failures and the role of reoperation. *Acta Neurol Scand, 111*(2), 126-133. doi:10.1111/j.1600-0404.2005.00371.x

Saling, M. M. (2009). Verbal memory in mesial temporal lobe epilepsy: beyond material specificity. *Brain, 132*(Pt 3), 570-582. doi:10.1093/brain/awp012

Saling, M. M., Berkovic, S. F., O'Shea, M. F., Kalnins, R. M., Darby, D. G., & Bladin, P. F. (1993). Lateralization of verbal memory and unilateral hippocampal sclerosis: evidence of task-specific effects. *J Clin Exp Neuropsychol, 15*(4), 608-618. doi:10.1080/01688639308402582

Sallie, B., Sarah, J. W., Gus, A. B., et al. (2019). Indications and expectations for neuropsychological assessment in epilepsy surgery in children and adults. Report of the ILAE Neuropsychology Task Force Diagnostic Methods Commission: 2017-2021 Neuropsychological assessment in epilepsy surgery. *Epileptic Disorders, 21*(3), 221-234. doi:10.1684/epd.2019.1065

Samarasekera, S. R., Wynd, A. W., McIntosh, A. M., & Berkovic, S. F. (2019). Predominantly nocturnal seizures post temporal lobectomy: Characteristics of an unusual outcome group. *Epilepsy Research, 155*, 106154. doi:10.1016/j.eplepsyres.2019.106154

Satz, P., Strauss, E., Wada, J., & Orsini, D. L. (1988). Some correlates of intra- and interhemispheric speech organization after left focal brain injury. *Neuropsychologia, 26*(2), 345-350. doi:10.1016/0028-3932(88)90087-5

Savic, I., Altshuler, L., Baxter, L., & Engel, J., Jr. (1997). Pattern of interictal hypometabolism in PET scans with fludeoxyglucose F 18 reflects prior seizure types in patients with mesial temporal lobe seizures. *Arch Neurol, 54*(2), 129-136. doi:10.1001/archneur.1997.00550140011006

Scheffer, I. E., Berkovic, S., Capovilla, G., et al. (2017). ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia, 58*(4), 512-521. doi:10.1111/epi.13709

Schmidt, D., & Sillanpää, M. (2017). Stopping epilepsy treatment in seizure remission: Good or bad or both? *Seizure - European Journal of Epilepsy, 44*, 157-161. doi:10.1016/j.seizure.2016.09.003

Schramm, J. (2008). Temporal lobe epilepsy surgery and the quest for optimal extent of resection: a review. *Epilepsia, 49*(8), 1296-1307. doi:10.1111/j.1528-1167.2008.01604.x

Schwartz, T. H., Jeha, L., Tanner, A., Bingaman, W., & Sperling, M. R. (2006). Late seizures in patients initially seizure free after epilepsy surgery. *Epilepsia, 47*(3), 567-573. doi:10.1111/j.1528-1167.2006.00469.x

Scoville WB, M. B. (1957). Loss of recent memory after bilateral hippocampal sclerosis. *J Neurol Neurosurg Psychiatry, 20*, 11-21.

Semah, F., Baulac, M., Hasboun, D., et al. (1995). Is Interictal Temporal Hypometabolism Related to Mesial Temporal Sclerosis? A Positron Emission Tomography/Magnetic Resonance Imaging Confrontation. *Epilepsia, 36*(5), 447-456. doi:10.1111/j.1528-1157.1995.tb00485.x

Shamim, S., Wiggs, E., Heiss, J., Sato, S., Liew, C., Solomon, J., & Theodore, W. H. (2009). Temporal lobectomy: resection volume, neuropsychological effects, and seizure outcome. *Epilepsy Behav, 16*(2), 311-314. doi:10.1016/j.yebeh.2009.07.040

Sherman, E. M., Wiebe, S., Fay-McClymont, T. B., et al. (2011). Neuropsychological outcomes after epilepsy surgery: systematic review and pooled estimates. *Epilepsia, 52*(5), 857-869. doi:10.1111/j.1528-1167.2011.03022.x

Shih, J. J., Fountain, N. B., Herman, S. T., et al. (2018). Indications and methodology for video-electroencephalographic studies in the epilepsy monitoring unit. *Epilepsia, 59*(1), 27-36. doi:10.1111/epi.13938

Shimamoto, S., Wu, C., & Sperling, M. (2019). Laser interstitial thermal therapy in drug-resistant epilepsy. *Curr Opin Neurol, 32*, 1. doi:10.1097/WCO.0000000000000662

Shin, H. W., Jewells, V., Sheikh, A., et al. (2015). Initial experience in hybrid PET-MRI for evaluation of refractory focal onset epilepsy. *Seizure, 31*, 1-4. doi:10.1016/j.seizure.2015.06.010

Shinozaki, Y., Shibata, K., Yoshida, K., et al (2017). Transformation of Astrocytes to a Neuroprotective Phenotype by Microglia via P2Y<sub>1</sub> Receptor Downregulation. *Cell Reports, 19*(6), 1151-1164. doi:10.1016/j.celrep.2017.04.047

Shtyrov, Y., Kujala, T., Ahveninen, J., Tervaniemi, M., Alku, P., Ilmoniemi, R. J., & Näätänen, R. (1998). Background acoustic noise and the hemispheric lateralization of speech processing in the human brain: magnetic mismatch

negativity study. *Neuroscience Letters, 251*(2), 141-144. doi:10.1016/S0304-3940(98)00529-1

Siclari, F., Prior, J. O., & Rossetti, A. O. (2013). Ictal cerebral positron emission tomography (PET) in focal status epilepticus. *Epilepsy Res, 105*(3), 356-361. doi:10.1016/j.eplepsyres.2013.03.006

Siddiqui, A., Kerb, R., Weale, M. E., et al. (2003). Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1. *N Engl J Med, 348*(15), 1442-1448. doi:10.1056/NEJMoa021986

Sidhu, M. K., Stretton, J., Winston, G. P., et al. (2013). A functional magnetic resonance imaging study mapping the episodic memory encoding network in temporal lobe epilepsy. *Brain, 136*(Pt 6), 1868-1888. doi:10.1093/brain/awt099

Sidhu, M. K., Stretton, J., Winston, G. P., et al. (2016). Memory network plasticity after temporal lobe resection: a longitudinal functional imaging study. *Brain, 139*(Pt 2), 415-430. doi:10.1093/brain/awv365

Silverman, I. E., Restrepo, L., & Mathews, G. C. (2002). Poststroke Seizures. *Arch Neurol, 59*(2), 195-201. doi:10.1001/archneur.59.2.195

Sinha, N., Dauwels, J., Kaiser, M., Cash, S. S., Brandon Westover, M., Wang, Y., & Taylor, P. N. (2017). Predicting neurosurgical outcomes in focal epilepsy patients using computational modelling. *Brain : a journal of neurology, 140*(2), 319-332. doi:10.1093/brain/aww299

Sinha, N., Wang, Y., Silva, N., et al. (2019). Node abnormality predicts seizure outcome and relates to long-term relapse after epilepsy surgery. *BioRxiv*, 747725 [Preprint] September 1, 2019. doi: 10.1101/747725

Smith, J. R., Sillay, K., Winkler, P., King, D. W., & Loring, D. W. (2004). Orbitofrontal Epilepsy: Electroclinical Analysis of Surgical Cases and Literature Review. *Stereotact Funct Neurosurg, 82*(1), 20-25. doi:10.1159/000076656

Smith, K., Blessing, M., Parisi, J., Britton, J., Mandrekar, J., & Cascino, G. (2019). Tau deposition in young adults with drug - resistant focal epilepsy. *Epilepsia, 60*. doi:10.1111/epi.16375

So, E. L., Radhakrishnan, K., Silbert, P. L., Cascino, G. D., Sharbrough, F. W., & O'Brien, P. C. (1997). Assessing changes over time in temporal lobectomy: outcome by scoring seizure frequency1Presented at the 48th Annual Scientific Meeting of the American Epilepsy Society, New Orleans, LA.1. *Epilepsy Research, 27*(2), 119-125. doi:10.1016/S0920-1211(97)01028-0

Soble, J. R., Eichstaedt, K. E., Waseem, H., et al. (2014). Clinical utility of the Wechsler Memory Scale--Fourth Edition (WMS-IV) in predicting laterality of temporal lobe epilepsy among surgical candidates. *Epilepsy Behav, 41*, 232-237. doi:10.1016/j.yebeh.2014.10.014

Sofroniew, M. V. (2009). Molecular dissection of reactive astrogliosis and glial scar formation. *Trends in neurosciences, 32*(12), 638-647. doi:10.1016/j.tins.2009.08.002

Sofroniew, M. V. (2014). Astrogliosis. *Cold Spring Harbor perspectives in biology, 7*(2), a020420-a020420. doi:10.1101/cshperspect.a020420

Spanaki, M. V., Kopylev, L., DeCarli, C., et al. (2000). Postoperative changes in cerebral metabolism in temporal lobe epilepsy. *Arch Neurol, 57*(10), 1447-1452.

Spanedda, F., Cendes, F., & Gotman, J. (1997). Relations Between EEG Seizure Morphology, Interhemispheric Spread, and Mesial Temporal Atrophy in Bitemporal Epilepsy. *Epilepsia, 38*(12), 1300-1314. doi:10.1111/j.1528-1157.1997.tb00068.x

Spencer, D., Gwinn R., Salinsky M., et al. (2011). Laterality and temporal distribution of seizures in patients with bitemporal independent seizures during a trial of responsive neurostimulation. *Epilepsy Res.*, 93(2-3):221-225.

doi:10.1016/j.eplepsyres.2010.12.010
Spencer, D. D., Spencer, S. S., Mattson, R. H., Williamson, P. D., & Novelly, R. A. (1984). Access to the Posterior Medial Temporal Lobe Structures in the Surgical Treatment of Temporal Lobe Epilepsy. *Neurosurgery, 15*(5), 667-671. doi:10.1227/00006123-198411000-00005
Spencer, S. S., Berg, A. T., Vickrey, B. G., et al. (2003). Initial outcomes in the Multicenter Study of Epilepsy Surgery. *Neurology, 61*(12), 1680-1685.
Springer, J. A., Binder, J. R., Hammeke, T. A., et al. (1999). Language dominance in neurologically normal and epilepsy subjects: A functional MRI study. *Brain, 122*(11), 2033-2046. doi:10.1093/brain/122.11.2033
Srikijvilaikul, T., Najm, I. M., Hovinga, C. A., Prayson, R. A., Gonzalez-Martinez, J., & Bingaman, W. E. (2003). Seizure Outcome after Temporal Lobectomy in Temporal Lobe Cortical Dysplasia. *Epilepsia, 44*(11), 1420-1424. doi:10.1046/j.1528-1157.2003.16703.x
Stanisic, M., Coello, C., Ivanovic, J., et al. (2015). Seizure outcomes in relation to the extent of resection of the perifocal fluorodeoxyglucose and flumazenil PET abnormalities in anteromedial temporal lobectomy. *Acta Neurochir (Wien), 157*(11), 1905-1916. doi:10.1007/s00701-015-2578-2
Steinhäuser, C., Seifert, G., & Bedner, P. (2012). Astrocyte dysfunction in temporal lobe epilepsy: K+ channels and gap junction coupling. *Glia, 60*(8), 1192-1202. doi:10.1002/glia.22313
Stephen, M., John, S., Mathew, E., Neal, F. K., Edward, K., & Ryder, G. (2016). Transcranial magnetic resonance–guided focused ultrasound for temporal lobe epilepsy: a laboratory feasibility study. *Journal of Neurosurgery JNS, 125*(6), 1557-1564. doi:10.3171/2015.10.JNS1542
Stewart, C. C., Swanson, S. J., Sabsevitz, D. S., Rozman, M. E., Janecek, J. K., & Binder, J. R. (2014). Predictors of language lateralization in temporal lobe epilepsy. *Neuropsychologia, 60*, 93-102. doi:10.1016/j.neuropsychologia.2014.05.021
Strauss, E., & Wada, J. (1983). Lateral Preferences and Cerebral Speech Dominance. *Cortex, 19*(2), 165-177. doi:10.1016/S0010-9452(83)80012-4
Streitfeld, B. D. (1980). The Fiber Connections of the Temporal Lobe with Emphasis on the Rhesus Monkey. *International Journal of Neuroscience, 11*(1), 51-71. doi:10.3109/00207458009147579
Stretton, J., Winston, G., Sidhu, M., et al. (2012). Neural correlates of working memory in Temporal Lobe Epilepsy--an fMRI study. *Neuroimage, 60*(3), 1696-1703. doi:10.1016/j.neuroimage.2012.01.126
Stroup, E., Langfitt, J., Berg, M., McDermott, M., Pilcher, W., & Como, P. (2003). Predicting verbal memory decline following anterior temporal lobectomy (ATL). *Neurology, 60*(8), 1266. doi:10.1212/01.WNL.0000058765.33878.0D
Sweeney, M. D., Montagne, A., Sagare, A. P., et al. (2019). Vascular dysfunction—The disregarded partner of Alzheimer's disease. *Alzheimer's & Dementia, 15*(1), 158-167. doi:10.1016/j.jalz.2018.07.222
Szelényi, A., Bello, L., Duffau, H., et al. (2010). Intraoperative electrical stimulation in awake craniotomy: Methodological aspects of current practice. *Neurosurgical FOCUS, 28*. doi:10.3171/2009.12.FOCUS09237
Tai, X., Koepp, M., Duncan, J., et al. (2016). Hyperphosphorylated tau in patients with refractory epilepsy correlates with cognitive decline: A study of temporal lobe resections. *Brain, 139*, aww187. doi:10.1093/brain/aww187
Takaya, S., Hanakawa, T., Hashikawa, K., et al. (2006). Prefrontal hypofunction in patients with intractable mesial temporal lobe epilepsy. *Neurology, 67*(9), 1674. doi:10.1212/01.wnl.0000242628.26978.e2

Takaya, S., Mikuni, N., Mitsueda, T., et al. (2009). Improved cerebral function in mesial temporal lobe epilepsy after subtemporal amygdalohippocampectomy. *Brain, 132*(Pt 1), 185-194. doi:10.1093/brain/awn218

Tasch, E., Cendes, F., Li, L. M., Dubeau, F., Andermann, F., & Arnold, D. L. (1999). Neuroimaging evidence of progressive neuronal loss and dysfunction in temporal lobe epilepsy. *Annals of Neurology, 45*(5), 568-576. doi:10.1002/1531-8249(199905)45:5<568::aid-ana4>3.0.co;2-p

Taylor, J., Kolamunnage-Dona, R., Marson, A. G., Smith, P. E. M., Aldenkamp, A. P., Baker, G. A., & on behalf of the, S. s. g. (2010). Patients with epilepsy: Cognitively compromised before the start of antiepileptic drug treatment? *Epilepsia, 51*(1), 48-56. doi:10.1111/j.1528-1167.2009.02195.x

Tellez-Zenteno, J. F., Dhar, R., & Wiebe, S. (2005). Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain, 128*(Pt 5), 1188-1198. doi:10.1093/brain/awh449

Tellez-Zenteno, J. F., Hernandez Ronquillo, L., Moien-Afshari, F., & Wiebe, S. (2010). Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. *Epilepsy Res, 89*(2-3), 310-318. doi:10.1016/j.eplepsyres.2010.02.007

Theodore, W. H., Bhatia, S., Hatta, J., Fazilat, S., DeCarli, C., Bookheimer, S. Y., & Gaillard, W. D. (1999). Hippocampal atrophy, epilepsy duration, and febrile seizures in patients with partial seizures. *Neurology, 52*(1), 132-136. doi:10.1212/wnl.52.1.132

Theodore, W. H., Kelley, K., Toczek, M. T., & Gaillard, W. D. (2004). Epilepsy duration, febrile seizures, and cerebral glucose metabolism. *Epilepsia, 45*(3), 276-279. doi:10.1111/j.0013-9580.2004.51803.x

Theodore, W. H., Sato, S., Kufta, C. V., Gaillard, W. D., & Kelley, K. (1997). FDG-positron emission tomography and invasive EEG: seizure focus detection and surgical outcome. *Epilepsia, 38*(1), 81-86.

Thevathasan, A., Naylor, J., Churilov, L., Mitchell, P., Dowling, R., Yan, B., & Kwan, P. (2017). Association between hemorrhagic transformation after endovascular therapy and poststroke seizures. *Epilepsia, 59*. doi:10.1111/epi.13982

Thom, M., Liu, J. Y. W., Thompson, P., et al. (2011). Neurofibrillary tangle pathology and Braak staging in chronic epilepsy in relation to traumatic brain injury and hippocampal sclerosis: a post-mortem study. *Brain, 134*(10), 2969-2981. doi:10.1093/brain/awr209

Thom, M., Mathern, G. W., Cross, J. H., & Bertram, E. H. (2010). Mesial temporal lobe epilepsy: How do we improve surgical outcome? *Ann Neurol, 68*(4), 424-434. doi:10.1002/ana.22142

Thompson, P. J., Baxendale, S. A., McEvoy, A. W., & Duncan, J. S. (2015). Cognitive outcomes of temporal lobe epilepsy surgery in older patients. *Seizure, 29*, 41-45. doi:10.1016/j.seizure.2015.03.017

Thompson, P. M., Andreassen, O. A., Arias-Vasquez, A., et al. (2017). ENIGMA and the individual: Predicting factors that affect the brain in 35 countries worldwide. *Neuroimage, 145*(Pt B), 389-408. doi:10.1016/j.neuroimage.2015.11.057

Tian, G.-F., Azmi, H., Takano, T., et al. (2005). An astrocytic basis of epilepsy. *Nature medicine, 11*(9), 973-981. doi:10.1038/nm1277

Trenerry, M. R., Westerveld, M., & Meador, K. J. (1995). MRI hippocampal volume and neuropsychology in epilepsy surgery. *Magnetic Resonance Imaging, 13*(8), 1125-1132. doi:10.1016/0730-725X(95)02022-L

Tsai, M.-H., Vaughan, D., Perchyonok, Y., Fitt, G., Scheffer, I., Berkovic, S., & Jackson, G. (2016). Hippocampal malrotation is an anatomic variant and has no

clinical significance in MRI - negative temporal lobe epilepsy. *Epilepsia*, *57*. doi:10.1111/epi.13505

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*(1), 273-289. doi:10.1006/nimg.2001.0978

Uijl, S. G., Leijten, F. S. S., Arends, J. B. A. M., Parra, J., Van Huffelen, A. C., & Moons, K. G. M. (2007). The Added Value of [18F]-Fluoro-D-deoxyglucose Positron Emission Tomography in Screening for Temporal Lobe Epilepsy Surgery. *Epilepsia, 48*(11), 2121-2129. doi:10.1111/j.1528-1167.2007.01197.x

Vakharia, V. N., Duncan, J. S., Witt, J.-A., Elger, C. E., Staba, R., & Engel, J., Jr. (2018). Getting the best outcomes from epilepsy surgery. *Annals of Neurology, 83*(4), 676-690. doi:10.1002/ana.25205

Vakharia, V. N., Sparks, R., Miserocchi, A., et al. (2019). Computer-Assisted Planning for Stereoelectroencephalography (SEEG). *Neurotherapeutics, 16*(4), 1183-1197. doi:10.1007/s13311-019-00774-9

van't Klooster, M. A., Huiskamp, G., Zijlmans, M., et al. (2014). Can we increase the yield of FDG-PET in the preoperative work-up for epilepsy surgery? *Epilepsy Res, 108*(6), 1095-1105. doi:10.1016/j.eplepsyres.2014.04.011

Vanicek, T., Hahn, A., Traub-Weidinger, T., et al. (2016). Insights into Intrinsic Brain Networks based on Graph Theory and PET in right- compared to left-sided Temporal Lobe Epilepsy. *Sci Rep, 6*, 28513. doi:10.1038/srep28513

Varrone, A., Asenbaum, S., Vander Borght, T., et al European Association of Nuclear Medicine Neuroimaging. (2009). EANM procedure guidelines for PET brain imaging using [18F]FDG, version 2. *Eur J Nucl Med Mol Imaging, 36*(12), 2103-2110. doi:10.1007/s00259-009-1264-0

Veersema, T. J., Ferrier, C. H., van Eijsden, P., et al. (2017). Seven tesla MRI improves detection of focal cortical dysplasia in patients with refractory focal epilepsy. *Epilepsia open, 2*(2), 162-171. doi:10.1002/epi4.12041

Verger, A., Lagarde, S., Maillard, L., Bartolomei, F., & Guedj, E. (2018). Brain molecular imaging in pharmacoresistant focal epilepsy: Current practice and perspectives. *Revue neurologique, 174*(1), 16-27. doi:10.1016/j.neurol.2017.05.001

Vermathen, P., Laxer, K. D., Schuff, N., Matson, G. B., & Weiner, M. W. (2003). Evidence of Neuronal Injury Outside the Medial Temporal Lobe in Temporal Lobe Epilepsy: N-Acetylaspartate Concentration Reductions Detected with Multisection Proton MR Spectroscopic Imaging—Initial Experience. *Radiology, 226*(1), 195-202. doi:10.1148/radiol.2261011668

Viard, A., Piolino, P., Desgranges, B., et al. (2007). Hippocampal activation for autobiographical memories over the entire lifetime in healthy aged subjects: an fMRI study. *Cerebral cortex (New York, N.Y. : 1991), 17*(10), 2453-2467. doi:10.1093/cercor/bhl153

Victoria, L. M., Baxter, P. R., Hernán, F. J. G., Sarah, E. G., & Dario, J. E. (2019). Characterization of postsurgical functional connectivity changes in temporal lobe epilepsy. *Journal of Neurosurgery JNS*, 1-11. doi:10.3171/2019.3.JNS19350

Vignal, J.-P., Maillard, L., McGonigal, A., & Chauvel, P. (2006). The dreamy state: hallucinations of autobiographic memory evoked by temporal lobe stimulations and seizures. *Brain, 130*(1), 88-99. doi:10.1093/brain/awl329

Vigneau, M., Beaucousin, V., Hervé, P.-Y., et al. (2011). What is right-hemisphere contribution to phonological, lexico-semantic, and sentence processing?:

Insights from a meta-analysis. *Neuroimage, 54*(1), 577-593. doi:10.1016/j.neuroimage.2010.07.036

Vinton, A. B., Carne, R., Hicks, R. J., Desmond, P. M., Kilpatrick, C., Kaye, A. H., & O'Brien, T. J. (2007). The extent of resection of FDG-PET hypometabolism relates to outcome of temporal lobectomy. *Brain, 130*(Pt 2), 548-560. doi:10.1093/brain/awl232

Vivash, L., Gregoire, M. C., Lau, E. W., et al. (2013). 18F-flumazenil: a gamma-aminobutyric acid A-specific PET radiotracer for the localization of drug-resistant temporal lobe epilepsy. *J Nucl Med, 54*(8), 1270-1277. doi:10.2967/jnumed.112.107359

Voets, N., Adcock, J., Stacey, R., Hart, Y., Carpenter, K., Matthews, P., & Beckmann, C. (2009). Functional and structural changes in the memory network associated with left temporal lobe epilepsy. *Human brain mapping, 30*, 4070-4081. doi:10.1002/hbm.20830

Voets, N. L., Beckmann, C. F., Cole, D. M., Hong, S., Bernasconi, A., & Bernasconi, N. (2012). Structural substrates for resting network disruption in temporal lobe epilepsy. *Brain, 135*(Pt 8), 2350-2357. doi:10.1093/brain/aws137

Vogt, V. L., Aikia, M., Del Barrio, A., et al. (2017). Current standards of neuropsychological assessment in epilepsy surgery centers across Europe. *Epilepsia, 58*(3), 343-355. doi:10.1111/epi.13646

Volk, H. A., Burkhardt, K., Potschka, H., Chen, J., Becker, A., & Löscher, W. (2004). Neuronal expression of the drug efflux transporter P-glycoprotein in the rat hippocampus after limbic seizures. *Neuroscience, 123*(3), 751-759. doi:10.1016/j.neuroscience.2003.10.012

Volterra, A., & Meldolesi, J. (2005). Astrocytes, from brain glue to communication elements: the revolution continues. *Nature Reviews Neuroscience, 6*(8), 626-640. doi:10.1038/nrn1722

von Lehe, M., & Parpaley, Y. (2017). Insular Cortex Surgery for the Treatment of Refractory Epilepsy. *Journal of Clinical Neurophysiology, 34*(4).

von Oertzen, T. J. (2018). PET and ictal SPECT can be helpful for localizing epileptic foci. *Curr Opin Neurol, 31*(2).

Vossler, D., Kraemer, D., Haltiner, A., et al. (2004). Intracranial EEG in Temporal Lobe Epilepsy: Location of Seizure Onset Relates to Degree of Hippocampal Pathology. *Epilepsia, 45*, 497-503. doi:10.1111/j.0013-9580.2004.47103.x

Walker, M. C., & Kullmann, D. M. (2020). Optogenetic and chemogenetic therapies for epilepsy. *Neuropharmacology, 168*, 107751. doi:10.1016/j.neuropharm.2019.107751

Walz, R., Castro, R. M., Velasco, T. R., et al. (2003). Surgical outcome in mesial temporal sclerosis correlates with prion protein gene variant. *Neurology, 61*(9), 1204-1210.

Warren, A., Harvey, A., Abbott, D., et al. (2017). Cognitive network reorganization following surgical control of seizures in Lennox-Gastaut syndrome. *Epilepsia, 58*. doi:10.1111/epi.13720

Waseem, H., Osborn, K., Schoenberg, M., et al. (2015). Laser ablation therapy: An alternative treatment for medically resistant mesial temporal lobe epilepsy after age 50. *Epilepsy & behavior : E&B, 51*, 152-157. doi:10.1016/j.yebeh.2015.07.022

Watabe, T., & Hatazawa, J. (2019). Evaluation of Functional Connectivity in the Brain Using Positron Emission Tomography: A Mini-Review. *Frontiers in neuroscience, 13*, 775-775. doi:10.3389/fnins.2019.00775

Weaver, D. F., & Pohlmann-Eden, B. (2013). Pharmacoresistant epilepsy: Unmet needs in solving the puzzle(s). *Epilepsia, 54*(s2), 80-85. doi:10.1111/epi.12191

Weber, J. P., Silbergeld, D. L., & Winn, H. R. (1993). Surgical resection of epileptogenic cortex associated with structural lesions. *Neurosurg Clin N Am*, 4(2):327-336.

Wechsler, D., (1999). *Wechsler Abbreviated Scale of Intelligence.*: San Antonio, TX: Harcourt Assessment.

Wechsler, D. (1945). A standardised memory scale for clinical use. *Journal of Psychology., 19*, 87-95.

Wehrl, H. F., Hossain, M., Lankes, K., et al. (2013). Simultaneous PET-MRI reveals brain function in activated and resting state on metabolic, hemodynamic and multiple temporal scales. *Nature medicine, 19*(9), 1184-1189. doi:10.1038/nm.3290

Weintrob, D. L., Saling, M. M., Berkovic, S. F., Berlangieri, S. U., & Reutens, D. C. (2002). Verbal memory in left temporal lobe epilepsy: evidence for task-related localization. *Ann Neurol, 51*(4), 442-447.

Weintrob, D. L., Saling, M. M., Berkovic, S. F., & Reutens, D. C. (2007). Impaired verbal associative learning after resection of left perirhinal cortex. *Brain, 130*(Pt 5), 1423-1431. doi:10.1093/brain/awm013

Wen-Han, H., Chao, Z., Kai, Z., Fan-Gang, M., Ning, C., & Jian-Guo, Z. (2013). Selective amygdalohippocampectomy versus anterior temporal lobectomy in the management of mesial temporal lobe epilepsy: a meta-analysis of comparative studies. *Journal of Neurosurgery JNS, 119*(5), 1089-1097. doi:10.3171/2013.8.JNS121854

Wetherington, J., Serrano, G., & Dingledine, R. (2008). Astrocytes in the Epileptic Brain. *Neuron, 58*(2), 168-178. doi:10.1016/j.neuron.2008.04.002

Wheatley, B. M. (2008). Selective amygdalohippocampectomy: the trans-middle temporal gyrus approach. *Neurosurgical Focus FOC, 25*(3), E4. doi:10.3171/FOC/2008/25/9/E4

Whiting P, G. R., Burch J, et al. . (2006). 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*, 1-250, iii-iv.

Whitney, E. P., Elizabeth, K. W., Chazen, J. L., Sumit, N. N., Rafael, U.-C., Michael, G. K., & Caitlin, E. H. (2019). Magnetic resonance–guided focused ultrasound for ablation of mesial temporal epilepsy circuits: modeling and theoretical feasibility of a novel noninvasive approach. *Journal of Neurosurgery JNS*, 1-8. doi:10.3171/2019.4.JNS182694

WHO. (2019). Epilepsy: a public health imperative.

Wiebe, S. (2000). Epidemiology of temporal lobe epilepsy. *Can J Neurol Sci, 27 Suppl 1*, S6-S21. doi:10.1017/s0317167100000561

Wiebe, S. (2016). Epilepsy: Does access to care influence the use of epilepsy surgery? *Nat Rev Neurol, 12*(3), 133-134. doi:10.1038/nrneurol.2016.7

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*(5), 311-318. doi:10.1056/nejm200108023450501

Wiebe, S., Blume, W. T., Girvin, J. P., & Eliasziw, M. (2011). Effectiveness and efficiency of surgery for temporal lobe epilepsy study group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N. Engl. J. Med., 345*, 311-318.

Wieser, H.-G., & Epilepsy, I. C. o. N. o. (2004). ILAE Commission Report. Mesial temporal lobe epilepsy with hippocampal sclerosis. *Epilepsia, 45*(6), 695-714. doi:10.1111/j.0013-9580.2004.09004.x

Wieser, H. G., Blume, W. T., Fish, D., et al. (2001). ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia, 42*(2), 282-286.

Willie, J. T., Laxpati, N. G., Drane, D. L., et al. (2014). Real-Time Magnetic Resonance-Guided Stereotactic Laser Amygdalohippocampotomy for Mesial Temporal Lobe Epilepsy. *Neurosurgery, 74*(6), 569-585. doi:10.1227/NEU.0000000000000343

Willmann, O., Wennberg, R., May, T., Woermann, F. G., & Pohlmann-Eden, B. (2007). The contribution of 18F-FDG PET in preoperative epilepsy surgery evaluation for patients with temporal lobe epilepsy A meta-analysis. *Seizure, 16*(6), 509-520. doi:10.1016/j.seizure.2007.04.001

Willment, K., & Golby, A. (2013). Hemispheric Lateralization Interrupted: Material-Specific Memory Deficits in Temporal Lobe Epilepsy. *Frontiers in Human Neuroscience, 7*, 546.

Wilson, C. L. (1995). Functional Pathways Underlying Ipsilateral and Contralateral Spread of Temporal Lobe Seizures. In A. G. Reeves & D. W. Roberts (Eds.), *Epilepsy and the Corpus Callosum 2* (pp. 153-173). Boston, MA: Springer US.

Wilson, S. J., & Baxendale, S. (2014). The new approach to classification: rethinking cognition and behavior in epilepsy. *Epilepsy Behav, 41*, 307-310. doi:10.1016/j.yebeh.2014.09.011

Wilson, S. J., Baxendale, S., Barr, W., et al. (2015). Indications and expectations for neuropsychological assessment in routine epilepsy care: Report of the ILAE Neuropsychology Task Force, Diagnostic Methods Commission, 2013-2017. *Epilepsia, 56*(5), 674-681. doi:10.1111/epi.12962

Wilson, S. J., Saling, M. M., Kincade, P., & Bladin, P. F. (1998). Patient Expectations of Temporal Lobe Surgery. *Epilepsia, 39*(2), 167-174. doi:10.1111/j.1528-1157.1998.tb01354.x

Winston, G. P., Stretton, J., Sidhu, M. K., Symms, M. R., & Duncan, J. S. (2014). Progressive white matter changes following anterior temporal lobe resection for epilepsy. *Neuroimage Clin, 4*, 190-200. doi:10.1016/j.nicl.2013.12.004

Wintermark, M., Druzgal, J., Huss, D. S., et al. (2014). Imaging Findings in MR Imaging–Guided Focused Ultrasound Treatment for Patients with Essential Tremor. *American Journal of Neuroradiology, 35*(5), 891. doi:10.3174/ajnr.A3808

Witt, J.-A., Alpherts, W., & Helmstaedter, C. (2013). Computerized neuropsychological testing in epilepsy: Overview of available tools. *Seizure : the journal of the British Epilepsy Association, 22*. doi:10.1016/j.seizure.2013.04.004

Wong, C. H., Bleasel, A., Wen, L., et al. (2010). The topography and significance of extratemporal hypometabolism in refractory mesial temporal lobe epilepsy examined by FDG-PET. *Epilepsia, 51*(8), 1365-1373. doi:10.1111/j.1528-1167.2010.02552.x

Wyler, A. R., Hermann, B. P., & Somes, G. (1995). Extent of medial temporal resection on outcome from anterior temporal lobectomy: a randomized prospective study. *Neurosurgery, 37*(5), 982-991. doi:10.1227/00006123-199511000-00019

Xu, S., Sun, Q., Fan, J., et al. (2019). Role of Astrocytes in Post-traumatic Epilepsy. *Frontiers in Neurology, 10*, 1149-1149. doi:10.3389/fneur.2019.01149

Yaşargil, M. G., Wieser, H. G., Valavanis, A., von Ammon, K., & Roth, P. (1993). Surgery and Results of Selective Amygdala-Hippocampectomy in One Hundred Patients with Nonlesional Limbic Epilepsy. *Neurosurgery Clinics of North America, 4*(2), 243-261. doi:10.1016/S1042-3680(18)30591-6

Yıldırım Capraz, I., Kurt, G., Akdemir, Ö., et al. (2015). Surgical outcome in patients with MRI-negative, PET-positive temporal lobe epilepsy. *Seizure - European Journal of Epilepsy, 29*, 63-68. doi:10.1016/j.seizure.2015.03.015

Ying, Z., Najm, I., Nemes, A., Pinheiro-Martins, A. P., Alexopoulos, A., Gonzalez-Martinez, J., & Bingaman, W. (2014). Growth-associated protein 43 and progressive epilepsy in cortical dysplasia. *Annals of Clinical and Translational Neurology, 1*(7), 453-461. doi:10.1002/acn3.69

Yogarajah, M., Focke, N. K., Bonelli, S. B., et al. (2010). The structural plasticity of white matter networks following anterior temporal lobe resection. *Brain, 133*(Pt 8), 2348-2364. doi:10.1093/brain/awq175

Yoon, H. H., Kwon, H. L., Mattson, R. H., Spencer, D. D., & Spencer, S. S. (2003). Long-term seizure outcome in patients initially seizure-free after resective epilepsy surgery. *Neurology, 61*(4), 445. doi:10.1212/01.WNL.0000081226.51886.5B

Youden, W. J. (1950). Index for rating diagnostic tests. *Cancer, 3*(1), 32-35. doi:10.1002/1097-0142(1950)3:1<32::aid-cncr2820030106>3.0.co;2-3

Zhang, C., & Kwan, P. (2019). The Concept of Drug-Resistant Epileptogenic Zone. *Frontiers in Neurology, 10*, 558.

Zhang, J., Liu, W., Chen, H., et al. (2014). Multimodal neuroimaging in presurgical evaluation of drug-resistant epilepsy. *Neuroimage Clin, 4*, 35-44. doi:10.1016/j.nicl.2013.10.017

Zimmer, E. R., Parent, M. J., Souza, D. G., et al. (2017). [(18)F]FDG PET signal is driven by astroglial glutamate transport. *Nature neuroscience, 20*(3), 393-395. doi:10.1038/nn.4492

Zubler, F., Seeck, M., Landis, T., Henry, F., & Lazeyras, F. (2003). Contralateral medial temporal lobe damage in right but not left temporal lobe epilepsy: a (1)H magnetic resonance spectroscopy study. *J Neurol Neurosurg Psychiatry, 74*(9), 1240-1244.

Zweig, M. H., & Campbell, G. (1993). Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clinical Chemistry, 39*(4), 561-577. doi:10.1093/clinchem/39.4.561

# Ethics & Published manuscripts

# Addition of Personnel to a Research Study

**Purpose**

For addition of research personnel to research projects submitted to the Melbourne Health Human Research Ethics Committee

**Procedure**

Complete the relevant sections of this form (Sections are reproduced from the Victorian Common Application Form) and submit along with an Amendment Request form and any other affected documents. Provide a justification of the personnel changes i.e. staff member no longer employed at Melbourne Health on the Amendment Request from.

**Other Related Documents**

Complete a Melbourne Health Investigator Curriculum Vitae for any personnel that are new to research at Melbourne Health and existing researchers if they have not submitted an updated CV within the past 3 years.

Completed CVs should be emailed to CVsFolder@mh.org.au. Hardcopy CVs will not be retained. It is the responsibility of investigators to inform the Office for Research should a researcher's position or registration change in a manner that affects the conduct of the study.

## 1. RESEARCHERS AND CONTACT INFORMATION

### List all the NEW researchers involved in this project

1.2 Copy this table and repeat for each **NEW Associate Researcher**.

| | |
|---|---|
| Title and Name | Dr Varduhi Carhill |
| Appointment | Clinical Epilepsy Fellow |
| Department | Neurology |
| Institution | Royal Melbourne Hospital |
| Mailing address | C/O Susan Belbin, Epilepsy Coordinator<br>Neurology Department<br>300 Grattan Street<br>Parkville, VIC 3050 |
| Describe what this researcher will do in the context of this project | This retrospective study will test a hypothesis about pre-operative PET data being an independent predictor of both, surgical and neurocognitive outcome in epilepsy patients. This will involve:<br>1. Pre-op and post-op neuroimaging processing (both PET and MRI) using Analyze/SPM software.<br>2. The MRI mages will be retrieved from Synapse local database; PET scans will be retrieved from Peter Mac upon request; old MRI scans will be retrieved from Biogrid upon our request.<br>3. Clinical data collection will be carried out accessing patients medical paper records, NeuroBase data and electronic data stored on the RMH S-drive. |
| Include a brief summary of relevant experience for this project | Advanced Neurology trainee (ST6) with interest in Epilepsy.<br>(Please kindly see my CV enclosed for further detail) |
| Phone | 0393427722 |
| Fax | 0393428628 |
| Mobile/pager | 0417494999 |
| email | varduhi.cahill@mh.org.au |

**Has the new Researcher submitted a CV to the Office for Research within the last three years? Yes (stored on hospital S-drive)**

## 2. TRAINING

Will any of the researchers require extra training to enable their participation in this project?

Yes ☐ No ☒

If *Yes*, list the researchers, describe the training that is required and who will provide this training.

| **Researcher** | **Training required** | **Who will provide training?** |
|---|---|---|
| Varduhi Cahill | Analyze/SPM software training | Lucy Vivash/Chris Steward |
| | | |

| | | |
|---|---|---|
| | | |
| | | |
| | | |

## 4. DECLARATION BY RESEARCHERS AND RESEARCH COORDINATORS

**Project Title: PET as an independent predictor of surgical and neurocognitive outcomes in epilepsy surgery patients.**

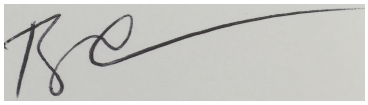
I, the researcher agree:

- To only start this research project after obtaining final approval from the Institution's Human Research Ethics Committee (HREC);
- To conduct this research project in accordance with the protocols and procedures as approved by the HREC;
- To only carry out this research project where adequate funding is available to enable the project to be carried out according to good research practice and in an ethical manner;
- To provide additional information as requested by the HREC;
- To maintain the confidentiality of all data collected from or about project participants;
- To agree to an audit if requested by the HREC;
- To only use data and any tissue samples collected for the study for which approval has been given;
- To only grant access to data to authorised persons; and
- To maintain security procedures for the protection of privacy, including (but not restricted to): removal of identifying information from data collection forms and computer files, storage of linkage codes in a locked cabinet and password control for access to identified data on computer files.

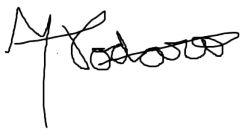
**I/we have read the NHMRC *National Statement on Ethical Conduct in Human Research (*2007) and will observe the principles set out in that document and in the *Declaration of Helsinki*.**

Name of principal researcher ……Prof Terence O'Brien…….
Signature Date

Name of researcher ……Dr Varduhi Cahill…….

Signature  Date 15/10/2015

Name of research co-ordinator ……Dr Marian Todaro……..

Signature  Date 15/10/2015

Austin Health

## AUSTIN HEALTH HUMAN RESEARCH ETHICS COMMITTEE

## ETHICAL APPROVAL FOR AMENDMENT

Professor Sarah Wilson
Department of Clinical Neuropsychology
Austin Health

30 March 2016

Dear Sarah Wilson

**AU RED HREC Reference Number:** HREC/14/Austin/603

**Austin Health Project Number:** ND 14/603

**Project Title:** Characterising the long-term cognitive and psychosocial outcomes of epilepsy surgery

---

I am pleased to advise that the above project amendment has **received ethical approval** from the Austin Health Human Research Ethics Committee (HREC). This HREC is organised and operates in accordance with the National Health and Medical Research Council's (NHRMC) National Statement on Ethical Conduct in Research Involving Humans (2007), and all subsequent updates, and in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), the Health Privacy Principles described in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988 (and subsequent Guidelines).

**Original HREC Approval Date:** 02/04/2015

**Approved Documents:**

The following documents have been reviewed and approved:

| Document | Date |
|---|---|
| Correspondence received from Professor Sarah Wilson re: Addition of Dr Charles Malpas as an associate investigator and Dr Varduhi Cahill as a student researcher to the study. | 04/03/2016 |

**Site Specific Assessment**:

A copy of this letter must be forwarded to all Principal Investigators at every participating site and must be submitted to the relevant Research Governance Officer at each site.

The HREC may conduct an audit of the project at any time.

Yours sincerely

K. Zlatic

Digitally signed by Kristina Zlatic
DN: cn=Kristina Zlatic, o=Manager HREC - Non-Drug Trials, ou=Office for Research Austin Health, email=kristina.zlatic@austin.org.au, c=AU
Date: 2016.03.30 14:14:04 +11'00'

RESEARCH ARTICLE

# Metabolic Patterns and Seizure Outcomes following Anterior Temporal Lobectomy

Varduhi Cahill, MD,[1,2,3] Benjamin Sinclair, PhD,[4,5] Charles B. Malpas, PhD,[1,5,6,7] Anne M. McIntosh, PhD,[1,5,8] Zhibin Chen, PhD,[1,5] Lucy E. Vivash, PhD,[1,5] Marie F. O'Shea, PhD,[9] Sarah J. Wilson, PhD,[7,9] Patricia M. Desmond, MD,[4] Salvatore U. Berlangieri, MBBS,[9] Rodney J. Hicks, MD,[10] Christopher C. Rowe, MD,[8,11] Andrew P. Morokoff, PhD, FRACS,[12] James A. King, PhD, FRACS,[12] Gavin C. Fabinyi, FRACS,[13] Andrew H. Kaye, MD, FRACS,[12] Patrick Kwan, MD, PhD,[1,5] Samuel F. Berkovic, MD, FRS,[8,9] and Terence J. O'Brien, MD[1,5]

**Objective:** We investigated the relationship between the interictal metabolic patterns, the extent of resection of $^{18}$F-fluorodeoxyglucose positron emission tomography ($^{18}$FDG-PET) hypometabolism, and seizure outcomes in patients with unilateral drug-resistant mesial temporal lobe epilepsy (MTLE) following anterior temporal lobe (TL) resection.
**Methods:** Eighty-two patients with hippocampal sclerosis or normal magnetic resonance imaging (MRI) findings, concordant $^{18}$FDG-PET hypometabolism, and at least 2 years of postoperative follow-up were included in this 2-center study. The hypometabolic regions in each patient were identified with reference to 20 healthy controls ($p < 0.005$). The resected TL volume and the volume of resected TL PET hypometabolism (TLH) were calculated from the pre- and postoperative MRI scans coregistered with interictal $^{18}$FDG-PET.
**Results:** Striking differences in metabolic patterns were observed depending on the lateralization of the epileptogenic TL. The extent of the ipsilateral TLH was significantly greater in left MTLE patients ($p < 0.001$), whereas right MTLE patients had significantly higher rates of contralateral (CTL) TLH ($p = 0.016$). In right MTLE patients, CTL hypometabolism was the strongest predictor of an unfavorable seizure outcome, associated with a 5-fold increase in the likelihood of seizure recurrence (odds ratio [OR] = 4.90, 95% confidence interval [CI] = 1.07–22.39, $p = 0.04$). In left MTLE patients, greater extent of resection of ipsilateral TLH was associated with lower rates of seizure recurrence ($p = 0.004$) in univariate analysis; however, its predictive value did not reach statistical significance (OR = 0.96, 95% CI = 0.90–1.02, $p = 0.19$).
**Interpretation:** The difference in metabolic patterns depending on the lateralization of MTLE may represent distinct epileptic networks in patients with right versus left MTLE, and can guide preoperative counseling and surgical planning.

**ANN NEUROL 2019;9999:1–10**

Epilepsy surgery remains the treatment option of choice in patients with drug-resistant mesial temporal lobe epilepsy (MTLE). However, despite a thorough multimodal presurgical evaluation, a significant proportion of patients

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.25405

Received Oct 25, 2017, and in revised form Dec 22, 2018. Accepted for publication Dec 24, 2018.

Address correspondence to
Prof Terence O'Brien, Department of Neuroscience and Neurology, Central Clinical School, Monash University, Alfred Centre, 99 Commercial Road, Melbourne, Victoria 3004, Australia.
Email: terence.obrien@monash.edu

From the [1]Departments of Medicine and Neurology, Melbourne Brain Centre, University of Melbourne, Royal Melbourne Hospital, Melbourne, Victoria, Australia[2]Manchester Centre for Clinical Neurosciences, Salford Royal NHS Foundation Trust, Salford, United Kingdom; [3]Division of Neuroscience and Experimental Psychology, School of Biological Sciences, University of Manchester, Manchester, United Kingdom; [4]Departments of Medicine and Radiology, University of Melbourne, Royal Melbourne Hospital, Melbourne, Victoria, Australia; [5]Departments of Neuroscience and Neurology, Alfred Health, Central Clinical School, Monash University, Melbourne, Victoria, Australia; [6]Murdoch Children's Research Institute, Melbourne, Victoria, Australia; [7]Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Victoria, Australia; [8]Epilepsy Research Centre, University of Melbourne, Austin Hospital, Melbourne, Victoria, Australia; [9]Comprehensive Epilepsy Program, Austin Hospital, Melbourne, Victoria, Australia; [10]Peter MacCallum Cancer Centre and the Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia; [11]Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, Victoria, Australia; [12]Department of Surgery, University of Melbourne, Royal Melbourne Hospital, Melbourne, Victoria, Australia; and [13]Department of Surgery, University of Melbourne, Austin Hospital, Melbourne, Victoria, Australia

Additional supporting information can be found in the online version of this article.

continue having seizures following surgery.[1,2] Accordingly, the need for reliable predictors of treatment outcomes in this era of personalized medicine remains ongoing. $^{18}$F-Fluorodeoxyglucose positron emission tomography ($^{18}$FDG-PET) is one of the most established functional imaging modalities employed in the evaluation of epilepsy surgery candidates and offers unique insights into cerebral glucose metabolism at the synaptic level.[3–6] The cost-efficiency of $^{18}$FDG-PET has long been recognized, and the wider availability of postacquisition processing techniques has increased its yield in surgical planning.[7–11]

With the advances in electroencephalography (EEG) and imaging technologies, including multimodal coregistration techniques, the role of $^{18}$FDG-PET in presurgical evaluation has been enhanced beyond being a useful diagnostic tool reserved for magnetic resonance imaging (MRI)-negative cases or clinical scenarios with discordant electroclinical and structural imaging findings.[12–16] There has been a growing body of evidence suggesting that the extent of the metabolic compromise correlates with the distribution of ictal EEG discharges.[17,18] Furthermore, the findings of recent $^{18}$FDG-PET and functional connectivity studies have been convergent in demonstrating the role of $^{18}$FDG-PET as a metabolic biomarker of the extent of the epileptic network dysfunction.[19,20] It has also been suggested that hypometabolic changes affecting the contralateral (CTL) temporal lobe (TL) may impact on seizure outcomes in patients with drug-resistant MTLE.[21–26] Although stereoelectroencephalography and intraoperative imaging coregistration technologies open new avenues for the use of $^{18}$FDG-PET in surgical planning,[8,9,27] studies on how the extent of the resection of $^{18}$FDG-PET hypometabolism affects long-term surgical outcomes have been sparse and contradictory, which could be explained by a modest patient cohort size and methodological differences.[28,29] Furthermore, the results of functional and metabolic connectivity studies have been suggestive of distinct functional connectivity patterns depending on the lateralization of MTLE, including higher rates of CTL TL involvement in patients with right MTLE.[20,30–33] The higher rates of bitemporal hypometabolism have been observed in patients with unilateral right MTLE;[19] however, the effect of this distinct metabolic pattern on seizure outcomes following anterior TL resection (ATLR) has not been demonstrated.

Our study investigated the role of $^{18}$FDG-PET in predicting surgical outcomes in a large, well-characterized cohort of patients with drug-resistant unilateral MTLE. The predictive value of the extent of the resection of $^{18}$FDG-PET hypometabolism and the influence of CTL TL $^{18}$FDG-PET changes on surgical outcomes in patients with right and left MTLE were evaluated.

## Subjects and Methods

### Study Subjects

This was a retrospective 2-center study. A total of 82 patients with drug-resistant unilateral MTLE who underwent an ATLR between 2001 and 2014 were included. Patients were identified from the prospectively administered Comprehensive Epilepsy Program databases at the Royal Melbourne and Austin Hospitals in Melbourne, Australia.

The inclusion criteria were: (1) age ≥ 16 years at the time of surgery, (2) preoperative MRI findings consistent with unilateral hippocampal sclerosis (HS) or no identifiable lesion ("MRI negative"), (3) concordant results of presurgical investigations and seizure semiology, (4) the presence of concordant ipsilateral TL $^{18}$FDG-PET hypometabolism on visual inspection of interictal $^{18}$FDG-PET, and (5) at least 2 years of follow-up following the ATLR.

The 2 centers adopted a similar presurgical evaluation protocol, which has been described previously.[12,28,34]

Briefly, this was comprised of at least one 5-day period of video-EEG telemetry including neurological examination, reevaluation of the clinical presentation and seizure semiology, expert neuroradiology review, and neuropsychiatric and neuropsychological assessment. Postoperatively, antiepileptic therapy was commonly rationalized within the first 6 to 12 months, depending on the seizure outcome. The study was approved by the Melbourne Health and Austin Health human research ethics committees.

### Seizure Variables Outcomes

Seizure outcomes were assessed at the time of last follow-up and categorized using Engel classification of postoperative outcomes as seizure-free (Engel class I) or not seizure-free (Engel class II–IV).[35] The duration of follow-up varied between the patients (Table 1); however, a minimum of 2 years of postoperative follow-up was achieved for all patients, consistent with the previous published work from our group evaluating predictors of surgical outcomes.[34]

"Worthwhile improvement" was set at a ≥ 75% reduction in seizure frequency compared to the preoperative seizure burden. Acute seizures occurring within the first week following surgery were discounted.[36] Postoperatively, only seizures manifesting with impaired awareness were counted toward seizure recurrence.[37]

### Neurosurgical Procedure

All patients underwent a Spencer-type resection, which is a type of ATLR also known as an anteromedial temporal lobectomy or a radical hippocampectomy.[38] In brief, it is a 2-step procedure involving the resection of the middle temporal gyrus and the inferior temporal gyrus 3 to 3.5 cm from the tip of the temporal pole, followed by resection of the mesial TL structures including the amygdala, hippocampus, and parahippocampal gyrus. It was the policy of our surgeons to do a less extensive neocortical resection, sparing the superior temporal gyrus, in patients with left (i.e., language dominant) MTLE. This is consistent with the results of previous studies that have

**TABLE 1. Patient Characteristics**

| Variable | Right MTLE | Left MTLE | $p$[a] |
|---|---|---|---|
| Gender, male, n (%) | 21/43 (48.8) | 20/39 (51.3) | 1.00 |
| Age of epilepsy onset, yr, median (IQR) | 17.0 (7.0–27.0) | 16.0 (4.0–26.0) | 0.50 |
| Duration of epilepsy, yr, median (IQR) | 19.0 (11.0–31.0) | 19.0 (9.0–30.0) | 0.91 |
| Age at operation, yr, median (IQR) | 40.0 (29.0–46.0) | 34.0 (29.0–47.0) | 0.58 |
| Duration of follow-up, yr, median (IQR) | 4.0 (3.0–8.0) | 5.0 (2.0–8.0) | 0.60 |

[a]Fisher exact test was used for categorical variables, and Mann–Whitney $U$ test was performed for continuous variables.
IQR = interquartile range; MTLE = mesial temporal lobe epilepsy.

reported a smaller volume of TL resections in patients undergoing left ATLR.[39,40]

The adequacy of the hippocampal resection was determined based on a postoperative MRI performed at least 3 months following surgery.

### $^{18}$FDG-PET and MRI Acquisition and Postprocessing

Preoperative $^{18}$FDG-PET and MRI examinations were carried out as part of the presurgical evaluation. $^{18}$FDG-PET scans were acquired on a Phillips Allegro (Phillips Medical Systems, Best, the Netherlands) at Austin Hospital with a voxel size of 2 × 2 × 2 mm or a GE Discovery 690 (GE Medical Systems, Milwaukee, WI) at Peter MacCallum Cancer Centre with a voxel size of 1.82 × 1.82 × 3.27 mm as described previously.[28] The median timing of the $^{18}$FDG-PET scans was 5 months preceding surgery (interquartile range = 3–10.25, range = 1–23 months).

Until 2005, MRI examinations were carried out on a Genesis Signa 1.5 T (GE Medical Systems); thereafter, the scans have been performed on a Magnetom Avanto 1.5 T and a Magnetom Trio Tim 3 T (Siemens Medical Solutions, Erlangen, Germany). Three-dimensional, T1-weighted, magnetization-prepared rapid acquisition gradient echo sequences were used for post-acquisition processing. All processing was conducted using Statistical Parametric Mapping (SPM) software, version 12 (Wellcome Department of Cognitive Neurology, University College London, London, UK) mounted on a MATLAB R2012-A (MathWorks, Natick, MA).

### $^{18}$FDG-PET Postprocessing

The images of the patients and 20 healthy controls were reoriented and nonlinearly normalized to SPM's built-in PET template using the default parameters within SPM's Old Normalise algorithm including grand mean scaling of 50 and a relative threshold of 0.8. Normalization parameters were saved for later use. Normalized images were smoothed with an 8 mm full width at half-maximum Gaussian kernel.

Hypometabolic regions of the brain were determined with reference to 20 healthy controls of an equivalent age range (16–65 years). For each patient, a general linear model was constructed to compare the patient to the 20 controls at each voxel, with a 2-sample $t$ test carried out for each subject. To optimize the detection of the total cerebral $^{18}$FDG-PET SPM hypometabolism (TCH), the modeling was conducted at every voxel within the whole brain mask (excluding the cerebellum) and a TL mask obtained from the Automated Anatomic Labeling atlas using the WFU Pick Atlas toolbox (Functional MRI Laboratory, Wake Forest University School of Medicine, Winston-Salem, NC).[41] This yielded a $t$ statistic image for each subject. $T$ statistic images were first transformed from the space of the PET atlas in which intersubject comparisons were made and then back to the native space of each patient's $^{18}$FDG-PET using the inverse of the normalization parameters.

### MRI Postprocessing

The resected tissue volume was estimated by deriving the difference through matching preoperative and postoperative MRIs. Preoperative and postoperative MRIs were nonlinearly registered using SPM's longitudinal registration toolbox with default parameters.[42] We opted for nonlinear registration because linear registration was not sufficient due to an inaccurate account of the postoperative brain changes, in particular the collapse of the brain tissue into the resection cavity. Preoperative and postoperative images were segmented into gray matter (GM), white matter (WM), and cerebral spinal fluid. The GM and WM partitions were added and thresholded at 0.1, resulting in an image of the brain tissue. A total cerebral volume image was constructed by taking the union of the preoperative and registered postoperative brain segmentations. The resection volume was measured as the difference between the preoperative and postoperative scans. To minimize the contribution of the pre- and postoperative image registration and segmentation errors, the largest cluster of the difference image was selected, which was invariably the resected tissue. To make this selection, the resected tissue was separated from the registration error by eroding the image by 2 voxels. Subsequently, the now separate resected tissue was selected, and dilated by 2 voxels to restore it to its original size. All resected tissue images were inspected by 2 independent operators to ensure the resected region on the postoperative MRI image was filled accurately. The volumes of resected tissue and of the total cerebral volume were calculated by summing the non-zero voxels and multiplying by the voxel size.

### Combined MRI and PET Postprocessing

To ascertain the extent of the $^{18}$FDG-PET hypometabolism resected, the patient's $^{18}$FDG-PET images were matched to their preoperative MRI. $^{18}$FDG-PET images were linearly coregistered to preoperative MRI using SPM's coregistration algorithm, which utilizes normalized mutual information to quantify similarity between 2 images of different modalities. The coregistered $^{18}$FDG-PET/MRI images were inspected by 2 independent operators to ensure the adequacy of the coregistration. This coregistration was used to transform the *t* statistic images from the native $^{18}$FDG-PET space to the native preoperative MRI space. The *t* statistic images were transformed to the preoperative MRI space, then thresholded (uncorrected $p = 0.005$, cluster extent >100 voxels) to elicit the region of hypometabolism and binarized. The optimal level of SPM thresholding was achieved through the identification of parameters whereby the $^{18}$FDG-PET hypometabolism was identifiable in the ipsilateral TL in all patients. Thresholding was undertaken in the MRI space, rather than the PET template space, to allow for the application of more accurate interpolation to a continuous image (i.e., the *t* statistic image), as opposed to a discontinuous image (i.e., a thresholded *t* statistic image). This resulted in a smoother hypometabolism boundary when applying the threshold in the higher-resolution MRI space, rather than the low-resolution PET template space.

The amount of hypometabolism resected was calculated by masking the hypometabolism image in the MRI space by the resected tissue image. The total amount of hypometabolism was calculated by masking the hypometabolism image by the total cerebral volume image. The voxels in these masked images were summed and multiplied by the voxel size to derive the volume of resected TL PET hypometabolism (TLH) and the volume of the TCH.

The proportion of the TLH resected was derived as follows:

$$\%\text{TLH resected} = (\text{volume of TLH resected} \times 100)/\text{volume of TLH}$$

The proportion of the resected TCH was calculated as follows:

$$\%\text{TCH resected} = (\text{volume of TLH resected} \times 100)/\text{volume of TCH}$$

The proportion that extratemporal hypometabolism (ETH) constituted within TCH was derived by first estimating the volume of ETH by subtracting TLH volume from TCH volume, followed by:

$$\%\text{ETH} = (\text{ETH volume} \times 100)/\text{TCH volume}$$

The SPM thresholded images were also inspected for the boundaries of the ipsilateral $^{18}$FDG-PET hypometabolism and the presence of ETH, including its distribution pattern.

In all patients, the $^{18}$FDG-PET SPM hypometabolism identifiable in the ipsilateral TL was confined to the TL region without extension into the neighboring regions (i.e., fronto-orbital, opercular, or the temporoparieto-occipital junction). The ETH areas were identified in the frontal regions (ipsilateral, CTL, and bilateral) and CTL TL region.

### Statistical Analysis

Univariate analyses using Mann–Whitney *U* test for continuous variables and Fisher exact test for categorical variables were performed to first explore the differences in pertinent demographic, seizure, preoperative and postoperative neuroimaging variables in patients with right versus left MTLE, and subsequently, to explore the differences within the subgroups, depending on seizure outcomes.

Pertinent neuroimaging variables with univariate $p < 0.1$ were included in multivariate logistic regression to explore the predictive value of neuroimaging variables on seizure outcomes in patients with right and left MTLE, respectively.

A 2-tailed *p* value <0.05 was considered statistically significant for all tests performed unless specified otherwise. All statistical analyses were performed using SPSS 21.0 (IBM, Armonk, NY).

## Results

### Patient Characteristics and Seizure Outcomes

There were 43 patients with right MTLE and 39 patients with left MTLE with comparable gender composition, age of epilepsy onset, epilepsy duration, age at surgery, and duration of postoperative follow-up (see Table 1).

The median postoperative follow-up period in patients with right MTLE was 4 years, ranging from 2 to 10 years, and 5 years in patients with left MTLE, ranging from 2 to 14 years. Preoperative seizure burden did not differ in patients with right and left MTLE ($p = 0.98$; Table 2).

The seizure outcomes, excellent (Engel class I) versus unfavorable (Engel class II-IV), did not differ in patients with right and left MTLE ($p = 1.00$), with excellent outcomes observed in 30 patients (68.9%) with right MTLE and 28 patients (71.8%) with left MTLE.

The striking differences in the interictal metabolic patterns observed in patients with right and left MTLE are outlined in Table 3. Importantly, the left MTLE patients were observed to have significantly higher rates in the extent of ipsilateral TLH ($p < 0.001$), with a markedly higher proportion of TCH being confined to the ipsilateral TL ($p < 0.001$). The right MTLE patients had a significantly higher proportion of TCH falling extratemporally ($p < 0.001$), with preferential CTL TLH occurrence in right MTLE patients ($p = 0.003$).

The estimated volumes of resected TL tissue in patients with right MTLE significantly exceeded those in patients with left MTLE ($p < 0.001$), consistent with the commonly employed more sparing approach to ATLR in patients with left MTLE.[39,43]

**TABLE 2. Preoperative Seizure Burden in Patients with Right (n = 43) and Left (n = 39) MTLE**

| Seizure Frequency | Right MTLE, n (%) | Left MTLE, n (%) |
|---|---|---|
| 4–10/day | 2 (4.7) | 1 (2.6) |
| 1–3/day | 5 (11.6) | 3 (7.7) |
| 1–6/wk | 17 (39.5) | 15 (38.5) |
| 1–3/mo | 16 (37.2) | 16 (40.9) |
| 4–11/yr | 1 (2.3) | 3 (7.7) |
| 1–3/yr | 2 (4.7) | 1 (2.6) |

MTLE = mesial temporal lobe epilepsy.

rates of seizure freedom; however, in the right MTLE cohort it was associated with unfavorable seizure outcomes ($p$ = 0.016; Table 5).

In the left MTLE cohort, excellent seizure outcomes were associated with greater resected TL tissue volumes ($p$ = 0.005) as well as greater extent of resection of ipsilateral TL hypometabolism ($p$ = 0.004; Table 6), which resonates with the findings of previous studies.[28,44]

Although the higher rates of HS on preoperative MRI (86.7% in right MTLE and 96.4% in left MTLE patients) in patients with excellent seizure outcomes were in keeping with previous studies,[34] they did not reach statistical significance in influencing seizure outcomes ($p$ = 0.10 and $p$ = 0.19 in patients with right and left MTLE, respectively).

**TABLE 3. Summary of Pre- and Postoperative Imaging Variables in Patients with Left versus Right MTLE/ATLR**

| Variable | Right MTLE/ATLR, n = 43, 52.4% | Left MTLE/ATLR, n = 39, 47.6% | $p$[a] |
|---|---|---|---|
| HS on preoperative MRI, n (%) | 34/43 (79.1) | 36/39 (92.3) | 0.12 |
| Volume of preoperative ipsilateral TL SPM hypometabolism, $mm^3$, median (IQR) | $3.79 \times 10^3$ ($1.67 \times 10^3$–$6.85 \times 10^3$) | $9.28 \times 10^3$ ($3.57 \times 10^3$–$14.58 \times 10^3$) | <0.001[b] |
| % of TCH confined to ipsilateral TL, median (IQR) | 29.9 (20.7–41.0) | 63.0 (49.8–73.5) | <0.001[b] |
| % TCH SPM hypometabolism distributed extratemporally, median (IQR) | 70.1 (59.0–79.3) | 37.0 (26.4–50.2) | <0.001[b] |
| Presence of contralateral TLH, n (%) | 17/43 (39.5) | 4/39 (10.3) | 0.003[b] |
| Volume of TL tissue resected, $mm^3$, median (IQR) | $21.9 \times 10^3$ ($17.7 \times 10^3$–$28.0 \times 10^3$) | $15.4 \times 10^3$ ($11.8 \times 10^3$–$21.3 \times 10^3$) | <0.001[b] |
| % TLH resected, median (IQR) | 59.1 (35.9–70.9) | 36.4 (23.6–58.3) | 0.008[b] |

[a]Fisher exact test was used for categorical variables and Mann–Whitney $U$ test was performed for continuous variables.
[b]Statistically significant.
ATLR = anterior temporal lobe resection; IQR = interquartile range; MRI = magnetic resonance imaging; MTLE = mesial temporal lobe epilepsy; SPM = Statistical Parametric Mapping; TCH = total cerebral hypometabolism; TL = temporal lobe; TLH = temporal lobe hypometabolism.

### *Pre- and Postoperative Imaging Variables in Relation to Seizure Outcomes*

Interestingly, the presence of SPM hypometabolism detected outside the ipsilateral TL was common (54/82, 65.9%) but significantly more prevalent in right MTLE patients (33/43, 76.7%; $p$ = 0.037). The most commonly sighted distributions of hypometabolism outside the ipsilateral TL in patients with right and left MTLE are outlined in Table 4. Hypometabolic changes in frontal regions were common and comparable in patients with right and left MTLE and were not associated with worse outcomes. The presence of CTL TLH in patients with left MTLE did not influence the

### *Predictors of Seizure Outcomes*

The results of the multivariate logistic regression exploring the predictive value of pertinent pre- and postoperative neuroimaging features, focusing on preoperative MRI findings and $^{18}$FDG-PET patterns in right MTLE patients and the extent of both the TL tissue resection and the ipsilateral TL hypometabolism in the left MTLE group, are shown in Tables 7 and 8, respectively.

In the right MTLE patients, the presence of CTL TLH was the strongest predictor of a heightened risk of unfavorable seizure outcomes and was associated with a nearly 5-fold increase in the risk of postoperative seizure

**TABLE 4. Distribution of ET Hypometabolism and Its Association with Seizure Outcomes**

| | Right MTLE Cohort, n (%) | | | Left MTLE Cohort, n (%) | | |
|---|---|---|---|---|---|---|
| ET Distribution | Engel I, 30/43 (69.8) | Engel II–IV, 13/43 (30.2) | $p$[a] | Engel I, 28/39 (71.8) | Engel II–IV, 11/39 (28.2) | $p$[a] |
| Ipsilateral frontal | 13/30 (43.3) | 8/13 (61.5) | 0.33 | 8/28 (28.6) | 4/11 (36.4) | 0.71 |
| Contralateral frontal | 14/30 (46.7) | 5/13 (38.5) | 0.74 | 8/28 (28.6) | 5/11 (45.5) | 0.45 |
| Bilateral frontal | 9/30 (30.0) | 4/13 (30.8) | 1.00 | 5/28 (17.9) | 3/11 (27.3) | 0.66 |
| Contralateral TL | 8/30 (26.7) | 9/13 (69.2) | 0.016[b] | 2/28 (7.1) | 2/11 (18.2) | 0.56 |

[a]Fisher exact test was used.
[b]Statistically significant.
ET = extratemporal; MTLE = mesial temporal lobe epilepsy; TL = temporal lobe.

recurrence (odds ratio = 4.90, 95% confidence interval = 1.07–22.39, $p = 0.04$).

In the left MTLE group, the predictive value of both the TL resection volume and the extent of the ipsilateral TL hypometabolism resection was explored; however, neither of the above predictors reached statistical significance ($p = 0.14$ and $p = 0.19$, respectively).

The presence of HS on preoperative MRI has long been shown to be an independent predictor of favorable seizure outcomes in patients with drug-resistant MTLE.[34] Our results corroborate with the above findings in that 76% of patients with HS on preoperative MRI achieved seizure freedom and only 42% of patients with normal MRI brain findings had a favorable outcome. The subgroup analysis of seizure outcome predictors is summarized in the Supplementary Table. The presence of CTL hypometabolism predicted an unfavorable seizure outcome ($p = 0.018$).

## Discussion

The results of our study demonstrated striking differences in metabolic patterns in patients with right and left MTLE, with significantly greater rates of bitemporal hypometabolic changes observed in patients with right MTLE, whereas the patients with left MTLE had more extensive ipsilateral TL $^{18}$FDG-PET hypometabolism.

Studies examining the evolution of the $^{18}$FDG-PET hypometabolism over time have been sparse and mostly focused on pediatric populations. Gaillard et al studied the temporal evolution of the $^{18}$FDG-PET changes in a mixed pediatric patient cohort, including a subgroup with drug-resistant epilepsy who were evaluated for epilepsy surgery, over a mean interval of 3 years.[45] They demonstrated no evidence of hypometabolism progression, with seizure frequency and time since the last seizure being the most important determinants of the differences in regional hypometabolism over the serial scans. In contrast, a recent study evaluating the interval changes in $^{18}$FDG-PET hypometabolism in a heterogenous group of pediatric patients with drug-resistant epilepsy did find progression in the PET hypometabolism over time, with the median interval between the scans being >4 years, in particular in patients with ongoing drug-resistant seizures.[46] In some of these cases, unilateral hypometabolism evolved into bilateral hypometabolism on the subsequent scans. In our study, the homogeneity of our cohort and the timing of the $^{18}$FDG-PET scans, with the median being 5 months preceding surgery, substantially diminish the possibility of dynamic changes influencing the findings. However, the possibility of interval changes cannot be excluded completely.

Remarkably, our findings resonate with the results of functional and metabolic connectivity studies,[20,30,32,33,47] demonstrating evidence of altered connectivity patterns in patients with MTLE, depending on the lateralization. In addition, although it remains unknown whether metabolic and functional asymmetry share the same underlying mechanisms, our findings corroborate the results of magnetic resonance spectroscopy studies by Zubler et al,[48] who demonstrated widespread abnormalities, with the involvement of CTL TL, in patients with right MTLE. It is not inconceivable, in light of the growing body of evidence demonstrating distinct aberrant metabolic and connectivity patterns, depending on the MTLE lateralization, that the right and left MTLE may represent two different entities where further research may not only advance our understanding of epileptogenesis but also influence patient management.

Our findings have shown that the overall extent of the ETH and hypometabolic changes in the frontal regions was not associated with adverse seizure outcomes,

**TABLE 5. Pre- and Postoperative Seizure Variables Pertinent to Seizure Outcomes in Patients with Right MTLE (Univariate Analyses)**

| Variable | Engel I, 30/43, 69.8% | Engel II–IV, 13/43, 30.2% | *p* |
|---|---|---|---|
| HS on MRI, n (%) | 26/30 (86.7) | 8/13 (61.5) | 0.10 |
| Estimated MRI volume of resected TL tissue, $mm^3$, median (IQR) | $22.17 \times 10^3$ ($18.22 \times 10^3$–$28.03 \times 10^3$) | $21.08 \times 10^3$ ($14.99 \times 10^3$–$26.52 \times 10^3$) | 0.58 |
| Volume of preoperative TLH, $mm^3$, median (IQR) | $3.62 \times 10^3$ ($1.70 \times 10^3$–$7.47 \times 10^3$) | $3.94 \times 10^3$ ($1.40 \times 10^3$–$6.16 \times 10^3$) | 0.94 |
| % TLH resected, median (IQR) | 58.67 (35.92–73.01) | 60.26 (45.98–65.27) | 0.63 |
| % of TCH confined to ipsilateral TL, median (IQR) | 30.72 (22.92–42.09) | 24.81 (14.55–36.35) | 0.17 |
| % TCH distributed in ET regions, median (IQR) | 69.28 (57.91–77.08) | 75.19 (63.65–85.45) | 0.17 |
| Patients with contralateral TLH, n (%) | 8/30 (26.7) | 9/13 (69.2) | 0.016[a] |

[a]Statistically significant.
ET = extratemporal; HS = hippocampal sclerosis; IQR = interquartile range; MRI = magnetic resonance imaging; MTLE = mesial temporal lobe epilepsy; TCH = total cerebral hypometabolism; TL = temporal lobe; TLH = temporal lobe hypometabolism.

**TABLE 6. Pre- and Postoperative Seizure Variables Pertinent to Seizure Outcomes in Patients with Left MTLE (Univariate Analyses)**

| Variable | Engel I, 28/39, 71.8% | Engel II–IV, 11/39, 28.2% | *p* |
|---|---|---|---|
| HS on MRI, n (%) | 27/28 (96.4) | 9/11 (81.8) | 0.19 |
| Estimated MRI volume of resected TL tissue, $mm^3$, median (IQR) | $17.78 \times 10^3$ ($12.89 \times 10^3$–$22.95 \times 10^3$) | $11.78 \times 10^3$ ($8.84 \times 10^3$–$14.56 \times 10^3$) | 0.005[a] |
| Volume of preoperative TLH, $mm^3$, median (IQR) | $9.75 \times 10^3$ ($4.60 \times 10^3$–$14.73 \times 10^3$) | $8.33 \times 10^3$ ($3.57 \times 10^3$–$11.42 \times 10^3$) | 0.83 |
| % TLH resected, median (IQR) | 46.22 (31.29–60.30) | 24.06 (18.01–29.42) | 0.004[a] |
| % of TCH confined to ipsilateral TL, median (IQR) | 63.31 (51.03–74.15) | 62.06 (49.82–69.77) | 0.62 |
| % TCH distributed in ET regions, median (IQR) | 36.69 (25.85–48.97) | 37.94 (30.23–50.18) | 0.62 |
| Patients with contralateral TLH, n (%) | 2/28 (7.1) | 2/11 (18.2) | 0.56 |

[a]Statistically significant.
ET = extratemporal; HS = hippocampal sclerosis; IQR = interquartile range; MRI = magnetic resonance imaging; MTLE = mesial temporal lobe epilepsy; TCH = total cerebral hypometabolism; TL = temporal lobe; TLH = temporal lobe hypometabolism.

regardless of the MTLE lateralization, and may represent changes associated with seizure propagation pathways.[49]

Conversely, in right MTLE patients the presence of CTL TLH heralded unfavorable seizure outcomes, heightening the risk of postoperative seizure recurrence 5-fold. The association of poor seizure outcomes in patients with unilateral MTLE and bitemporal hypometabolism has been reported previously,[21–26] with Joo et al reporting higher rates of nonlateralizing EEG patterns in patients with bitemporal hypometabolism.[21]

We found that the patients with right MTLE had higher rates of CTL TL hypometabolism, and to our knowledge, it has not been described previously in conjunction with the lateralization of MTLE.

**TABLE 7. Predictors of Postoperative Seizure Recurrence in Right MTLE Patients**

| Variable | OR | 95% CI | *p* |
|---|---|---|---|
| MRI findings, HS vs HS-negative | 2.13 | 0.39–11.73 | 0.38 |
| Presence of CTL hypometabolism | 4.90 | 1.07–22.39 | 0.04[a] |

[a]Statistically significant.
CI = confidence interval; CTL = contralateral; HS = hippocampal sclerosis; MRI = magnetic resonance imaging; MTLE = mesial temporal lobe epilepsy; OR = odds ratio.

**TABLE 8. Predictors of Postoperative Seizure Recurrence in Left MTLE Patients**

| Variable | OR | 95% CI | *p* |
|---|---|---|---|
| Estimated MRI volume of resected TL tissue, $mm^3$ | 1.00 | 1.00–1.00 | 0.14 |
| % TLH resected | 0.96 | 0.90–1.02 | 0.19 |

CI = confidence interval; MRI = magnetic resonance imaging; MTLE = mesial temporal lobe epilepsy; OR = odds ratio; TL = temporal lobe; TLH = temporal lobe hypometabolism.

Within the limitations of the current study, we therefore propose that it is not the extent but the location of the ETH that is the ultimate determinant of unfavorable seizure outcomes.

Interestingly, in the left MTLE cohort, the greater TL resection volume was associated with excellent seizure outcomes, and so was greater extent of resected ipsilateral TL $^{18}$FDG-PET hypometabolism, in keeping with previous studies,[28,44] albeit none of these potential predictors reached statistical significance. It has been proposed that the extent of $^{18}$FDG-PET hypometabolism is a metabolic biomarker of the extent of neural network dysfunction in patients with MTLE.[19,28,50,51] It might be, in light of potentially distinct networks implicated in right versus left MTLE, that neuronal dysfunction in left MTLE patients tends to be more confined within the ipsilateral TL, and further studies looking into the influence of the extent of resection of the ipsilateral TL $^{18}$FDG-PET hypometabolism would be warranted with the focus on the left MTLE cohort.

Moreover, it has been shown that the greater TL resection volumes were associated with favorable seizure outcomes on several occasions,[44,52] and yet the quest for the optimal volume of TL resection remains ongoing to this day.[53] In reality, left ATLR procedures tend to be more sparing, with the left superior temporal gyrus being commonly preserved, resulting in a less extensive TL resection in left MTLE patients.[39,43] Our findings demonstrate distinct metabolic patterns with more extensive ipsilateral TL involvement in left MTLE patients and preferential CTL involvement in patients with right MTLE, which may help to explain the disparity between the extent of the TL resection volume and the seizure freedom rates. Further studies are warranted to explore the potential value of $^{18}$FDG-PET tailored resections in patients with left MTLE.

### *Conclusions*

Our findings demonstrate striking differences in the metabolic patterns in patients with right versus left MTLE and offer further insights into potentially distinct epileptogenic network dysfunction, depending on the lateralization of the MTLE.

From a practical standpoint, our findings call for the extended role of $^{18}$FDG-PET in presurgical planning. Current guidelines reserve the use of $^{18}$FDG-PET for MRI-negative cases and for patients with discordant MRI and electroclinical findings. With the results of our study demonstrating CTL TH to be a strong predictor of unfavorable seizure outcomes heralding a 5-fold increase in seizure recurrence in patients with right MTLE, the wider use of $^{18}$FDG-PET can influence stratification of surgical candidates and improve presurgical counseling, in line with the expectations of personalized patient care.

## Acknowledgment

This study was supported by the Melbourne International Research Scholarship and the Melbourne International Fee Remission Scholarship (V.C.).

We thank J. Callaghan, G. O'Keefe, and C. Stewart for their assistance in the retrieval of the PET and MRI scans.

## Author Contributions

V.C., T.J.O., P.K., S.F.B., B.S., and A.M.M. contributed to the concept and study design. V.C., B.S., Z.C., A.M.M., S.F.B., C.B.M., M.F.O., S.U.B., S.J.W., R.J.H., A.H.K., J.A.K., A.P.M., C.C.R., P.M.D., L.E.V., and G.C.F. contributed to data acquisition and analysis. V.C., T.J.O., and P.K. drafted the manuscript and tables. All authors approved the final version.

## Potential Conflicts of Interest

Nothing to report.

## References

1. McIntosh AM, Wilson SJ, Berkovic SF. Seizure outcome after temporal lobectomy: current research practice and findings. Epilepsia 2001;42:1288–1307.

2. Tellez-Zenteno JF, Hernandez Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. Epilepsy Res 2010;89:310–318.
3. Willmann O, Wennberg R, May T, et al. The contribution of 18F-FDG PET in preoperative epilepsy surgery evaluation for patients with temporal lobe epilepsy: a meta-analysis. Seizure 2007;16:509–520.
4. Knowlton RC. The role of FDG-PET, ictal SPECT, and MEG in the epilepsy surgery evaluation. Epilepsy Behav 2006;8:91–101.
5. Duncan JS, Winston GP, Koepp MJ, Ourselin S. Brain imaging in the assessment for epilepsy surgery. Lancet Neurol 2016;15:420–433.
6. Gaillard WD, Cross JH, Duncan JS, et al. Epilepsy imaging study guideline criteria: commentary on diagnostic testing study guidelines and practice parameters. Epilepsia 2011;52:1750–1756.
7. O'Brien TJ, Miles K, Ware R, et al. The cost-effective use of 18F-FDG PET in the presurgical evaluation of medically refractory focal epilepsy. J Nucl Med 2008;49:931–937.
8. Murphy M, O'Brien TJ, Morris K, Cook MJ. Multimodality image-guided epilepsy surgery. J Clin Neurosci 2001;8:534–538.
9. Zhang J, Liu W, Chen H, et al. Multimodal neuroimaging in presurgical evaluation of drug-resistant epilepsy. Neuroimage Clin 2014;4: 35–44.
10. Whiting P, Gupta R, Burch J, et al. 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 2006;10:1–250, iii–iv.
11. Rathore C, Dickson JC, Teotonio R, et al. The utility of 18F-fluorodeoxyglucose PET (FDG PET) in epilepsy surgery. Epilepsy Res 2014;108:1306–1314.
12. Carne RP, O'Brien TJ, Kilpatrick CJ, et al. MRI-negative PET-positive temporal lobe epilepsy: a distinct surgically remediable syndrome. Brain 2004;127(pt 10):2276–2285.
13. Neuroimaging Subcommision of the International League against Epilepsy. Commission on diagnostic strategies: recommendations for functional neuroimaging of persons with epilepsy. Epilepsia 2000;41:1350–1356.
14. Knowlton RC, Elgavish RA, Limdi N, et al. Functional imaging: I. Relative predictive value of intracranial electroencephalography. Ann Neurol 2008;64:25–34.
15. Pittau F, Grouiller F, Spinelli L, et al. The role of functional neuroimaging in pre-surgical epilepsy evaluation. Front Neurol 2014;5:31.
16. LoPinto-Khoury C, Sperling MR, Skidmore C, et al. Surgical outcome in PET-positive, MRI-negative patients with temporal lobe epilepsy. Epilepsia 2012;53:342–348.
17. Lamarche F, Job AS, Deman P, et al. Correlation of FDG-PET hypometabolism and SEEG epileptogenicity mapping in patients with drug-resistant focal epilepsy. Epilepsia 2016;57:2045–2055.
18. Guedj E, Bonini F, Gavaret M, et al. 18FDG-PET in different subtypes of temporal lobe epilepsy: SEEG validation and predictive value. Epilepsia 2015;56:414–421.
19. Chassoux F, Artiges E, Semah F, et al. Determinants of brain metabolism changes in mesial temporal lobe epilepsy. Epilepsia 2016;57: 907–919.
20. Vanicek T, Hahn A, Traub-Weidinger T, et al. Insights into intrinsic brain networks based on graph theory and PET in right- compared to left-sided temporal lobe epilepsy. Sci Rep 2016;6:28513.
21. Joo EY, Lee EK, Tae WS, Hong SB. Unitemporal vs bitemporal hypometabolism in mesial temporal lobe epilepsy. Arch Neurol 2004;61: 1074–1078.
22. Choi JY, Kim SJ, Hong SB, et al. Extratemporal hypometabolism on FDG PET in temporal lobe epilepsy as a predictor of seizure outcome after temporal lobectomy. Eur J Nucl Med Mol Imaging 2003; 30:581–587.
23. Wong CH, Bleasel A, Wen L, et al. The topography and significance of extratemporal hypometabolism in refractory mesial temporal lobe epilepsy examined by FDG-PET. Epilepsia 2010;51:1365–1373.
24. Kim MA, Heo K, Choo MK, et al. Relationship between bilateral temporal hypometabolism and EEG findings for mesial temporal lobe epilepsy: analysis of 18F-FDG PET using SPM. Seizure 2006;15: 56–63.
25. Koutroumanidis M, Hennessy MJ, Seed PT, et al. Significance of interictal bilateral temporal hypometabolism in temporal lobe epilepsy. Neurology 2000;54:1811–1821.
26. Blum DE, Ehsan T, Dungan D, et al. Bilateral temporal hypometabolism in epilepsy. Epilepsia 1998;39:651–659.
27. Lee KK, Salamon N. [18F] Fluorodeoxyglucose-positron-emission tomography and MR imaging coregistration for presurgical evaluation of medically refractory epilepsy. AJNR Am J Neuroradiol 2009; 30:1811–1816.
28. Vinton AB, Carne R, Hicks RJ, et al. The extent of resection of FDG-PET hypometabolism relates to outcome of temporal lobectomy. Brain 2007;130(pt 2):548–560.
29. Stanisic M, Coello C, Ivanovic J, et al. Seizure outcomes in relation to the extent of resection of the perifocal fluorodeoxyglucose and flumazenil PET abnormalities in anteromedial temporal lobectomy. Acta Neurochir (Wien) 2015;157:1905–1916.
30. Dupont S, Samson Y, Van de Moortele PF, et al. Bilateral hemispheric alteration of memory processes in right medial temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 2002;73:478–485.
31. Coito A, Genetti M, Pittau F, et al. Altered directed functional connectivity in temporal lobe epilepsy in the absence of interictal spikes: a high density EEG study. Epilepsia 2016;57:402–411.
32. Englot DJ, Konrad PE, Morgan VL. Regional and global connectivity disturbances in focal epilepsy, related neurocognitive sequelae, and potential mechanistic underpinnings. Epilepsia 2016;57:1546–1557.
33. Haneef Z, Lenartowicz A, Yeh HJ, et al. Functional connectivity of hippocampal networks in temporal lobe epilepsy. Epilepsia 2014;55: 137–145.
34. Berkovic SF, McIntosh AM, Kalnins RM, et al. Preoperative MRI predicts outcome of temporal lobectomy: an actuarial analysis. Neurology 1995;45:1358–1363.
35. Engel J Jr, Van Ness P, Rasmussen TB, Ojemann LM. Outcome with respect to epileptic seizures. In: Engel JJ, ed. *Surgical treatment of the epilepsies*. New York, NY: Raven Press, 1993:609–621.
36. Malla BR, O'Brien TJ, Cascino GD, et al. Acute postoperative seizures following anterior temporal lobectomy for intractable partial epilepsy. J Neurosurg 1998;89:177–182.
37. McIntosh AM, Kalnins RM, Mitchell LA, Berkovic SF. Early seizures after temporal lobectomy predict subsequent seizure recurrence. Ann Neurol 2005;57:283–288.
38. Fried I. Anatomic temporal lobe resections for temporal lobe epilepsy. Neurosurg Clin N Am 1993;4:233–242.
39. Yogarajah M, Focke NK, Bonelli SB, et al. The structural plasticity of white matter networks following anterior temporal lobe resection. Brain 2010;133(pt 8):2348–2364.
40. Bonelli SB, Powell RH, Yogarajah M, et al. Imaging memory in temporal lobe epilepsy: predicting the effects of temporal lobe resection. Brain 2010;133(pt 4):1186–1199.
41. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002;15:273–289.
42. Ashburner J, Ridgway GR. Symmetric diffeomorphic modeling of longitudinal structural MRI. Front Neurosci 2013;6:197.

43. Shamim S, Wiggs E, Heiss J, et al. Temporal lobectomy: resection volume, neuropsychological effects, and seizure outcome. Epilepsy Behav 2009;16:311–314.

44. Thom M, Mathern GW, Cross JH, Bertram EH. Mesial temporal lobe epilepsy: how do we improve surgical outcome? Ann Neurol 2010; 68:424–434.

45. Gaillard WD, Weinstein S, Conry J, et al. Prognosis of children with partial epilepsy: MRI and serial 18FDG-PET. Neurology 2007;68:655–659.

46. Govil-Dalela T, Kumar A, Behen ME, et al. Evolution of lobar abnormalities of cerebral glucose metabolism in 41 children with drug-resistant epilepsy. Epilepsia 2018;59:1307–1315.

47. Coito A, Plomp G, Genetti M, et al. Dynamic directed interictal connectivity in left and right temporal lobe epilepsy. Epilepsia 2015;56: 207–217.

48. Zubler F, Seeck M, Landis T, et al. Contralateral medial temporal lobe damage in right but not left temporal lobe epilepsy: a (1)H magnetic resonance spectroscopy study. J Neurol Neurosurg Psychiatry 2003;74:1240–1244.

49. Van Paesschen W, Dupont P, Sunaert S, et al. The use of SPECT and PET in routine clinical practice in epilepsy. Curr Opin Neurol 2007;20:194–202.

50. Chassoux F, Semah F, Bouilleret V, et al. Metabolic changes and electro-clinical patterns in mesio-temporal lobe epilepsy: a correlative study. Brain 2004;127(pt 1):164–174.

51. Chassoux F, Artiges E, Semah F, et al. 18F-FDG-PET patterns of surgical success and failure in mesial temporal lobe epilepsy. Neurology 2017;88:1045–1053.

52. Joo EY, Han HJ, Lee EK, et al. Resection extent versus postoperative outcomes of seizure and memory in mesial temporal lobe epilepsy. Seizure 2005;14:541–551.

53. Schramm J. Temporal lobe epilepsy surgery and the quest for optimal extent of resection: a review. Epilepsia 2008;49:1296–1307.