EPISODIC MEMORY IN TEMPORAL LOBE EPILEPSY

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PERSONAL DECLARATION

I, Meneka Kaur Sidhu, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated and referenced throughout the thesis.

The scientific studies presented in this thesis reflect the contributions of a team of researchers including other colleagues from the Department of Clinical and Experimental Epilepsy, ION, UCL and Wellcome Trust Centre for Neuroimaging, UCL. All neuropsychometry presented in this thesis was performed by the Neuropsychologists at the National Hospital for Neurology Neurosurgery and the Epilepsy Society. Dr Gavin Winston and Mr Jason Stretton studied diffusion tensor imaging and working memory fMRI respectively in the same patients and we shared the task of imaging all controls and patients in this study.

I performed all the fMRI data analyses, interpretation of results and data presentation in this thesis. I have outlined my individual contribution to studies performed with collaborators in the relevant chapters.

Dr Meneka Kaur Sidhu

ABSTRACT

Individuals with temporal lobe epilepsy (TLE) have significant material specific episodic memory impairments with greater verbal and visual memory deficits accompanying left and right TLE respectively. More recently, however, widespread cognitive deficits have been described in patients with TLE in keeping with morphological and functional abnormalities that extend beyond the temporal lobes. Functional magnetic resonance imaging (fMRI) has demonstrated reorganisation of memory encoding networks within the temporal lobe in TLE, but little is known of the extra-temporal networks in these patients. Memory fMRI as a tool for predicting memory decline after anterior temporal lobe resection has been explored but a clinically applicable algorithm has yet to be defined. Fewer studies have described the changes in the memory encoding networks after temporal lobe surgery.

This thesis presents methodological developments and novel applications to describe the pre-operative and post-operative verbal and visual memory networks in those with unilateral TLE. Pre-operatively, I investigated extra-temporal areas of memory reorganisation in left and right TLE patients, quantitatively compared to healthy controls. Novel findings include the 'efficiency' of extra-temporal reorganisation to successful memory formation. Next, using clinical parameters such as age at onset of epilepsy, epilepsy duration and seizure frequency as continuous regressors, I described the factors affecting verbal and visual memory reorganisation in TLE.

In a separate pre-operative study, I used an alternative fMRI analysis method, multi-voxel pattern analysis (MVPA) that focuses on the patterns of activity across voxels

in specific brain regions that are associated with individual memory traces. I used MVPA-fMRI to assess the functional integrity of the hippocampi and other medial temporal lobe structures in patients with unilateral TLE.

Next, I explored the predictive ability of temporal and extra-temporal activations in predicting post-operative verbal memory decline in left and right TLE patients and described a method of using memory fMRI as a clinically applicable tool in patients who had anterior temporal lobe resection.

Finally, I explored memory encoding network plasticity four and 12 months after anterior temporal lobe resection. In this study, controls were also scanned at similar time intervals to patients. I report for the first time, dynamic changes in the memory encoding network four and 12 months after surgery, relative to changes in controls. Novel findings also include the efficiency of these post-operative networks. In this thesis, I also discuss methodological constraints, clinical applications and future directions.

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LIST OF ABBREVIATIONS

AED = Antiepileptic drugs

ACC = Anterior cingulate cortex

Ant = Anterior

ANOVA = Analysis of variance

ANCOVA = Analysis of covariance

ATLR = Anterior temporal lobe resection

AVM = Arterio-venous malformation

BOLD = Blood oxygen level dependent

CTR = Controls

C = Cortex

CT = Computed tomography

DL = Design learning

DMN = Default mode network

DNET = Dysembryoplastic neuroepithelial tumour

EEG = Electroencephalography

EEG-fMRI = Simultaneous electroencephalography and functional magnetic resonance imaging

EPC = Entorhinal / perirhinal cortex combined

FCD = Focal cortical dysplasia

FDG = Fluoro deoxy-glucose

FFam = Faces familiar

FFo = Faces forgotten

FG = Fusiform gyrus

fMRI = Functional magnetic resonance imaging

FRem = Faces remembered

FWE = Family wise error

G = Gyrus

HFO = High frequency oscillations

HRF = Haemodynamic response function

HS = Hippocampal sclerosis

icEEG-fMRI = Intracranial electroencephalography and functional magnetic resonance imaging

IFG = Inferior frontal gyrus

ILAE = International league against epilepsy

Inf = Inferior

IFG = Inferior frontal gyrus

IPL = Inferior parietal lobe

ITG = Inferior temporal gyrus

IQR = inter quartile range

Lt = left

Lat = Lateral

LI = lateralisation index

LHS = Left hippocampal sclerosis

LTLE = Left temporal lobe epilepsy

Med = medial

MEG = Magneto-encephalography

MFG = Middle frontal gyrus

MNI = Montreal neurological institute

MTG = middle temporal gyrus

MTS= Mesial temporal sclerosis

MOG = middle occipital gyrus

MVPA = multivariate pattern analysis

MTG = Middle temporal gyrus

n/a = not applicable

NHNN = National Hospital for Neurology and Neurosurgery

N/S = No significant activations

OFC = Orbitofrontal Cortex

PCC = Posterior cingulate cortex

PET = Positron emission tomography

PMC = Pre-motor cortex

Post = Posterior

RA = Recognition accuracy

RF = Radio frequency

RHS = Right hippocampal sclerosis

ROI = Region of interest

RTLE = Right temporal lobe epilepsy

RP = Realignment parameters

Rt= Right

SD = Standard deviation

SEM = Standard error of mean

SFG = Superior frontal gyrus

SGS = Secondary generalized seizure

SISCOM = Subtraction of ictal and interictal scans

SPECT = Single photon emission computed tomography

SPM = Statistical parametric mapping

STG = Superior temporal gyrus

SVM = Support vector machine

T = Tesla

TLE = Temporal lobe epilepsy

TR = Time repeat

UCL = University College London

UCLH = University College London Hospitals

VL = Verbal learning

WFam = Words familiar

WFo = Words forgotten

WR = Words remembered

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PUBLICATIONS

Experimental studies detailed in chapters 6 – 9 have been published or accepted for publication as first author publications in international peer-reviewed journals.

Chapter 6

- A functional magnetic resonance imaging study mapping the episodic memory encoding network in temporal lobe epilepsy. **Sidhu MK**, Stretton J, Winston GP, Bonelli S, Centeno M, Vollmar C, Symms M, Thompson PJ, Koepp MJ, Duncan JS. ***Brain*** 2013 Jun;136(Pt 6):1868-88.2013

Chapter 7

- Factors affecting memory Reorganisation in Temporal Lobe Epilepsy. **Sidhu MK**, Stretton J, Winston G, Bonelli S, Thompson PJ, Symms M, Koepp MJ ,Duncan JS. ***Epilepsy Research***, 2015 Feb;110:1-9. doi: 10.1016/j.eplepsyres.2014.11.001. Epub 2014 Nov 11.

Chapter 8

This study was a collaboration with Professor Eleanor Maguire at the functional imaging laboratory, Queen Square London. Dr. Bonnici and I share first authorship for this publication

- Assessing hippocampal functional reserve in temporal lobe epilepsy: A multi-voxel pattern analysis of fMRI data. Bonnici HM*, **Sidhu M*,** Chadwick MJ, Duncan JS, Maguire E. ***Epilepsy Res*** 2013 Jul;105(1-2):140-9.doi: 10.1016/j.eplepsyres.2013.01.004

Chapter 9

- Memory fMRI predicts Verbal Memory Decline after Left Anterior Temporal Lobe Resection. **Sidhu MK**, Stretton J, Winston G, Symms M, Thompson PJ, Koepp MJ, Duncan JS. ***Neurology***, April 14, 2015 vol. 84 no. 15 1614

Chapter 10

- Memory network plasticity after temporal lobe resection: a longitudinal fu**nctional** imaging study. **Sidhu MK**, Stretton J, Winston G, McEvoy A, Symms M, ***Thompson*** PJ**,** Koepp MJ, Duncan JS. Submitted to ***Brain*** (BRAIN-2015-00632).

PRESENTATIONS

NATIONAL/ INTERNATIONAL

May 2014 **Memory fMRI predicts verbal memory decline after anterior temporal lobe resection**

Platform presentation, EFNS/ENS Joint Congress of European Neurology, Istanbul 2014

Oct 2012 **Memory encoding after left anterior temporal lobe resection**

Platform presentation, 10th European Congress on Epileptology, London. Best poster award.

Jun 2012 **Frontal Lobe activations in Temporal Lobe Epilepsy**

18th Annual meeting for the Organisation of Human Brain Mapping Conference, Beijing China

May 2012 **Factors affecting memory reorganisation in Temporal Lobe Epilepsy; an fMRI study**

Platform Presentation, Association of British Neurologists Annual Meeting, Brighton

Dec 2011 **Special Interest Group: Frontal Lobe Epilepsy, the Effect of Frontal Lobe Epilepsy on the Developing Brain**

Invited speaker: American Epilepsy Society, Annual Meeting, Baltimore, Maryland

Dec 2011 **Frontal Lobe Activity during memory encoding in Temporal Lobe Epilepsy**

Poster Presentation, American Epilepsy Society, Annual Meeting, Baltimore, Maryland

Oct 2011 **Memory in Temporal Lobe Epilepsy; an fMRI study**

Platform Presentation, Association of British Neurologists Annual Meeting, Gateshead, Newcastle

Aug 2011 **Frontal Lobe Activity during memory encoding in Temporal Lobe Epilepsy**

Poster Presentation, International Epilepsy Congress, Rome

Mar 2011 **Memory Encoding: Beyond the Hippocampus**

London-Salzburg Functional Imaging Symposium
Inter-department imaging collaboration, Department of Epilepsy, Salzburg

LOCAL PRESENTATIONS

Oct 2012 **Functional imaging in Epilepsy**
Invited Speaker: Journal club, Neuroscience Directorate, Hope Hospital Manchester

Apr 2011 **Multivariate Pattern Analysis; Decoding the Hippocampus**
Departmental meeting, Epilepsy Society, Buckinghamshire,

BURSARIES & GRANTS

May 2014 ***EFNS/ENS Joint Congress of European Neurology Bursary***
EFNS/ENS Joint Congress of European Neurology, Istanbul

Oct 2012 **International League Against Epilepsy *Bursary***
10th European Congress on Epileptology, London

Jul 2012 ***University College London, Graduate Fund: Major Grant***
18th Annual meeting for the Organisation of Human Brain Mapping Conference, Beijing China

Jul 2012 ***Epilepsy ActionTravel Bursary***
18th Annual meeting for the Organisation of Human Brain Mapping Conference, Beijing China

Jul 2011 ***Epilepsy Action Travel Bursary***
International Epilepsy Congress, Rome

Sept 2011 ***University College London, Graduate Fund: Minor Grant***
International Epilepsy Congress, Rome

AWARDS

Oct 2012	***Best Poster Award*** 10th European Congress on Epileptology, London
Dec 2011	***Young Investigator Award*** American Epilepsy Society Annual Meeting, Baltimore, Maryland

Section 1: Literature Review

Epilepsy is a common condition affecting 50 million people worldwide, 80 % of which live in the developing world (Meyer et al., 2010). TLE is the most common focal epilepsy syndrome. Apart from the burden of continued seizures patients with refractory epilepsy develop significant co-morbidities in the form of physical impairment from seizures, cognitive and language impairment and behavioural disruption causing significant psychosocial impairment and stigmatisation (de Boer et al., 2008). At the 2007 conference sponsored by the National Institutes of Neurological Diseases and Stroke (Curing Epilepsy 2007: Translating Discoveries into Therapies), the prevention and reversal of the comorbidities of epilepsy were identified as primary benchmark areas for research(Kelley et al., 2009).

The aim of this 3 year PhD study was to investigate the episodic memory network in those with TLE and to predict the consequences of temporal lobe resection on cognitive function.

Chapter 1: Epilepsy

1.1 History and Definition

Epilepsy is a condition with a mythical past, with the earliest description as early as 600BC attributed to supernatural causes (Reynolds and Kinnier Wilson, 2008; Wilson and Reynolds, 1990). Semiologies now recognised as generalised tonic clonic seizures, gelastic seizures, nocturnal seizures and post ictal states were thought to be the effect of demons and ghosts. Indeed, the word 'epilepsy' is derived from the Greek word meaning to 'seize upon' or 'taking hold of', acts thought to be orchestrated by a god or demon. Accordingly, treatments used included fumigation with kindled jets and bathing new-borns in undiluted wine. Magicians and witch doctors were frequently sought to ward off evil during attacks using mineral stones, camel hair and even human blood and bones (Chaudhary et al., 2011).

Hippocrates was the first philosopher to challenge these myths and postulated the brain as source of epilepsy and attributed this to excess phlegm in the blood stream. Although advances in the understanding of epilepsy were seen from the early 1700s, the greatest surge in modern epileptology concepts that are still widely accepted today have been attributed to the work of Sir John Hughlings Jackson (for review see- (Chaudhary et al., 2011). He defined epilepsy as occasional, sudden, excessive, rapid, and local discharges of gray matter lesions. He emphasized lesion localisation by semiology and combined this with pathology from neuroanatomical dissections to study mechanisms of seizure spread. He proposed that gray matter in cerebral cortex is the focus of epilepsy, but recognised the role of deeper gray matter structures in the corpus striatum (Reynolds, 1988).

Although Sir Hughlings Jackson has been widely credited with the electrical theory of epilepsy, it was in fact Robert Bentley Todd (1809–60) who was the real pioneer and

developed an electrical theory of epilepsy many years before Jackson did. He was influenced by the electrical discoveries of his contemporary, Michael Faraday, and thought of the brain as having battery like properties that led to the sudden discharge of electrical energy (nervous force) in epilepsy. Being a physiologist himself, he performed remarkable experiments on rabbits to support his hypothesis. All of this work is described in Todd's own Lumleian lectures, "On the pathology and treatment of convulsive diseases", to the Royal College of Physicians, which were published in the *London Medical Gazette* in 1849. Hughlings Jackson made no reference to Todd's findings in his later Lumleian lectures on the same subject (Reynolds).

An epileptic seizure is now widely accepted as a sudden abnormal paroxysmal synchronous discharge of neuronal activity culminating in clinical signs and symptoms representative of the area of aberrant neuronal discharge and propagation. The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) have come to a consensus definition of epilepsy as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition (Fisher et al., 2005).

1.2 Classification

After the advent of the electro encephalogram (EEG) the earliest classification of epilepsy was proposed by Gastaut in 1967 into partial, generalised, unilateral and unclassified, incorporating clinical features, anatomical substrates, age at onset, aetiology, ictal and inter-ictal EEG findings (Gastaut, 1970). In 1981, the ILAE developed an international classification of epileptic seizures where anatomical substrates, aetiology and age at onset were discarded and partial onset seizures were divided on the basis of retained or loss of consciousness; simple and complex

partial seizures respectively (1981). In 1985 the terms ‘primary’, ‘secondary’ and ‘localisation related epilepsy’ were replaced by ‘idiopathic’, ‘symptomatic’ and ‘partial’ epilepsy respectively and in 1989, epilepsy syndromes were better categorised (1985; 1989).

Epilepsy is heterogeneous and classification was proposed to better understand and treat subgroups and also for standard descriptive nomenclature to be used. The 1989 classification although widely used was deemed unsatisfactory in identifying subgroups of epilepsy hence four documents were proposed that were aimed at descriptive terminology for ictal phenomena (Luders et al., 1998), classification of epileptic seizures, classification of epilepsy syndromes and classification of functional disability (Engel, 1998).

In 2001 the ILAE task force introduced specific criteria for identification of specific epileptic seizure types and specific epilepsy syndromes as unique diagnostic entities. A 5–axis diagnostic scheme was proposed especially to be used in the context of epilepsy surgery[2] :

Axis 1: Descriptive ictal terminology.

Axis 2: Seizure type, from the List of Epileptic Seizures with specific brain location, if known.

Axis 3: Syndrome, from the List of Epilepsy Syndromes, not always possible.

Axis 4: Aetiology, including specific genetic defects or pathologic substrates.

Axis 5: Impairment, optional but useful parameter can be derived from the WHO ICIDH-2 impairment classification.

In 2006, the classification was refined further with the reintroduction of parameters such as age at onset. Other parameters considered in the classification criteria included seizure types, nature of progression, inter ictal EEG, pathophysiological mechanisms and genetics, detailed below (Engel, 2006), Table 1.1**.**

Table 1.1: Seizure Classification
Classification by Seizure Types
Self-limited epileptic seizures
I. Generalized onset
A. Seizures with tonic and/or clonic manifestations
    1. Tonic-clonic seizures
    2. Clonic seizures
    3. Tonic seizures
B. Absences
    1. Typical absences
    2. Atypical absences
    3. Myoclonic absences
C. Myoclonic seizure types
    1. Myoclonic seizures
    2. Myoclonic astatic seizures
    3. Eyelid myoclonia
D. Epileptic spasms
E. Atonic seizures

II. Focal onset (partial)
A. Local
1. Neocortical
a. Without local spread
    i Focal clonic seizures
    ii Focal myoclonic seizures
    iii Inhibitory motor seizures
    iv Focal sensory seizures with elementary symptoms
    v Aphasic seizures
b. With local spread
    i Jacksonian march seizures
    ii Focal (asymmetrical) tonic seizures
    iii Focal sensory seizures with experiential symptoms
2. Hippocampal and parahippocampal

B. With ipsilateral propagation to:
1. Neocortical areas (includes hemiclonic seizures)
2. Limbic areas (includes gelastic seizures)

C. With contralateral spread to:
1. Neocortical areas (hyperkinetic seizures)
2. Limbic areas (dyscognitive seizures with or without automatisms [psychomotor])

D. Secondarily generalized
1. Tonic-clonic seizures
2. Absence seizures
3. Epileptic spasms (unverified)

III. **Neonatal seizures**
Status epilepticus
I. Epilepsia partialis continua (EPC)
    A. As occurs with Rasmussen syndrome
    B. As occurs with focal lesions
    C. As a component of inborn errors of metabolism
II. Supplementary motor area (SMA) status epilepticus
III. Aura continua
IV. Dyscognitive focal (psychomotor, complex partial) status epilepticus
    A. Mesial temporal
    B. Neocortical
V. Tonic-clonic status epilepticus
VI. Absence status epilepticus
    A. Typical and atypical absence status epilepticus
    B. Myoclonic absence status epilepticus
VII. Myoclonic status epilepticus
VIII. Tonic status epilepticus
IX. Subtle status epilepticus

Epilepsy syndromes by age of onset and related conditions
Neonatal period
Benign familial neonatal seizures (BFNS)
Early myoclonic encephalopathy (EME)
Ohtahara syndrome
Infancy
Migrating partial seizures of infancy
West syndrome
Myoclonic epilepsy in infancy (MEI)
Benign infantile seizures
Dravet syndrome
Myoclonic encephalopathy in non-progressive disorders
Childhood
Early onset benign childhood occipital epilepsy
(Panayiotopoulos type)
Epilepsy with myoclonic astatic seizures
Benign childhood epilepsy with centro-temporal spikes (BCECTS)
Late onset childhood occipital epilepsy (Gastaut type)
Epilepsy with myoclonic absences
Lennox-Gastaut syndrome (LGS)
Epileptic encephalopathy with continuous spike-and-wave during
sleep (CSWS) including Landau-Kleffner syndrome (LKS)
Childhood absence epilepsy (CAE)
Adolescence

Juvenile absence epilepsy (JAE)
Juvenile myoclonic epilepsy (JME)
Progressive myoclonus epilepsies (PME)
Less Specific Age Relationship
Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
Familial temporal lobe epilepsies
Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
Rasmussen syndrome
Gelastic seizures with hypothalamic hamartoma
Special epilepsy conditions
Symptomatic focal epilepsies not otherwise specified
Epilepsy with generalized tonic-clonic seizures only
Reflex epilepsies
Febrile seizures plus (FS+)
Familial focal epilepsy with variable foci
Conditions with epileptic seizures that do not require a diagnosis of epilepsy
Benign neonatal seizures (BNS)
Febrile seizures (FS)

Electroclinical syndromes and other epilepsies
Electroclinical syndromes arranged by age at onset
Neonatal period
Benign familial neonatal epilepsy (BFNE)
Early myoclonic encephalopathy (EME)
Ohtahara syndrome
Infancy
Epilepsy of infancy with migrating focal seizures
West syndrome
Myoclonic epilepsy in infancy (MEI)
Benign infantile epilepsy
Benign familial infantile epilepsy
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders
Childhood
Febrile seizures plus (FS+) (can start in infancy)
Panayiotopoulos syndrome
Epilepsy with myoclonic atonic (previously astatic) seizures
Benign epilepsy with centrotemporal spikes (BECTS)
Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
Late onset childhood occipital epilepsy (Gastaut type)
Epilepsy with myoclonic absences
Lennox-Gastaut syndrome
Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
Landau-Kleffner syndrome (LKS)
Childhood absence epilepsy (CAE)
Adolescence – Adult
Juvenile absence epilepsy (JAE)

Juvenile myoclonic epilepsy (JME)
Epilepsy with generalized tonic–clonic seizures alone
Progressive myoclonus epilepsies (PME)
Autosomal dominant epilepsy with auditory features (ADEAF)
Other familial temporal lobe epilepsies
Less specific age relationship
Familial focal epilepsy with variable foci (childhood to adult)
Reflex epilepsies
Distinctive constellations
Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
Rasmussen syndrome
Gelastic seizures with hypothalamic hamartoma
Hemiconvulsion–hemiplegia–epilepsy

Epilepsies that do not fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)

Epilepsies attributed to and organized by structural-metabolic causes
Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
Tumor
Infection
Trauma
Angioma
Perinatal insults
Stroke
Epilepsies of unknown cause
Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se.
Benign neonatal seizures (BNS)
Febrile seizures (FS)

The most recent report of the ILAE Commission Core Group was published recently in 2010 where revisions to terminology and concepts of seizure classification were proposed (Berg et al., 2010). The terms generalised, symptomatic and idiopathic have been replaced by the terms genetic, structural/metabolic and unknown respectively. Focal seizures with secondary generalisation is now termed discrete onset with bilateral synchronisation. These changes provide more background to the classification however no changes have been made to the electro-clinical syndromes

that had already been updated by the Task force in 2006, detailed above. The descriptive terms of focal seizures have been changed to reflect changes in consciousness of awareness:

a) Without impairment of consciousness or awareness. This corresponds to the concept of ‘simple partial seizure’. These can be described according to the semiological classification (Luders et al., 1998) or the glossary of ictal semiology (Blume et al., 2001)

b) With impairment of consciousness or awareness. This corresponds to the concept of complex partial seizure. ‘Dyscognitive’ is a term that is widely accepted for this concept.

Focal seizures evolving to bilateral, convulsive seizure (either tonic, clonic, or tonic and clonic components) replaced the term ‘secondarily generalized seizure.’ Other changes proposed included changes to classification of seizure types. The classification of absence seizures had been simplified and myoclonic absence and eyelid myoclonia were allocated under this umbrella heading. Epileptic spasms were classified as unknown. Myoclonic astatic seizures were renamed myoclonic atonic seizures. Neonatal seizures were no longer considered a separate entity. Dravet syndrome is now considered a genetic epilepsy. Epilepsies with structural or metabolic causes are now labelled so their localisation and aetiology is described eg. Epilepsy with focal seizures secondary to cavernous angioma in the frontal lobe. Finally, the concept of epileptic encephalopathy has been recognised.

The revised classification is shown below:

Classification of seizures[a]

Generalized seizures
- Tonic–clonic (in any combination)

Absence
- Typical
- Atypical
- Absence with special features — Myoclonic absence; Eyelid myoclonia

Myoclonic
- Myoclonic
- Myoclonic atonic
- Myoclonic tonic

Clonic

Tonic

Atonic

Focal seizures

Unknown
- Epileptic spasms

[a]Seizures that cannot be clearly diagnosed into one of the preceding categories should be considered unclassified until further information allows their accurate diagnosis. This is not considered a classification category, however.

There are several pros to the revised 2010 criteria, particularly in the context of epilepsy surgery. The new classification allows flexibility to describe syndromes incorporating multiple axes. The use of descriptive terminology (Blume et al., 2001; Luders et al., 1998) aids in the clinical localisation of seizures and in conjunction with aetiology, using the proposed database by Shorvon (Shorvon, 2011), proves particularly advantageous in the context of epilepsy surgery. Aetiological classification also informs prognosis and outcome measures (Menzler et al., 2011; Moshe, 2011).

1.3 Epidemiology and Prognosis

Epilepsy is a common condition affecting 50 million people worldwide, 80 % of which live in the developing world. The cumulative lifetime risks for epilepsy and for any unprovoked seizure are 3.1% and 4.1%, respectively, in industrialized countries. In developed countries the annual incidence is as high as 43 cases per 100,000 (Meyer et al., 2010). In up to 70% of people with epilepsy, seizures are well controlled on anti-epileptic medication within 5 years of diagnosis however some continue to have refractory epilepsy (Sander, 2003). Apart from the burden of continued seizures patients with refractory epilepsy develop significant co-morbidities in the form of physical impairment from seizures, cognitive and language impairment and behavioural disruption causing significant psychosocial impairment and stigmatisation (de Boer et al., 2008). At the 2007 conference sponsored by the National Institutes of Neurological Diseases and Stroke (Curing Epilepsy 2007: Translating Discoveries into Therapies), the prevention and reversal of the comorbidities of epilepsy were identified as primary benchmark areas for research (Kelley et al., 2009).

The Rochester Epidemiology project and several studies have reported a lower incidence of epilepsy and unprovoked seizures in females. Conversely, idiopathic generalized epilepsies (IGEs) are more common among females. Medial temporal lobe epilepsy (TLE) is the most common form of focal epilepsy and patients with TLE typically have a signature deficit in episodic memory. In carefully selected refractory TLE patients, anterior temporal resection is curative of seizures in up to 50% of patients (de Tisi et al., 2011) however surgery can compound existing cognitive deficits.

1.4 Mesial Temporal Lobe Epilepsy (MTLE)

60 – 70% of focal epilepsies are thought to arise from the temporal lobe. TLE is characterised by simple and complex partial seizures with features that can be used to further localise seizure onset within the temporal lobe. Seizures are either mesial or lateral neocortical with the former being more common. The mean age of seizure onset is towards the second half of the first decade. The most common pathology associated with mesial TLE is mesial temporal sclerosis (MTS).

1.4.1 Structure and connections of the mesial temporal lobe (MTL)

The mesial temporal lobe comprises the hippocampus, amygdala, entorhinal, perirhinal and parahippocampal neocortical regions. The hippocampus proper is composed of the four CA (Cornu Ammonis) subregions, CA 1-4, whereas the hippocampal formation includes the dentate gyrus, and the subicular complex. The hippocampal components are comprised of a 3 layered allocortex compared to the adjacent six layered mesial temporal neocortex. A layer of white matter, alveus linea is on the ventricular surface of the hippocampus and contains afferent and efferent axons (Duvernoy, 1998). The mesial temporal lobe has local and more distant reciprocal connections with the prefrontal cortex including the orbitofrontal cortex (Simons and Spiers, 2003).

1.4.1.1 Connections within the MTL

The major input to the hippocampus is from the entorhinal cortex, via the perforant path to the dentate gyrus. From here, the dentate granule cells project to the CA3 field of the hippocampus via efferent mossy fibres. The CA3 pyramidal cells in turn project to the CA1 field via the Schaffer collaterals . The principal neurotransmitter of these pathways is glutamate. The primary output from the hippocampus to the

temporal lobe is from the CA1 field to the subicular complex which projects to the entorhinal cortex, creating a loop involving the hippocampus (Duvernoy, 1998).

1.4.1.2 MTL - Pre Frontal Cortex (PFC) connections

A seminal paper suggested that amnesia may occur as a result of disconnection between the frontal and temporal lobes (Warrington and Weiskrantz, 1982). This is in keeping with a vast amount of literature showing functional connections between the two lobes. There are large cortico-cortical direct reciprocal connections between the PFC and the mesial temporal lobe, passing through the uncinate fascicle, anterior temporal stem and anterior corpus callosum. The orbitofrontal and dorsolateral cortices have strong reciprocal connections with the perirhinal and entorhinal cortices(Rempel-Clower and Barbas, 2000). There are more top down connections from the PFC to the perirhinal cortex (Lavenex and Amaral, 2000) than vice-versa.

The CA1 region has unidirectional projections to the caudal region of the medial prefrontal cortex (Barbas and Blatt, 1995; Rosene and Van Hoesen, 1977) whilst the subicular complex and neocortical medial temporal regions have reciprocal connections with this region (Goldman-Rakic et al., 1984). The MTL also receives connections from sensory association areas including parietal and temporal sensory areas (Suzuki and Amaral, 1994) that in turn have reciprocal connections with the PFC (Barbas et al., 1999).

1.4.2 Mesial Temporal Sclerosis

1.4.2.1 Neuropathology and epileptogenesis

MTS is associated with a relatively uniform clinical syndrome of high epileptogenicity. The hippocampus has been implicated as the epileptogenic region in non-convulsive seizures since the late 19th century. MTS is defined by its anatomical characteristics, namely gliosis and loss of neurones in the hippocampus, subiculum, parahippocampal gyrus and inferomedial temporal cortex. Wilhelm Sommer first described selective neurone loss in the CA 1 region (Sommer, 1880) which remains the primary area of pathology. Other areas include CA4, hilus of the dentate gyrus with relative sparing of the dentate gyrus granule cells, CA2 and CA 3 (Figure 1.1).

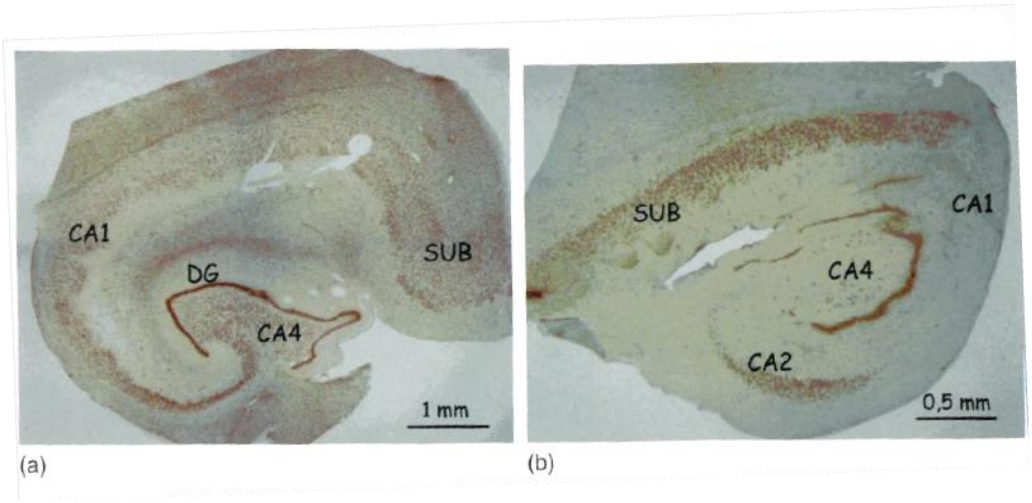


Fig 1.1: Neuropathological finding in MTS

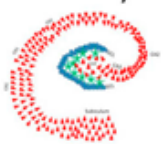
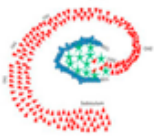
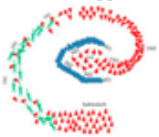
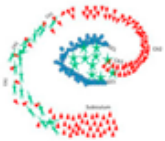
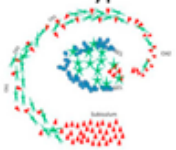
(a) Histograph of a human hippocampus obtained from autopsy. Pigment- Darrow red staining. Significant atrophy in (b) (Blumcke, 2008). Segmental pyramidal loss affecting CA1 and CA4 sectors. In contrast, CA2 pyramidal and dentate gyrus(DG) granule cells are most seizure resistant. Subiculum (SUB).

MTS may co-exist with other pathologies including cortical dysplasias, neoplasms and vascular malformations. Hippocampal sclerosis (HS) is a neuropathological condition with severe neuronal cell loss and gliosis in the hippocampus, specifically in the CA1 and subiculum of the hippocampus. It is typically unilateral (Quigg et al.,

1997), described structurally using various neuroimaging modalities. If bilateral hippocampal atrophy is seen it is, it is often asymmetrical, with greater cell loss on the epileptogenic side (Mathern et al., 1996). In 1966, Margerison and Corsellis reported clinical, EEG and post-mortem findings of 55 patients with epilepsy. HS was identified in 36 of 55 cases and interestingly, in 17 of these cases HS was present bilaterally (Margerison and Corsellis, 1966). Whether modern neuroimaging would have identified these cases as bilateral, remains a mystery.

In severe HS all hippocampal subfields, including the granule cells of the dentate gyrus may be involved, so called ‘total’ hippocampal sclerosis . End folium sclerosis, seen in 3-4% of surgical cases, describes a pattern of neuronal damage confined to the hilar and CA4 pyramidal cells. This may be undetectable with neuroimaging, associated with a later onset of epilepsy and a worse post-operative seizure outcome. Table 1.1 below summarises various classification schemes adopted for the patterns of HS in recent eras (Thom, 2014).

Table 1.2: Summary of various classification schemes adopted for the patterns of HS in recent years

	Main pathology findings					
	No HS  No HS	Gliosis only  End folium gliosis	ILAE type 3  End folium sclerosis	ILAE type 2  CA1 predominant	ILAE type 1  Classical HS	ILAE type 1 
Classification system/era	*No neuronal loss and no gliosis*	*Gliosis only (often involving the subgranular zone)*	*Neuronal loss and gliosis in CA4 subfield (endplate/hilus)*	*Neuronal loss and gliosis predominant in CA1 subfield*	*Neuronal loss and gliosis in CA1 > CA4, CA3 with sparing of CA2*	*Extensive neuronal loss (and gliosis) in all subfields including the dentate gyrus*
Corsellis/Bruton (1966 to 1988)	No HS		End folium sclerosis	Not identified	Classical Sclerosis	Total Sclerosis
Wyler (1996)	Grade 0	Grade 1	Grade 2 (end folium pattern)	Grade 2	Grade 3	Grade 4
Blumcke/ILAE (2007 to 2013)	No HS	Gliosis only	ILAE type 3 HS	ILAE type 2 HS	ILAE type 1 HS	
Approximate proportion*	10–30%	Unknown	3–7.4%	5–10%	60–80%	
Clinicopathological correlations in temporal lobe epilepsy surgical series†	(1) Poorer postsurgical seizure-free outcomes (42–58% seizure free) (2) FS – less common	Unknown specificity for TLE	(1) Pattern of HS most often associated with a second (dual) pathology (e.g. DNT, cavernoma) (2) Older age at onset of epilepsy† (3) Poorer postsurgical seizure-free outcomes in some series	(1) Older age at onset of epilepsy in some series (2) Poorer postsurgical seizure-free outcomes in some series	(1) Highest rates of seizure freedom (~70–85% seizure freedom post-operatively at 2 years, ~50% at 10 years) (2) Common association with febrile seizures 50–76%	

*This refers to the relative incidence of the patterns of sclerosis in surgical epilepsy series where HS/mesial temporal lobe sclerosis is considered, both electroclinically and/or by MRI, to be the cause of epilepsy.
†Clinicopathological correlations for different subtypes have been reported in some, but not all, epilepsy surgical series.
In the diagrams pyramidal neurones of hippocampal subfields and subiculum are shown in red, granule cells in blue and astrocytosis in green.
ILAE, International League Against Epilepsy; FS, febrile seizures; DNT, dysembryoplastic neuroepithelial tumour.

Patients undergoing anterior temporal lobe resection have a better outcome linked to different patterns of MTL neuronal loss (Thom et al., 2010). Patients with early precipitating injuries tend to have HS type 1 whilst later seizure onset has been associated with HS types 2 and 3 (Blumcke, 2008).

Although the hippocampus remains the main focus of research into the molecular and cellular causes of epilepsy the entorhinal cortex may have importance in the initiation of mesial temporal lobe seizures or the initiation of HS. Early observations noted selective loss of layer III of the medial EC in patients with TLE with or without HS (Du et al., 1993). Animal studies have replicated this finding with relative preservation of parvalbumin –positive inhibitory interneurones suggesting that excitotoxicity was the mechanism of neuronal death (Du et al., 1995).

Dispersion of granule cells in the molecular layer has been seen in up to 40-50% of patients with HS. Although the functional significance as well as the cause of this dispersion is not fully understood it may be that following stimulation by seizures, an increased rate of granule cell neurogenesis occurs leading to the abnormal cell localisation and reorganisation observed in HS (Thom, 2011). Another neuropathological feature recognized in both rat models and humans and believed to be a key event in the development of chronic seizures, is the aberrant axonal reorganisation, or mossy fibre sprouting. Mossy fibres as described earlier are the excitatory, glutamatergic axons of the dentate gyrus. Over 90% of these mossy fibres make synaptic contact with apical dendrites and spines of the granule cells creating a pro epileptogenic ‘short circuit’ (Thom, 2011). In summary, mechanisms of epileptogenesis in HS include, alteration between excitatory and inhibitory neuronal connections, altered intrinsic cell firing properties, astrocyte dysfunction in areas of

gliosis, mossy fibre sprouting and activation of microglial cells and inflammatory pathways (Thom, 2011).

Many retrospective studies have shown a significant risk of developing HS in patients with a history of prolonged febrile convulsions. Whether this is an epiphenomenon or a causative factor is not fully understood. It has been suggested that MTS occurs as a consequence of hypoxia in a prolonged febrile convulsion thereby increasing the risk of MTLE (Taylor and Ounsted, 1971). This relationship has been debated as other retrospective and prospective studies have failed to replicate this relationship. A genetic predisposition is an important factor in MTS and in several sub-syndromes presenting with febrile seizures (Hauser et al., 1985; Ottman et al., 1985). Other studies have suggested that an underlying malformation of the hippocampus predisposes to both MTS and febrile convulsions. Evidence from neuroimaging has suggested subtle hippocampal malformations as a cause of familial febrile convulsions and subsequent hippocampal sclerosis (Fernandez et al., 1998). Studies have also demonstrated the coexistence of HS with subtle cytoarchitectural malformations in the neocortex, also called microdysgenesis (Hardiman et al., 1988). It is possible that these epileptogenic extra-hippocampal lesions ‘kindle’ the hippocampal neuronal loss, leading to the development of HS.

1.4.3 Seizure characteristics of MTLE

Seizures arising from the temporal have a gradual evolution over 1-2 minutes. They can range from a subjective epileptic aura with no loss of awareness to objective with loss of awareness and sometimes consciousness. They tend to last longer than extra-temporal seizures. Three components, aura, motor arrest and automatisms are usually seen (Diehl and Duncan, 2011).

1.4.3.1 Aura

An aura or simple partial seizure is a subjective description which can help to localise the ictal onset zone. It can occur in isolation or as the initial manifestation of a complex partial seizure (CPS). The most common aura is a rising epigastric sensation which is most likely to be due to the spread of the epileptogenic discharge to the insula cortex (Luders, 2008). Others include visceral, cephalic, gustatory, olfactory, dysmnestic, experiential or affective symptoms and fear. Seizures arising from the amygdala are strongly associated with an intense feeling of fear and may be associated with autonomic symptoms, including changes in skin colour, blood pressure, heart rate, and pupil size. There is usually reduced speech. Other localising auras include a hissing, humming or roaring sound implicating the superior temporal gyrus (Heschl's gyrus) and olfactory sensations can signal the start of seizures in the sylvian or ento-rhinal cortex. Complex illusionary auras may occur in seizures arising in association areas. Depth recordings show that seizures arise from the hippocampus but electrical stimulation suggests that the symptoms that occur are due to spread of the epileptiform activity to adjacent areas (Luders, 2008).

1.4.3.2 Motor arrest

Motor arrest, or a dialeptic state, is a prominent feature of progression of the aura to a CPS and was introduced as part of the semiological classification in 1998 (Luders et al., 1998). Predominant ictal features include alteration of consciousness, staring and loss, or minimal motor activity. When the aura is short, this is often the first manifestation of the seizure noticed by eyewitnesses.

1.4.3.3 Automatism

Automatisms are semi-purposeful involuntary motor activity occurring when there is loss of awareness and can help to lateralise the hemisphere of seizure onset

clinically (Loddenkemper and Kotagal, 2005). Automatisms in TLE are typically less violent than in frontal lobe seizures, and are usually oro-alimentary (e.g. lip-smacking, chewing, swallowing) or manual (e.g. fumbling, fidgeting, repetitive motor actions, undressing, walking, and sexually-directed actions). They can sometimes be prolonged or semi-purposeful, e.g. rearranging items on a desk. Limb automatisms are usually implicate the ipsilateral hemisphere whilst dystonic posturing is seen in the limb contralateral to the hemisphere of seizure onset. Vocalisation of identifiable words suggests a non-dominant seizure focus.

Post-ictal confusion and headache are common and if dysphasia is present after the seizure, this is a useful lateralising sign indicating seizure origin in the dominant temporal lobe. Post-ictal nose-rubbing is seen in 90% of cases and is usually ipsilateral to the focus in 90% (Geyer et al., 1999). Secondary generalisation may occur but less frequently than in extra-temporal epilepsy. Versive head turning just prior to secondary generalisation is a good indicator of ictal onset contralateral to the direction of head turning. Some patients suffer from prolonged post ictal amnesia and may have psychiatric or behavioural disturbances.

1.4.4 EEG findings in MTLE

1.4.4.1 Inter-ictal

From the point of identifying the epileptogenic zone the inter-ictal recording may provide vital clues. Prolonged or consistent epileptiform discharges, exclusively unilaterally are highly predictive of seizure onset in that region (Holmes et al., 2000; Lee et al., 2000). In MTLE, there may be anterior or mid temporal spikes or there may be persistent slow activity over the temporal lobes.

1.4.4.2 Ictal

The most common EEG changes associated with auras is a run of fast activity progressively increasing in amplitude and slowing in frequency, followed by slow or spike-wave activity. Often auras occur with no scalp EEG changes (Devinsky et al., 1989). Complex partial and secondarily generalised seizures are usually accompanied by lateralised rhythmic discharges that are evolving over time in frequency, amplitude and location. Rhythmic theta (7Hz) are the most common finding of seizures arising from the MTL (Risinger et al., 1989) but rhythmic alpha (8-12Hz) , delta(1-3 Hz), repetitive spike discharges, fast activity, generalised or focal attenuation (<10 μV), bilateral synchronous spikes and localised spike-wave complexes are other changes seen in the ictal EEG recording (Holmes, 2006). Postictally, the EEG may exhibit focal or generalised slow activity or return rapidly to normal.

1.4.4.3 Intra-cranial EEG and High Frequency Oscillations

Intra cranial EEG is less subject to artifactual distortion compared to scalp recordings. A variety of ictal patterns have been shown including voltage attenuation, rhythmic potentials at faster frequencies (>12 Hz), repetitive spike or multispike complexes (Holmes, 2006). The timing of the first electrographic seizure and clinical manifestation has important implications. Should a clinical seizure preceed EEG findings, it may suggest seizure onset is not at the site of the electrodes.

Transient waveforms with spectral content at frequencies above 80 Hz, generally referred to as high frequency oscillations (HFOs), are observable in human intracranial EEG recordings (Bragin et al., 2010; Chatillon et al., 2013) . HFO activity has been shown to be increased in the primary ictal onset zone (Worrell et al., 2008). It is a better predictor of surgical outcomes compared to the clinically identified ictal

onset zone (Jacobs et al., 2010), and is associated with seizure freedom when resected (Wu et al., 2010). These frequencies have been widely studied for research purposes and promisingly, recent advances have seen clinical systems developed for the visualisation of HFOs in clinical practise (Kondylis et al., 2014).

Chapter 2: EPILEPSY SURGERY

….Hippocrates, speaking generally, says, where medicine fails, steel may cure, where steel fails, fire may cure; where fire fails, the disease is incurable (Schmidt and Meencke, 2008).

2.1 Introduction

An estimated one third of patients with epilepsy remain refractory to anti epileptic drug treatment (Laxer et al., 2014). In a recent study, eight percent of patients with refractory epilepsy remained seizure free for at least one year with optimisation of anti-epileptic medication (Neligan et al., 2012). This benefit has previously been shown to be specific to epilepsy syndromes with the greatest benefit being described in idiopathic generalised epilepsies (Luciano and Shorvon, 2007). In patients with temporal lobe epilepsy, anterior temporal lobe resection (ATLR) has been shown to bring remission in up to 50 % of patients with refractory temporal lobe epilepsy (de Tisi et al., 2011), a much higher probability than drug changes alone. In clinical practise, all patients with focal epilepsy who fail a trial of two or more anti –epileptic drugs at therapeutic doses should be investigated for the possibility of epilepsy surgery.

2.2 History

2.2.1 Functional Localisation

It was in the late nineteenth century that epilepsy surgery as we know it came into practice. Informed by cortical mapping studies in monkeys, Sir Victor Horsley and Hughlings Jackson first postulated cortical irritability as a cause for focal seizures in humans (Horsley and Schafer, 1886), (Figure 2.1). The first successful invivo cortical

mapping led to successful cortical resection of a tuberculoma in a boy with Jacksonian epilepsy.

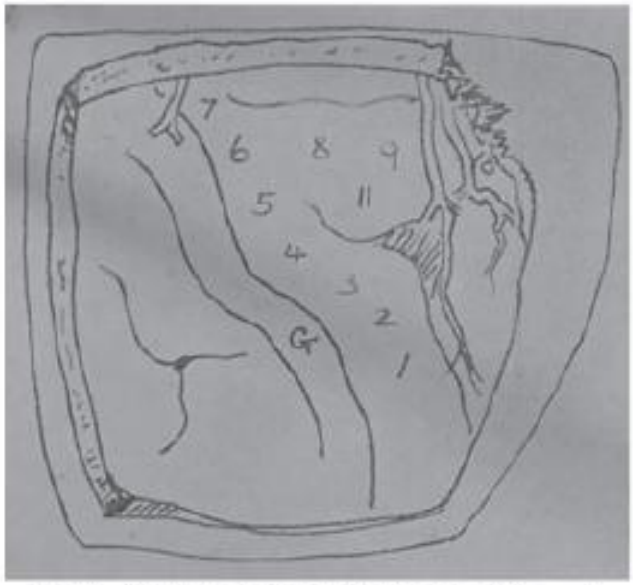


Fig. 4.—Sketch of operation field in case of Hn., made immediately after operation, showing cut edge of bone. Fissure of Rolando or central fissure passes in front of G. The sulcus pre-centralis inferior is shaded. The numbers indicate the points stimulated. (See text.)

Fig. 11.—Outline of the gyrus pre-centralis removed. Abd., abduction; ret., retraction; e.e., elbow extend; w.e., wrist extend; w.f., wrist flexed; ul. ad., ulnar adduction; f.f., fingers flex.

Fig 2.1: Victor Horsley's sketches of stimulation points on the motor cortex at operation (left) and from the excised specimen of cortex (right).

Fedor Krause, studied 96 patients with Jacksonian epilepsy extensively (Krause F, 1912) (Figure 2.2). He created galeal flaps to relieve increased CSF pressure, which was thought to cause epilepsy. Although this surgical technique failed to improve outcome, Krause's utilization of faradic stimulation during surgery not only confirmed Horsley's discrete functional localization theory but also provided the first detailed mapping of motor cortex (Horsley, 1909). Krause first recognised the area around the right arm cortex as a speech generation area. Harvey Cushing provided similar mapping data for sensory cortex in 1909.

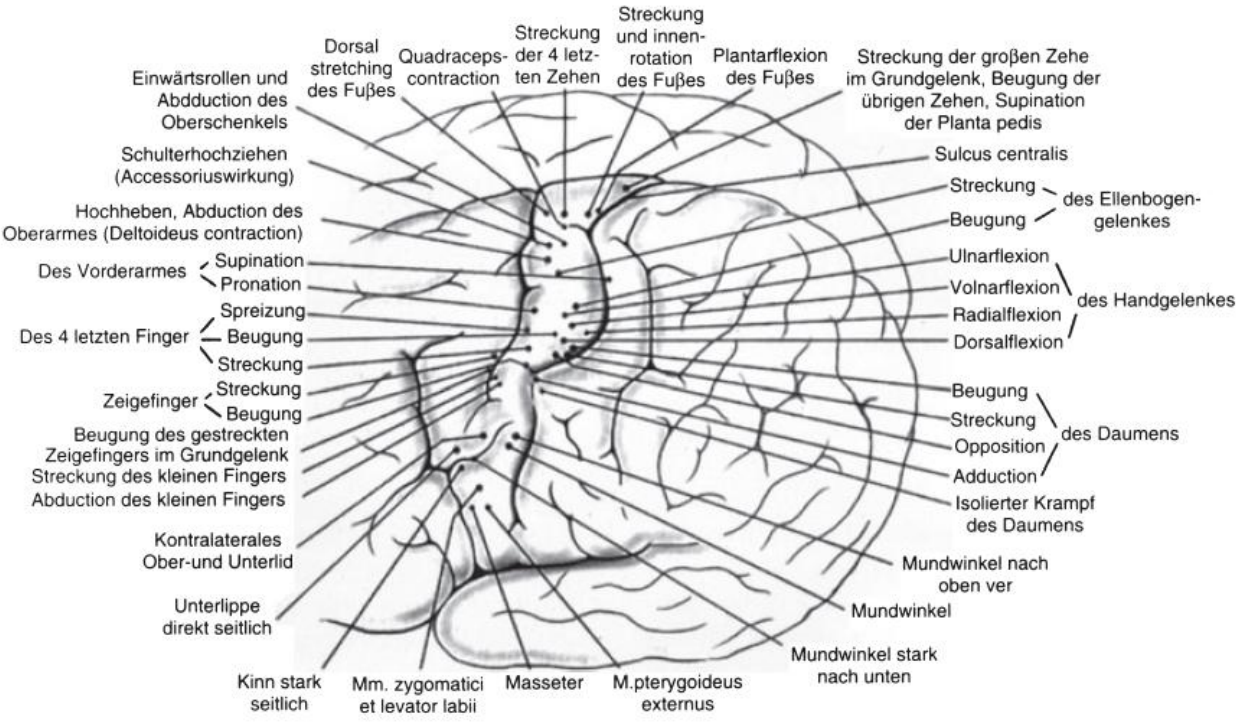


Fig 2.2 Motor map from electrical stimulation. Krause 1912.

Otfrid Foefster, a German neurologist who retrained as a neurosurgeon, developed techniques to better localise seizure onset in patients under local anaesthetic using stimulation, traction on the epileptogenic scar and intra-operative hyperventilation as techniques to elicit a habitual attack (Feindel et al, 2010).

Two decades later, Wilder Penfield, considered the most influential neurosurgeon in the advancement of epilepsy surgery performed surgical techniques of cortical mapping under local anaesthetic (Foerster 1930) and described the homunculus (Penfield et al, 1937), and mapped other eloquent areas of cortex that subserve speech, hearing, vision and memory (Feindel, 1977). The first anterior temporal lobe resection was performed by Penfield in 1928 in a patient with refractory post traumatic epilepsy but seizure freedom was only seen after the third operation in this patient when an area of scarred cortex was removed from the temporal lobe. A

decade later, electroencephalography (EEG) was used as a clinical tool for ictal onset localisation which led to the close collaboration between Penfield and the neurophysiologist Jasper at the Montreal Neurological Institute. Jasper performed pre and intraoperative EEG on Penfield's patients and if patients did not have a lesion at the site indicated by EEG, resective surgery was not performed.

It was not until 1952 when Penfield with Maitland Baldwin published a report favouring mesial over anterolateral subtotal temporal lobectomy when Penfield wrote, 'the abnormal, sclerotic area of cortex, which must be removed in most cases, lies in the deepest, most inferior and mesial portion of the temporal lobe' (Penfield 1952). In 1991, a relatively large follow up study confirmed the role of standard subtotal lobectomy with minimal hippocampal resection for temporal lobe epilepsy (Feindel and Rasmussen, 1991). In this review, patients who had amygdala resection with minimal hippocampal resection had the same seizure outcome as patients who had half or more of the hippocampus resected. Refinements of this procedure led to anterior temporal lobe resection as is performed to date.

2.3 Temporal lobe surgeries

2.3.1 Standard anterior temporal lobe resection

This technique was pioneered by Penfield in 1952 and was termed the 'Montreal Procedure'. The standard anterior temporal lobe resection involves resection of the anterolateral neocortex, entering the temporal horn deep to the temporal gyri. The ventricle forms the roof of the hippocampus which is visible once the ventricle is entered. The anterior hippocampus is then resected, at the junction of the body and the tail of the hippocampus. Alternatively, a subtemporal approach is used where the basal temporal lobe is exposed and the ventricle is entered inferiorly. The important

anatomical landmarks for removal of the hippocampus are the temporal horn of the lateral ventricle, the choroidal fissure and the medial structures including the internal carotid artery, brainstem and oculomotor nerve. Neocortical resection extends from the temporal pole along the superior temporal gyrus to the level of the central sulcus and precentral sulcus in non-dominant and dominant resections respectively. The anterior parahippocampal gyrus, the uncus and 4/5 of the amygdala is also removed (Ojemann and Park, 2004), (Figure 2.3).

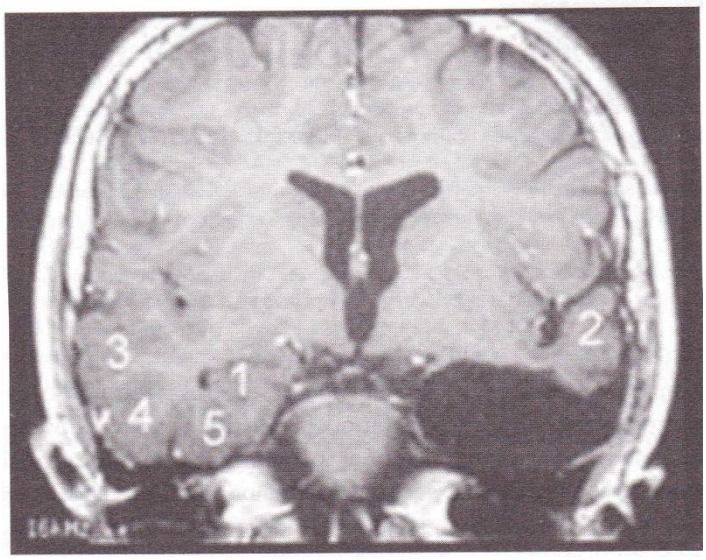


Fig 2.3: Post-operative coronal T1 weighted MRI following standard anterior temporal lobe resection. The hippocampus has been resected (labelled 1 on the contralateral side). The superior temporal gyrus is spared (labelled 2). Resected structures (shown on the contralateral side) include the middle temporal gyrus (3), inferior temporal gyrus (4) and fusiform gyrus (5)(Ojemann and Park, 2004).

2.3.2 Other temporal lobe surgeries

In patients without an identifiable lesion on MRI scanning, intracranial EEG electrodes are implanted and a period of EEG monitoring is observed in an attempt to capture a habitual seizure. Using this technique, the extent of resection can also be investigated by direct brain mapping through grid stimulation. If an epileptogenic

zone is identified, the craniotomy is re-opened and the lesion is resected or a standard anterior temporal lobe resection is performed as appropriate. Risks of this procedure include infection, bleeding and infarction including venous infarction. In non-lesional patients who have concordant anterior temporal hypometabolism on FDG-PET scanning with ictal EEG findings, particularly in the non-dominant hemisphere, intracranial EEG may not be necessary.

Other techniques used include selective amygdalohippocampectomy (SAH) where most of the lateral neocortex is spared and more directed lesionectomies. SAH s may be preferred in some centres when the pathology is limited to the medial temporal lobe. Lesionectomies may be indicated for pathologies such as cortical dysplasia, low grade dysembryoplatic neuroepithelial tumour, areas of cortical infarction, areas of injury and vascular malformations (Frater et al 2000). Intracranial EEG and mapping are often used to delineate the extent of resection to ensure adequate resection with preservation of eloquent cortex in such cases.

2.4 The pre-surgical process

2.4.1 Clinical semiology and video telemetry

The aim of presurgical testing is to identify a concordant epileptogenic zone and estimate the risks involved should surgery be deemed appropriate. The first component is the clinical history. The semiology of the seizure may aid lateralisation and localisation. Physical examination and other intercurrent illness that may preclude surgery are explored. Next, localising patterns of the inter-ictal EEG such as focal slowing or spike wave discharges may infer the lateralisation and localisation of the EEG abnormalities. Video-EEG telemetry is then performed to capture habitual seizures.

2.4.2 Structural Imaging

Should clinical and electrophysiological tests be concordant, MRI is preferably the first choice investigation in all patients with epilepsy except those patients who have a definite diagnosis of idiopathic generalized epilepsy or other types of epilepsy known to have no structural abnormality (Duncan, 1997). The indications in patients with epilepsy include the onset of focal seizures at any age, onset of generalized or unclassified seizures in the first year of life or adulthood, evidence of a fixed neurological or neuropsychological deficit, difficulty in obtaining seizure control with antiepileptic drugs and loss of seizure control or a change in seizure pattern (Duncan, 2010).

The most common abnormalities detected on MRI in patients with epilepsy include: HS, malformations of cortical development, vascular malformations, tumours (DNET and glioma), cavernomas, granulomas especially cysticercosis, traumatic injuries, haemorrhages and ischemic damage. MRI at 3 Tesla is the gold standard for epilepsy imaging, with higher rates of detection of more subtle pathology such as focal cortical dysplasia (Strandberg et al., 2008) than conventional 1.5 Tesla MRI. MR quantification techniques such as voxel based morphometry have been performed on structural MR scans to increase the yield of identifying more subtle structural pathology (Focke et al., 2008; Salmenpera et al., 2007).

Diffusion tensor imaging allows the mapping of white matter tracts by imaging the diffusion of water molecules. In epilepsy surgery, mapping of the optic radiation and pyramidal tracts are frequently performed to aid resection and spare eloquent function. Diffusion tensor imaging has shown diffusion abnormalities in 50% of patients with refractory focal epilepsy which were concordant with epileptiform

abnormalities on EEG (Guye et al., 2007). The diffusivity of water increases in the sclerotic hippocampus, so in TLE patients who are surgical candidates, the apparent diffusion coefficient measurements might provide a useful post-operative prognostic indicator (Goncalves Pereira et al., 2006). In patients with an apparently normal conventional MRI diffusion abnormalities have been shown in hippocampus ipsilateral to seizure onset (Wehner et al., 2007).

Further discussion of structural abnormalities seen in TLE patients is detailed in section 2.5 below.

2.4.3 Functional Imaging

Functional imaging is performed to investigate the epileptogenic zone in patients in whom a structural lesion is not identified despite optimal imaging or if an MRI lesion is discordant with clinical and EEG data.

2.4.3.1 Positron emission tomography (PET)

Positron emission tomography (PET) utilizes positron emitting radionucleotide such as 18F-fluoro deoxy-glucose (FDG) in combination with X-ray,CT-scan or MRI. It is usually obtained in the inter-ictal state and hypometabolism is seen in areas of cerebral dysfunction during interictal periods in patients with focal seizures. It has been shown that PET can identify focal areas of hypometabolism in up to 80% of patients with inter ictal discharges on EEG (Theodore, 1989) and this area is often more extensive that the area of structural pathology (Duncan, 2010)

PET imaging has been shown to influence clinical decision making in 53% of patients without or with discordant abnormalities on structural imaging (Rathore et al., 2014). In such cases, re-review of structural imaging in the light of PET findings

may reveal a subtle lesion in the area of hypometabolism. The area of hypometabolism can also serve as a guide for the placement of intracranial electrodes to identify seizure focus during presurgical evaluation (Duncan, 2010). Ipsilateral hypometabolism on FDG PET scans has also been shown to be a predictor of good post-operative outcome (Van Bogaert et al., 2000).

2.4.3.2 Ictal single photon emission computed tomography (Ictal SPECT)

Ictal SPECT measures regional cerebral blood flow and is used on the basis that there is increased neuronal activity and thus blood flow during seizures. Although both interictal and ictal SPECT have been used in localisation and lateralization of seizure activity, higher sensitivity has been shown with the latter (73-97% vs 50%) in temporal lobe epilepsy (Spanaki et al., 1999). Technetium hexa-methyl-propylene-amine-oxime (99mTc-HMPAO) and technetium ethyl cysteinate dimer (99mTc-ECD) are preferred radio tracers used as peak activity is reached within 2 minutes of injection. Using digital analysis techniques, ictal and inter-ictal scans can be subtracted, SISCOM. SISCOM has been used in predicting postsurgical outcome with better prognosis when SISCOM findings lie within the margins of the resected area (Ahnlide et al., 2007; Wichert-Ana et al., 2008a; Wichert-Ana et al., 2008b).

Similar to PET scanning, ictal SPECT is used when no concordant structural abnormality is visible on MRI scan. If the area of hyperperfusion on ictal SPECT is concordant with electroclinical information with little risk to eloquent cortex, resection can be recommended without confirmation with invasive intracranial EEG recordings. In more complicated patients, the findings of ictal SPECT can be used as a guide for the placement of intracranial electrodes during presurgical assessment (Van Paesschen et al., 2007).

2.4.3.3 Magnetoencephalography (MEG)

In patients with frequent inter-ictal spikes, magnetoencephalography (MEG) may be helpful in seizure localisation (Knake et al., 2006). MEG scans require $4cm^2$ for a visually appreciable spike to be seen and is more sensitive that scalp EEG in the detection of inter-ictal spikes from the orbitofrontal cortex, interhemispheric region and neocortex but not the medial temporal lobes (Agirre-Arrizubieta et al., 2009) where scalp EEGs remain more sensitive. As such, both modalities are complimentary to one another.

2.4.3.4 Functional Magnetic Resonance Imaging (fMRI)

FMRI was developed in the 1990s and relies on the blood oxygen level dependent (BOLD) changes associated with physiological and pathological processes in the brain (Ogawa et al., 1990a; Ogawa et al., 1990b). Over the last three decades fMRI has been used to describe networks including those involved in cognitive and motor tasks and resting state networks. Invasive techniques such as intracarotid amobarbital testing (IAT) have been used to assess pre-operative language and memory. This technique involved causing temporary dysfunction of one hemisphere via the anterior cerebral circulation. fMRI as a technique for language mapping became a favoured method due to many advantages; non-invasive, greater spatial and temporal resolution than IAT, safe means of repeated testing and a means of testing a greater stimulus set. IAT may pose risks of embolism and intra-arterial injury (Bendszus et al., 2004; Haag et al., 2008). Early language studies showed concordance of language fMRI lateralisation with IAT testing in TLE patients (Binder et al., 1996; Desmond et al., 1995; Fernandez et al., 2003; Liegeois et al., 2002; Woermann et al., 2003) and fMRI is now a clinically validated tool to assess

language lateralisation in pre-operative TLE patients in some surgical centres. Language paradigms to localise in addition to lateralising language function have been described (Binder et al., 2008b) and further refinements are being developed.

Memory fMRI has been used to describe memory network disruptions seen in TLE and also to investigate this modality as a tool for predicting post surgical memory decline (Binder et al., 2010; Bonelli et al., 2010; Janszky et al., 2005; Powell et al., 2008; Richardson et al., 2004; Richardson et al., 2006). The methodological details and applications of memory fMRI are discussed in Chapter 3 and 4.

2.4.3.5 Simultaneous EEG and fMRI (EEG-fMRI)

Simultaneous EEG and fMRI (EEG–fMRI) can map the BOLD signal changes associated with interictal epileptic discharges (IED) and ictal activity. Standard EEG-fMRI takes 40 minutes to acquire and refractory TLE patients with frequent IEDs on scalp EEG will have an IED during EEG-fMRI recording. 50% of these patients will show an identifiable BOLD change (for review see- (Chaudhary et al., 2013; Gotman et al., 2004).

Electrical source imaging (ESI) on EEG–fMRI can improve temporal resolution to resolve propagation patterns (Vulliemoz et al., 2010). In some patients, localisation of the seizure focus remains difficult despite these non-invasive tests and intracranial EEG assessment is required. In patients who have intracranial EEG assessments a time of flight venogram is recommended to investigate the venous vasculature to guide the placement of grid and depth electrodes.

2.4.4 Neuropsychological and Neuropsychiatric assessments

Neuropsychological assessment is carried out as part of routine pre-surgical assessment to ascertain if cognitive deficits are concordant with other data. Neuropsychiatric evaluation is mandatory as patients with epilepsy often have co-existing psychiatric illness that may need optimisation prior to surgery and close post-surgical follow up (Foong and Flugel, 2007). Neuropsychological deficits in TLE are detailed in section 4.3.

2.5 Consequences of temporal lobe resection

The main aim of epilepsy surgery is to completely resect the epileptogenic focus with little consequence on eloquent function such as vision, language, memory, sensory and motor functions. Significant deficits in language function have been described after surgery in the dominant hemisphere. Although deterioration of both verbal and visual episodic memory has been described as a consequence of surgery, verbal memory decline after dominant anterior temporal lobe resection (ATLR) remains the most consistent finding. About a 1% risk of serious adverse effects such a stroke and death have been quoted as a consequence of ATLR.

2.5.1 Vision

During ATLR, there may be disruption to the Myers loop and in up to 10% of patients a superior temporal quadrantanopia may ensue, precluding driving in a minority of these patients (Winston et al., 2011). Recent advances in techniques such as diffusion based tractography to map the visual cortex have been used intra-operatively (I-MRI) to guide resection during surgery. In a recent study, all patients undergoing I-MRI had no visual deficits compared to 13% of patients who had

anterior temporal lobe resection without I-MRI guidance. Importantly, seizure outcome did not differ between the two groups (Winston, 2013).

As part of the presurgical evaluation process functional and structural MRI is performed either as a standard clinical test (language fMRI) or as part of a study (diffusion tensor imaging of visual tracts and memory fMRI). Prediction of language and memory deficits using language fMRI is discussed later in the thesis (section 4.5.2).

2.5.2 Language

Reorganisation of language networks pre-operatively and after ATLR (Bonelli et al., 2012) has been described and onset of dominant TLE in childhood is associated with atypical language dominance (Gaillard et al., 2007; Liegeois et al., 2004). Functions located close to pathology can relocate contralaterally, whilst more remote functions may remain in the ipsilateral hemisphere (Berl et al., 2005).

As a consequence of epilepsy surgery in the dominant hemisphere, expressive language dysfunction in particular naming decline has been described in ≤40% of patients (Davies et al., 1998). Receptive language functions involve the posterior temporal and parietal cortex that are anatomically spared during resection. As such, receptive language mapping is performed when more posterior temporal resection in a language dominant hemisphere in considered. Should resection near critical language areas be considered, awake craniotomy with intra-operative cortical stimulation can be performed (Giussani et al., 2010).

Pre operative language tasks have been used to predict both significant language (Sabsevitz et al., 2003) and memory (Binder, 2011) decline.

2.5.3 Memory

ATLR brings remission in up to 50 % of patients with refractory TLE (de Tisi et al., 2011) but significant verbal memory impairment may ensue in 30 % of temporal lobe resections in speech-dominant hemispheres, with a significant effect on daily life and work (Chelune et al., 1991; Helmstaedter and Elger, 1996; Sabsevitz et al., 2001; Saykin et al., 1989). Visual memory decline after non-dominant temporal resection has been described, albeit less consistently. Cognition in TLE is discussed in detail in chapter 4.

2. 6 Seizure outcome

The chances of a good outcome depend on the concordance of the results of the above investigations, and any discordant result markedly reduces the chances of a good outcome. In patients with TLE, a resectable lesion on MRI and fully concordant electro-clinical and neuropsychological data have a high chance of seizure freedom as described above. At the other end of the spectrum, patients with frontal lobe epilepsy, no definite pathology and poorly congruent data may have a less than 10% chance of becoming seizure-free. Factors such as seizure duration of less than 10 years, presence of a structural lesion on MRI imaging particularly hippocampal sclerosis, presence of febrile seizures and unilateral localised EEG spike wave discharges have been shown to be associated with better seizure outcome after surgery (Savitr Sastri et al.; Stefan et al., 2009; Sun et al., 2014), Factors associated with poorer outcome included a positive family history of epilepsy, younger age at onset of epilepsy and dysphoric symptoms 3 months after surgery (Kanchanatawan et al., 2014).

Two scales are commonly used to classify seizure recurrence after surgery. Engels classification has been widely used for decades (Engel et al., 1993) (Table 2.1).

Class I: Free of disabling seizures
A: Completely seizure free since surgery
B. Non disabling simple partial seizures only since surgery
C. Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
D. Generalized convulsions with AED discontinuation only
Class II: Rare disabling seizures ("almost seizure free")
A. Initially free of disabling seizures but has rare seizures now
B. Rare disabling seizures since surgery
C. More than rare disabling seizures since surgery, but rare seizures for the last 2 years
D. Nocturnal seizures only
Class III: Worthwhile improvement
A. Worthwhile seizure reduction
B. Prolonged seizure-free intervals amounting to greater than half the followed-up period, but not <2 years
Class IV: No worthwhile improvement
A. Significant seizure reduction
B. No appreciable change
C. Seizures worse

Table 2.1: Engels classification of seizure outcome

This classification was thought to be more ambiguous by some, as what may be deemed ‘disabling’ or ‘worthwhile improvement’ is subjective.

The more recent ILAE scale has six outcomes based on a more objective scale of number of seizures after surgery (Wieser et al., 2001) (Table 2.2).

Outcome	1	Completely seizure free; no auras
	2	Only auras; no other seizures
	3	One to three seizure days per year; ± auras
	4	Four seizure days per year to 50% reduction of baseline seizure days; ± auras
	5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ± auras
	6	More than 100% increase of baseline seizure days; ± auras

Table 2.2: ILAE seizure outcome classification

Reassuringly, good inter-rater reliability between the two scoring methods has been shown (Durnford et al., 2011).

Chapter 3: Magnetic Resonance Imaging

3.1 Basic MR physics

3.1.1 Nuclear magnetic resonance

The basic principle of nuclear magnetic resonance was described by Block and Purcell in 1940s. That is, *if certain nuclei are placed in a magnetic field, they are able to 'absorb' energy in a specific radiofrequency range, and signal can be recorded as a result of this energy exchange as these nuclei return to their original state*.

The technique of MRI is based on the intrinsic properties of atomic charge and spin. This spinning motion induces a local magnetic field, a magnetic moment that can be thought of as a small magnet. The combination of spin and nuclear magnetisation confers the properties on the nuclei akin to a spinning top that has tipped from the vertical position (Kuzniecky and Jackson, 2005).

The signal measured during MRI arises from atomic nuclei that contain an odd number of nuclear spins. In the human body, the strongest signal is obtained form hydrogen atoms due to its abundance. When an external magnetic field, B0 is applied the hydrogen nucleus rotates around both the direction of B0 and its own axis. The frequency of this precession around the magnetic field is characteristic of that particular nucleus and is directly proportional to the field strength. This frequency is known as the Larmor frequency, w0.

w0 = g**B0**

w0 = the precessional frequency of the magnetic dipole of the spinning nucleus in radians per second

B0 = field strength in Tesla

g = the gyro-magnetic ratio for the nucleus in question in radians per second per Tesla.

The improvement in signal to noise ratio seen in 3T compared to 1.5 T scanner is due to the doubling of precession frequency as this relationship predicts.

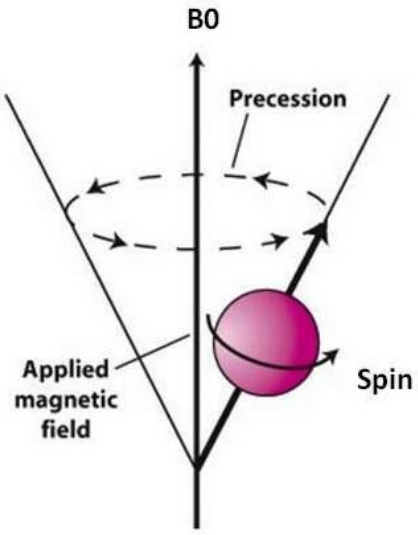


Fig 3.1: Spin and precession of a single proton.

The proton possesses the intrinsic property of spin (black arrow). In an external magnetic field, the proton precesses (black dashed arrow) around the longitudinal magnetisation vector (B0)(http://www.rise.duke.edu/apep/pages/page.html?001009).

The hydrogen nuclei align either along the direction (aligned) or opposite (anti-aligned) to the applied field. The former state is preferred and a majority of nuclei in a collection will assume this ‘low energy’ state. A small population of nuclei are anti-aligned in the ‘high energy’ state. It is this population difference that underlies the phenomenon of NMR. The sum of all the individual magnetic moments precessing around B0 yield a single bulk magnetisation vector, **M** aligned along B0. The magnetisation can be described using a coordinate system, z-axis, running in the direction of the magnetic field B0. **M** can be viewed in a frame rotating with respect

to the laboratory frame, known as the rotating frame, an x-y axis that rotates about z at the Larmor frequency.

At equilibrium **M** lies along the direction of B0. When a radiofrequency (RF) pulse B1 is applied perpendicular (transverse or x-y plane) to B0, protons are excited from the low to the high energy state. For this to occur, B1 should be the same frequency as the Larmor frequency (i.e. 128 MHz for a proton in a 3T field). This resonance has the effect of tilting **M** away from the z axis, and towards the transverse (x-y) plane. The degree to which **M** is tilted (flip angle) can be controlled by manipulating the amplitude and duration of the RF pulse. A 90^0 flip angle causes M to be rotated into the x-y plane. This oscillating magnetic field induces a voltage in a receiver coil and it is this transverse component that gives rise to the detectable MR signal. Signals cannot be detected in the longitudinal plane.

Following this perturbed state, nuclei return to their original energy state with realignment of **M** along the z axis. As a consequence of this 'relaxation' there is signal decay that is measured by the receiver coil.

There are two types of relaxation, T1 or spin-lattice relaxation characterised by the recovery in the z direction and T2 or spin-spin relaxation characterised by the decay of the magnetisation in the x-y plane. The line width of an NMR signal is determined by T2 (short *T*2 means broader lines) and maximum repetition rate during acquisition of an NMR signal is governed by T1 (short T1 means signal can be acquired faster). There is an exchange of energy during relaxation that desynchronises the rotation of the spin, reducing the coherence of the transverse magnetisation. This dephasing represents a mechanism of loss of transverse magnetisation and may occur without T1 relaxation. T2 relaxation is faster than T1 relaxation.

In the static magnetic field, nuclei have a different resonant frequency due to technical and sample factors. As a consequence, nuclei become out of phase leading to a loss of transverse magnetisation. This decay is characterised by the exponential time constant T2*, which is faster than T2. T2 * is thus affected by field inhomogeneity caused by the properties of the sample.

3.1.2 Spin and gradient echo pulse sequences

The spin echo sequence is routinely used in MRI and involves the use of both a basic excitatory 90^0 RF pulse and an additional 180^0 RF pulse. This 180^0 pulse refocuses the dephasing of nuclei due to inhomogeneities in the magnetic field . The 90^0 pulse produces transverse magnetisation along the *x* axis. This dephases due to local field inhomogeneities. At time *t (*TE/2 where TE is the echo time), a 180^0 pulse then flips the spins from the *x* axis to the *–x* axis. The spins continue to precess in the same direction and at the same speed as before the 180^0 pulse was applied, leading to rephasing of the transverse magnetisation. The spins rephase at a time *2t* to produce a spin echo signal which can be detected. The time *2t* is called the echo time TE. This pulse refocuses the transverse magnetisation producing a ‘rephased’ signal, known as ‘spin echo’.

Although the 180^0 pulse cancels out the effects of T2*, the recovered signal at the echo is less than its original height. This is due to T2-relaxation. T2-relaxation is the second contributor to magnetisation dephasing, which cannot be refocused with a spin-echo as it results from spatial and temporal variations in the intrinsic magnetic environment of each nucleus. Echoes can also be formed by using magnetic field gradients to rephase the nuclei dephased by the initial RF pulse. Rephasing leads to a signal which can be detected by the receiver coil, and this is called a gradient echo. In this type of sequence, lower flip angles can be used leading to faster

recovery of longitudinal magnetisation (T1) allowing the use of a shorter repetition time, TR (the time between consecutive 90^0 pulses). Gradient echo imaging is therefore frequently used in fast imaging sequences but is susceptible to magnetic field inhomogeneities. These inhomogeneities may be the result of either intrinsic defects in the magnet itself or of susceptibility-induced field distortions produced by tissue or haemoglobin.

3.1.3 Echo planar imaging

Echo planar imaging (EPI) is the fastest imaging sequence available and can produce tomographic images at video rates. The commonly used spin-echo sequences can take up to minutes to acquire each slice (Kuzniecky and Jackson, 2005).

The major difference between EPI and other MR imaging sequences is the way in which the data is sampled. Typical spin-echo and gradient-echo sequences sample a single line of kspace after each RF pulse whereas a fast sequence such as EPI samples all lines of k-space after a single RF excitation. Imaging times are in the order of 100ms for a 128 x 128 matrix. An initial 90^0 (gradient-echo EPI) or 90^0- 180^0 (spin-echo EPI) combination of pulses tips the magnetisation into the transverse plane. A rapid switching of a strong gradient then forms a series of gradient echoes, each with a different degree of phase encoding. This allows an entire image to be acquired in a single excitation. EPI therefore greatly reduces imaging time and makes it an ideal sequence for dynamic MRI techniques such as fMRI. The main technical problem when using EPI sequences, especially within the temporal lobes, is that of susceptibility artefact. In the absence of an applied gradient, there would be a homogenous magnetic field within the bore of the MRI scanner. Field inhomogeneities are introduced due to the different magnetic properties of bone,

tissue and air. Brain regions closest to borders between sinuses and brain or bone and brain are most affected and therefore especially likely to suffer geometric distortions or signal loss (Jezzard and Clare, 1999). Geometric distortions of the EPI data make it difficult to directly overlay fMRI activations directly on coregistered high-resolution scans. They can be unwarped using techniques including mapping of the local field B0 (Jezzard and Balaban, 1995), but this can introduce extra noise into the corrected EPI data (Hutton et al., 2002).

EPI data may also be subject to signal loss or drop out, and thus sensitivity loss which is irrecoverable by image processing techniques. Some of these artefacts can be corrected by shimming, a process whereby the static magnetic field is made more homogenous over the region of interest (Jezzard and Clare, 1999). Other approaches to removing dropout often involve acquiring extra images, leading to a loss of temporal resolution (Deichmann et al., 2002).

3.1.4 Image contrast

The contrast in an image is based on differences in signal intensity. The objective of imaging is to accurately distinguish structures in an image with accuracy. The contrast of an image is dependent on ‘extrinsic’ and ‘intrinsic’ factors. The magnetic field strength is an example of extrinsic contrast factors. Intrinsic factors include differences in signal intensity generated by particular tissues, including the T1 and T2 relaxation times, and the proton density (PD) of the tissue. The composition of tissue affects T1 and T2 relaxation times, with protons in water having longer T1s than those in fat. A T1-weighted image is one where the difference in signal intensity between tissues, is due to their differences in T1 relaxation times.

The relative contribution of T1, T2 and PD, of the image, may be manipulated by controlling the parameters of the spin echo pulse sequence, in particular the echo time, TE and the repetition time, TR. Different combinations of TR and TE will produce different degrees of contrast between tissues. Changing the TR changes the contrast between tissues with different T1 relaxation times while changing TE will change the contrast between tissues with different T2s. A short TE and a short TR produces images which are T1-weighted, a long TE and a long TR produces images which are T2-weighted, and a short TE and long TR gives PD weighting.

3.1.5 Image Formation

Creating an image requires the use of additional magnetic fields (gradient fields) to spatially encode the protons and employs the fact that the resonance frequency (or Larmor frequency) of protons is directly proportional to the magnetic field as discussed above. A gradient field varies the magnetic field across the object and the Larmor frequencies of the protons will therefore be determined by their location along the gradient. The combination of the RF pulse and gradient fields, applied at very specific times, is used to obtain slice selection (SS), frequency encoding (FE) and phase encoding (PE) as desired (Figure 3.2). The application of an RF pulse of the appropriate frequency and bandwidth in the presence of a slice select gradient excites a small slice of the sample, allowing the sample to be studied slice by slice.

1.

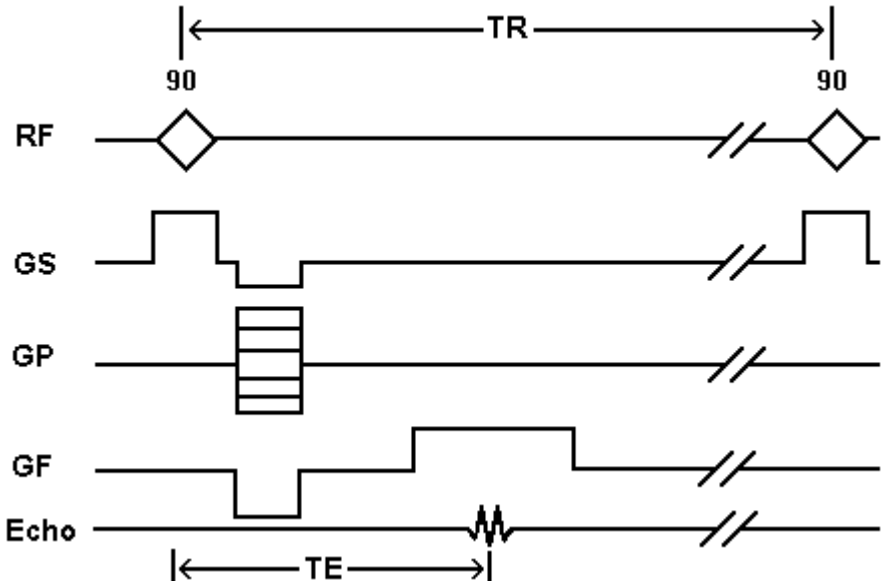


Fig 3.2: Pulse sequence diagram from a gradient echo sequence (http://www.mritutor.org/mritutor/gre.htm)

The repetition time (TR) is the interval between two successive pulse cycles in milliseconds (ms) and the echo time (TE) is the time taken from the application of the RF pulse to the measurement of the MR signal in ms. A combination of three gradient fields; slice selection (GS), frequency encoding (GF) and phase encoding (GP), are used to spatially encode the protons.

Raw MR data lies in a matrix called k-space. Fourier transformation is applied to this matrix to produce an image. This mathematical manipulation converts signal from the time domain into the frequency domain. All points in k-space contain data from all locations in an MR image. Points near the centre of k-space have low spatial frequencies and convey the overall form of the image. Points at the periphery of k-space have high spatial frequencies and convey the fine edge detail of the image. The representations of image resolution and field of view are inversely related for physical image space, compared to k-space. Sampling a larger area of k-space leads to increased spatial resolution in the image, whereas decreasing the distance

between points of k-space increases the image field of view. After Fourier Transformation, the image is represented by a grid of small cubes called voxels. Within each voxel, the protons experience the same frequency and phase encoding and the signal from a voxel is the sum of all the protons within it. The resolution of an image depends on the size of the voxels, which is determined by the step size of the gradients. To get a typical 128 x 128 matrix, frequency encoding is done at 128 points for each phase encoding step, and a total of 128 phase encoding steps are carried out. This produces 128 lines of data, each one of 128 points. Reducing the number of steps leads to an increased voxel size. Larger voxels have greater signal to noise with greater partial volume effect. Signal to noise is proportional to voxel volume to the square root of the number of phase encoding steps.

3.2 fMRI and the BOLD contrast

As described briefly section 2.4.3.2 this technique relies on the fact that cerebral blood flow and neuronal activation are coupled. When an area of the brain is in use, blood flow to that region increases. fMRI is performed using T2*-weighted EPI and makes use of the differing magnetic properties of oxygenated and deoxygenated haemoglobin. Deoxyhaemoglobin is a paramagnetic molecule and causes local field inhomogeneity, increasing the effects of T2* and thus shortening the decay in transverse magnetization. Conversely oxyhaemoglobin is diamagnetic and has little effect on MR images. On heavily T2*-weighted sequences, changing the ratio of oxy- to deoxyhaemoglobin produced detectable contrast changes in blood vessels and in their surrounding tissues (Ogawa et al., 1990a), termed the blood oxygenation level-dependent (BOLD) effect. The BOLD effect mainly represents synaptic activity (local

field potentials) where there is increased glucose and oxygen utilisation (Logothetis, 2003).

Several important factors have to be accounted for in fMRI statistical analysis. There is an initial decrease in oxygen concentration, followed by the compensatory increase in local blood flow and oxygenation in the local capillaries and draining veins (Villringer and Dirnagl, 1995). Thus, in the neurovascular response the BOLD response takes a number of seconds to evolve and this time lag must be accounted for in the statistical analysis of fMRI time series. Blood occupies only a small fraction of grey matter so the corresponding BOLD signal changes are of the order of a few percent. These small signal changes require the implementation of sophisticated image processing and analysis techniques to ensure that observations reflect true BOLD signal and not noise.

3.3 Statistical analysis of fMRI data

FMRI analysis begins with a series of pre processing steps that aim to first correct for motion and ‘transform’ images to conform with standard accepted anatomical space. Then, these images are used in a statistical model to draw inferences about differences in regional brain activity between different conditions or states. A number of different packages exist for carrying out these steps including statistical parametric mapping (SPM)(Friston, 1995).

3.3.1 Spatial preprocessing

3.3.1.1 Realignment

A typical fMRI data series consists of a number of 3D whole brain volumes, with one volume for each time point. Even small head motion can give rise to major artefacts therefore the first preprocessing step involves realigning the imaging time series to a common reference frame (generally the first slice) to correct head movement during scanning. The t-test that is used by SPM is based on the signal change relative to the residual variance. This signal is computed from the sum of squared differences between the data and the linear model to which it is fitted. Movement artefacts will add up to the residual variance and therefore reduce sensitivity.

3.3.1.2 Normalisation

After realignment the data is transformed into standard anatomical space allowing inferences to be made about group analyses and permits data reporting within a standardized reference co-ordinate system. The functional mean realigned image produced during the realignment step above is warped directly to the SPM EPI template that is in standard anatomical space(Talairach and Tournoux, 1988). The resulting transformation parameters are then applied to every image in the time course.

3.3.1.3 Smoothing

Spatial smoothing is primarily carried out to increase signal to noise ratio and to meet the assumptions of Gaussian field theory. Data points are averaged with their neighbours in a series, such as a time series, or image. This has the effect of reducing the variation in high frequency data, ‘blurring the sharp edges’. Smoothing in SPM is carried out by applying a Gaussian kernel of known width to each voxel. It is usual to describe the width of the Gaussian with another related measure, the Full

Width at Half Maximum (FWHM). The FWHM is the width of the kernel, at half of the maximum of the height of the Gaussian. Smoothing also allows averaging across subjects.

3.3.2 The general linear model

The experimentally induced changes at each voxel can be tested independently and simultaneously using the univariate General Linear Model (Figure 3.3). The null hypothesis is that there is no effect at each voxel, generating a t-statistic for each voxel. A Z-score equivalent is then computed before an image of t-statistics is generated. This is called a statistical parametric map. Finally, an inference is drawn from this SPM, reliably locating voxels where an effect is present limiting the possibility of false positives. SPM uses much of the same underlying mathematics as other statistics packages and commonly used statistical tests such as linear regression, t-tests and analysis of variance (ANOVA). This model explains variation in the response variable (i.e. the measured data for a given voxel) Y, in terms of a combination of the explanatory variables (or regressors) x;

$$Y_j = x_{j1}\beta_1 + \ldots + x_{jl}\beta_l + \ldots + x_{jL}\beta_L + \varepsilon_j$$

where β are unknown parameters, corresponding to each of the explanatory variables for Y, and ε are the residual errors.

This model can be expressed as a matrix;

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$$

Where **Y** is the data matrix, **X** is the design matrix which has one row per scan, and one column per model parameter and **ε** is the error matrix. **β** is the matrix of parameters that need to be estimated that best fit the data and this is done by least squares.

The design matrix **X** is displayed graphically by SPM and consists of a number of columns, each one corresponding to a regressor of the experiment (Figure 3.3). The relative contribution of each of these columns to the experimental variance (i.e. the parameter estimate for each column) is assessed by using least squares of the residuals. We can test the null hypothesis that there is no relationship between our experimental model and the voxel data by calculating t-statistics for specific linear combinations or 'contrasts' of parameter estimates, by dividing the contrast of parameter estimates by the standard error of that contrast. The standard error can be worked out using the remaining error, matrix **ε** above and is the variance of the residuals about the least squares fit. fMRI time series are filtered to remove any low-frequency noise due, for example to scanner drift. The regressors are convolved with the haemodynamic response function (HRF) of the BOLD effect in order to account for the lag of the response described above. The general linear model imposes a temporal smoothing function on the time-series as data from one scan to the next are correlated.

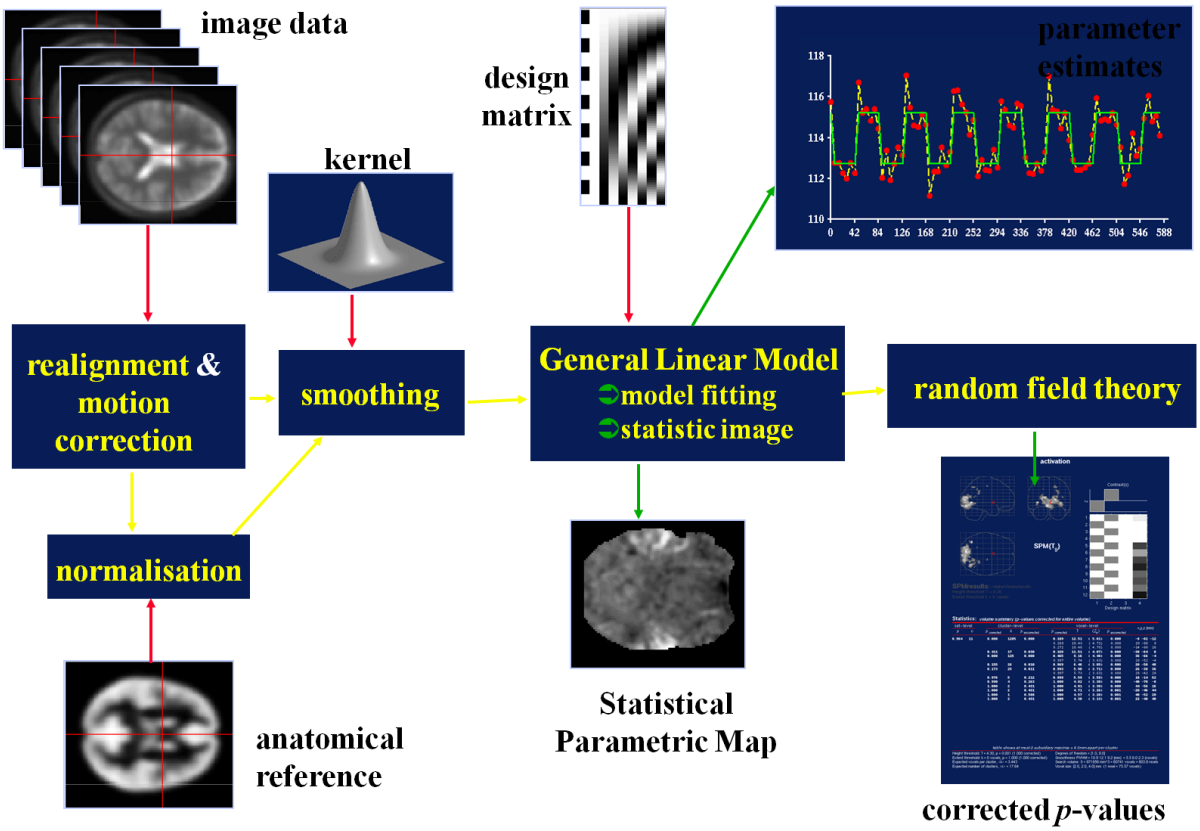


Fig 3.3: Schematic of fMRI statistical analysis

Schematic of steps involved in fMRI statistical analysis. Pre processing steps include realignment, normalisation and smoothing. The resultant images are then entered into a general linear model.

3.3.3 Thresholding and random field theory

The null hypothesis for a particular statistical comparison will be that there is no change in any voxel anywhere in the brain. Each SPM map computes a statistic for each voxel therefore there are bound to be some false positives at standard statistical thresholds of $p<0.05$ or $p<0.01$. This is the problem of multiple comparisons and a correction is required for the number of statistical tests

performed. One solution is the application of the Bonferroni correction, which is a conservative threshold where the p value threshold is divided by the number of tests performed. In most cases however this will be considerably too conservative. For most SPMs, the Z scores at each voxel are highly correlated with their neighbours. The correction used by SPM is based on Gaussian field theory. Neighbouring voxels are not independent and the process of spatial smoothing using FWHM kernel described above yields units called resels. Resels are the number of spatial elements in and are used to correct for multiple corrections in SPM. This correction is similar to a Bonferroni correction for multiple comparisons but less conservative provided that the data are sufficiently smooth. If an apriori region of interest has been identified, data can be appropriately corrected for this volume (small volume correction) (Brett et al., 2003).

3.3.4 fMRI experimental design

3.3.4.1 Blocked experimental design

In the blocked experimental design, multiple repetitions from a given experimental condition are strung together in a condition block which alternates between one or more condition blocks or control blocks. For example, in a comparison of activation against rest, the null hypothesis would be that there are no differences between the scans in the activation condition, and the scans in the rest condition. The advantage of blocked designs is that the scans from each block are additive therefore this is the most sensitive design (Bandettini and Cox, 2000). The disadvantages include the reduced specificity for studying different conditions such as memory.

3.3.4.2 Event-related fMRI

Event-related fMRI is defined as the detection of transient haemodynamic responses to brief stimuli or tasks. This technique, enables trial-based rather than block-based experiments to be carried out. Trial-based designs have a number of methodological advantages, in particular that the trial order can be randomised, thus avoiding some of the confounds of blocked designs, and that trials can be 'back-sorted' according to a subject's performance on a subsequent test (Josephs and Henson, 1999; Powell and Duncan, 2005). When analysing event-related data, the explanatory variables are created by convolving a set of delta functions, indicating the onset times of a particular event with a set of basis functions that model the haemodynamic responses to those events. Event-related experiments may be more vulnerable to alterations in the HRF and there may be more overlapping of the BOLD signal. This effect may be reduced by introducing 'jitter' (variable length of inter trial interval). The signal can also be convolved with the other basis functions of the HRF; temporal and dispersion derivative. The temporal derivative models the differences in the latency of the peak responses while the dispersion derivative models the differences in the duration of the peak response (Friston et al., 1998). The disadvantage of the event related design is reduced statistical power. This can be reduced by ensuring adequate trials of the experimental condition.

3.3.4.3 Group analyses

Group analyses can either be a fixed- effects or random-effects analysis. A fixed-effects analysis assumes that the variance between subjects are fixed and inference can only be drawn from the individuals studies and not of the group. By contrast, a random-effects analysis assumes that measurements are from a random sample drawn from a larger population, and therefore the variance between them is different.

This allows inference to be made about a population, which is crucial for neuroimaging studies.

One observation per subject per condition is entered into a random effects analysis (usually a contrast of parameter estimates from a 1st level analysis). Hence the effect size is compared against the between subject variability in these contrasts. This type of analysis is, therefore, not at risk of being biased by strong effects in a subset of subjects. At the second level of the random effects analysis, a single contrast image for each subject is entered into a one-sample t-test to examine effects across the whole group, testing whether the estimated effect size is significantly greater than zero across all subjects. Two-sample t-tests or an analysis of variance (ANOVA) can be used to compare two or more groups respectively. Regression analyses can be performed between a particular contrast and a covariate of interest to investigate brain areas that correlate with the variable tested.

3.4 Multivariate Pattern Analysis (MVPA)

In recent years an alternative analysis approach has emerged which exploits the intrinsically multivariate nature of fMRI data. This is motivated by the view that there may be information present in the distributed patterns of activation across voxels that is missed when looking at each voxel independently as in the mass-univariate conventional fMRI method (Haynes and Rees, 2006; Norman et al., 2006). This multivariate approach is commonly known as multi-voxel pattern analysis (MVPA), or decoding. It involves training a support vector machine (SVM) classifier to recognise the patterns of activity across voxels associated with particular stimuli (e.g. specific memories). The classifier is then applied to a previously unseen portion of the data that was not used for training. If the classifier is successful at predicting (or

decoding) which particular memory was being recalled in this test data set, this indicates that there is information about that memory represented in the brain region where the pattern of voxels was successfully identified.

3.4.1 Why classify?

In combination with high-resolution fMRI, pattern-information analysis can detect fine-grained activity-pattern information. It tests for mutual information between experimental stimuli and regional fMRI response patterns in an attempt to 'decode' brain activity and enhance our understanding of neural representations during cognitive tasks. Conventional fMRI is used to delineate eloquent areas *involved* in specific mental tasks. fMRI activation focuses on the spatial involvement of an area which necessitates steps such as smoothing. MVPA investigates the *representational* content of a region during a task.

The main differences between fMRI and MVPA are shown in Figure 3.4 below (Mur et al., 2009).

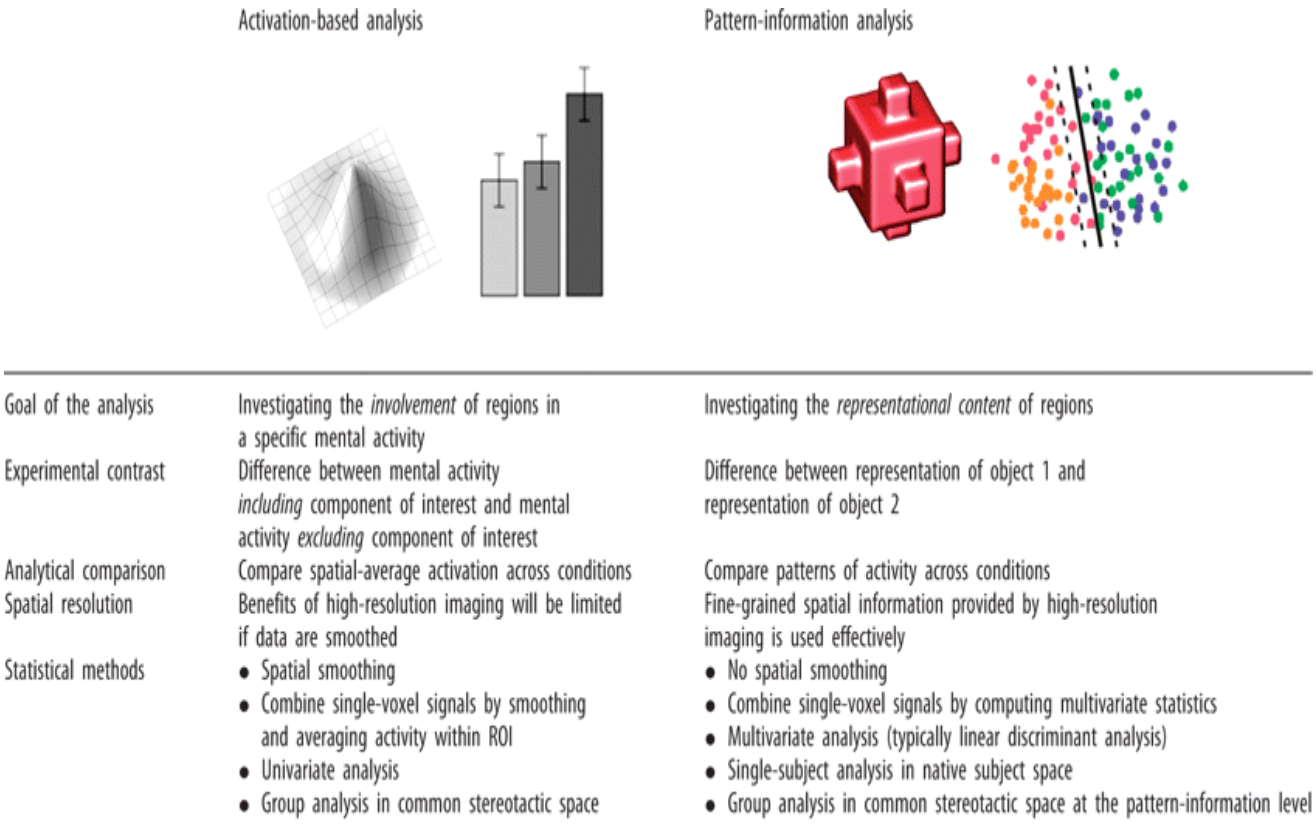


Fig 3.4:Differences between activation-based analyses (conventional fMRI) and pattern-information analysis (MVPA).

First, the GLM is a univariate analysis whilst MVPA is a multivariate voxel comparison. Second, as part of the preprocessing, voxels are not smoothed as in the univariate approach. Finally, univariate GLM analysis is performed in the standard stereotactic state whilst MVPA is performed on a single subject basis in native subject space and only group analyses are performed in the common sereotactic space.

BOLD fMRI shows neural activity related to a stimulus and can be affected by noise. Successful pattern analysis relies on a high voxel resolution during scanning. Previous literature has used pattern information studies from beta estimates (De Martino et al., 2008; Haxby et al., 2001)(De Martino et al., 2008), t-values (Kriegeskorte et al., 2008; Martinez-Ramon et al., 2006) and raw fMRI inputs as

percentage signal change (Cox and Savoy, 2003; LaConte et al., 2005). Both block design and event-related designs have been used with block designs tending to have a greater signal to noise ratio as in univariate analyses. An event related analysis however confers the benefit of a greater number of conditions. Another advantage is that they yield more independent data points than block designs that produces a better estimate of the shape of each condition's multivariate response distribution. This can improve sensitivity and classification performance.

MVPA is not restricted to areas showing activation using conventional fMRI –GLM and can be used to investigate patterns across a wide distributed network or to map regions containing the most patterns using a multivariate search light “information-based brain mapping” ((Chadwick et al., 2010; Kriegeskorte and Bandettini, 2006; Kriegeskorte et al., 2007).

3.4.2 Which Classifier

Above chance classifier accuracy suggests that patterns contain information about the stimulus category, however the sensitivity is dependent upon the classifier type. Classifiers differ in the shape that they allow for a decision boundary of classifying voxels (Mur et al., 2009). There are linear and non-linear classifiers (Figure 3.5) Linear or hyperplane classifers use a linear decision boundary to classify data. These include, minimum distance classifier, Fischers linear distance classifier, (FLDA) and linear support vector machine (lin SVM). Non-linear classifers have a more flexible boundary and include k– nearest neighbour (KNN), radial SVM and non linear Gaussian naïve Bayes (GNB). Most classifiers applied to fMRI data were developed in statistical and machine models.

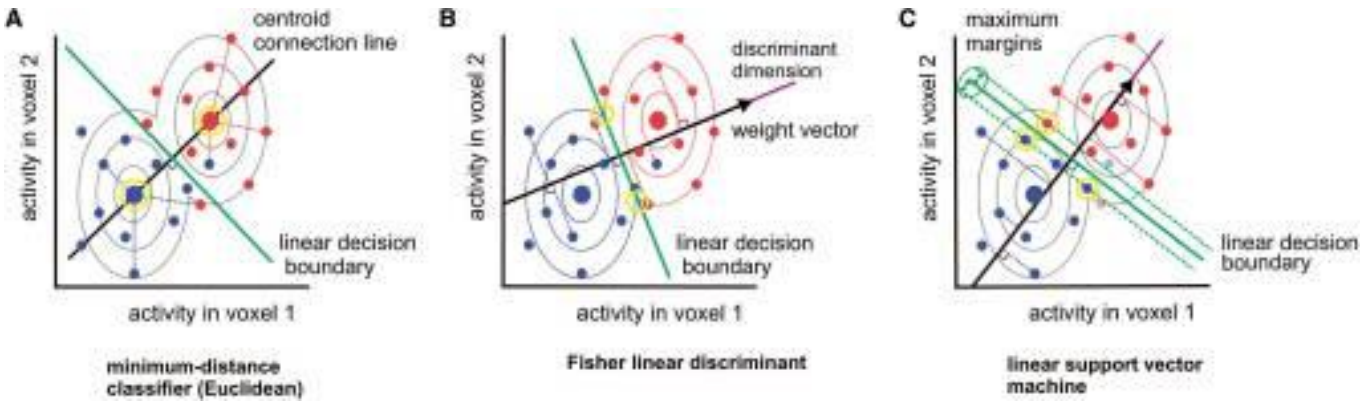


Figure 3.5: Linear/ hyperplane classfiers (Mur et al., 2009)

Performance is dependent upon the synchrony of classifiers' implicit assumption (inductive bias), the domain or application and the available data. The inductive bias needs to be suited to:

a) The neural representations investigated
b) fMRI components eg. noise
c) Dimensionality (no of voxels considered)
d) Number of training patterns available

The more flexible the decision boundary, the greater the chance of separating the stimulus categories in the training set. However, with a more flexible boundary, there is an increased risk of the boundary adapting to noise in the training dataset; a concept known as 'overfitting'. That is why statistical inference is performed on a data set independent of the training set to prevent statistical circularity.

The most rigid decision boundary, a hyperplane tends to suffer less from overfitting than non-linear classifiers. In linear classifiers however the placement of the boundary itself can cause overfitting as although rigid in shape, a hyperplane in d-dimensional space requires d-parameters to define its placement. In fMRI, overfitting

can occur even in liner classifiers as often the number of voxels in the ROI is similar to the number of training patterns.

Reducing the hypothesis space is one method of reducing overfitting. Another method is regularisation; using prior assumptions to constrain the way in which the boundary is shaped and shifted to discriminate the categories in the training set. Different classifiers utilise different implicit assumptions for this purpose. For each classifier, dimensionality reduction can increase accuracy by voxel selection. This can be done using a multivariate feature selection procedure as described above.

Previous classifier comparisons argued a better classifier accuracy using linear classifiers as detailed below:

1) Cox and Savoy 2003 (Cox and Savoy, 2003) – compares linear and polynomial SVM to classify categories of visually presented material. Block design was employed. Linear SVM proved superior to polynomial suggesting that the polynomial suffered overfitting.
2) La conte 2005 (LaConte et al., 2005) – linear SVM superior to nonlinear for decoding block-design fMRI data
3) Mitchell 2004 – compared non linear GNB (Gaussian naïve Bayes), SVM and KNN .KNN was inferior to SVM and GNB.
4) Ku 2008 – compared linear classifiers, FLDA, linear SVM to non linear GNB. All linear classifiers performed equally well over the non linear GNB which utilises quadratic decision boundaries.
5) Misaki 2010 (Misaki et al., 2010)- compared 6 classifers; 3 linear and 3 non-linear using a event related analysis. Accuracy of classifiers was greatest

using linear classifiers with the most accurate being the FLDA and linear SVM.

Linear classifiers may have been superior as data available for each subject may have been inadequate to capitalize on their ability to model a nonlinear optimal decision boundary, but Mumford et al (Mumford et al., 2011) showed that the radial SVM classified event related data better than linear SVM and GNB.

Misaki et al showed that t-values were better classified than beta estimates by the linear classifiers due to down weighting of the noisy voxels. There was also no advantage of normalisation of the t-values to classifier accuracy.

In summary, the most popular method is linear classification, which analyzes a region's activity patterns by means of a weighted sum of the single-voxel responses, with the weights chosen to maximally discriminate different conditions.

Previous studies have successfully used a linear SVM to describe a topographical hierarchy within the temporal lobe with the hippocampus containing significantly more episodic memory representation than other MTL structures (Chadwick et al., 2010). Given the above evidence we performed an MVPA experiment detailed in chapter 8 using a linear support vector machine. Methodological details are provided in this chapter.

Chapter 4: Cognition in TLE

4.1 Memory

Memory formation is a complex dynamic process that is carried out by representational systems in the brain; distinguished by the nature of the information and task presented (Nadel and Hardt, 2011).

Short and long term memory systems serve distinct roles in everyday life as first proposed by Hebb in 1949 (Hebb, 1949). Short term memory or working memory refers to the temporary storage and manipulation of information whilst long term memory allows longer term storage and retrieval of information and is associated with more permanent neurochemical changes in the brain.

Long term memory is made up of explicit (declarative) and implicit (non-declarative) memory systems (Squire, 1992). Explicit memory allows conscious recall and is sub-divided into semantic memory; the conscious recall of factual knowledge and episodic memory; recall of individual events in spatial and context order. Critical steps of episodic memory include the formation of distinct neural traces during memory encoding, memory storage and, for subsequent recollection, memory retrieval (Tulving, 1973).

Implicit memory processes utilise previous experiences to facilitate a task without conscious recall of this past experience and is sub –divided into procedural memory, perception and priming (Schacter, 1987), Figure 4.1.

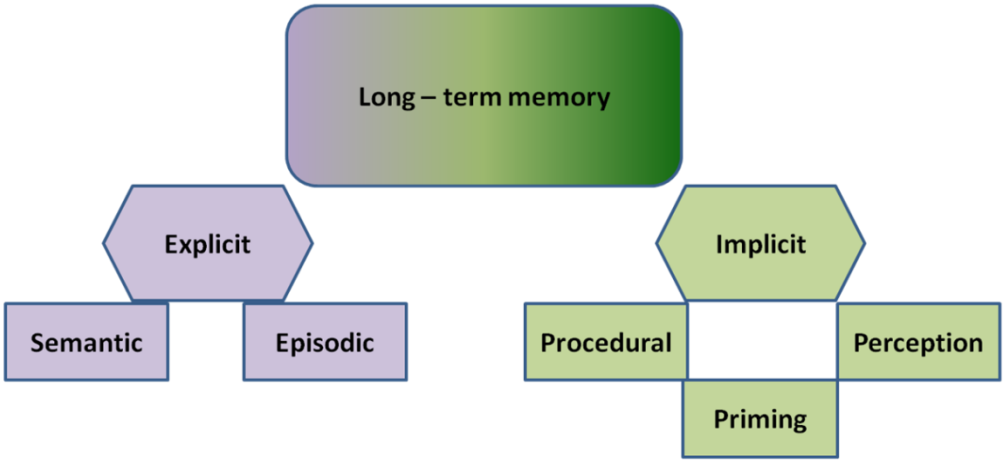


Figure 4.1: Long –term memory systems.

Recent models of working memory introduce the concept of an 'episodic buffer' (Baddeley, 2000) which proposes a multidimensional work space linking the subsystems of working memory to long term episodic memory processes in the formation of distinct neural episodic memory traces.

4.2 Neuroanatomy of the memory encoding network

The hippocampus is thought to be the main memory index for a more widespread neocortical representation of episodic memory (Marr, 1971) and is thought to be at the top of the sensory cortical hierarchy (Squire et al., 2004) supporting this widely acknowledged role.

Critical involvement of the medial temporal lobe to memory encoding was first recognised when patient HM was rendered amnesic after bilateral anterior temporal lobe resection with partial hippocampal resection to treat epilepsy (Scoville and Milner, 1957). This was in tandem with a report by Papez in 1937 who proposed a network that begins and ends in the hippocampal formation as the main network for

emotion (Papez, 1995) but was later recognised as as a mnemonic circuit. This proposed circuit included the hippocampus (subiculum), fornix, mamillary bodies, mamillothalamic tract, anterior thalamic nucleus, cingulum, entorhinal cortex and back to the hippocampal formation. In 1957, McLean modified this circuit to include the amygdala for emotion and coined the term the 'limbic system' (Newman and Harris, 2009). It was only subsequently that theta wave experiments showed the critical involvement of these regions to memory encoding (Vertes and Kocsis, 1997; Vertes et al., 2001). Advances in lesional, functional imaging and computational analyses have all corroborated the involvement of these anatomical regions to memory encoding (Simons and Spiers, 2003; Squire et al., 2004). More recently, the prefrontal cortex (PFC) has also been shown to be involved in successful memory encoding and intact fronto-temporal connections are essential for successful memory encoding and retrieval (Simons and Spiers, 2003; Squire et al., 2004).

The PFC is cytoarchitectonically and functionally heterogeneous (Petrides, 2005; Ramnani and Owen, 2004). The lateral PFC is typically involved in goal-directed cognitive processes such as memory encoding (Fletcher and Henson, 2001) which integrates critical processes such as semantic and phonologic elaborations in the inferior frontal gyrus (IFG) (Otten and Rugg, 2001), material organisation in the dorsal middle frontal gyrus (MFG) (Wig et al., 2004) with subsequent manipulation in the anterior PFC (Dumontheil et al., 2010). More extensive cortical areas can be recruited to adapt to meet task demands (Duncan and Owen, 2000). Lesional studies in the lateral PFC have been associated with memory deficits particularly with source memory (Janowsky et al., 1989), memory for temporal order (Kesner et al., 1994) and associative learning ; all of which are necessary for the formation of long term memories.

The orbitofrontal cortex (OFC) is widely connected to limbic structures including the amygdala, hippocampus, temporal pole, entorhinal, perirhinal and parahippocampal cortices (Carmichael and Price, 1995; Insausti et al., 1987; Lavenex et al., 2002) and is now thought to be critical to memory encoding along with the MTL. A lesional study of the OFC in 8 rhesus monkeys revealed impairments in recognition memory to the same degree as seen after medial temporal lesions (Meunier et al., 1997). In a PET study of a visual memory encoding paradigm, the OFC and parahippocampal gyrus were the only regions that showed more activity with increasing encoding demands (Frey and Petrides, 2002).

Functional MRI has been used to investigate short and long-term memory processes. fMRI has consistently shown MTL activation in episodic memory tasks (Cabeza and Nyberg, 2000). Some functional imaging studies have proposed a mnemonic lateralisation of MTL and prefrontal activity; left for encoding and right for retrieval, positing a framework for the hemispheric encoding/retrieval asymmetry (HERA) model (Grady et al., 1995; Tulving et al., 1994). Other fMRI studies have shown a material specific lateralisation of verbal and non-verbal encoding and retrieval to the left and right PFC and MTL respectively (Kelley et al., 1998). This implies interdependence between these two memory modes and is concordant with neuropsychological data (Elger et al., 2004; Milner, 1971) and lesion deficit studies showing a deficit in verbal and non-verbal episodic memory with left (Frisk and Milner, 1990) and right lesions (Smith and Milner, 1981) respectively.

Memorisation commonly involves semantic association strategies which aid subsequent recall (Craik, 2002). fMRI has also shown that explicit task designs where memorisation is encouraged is associated with greater subsequent memory and corresponding increase in fMRI activations compared to implicit memory tasks

that rely on incidental encoding (Frey and Petrides, 2002). Successful encoding is therefore also dependent upon the specific task process engaged during memorisation.

4.3 Cognition in Temporal lobe epilepsy

Individuals with TLE have significant material specific episodic memory impairment reflective of perturbation of the underlying temporal lobe function. Neuropsychometry has consistently shown deficits in verbal memory in left TLE patients (Hermann et al., 1997). In right TLE, although studies have shown specific deficits in visuo-spatial tasks such as the identification of famous faces (Glosser et al., 2003), delayed face recognition (Milner, 2003) and emotional facial recognition (Benuzzi et al., 2004) visual memory deficits have been shown to be less consistently lateralising for right TLE and deficits have been described in both patient groups (Alessio et al., 2004). Deficits in episodic memory with relative preservation of semantic memory has been described in TLE patients suggesting a functional segregation of consolidation of these long-term memory processes within the temporal lobe (Tramoni et al., 2011).

Within the temporal lobe itself, there exists a functional hierarchy of verbal episodic memory and different tasks employed show activation accordingly. List learning has been shown to be a task involving the lateral temporal cortex. It has been reported that patients with more proficient list learning pre-operatively have a greater decline in memory performance post-operatively. In a study by Helmstaedter, reporting cognitive outcomes post different surgical approaches, patients with hippocampal sclerosis who underwent selective amygdalohippocampectomy versus ATLR showed similar long-term decline in delayed memory. The ATLR group however

showed additional deficits in learning of new verbal learning ability reflecting the role of the lateral temporal neocortex (Helmstaedter, 2013).

Over the last decade, neuropsychological dysfunction remote to the affected medial temporal lobes has been increasingly reported in TLE patients (Helmstaedter and Kockelmann, 2006; Hermann et al., 2002). Deficits have been noted in global intellectual functioning (IQ), executive functions, language and sensorimotor skills (Oyegbile et al., 2004). Several clinical factors have been shown to influence the severity of cognitive dysfunction in TLE patients. In a study of 1156 patients with refractory TLE, patients with hippocampal sclerosis had worse verbal learning and memory scores compared to any other pathology (Helmstaedter and Elger, 2009). Patients with less severe pathology on MR scanning and larger hippocampal volumes were noted to have superior pre-operative cognitive function and suffered the greatest decline post-operatively. Conversely worse pathology and smaller volumes were associated with poorer pre-operative cognitive function and minimal cognitive decline or even improvement post-operatively (Trenerry et al., 1993). In a recent study of 382 patients with TLE, it was shown that side of pathology and gender were significant factors affecting the cognitive profile of TLE patients with female and left hippocampal sclerosis patients at greatest risk of widespread cognitive deficits (Baxendale et al., 2010).

It is difficult to postulate if cognition is affected before the onset of epilepsy in structural and metabolic (symptomatic) focal epilepsy. Oostrom et al showed cognitive and behavioural dysfunction in pre-treatment early new onset epilepsy in children compared to their peers or siblings (Oostrom et al., 2003). Aikia et al showed verbal memory deficits in new onset as well as chronic TLE patients (Aikia et al., 2001). In a separate study Roeschl-Heils described cognitive decline in all

domains including IQ in TLE patients compared to their siblings. Interestingly, there was no relationship between the discrepancy in cognitive scores and duration of epilepsy implying that this difference was present at the onset of epilepsy (Roeschl-Heils et al., 2002).

Earlier age at onset of epilepsy has been shown to interfere with brain maturation (Hermann et al., 2010) with greater intellectual deficits reported in children with an earlier age at onset of epilepsy (Cormack et al., 2007). Cognitive deficits accrued have been further characterised and it was reported that adolescents failed to build learning and memories to the same ability as age matched controls and reached a peak capacity at and earlier age than controls. The decline thereafter followed a similar trajectory of age dependent losses seen in controls however due to the inherent bias of reduced cognitive abilities, patients reached a level of very poor performance before healthy controls (Helmstaedter and Elger, 2009). The so called early ‘dementia’ seen in patients was therefore a consequence of the initial cognitive hit.

The effect of duration of epilepsy and in particular ongoing seizures has been extensively studied. A review of longitudinal adult and children studies by Dodrill on the effect of seizures on neuropsychological abilities concluded that cognitive losses over multiple domains do occur over time in patients with uncontrolled seizures (Dodrill, 2004). In particular, TLE patients with generalised tonic-clinic seizures have been noted to have impaired frontal lobe functions (Jokeit et al., 1997). There has been much debate on the effects of inter-ictal epileptiform activity on cognition. Whilst some reports describe transient cognitive impairment (Aldenkamp and Arends, 2004; Binnie, 2003), it was concluded that interictal activity had a non-

significant role on persistent cognitive deterioration in TLE (Aldenkamp and Arends, 2004).

4.4 Structural deficits in Temporal lobe epilepsy

Increased sensitivity of detection of hippocampal pathology beyond conventional MR imaging parameters, has been shown with quantitative magnetic resonance T_2 relaxometry and is employed at most surgical centres (Bartlett et al., 2007; Bernasconi et al., 2000; Jackson et al., 1993; Woermann et al., 2001).

The widespread cognitive disruption described in TLE is in concert with extra-temporal structural changes reported in these patients. The earliest description of widespread structural changes investigated in a quantitative whole brain analysis was performed by Sisodiya et al in 1997. A retrospective quantitative analysis of cortical and subcortical grey and white matter in pre-operative MRI scans in TLE patients showed ipsilateral and contralateral extra-temporal abnormalities in 13 of 14 patients who continued to have seizures post ATLR (Sisodiya et al., 1997).

4.4.1 Voxel based morphometry (VBM)

VBM is a technique that allows voxel by voxel whole brain analysis with greater spatial precision that standard MR quantification techniques. An elegant review by Keller and Roberts on VBM studies in TLE, report 26 brain regions with reduced brain volumes and concentration compared to healthy controls (Keller and Roberts, 2008). The changes noted were primarily ipsilateral reduction in grey matter (GM) within the MTL. Contralateral GM volume reduction was also noted in the hippocampus, parahippocampal gyrus, amygdala, fusiform gyrus, inferior, middle and superior temporal gyri however to a significantly less degree. No contralateral volume loss was noted in the fornix or the perirhinal cortex. Relatively bilateral

changes were noted in extra-temporal regions such as the thalamus, cingulate gyrus, insula, cerebellum, parietal cortex, dorsal frontal and orbitofrontal cortex. In patients with unilateral hippocampal sclerosis Lin et al reported up to 30% decrease in cortical thickness in the frontal poles, frontal operculum, orbitofrontal, lateral temporal and occipital regions bilaterally (Lin *et al.*, 2007). Additionally, duration of epilepsy significantly correlated with ipsilateral cortical thickness reduction in the superior frontal and parahippocampal gyri. VBM analyses have also shown increase in grey matter concentration in the ipsilateral medial temporal and lateral temporal lobe, dorsal frontal cortex, insula, cingulum and globus pallidus (Keller and Roberts, 2008). The authors discuss the possibility of other cortical malformations particularly within the temporal lobe that can mar the grey white matter interface on MR causing this apparent increase in concentration. Of note, no volume increase was noted. In contrast, a recent study contrasting VBM analysis in early vs late onset of TLE patients showed markedly increased grey matter volume in early onset patients particularly frontally within the superior and middle frontal gyri (Kaaden et al., 2011). Other areas of increased volume reported include post central gyrus, rolandic operculum and precuneus. Early onset of TLE is thought to disrupt normal brain maturation that occurs in an anterior-posterior fashion causing dysregulation of pruning processes particularly within the frontal lobes.

VBM and volumetric studies have also shown correlations of cognitive impairment with structural pathology in TLE. Bonilha et al showed that reduced verbal and general memory in left TLE patients was associated with reduced grey matter concentration in the left MTL, cingulum and OFC (Bonilha et al., 2007).

Changes were more severe in left compared to right TLE patients. Keller et al reported ipsilateral hippocampal and bilateral PFC volume atrophy in patients with

unilateral TLE that correlated with executive dysfunction in these patients (Keller et al., 2009). MR volumetric analysis of the corpus callosum in TLE patients showed that callosal atrophy correlated significantly with poorer performance across non-verbal measures such as performance IQ, immediate memory, complex psychomotor processing and speeded motor dexterity (Hermann et al., 2003). Greater volume reduction was seen in patients with an earlier onset of epilepsy compared to later onset patients and controls.

This pattern of structural changes is suggestive of disconnection involving preferentially frontolimbic pathways in patients with pharmacologically intractable TLE.

4.4.2 Diffusion Tensor Imaging (DTI)

Disruption in white matter tracts in the limbic system within the fornix and cingulum have been described in TLE using DTI (Concha et al., 2005). DTI is a magnetic resonance technique that provides information about the microstructure of white matter by assessing the Brownian motion of water in tissues. Fractional anisotropy (FA) is the primary measure of white matter integrity and is a measure of the degree of directionality of diffusion. Mean diffusivity (MD) reflects the total magnitude of diffusion in the corresponding voxel. Disrupted white matter with poor organisation has a low FA and high MD (Le Bihan et al., 2001). Widespread disruptions have been described in whole brain voxel-based DTI studies in TLE. Focke et al describe disrupted ipsilateral temporal lobe, arcuate fasciculus (AF), cingulum, thalamus, cerebellar and occipito-temporal connections in left TLE patients. Right TLE patients showed relatively less structural disruptions however showed greater contralateral temporal and inferior frontal lobe WM disruption (Focke et al., 2008). DTI studies have paralleled VBM findings of greater structural deficits in left TLE patients

compared to right (Ahmadi et al., 2009; Kemmotsu et al., 2011). Furthermore, Kemmotsu et al showed that earlier age at onset of epilepsy was a strong predictor for more disrupted fibre tract integrity in left TLE patients whilst no correlation with age at onset was seen in right TLE patients (Kemmotsu et al., 2011).

Several studies have linked cognitive deficits with structural deficits on DTI. Yogarajah et al showed reduced ipsilateral connections in parahippocampal gyrus (PHG) and reduced FA in left TLE patients only. A material specific correlation with FA was seen in left TLE where left PHG FA correlated with verbal learning and right PHG FA to design learning. No correlations were seen in right TLE patients (Yogarajah et al., 2008). Diehl et al showed bilateral changes in the uncinate fasciculus (UF) in right and left TLE patients. Again, only left TLE patients showed material specific correlations with UF dysfunctions where left UF dysfunction correlated significantly with reduced auditory delayed memory and right with delayed visual memory scores (Diehl et al., 2008). In a study of left and right TLE patients, left sided increase in MD in the UF, parahippocampal gyrus and inferior frontal-occipital fasciculus (IFOF) were associated with impaired delayed verbal memory. No correlations were seen with visual memory.

4.4.3 Multimodal imaging

Over recent years, multiple imaging modalities have been used in combination to investigate the widespread structural abnormalities in those with TLE. In a study of 9 left TLE patients, volumetric studies were combined with DTI. Ipsilateral caudate atrophy greater than controls with reduced connections from specific caudate regions to the dorsal and ventro-lateral PFC, anterior cingulate and orbitofrontal cortex were shown with corresponding reductions in executive functions (Riley et al., 2011). A novel method of combining functional connectivity analysis using a tensor

independent component analysis and DTI showed reduced functional connectivity in the OFC with corresponding fornix tract abnormalities in 9 left TLE patients (Voets et al., 2009).

A recent study combined structural T1 weighted volumes, T1 and T2 relaxometry data and DTI to determine thalamo-cortical connectivity using connectivity based segmentation (Keller et al., 2014). In addition, T1 and T2 values and volumes were calculated from each thalamo-cortical segment. Thalamic segments preferentially connected to the temporal lobes were the anterior, dorsomedial and pulvinar regions. Only in these regions were there increased T2 values, volume loss and reduced connectivity ipsilateral to the epileptogenic temporal lobe. The same group then showed that patients with TLE who continued to have seizures after epilepsy surgery had reduced thalamo-cortical connectivity and volume loss within these thalamic segments bilaterally compared to patients who were seizure free post-operatively (Keller et al., 2015).

In summary, there is a building repertoire of studies showing widespread structural disruptions correlating with the complex cognitive deficits described in patients with TLE. Left sided epilepsy and earlier age at onset are clinical variables known to be associated with greater cognitive and structural deficits in TLE.

4.5 Memory fMRI

The challenge of epilepsy surgery is to completely resect the epileptic zone without causing significant cognitive complications. This is aided by understanding the pre-operative functional anatomy of the cognitive network in TLE patients. Invasive techniques such as intracarotid amobarbital testing (IAT) have been used to assess pre-operative language and memory functions. This technique involved causing

temporary dysfunction of one hemisphere via the anterior cerebral circulation, however the hippocampus is largely perfused by the posterior circulation making this a less specific technique for memory testing. Other limitations include the limited time to perform a full neuropsychometric assessment and the lack of spatial resolution beyond lateralising to the whole hemisphere, the cost and the risk. IAT was therefore largely used to identify patients at risk of global amnesia that may be due to undetermined contralateral MTL pathology; a finding that would contraindicate surgery. This role of IAT has been much reduced by the ability of MRI to determine whether there is abnormal contra-lateral MTL structure.

4.5.1 Functional neuroanatomy of the memory encoding network in TLE

4.5.1.1 MTL activations in memory fMRI

4.5.1.1.1 Blocked Design Analyses

Early memory encoding fMRI studies utilising blocked designs investigated the concordance of asymmetry of MTL activations with intra carotid amobarbital memory lateralisation indices (Bellgowan et al., 1998; Detre et al., 1998; Golby et al., 2002) with promising results (Powell and Duncan, 2005).

These early studies utilised blocked designs of tasks known to activate the MTL bilaterally; complex scene encoding (Detre et al., 1998) and Roland's hometown walking (Jokeit et al., 2001), to show reduced ipsilesional MTL activations. Golby et al were the first to investigate activation patterns in TLE patients across different material types and to show 'functional reorganisation' to involve the contralateral MTL. They confirmed material specific activations within the MTL in controls with left sided activations during word encoding and right during visual encoding. Patients not

only showed an ipsilesional reduction in MTL activations concordant with previous studies, but also material specific reorganisation of activations to involve the contralesional MTL (Golby et al., 2002).

It therefore became apparent that material specific paradigms were relevant to fully investigate memory encoding networks in patients with unilateral TLE.

4.5.1.1.2 Event-related analyses

Event related analyses have been used to investigate the neural basis of successful memory formation. Subtraction contrasts, for example, items remembered minus items forgotten yield a more specific contrast for subsequent memory formation. Over the last decade, there have been a surge of event related material specific experiments that consistently described reorganisation of MTL activations to involve the contralateral medial temporal lobe in TLE patients. Standard neuropsychology memory parameters such as list learning and delayed recall (Coughlan AK, 2007) known to be sensitive to temporal lobe pathology (Baxendale et al., 2006) have been used in correlations with memory fMRI activations to further assess if areas of reorganisation were involved in successful memory formation, or were inefficient and represented aberrant reorganisation. Reorganisation of verbal and visual memory encoding to both the contralateral MTL (Powell et al., 2007; Richardson et al., 2003) and the ipsilateral posterior MTL (Bonelli et al., 2010) in left and right TLE patients have been described in event related subsequent memory analyses.

Richardson et al studied verbal memory encoding in a group of 24 left TLE patients with intact episodic memory gauged by standard neuropsychometry (Richardson et al., 2003). Patients were divided into two groups, one with hippocampal sclerosis (HS) only and the other also with amygdala pathology, as assessed by pathological

T2 relaxation values. The verbal paradigm used incorporated emotionally neutral and aversive words as the amygdala has been shown to be activated in encoding emotional stimuli. All subjects performed a task in which a decision of living vs non-living was made on each word via a button box. An implicit paradigm was used where memorisation was not encouraged and a 'surprise' recognition test was performed post scanning. Patients indicated if words were remembered, familiar or forgotten. Recognition accuracy for each category of remembered, familiar and forgotten were calculated as a correct judgement of each vs misses. Repeated-measures ANOVA of recognition accuracies revealed no difference between controls and patients in either remembered or familiar recognition judgements but a significant difference in 'new' reflecting better identification of "new" stimuli by normal subjects. Therefore, to best match performance between patients and controls, a contrast of remember – familiar was used. This subsequent memory contrast showed left hippocampal activations in controls. All left TLE patients showed additional right hippocampal activations. Patients with a pathological left amygdala showed reorganisation of activation from the left amygdala to the right. This patient group had larger left hippocampus than patients with left HS alone and additionally showed activation in the left HC to emotionally neutral words. This study was the first event related study to show successful memory reorganisation of verbal encoding network to involve the contralateral medial temporal lobe.

In 2007, the same group tested subsequent memory using a difference image of subsequently remembered - forgotten items (Powell et al., 2005). Additionally, fMRI activations were correlated with standard neuropsychology measures and hippocampal volumes. In this study, Powell et al studied the effect of encoding pictures, faces and words in a single scanning session in a group of 7 right and 7 left

HS patients. As in the Richardson study, an implicit encoding paradigm was employed. They contrasted activations using both the block and event related analyses within hippocampal and parahippocampal regions of interests. An identical study was performed in 10 healthy controls (Powell et al., 2005). Differences to controls were assessed in a quantitative fashion. At the group level, left HS patients showed no medial temporal lobe activations for word and picture encoding in the event related design but compared to controls, a significant right medial temporal lobe cluster was seen during word encoding implying contralateral reorganisation to the right PHG was an efficient process. These activations were correlated with out of scanner neuropsychology memory measures as a further analysis of the efficiency of reorganised networks. In both patient groups, left HC volume correlated with better verbal memory whilst right HC volume correlated with better visual memory.

In a large group of TLE patients (41 LTLE, 31RTLE) Bonelli et al (Bonelli et al., 2010) studied the patterns of memory reorganisation in a similar paradigm to Powell et al (Powell et al., 2007). Similar to the studies described above, an event related analysis in which subsequent memory is analysed was used. Interestingly only the material specific paradigm of face and word encoding showed activation differences compared to controls with reduced left sided activation during word encoding and right sided activation during face encoding, in left and right TLE patients respectively. No differences compared to controls were seen at picture encoding. The integrity of reorganised networks was assessed similarly by correlating fMRI activations with out of scanner neuropsychology measures. This showed that better verbal memory correlated with left sided activations in left TLE patients whilst right sided activations correlated with better visual memory in right TLE patients.

Fugueridо et al used abstract words and line drawings with a subsequent recognition analysis to investigate memory encoding in ten right TLE patients compared to controls (Figueiredo et al., 2008). A blocked design was used. To investigate efficiency of networks, mean signal change within medial temporal lobe regions of interest were correlated with recognition scores. They showed that activation of the left anterior and posterior hippocampus represented efficient 'adaptive' reorganisation as activation in these regions of interest correlated with better recognition memory. A caveat of the study was that there was no significant difference between patients and controls in the subsequent recognition memory scores. It is not known if these patients had impaired memory compared to controls using standard neuropsychology memory measures. Correlations with this clinical measure may have been more meaningful to investigate the integrity of reorganised memory encoding networks.

In a non-material specific picture encoding task Guedj et al showed that in patients with intact recognition memory, there was increased activations within the parahippocampal and fusiform gyri bilaterally (Guedj et al., 2011)

In summary, patients with TLE have been shown to have an altered memory network within the MTL. Over the last decade fMRI studies in TLE patients have consistently shown atypical material-specific involvement of the MTL in episodic memory encoding, with reorganisation to the contralesional side (Figueiredo et al., 2008; Golby et al., 2002; Powell et al., 2007; Richardson et al., 2003). The functional integrity of these reorganised networks has been investigated with varied results (Bonelli et al., 2010; Figueiredo et al., 2008; Guedj et al., 2011; Powell et al., 2007; Richardson et al., 2003).

4.5.1.2 Prefrontal cortex activations

There have been relatively fewer studies showing PFC activations during memory encoding in left and right TLE patients with inconsistent findings (Alessio et al., 2011; Dupont et al., 2000; Dupont et al., 2002; Guedj et al., 2011; Maccotta et al., 2007; Wagner et al., 2008). The earliest study in TLE describing frontal activations was performed by Dupont et al in LTLE patients (Dupont et al., 2000) and subsequently in RTLE patients (Dupont et al., 2002). In a verbal list learning task, controls and LTLE patients activated the left inferior frontal gyrus (IFG) whilst RTLE patients showed no activations within the IFG. LTLE patients additionally activated the middle frontal gyrus (MFG) bilaterally whilst RTLE patients showed increased left MFG activations compared to controls, who did not activate the MFG (Dupont et al., 2002). In contrast, Alessio et al performed a similar word encoding task and reported no IFG activations but bilateral MFG activations in controls. LTLE patients activated the IFG and MFG bilaterally whilst RTLE patients showed bilateral IFG and left MFG activations (Alessio et al., 2011).

In a verbal encoding task, Wagner et al presented fMRI activations during a verbal memory encoding task as asymmetry of activations within three regions of interest (ROI), the hippocampus, lateral temporal lobe and IFG (Wagner et al., 2008). 29 TLE patients (15 left) were studied. Only activation asymmetry within the hippocampal ROI differed between right and left TLE patients with greater right sided hippocampal activation in left TLE patients and greater left hippocampal activation in right TLE patients. Activation during verbal encoding was left lateralised within the IFG in both patient groups. In this study, no comparison was made to a healthy control group therefore it is not known which activations represent reorganised networks. Using a verbal recognition paradigm, temporal and frontal lobe epilepsy patients showed

activation within the right insula, left cuneus and bilateral anterior cingulate cortex that was not present in healthy controls. In this study, although a blocked design analysis was performed, patients were not amnesic therefore activations were thought to represent part of an 'efficient' encoding network (Eliassen et al., 2008). Of note, this study was conducted in 12 patients (5 right hemispheric epilepsy) and both temporal and frontal lobe epilepsy patients were analysed together.

All the memory fMRI studies that investigated extra-temporal activations to date employed a block design that is sensitive but not specific to memory processes. Thus, no inference on whether extra-temporal activations are involved in successful memory formation can be drawn.

4.5.2 Prediction of the effects of temporal lobe resection on post-operative memory outcome using fMRI

Previously, IAT was used to investigate pre-operative language and memory function and used to predict the risk of amnesia following ATLR (Bell et al., 2000; Loring et al., 1994). Language fMRI has replaced IAT to determine language lateralisation and assist prediction of verbal memory outcome after ATLR in some surgical centres (Baxendale, 2002; Binder et al., 2008a; Binder et al., 2010). Other non-invasive measures showing predictive value for post-operative memory outcome include severity of hippocampal sclerosis assessed by hippocampal volume, type of pathology, neuropsychological memory measures, age at onset and duration of epilepsy (Baxendale et al., 2006; Baxendale et al., 2012; Helmstaedter et al., 2011; Trenerry et al., 1993).

As understanding of the pre-operative functional neuroanatomy expanded, investigators began exploring the predictive ability of pre-operative temporal fMRI

activations to post-operative decline; a valuable tool for surgical counselling for epilepsy surgery. The predictive value of extra-temporal activations has not been investigated in previous memory fMRI studies.

Chelune et al proposed two contrasting theories about post-operative memory function; hippocampal reserve vs functional adequacy (Chelune, 1995). The functional adequacy model suggests that post-surgical memory decline is inversely proportional to the function of the 'to-be-resected' tissue whilst the hippocampal reserve model suggests that it is the function of the contralateral hippocampus to sustain memory function after surgery that determines memory outcome after surgery (Chelune, 1995).

fMRI studies have favoured the functional adequacy model as asymmetry of hippocampal activation with greater activation within the to be resected hippocampus being predictive of memory decline after anterior temporal lobe resection. Further, fMRI has been shown to be the strongest predictor of post-operative verbal and visual memory decline compared to other parameters such as pre-operative neuropsychology scores, hippocampal volumes and language lateralisation (Bonelli et al., 2010; Richardson et al., 2004).

Earlier fMRI studies have used a scene encoding task to predict memory change after ATLR. Rabin et al. examined 23 patients undergoing anterior temporal lobe resection (10 left, 13 right) using this non-material specific task that activated the posterior medial temporal lobe bilaterally. Patients were tested for delayed recognition of the same pictures immediately after scanning. This paradigm was repeated after surgery. Extent of activation within the to-be resected hippocampus

correlated with recognition memory decline but was not predictive of verbal memory decline on standard verbal memory tests (Rabin et al., 2004).

Using an event related fMRI 'asymmetry image' analysis Richardson et al 2004 showed that activation in the left MTL in left HS patients during a word encoding task was predictive of greater verbal memory loss post left ATLR (Richardson et al., 2004; Richardson et al., 2006). Powell et al corroborated this finding and additionally showed that greater right amygdala activation during visual encoding in right HS patients was predictive of post operative decline in visual memory (Powell et al., 2008). In a visuo-spatial memory task, the Roland's Hometown walking test, Janszky et al showed that reduced right hippocampal activation, as reflected by a more positive asymmetry index, was associated with better post-operative design learning scores in RTLE patients. In this study compared to the studies discussed above, patients were imaged during memory retrieval rather than encoding and a blocked rather than an event related analysis was used. Despite these differences, their findings corroborate other fMRI prediction studies described above (Janszky et al., 2005). In all the above studies, group activations were reported. The predictive ability of individual patient activations were not studied.

To date, the only memory FMRI paradigm that successfully predicted memory decline on an individual subject basis was described by Bonelli et al (Bonelli et al., 2010). In this study, an 'asymmetry value' within a 10 mm sphere in the ipsilesional hippocampus was predictive of verbal and visual memory decline after left and right anterior temporal lobe resection respectively. Whilst this study is a great leap in using memory fMRI as a clinical tool to predict memory decline after epilepsy surgery, there are several limitations. Firstly, the asymmetry value within a 10mm sphere was obtained from a peak voxel of a group analysis of the same patients and

may not be applicable as a clinical tool to a newly encountered patient. Second, the computationally complex and time consuming steps may not be feasible to employ in less specialised centres. Asymmetry images involve first conducting an event related analysis of items remembered – forgotten. Contrasts generated are flipped and subtracted from the original unflipped contrast to generate an asymmetry image for each individual. Finally, in this study, there was no objective value of 'asymmetry' within this 10mm sphere that predicted decline. Therefore, prospective application of this model without a clear value of asymmetry beyond which memory decline is expected remains difficult.

In studies in which asymmetry images rather than absolute activations were used, the authors were unable to comment on the hippocampal reserve model as activations in asymmetry images represent either left>right activations or vice-versa (Richardson et al., 2006).

Despite very similar paradigms, peak areas of activation on verbal and non- verbal memory tasks have been divergent in functional imaging studies (Bonelli et al., 2010; Powell et al., 2007; Richardson et al., 2006). Whilst this may be explained by differing patient characteristics and imaging parameters, a recent study employing seven different memory fMRI protocols performed on three separate scanning sessions in the same participants showed only modest reliability in localisation and magnitude of activations with some tasks being more reliable than others. By contrast, laterality of activations assessed by calculating the lateralisation index within the temporal lobe was more reliable (Towgood et al., 2015). This suggests that a prediction models using a large anatomical or functional region of interest may be more accurately applicable to a newly encountered patient.

Several memory fMRI studies have investigated the value of absolute activations rather than asymmetry images in the prediction of post-surgical verbal memory decline using a lateralisation index within MTL anatomical regions of interest(for review see (Binder, 2011)). To date this has only been performed in non-material specific memory encoding paradigms investigating only the predictive value of medial temporal activations (Binder et al., 2010; Mechanic-Hamilton et al., 2009; Rabin et al., 2004). In an object location task, hippocampal lateralisation index correlated with verbal memory change in a group of left and right TLE patients, but in the individual right TLE and left TLE groups, this effect was not significant (Frings et al., 2008).

To date, a memory fMRI method that is easily applied and tested across centres has not been described. We conclude that for memory fMRI to be widely used as a clinical predictive tool, it is mandatory that:

1) patients are able to perform the task
2) the paradigm used is sensitive, eliciting robust activations on a single subject level and
3) imaging and analysis can be performed in a time efficient manner with simple computational methods.

4.5.3 Post-operative network plasticity

Plasticity in the memory encoding networks within the medial temporal lobe after anterior temporal lobe resection has only described in a few memory encoding studies and case reports (Bonelli et al., 2013; Cheung et al., 2009; Korsnes et al., 2009) with one study reporting extra-temporal post-operative memory network plasticity albeit within a small frontal region of interest (Maccotta et al., 2007).

Using a material specific word encoding task Bonelli et al showed that memory reorganisation to the posterior hippocampus pre-operatively was predictive of preserved verbal memory function after left ATLR. Conversely, if reorganisation to the ipsilesional posterior hippocampus occurred after surgery, this correlated with worse memory performance 4 months after surgery (Bonelli et al., 2013). No significant memory reorganisation was described in right TLE patients after right ATLR. This study did not examine extra-temporal post-operative memory reorganisation.

One study examined extra-temporal network plasticity after surgery in TLE patients but in a limited inferior frontal gyrus (IFG) region of interest (ROI) (Maccotta et al., 2007). Pre and post operative signal change within this ROI was compared quantitatively in this word and face classification study. Reduced right frontal activation was shown post-operatively during word encoding in LTLE patients suggesting a more left lateralised network post-operatively. No differences were described at visual encoding.

In a fMRI study of 17 temporal lobe (9 left) epilepsy, plasticity after selective amygdalohippocampectomy and anterior temporal lobe resection was described 12 months after surgery. This is the only 12 month post-operative fMRI study to date. (Cheung et al., 2009). In this study a non-material specific scene encoding task was used. The authors report that the contralateral medial temporal lobe played an efficient compensatory role in maintaining verbal and visual episodic 12 months after surgery (Cheung et al., 2009). Although more sensitive, blocked design analysis is less specific to activations that represent successful memory formation.

In controls, although memory encoding test-retest studies have shown stable hippocampal activations at least 3 months after initial scanning (Atri et al., 2011; Putcha et al., 2011) task similarities may incur practise effects and altered memory encoding strategies in healthy controls (Siders et al., 2006) leading to differential engagement of the frontal lobes (Fletcher and Henson, 2001). There have been no studies to date describing quantitative post-operative network plasticity changes compared to changes in controls imaged across similar time intervals.

In summary, studies to date have suggested that whilst ipsilesional reorganisation of the memory encoding network is protective against verbal memory decline, further posterior ipsilesional reorganisation after surgery is not effective. 12 months after surgery the contralateral hippocampus is involved in memory encoding. As the latter 12 month study was performed in a non-material specific task using a blocked rather than event related analysis, it is not known if contralateral reorganisation occurs for both verbal and visual memory and if contralateral hippocampal activations represent a network that contributes to successful memory formation.

4.6 Main objectives

Memory reorganisation that occurs as a consequence of unilateral TLE within the temporal lobe has been eloquently described using material specific event related studies where activations seen represent activations involved in subsequent memory formation. Extra-temporal activations remain to be described in detail. Although efforts have been made at using memory fMRI as a clinical tool to predict memory decline after epilepsy surgery, a clinically applicable tool that can be applied to a newly encountered patient has yet to be described. It is also not known if pre-

operative extra-temporal activations are predictive of memory decline, as has been shown for pre-operative medial temporal activations.

There are no memory fMRI studies describing longitudinal changes within both temporal and extra-temporal brain areas involved in successful memory reorganisation at intervals after anterior temporal lobe resection. An understanding of this latter network may be the basis of understanding and predicting memory improvement after memory rehabilitation in temporal lobe epilepsy patients after surgery.

These observations form the basis of the main objectives of this thesis:

1) Pre-operative

- Describe pre-operative temporal and extra-temporal material specific memory reorganisation compared to healthy controls.
- Explore the efficiency of reorganised networks at a whole brain level using an event related analysis and correlations with neuropsychometry memory measures.
- Explore the use of MVPA in investigating memory representations within the MTL in TLE patients as had been previously described in healthy controls (Chadwick et al., 2010).

2) Prediction of memory decline after ATLR

- Investigate temporal and extra-temporal brain activations predictive of post-surgical memory outcome using a material specific paradigm.
- Attempt to design a clinically applicable prediction algorithm that can be used on a single subject basis.

3) Post-operative

- Describe longitudinal network plasticity in the material specific memory encoding networks at separate time intervals after ATLR compared to changes in healthy controls imaged across similar time intervals.

SECTION II: COMMON METHODOLOGY

CHAPTER 5

This chapter describes the methods which are common to the studies described in subsequent chapters. Details of subject recruitment, MR data acquisition, the cognitive task paradigms and neuropsychological tests used are included in this section. Individual results chapters refer back to this section with additional details included should this be individual to the experiment conducted.

5.1 Subject Recruitment

Patients were recruited from the epilepsy clinics at the National Hospital for Neurology and Neurosurgery (NHNN), London, UK, and the Epilepsy Society, Chalfont St Peter, UK. All had medically refractory TLE and were undergoing pre-surgical evaluation at the National Hospital for Neurology and Neurosurgery. Further details on patient demographics, neurological and neuropsychological test results, and surgical outcome data where relevant, are included in each chapter.

Control subjects were all English-speaking healthy volunteers with no history of neurological or psychiatric disease. Volunteers included patient relatives, staff at the Epilepsy society and members of the general public who responded to flyers posted in local shops. All studies were approved by the NHNN and the Institute of Neurology Joint Research Ethics Committee and informed written consent was obtained from all subjects.

5.2 Acquisition of clinical data

All subjects had undergone structural MRI at 3T, including quantification of hippocampal volumes and T2 relaxation times. Electro-clinical assessment had been

carried out with video-EEG at the National Hospital. All patients received antiepileptic medication and spoke fluent English. Handedness and language dominance were determined using a standardized questionnaire (Oldfield, 1971) and language fMRI tasks (Powell et al., 2006) respectively. Expressive language lateralisation within an inferior and middle frontal gyrus mask was calculated (Bonelli et al., 2010) in all subjects.

5.3 Neuropsychometry

All patients underwent detailed presurgical neuropsychometry. This was repeated 3 and 12 months after temporal lobe surgery and at similar time intervals in controls. These included measures of intellectual functioning; IQ (Nelson and O'Connell, 1978; Wechsler, 1997) and measures of verbal learning and design learning (Coughlan AK, 2007) previously demonstrated as sensitive to the integrity of temporal structures (Baxendale et al., 2006).

In the verbal learning task the subject is read a list of 15 words five times and on each presentation has to attempt to recall as many of the words as possible. The percentage of correct responses was used as a second measure of verbal memory efficiency. In the figure recall task the subject firstly copies a complex design and reproduces it from memory immediately and at a 30 minute delay. The percentage of the figure remembered following the delay was employed as a measure of non-verbal memory competence. In the design learning task the subject is presented with a design on five occasions with recall being tested after each presentation. The percentage of correct responses over the five trials was used as a second measure of non-verbal memory efficiency.

5.4 Functional MRI

5.4.1 Memory fMRI data acquisition

Studies were performed using a 3T General Electric Excite HDx MRI scanner with a gradient strength of 40mTm^{-1} and slew rate 150Tm-1s-1. For the fMRI, gradient-echo echo planar T2*-weighted images were acquired, providing blood oxygen level dependent contrast (BOLD). Each volume comprised 36 contiguous oblique axial slices, slice thickness 2.5mm (0.3 mm gap), field of view 24cm, matrix 96 x 96 interpolated to 128 x 128 during image reconstruction, in-plane resolution 2.5, SENSE factor 2.5, Echo time (TE) 25ms, TR 2.75s. The field of view was positioned to cover the temporal and frontal lobes with the slices aligned with the long axis of the hippocampus on the sagittal view.

5.4.2 Language fMRI data acquisition

Each volume comprised 58 contiguous 2.5 mm oblique axial slices, through the temporal and frontal lobes with a 24 cm field of view, 96 x 96matrix, reconstructed to 128 x 128. TE30 ms and TR 4.5 s. The field of view was positioned to maximize coverage of the frontal and temporal lobes in both patient groups.

5.4.3 Paradigms used

5.4.3.1 Memory task

Two material types, visual (faces) and verbal (words) were visually presented to patients during a single scanning session.

Black and white photographs of non-famous faces unfamiliar to the subjects and single concrete nouns were presented on an MR compatible screen viewed via a mirror (Bonelli et al., 2010). Each item was presented for 3 seconds in 60 second blocks. We used a different inter-stimulus interval (3 seconds) to our TR of 2.75 s to introduce jitter and facilitate random sampling. Each block consisted of 10 faces and

10 words followed by 15s cross hair fixation. We presented a total of 10 blocks (100 faces and 100 words). Participants were explicitly instructed to memorise items for subsequent out of scanner recall. A deep encoding task (Craik, 2002) which involved a subjective decision on whether each stimulus was pleasant or unpleasant, using a joystick was performed.

Forty minutes after scanning face and word recognition was tested separately in an out-of-scanner recognition task. In each recognition task, subjects were shown the same 100 items intermixed with an additional 50 novel faces/words as foils in random order at the same speed as items were displayed within the scanner.

A button box was used to indicate if items were remembered, familiar or novel. A meta-analysis across a variety of stimulus materials showed that regardless of level of contextual retrieval, the human anterior MTL particularly the perirhinal cortex is sensitive to familiarity of stimuli experienced in an experimental context (Henson et al., 2003). For this reason, we included a familiarity judgement to the out scanner recognition assessment. These responses were used to sort each item shown in the scanner to items remembered, familiar and forgotten. Recognition accuracy (%) was calculated for both faces and words (true positive – false positive). For a more specific contrast of subsequent memory we used the contrast remember minus (familiar plus forgotten).

Richardson et al used a contrast of remembered- familiar for reasons discussed in section **4.5.1.1.2** (Richardson et al., 2003). In brief, this was because patients did not identify as many foil words as new words. Of note there was no difference in recognition accuracy of remembered and familiar words. To keep controls and patients matched, rememberedd- familiar was used. The patients I studied were

amnestic and had significantly lower verbal and visual neuropsychological memory scores and lower recognition accuracies than controls. Across all of the categories; remembered, familiar and forgotten, patients differed from controls which is a reflection of the neuropsychological deficits seen in patients with TLE (see section **4.3**). Controls and patients were matched for age and IQ as far as possible. As the neuro-anatomical substrates for subsequently forgotten and familiarity judgements differ from subsequently remembered items (Hongkeun, 2011; Simons and Spiers, 2003), I chose to the contrast remembered – (familiar plus forgotten) as the most specific contrast for subsequently memory.

5.4.3.2 Language tasks

In the verbal fluency task, subjects were instructed to covertly generate different words beginning with a visually presented letter (A, S, W, D, and E) during the activated phase contrasted by crosshair fixation as rest condition. A blocked experimental design with 30-s activation blocks alternating with 30-s of cross-hair fixation over 5.5 min was employed (Bonelli et al., 2012; Powell et al., 2006). During the verb generation task concrete nouns were visually presented every 3s in blocks of 10 nouns. Subjects were instructed to covertly generate verbs from the nouns during the task block and to silently repeat the nouns during the rest block. These paradigms were used to identify anterior language regions in the inferior and middle frontal gyri.

5.4.4 Data Analysis

Analysis was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). The imaging time series was realigned, normalized into standard anatomical space (using a scanner specific template created from 30 healthy controls, 15 patients with left

hippocampal sclerosis (HS) and 15 patients with right HS using the high resolution whole brain EPI) and smoothed with a Gaussian kernel of 8mm full-width at half maximum.

5.4.4.1 Blocked Design

Regressors of interest were formed by creating two box-car functions for faces and words convolved with the canonical HRF. Movement parameters were included as confounds and parameter estimates for the regressors were calculated for each voxel. Contrasts were generated for both ‘words’ and ‘faces’ corresponding to the main effect of material-specific encoding. These contrast images were used for the second-level analysis.

All results for the main effects are shown corrected for multiple comparisons (family wise error (FWE)), $p<0.05$ and group comparisons at $p<0.001$ uncorrected unless otherwise stated. Activations within the medial temporal lobe are shown corrected for multiple comparisons using a small volume correction within a sphere of 6 mm, FWE $p<0.001$ (Bonelli et al., 2010).

5.4.4.2 Event-related analysis

Event related analysis on a blocked designed experiment have been performed in memory studies (Bonelli et al., 2010; Powell et al., 2007; Richardson et al., 2003) and other cognitive tasks (Mechelli et al., 2003; Seghier et al., 2012; Seghier and Price, 2012). We compared the encoding-related responses for stimuli that were subsequently remembered versus stimuli that were subsequently forgotten or rated familiar. A two-level event-related random-effects analysis was employed. At the first level, trial specific delta functions were convolved with the canonical HRF and its temporal derivative for each subject. Six regressors of interest for each of the event

types, words remembered (WR), words familiar (WFam), words forgotten (WF), faces remembered (FR), faces familiar (FFam) and faces forgotten (FF) were created.

A random effects analysis was performed at the second level, for both the blocked and event related analyses. A one-sample t-test was performed to examine the group effect of each contrast. An analysis of variance (ANOVA) was performed to quantitatively assess statistically different brain activations between all three groups.

5.4.4.3 Language fMRI

Similar to the memory task, a random effects analysis was employed. At the first level, a blocked design was used to form a regressor of interest by creating a box-car function for the activation phase of the verbal fluency paradigm, and verb generation and repetition for the verb generation task. For verb generation a contrast of verb generate minus verb repeat was produced for each subject.

For both the fluency and generation paradigms, an anatomical mask incorporating the inferior and middle frontal gyrus was created using an automated method the WFU PickAtlas in SPM8 (Maldjian et al., 2003). Asymmetry of expressive language activation was calculated within the mask by using a bootstrap method to calculate language lateralisation index (LI) using the Lateralisation Index toolbox in SPM 8 (Bonelli et al., 2012). A LI of ≥ 0.5 or - ≤0.5 was deemed strongly left or right lateralised respectively.

SECTION III: RESULTS

Chapter 6: Mapping the pre-operative episodic memory encoding network in temporal lobe epilepsy

Abstract

Functional magnetic resonance imaging has demonstrated reorganisation of memory encoding networks within the temporal lobe in temporal lobe epilepsy, but little is known of the extra-temporal networks in these patients. We investigated the temporal and extra-temporal reorganisation of memory encoding networks in refractory temporal lobe epilepsy and the neural correlates of successful subsequent memory formation.

I studied 44 patients with unilateral temporal lobe epilepsy and hippocampal sclerosis (24 left) and 26 healthy controls. All participants performed a functional magnetic resonance imaging memory encoding paradigm of faces and words with subsequent out of scanner recognition assessments. A blocked analysis was used to investigate activations during encoding and neural correlates of subsequent memory were investigated using an event related analysis. Event related activations were then correlated with out-of-scanner verbal and visual memory scores.

During word encoding, controls activated the left prefrontal cortex and left hippocampus whilst left hippocampal sclerosis patients showed significant additional right temporal and extra-temporal activations. Controls displayed subsequent verbal memory effects within left parahippocampal gyrus, left orbitofrontal cortex and fusiform gyrus whilst left hippocampal sclerosis patients activated only right posterior hippocampus, parahippocampus and fusiform gyrus. Correlation analysis showed that left hippocampal sclerosis patients with better verbal memory additionally

activated left orbitofrontal cortex, anterior cingulate cortex and left posterior hippocampus.

During face encoding, controls showed right lateralised prefrontal cortex and bilateral hippocampal activations. Right hippocampal sclerosis patients showed increased temporal activations within the superior temporal gyri bilaterally and no increased extra-temporal areas of activation compared to controls. Controls showed subsequent visual memory effects within right amygdala, hippocampus, fusiform gyrus and orbitofrontal cortex. Right hippocampal sclerosis patients showed subsequent visual memory effects within right posterior hippocampus, parahippocampal and fusiform gyri, and predominantly left hemisphere extra-temporal activations within the insula and orbitofrontal cortex. Correlation analysis showed that right hippocampal sclerosis patients with better visual memory activated the amygdala bilaterally, right anterior parahippocampal gyrus and left insula.

Right sided extra-temporal areas of reorganisation observed in left hippocampal sclerosis patients during word encoding and bilateral lateral temporal reorganisation in right hippocampal sclerosis patients during face encoding were not associated with subsequent memory formation. Reorganisation within the medial temporal lobe however, is an efficient process. The orbitofrontal cortex is critical to subsequent memory formation in controls and patients. Activations within anterior cingulum and insula correlated with better verbal and visual subsequent memory in left and right hippocampal sclerosis patients respectively, representing effective extra-temporal recruitment.

6.1 Introduction

Lesional, functional imaging and computational analyses have indicated that the MTL and PFC and subcortical structures are involved in episodic memory processes (Simons and Spiers, 2003; Squire et al., 2004). A recent meta-analysis of fMRI event related studies, identified other brain regions critical to memory encoding such as the fusiform gyrus, posterior parietal and pre-motor cortex in healthy individuals (Hongkeun, 2011).

Specific processes that mediate memory encoding have been shown to occur in different subregions of the PFC as detailed in section 4.2. The OFC with its close anatomical connections to the MTL, (Carmichael and Price, 1995) is thought to be critical to the successful encoding of both verbal (Savage et al., 2001) and visual material (Frey and Petrides, 2002). Individuals with TLE have significant material specific episodic memory impairments with greater verbal and visual memory deficits with left and right TLE respectively. More recently however widespread cognitive deficits have been described with variable memory performance between patients despite a homogenous clinical presentation (Elger et al., 2004; Helmstaedter et al., 2003). This is in concert with more widespread morphological (Woermann et al., 1999) and functional abnormalities with disrupted connectivity as remote as the OFC and occipital cortex being described (Voets et al., 2009).

FMRI studies in healthy controls have shown a material specific functional hemispheric lateralisation of verbal and visual memory encoding to the left and right hemispheres respectively (Golby et al., 2002; Kelley et al., 1998). FMRI studies in TLE patients have consistently shown atypical material-specific involvement of the MTL in episodic memory encoding, with reorganisation of memory functions to the

contralesional side (Golby et al., 2002; Powell et al., 2007; Richardson et al., 2003). Extra-temporal activations during verbal and visual memory encoding in TLE have only been investigated in relatively small studies in which differences in the encoding network compared to controls has been described within the PFC, lateral temporal, parietal and occipital cortex (Alessio et al., 2011; Dupont et al., 2000; Dupont et al., 2002; Maccotta et al., 2007). These studies were analysed using a blocked model and no correlations were made to memory performance therefore it is not known if these extra-temporal regions are involved in subsequent memory formation.

Several subsequent memory studies using an event related analysis of fMRI comparing activations related to items that are subsequently remembered to those forgotten have been reported within the MTL (Bonelli et al., 2010; Powell et al., 2007; Richardson et al., 2003; Richardson et al., 2006). By contrast, extra-temporal subsequent memory effects have been less well described. The extra-temporal functional anatomy of episodic memory processes in those with TLE has not been investigated in detail. This is an important consideration for patients who may be candidates for epilepsy surgery.

The blocked analysis investigates neural correlates during the encoding task and provides a good reflection of strategies employed during encoding. Whilst it is more sensitive than an event related analysis, the latter addresses a more specific issue of successful subsequent memory (Powell et al., 2005). We employed a blocked analysis to test the hypotheses that:

1) Healthy controls have a material specific representation of memory encoding; left hemispheric activations for verbal memory and right for visual.

2) Patients with left and right TLE have greater activations for verbal and visual memory encoding within the contralateral 'healthy' hemisphere.

Additionally, we investigated the neural correlates of successful subsequent memory in TLE patients at a whole brain level using an event related analysis. Further correlations of out-of-scanner visual and verbal memory performance with subsequent memory activations were conducted to investigate the effectiveness of subsequent memory activations (Powell et al., 2007).

6.2 Materials and Methods

Methodological details have been presented in chapter 5. Methods specific to this study are detailed below.

6.2.1 Subjects

We studied 44 patients with medically refractory TLE (24 left: median age 42 years (range 19-54), 20 right: median age 42.5, range 21-56) due to unilateral HS. 26 healthy native English speaking controls, median age 37 years (range 19-58) with no neurological or psychiatric history were also studied. All subjects underwent neuropsychological testing (Table 6.1).

6.2.2 Memory encoding paradigm and data analysis

Visual (faces) and verbal (words) stimuli were visually presented to patients during a single scanning session and recognition was checked after scanning (section 5.4.3.1). Image preprocessing, blocked and event related analyses were performed as detailed in section 5.4.4. Subjects were divided into three groups: controls, left

hippocampal sclerosis (LHS) and right hippocampal sclerosis (RHS) patients. A one-sample t-test was performed to examine the group effect of each contrast. An analysis of variance (ANOVA) was performed to quantitatively assess statistically different brain activations between all three groups. To ensure that only differences in activation were analysed, the difference maps were masked with the main effect of condition. Statistical thresholds for reporting as detailed in section.

As part of standard preoperative neuropsychometry, measures of verbal learning and design learning (Coughlan AK, 2007) previously demonstrated as sensitive to the integrity of temporal structures (Baxendale et al., 2006) were acquired. Verbal and visual subsequent memory activations from the event related analyses were correlated with verbal (VL) and design learning (DL) scores respectively in controls, LHS and RHS patients. Positive and negative correlations were explored using memory scores as a continuous regressor in an analysis of covariance (ANCOVA), using the group verbal and visual activation maps as a mask. All correlations are reported at $p<0.001$ uncorrected. MTL activations are shown corrected for multiple comparisons using a small volume correction within a sphere of 6 mm (FWE $p<0.05$) unless otherwise stated**.**

6.3 Results

6.3.1 Behavioural

Controls performed significantly better than both LHS and RHS patients on both word [mean % (SD), 75 (12.1), 49 (15.7), 59 (20.6) respectively] and face [27 (12.2), 15 (9.4), 14 (9.7)] recognition. There was no significant difference between the patient groups in word and face RA. Both controls and patients had significantly higher recognition accuracy (RA) for words than faces (Table 6.1, Fig 6.1).

Controls performed better than both LHS and RHS patients on the VL task [57.4 (8.9), 44.5 (10.9), 44 (10)]. There was no significant VL difference between LHS and RHS patients. Both controls and LHS patients performed significantly better than RHS patients on the DL task [39.3 (5.3), 34.2 (7.4), 27 (90] (Table 6.1).

	Age (years)	Age at onset (years)	Duration (years)	No. of AEDs	Language LI within frontal ROI	Right HC Volume (cm^3)	Left HC Volume (cm^3)	IQ	List Learning /75	Design Learning /45	RA Words %	RA Faces %
C	37 (23.3)	n/a	n/a	n/a	-0.82 (0.13)	2.76 (0.21)	2.70 (0.3)	111.5 (11)	57.4 (8.9)	39.3 (5.3)	75 (12.1)	27 (12.2)
LHS	52 (9.3)	15.8 (2.8)	24.1 (14)	3 (1)	-0.76 (0.12)	2.76 (0.35)	1.82* (0.4)	97* (9.8)	44.5* (10.9)	34.2 (7.4)	49* (15.7)	15* (9.4)
RHS	42.5 (13.5)	13.5 (2.5)	28.7 (16.5)	3 (1)	-0.75 (0.14)	1.92* (0.41)	2.74 (0.32)	99* (14.7)	44* (10)	27* μ (9)	59* (20.6)	14* (9.7)

Table 6.1: Demographic details and results of standard neuropsychometry in controls (C) and patients. Age and No of AEDs (Number of anti-epileptic drugs) are shown as median (IQR), all others shown as mean (SD). LI (lateralisation index), ROI (region of interest), HC (hippocampus), RA (recognition accuracy). * Controls> patient group indicated p<0.001, $^{\mu}$ LHS>RHS, p= 0.004.

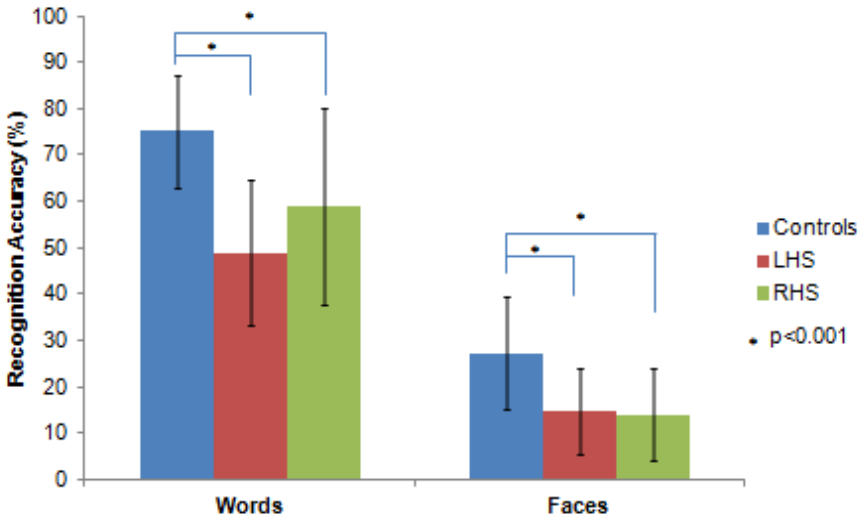


Fig 6.1: Histograms showing mean percentage Recognition Accuracy with error bars (+/- 1 SD) for word and face recognition across all groups.

6.3.2 Main Effects: Word Encoding

All 3 groups showed activations in the left IFG, MFG, anterior PFC, left pre-central and bilateral fusiform gyri (FG). Although activations were left lateralised within the PFC, controls also showed activations in the right MFG. LHS patients showed activations in the right MFG, IFG, angular gyrus, superior parietal lobule and left post-central gyrus that were not seen in the other groups. Qualitatively, both patient groups showed activations in the left inferior temporal gyrus and inferior parietal lobule that was not seen in controls. Controls and both patient groups activated the left HC during word encoding. LHS patients also showed contralateral right HC and amygdala activation. RHS patients also activated the left PHG (Table 6.2, Figure 6.2).

6.3.3 Main Effects: Face Encoding

Controls and LHS patients showed right lateralised PFC activations. RHS patients showed bilateral albeit reduced PFC activations. All 3 groups activated the right superior parietal lobule, bilateral FG, left pre and post central gyri and left insula. Only controls activated the right OFC, anterior PFC and left occipital cortex. LHS patients also activated the right inferior temporal gyrus and temporal poles bilaterally. Controls showed bilateral activations within the HC, PHG and amygdala. Both patient groups showed qualitatively more activations in the contralesional MTL (Table 6.3, Figure 6.3).

6.3.4 Group comparisons: Word Encoding

Quantitative analysis revealed significantly greater right hemispheric activations within the MFG, IFG and superior temporal gyrus (STG) in LHS patients compared to

controls whilst RHS patients activated the right STG and MFG bilaterally greater than controls (Table 6.4,Figure 6.2).

Both patient groups showed reduced left hemispheric activations compared to controls. In LHS patients this reduction was seen at a lower threshold; left middle temporal gyrus (MTG) (p=0.002) and left inferior frontal operculum (p=0.007) (Table 6. 4).

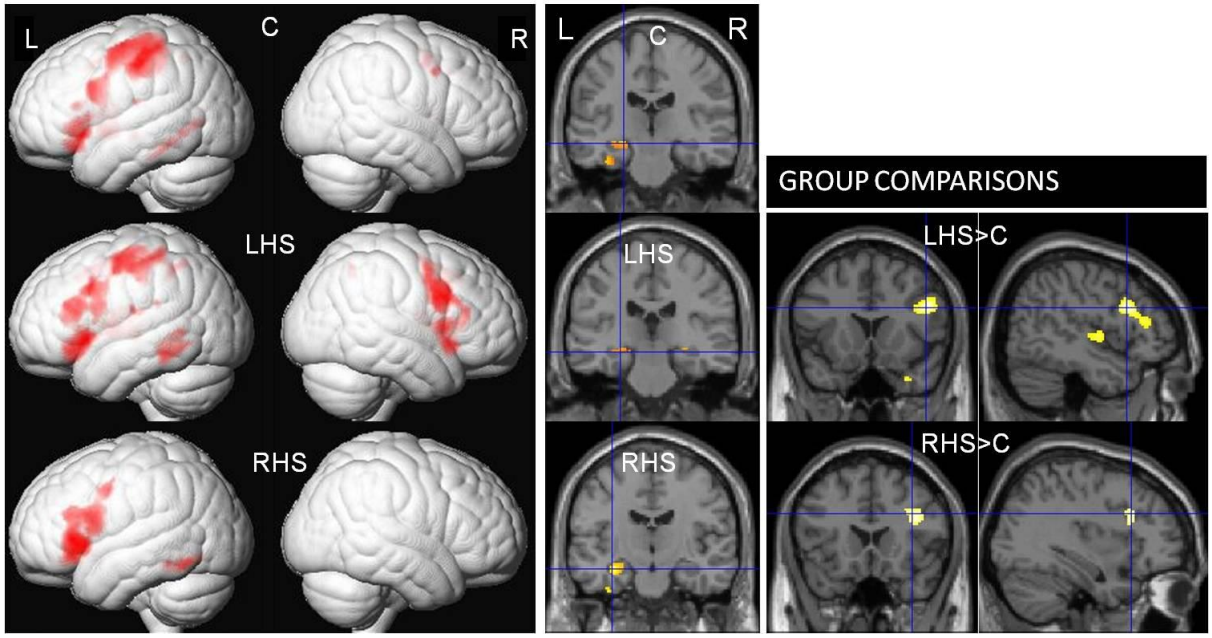


Fig 6.2: Rendered image showing whole brain activations, coronal image showing medial temporal lobe activations and group comparisons during word encoding in controls (C), LHS and RHS patients. Controls and RHS patients showed robust left lateralised prefrontal cortex and hippocampal activations while LHS patients activated the prefrontal cortex and hippocampus bilaterally. Group comparisons showed greater right prefrontal cortex activations in LHS patients than controls. RHS patients activated the prefrontal cortex bilaterally greater than controls; only right prefrontal cortex activation greater than controls is shown in this image.

6.3.5 Group comparisons: Face Encoding

LHS patients showed significantly greater right hemispheric activations within the IFG, STG and supramarginal gyrus compared to controls whilst RHS patients

showed greater bilateral STG activations compared to controls during face encoding. No significant extra-temporal increased activation was seen in RHS patients compared to controls (Table 6.4, Figure 6.3).

Both patient groups showed significantly less medial OFC activation than controls. LHS patients also showed significantly less left hemisphere activations within the IFG, lateral OFC, middle occipital gyrus, amygdala and HC than controls, whilst RHS patients showed significantly less right hemisphere activations within the MFG, middle occipital gyrus and amygdala than controls (Table 6. 4).

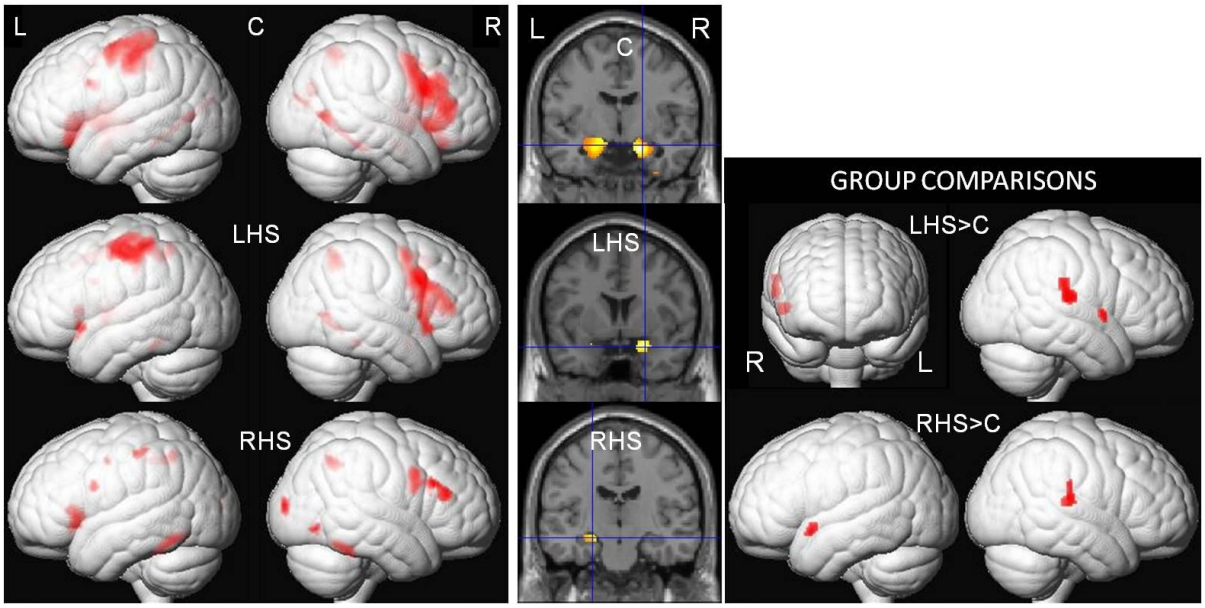


Fig 6.3: Rendered image showing whole brain activations, coronal image showing medial temporal lobe activations and group comparisons during face encoding in controls (C), LHS and RHS patients. Controls showed bilateral prefrontal cortex (right lateralised) and medial temporal lobe activations during face encoding. LHS patients activated predominantly the right prefrontal cortex and medial temporal lobe whilst RHS patients showed lesser activations than controls in the right prefrontal cortex and only left medial temporal lobe activation. Group comparisons are shown on a rendered image. LHS patients activated the right prefrontal cortex, superior temporal gyrus and supramarginal gyrus more than controls. RHS patients activated the superior temporal gyri bilaterally (anterior on left, posterior on right).

FWE p<0.05	WORD ENCODING											
	LEFT HEMISPHERE						RIGHT HEMISPHERE					
	Controls	**Z**	**LHS**	**Z**	**RHS**	**Z**	**Controls**	**Z**	**LHS**	**Z**	**RHS**	**Z**
Ant PFC	-4 52 -22	4.89	-38 30 -14	5.54	-34 30 -12	5.64						
	-42 28 -18	5.07										
Inf Frontal G	-42 24 -4	5.41	-46 24 -6	5.97	-48 30 4	6.87			40 32 16	6.27		
	-44 16 6	5.03	-48 28 20	6.18	-46 18 22	6.16			36 26 8	6.14		
	-38 24 14	5.06	-50 16 -4	6.1	-44 6 24	6.13			5018 -10	6.08		
	-40 6 28	6.54	-48 8 22	5.72	-50 28 -10	5.95			54 14 6	6		
			-52 10 10	4.78	-56 10 12	5.78						
Mid Frontal G	-36 -4 56	6.37	-48 12 36	6.24	-52 28 22	5.85	38 0 50	5.14	5814 30	5.88		
			-40 2 36	5.36					40 2 52	5.51		
									36 44 28	4.78		
Med Frontal G	-6 4 54	6.19	-4 12 50	6.44					10 12 48	5.87		
	-2 -4 56	6.04							6 2 56	5.75		
Insula	-32 24 2	5.25	-48 -26 18	5.07			36 26 -2	4.84	32 20 4	5.59		
	-40 0 12	4.69										
Pre-central G	-32 -10 64	6.71	-40 -16 54	5.56	-44-16 58	4.89	56 8 42	5.05	50 8 30	6.7		
	-38 -24 58	6.21			-54 0 42	5.71						
	-36 -14 60	6.26										
Post-central G			-42 -40 62	5.61								
			-38 -26 52	5.52								
			-50 -14 54	5.44								
Angular G									30 -5846	4.88		
Supramarginal	-52 -22 18	5.28	-54 -38 24	5.01								
Sup Parietal L	-26 -58 52	5.08							34-58 54	4.92		
Inf Parietal L			-32 -48 46	5.1	-32 -60 52	4.88						
Thalamus			-14 -12 4	5.84					14 -6 -2	4.95		
Putamen	-26 0 -6	5.53					18 6 8	4.81				
							24 4 8	4.95				
Fusiform G	-42 -52 -14	6.01	-42-54 -16	6.25	-46-58 -18	5.41	34-38 24	3.85	32-38-24	4.65	42 -52-24	4.32
	-36 -38 -24	5.57	-34 -64 -8	4.23	-44-46-22	4.63			38-52-12	4.47		
	-40 -56 -10	6.36	-40 -24 -8	5.83	-46 -58-18	5.41			34-6-46	3.71		
Inf Temporal G			-50-52-10	5.62	-37-14 -36	4.23						
			-50-44 -10	5.96								

				-46 -66 -6	4.87							
Mid Temporal G				-48 -54 -2	5.27							
Occipital	-40 -58 -8	6.65				-54-64 -16	-	5.60				
Cerebellum				-28 -48 -22	-	5.59			4-56 10	-	5.53	6 -60-18	4.74
MTL activations, Family wise error correction within a 6mm sphere, p<0.001												
Hippocampus	-30-18-12	4.65		-26 -24 -8	4.38	-32-14-18		5.08				32-20 -8	4.45
	-24-22 10	-	4.69	-32-22-10	4.1	-26-22-14		4.65				28 -24 -8	4.31
	-14-28-10		4.23	-28-28-6	4.38							32 -16-12	3.69
	-12 -6 -16		4.39	-16-26-8	4.01								
PHG						-14 10	-30-	3.74					
Amygdala	-22 -8 -12		4.24	-26 2 -16	4.01							22 6 -16	3.39
	-26 -2 -16		3.38										

Table 6.2: Whole brain activations in controls, LHS and RHS patients during word encoding shown corrected for multiple comparisons (Family Wise Error Correction, FWE) p<0.05. Medial temporal lobe activations (MTL) are shown corrected for multiple comparisons using a small volume correction within a sphere of 6 mm, FWE p<0.001. All groups showed left prefrontal (PFC) activations during word encoding. LHS patients additionally activated the right middle frontal gyrus and inferior frontal gyrus. RHS patients showed no right PFC activation but showed activations in the left inferior temporal gyrus and parahippocampal gyrus (PHG) that was not seen in controls. Ant (anterior), Med (medial), G (gyrus), L (lobule), Sup (superior), Mid (middle), Inf (inferior).

FACE ENCODING												
FWE p<0.05	LEFT HEMISPHERE						RIGHT HEMISPHERE					
	Controls	**Z**	**LHS**	**Z**	**RHS**	**Z**	**Controls**	**Z**	**LHS**	**Z**	**RHS**	**Z**
Ant PFC	-38 30 -20	5.74					2 52 -20	5.34				
							10 62 -10	4.79				
							32 32 -20	5.65				
Inf Frontal G	-40 6 28	5.38	-36 8 30	5.1	-42 6 26	5.34	46 18 24	6.69	48 8 30	7	42 8 22	5.68
					-30 26 -10	5.17	50 36 10	6.24	46 32 14	5.77	50 32 24	5.36
							30 26 -14	5.26	52 16 6	5.76		
Mid Frontal G							40 4 42	5.72	42 2 52	5.76	48 10 34	5.37
							44 28 36	5.13				
Med Frontal G	-6 6 52	6.21	-4 10 52	6.76			6 18 46	5.82	0 18 50	6.11		
	-2 -8 54	5.65										
Insula	-42 -2 10	4.77	-36 18 8	5.2	-34 22 4	5.36	38 26 -2	6.69	34 22 4	4.87		
	-30 16 4	5.34										
Pre-central G	-32 -10 64	6.36	-40 -26 62	5.9	-38 -4 46	5.19	52 8 44	6.12				
Post-central G	-38 -24 60	6.14	-46 -38 62	6.17	-50 -34 54	5.09						
			-54 -18 54	5.95								
Angular G							32 -56 44	4.91				
Sup Parietal L							32 -58 56	6.21	30 -56 46		34 -60 44	5.44
Inf Parietal L					-28 -50 48	5.41						
Putamen	-22 -4 0	7.07	-26 -2 2	5.44			18 2 -2	6.85	22 6 6	5.08		
Fusiform G	-38 -46 -18		-40 -44 -22	5.65	-38 -52 -24	5.84	44 -42 20	6.41	44 -54 -8	5.42	38 -50 -24	5.57
					-36 -62 -18	5.44	44 -52 -12	6.03	42 -38 -22	5.26		
							34 -38 -24	5.74				
Temporal Pole			-48 16 -10	5.2					54 18 -10	5.93		
Inf Temporal									44 -40 -20	5.46		
Occipital	-38 60 -8	6.44					44 -64 -2	5.96			24 -100 10	6.01
	-38 -70 0	5.61					32 -84 14	6.27			42 -74 -12	4.90
Cerebellum					-36 -54 -24	5.93	4 -56 -10	5.45			36 -52-26	6.13

												26 -48 - 26	5.68
MTL activations, Family wise error correction within a 6mm sphere, p<0.001													
Hippocampus	-26 -24 -8	5.18				-22 -16 -14	-	4.83	20 -30 -8	5.53	26 -22 -10	-	4.2
									28 -20 -10	- 4.3	14 -4 -16	-	4.51
Amygdala/ PHG	22 -2 -24	5.43	-24 -2 -16		4.22	-18 -4 -14		4.68	18 -6 -22		20 2 -20	-	5.29

Table 6. 3: Whole brain activations in controls, LHS and RHS patients during face encoding shown corrected for multiple comparisons (Family Wise Error Correction, FWE) p<0.05. Medial temporal lobe activations (MTL) are shown corrected for multiple comparisons using a small volume correction within a sphere of 6 mm, FWE p<0.001. Only controls activated the anterior prefrontal cortex (Ant PFC). Although all groups activated the right middle and inferior frontal gyri, RHS patients showed reduced activations in these regions. Ant (anterior), Med (medial), G (gyrus), L (lobule), Sup (superior), Mid (middle), Inf (inferior), PHG (parahippocampal gyrus).

Group Differences: Word Encoding							
Region	**Coordinate**	**P value**	**Z score**	**Region**	**Coordinate**	**P value**	**Z score**
LHS<C				**RHS<C**			
Lt Mid Temporal G	-62 -14 -14	0.002	2.87	Lt Post central G	-54 -20 40	0.000	3.37
Lt Frontal Operculum	-38 6 18	0.007	2.47				
LHS>C				**RHS>C**			
Rt Mid Frontal G	48 16 26	0.000	4.19	Rt Sup Temporal G	56 2 -2	0.000	3.32
Rt Inf Frontal G	52 26 20	0.000	3.37	Rt Mid Frontal G	40 20 24	0.001	3.22
Rt Sup Temporal G	60 -24 14	0.001	3.08	Lt Mid Frontal G	-32 40 10	0.001	3.01
Group Differences: Face Encoding							
Region	**Coordinate**	**P value**	**Z score**	**Region**	**Coordinate**	**P value**	**Z score**
LHS<C				**RHS<C**			
Medial OFC	4 56 -18	0.000	4.26	Medial OFC	2 58 -12	0.000	3.46
Lt Mid Occipital	-30 -90 16	0.000	3.33	Rt Mid Occipital G	32 -78 24	0.000	3.63
Rt Post Central G	40 -32 44	0.000	3.32	Rt Mid Frontal G	44 2 42	0.000	3.46
Lt OFC	-38 28 -16	0.001	3.07	Rt Amygdala	18 -2 -22	* 0.06	2.40
Lt Inf Frontal G	-42 24 -6	0.001	2.97				
Lt Hippocampus	-14 -2 -14	*0.021	2.89				
Lt Amygdala	-22 -8 -12	*0.028	2.77				
LHS>C				**RHS>C**			
Rt Sup Temporal G	66 -24 16	0.000	3.62	Rt Sup Temporal G	66 -26 16	0.001	3.18
Rt Inf Frontal G	54 6 0	0.000	3.33	Lt Sup Temporal G	-48 8 -10	0.001	2.98
Rt Supramarginal G	66 -24 28	0.001	2.99				

Table 6.4: Coordinates, p-values and z-scores of whole brain group differences in activations comparing controls, LHS and RHS patients during word and face encoding. * Family wise error corrections p<0.05 using a small volume correction within a sphere of 6mm for MTL activations. Lt (left), Rt (right), Inf (inferior), Mid (middle), Sup (superior), G (gyrus), OFC (orbitofrontal cortex), NS (no significant activations).

6. 3.6 Event related analysis

6.3.6.1 Verbal subsequent memory

In controls, verbal subsequent memory activations were seen within the left OFC, PHG and fusiform gyrus. LHS patients showed subsequent memory effects within the right posterior PHG and HC, right fusiform gyrus and inferior temporal gyrus (ITG) bilaterally. No extra-temporal subsequent memory activations were seen in LHS patients. RHS patients activated the left OFC and IFG, right insula and bilateral PHG, pre-central gyrus and temporal poles during verbal subsequent memory. The

extra-temporal areas of significantly increased activation compared to controls during word encoding in both LHS (right MFG and IFG) and RHS (bilateral MFG) patients were not involved in subsequent verbal memory formation (Table 6.5, Fig 6.4).

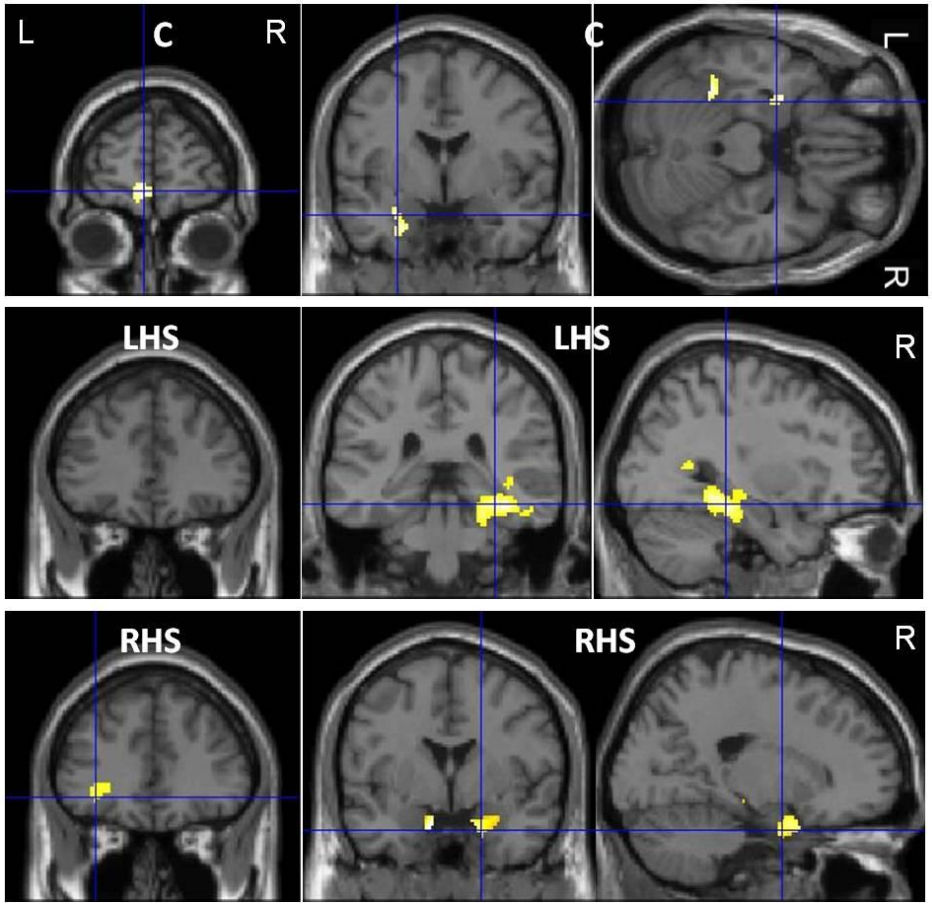


Fig 6.4: Whole brain verbal subsequent memory in controls (C), LHS and RHS patients. Top row: activations in controls, middle row: LHS patients and bottom row RHS patients. Medial temporal lobe activations are displayed at a threshold of $p<0.01$, uncorrected. Controls showed verbal subsequent memory effects within the left medial orbitofrontal cortex, parahippocampal gyrus and fusiform gyrus. LHS patients showed no orbitofrontal cortex activations and only right sided activations within the hippocampus, parahippocampal gyrus and fusiform gyrus. RHS patients showed left orbitofrontal cortex, and bilateral parahippocampal gyrus activations.

Words: Remembered - Familiar Forgotten							
	LEFT HEMISPHERE			RIGHT HEMISPHERE			
Region	**Coordinate**	**P value**	**Z score**	**Region**	**Coordinate**	**P value**	**Z score**
CONTROLS							
Medial OFC	-4 60 -8	0.000	3.36				
PHG	-24 0 -30	0.058*	2.49				
Fusiform G	-32 -42 -22	0.05*	2.53				
LHS							
Inf Temporal G	-46 -6 -36	0.001	3.18	Posterior PHG/ Hippocampus	38 -32 -16	0.03*	3.46
				Inf Temporal G	50 -12 -26	0.000	3.40
				Fusiform G	28 -42 -8	0.001	3.23
RHS							
Pre-central G	-40 -6 -34	0.000	3.85	Temporal pole	32 12 -26	0.000	3.94
Caudate	-10 -4 16	0.000	3.66	Insula	32 2 14	0.000	3.62
PHG	-12 0 -26	0.005*	3.41	Caudate	10 2 16	0.000	3.50
Temporal pole	-34 14 -24	0.000	3.4	Pre-central G	40 -14 36	0.001	3.20
OFC	-30 36 -4	0.001	3.10	PHG	18 0 -28	0.019*	2.97
Inf Frontal G	-44 4 24	0.001	3.00				
Inf Frontal G	-50 16 16	0.001	2.97				

Table 6.5: Coordinates, p-values and z-scores of whole brain verbal subsequent memory activations in controls, LHS and RHS patients. * Family wise error corrections $p<0.05$ using a small volume correction within a sphere of 6mm for MTL activations. Lt (left), Rt (right), OFC (orbitofrontal cortex), Sup (superior), Inf (inferior), G (gyrus), C (cortex), PHG (parahippocampal gyrus), NS (no significant activations).

6.3.6.2 Correlation of verbal subsequent memory activations with out of scanner verbal learning (VL) scores

Controls showed no significant positive correlations. Activations within the posterior cingulate cortex (PCC) bilaterally correlated negatively with VL scores in controls. Although LHS patients showed no extra-temporal verbal subsequent memory effects as a group, correlation with VL scores showed a positive correlation with extra-temporal activation within the left OFC and anterior cingulate cortex (ACC). Positive correlation was also seen with temporal activations within the right posterior PHG and HC, bilateral MTG and left posterior HC activations (left posterior HC activation

was seen at a lower threshold (uncorrected p=0.01)). In RHS patients, left HC, bilateral anterior PHG, right posterior PHG and HC activations correlated positively with VL scores. No negative correlations with VL scores were seen in either patient group (Table 6.6, Fig 6.5).

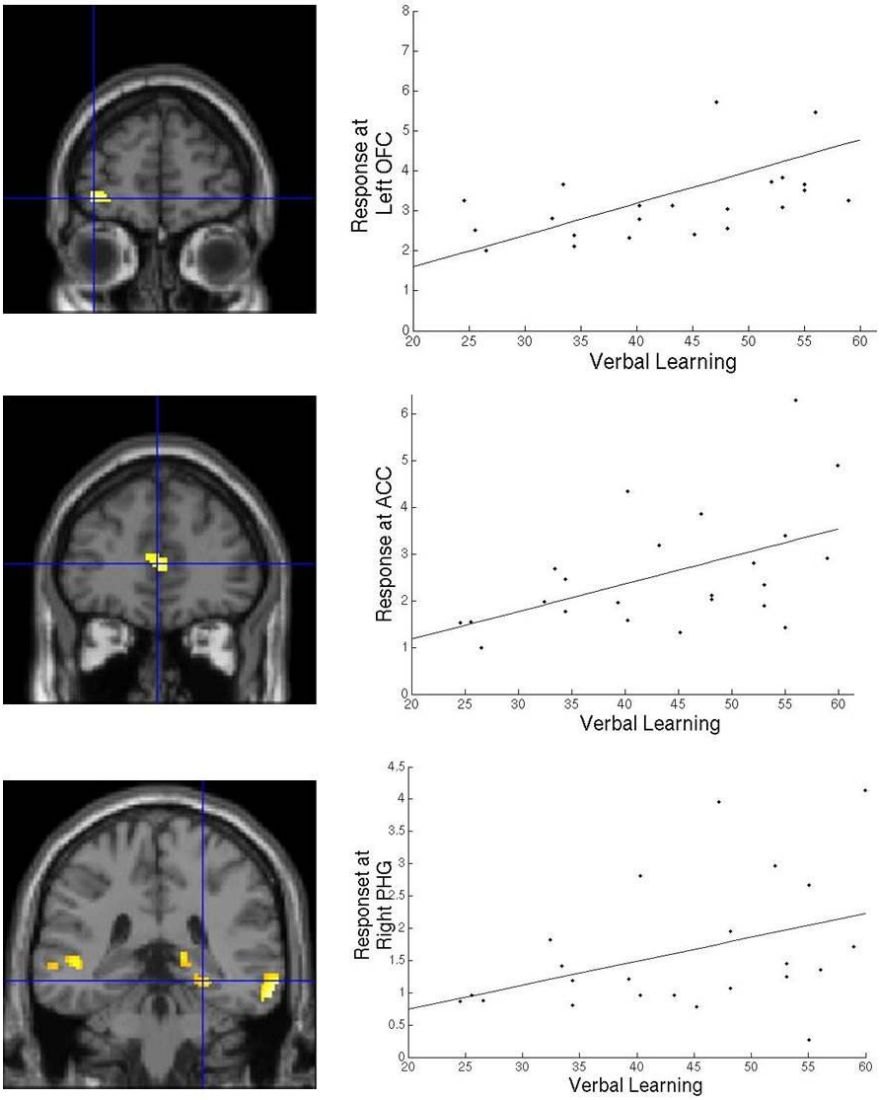


Fig 6.5: Positive correlation of verbal subsequent memory activations with verbal learning in LHS patients. Correlation maps are shown on a coronal image with their corresponding dot plot graphs plotted on SPM 8 shown on the right. Medial temporal lobe activations are displayed at a threshold of p<0.01, uncorrected. The top row shows correlations with left orbitofrontal cortex activation (OFC), middle row, activations within the anterior cingulate cortex (ACC) and bottom row, activation correlation within the right posterior parahippocampal gyrus (PHG). The coronal image on the bottom row also shows activations within the right and left middle temporal gyri and right posterior hippocampus that correlate positively with verbal learning in LHS patients.

Correlations with verbal (VL) and visual memory (DL) scores					
		Coordinate	**P value**	**Z score**	**Region**
Controls					
	Better VL		NS		
	Worse VL	6 -38 16	0.000	3.87	Rt posterior Cingulate C
		-12 44 16	0.000	3.84	Lt posterior Cingulate C
	Better DL		NS		
	Worse DL	16 -16 56	0.000	4.74	SMA / Rt Mid Cingulate C
		14 -12 30	0.000	3.61	Mid Cingulate C
LHS					
	Better VL	64 -26 -16	0.000	3.97	Rt Mid Temporal G
		-50 -38 2	0.001	3.26	Lt Mid Temporal G
		-36 56 -6	0.001	3.21	Lt OFC
		2 42 10	0.001	3.05	Anterior Cingulate C
		26 -36 -10	0.048*	2.57	Rt posterior PHG
		18 -32 -4	0.01*	2.54	Rt posterior HC
		-20 -36 2	0.01	2.25	Lt posterior HC
	Worse VL		NS		
	Better DL		NS		
	Worse DL		NS		
RHS					
	Better VL	-34 -30 -10	0.001*	3.88	Lt HC
		24 0 -26	0.003*	3.62	Rt anterior PHG/ amygdala
		18 -30 -12	0.008*	3.28	Rt posterior PHG
		-14 -2 -22	0.032*	2.74	Lt anterior PHG
		36 -36-4	0.048*	2.57	Rt posterior HC
	Worse VL		NS		
	Better DL	24 2 -24	0.017*	3.18	Rt amygdala/ anterior PHG
		-1 0 -18	0.059*	2.62	Lt amygdala
		-42 2 -2	0.001	3.06	Lt insula
	Worse DL		NS		

Table 6.6: Coordinates, p-values and z-scores of positive and negative correlations of verbal and visual subsequent memory activations with verbal memory (VL) and visual memory (DL) performance in controls, LHS and RHS patients. * Family wise error corrections $p<0.05$ using a small volume correction within a sphere of 6mm for MTL activations. Lt (left), Rt (right), OFC (orbitofrontal cortex), C (cortex), G (gyrus), Mid (middle), HC (hippocampus), PHG (parahippocampal gyrus), SMA (supplementary motor area), NS (no significant activations).

6.3.6.3 Visual subsequent memory

Controls activated the right OFC, fusiform gyrus, HC, amygdala and ITG. Activations were also seen in the left PHG, left temporal pole and MTG bilaterally. In LHS patients activations were seen in the right anterior PHG and amygdala, left insula, left superior and middle temporal gyri and left ACC. RHS patients activated the left insula, OFC, pre-central and post-central gyri, right anterior and posterior PHG and right posterior HC (Table 6.7, Fig 6.6).

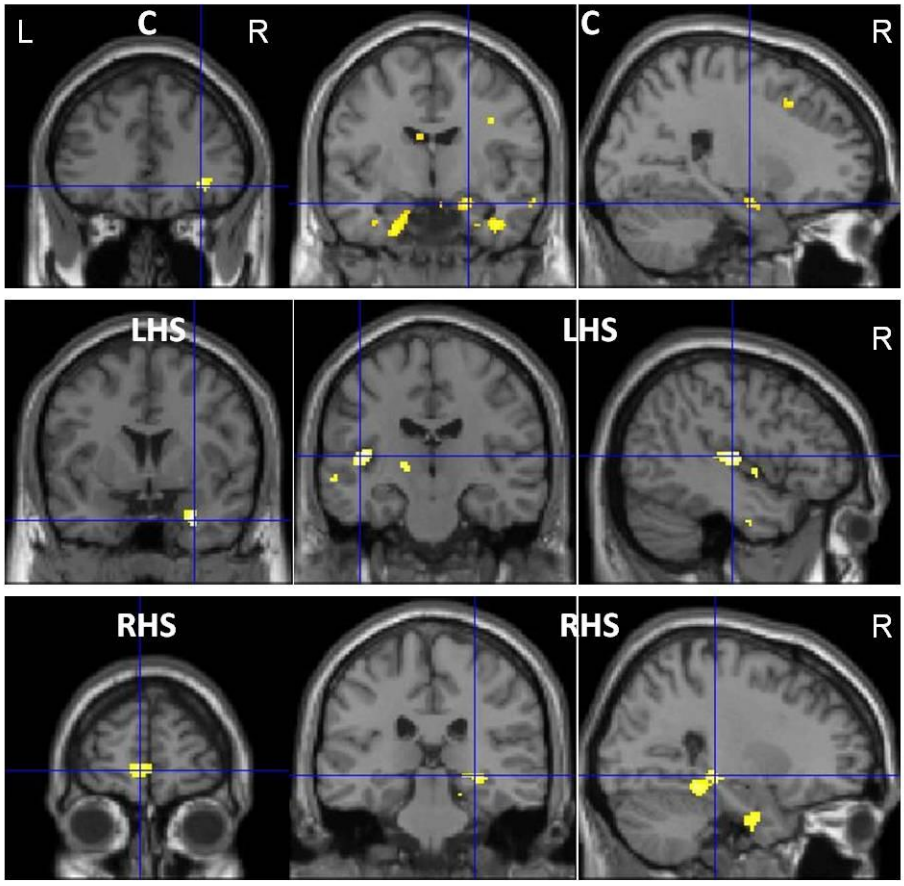


Fig 6.6: Whole brain visual subsequent memory in controls (C), LHS and RHS patients. Top row: activation in controls, middle row: LHS patients and bottom row: RHS patients. Medial temporal lobe activations are displayed at a threshold of $p<0.01$, uncorrected. Controls showed visual subsequent memory effects within the right orbitofrontal cortex, right hippocampus and parahippocampal gyri bilaterally. In LHS patients visual subsequent memory effects within the right parahippocampal gyrus and left insula are shown. In RHS patients, visual subsequent memory effects within the left medial orbitofrontal cortex, right posterior hippocampus and parahippocampal gyrus are shown.

Faces: Remembered - Familiar Forgotten							
LEFT HEMISPHERE				**RIGHT HEMISPHERE**			
Region	**Coordinate**	**P value**	**Z score**	**Region**	**Coordinate**	**P value**	**Z score**
CONTROLS							
Temporal pole	-34 16 -34	0.000	3.46	Mid Temporal G	58 0 -24	0.001	3.52
Mid temporal G	-54 4 -22	0.001	3.09	OFC	34 36 -9	0.000	3.34
PHG	-24 2 -36	0.024*	3.06	Amygdala	20 -2 -20	0.015*	3.15
PHG	-20 -2 -32	0.025*	2.95	Fusiform G	32 -2 -46	0.001	3.15
				Hippocampus	34 -14 -18	0.046*	2.70
				Inf Temporal G	42 -6 -32	0.001	3.04
LHS							
Insula / Sup Temporal G	-44 -18 8	0.000	4.43	PHG/ Amygdala	30 4 -32	0.051*	2.53
Sup Temporal G	-62 -38 16	0.001	3.11				
Mid Temporal G	-60 -22 -4	0.001	3.10				
Ant Cingulate C	-4 6 28	0.001	2.98				
RHS							
Insula	-40 -16 22	0.000	3.59	Sup Temporal G	60 -32 18	0.001	3.09
Pre-central G	-52 -6 50	0.000	3.31	Posterior PHG	32-38-12	0.026*	2.83
OFC	-4 62 -2	0.000	3.30	Posterior HC	22 -32 -4	0.044*	2.60
Post-central G	-60 -16 20	0.001	3.22	Anterior PHG/ Fusiform G	34 -4 -40	0.055*	2.50

Table 6.7: Coordinates, p-values and z-scores of whole brain visual subsequent memory activations in controls, LHS and RHS patients. *Family wise error corrections using a small volume correction within a sphere of 6mm for MTL activations. Lt (left), Rt (right), OFC (orbitofrontal cortex), Sup (superior), Mid (middle), Inf (inferior), G (gyrus), C (cortex), Ant (anterior), PHG (parahippocampal gyrus), NS (no significant activations).

6.3.6.4 Correlation of visual subsequent memory activations with out of scanner design learning (DL) scores

Controls showed no significant positive correlation. Activations within the middle cingulate cortex (MCC) and supplementary motor area correlated negatively with DL scores in controls. RHS patients showed significant positive correlation with right anterior PHG and amygdala, left amygdala and left insula activations (Table 6.6, Fig 6.7). No negative correlation with DL scores was seen in RHS patients. LHS patients showed neither positive nor negative correlation with DL scores.

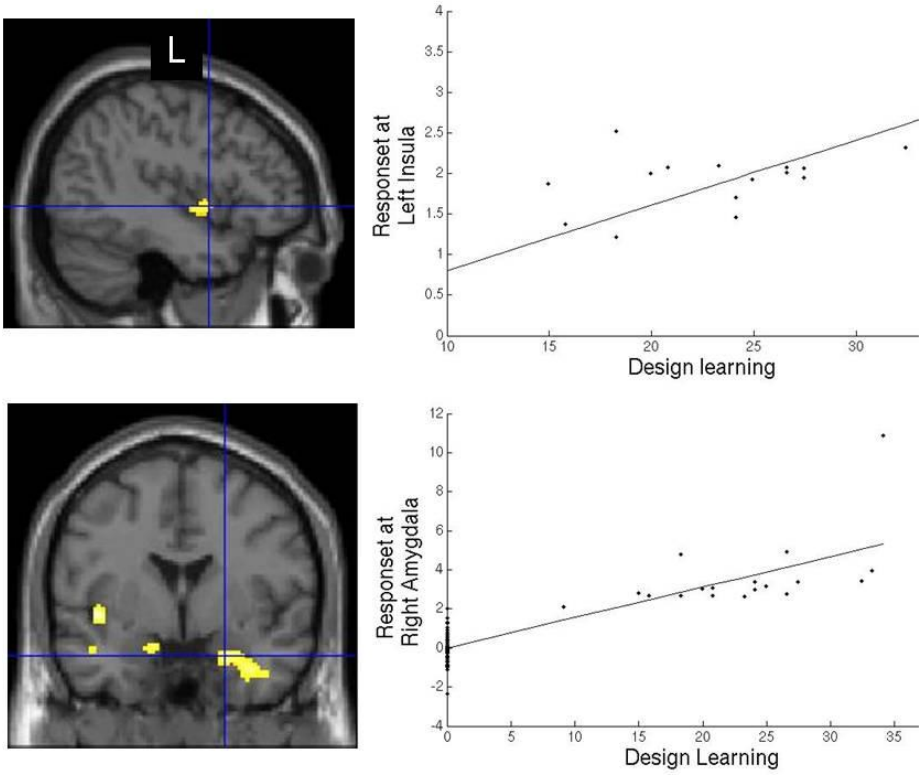


Fig 6.7: Positive correlations of visual subsequent memory activations with design learning (DL) in RHS patients. Medial temporal lobe activations are displayed at a threshold of $p<0.01$, uncorrected. Correlation maps are shown on the left with corresponding dot plot graphs plotted on SPM8 on the right. The top row shows correlation with left insula activation and bottom row shows right amygdala and anterior parahippocampal gyrus (PHG) correlation with DL scores in RHS patients. The bottom image also shows activation in the left amygdala that correlate positively with DL scores in RHS patients.

6.3.7 Effect Size Analysis

In our event related analysis above we showed brain regions that were important for successful memory formation in patients but not in controls. To further strengthen the methodology and validity of our findings we performed a post-hoc analysis where we investigated the effect size of brain activations for remembered, familiar and forgotten trials individually in a brain region that was important for subsequent memory in patients but not controls. Effect size quantification was performed within

the left insula where we showed significant successful subsequent visual memory activation in RHS patients but not in controls in the event related analysis.

Effect size quantification was performed by extracting the mean BOLD percentage signal change for remembered, familiar and forgotten faces individually using the MarsBar toolbox in SPM8 (Brett et al., 2002). This was performed in all RHS patients and controls at the single subject level. There was a significant difference in percentage signal change between the remembered, familiar and forgotten faces [mean % signal change (SEM), 0.035 (0.012), -0.002 (0.014), 0.008 (0.017) respectively] in RHS patients (paired t-test, $p<0.05$) with the highest positive percentage signal change for remembered faces. There was a negative percentage signal change for faces remembered, familiar and forgotten [-0.003 (0.012), -0.021 (0.013), -0.012 (0.014) respectively] in controls at the left insula with no significant difference in effect size between the three trials ($p>0.05$, paired t-test; Fig 6. 8). RHS patients showed a significantly higher percentage signal change for faces remembered compared to controls ($p< 0.05$, independent sample t-test).

A significant difference in effect size between remembered, familiar and forgotten faces was only seen in RHS patients but not in controls. There was a higher percentage signal change for faces remembered in RHS patients compared to controls. These findings corroborate the findings from the event related analysis above, that the left insula was significantly involved in subsequent memory formation for faces in RHS patients but not in controls.

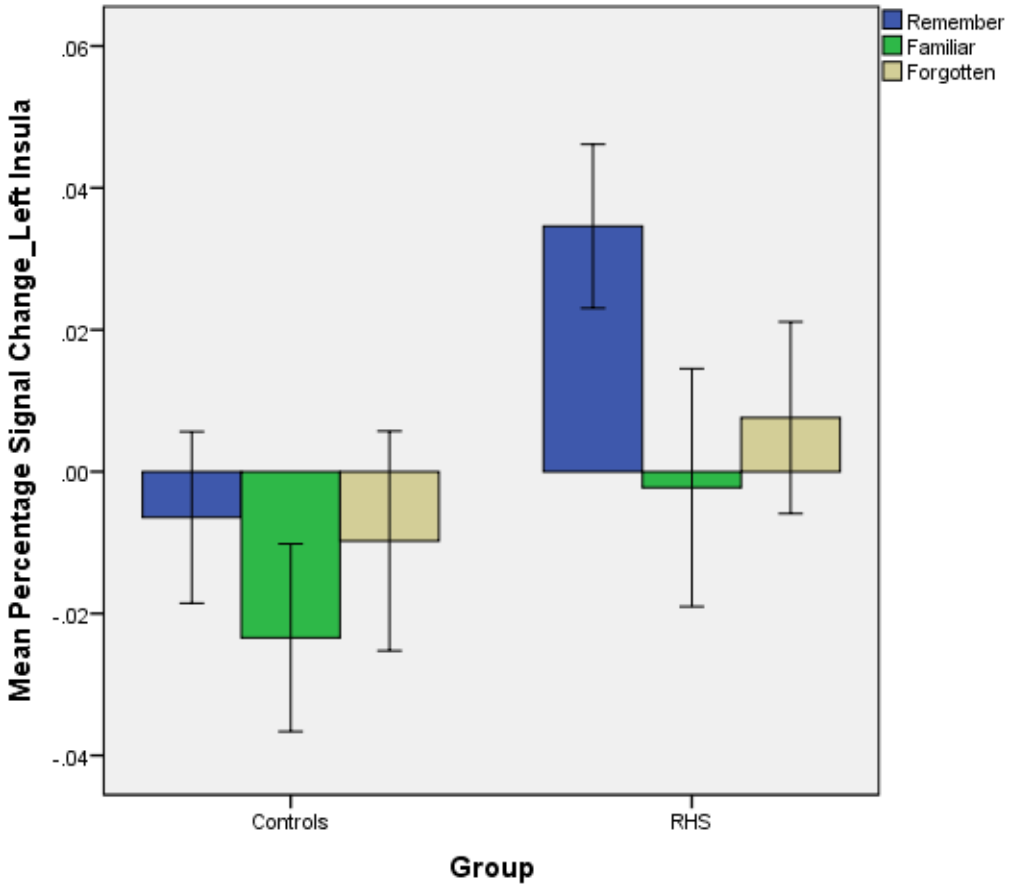


Fig 6.8: Mean percentage signal change and standard error (SEM) at the left insula for faces remembered, familiar and forgotten in right hippocampal sclerosis (RHS) patients and controls.

Summary of Verbal Memory Findings in LHS patients		
Word Encoding (Blocked analysis) **LHS>Controls**	**Verbal Subsequent Memory** (Event related analysis)	**Positive Correlation** of verbal subsequent memory with **Verbal Learning** scores
Rt Superior Temporal G	Rt posterior PHG and Hippocampus	Rt Mid Temporal G
Rt Inferior Frontal G	Rt Inferior Temporal G	Lt Mid Temporal G
Rt Middle Frontal G	Rt Fusiform G	Lt Orbitofrontal Cortex
	Lt Inferior Temporal G	Anterior Cingulate Cortex
		Rt posterior PHG
		Rt posterior Hippocampus
		Lt posterior Hippocampus
Summary of Verbal Memory Findings in RHS patients		
Word Encoding RHS>Controls	**Verbal Subsequent Memory**	**Positive Correlation** of verbal subsequent memory with **Verbal Learning** scores
Rt Superior Temporal G	Lt Pre-central G	Lt Hippocampus
Rt Middle Frontal G	Lt Parahippocampal G	Lt anterior Parahippocampal G
Lt Middle Frontal G	Lt Temporal pole	Rt posterior PHG and hippocampus
	Lt Orbitofrontal Cortex	Rt anterior PHG and amygdala
	Lt Inferior Frontal G	
	Rt Temporal pole	
	Rt Insula	
	Rt Pre-central G	
	Rt Parahippocampal G	

Table 6.8: Summary of verbal memory findings in LHS and RHS patients. Lt (left), Rt (right), G (gyrus), C (cortex), PHG (parahippocampal gyrus).

Summary of Visual Memory Findings in LHS patients		
Face Encoding (Blocked analysis) **LHS>Controls**	**Visual Subsequent Memory** (Event related analysis)	**Positive Correlation** of visual subsequent memory with **Design Learning** scores
Rt Superior Temporal G Rt Inferior Frontal G Rt Supramarginal G	Rt Anterior PHG and amygdala Lt Insula Lt Superior Temporal G Lt Middle Temporal G Lt Anterior Cingulate Cortex	No significant correlation seen
Summary of Visual Memory Findings in RHS patients		
Face Encoding RHS>Controls	**Visual Subsequent Memory**	**Positive Correlation** of visual subsequent memory with **Design Learning** scores
Rt Superior Temporal G (posterior) Lt Superior Temporal G	Rt Superior Temporal G (anterior) Rt Posterior PHG and hippocampus Rt anterior Parahippocampal G Rt Fusiform G Lt Insula Lt Pre-central G Lt Orbitofrontal Cortex Lt Post-central G	Rt anterior PHG and amygdala Lt amygdala Lt insula

Table 6.9: Summary of visual memory findings in LHS and RHS patients. Lt (left), Rt (right), (G (gyrus), PHG (parahippocampal gyrus).

6.4 Discussion

6.4.1 Summary of results (Tables 6.8 and 6.9)

Controls showed material-specific memory encoding activations with predominantly left hemispheric activations for word encoding and right for face encoding.

LHS patients showed greater right-sided activations both temporally (STG) and extra-temporally for word (MFG and IFG) and face (supramarginal gyrus, IFG) encoding. RHS patients similarly showed increased activations both temporally (right STG) and extra-temporally (bilateral MFG) for word encoding but increases in activation were limited to the temporal lobe (bilateral STG) for face encoding. Whilst

LHS patients showed predominantly right hemispheric increases for word and face encoding, RHS patients showed increased activation bilaterally.

Subsequent memory activations in controls were material specific with predominantly left sided activations for verbal subsequent memory and similar right sided activations for visual subsequent memory. LHS patients showed predominantly right temporal verbal subsequent memory activations and no extra-temporal activations. By contrast, RHS patients showed bilateral temporal and extra-temporal verbal subsequent memory effects. Both LHS and RHS patients showed visual subsequent memory activations within the right anterior MTL (anterior PHG, amygdala) but RHS patients additionally showed activations within the right posterior PHG and HC. Both patient groups showed left extra-temporal visual subsequent memory activations. Across both tasks, RHS patients showed greater extra-temporal subsequent memory effects than LHS patients.

Although LHS patients as a group showed only right temporal subsequent memory activations and no extra-temporal activations, patients with a better verbal memory showed additional activations within the left OFC, ACC and left posterior HC correlating positively with verbal learning scores. In RHS patients with a better verbal memory, activations within the left HC and right posterior hippocampus in addition to the bilateral anterior PHG activation correlated positively with verbal learning scores. RHS patients with a better visual memory showed significant correlations with activation within the left amygdala in addition to activations within the right anterior PHG and left insula that were seen in the visual subsequent memory analysis. No additional areas correlated with design learning in LHS patients.

The areas of significantly increased activation observed in patients compared to controls on word and face encoding were not associated with subsequent memory formation across both material types but additional contralateral MTL activations correlated with better memory performance within the patient groups. Extra-temporally, the OFC is involved in successful verbal and visual subsequent memory in controls and RHS patients and is activated in verbal subsequent memory in LHS patients with better verbal memory. The OFC therefore appears to be a critical region for encoding in controls and patients. Activations within anterior cingulum and insula correlated with better verbal and visual subsequent memory only in left and right hippocampal sclerosis patients respectively, but not in controls.

6.4.2 Memory Performance

Both patient groups performed significantly worse than controls in the out of scanner verbal learning task. In the design learning task however, LHS patients showed no significant difference to controls. RHS patients were significantly worse than controls and LHS patients. In the recognition task within the scanner both patient groups had significantly worse word and face recognition accuracy than controls. Both controls and patients had significantly lower face recognition than word recognition accuracy. This is possibly due to the fact that memorising words that are familiar and are associated with semantic inferences is an ‘easier’ task than memorising unfamiliar faces.

Both patient groups were impaired across both visual and verbal domains in line with current evidence suggesting a shift away from the material specific model of memory deficits in TLE (Baxendale, 1998; Gleissner et al., 2002; Glikmann-Johnston et al., 2008; Saling, 2009). In 1966, Margerison and Corsellis reported bilateral HS in

17 of 33 cases with mTLE on post-mortem examination (Margerison and Corsellis, 1966). Both widespread physiologic dysfunction due to ongoing seizure activity (Hermann et al., 2006) and extensive structural deficits beyond the lesional temporal lobe (Margerison and Corsellis, 1966,Focke et al., 2008; Keller et al., 2009) have been associated with widespread cognitive deficits seen in TLE patients.

6.4.3 Memory in controls

During memory encoding, controls showed widespread material specific frontal, parietal, temporal and occipital activation; left for verbal and right for visual encoding. During subsequent memory analyses although still material specific, the extra-temporal activations were limited to the left OFC for verbal subsequent memory and right OFC and IFG for visual subsequent memory.

Memory encoding is a complex dynamic process with activations representing a task specific network (Fletcher and Henson, 2001). IFG activations are seen during semantic and phonologic elaborations (Otten and Rugg, 2001) with material organisation and manipulation mediated within the MFG (Wig et al., 2004). A fronto-parietal interaction between the premotor cortex and posterior parietal cortex has been shown to be critical to attention during encoding (Corbetta et al., 2008). The MTL has been widely recognised for its key storage function of these memory representations for subsequent recall (Squire et al., 2004).

Robust activations that we showed in controls during encoding reflect the global cognitive state during the task and include strategies and stages of memory encoding as described above. Subsequent memory paradigms however are specific to activations that represent successful memory formation and bear some relevance to memory storage function (Hongkeun, 2011). Extra-temporally, we showed that the OFC was involved in both verbal and visual subsequent memory in controls.

The OFC is well connected to limbic structures including the amygdala, hippocampus, temporal pole, entorhinal, perirhinal and parahippocampal cortices (Carmichael and Price, 1995; Insausti et al., 1987; Lavenex et al., 2002) and may explain its critical role to successful memory formation along with MTL structures. A lesional study of the OFC in rhesus monkeys revealed impairments in recognition memory similar to that seen after medial temporal lesions (Meunier et al., 1997). In a PET study of a visual memory encoding paradigm, the OFC and PHG were the only regions that showed more activity with increasing encoding demands (Frey and Petrides, 2002).

The discrepancy in activation seen during encoding and subsequent memory analyses is due to the task differences explored by the two different analysis methods. Encoding explores the global cognitive task irrespective of whether an item is successfully encoded whilst subsequent memory paradigms specifically investigate activations for items successfully encoded.

6.4.4 Verbal memory encoding in TLE

Reorganisation of memory function to the contralesional hemisphere in patients with TLE has been consistently described particularly within the MTL (Bonelli et al., 2010; Powell et al., 2007; Richardson et al., 2003). This process is thought to occur as a ‘compensatory’ effort in TLE patients who have been shown to have widespread physiologic and structural deficits. Both LHS and RHS patients showed increased recruitment of the right STG compared to controls. Extra-temporally, LHS patients showed significantly greater right IFG and MFG activations whilst RHS patients showed bilateral MFG increases.

A few other studies have reported extra-temporal activations during verbal memory tasks in both LTLE and RTLE patients, but these have been small (Alessio et al., 2011; Dupont et al., 2000; Dupont et al., 2002; Maccotta et al., 2007). In a heterogenous group of right and left TLE patients Macotta et al showed reorganisation to the right IFG in both patient groups, left TLE greater than right TLE, compared to controls. As activations were explored within a limited IFG region it is not known if there were differences in other frontal lobe regions (Maccotta et al., 2007). Dupont et al showed increased bilateral with right more than left MFG activations in LHS patients, whilst RHS patients only showed increased left MFG activations. In this study controls only activated the left IFG (Dupont et al., 2002). In contrast, Alessio et al showed no difference in MFG activations in LHS patients compared to controls during a similar word encoding task but both LHS and RHS patients showed bilateral IFG activations that were lateralised to the contralesional hemisphere; activations that was not seen in controls (Alessio et al., 2011). Areas of reorganisation described in the latter two studies above were reported qualitatively based on group activation maps therefore it is not known if inter-group differences were statistically significant.

6.4.5 Visual memory encoding in TLE

LHS patients showed both temporal and extra-temporal reorganisation compared to RHS patients who only showed temporal reorganisation during face encoding. Although we described reduced medial OFC and ipsilesional MTL activations in both patient groups compared to controls, LHS patients showed greater network dysfunction compared to RHS patients with additional regions of reduced extra-temporal activation both ipsilesionally (left IFG and OFC) and contralesionally (right

post-central gyrus) positing an explanation for the more widespread reorganisation seen in LHS patients.

Few studies have investigated the extra-temporal neural correlates of visual encoding (Alessio et al., 2011; Maccotta et al., 2007). In an abstract pattern encoding task, Alessio et al reported right frontal activations in controls and bilateral frontal activations within the superior frontal gyrus and IFG in RHS and LHS patients. All 3 groups showed bilateral parieto-occipital activations. Group differences, however, were only reported qualitatively (Alessio et al., 2011).

Macotta et al reported right lateralised frontal activations in controls and right and left TLE patients in a visual encoding task. Although patients performed significantly worse than controls in a subsequent recognition test, no differences in the visual encoding network were seen between controls and patient groups. In this study, group differences were only explored within a limited IFG region of interest and an implicit encoding task in which memorisation was not encouraged was performed (Maccotta *et al.*, 2007). Greater IFG activation has been shown in explicit paradigms in which memorisation is encouraged (Dove et al., 2006). These factors may explain the lack of network differences reported.

During verbal and visual encoding, we showed extra-temporal contralesional reorganisation in LHS patients. RHS patients in contrast showed increased extra-temporal reorganisation bilaterally at word encoding but reorganisation was limited to the temporal lobe for face encoding.

6.4.6 Subsequent memory: Event related analysis

Activations in the event related design represent activations associated with successful memory formation in controls and patients. Though a less efficient network than controls (as patients perform significantly worse than controls across both tasks) activations in this specific paradigm represent a ‘necessary’ network for patients for subsequent memory formation. These activations were further correlated with neuropsychological memory performance measures. Activations that correlated positively represent areas of effective recruitment in patients who performed better.

6.4.6.1 Verbal subsequent memory and correlation with verbal learning performance

Controls showed predominantly left hemisphere verbal subsequent memory activations. As most controls performed uniformly well, no positive correlation with VL was seen. Negative correlation was seen with activation within the posterior cingulate, a region that is typically activated as part of the default mode network (Raichle et al., 2001), implying that poor performance in controls is likely to be due to distraction or reduced attention during the task.

During verbal subsequent memory, LHS patients as a group showed predominantly right temporal activations with no extra-temporal activations however in LHS patients who performed better, positive correlation was seen with additional activations temporally within the ipsilesional posterior hippocampus and extra-temporally within the left OFC and ACC implying areas of effective recruitment in this patient group.

By contrast, RHS patients showed bilateral temporal and extra-temporal verbal subsequent memory activations. RHS patients who performed better showed

positive correlation with activation within the anterior medial temporal lobes bilaterally and right posterior MTL implying effective recruitment of these regions for verbal memory performance.

In both our patient groups recruitment of the ipsilesional posterior HC and bilateral MTL was an efficient process for verbal subsequent memory.

6.4.6.2 Visual subsequent memory and correlation with design learning performance

Predominantly right extra-temporal activations were seen in controls for visual subsequent memory. As in verbal learning, no positive correlation was seen in controls with design learning and negative correlation was seen with activation within the default mode system.

In contrast to bilateral extra-temporal activations for verbal subsequent memory, RHS patients showed mainly left extra-temporal visual subsequent memory activations (left insula, OFC, left precentral and postcentral gyri). RHS patients showed widespread areas of reduced right extra-temporal activations compared to controls during face encoding which may explain the 'compensatory' left extra-temporal recruitment in these patients during visual subsequent memory. RHS patients as a group showed visual subsequent memory activations within the right temporal lobe (PHG, amygdala, and posterior HC) however patients who performed better showed positive correlation with design learning scores with activations within the left amygdala in addition to right amygdala and left insula activations. Left amygdala and insula activation was not seen in controls and represent areas of efficient recruitment in RHS patients for visual memory.

LHS patients showed right MTL activations for visual subsequent memory as in verbal subsequent memory but also showed significant extra-temporal visual subsequent memory activations within the left insula and ACC that were not seen for verbal subsequent memory. No correlation with design learning was seen in LHS patients possibly because LHS patients did not perform significantly worse than controls on the design learning task.

6.4.6.3 Medial temporal subsequent memory effects

In both patient groups bilateral MTL activation correlated positively with verbal and visual memory performance implying efficient network reorganisation within these structures. Several verbal (Richardson et al., 2003) and visual (Guedj et al., 2011) event-related studies have shown subsequent memory effects and correlations within the MTL in left and right TLE patients (Bonelli et al., 2010; Powell et al., 2007). Richardson et al showed that activation within the right MTL in LHS patients was an efficient process during verbal subsequent memory (Richardson et al., 2003). Powell et al however showed that only left MTL activations during verbal subsequent memory correlated with better memory performance. Bonelli et al and Powell et al showed that only right MTL activation represented efficient reorganisation in a face encoding task however Guedj et al showed that bilateral MTL activation represented an efficient network.

To assess subsequent memory, we used a robust paradigm of, 'remember–familiar+forgotten' whilst a paradigm of 'remember–forgotten' was used by Powell et al and Bonelli et al, 'remember-familiar' by Richardson et al and 'remember' by Guedj et al. Powell et al acquired fMRI data on a 1.5T scanner, Richardson et al on a 2T scanner whilst we used a 3T scanner. These methodological differences as well

as the differences in number of patients and pathology may account for the differences seen.

6.4.6.4 Extra-temporal subsequent memory effects

Both patient groups did not activate the ipsilesional OFC as controls did. In an electrical stimulation study, responses in the OFC were detected upon stimulation of the hippocampus positing a role of the OFC in propagation of MTL seizures (Wilson and Engel, 1993). The lesser activation we observed in patients may therefore be a result of either network dysfunction caused by propagation of epileptic activity, be due to concomitant frontal structural deficits (Bonilha et al., 2007), or both.

The importance of the OFC to successful verbal memory formation was demonstrated in LHS patients where only those with a better verbal memory showed significant positive correlation with activation within the left OFC. In a verbal encoding study, healthy participants who spontaneously used a semantic strategy to memorise items showed greater activation in the OFC, indicating that OFC activation predicted which subjects would initiate effective verbal learning strategies (Savage et al., 2001). In LHS patients who perform better, left OFC activation may reflect the effective strategies employed. The left OFC was also seen in RHS patients during both verbal and visual subsequent memory analyses.

In a verbal subsequent memory study of non-amnesic temporal and frontal lobe epilepsy patients, activation within the right insula, left cuneus and bilateral anterior cingulate cortex was reported to be an efficient network (Eliassen et al., 2008). Using correlation analysis in a larger homogenous group of LHS patients we showed that anterior cingulate cortex activation similarly represents effective recruitment for verbal subsequent memory in LHS patients but not in controls. Anterior cingulate cortex activation has been shown to be related to motivation, goal directed behaviour

(Devinsky et al., 1995) and is activated particularly in tasks with greater difficulty (Fu et al., 2002). This may explain anterior cingulate activation in LHS patients who performed better.

Left insula visual subsequent memory activations were seen in both LHS and RHS patients but not in controls. The insula has been functionally implicated in higher order cognition and emotional recognition from facial expression (Calder et al., 2000; Singer et al., 2004) and atrophy in the insula has been associated with a reduced ability to discern facial expression in patients with dementia (Hsieh et al., 2012). Encoding emotional faces has been shown to be associated with better subsequent recognition memory (Nomi et al., 2012). In RHS patients, insula activation was associated with better visual memory implying efficient recruitment. This may be attributed to better emotional recognition in patients who performed better.

6.4.7 Strengths and limitations

This study has several methodological strengths. Activations within the MTL are susceptible to geometric distortions and signal loss. Factors that influence this include scanning parameters such as slice thickness, echo time and gradients used (Powell et al., 2005). In whole brain blocked design studies, no MTL activations were seen during memory encoding (Alessio et al., 2011; Dupont et al., 2000). We scanned in the oblique axial plane on a 3T scanner with a slice thickness of 2.5 mm, echo time of 25 ms and showed significant anterior HC and amygdala activations in both the blocked design and event related analysis.

Second, we included a relatively large homogenous cohort of HS patients who were all left language dominant to ensure that there was no inherent bias to contralateral activations during the verbal encoding task.

Third, during memory encoding, activations within the PFC, MTL and parietal lobe have been described with familiarity judgements (Skinner and Fernandes, 2007). We therefore assessed successful memory formation by subtracting activations that represented neural correlates of not just items forgotten but also items deemed familiar, to generate a more specific model of successful subsequent memory.

Fourth, we applied robust analysis methods and used conservative statistical thresholds that allow inferences to be made about HS patients as a population.

There are several limitations to our study. For an event related analysis it is important that there are adequate stimuli to create events for items remembered and those deemed familiar and forgotten. In controls and higher functioning patients there can be relatively fewer familiar or forgotten responses particularly for words so in our study we incorporated greater number of stimuli than previously used (Powell et al., 2007). Whilst this has conferred greater sensitivity to our event related analysis, this imbalance remains a methodological limitation.

Although we attempted maximal brain coverage, our field of view did not incorporate the whole of the superior frontal gyrus. Anti-epileptic drugs may have a detrimental effect on cognition. Although both patient groups were on equal numbers of antiepileptic drugs, this effect was not accounted for in our analysis.

6.4.8 Clinical implications and future work

In well selected patients with refractory TLE, temporal lobe resection may render up to 50% of patients seizure free (de Tisi et al., 2011) however reports from as early as 1958 have shown that amnesia may ensue from unilateral temporal lobe resection (Kapur and Prevett, 2003; Penfield and Milner, 1958). FMRI is a useful tool in

predicting decline of memory after anterior temporal lobe resection. Asymmetry of MTL activations and absolute hippocampal activations pre-operatively have been correlated with memory performance post-operatively to predict memory change (Bonelli et al., 2010; Powell et al., 2008; Rabin et al., 2004; Richardson et al., 2003). Whilst these studies describe correlations of post-operative memory decline to pre-operative MTL activations, little is known of the predictive value of pre-operative extra- temporal activations for post operative memory change.

We are investigating the predictive ability of the extra-temporal activations shown in this study to memory function post-operatively.

6.4.9 Conclusion

Both right and left TLE due to HS have altered memory networks with a predominantly ipsilesional hemisphere reduction in activations during encoding. LHS patients engaged contralateral extra-temporal and temporal regions during both word and face encoding greater than controls whilst RHS patients show bilateral extra-temporal increases during word encoding and only temporal increases during face encoding. These areas of reorganisation in LHS and RHS patients were not involved in subsequent memory formation. The neural correlates of subsequent memory formation differed between controls and patients with HS. Both LHS and RHS patients who performed better showed effective recruitment of the contralesional medial temporal lobe during verbal and visual encoding respectively. The orbitofrontal cortex is critical to subsequent memory formation in controls and patients. Activations within anterior cingulum and insula correlated with better verbal and visual subsequent memory in left and right hippocampal sclerosis patients respectively, representing areas of effective extra-temporal recruitment.

Chapter 7: Factors affecting reorganisation of memory encoding networks in Temporal Lobe Epilepsy

Abstract

Aims

As described in chapter 6, distinct areas of reorganisation have been shown to be efficient when associated with successful subsequent memory formation or inefficient when not associated with successful subsequent memory. We investigated the effect of clinical parameters that modulate memory functions: age at onset of epilepsy, epilepsy duration and seizure frequency in a large cohort of patients.

Methods

I studied 53 patients with unilateral TLE and HS (29 left). All participants performed a fMRI encoding paradigm of faces and words. A continuous regression analysis was used to investigate the effects of age at onset of epilepsy, epilepsy duration and seizure frequency on the activation patterns in the memory encoding network.

Results

Earlier age at onset of epilepsy was associated with left posterior hippocampus activations that were involved in successful subsequent memory formation in left hippocampal sclerosis patients. No association of age at onset of epilepsy was seen with face encoding in right hippocampal sclerosis patients. In both left hippocampal sclerosis patients during word encoding and right hippocampal sclerosis patients during face encoding, shorter duration of epilepsy and lower seizure frequency were associated with medial temporal lobe activations that were involved in successful memory formation. Longer epilepsy duration and higher seizure frequency were

associated with contralateral extra-temporal activations that were not associated with successful memory formation.

Conclusion

Age at onset of epilepsy influenced verbal memory encoding in patients with TLE due to hippocampal sclerosis in the speech-dominant hemisphere. Shorter duration of epilepsy and lower seizure frequency were associated with less disruption of the efficient memory encoding network whilst longer duration and higher seizure frequency were associated with greater, inefficient, extra-temporal reorganisation.

7.1 Introduction

Memory in TLE has been related to several clinical factors including duration of epilepsy (Cheung et al., 2006), age at onset and seizure frequency (Hermann et al., 2002; Kaaden and Helmstaedter, 2009). Age at onset and duration of epilepsy have also been shown to be predictive of memory outcome after anterior temporal lobe resection (Baxendale et al., 2006; Baxendale, 2008).

fMRI studies have shown that memory reorganisation within MTL structures are influenced by age at onset of epilepsy, epilepsy duration and seizure frequency. Cheung et al showed that longer duration of epilepsy was associated with reduced medial temporal lobe activation (Cheung et al., 2006) whilst greater reorganisation to the contralateral medial temporal lobe has been associated with a lower seizure frequency (Figueiredo et al., 2008). In a non-material specific complex scene encoding task, earlier age at onset of epilepsy was associated with greater asymmetry of medial temporal lobe activations, conferred by predominant contralateral activations (Mechanic-Hamilton et al., 2009). To date, factors influencing extra-temporal memory reorganisation have not been investigated.

In chapter 6, we showed an ipsilateral reduction in network activation during both verbal and visual encoding. Left HS patients showed greater contralesional temporal and extra-temporal activations compared to controls across both verbal and visual encoding whilst right HS patients showed bilateral increases. In both LHS and RHS patients encoding activations within the contralateral MTL during word and face encoding were associated with successful subsequent memory formation. Extra-temporally, encoding activations within the left orbitofrontal and anterior cingulate cortex in LHS patients during word encoding and left insula activation in RHS

patients during face encoding were associated with successful subsequent memory formation.

In this study I investigated the effect of age at onset of epilepsy, duration of epilepsy and the effect of seizure burden on both temporal and extra-temporal memory reorganisation. I hypothesized that:

1) Patients with an earlier age at onset, longer duration of epilepsy and greater seizure frequency would have greater alteration of the memory encoding network with predominantly ipsilesional temporal and extra-temporal reduction in activations and more extensive reorganisation contralateral to the lesion.
2) Patients with a shorter duration of epilepsy, later age at onset and lower seizure frequency would have less disruption of the memory encoding network with greater activations in brain areas shown to be associated with subsequent memory formation in chapter 6.

7.2 Materials and Methods

7.2.1 Subjects

53 patients with medically refractory TLE (29 left: median age 40 years (range 19-54), 24 right: median age 42.5, range 21-56) due to unilateral HS having pre-surgical evaluation at NHNN were studied (Table 7.1). These were the same patients studied in chapter 6 with the addition of a further five LHS and four RHS patients. 26 healthy native English speaking controls, median age 37 years (range 19-58) with no neurological or psychiatric history were also studied.

Seizure frequency was calculated as the number of complex partial seizures per month. There was no significant difference between patient groups in age, age at

onset of epilepsy, epilepsy duration, seizure frequency, hippocampal volumes, number of AEDs or language lateralisation (Independent sample two-tailed t-test, $p>0.05$,Table 1). fMRI paradigms, data acquisition, data analysis and memory testing is detailed in chapter 5.

7.2.2 Statistical Analysis

Statistical analyses were performed using PASW Statistics 18.0 (IBM, Armonk, USA). Correlations between age, age at onset of epilepsy, duration, hippocampal volume, number of AEDs frequency of CPS per month and language lateralization were performed with the verbal and visual memory test scores described above.

7.2.3 Factors affecting memory reorganisation

The effect of age at onset of epilepsy, epilepsy duration and seizure frequency on word and face memory encoding networks was explored separately in LHS and RHS patients. These parameters were entered as continuous regressors in an ANCOVA against the word and face whole brain blocked design encoding activations in each patient group.

As age at onset was highly correlated to duration of epilepsy (Pearson correlation coefficient 0.75, $p<0.001$), the ANCOVA was performed with either age at onset or duration used as a covariate to investigate the effect of these clinical parameters in turn on face and word encoding networks in LHS and RHS patients. The number of CPS per month at the time of the scan was used as a measure of current seizure frequency. As there was no correlation between age at onset or duration of epilepsy and seizure frequency (Pearson correlation < 0.5), neither of these were used as an additional covariate in this analysis.

Regression analyses were reported at $p<0.005$ uncorrected. Medial temporal lobe activations were reported corrected for multiple comparisons, FWE $p<0.05$ using a small volume correction within a 12mm diameter sphere (Bonelli et al., 2010; Sidhu et al., 2013).

7. 3 Results

7.3.1 Neuropsychological memory test performance

There was no significant difference between the patient groups on the verbal memory measures (Independent sample t-test, $p>0.05$) but LHS patients performed significantly better than RHS patients in the design learning and delayed design recall tasks (Independent sample two-tailed t-test $p<0.01$), (Table 7.1).

In LHS patients, neither verbal list learning nor delayed verbal recall correlated with age at onset, duration of epilepsy, seizure frequency, hippocampal volumes or language lateralisation ($p>0.05$).

In RHS patients, shorter duration of epilepsy was associated with better design learning (Pearson correlation 0.57, $p =0.007$). Neither design list learning nor delayed design recall correlated with age at onset, language lateralisation, seizure frequency or hippocampal volumes ($p>0.05$).

	Age (yrs)	Age at onset (yrs)	Duration (yrs)	Language LI	L15 (/75)	L6 /15	D15 /45	D6 /9	RHV cm^3	LHV cm^3	CPS /mth	AED
LHS	40 (7.5)	14.6 (10.9)	23.8 (14.4)	-0.69 (0.3)	43.5 (10.4)	7.9 (3.1)	34* (7.4)	7.2* (1.7)	2.8 (0.4)	1.8 (0.4)	8.4 (10.8)	2 (1)
RHS	42.5 (14.5)	13.2 (10.3)	29.1 (16.2)	-0.64 (0.4)	43.3 (9.8)	9.3 (3)	28.3 (7.8)	5.5 (3)	1.9 (0.4)	2.7 (0.3)	5.7 (6)	2 (1)

Table 7.1: Demographic details and results of standard memory tests in patients, Mean (SD) of AED (Number of anti-epileptic drugs),LI (lateralisation index), HV (hippocampal volume), L15 (verbal list learning), L6 (delayed verbal recall), D15 (design learning), D6 (delayed visual recall), * LHS> RHS $p<0.01$

7.3.2 fMRI Results: Regression Analyses

7.3.2.1 Age at onset

Word encoding: In LHS patients, earlier age at onset was associated with significant activations within the posterior left HC, middle occipital gyrus (MOG), post-central gyrus and bilateral posterior MTG. Older age at onset was associated with left anterior fusiform gyrus activations (Fig 7.1, Table 7.2). No significant correlation of age at onset was seen in RHS patients during word encoding.

WORD ENCODING LHS Patients: Earlier age at onset							
	Left Hemisphere			Right Hemisphere			
Region	**Coordinate**	**P value**	**Zscore**	**Region**	**Coordinate**	**Pvalue**	**Zscore**
Mid Occipital G	-50 -78 10	0.000	3.40	Inf Temporal G	44 -52 -8	0.001	3.21
Hippocampus	-26 -20 -18	0.002*	2.89	Mid Temporal G	60 -36 -6	0.002	2.91
Mid Temporal G	-54 -34 -6	0.003	2.80				
Post. Hippocampus	-30 -36 0	0.036*	2.78				
Post- Central G	-56 -12 38	0.003	2.77				
Left HS Patients: Later age at onset							
	Left Hemisphere			Right Hemisphere			
Region	**Coordinate**	**P value**	**Zscore**	**Region**	**Coordinate**	**Pvalue**	**Zscore**
Fusiform G	-30 -10 -40	0.000	3.72				

Table 7.2 Coordinates, p-values and z-scores of whole brain activations associated with age at onset of epilepsy in LHS patients. * Family wise error corrections p<0.05 using a small volume correction within a sphere of 6mm for medial temporal lobe activations. Mid (middle), Inf (inferior), Post (posterior) G (gyrus).

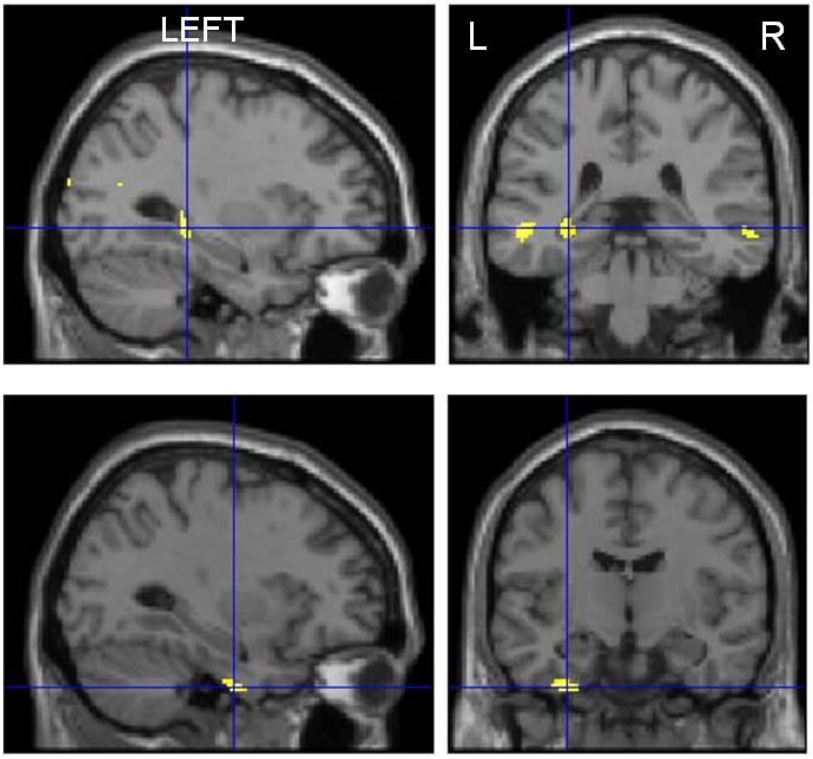


Fig 7.1: Correlation of word encoding with age at onset of epilepsy. Upper panel: left posterior hippocampal and bilateral posterior medial temporal lobe activations associated with an earlier age at onset of epilepsy. Lower panel: Left anterior fusiform gyrus activations associated with older age at onset of epilepsy.

Face encoding:

Neither LHS nor RHS patients showed a significant correlation between face encoding and age at onset of epilepsy.

7.3.2.2 Duration of epilepsy

Word encoding: In LHS patients, longer duration correlated significantly with right hemispheric activations within the pre-central gyrus, MFG and supramarginal gyrus. Shorter duration correlated predominantly with left hemispheric activations in HC, MOG,MTG, postcentral gyrus, medial OFC and IFG. Significant right PHG correlation was also seen. No significant correlation was seen in RHS patients (Fig 7.2, Table 7.3).

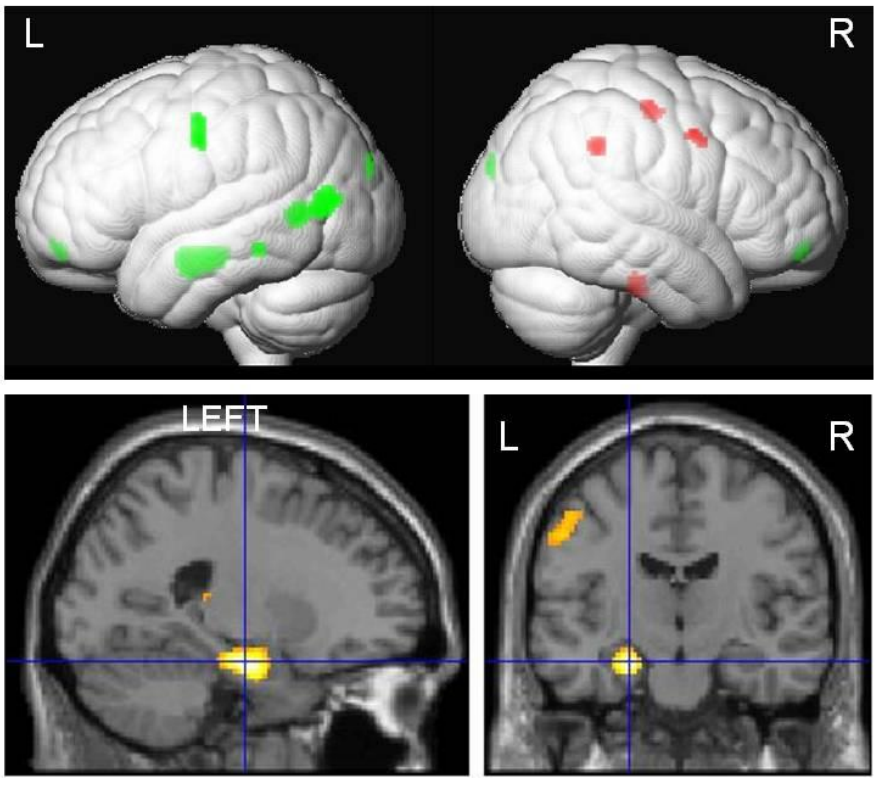


Fig 7.2: Correlation of word encoding with duration of epilepsy. Upper panel: Render image showing predominantly left hemispheric activations (green) associated with a shorter duration and right hemispheric activations (red) associated with longer duration of epilepsy. Lower panel: Sagittal and axial image showing left medial temporal lobe activations associated with a shorter duration of epilepsy

Face encoding: In LHS patients, shorter duration of epilepsy correlated significantly with right amygdala and left hippocampus, OFC and STG activations. Longer duration of epilepsy correlated with activations within the right supramarginal gyrus, pre-central gyrus and left inferior parietal lobule.

In RHS patients, shorter duration correlated with left PHG and hippocampal activations whilst longer duration correlated with left post-central gyrus activation (Fig 7.3, Table 7.3).

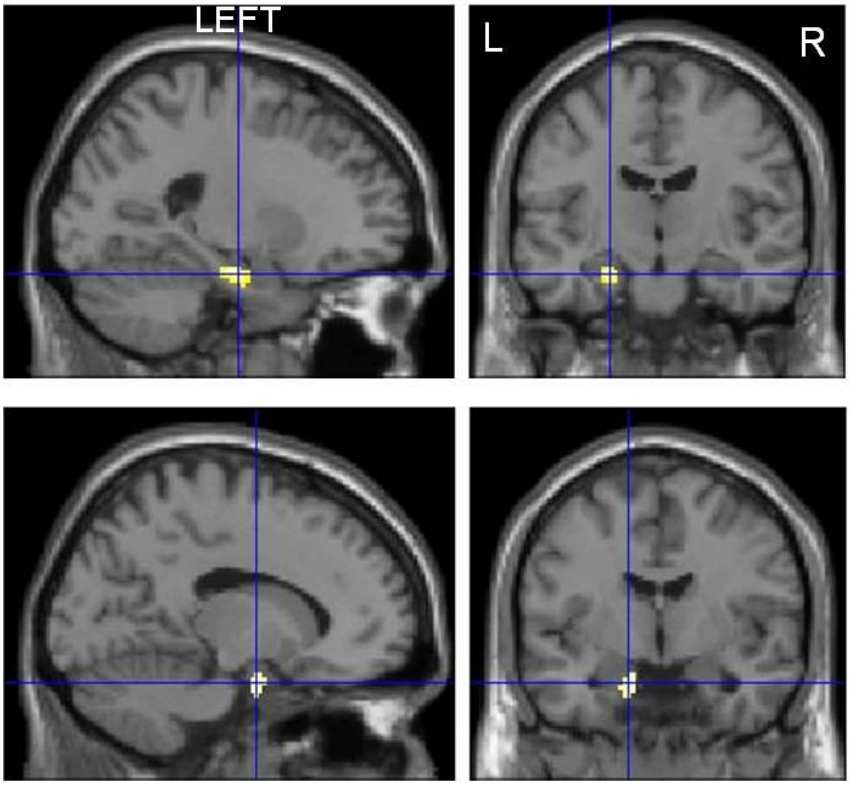


Fig 7.3: Correlation of face encoding with shorter duration of epilepsy. Left medial temporal lobe activations associated with a shorter duration of epilepsy in LHS patients (upper panel) and RHS patients (lower panel) during face encoding.

WORD ENCODING							
LHS Patients: Shorter duration of epilepsy							
	Left Hemisphere			**Right Hemisphere**			
Region	**Coordinate**	**P value**	**Zscore**	**Region**	**Coordinate**	**Pvalue**	**Zscore**
Hippocampus	-22 -14 -20	0.000*	4.51	Parahippocampal	18 0 -20	0.048*	2.54
Mid Occipital G	-42 -62 4	0.000	3.46				
Mid Temporal G	-50 -72 6	0.001	2.99				
Post-central G	-54 -12 40	0.001	3.18				
Med Orbito-frontal	-4 58 -14	0.001	3.01				
Inf Frontal G	-36 16 12	0.003	2.74				
LHS Patients: Longer Duration of epilepsy							
`				Pre-central G	24 -18 58	0.000	3.63
				Mid Frontal G	32 4 44	0.003	2.78
				Supramarginal G	40 -44 36	0.004	2.63
FACE ENCODING							
LHS Patients: Shorter duration of epilepsy							
	Left Hemisphere			**Right Hemisphere**			
Region	**Coordinate**	**P value**	**Zscore**	**Region**	**Coordinate**	**Pvalue**	**Zscore**
Hippocampus	-24 -14 -20	0.000	3.52	Amygdala	26 -2 -28	0.036*	2.61
Orbito-Frontal C	-30 56 -8	0.005	2.58				
Sup Temporal G	-38 22 -32	0.003	2.72				
LHS Patients: Longer duration of epilepsy							
	Left Hemisphere			**Right Hemisphere**			
Region	**Coordinate**	**P value**	**Zscore**	**Region**	**Coordinate**	**Pvalue**	**Zscore**
Inf. Parietal L	-58 -30 50	0.000	3.54	Supramarginal G	44 -42 32	0.000	3.58
	-24 -10 44	0.001	3.28	Pre-central G	24 -18 58	0.001	3.01
FACE ENCODING RHS Patients: Shorter duration of epilepsy							
	Left Hemisphere			**Right Hemisphere**			
Region	**Coordinate**	**P value**	**Zscore**	**Region**	**Coordinate**	**Pvalue**	**Zscore**
Parahippocampal G	-14 -2 -24	0.026*	2.74				
RHS Patients: Longer duration of epilepsy							
Post-central G	-42 -36 54	0.005	2.55				

Table 7.3: Coordinates, p-values and z-scores of whole brain activations associated with duration of epilepsy during word encoding in LHS patients and face encoding in LHS and RHS patients. There was no correlation of epilepsy duration and word encoding in RHS patients. * Family wise error corrections $p<0.05$ using a small volume correction within a sphere of 6mm for medial temporal lobe activations. Sup (Superior), Mid (Middle), Inf (Inferior), Med (Medial), G (gyrus), L (lobule), C (cortex).

7.3.2.3 Seizure Frequency

Word Encoding: In LHS patients lower seizure frequency was associated with activations within the left IFG, right STG, PHG, rolandic operculum and bilateral HC activations. Higher seizure frequency correlated with right OFC activation.

In RHS patients, lower seizure frequency was associated with left MTL activation within the PHG and hippocampus whilst higher frequency was associated with activation within the left rolandic operculum (Fig 7.4, Table 7.4).

Face encoding: In LHS patients, lower seizure frequency correlated with activations within the right HC, STG, MTG, left amygdala and bilateral IFG. Higher seizure frequency correlated with activations within the left paracentral lobule.

In RHS patients, lower seizure frequency correlated significantly with activations within the left PHG and HC and right amygdala and PHG whilst a higher seizure frequency correlated with activations within the left post-central gyrus and inferior parietal lobule (Fig 7.4, Table 7.4).

WORD ENCODING LHS Patients: lower CPS frequency							
	Left Hemisphere			**Right Hemisphere**			
Region	**Coordinate**	**P value**	**Zscore**	**Region**	**Coordinate**	**Pvalue**	**Zscore**
Hippocampus	-20 -20 -14	0.027*	2.77	Hippocampus	36 -28 -6	0.001*	4.08
Inf Frontal G	-42 12 28	0.003	2.73	Parahippocampal G	30 -6 -32	0.001*	3.76
				Sup Temporal G	56 -22 8	0.001	3.11
				Rolandic operculum	38 -26 24	0.001	
LHS Patients: higher CPS frequency							
				OFC	18 60 -10	0.001	3.13
RHS Patients: higher CPS frequency							
Rolandic operculum	-42 -34 22	0.004	2.64				
RHS Patients: lower CPS frequency							
PHG/hippocampus	-32 -28 -14	0.026*	2.93				
FACE ENCODING LHS Patients: lower CPS frequency							
	Left Hemisphere			**Right Hemisphere**			
Region	**Coordinate**	**P value**	**Zscore**	**Region**	**Coordinate**	**Pvalue**	**Zscore**
Inf Temporal G	-46 -50 -10	0.000	3.52	Mid Temporal G	60 -48 -6	0.000	4.77
Inf Frontal G	-42 12 28	0.003	2.79	Hippocampus/PHG	28 -28 -6	0.000*	4.28
Amygdala		0.038*	2.59	Sup Temporal G	58 -24 4	0.000	3.78
				Inf Frontal G	48 18 24	0.003	2.73
LHS Patients: higher CPS frequency							
Paracentral lobule	-12 -32 58	0.000	3.33				
RHS Patients: lower CPS frequency							
PHG/ Hippocampus	-32 -18 -20	0.034*	2.65	Amygdala/PHG	36 0 -24	0.026*	2.76
				Hippocampus	24 -12 -18	0.021*	2.55
RHS Patients: higher CPS frequency							
Post-central G	-48 -12 32	0.001	3.14				
Inf Parietal L	-46 -32 24	0.002	2.95				

Table 7.4: Coordinates, p-values and z-scores of whole brain activations associated with seizure frequency during face and word encoding in LHS and RHS patients.* Family wise error corrections $p<0.05$ using a small volume correction within a sphere of 6mm for medial temporal lobe activations. CPS (complex partial seizure), Sup (Superior), Inf (inferior), G (gyrus), PHG (parahippocampal gyrus), Mid (middle), L (lobule)

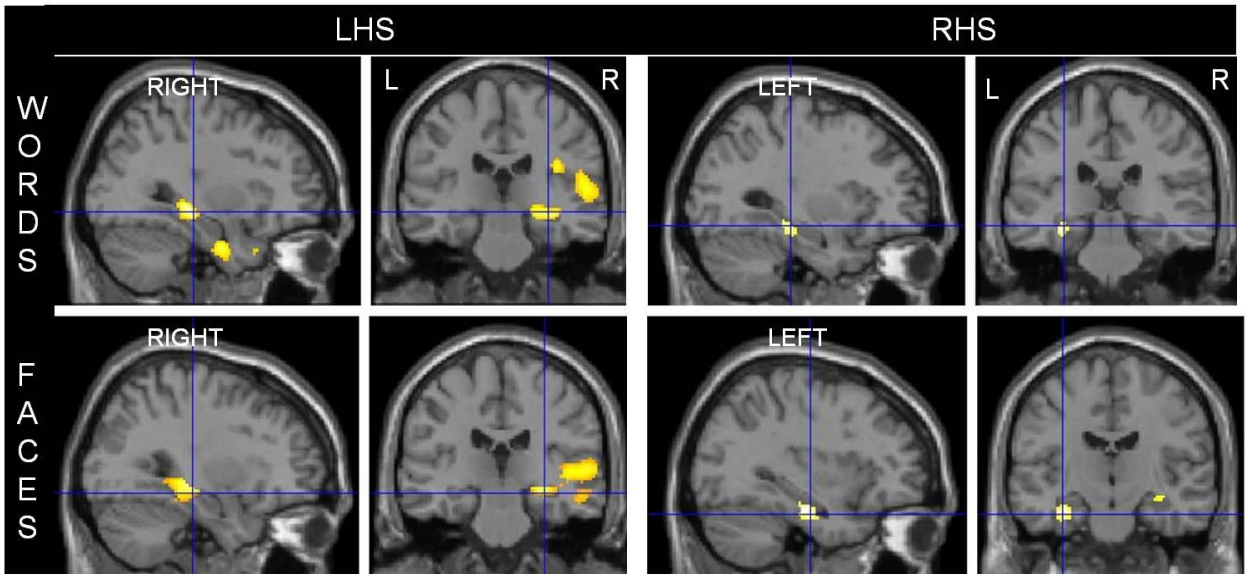


Figure 7.4: Correlation of lower seizure frequency with word (upper panel) and face encoding (lower panel) in LHS and RHS patients. Predominantly right medial and lateral temporal lobe activations associated with a lower seizure frequency in LHS patients during word encoding and face encoding. Conversely, predominantly left medial temporal lobe activations associated with lower seizure frequency in RHS patients during word and face encoding.

7.4 Discussion

7.4.1 Summary of findings

Earlier age at onset of epilepsy influenced the word encoding network in LHS patients. Patients with earlier age of onset showed left posterior HC, bilateral posterior MTH and occipital activations.

Duration of epilepsy and seizure frequency significantly influenced both verbal and visual memory encoding. In LHS patients, shorter duration of epilepsy was associated with bilateral MTL activations during word and face encoding whilst in RHS patients, shorter duration was associated with left MTL activation during face encoding. LHS patients showed particularly left extra-temporal activations correlating with shorter duration for both word and face encoding whilst longer duration in both

LHS and RHS patients associated with contralesional extra-temporal reorganisations.

In LHS patients, contralateral MTL activations were associated with lower seizure frequency for both word and face encoding. In RHS patients, bilateral MTL activations during face encoding and left MTL activations during word encoding were associated with a lower seizure frequency. Higher seizure frequency was associated with greater extra-temporal activations.

7.4.2 Age at onset of epilepsy

Previously, we showed that activations in the left posterior HC and posterior middle temporal MTG bilaterally were associated with successful verbal memory formation in LHS patients (Chapter 6). In this study we showed that this reorganisation was influenced by an earlier age at onset of epilepsy. Early onset of epilepsy appears to compromise the normal functioning of the anterior left HC. Age at onset was not seen to influence word encoding in RHS patients or face encoding in either patient group.

Post-natal brain development continues into adolescence with brain myelination occurring in a posterior to anterior fashion so frontal lobe myelination occurs last. In TLE patients, early age at onset of epilepsy affected white matter maturation with a lag in the frontal and parietal but not the occipital lobes (Hermann et al., 2010).

The hemispheric asymmetry of brain maturation suggests that the left hemisphere matures later than the right. Regional cerebral blood flow at rest was maximal in the right hemisphere at 1 year and in the left hemisphere at age 3, in keeping with the cadence of skill acquisition in children namely visuo-spatial (right dominant) skills

followed by language acquisition (left dominant) (Chiron et al., 1997). Disruption of this maturation process by early onset epilepsy may therefore preferentially influence 'dominant' functions including verbal memory. Another possible explanation for the modulation of the verbal encoding network only in LHS patients is that structural and morphological changes described in early onset epilepsy may be greater in left TLE than in right TLE patients (Kemmotsu et al., 2011; Riederer et al., 2008).

This hemispheric and anterior-posterior maturation asymmetry renders the left hemisphere and frontal lobes more vulnerable to early insults such as that incurred from early seizures which may explain why there appeared to be a selective effect of earlier age at onset of epilepsy in LHS patients.

7.4.3 Duration of epilepsy

In TLE patients, Cheung et al showed reduced MTL activations associated with longer duration of epilepsy in a scene encoding task where controls showed bilateral MTL activations (Cheung et al., 2006). This task was not material specific therefore contralateral activation due to reorganisation could not be assessed. Using a material specific paradigm, we showed that in a left lateralised task of word encoding in LHS patients a longer duration of epilepsy was associated with less MTL activation. Conversely, longer duration correlated with contralateral extra-temporal activations that we previously showed to be unrelated to successful subsequent memory formation (Chapter 6). Shorter duration correlated with left extra-temporal hemispheric activation including the left OFC during verbal encoding. We showed in Chpater 6 that left OFC activations in LHS patients during verbal encoding were associated with successful subsequent memory formation.

In RHS patients during face encoding, shorter duration of epilepsy correlated with left MTL activation whilst longer duration correlated with left post-central gyrus activations that were not associated with subsequent memory formation in our previous study (Chapter 6). This implies that longer duration of epilepsy is associated with greater disruption of the MTL functions in individuals with LHS and RHS with more engagement of neocortex that is not efficient. In RHS patients, this corroborates the finding that better visual memory correlated with shorter duration of epilepsy. In pharmacoresistant epilepsy, anterior temporal lobe resection has up to a 80% chance of resulting in seizure remission (de Tisi et al., 2011) and early surgical intervention has been shown to prevent permanent disability (Engel, 2008). My findings of greater disruption of the encoding networks with longer duration of epilepsy support early consideration of surgical treatment.

7.4.4 Seizure Frequency

Pathological studies have suggested that repeated complex partial seizures might cause neuronal injury (Dam, 1980) and negatively impact on cognition in TLE (Hermann et al., 2002).

I did not find that current seizure frequency correlated with memory test performance or hippocampal volume but found significant correlations between seizure frequency and fMRI activations during verbal and visual encoding. Lower complex partial seizure frequency correlated with anterior MTL activations in both LHS and RHS patients during face and word encoding. In LHS patients lower seizure frequency correlated with involvement of the right MTL; an activation shown in chapter 6 to be associated with subsequent memory formation. Fewer seizures also correlated with left IFG and left HC activations that have been shown to be associated with successful verbal memory formation in controls (Hongkeun, 2011).

In RHS patients lower complex partial seizure frequency was associated with greater activation within the left PHG at word encoding and bilateral PHG on face encoding, activations that we showed to be associated with successful subsequent memory in right HS patients in chapter 6.In both LHS and RHS patients during word and face encoding higher seizure frequency was associated with extra-temporal activations that were not associated with successful memory formation. Our findings concur with a study of 10 RHS patients, in which a lower seizure frequency correlated with MTL activation that was relevant to subsequent recognition performance during visual encoding (Figueiredo et al., 2008).

The overall inference is that, in TLE with HS, more frequent seizures are associated with greater disruption of normal encoding networks and the recruitment of other cerebral areas did not compensate for this.

7.4.5 Strengths and limitations

I included a large homogenous cohort of HS patients and applied robust analysis methods and used conservative statistical thresholds that allow inferences to be made about HS patients as a population. As age at onset and duration are highly correlated clinical variables we performed all correlation analyses controlling for each of these factors in turn.

I estimated current CPS frequency as the best measure of seizure frequency in our patients but this may not be a true reflection of total lifetime seizure burden. Gender was fairly balanced in the left TLE group (16 female and 13 male) but not in the right TLE group (5 female and 19 male). This discrepancy was not accounted for in our analysis. We investigated only patients with TLE and HS therefore generalisability to other forms of TLE remains to be investigated.

I report our findings as a group inference. Further research using objective parameters would be necessary to be able to apply these findings to an individual patient.

7.4.6 Neurobiological and clinical implications

I showed that age at onset of epilepsy, epilepsy duration and seizure frequency significantly affected memory encoding networks in TLE patients. Early age at onset was associated with successful memory reorganisation to the left posterior medial and bilateral lateral temporal lobes. Shorter duration of epilepsy and fewer complex partial seizures were associated with MTL and neocortical activations predictive of successful subsequent memory formation whilst longer epilepsy duration and greater burden of seizures were associated with 'inefficient' neocortical activations.

Anterior temporal lobe resection for refractory TLE has up to an 80% chance of inducing seizure remission for years at a time (de Tisi et al., 2011). An important consideration, however, is the memory deficits that may ensue. The patterns of organization and reorganisation of memory encoding networks visualized using fMRI have been shown to be an important predictor of memory decline following surgery (Bonelli et al., 2010; Powell et al., 2008; Richardson et al., 2004). Bonelli et al showed that pre-operative reorganisation of both verbal and visual memory to the posterior HC was associated with a lower risk of memory decline post-operatively and activation in the 'to-be resected' anterior hippocampus was predictive of memory decline post-operatively (Bonelli et al., 2010). I showed that age at onset, duration of epilepsy and seizure frequency, significantly influenced memory reorganisation and these factors may contribute to the prediction of memory outcome after surgery.

7.4.7 Conclusion

Earlier age of onset of epilepsy influences verbal memory reorganisation in left HS patients, being associated with left posterior HC and temporal activations. Duration of epilepsy and seizure frequency significantly influenced memory encoding networks in both LHS and RHS patients during verbal and visual encoding. Shorter duration and lower seizure frequency were associated with memory activations in brain regions that were involved in successful memory formation, with longer duration and higher seizure frequency associated with extra-temporal memory reorganisation to brain regions that did not contribute to successful memory formation. Investigating the pre-operative memory encoding network and understanding factors that influence memory reorganisation has important implications when considering the possible effects of epilepsy surgery on memory.

Chapter 8: Assessing hippocampal functional reserve in temporal lobe epilepsy: A multi-voxel pattern analysis of fMRI data

This study was performed in collaboration with Professor Eleanor Maguire at the Functional Imaging Laboratory, Wellcome Trust Centre for Neuroimaging, University College London. I was involved in patient recruitment, scanning, statistical analysis and drafting of manuscript with Dr Heidi Bonnici.

Abstract

Assessing the functional reserve of key memory structures in the MTL of pre-surgical patients with intractable TLE remains a challenge. Conventional fMRI memory paradigms have yet to fully convince of their ability to confidently assess the risk of a post-surgical amnesia. An alternative fMRI analysis method, MVPA, focuses on the patterns of activity across voxels in specific brain regions that are associated with individual memory traces. This method makes it possible to investigate whether the HC and related structures contralateral to any proposed surgery are capable of laying down and representing specific memories.

We used MVPA-fMRI to assess the functional integrity of the HC and MTL in patients with long-standing medically refractory TLE associated with unilateral HS. Patients were exposed to movie clips of everyday events prior to scanning, which they subsequently recalled during high-resolution fMRI. MTL structures were delineated and pattern classifiers were trained to learn the patterns of brain activity across voxels associated with each memory.

Predictable patterns of activity across voxels associated with specific memories could be detected in MTL structures, including the HC, on the side contralateral to

the HS, indicating their functional viability. By contrast, no discernible memory representations were apparent in the sclerotic HC, but adjacent MTL regions contained detectable information about the memories.

These findings suggest that MVPA in fMRI memory studies of TLE can indicate hippocampal functional reserve and may be useful to predict the effects of hippocampal resection in individual patients.

8.1 Introduction

In recent years an alternative analysis approach has emerged which exploits the intrinsically multivariate nature of fMRI data. This is motivated by the view that there may be information present in the distributed patterns of activation across voxels that is missed when looking at each voxel independently as in the mass-univariate method (Haynes and Rees, 2006; Norman et al., 2006). This multivariate approach is commonly known MVPA, or decoding. It involves training a support vector machine (SVM) classifier to recognise the patterns of activity across voxels associated with particular stimuli (e.g. specific memories). The classifier is then applied to a previously unseen portion of the data that was not used for training. If the classifier is successful at predicting (or decoding) which particular memory was being recalled in this test data set, this indicates that there is information about that memory represented in the brain region where the pattern of voxels was successfully identified. MVPA therefore affords the opportunity to examine the neural substrates of specific memory traces in individual participants, localised to brain regions of interest.

Recent studies in healthy subjects have documented the power of this method for investigating neural information at the level of individual memory representations (Rissman and Wagner, 2012). A number of these studies specifically focused on the HC and surrounding MTL structures and successfully interrogated their capacity to represent various types of memory (Bonnici et al., 2012b; Chadwick et al., 2010; Chadwick et al., 2011; Chadwick et al., 2012; Hassabis et al., 2009).

The ability to establish the functional capacity of the contralesional MTL to sustain specific memories on an individual patient level has clear implications for surgical

planning. Here we describe a novel approach of decoding specific neural signatures of memory representations within the MTL using MVPA-fMRI in patients with TLE. Initially, we sought to ascertain whether this approach would provide results that were concordant with established clinical features in individuals with well-defined unilateral HS and memory profiles concordant with the laterality of their pathology. If MVPA has potential utility in the context of TLE, we would expect the classifier operating on voxels in the sclerotic HC to perform at chance, as viable memory traces are unlikely to be laid down there. By contrast, the contralesional HC should contain memory representations that a classifier can detect.

We employed a paradigm devised by Chadwick et al (Chadwick et al., 2010) in which participants viewed three short movies of everyday events prior to scanning, and then recalled them during high-resolution fMRI. This task had a number of advantages for our purpose; the memories involved were realistic and close to the experiences of day-to-day life, all participants were exposed to the same events permitting greater experimental control, and the task was simple and suitable for a range of abilities. Most importantly, this task revealed that decodable information about the memories was present bilaterally within the hippocampi, entorhinal/perirhinal and parahippocampal cortices in healthy subjects, making it suitable for use in individuals with both left and right HS. We therefore tested the hypothesis that the contralesional HC and MTL would show the same pattern of findings as in the healthy controls (Chadwick et al., 2010) while results for the sclerotic hippocampus would be at chance.

8.2 Methods

8.2.1 Participants

Ten patients (8 female; 9 right handed) with a median age of 41 years, IQR 16.75, took part (Table 8.1). All had long-standing medically refractory TLE associated with unilateral HS, which had been identified on 3T structural MRI scans following qualitative assessment by expert neuroradiologists and quantification of HC volumes and T2 relaxation times showing unilateral HS and normal contralateral MTL structures. Nine individuals had left HS, and one had right HS, and all were taking anti-epileptic medication at the time of the study.

Neuropsychological assessment (Table 8.1) showed that their overall intellectual level was low average to average (WASI-III; Wechsler, 1997). Three patients with left HS had some mild word-finding difficulties (Graded Naming Test) but all could read proficiently and readily comprehended and complied with the task instructions. Executive function (The Weigl Colour-Form Sorting Test) and visual perception (subtests from the Visual Object Space Perception Battery) were within the average range. Memory (recall and recognition; visual and verbal) was assessed using several British-normed tests: the BMIPB, the Camden Memory Tests, and the Recognition Memory Tests. In general memory scores echoed the laterality of pathology, i.e. impaired or weaker verbal compared to visual memory in patients with left HS, and the opposite pattern in the patient with right HS (Table 8.1).

Our main interest was in comparing the affected MTL with the contralesional MTL within subjects, with patients effectively acting as their own controls. In this way it was possible to control completely for factors such as age, IQ, seizure history and medication regimen. However, in order to establish how the patients performed more

generally, we also compared their fMRI data to a group of healthy control participants (also n=10; six female; mean age 21.1 years, SD 1.8) who had previously performed the same task (Chadwick et al., 2010).

ID	Gender	Age (yrs)	H'ess	Cognitive summary[a]	Age at onset (yrs)	Duration (yrs)	MRI	Seizure type and frequency
1	F	41	R	IQ low average; verbal mem imp; visual mem average	32	9	LHS	CPS: 2–3/month; SGS: 2/month
2	F	51	R	IQ average; verbal mem average; visual mem above average	20	31	LHS	CPS: 1/year; SGS: 2 in the past
3	M	20	L	IQ average; verbal mem average; visual mem average	13	7	LHS	CPS: 4–8/month; SGS: 2/year
4	F	55	R	IQ average; verbal mem borderline imp; visual mem low average	14	41	LHS	CPS: 2/week; SGS: 2/year
5	F	42	R	IQ average; verbal mem imp; visual mem low average	11	31	LHS	CPS: 3–4/month
6	M	29	R	IQ average; verbal mem imp; visual mem average	6	23	LHS	CPS: 1/month; SPS: 1/month; SGS: 1/year
7	F	44	R	IQ low average; verbal mem imp; visual mem above average	18	26	LHS	Previously CPS: 2–3/month; currently controlled on AED
8	F	52	R	Chose not to attend for cognitive testing	12	40	LHS	CPS: 1/month; SGS: 1/year
9	F	50	R	IQ average; verbal mem imp; visual mem above average	35	15	LHS	CPS: 16/month; SGS: 2/year
10	F	37	R	IQ average; verbal mem low average; visual mem imp	2	35	RHS	CPS: 4–6/month; SGS S: 2/year

Table 8.1: yrs = years; H'ess = handedness; R = right; L = left; imp = impaired; mem = memory; LHS = left hippocampal sclerosis; RHS = right hippocampal sclerosis; CPS = complex partial seizure; SGS = secondarily generalised tonic–clonic seizure; SPS = simple partial seizure; AED = anti-epileptic drugs. Impaired = <2nd percentile; borderline impaired = 2nd–9th percentile; low average = 10th–24th percentile; average = 25th–75th percentile; above average = 76th–90th percentile; superior = 91st + percentile.

8.2.2 Pre-scan training

The experimental protocol was the same as that employed by (Chadwick et al., 2010), and the key features are reprised here for convenience. During a pre-scan training period, a patient viewed three film clips of everyday events. Each clip was 7s long and featured a woman (a different one in each clip) carrying out a short series of actions. The films were shot outdoors in three different urban settings. These stimuli ensured that memories would be episodic-like in nature, and that all participants recalled the same set of memories. One clip featured a woman taking a letter out of her handbag, posting it in a post box (mailbox), and then walking off. Another clip featured a woman taking a drink from a disposable coffee cup, putting the cup in a rubbish bin (trashcan), and then walking off (Fig. 8.1). The final clip featured a woman picking up a bicycle that was leaning against some railings, adjusting her helmet and walking off with the bicycle. Patients viewed each clip 15 times and practiced recalling them as vividly as possible and within the 7s timeframe. Patients were also trained on a rating procedure where they evaluated each recall period for the level of vividness as well as how consistent the recall had been relative to previous recollections of the same memory. This practice period therefore ensured that the memory traces for the three movies were stable before going into the scanner, a pre-requisite for the subsequent MVPA analysis.

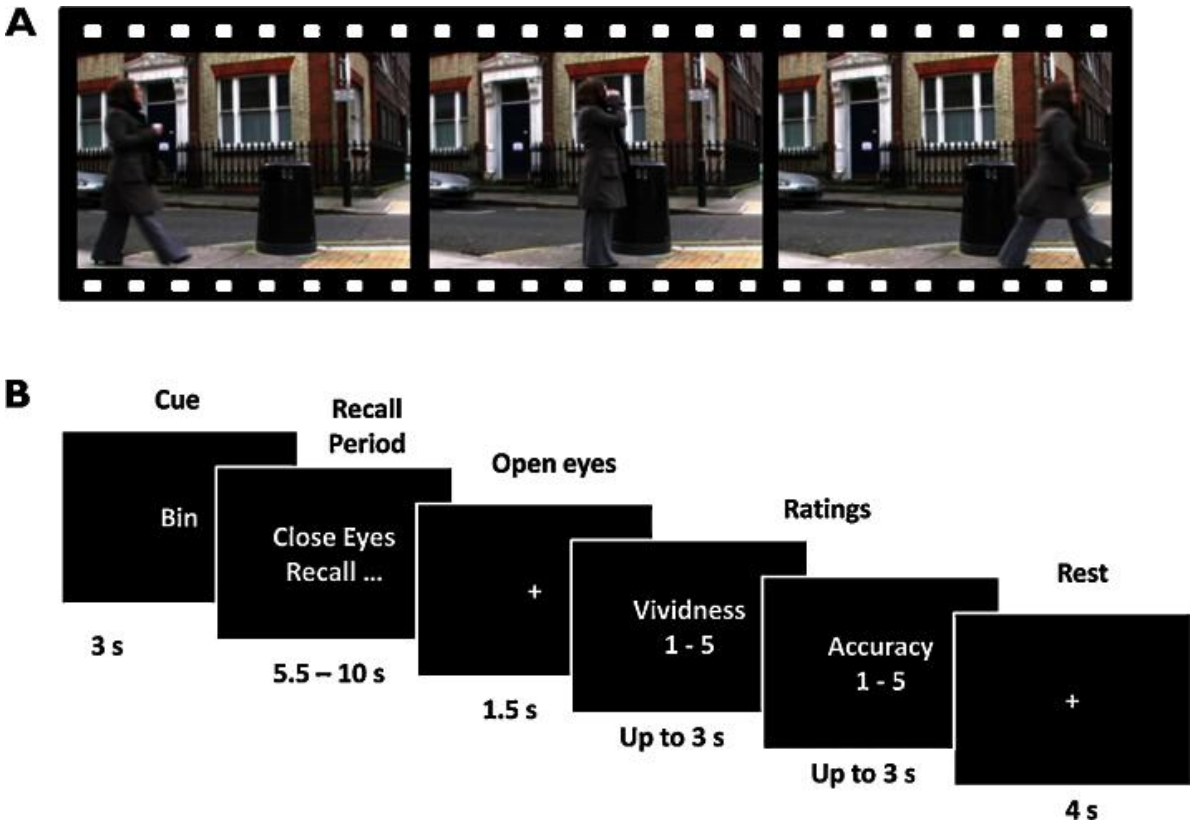


Fig 8.1: The experimental protocol. (A) Still photographs taken from one of the film clips viewed during pre-scan training. The clip depicted a woman taking a drink from a disposable coffee cup and then putting it in a bin (trashcan). (B) Timeline of an example trial during fMRI scanning.

8.2.3 Scanning task

During scanning patients recalled each movie twenty times in a pseudo-random order, ensuring that the same memory was not repeated two or more times in a row. On each trial (see Fig 8.1B) the patient viewed a cue on screen indicating which of the three film events they should recall. Patients were instructed not to begin the recall process until the cue to close their eyes and recall appeared. To ensure the patients were concentrating, and that the recall approximated the original 7s length of a clip, the patient had to press a button (using a scanner-compatible button-box) when they had finished recalling the clip. If the button was pushed too soon (<5.5s) or they failed to push it within 10s then a tone would sound, and a message would

appear for 1.5s indicating that their recall had been too fast or too slow. Any such trials were excluded from the subsequent analysis. If the patient pressed the button between 5.5-10s, a fixation cross appeared onscreen for 1.5s. Patients were trained to open their eyes as soon as they had pressed the button or if they heard the tone. Following this, the patient was required to provide ratings about the preceding recall trial using the button-box, just as they had been trained to do during the pre-scan training session. First, they rated how vivid the preceding recall trial was (scale: 1 – 5, where 1 was not vivid at all, and 5 was very vivid). Second, they rated how accurately the recalled memory reflected the actual film clip (scale: 1 – 5, where 1 was not accurate at all, and 5 was very accurate). Any trials where a participant recorded a rating of less than 3 were excluded from the subsequent analysis. Following the ratings, participants rested for 4s before starting the next trial. Once excluded trials were discounted (and similar to the control data in Chadwick et al., 2010), this resulted in an average of 12.3 (SD 1.34) trials for memory 1, 12.5 (SD 2.42) trials for memory 2 and 12.9 (SD 1.97) trials for memory 3 making an average of 36 trials in total per patient being entered into the MVPA analysis.

8.2.4 Data acquisition

Using high-resolution fMRI (Carr et al., 2010) we acquired data in a limited volume focussing on the medial temporal lobe, particularly the hippocampus entorhinal/perirhinal and posterior parahippocampal cortices. A 3T Magnetom Allegra head only MRI scanner (Siemens Healthcare, Erlangen, Germany) operated with the standard transmit-receive head coil was used to acquire the functional data with a T2*-weighted single-shot EPI sequence in a single session (in-plane resolution = 1.5 x 1.5 mm^2; matrix = 128 x 128; field of view = 192 x 192 mm^2; 35 slices acquired in interleaved order; slice thickness = 1.5mm with no gap between

slices; echo time TE = 30ms; asymmetric echo shifted forward by 26PE lines; echo spacing = 560 μs; TR = 3.5s; flip angle α = 90°). All data were acquired at 0° angle in the anterior-posterior axis. An isotropic voxel size of 1.5 x 1.5 x 1.5 mm was chosen for an optimal trade-off between BOLD sensitivity and spatial resolution. Further, the isotropic voxel dimension reduced re-sampling artefacts when applying motion correction. To ensure optimal data quality, images were reconstructed online and underwent online quality assurance (Weiskopf et al., 2007). For distortion correction (Hutton et al., 2002), field maps were acquired with the standard manufacturer's double echo gradient echo field map sequence (TE = 10.0 and 12.46 ms, TR 1020ms; matrix size, 64x64), using 64 slices covering the whole head (voxel size 3 x 3 x 3 mm). In addition to the functional scans, a whole brain T1-weighted 3D FLASH sequence was acquired with a resolution of 1 x 1 x 1 mm. A T1-weighted high-resolution 3D modified driven equilibrium Fourier transform whole-brain structural MRI scan was acquired for each patient after the main scanning session with 1mm isotropic resolution (Deichmann et al., 2004).

8.2.5 Region of interest (ROI) segmentation

Given our specific interest in the HC and MTL, manual segmentation of the HC, entorhinal/perirhinal cortex combined (EPC) and parahippocampal cortex (PHC) was performed using ITK-SNAP (Yushkevich et al., 2006)– www.itksnap.org) using the 1x1x1mm T1 structural images (see example in Fig 8.2). Hippocampal anatomy was identified using the Duvernoy hippocampus atlas (Duvernoy, 2005). The EPC and PHC were segmented according to the protocol described by (Insausti et al., 1998). Author HMB performed the segmentations, and inter-rater reliability was calculated on a random selection of four patient scans which had also been segmented by author MS. The Dice overlap metrics (Dice, 1945) were as follows: HC 0.81, EPC

0.63, PHC 0.60. Mean volumes (in cubic mm) and standard deviations (SD) for the ROIs in the left (L) and right (R) MTL in the group of nine LHS patients were as follows: HCL 2435.11 (SD 467.94), HCR 3415.89 (453.01), EPCL 3085.33 (45301), EPCR 3159.33 (326.71), PHCL 1591.22 (386), and PHCR 1543.56 (272.99). A repeated measures ANOVA revealed a significant hemisphere by region interaction ($F=24.37$, $p<0.0001$). Further investigation of this effect using paired t-tests confirmed that a volume difference between the left and right HC drove this result ($t=-6.06$, $p<0.0001$) with the right HC volume greater than the left. There were no differences in volume between the left and right sides for the other MTL structures (EPC: $t=-1.07$, $p=0.32$; PHC: $t=0.42$; $p=0.69$). For the patient with right HS, the hippocampal volume difference was also apparent, but with the left greater than the right: HCL 3503, HCR 2059, EPCL 2569, EPCR 2956, PHCL 1297, and PHCR 1433.

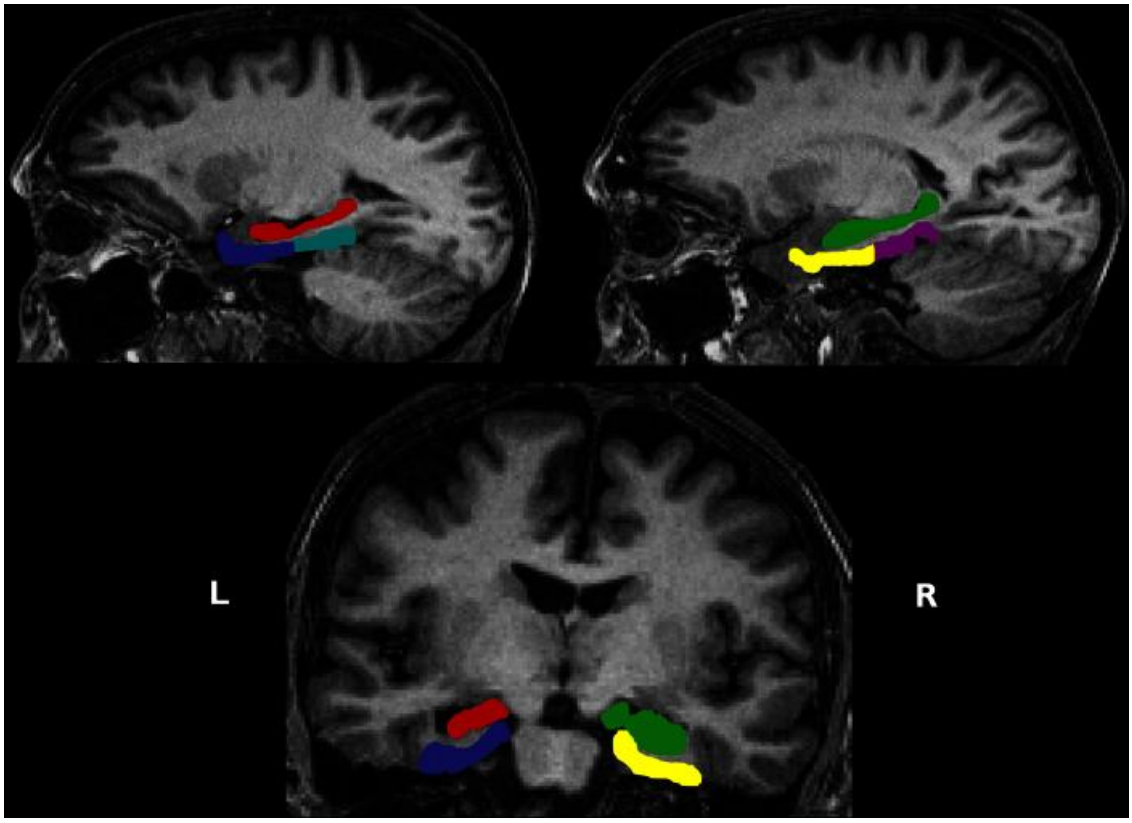


Fig 8.2: Brain regions of interest. The top panel shows sagittal views through the left and right hemispheres, and the lower panel a coronal section, from the structural MRI scan of one of the patients with left HS; L = left side of the brain, R = right side of the brain. The left hippocampus (sclerosed) is coloured in red, the right hippocampus in green, the left EPC in blue, the right EPC in yellow, the left PHC in turquoise, and the right PHC in magenta.

8.2.6 Image pre-processing

Pre-processing of the fMRI data was performed using SPM8 (www.fil.ion.ucl.ac.uk/SPM). The first six EPI volumes were discarded to allow for T1 equilibration effects (Frackowiak, 2004). The remaining EPI images were then realigned to correct for motion effects, and minimally smoothed with a 3mm FWHM Gaussian kernel. A linear detrend was run on the images to remove any noise due to scanner drift (LaConte et al., 2005). Next the data were convolved with the HRF to increase the signal-to-noise ratio (Frackowiak, 2004). This HRF convolution effectively doubled the natural BOLD signal delay, giving a total delay of

approximately 12s. To compensate for this delay, all onset times were shifted forward in time by three volumes, yielding the best approximation to the 12s delay given a TR of 3.5s and rounding to the nearest volume (Duda, 2001). Functional volumes were extracted from the vivid recall period of each trial, leading to a total of four functional volumes per trial.

8.2.7 Multivariate classification

A SVM classifier was created for each region of interest. Each classifier was trained on a portion of the fMRI data relating to the three episodic memories and then tested on an independent set of instances of these memories. We used a standard MVPA procedure that has been described elsewhere (Bonnici et al., 2012a; Chadwick et al., 2010). Briefly, the overall classification procedure involved splitting the fMRI data into two segments: a “training” set used to train a classifier with fixed regularization hyperparameter C = 1, in order to identify response patterns related to the memories being discriminated, and a “test” set used to independently test the classification performance (Duda, 2001), using a cross-validation procedure. We used a standard k-fold cross-validation testing regime wherein k equalled the number of experimental trials, with the data from each trial set aside in turn as the test data, and the remaining data used as the training set. This therefore generated k sets of SVM training and test sets which produced an overall classification accuracy from the proportion of correct classification “guesses” across all k folds of the cross-validation. The classification was performed using the LIBSVM implementation (Chang and Lin, 2011).

Prior to multivariate classification, feature selection (Guyon and Elisseeff, 2003) was performed on the data from the training set, thereby ensuring that this step was fully

independent from final classification, which is critical for avoiding “double-dipping” -(Kriegeskorte et al., 2009). The purpose of feature selection is to reduce the set of features (in this case, voxels) in a dataset to those most likely to carry relevant information. This is effectively the same as removing voxels most likely to carry noise, and is a way of increasing the signal-to-noise ratio. This was conducted using a standard multivariate searchlight strategy within the given ROI. For a given voxel, we first defined a small sphere with a radius of three voxels centred on the given voxel (Hassabis et al., 2009; Kriegeskorte et al., 2009) (Bonnici et al., 2012a; Chadwick et al., 2010; Hassabis et al., 2009). Note that the spheres were restricted so that only voxels falling within the given region of interest were included. Therefore, the shape of the sphere and the number of voxels within it varied depending on the proximity to the region of interest’s borders. This procedure then allowed the selection of the searchlight voxel set that contained the greatest degree of decoding information within the training dataset. Using this voxel subset, the SVM classifier was trained to discriminate between the three episodic memories using the “training” dataset, and tested on the independent “test” dataset.

Standard SVMs are binary classifiers that operate on two-class discrimination problems, whereas our data involved a three-class problem (i.e. three memories). The SVM can, however, be arbitrarily extended to work in cases in which there are more than two classes. Typically this is done by reducing the single multiclass problem into multiple binary classification problems that can be solved separately and then recombined to provide the final class prediction(Allwein et al., 2000). We used the well-established Error Correcting Output Codes approach (Dietterich and Bakiri, 1994) and computing of the Hamming distance (Chadwick et al., 2010; Hassabis et al., 2009).

8.2.8 Data analysis

The classifier accuracy values for each brain region were compared to chance using one-tailed t-tests. Because there were three memories, chance was 33% in this study. Other within-subjects comparisons were made using repeated measures ANOVA and paired t-tests. We report formal statistical analyses for the group (n=9) of left HS patients, and present the individual data of the right HS patient. We also compared the performance of the patients (n=9 with left HS) with the 10 healthy participants reported by Chadwick et al. (2010) using ANOVA. A threshold of $p<0.05$ was employed throughout.

8.3 Results

In order to contextualise the current findings, it is worth noting that when using this paradigm in healthy subjects, Chadwick et al. (2010) found that all three MTL regions produced classification results that were significantly above chance, showing that it was possible to detect information about individual episodic-like memories from activity patterns within the HC and surrounding MTL (Fig 8.3 A). The results were highly similar for left and right MTL. They also found that classification accuracy for the HC was significantly better than for the other MTL regions, suggesting that episodic-like memories may be more distinct within the HC than the surrounding cortex.

In a similar vein, we found that in the patients, classifiers operating on the patterns of activity across voxels in each region of the contralesional MTL predicted which memory was being recalled significantly above chance (HCR: $t=7.299$, $p=0.0001$; EPCR: $t=2.206$, $p=0.029$; PHCR: $t=2.450$; $p=0.020$) (Fig 8.3B). Classification accuracy was significantly higher in the hippocampus compared to the EPC ($t=2.551$,

p=0.034; not significant compared to the PHC t=1.788, p=0.112). This shows that the episodic-like memories of the movies were represented in the hippocampus in particular, and also in adjacent MTL structures, suggesting operational memory capacity of these contralateral MTL regions.

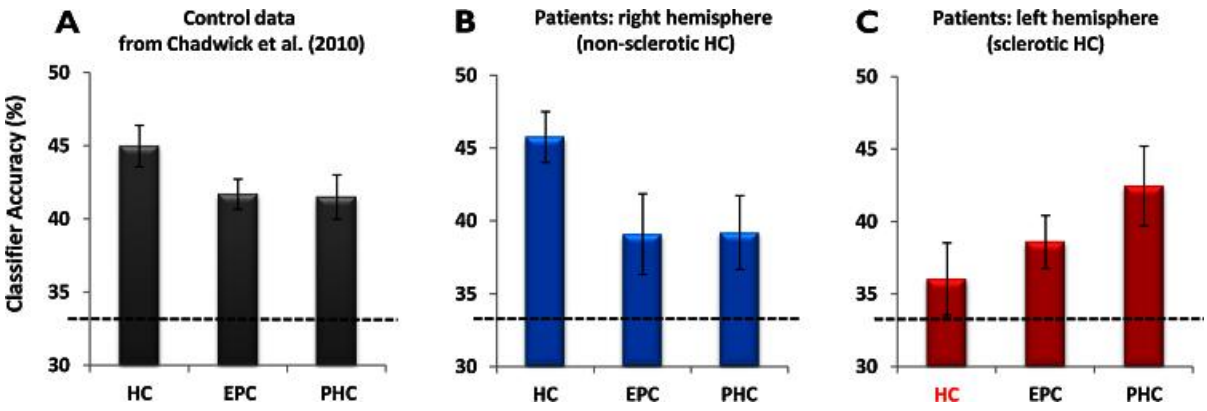


Fig 8.3: Results of the MVPA analyses. (A) Control data (*n* = 10, collapsed across hemispheres) from Chadwick et al. (2010) using the same task as that employed in the current study. Mean classifier accuracy performances (± one standard error of the mean) are shown; chance was 33% (represented by the black dashed line). HC = hippocampus; EPC = entorhinal/periphinal cortex; PHC = parahippocampal cortex. (B) Data for the contralesional right MTL (from the 9 patients with left HS). (C) Results for the affected left MTL, where classifier performance for the sclerosed hippocampus (highlighted in red on the *x*-axis) was not significantly different to chance. Classifier performances in the other left MTL regions and all areas in the contralesional MTL were significantly above chance.

By contrast, the classifier accuracy within the sclerotic left HC for the three memories was not significantly greater than chance (HCL: t=1.225, p=0.128; Fig. 8.3C), while classifier performances in the surrounding MTL regions were significantly above chance (EPCL: t=3.067, p=0.008; PHCL: t=3.444, p=0.004). Classification accuracy was significantly higher in the parahippocampal cortex than the sclerotic hippocampus (t=-3.853, p=0.005). This suggests that discernable memory representations were absent in the sclerotic hippocampus, but present in adjacent

MTL structures. Having examined MTL structures in each hemisphere separately, we then made direct comparisons using a repeated-measures ANOVA. There was a significant interaction between the two factors of hemisphere and region ($F=4.561$; $p=0.026$), that was driven by a significant difference in classifier performance between the sclerotic and contralesional HC ($t=-3.989$, $p=0.004$), with the classifier operating on voxels in the sclerotic left HC unable to distinguish between the three episodic memories.

Eight of the nine left HS patients showed a difference in performance between the HC in the predicted direction; the performance of the classifier operating on voxels in the contralesional right HC was greater than that of the sclerotic left HC (mean classifier performance HCL=34.94%, SD=7.16; HCR=46.10%, SD=5.51). Data for the one patient with right HS was also in the expected direction, with deceased classifier accuracy within the sclerosed right HC (HCL 44.44%, HCR 36.67%). We also examined whether the at-chance result in the sclerotic HC might have been associated with its smaller volume. No correlation between classification accuracy and hippocampal volume was found (Pearson $r=0.511$, $p=0.16$).

The ninth left HS patient's results were equivocal (patient 9: HCL=44.95%, HCR=43.12%; volumes for this patient: HCL 2970, HCR 3478). To investigate if this was related to clinical factors, correlations of classifier accuracy with variables such as patients' current age, age of epilepsy onset, epilepsy duration and seizure frequency were performed. No significant correlations were observed, although this may be due to the relatively small sample size.

Finally, we directly compared the fMRI data from the nine left HS patients with that of the ten healthy control participants reported by Chadwick et al. (2010). Despite the

controls being younger than the patients, there were no significant differences in classifier accuracies between the patient and controls for any MTL region except the left HC, where classifier accuracy was significantly less in the patients (HCL $F=6.52$, $p=0.02$; HCR $F=0.001$, $p=0.97$; EPCL $F=1.57$, $p=0.23$; EPCR $F=0.94$, $p=0.35$; PHCL $F=0.7$, $p=0.41$; PHCR $F=1.3$, $p=0.27$). Of particular note, there was no difference between the groups in classifier accuracy for the right HC. These findings therefore affirm the view that the sclerotic left HC in the patients were dysfunctional, while the right HC retained a normal level of mnestic functioning.

8.4 Discussion

We found that predictable patterns of activity across voxels associated with specific memories could be detected in MTL structures, including the HC, on the side contralateral to focal unilateral HS in a group of patients with TLE. By contrast, no discernible memory representations were apparent in the sclerotic HC, although the adjacent MTL regions on that side contained detectable information about the memories. To our knowledge, this is the first MVPA-fMRI study to be reported in TLE, and therefore shows that the MVPA technique, designed to detect specific memory representations in patterns of fMRI data, permits interrogation of MTL functionality and in particular hippocampal functional reserve, complementing existing investigative protocols in TLE.

The paradigm we employed involved exposing all patients to the same set of movies that depicted everyday events. Memories of these naturalistic stimuli have been found to be encoded and represented in the left and right HC of healthy controls, such that recall of these memories could be predicted from patterns of fMRI brain

activity across hippocampal voxels (Chadwick et al., 2010). By capitalising on the bilateral nature of the memory traces associated with these episodic-like memories, we could examine and compare the memory capacity of the HC in patients in whom one hippocampus was sclerotic. In this study we therefore deliberately focussed on patients where the structural imaging and neuropsychological tests pointed to selective involvement of one sclerotic HC. That this damage compromised the mnestic capacity of that hippocampus was clear in the at-chance performance of the pattern classifier, which could not discern any reliable patterns of activity associated with the memories. This was in direct contrast to the contralateral HC in which the memory traces were readily detected. Moreover, the contralateral HC contained similar amounts of information about the memories when the patients were compared to healthy control participants, while the sclerotic hippocampus was severely compromised. Overall, therefore, the within- and between-subjects effects we observed suggest the MVPA approach is reliable, and offers new insights into hippocampal functional reserve in TLE.

This method was not only able to interrogate the functional status of the hippocampus, but also the surrounding MTL tissue. The EPC and PHC in the contralesional hemisphere of the patients contained decodable information about the memories, and less so than the HC, confirming the functional integrity, and functional hierarchy, of the wider MTL memory system on that side. Of particular note was the status of the EPC and PHC on the affected side, as information about the memories was detectable in these structures. This shows that in the presence of HS, adjacent MTL regions can retain a capacity to contribute to memory recall. The classifier operating on voxels in the PHC on the affected side seemed to perform better than its counterpart on the unaffected side perhaps indicating a compensatory

mechanism. However, when directly compared, there was no significant difference between the two and no difference when compared to the control participants.

How do our MVPA findings relate to results from conventional fMRI memory studies in TLE? After all, asymmetric MTL activations have also been observed using standard fMRI paradigms, and much information can be gleaned from such studies. For instance, in tasks that were associated with bilateral activity within the MTL in healthy control participants, patients showed significantly reduced MTL activation ipsilesionally (Detre et al., 1998; Jokeit et al., 2001; Mechanic-Hamilton et al., 2009). In a complex scene encoding task seven patients with left TLE and three with right TLE were studied using a simple block design fMRI protocol. Patients showed asymmetry of activation with greater activation in the non-lesional MTL. However, fMRI activations were not correlated with neuropsychological performance, therefore it could not be definitively ascertained if contralateral activations were specifically related to successful memory encoding (Detre et al., 1998). Jokeit et al 2001(Jokeit et al., 2001) employed a spatial navigation task in a group of thirty patients with refractory TLE. Asymmetry of activation was seen in 90% of patients. Rank correlation was performed between the number of activated voxels within the MTL, out of scanner neuropsychological variables, and Wada test hemispheric memory performance. Correlations between visuospatial memory performance and right MTL activation but not left MTL activation were found. Left MTL activation was correlated with Wada hemispheric memory performance for visually presented objects. These correlations suggested that MTL activations during the task were related to the memory encoding process.

These examples illustrate that conventional fMRI BOLD activations typically index the involvement of brain regions in an experimental task. However, to more directly

link the engagement of a brain area to successful memory function, further correlation with neuropsychological variables or subsequent memory paradigms using, for example, an event-related analysis is necessary (Powell et al., 2007). MVPA, however, offers the important added value of being able to assess the function of MTL structures at the level of fine-grained individual memory representations, which is a more direct reflection of the capacity of the MTL structures. This method provides the additional benefit of being able to distinguish specific neural representations within relatively small sub-regions of the medial temporal lobe in individual patients, thereby offering another dimension to delineating the functional topography of memory representations in the context of TLE.

Conventional fMRI memory encoding studies have also examined material-specific effects and some have observed memory reorganisation involving the contralesional MTL (Golby et al., 2002; Powell et al., 2007). In left TLE patients subsequent memory studies using an event-related analysis showed reorganisation of verbal memory encoding to the contralateral HC (Richardson et al., 2003) and in right TLE patients reorganisation of visual encoding to involve the left HC (Powell et al., 2007). It will be interesting for future studies to employ MVPA in this context to investigate the capacity for effective reorganisation in unilateral TLE.

In a similar vein, pre-operative conventional fMRI activations have been shown to be important predictors of post-surgical memory outcome in both material-specific memory paradigms (Bonelli et al., 2010; Powell et al., 2008; Richardson et al., 2004) and tasks that are more bilaterally represented within the MTL (Janszky et al., 2005; Mechanic-Hamilton et al., 2009) in group studies. Because MVPA indexes the presence of predictable and useful information pertaining to specific memories, and given that we have shown evidence for functional capacity within the MTL even on a

single subject basis, this leads to the exciting possibility that pre-operative MVPA could also predict post-operative memory change in patient groups but also, crucially, at the level of individual patients.

Overall, our findings indicate that MVPA-fMRI could prove a useful non-invasive method of assessing pre-surgical memory capacity within the MTL. Despite our small sample size, our results illustrate that the MVPA approach to fMRI memory studies in the context of TLE can give an insight into hippocampal functional reserve. While this MVPA-fMRI method for assessing memory reserve shows promise, our study reveals clear targets for future inquiries. Here we examined memory recall in individuals with clear-cut unilateral HS (mostly left-sided) and memory profiles that echoed the laterality of this pathology. This was the logical first step in evaluating MVPA-fMRI because if the results did not concur with known pathology, this would discourage its future use. As it is, MVPA may be useful not only in addition to existing structural and functional MRI and neuropsychological data in straightforward cases, but could play a particularly useful role in patients in whom existing information is ambiguous. In those situations, MVPA-fMRI could give insights into the memory reserve of the HC and surrounding MTL structures that may have a direct bearing on surgical decisions. Further work is now required to assess the validity of the MVPA-fMRI approach in larger cohorts, and patients with unilateral left and right HS as well as more complex cases.

Finally, MVPA as it is commonly implemented including its use here, involves training support vector machine classifiers. This requires multiple presentations of the same stimuli in order to accrue enough examples of the brain activity patterns associated with each stimulus for training to be viable. As such, the technique depends on brain activity being stable from one instance of stimulus presentation to

the next. Certain types of design, therefore, become more challenging, including learning paradigms in which the neural signatures of stimuli may be more dynamic. However, decoding methods are constantly evolving (Chadwick et al., 2012) and it is likely that opportunities for new applications in the context of pre-surgical evaluation of TLE patients will arise.

Chapter 9: Pre-operative memory fMRI predicts verbal memory decline after left anterior temporal lobe resection

Abstract

Objective: To develop a clinically applicable memory fMRI method of predicting post-surgical memory outcome in individual patients.

Methods: A prospective cohort study where 50 patients with TLE (23 left) and 26 controls performed an fMRI memory encoding paradigm of words with a subsequent out of scanner recognition assessment was performed. Neuropsychological assessment was performed pre-operatively and four months after anterior temporal lobe resection, and at equal time-intervals in controls. An event related analysis was used to explore brain activations for words remembered and change in verbal memory scores 34 months after surgery was correlated with pre-operative activations. Individual lateralisation indices were calculated within a medial temporal and frontal region and compared with other clinical parameters (hippocampal volume, pre-operative verbal memory, age at onset of epilepsy and language lateralisation) as a predictor of verbal memory outcome.

Results: In left temporal lobe epilepsy patients, left frontal and anterior medial temporal activations correlated significantly with greater verbal memory decline whilst bilateral posterior hippocampal activation correlated with less verbal memory decline post-operatively**.** In a multivariate regression model, left lateralised memory lateralisation index (≥0.5) within a medial temporal and frontal mask was the best predictor of verbal memory outcome after surgery in the dominant hemisphere in individual patients. Neither clinical nor functional MRI parameters predicted verbal memory decline after non-dominant temporal lobe resection.

Conclusion: I propose a clinically applicable memory fMRI paradigm to predict post-operative verbal memory decline after surgery in the language dominant hemisphere in individual patients.

9.1Introduction

ATLR brings remission in up to 80% of patients with refractory TLE (de Tisi et al., 2011) but significant verbal memory loss may ensue in 30% of temporal lobe resections in the speech-dominant hemisphere.(Chelune et al., 1991; Helmstaedter and Elger, 1996; Sabsevitz et al., 2001; Saykin et al., 1989). Verbal memory decline may also occur after non-dominant temporal lobe resections albeit less frequently.

Over the last decade, the utility of material specific memory encoding paradigms that predominantly activate the left (verbal) and right (visual) hemispheres have been investigated to predict memory decline after ATLR (Bonelli et al., 2010; Powell et al., 2008; Richardson et al., 2004).

During a verbal encoding task, greater left than right activation within the anterior MTL assessed by 'asymmetry images' was a better predictor of verbal memory decline than pre-operative list learning scores and fMRI language lateralisation index (Bonelli et al., 2010). This 'asymmetry value' was obtained within a 10mm sphere, identified in a group analysis and may be difficult to apply in a newly encountered patient. In the studies by Powell et al, Bonelli et al and Richardson et al, despite very similar paradigms, the areas and extent of activation for verbal and visual memory encoding within the MTL varied considerably (Bonelli et al., 2010; Powell et al., 2008; Richardson et al., 2004). Towgood et al investigated the variability of effect size, location of activation and activation lateralisation in 16 TLE patients imaged on three separate sessions using the same paradigms (Towgood et al., 2015). Despite

investigating the same individuals, there were significant differences in the location and extent of activations within the MTL possibly related to noise. Hence, the use of a large region of interest such as an anatomical mask of the MTL may be a more reliable way of investigating laterality effects for the purpose of outcome prediction.

Several memory fMRI studies have investigated the value of lateralisation of absolute activations within a large MTL ROI in the prediction of post-surgical verbal memory with encouraging results (Binder, 2011). In an object location task, hippocampal lateralisation index correlated with verbal memory change in a group of left and right TLE patients, but in the individual right TLE (RTLE) and left TLE (LTLE) patients this effect was not significant (Frings et al., 2008). To date, lateralisation of absolute activations as a method of predicting memory decline has only been investigated within the MTL (Binder et al., 2010; Mechanic-Hamilton et al., 2009; Rabin et al., 2004). Using a verbal memory encoding paradigm I showed that both extra-temporal (particularly frontal) and temporal activations were involved in successful verbal memory formation (Chapter 6), suggesting that pre-operative extra-temporal activations may play a role in predicting post-operative verbal memory decline.

The purpose of this study was to develop a method of using memory fMRI as a clinically applicable tool for predicting post-surgical memory decline in individual patients. I:

1) Investigated which temporal and extra-temporal brain activations were predictive of post-surgical verbal memory outcome using an event related word encoding task inLTLE and RTLE patients.

2) Devised a clinically applicable prediction algorithm using objective fMRI lateralisation index parameters from an anatomical MTL and frontal region of interest to predict post-surgical verbal memory decline in individual patients.

3) Compared memory fMRI to language fMRI and standard clinical parameters including age at onset of epilepsy, pre-operative hippocampal volume and pre-operative memory score as a predictive tool for post-surgical memory outcome.

9.2 Methods

9.2.1 Subjects

57 patients (27 left) with medically refractory TLE who underwent pre-surgical evaluation and surgery at NHNN were prospectively studied. Inclusion criteria included patients who underwent standard en-bloc anterior temporal lobe resections which involved opening of the temporal horn, and resection of the hippocampus with a posterior resection margin at the mid brainstem level. 4 patients (3 LTLE) were excluded as resection did not include the hippocampus. 1 RTLE patient was excluded due to previous lesionectomy that included part of the anterior MTL. 2 patients with IQ <70 (1 LTLE) were excluded. In total, 50 patients (23 LTLE) were included in the study (Table 9.1, Appendix 1).

All patients had structural MRI at 3T including quantification of hippocampal volumes (Table 1). All patients received antiepileptic medication and spoke fluent English. Detailed neuropsychometry was performed before and months after ATLR.

26 healthy native English speaking controls were also studied (Table 1, Appendix 4).

All participants underwent neuropsychological testing (chapter 5 for methodological details). All 26 controls were assessed at baseline. 18 were reassessed 6 – 10 months after initial assessment. Using RCI based on control data, significant decline with 90% confidence interval(Bonelli et al., 2010) was defined as a ≥ 10 point decline at 4 months after surgery.

9.2.2 Event related analysis

I compared the encoding-related responses for stimuli that were subsequently remembered. A two-level event-related random-effects analysis was employed.

For each subject, delta functions of words remembered (WR) were convolved with the canonical haemodynamic response and its temporal derivative. The generated 'WR' contrast image for each subject was used in the second-level analysis.

One-sample t-tests were used to examine the group effect of each contrast in each group. Group differences were explored using an ANOVA between the groups. I determined the relevance of fMRI memory activations using a simple regression model of WR activations with pre-operative list learning.

Pre-operative brain activations associated with greater / less post-surgical verbal memory decline were investigated using a simple regression model of change in list learning scores against WR activations. Language LIs were used as a covariate in all second level analyses.

All group activations were shown corrected for multiple comparisons family wise error FWE, $p<0.05$. Group differences and correlations are reported at $p<0.001$, uncorrected. All activations within the MTL are corrected for multiple comparisons FWE, within a small volume, 12mm diameter sphere unless otherwise stated.

9.2.3 Individual patient memory Lateralisation Index Calculation

An anatomical mask incorporating frontal and medial temporal lobes (amygdala, PHG, HC, MFG,IFG) was created using the WFU PickAtlas in SPM8 (Maldjian et al., 2003). The frontal regions selected were the same as those used to calculate expressive LI. A bootstrap method was used to calculate lateralisation index within the fronto-temporal mask in all patients using the LI toolbox in SPM 8. LI of ≥ 0.5 was deemed strongly left lateralised.

9.2.4 Linear regression

Linear regression was used to investigate the utility of memory LI, language LI and predictive clinical variables (pre-operative hippocampal volume, pre-operative list learning and age at onset of epilepsy) (Bonelli et al., 2010) in predicting post-operative post-operative verbal memory decline. These parameters were entered into a multivariable regression model to investigate the variable that has predictive power over and above the other variables studied.

Statistical analyses used PASW Statistics 18.0 (IBM, Armonk, USA).

9.3 Results

9.3.1 Behavioural

LTLE and RTLE patients performed significantly worse than controls in the recognition test pre and post-operative post-operatively ($p<0.005$). LTLE patients showed a decline in recognition accuracy whilst RTLE patients improved, but not significantly, in recognition accuracy after surgery ($p>0.1$) (Table 9.1).

	Age (years)	Age at onset (years)	Duration of epilepsy (years)	HV cm3	NART IQ	Preop VL	Postop VL	Preop RA (%)	Postop RA (%)
C	37 (24)	NA	NA	2.15 (1.1)	111.5 (11)	57.4 (8.9)	57.3 (5.5) (retest)	76 (5.1)	75.2 (19.5) (retest)
LTLE	34 (17)	11 (21)	18 (27)	1.9* (0.7)	93.1* (10.3)	43.1* (10.7)	39.3* (14.6)	54.1 (24.0)	47.4* (22.5)
RTLE	35 (22)	17 (12)	17 (24)	2.4 (0.5)	100.2* (11.1)	48.4* (8.9)	44.3* (11.6)	55 (24.1)	59.7* (19.2)

Table 9.1: Age, age at onset of epilepsy and duration of epilepsy as median (inter quartile range). Hippocampal volume, NART IQ, pre-operative (preop VL), post-operative (Postop VL) verbal learning, pre-operative recognition accuracy (Preop RA) and post-operative recognition accuracy (postop RA) as mean (standard deviation). Controls (C). *C>patient group indicated, 2-tailed t-test $p<0.005$.

9.3.2 Neuropsychological Performance and Clinical Parameters

Both LTLE and RTLE patients had significantly lower IQs and performed significantly less well than controls on the verbal learning task, pre and post-operatively (two-tailed t-test $p<0.005$ (Table 9.1)). LTLE and RTLE patients did not differ significantly in age, age at onset of epilepsy, epilepsy duration, or verbal learning (two-tailed t-test $p>0.1$), (Table 9.1).

Of the 23 LTLE patients assessed 4 months after surgery, 14 showed verbal memory decline (8 significant), 1 showed no change and 8 showed improvement (3 significant). The mean change in verbal learning was -3.7 (SD 13.7) with a range of -32 to +27. 18 RTLE patients showed verbal memory decline (7 significant) and 9 showed improvements (2 significant). Mean change in verbal learning was -4.2 (SD 9.4). One RTLE patient was right dominant for language and showed significant verbal memory decline after right ATLR (Appendix 1).

9.3.3 Main Effects and group comparisons

Controls activated the left fusiform gyrus, pre and post central gyrus, IFG, MOG,OFC, left HC and PHG. LTLE patients activated the left fusiform gyrus, IFG, precentral gyrus, ITG, IPL, HC and PHG. Significant right sided activations were seen within the SFG, IPL and HC. RTLE patients activated the left HC, precentral gyrus, ITG, IFG OFC and SMA. LTLE patients showed significantly less activation in the left fusiform gyrus, anterior PHG, body of HC, MTG and medial frontal lobe, and greater right IFG activation than controls. No quantitative activation differences were seen between RTLE patients and controls (Fig 9.1, Table 9.2).

Region	Coordinates	T score	Z score	P value
Controls_FWE				
L Fusiform G	-40 -54 -10	10.49	7.49	0.000
	-34 -36 -26	6.3	5.10	0.000
L pre and postcentral G	-36 -30 64	10.32	7.42	0.000
L Orbito-frontal C	-44 24 -14	7.80	6.22	0.000
L Inf. Frontal G	-42 8 24	7.31	5.94	0.000
L Mid. Occipital G	-34 -86 12	6.38	5.39	0.000
MTL activations, FWE correction within a small volume				
L Hippocampus	-24 -20 -10	6.38	5.39	* 0.000
LTLE_FWE				
L Fusiform G	-40 -54 -10	8.76	6.71	0.000
L Precentral G	-46 8 30	7.24	5.90	0.000
R Sup Frontal G	6 24 42	7.08	5.81	0.000
L Inf Frontal G	-46 30 12	6.54	5.48	0.000
R Inf Parietal Lobule	56 20 24	6.34	5.37	0.000
L Inf Parietal Lobule	30 -52 38	5.87	5.06	0.000
L Inf Temporal G	-42 -32 -33	5.54	4.84	0.000
MTL activations, FWE correction within a small volume				
L Hippocampus and PHG	-12 -6 -8	4.97	4.43	*0.000
R Hippocampus	14 -4 -18	2.88	2.75	*0.000
LTLE<Controls				
L Ant PHG and Fusiform G	-30 2 -38	2.68	2.57	*0.05
L Mid Temporal G	-62 -10 -14	2.68	2.57	0.005
L Med Frontal G	-12 50 6	2.67	2.56	0.005
L HC body, PHG	-16 64 -2	2.56	2.46	*0.076
LTLE>Controls				
R Inf Frontal G	54 22 22	3.25	3.07	0.001
RTLE_FWE				
L Supplementary Motor C	-4 12 50	9.37	7.08	0.000
L Inf Temporal G	-44 -52 -14	9,19	7	0.000
L Orbito-Frontal C	-4 54 -20	6.10	5.25	0.000
R insula	32 26 -2	5.8	5.04	0.000
L Inf Frontal G	-38 24 -2	8,11	6.45	0.000
L Precentral G	-42 8 30	8.24	6.52	0.000
MTL activations, FWE correction				
L Hippocampus	-28 -16 -12	5.69	5.98	0.000
RTLE<Controls				
Nil significant				
RTLE>Controls				
Nil significant				

Table 9.2: Coordinates, p-values T and z-scores of whole brain activations and differences in activations in controls, left (LTLE) and right (RTLE) temporal lobe epilepsy patients. * Family wise error (FWE) corrections using a small volume correction within a sphere of 12mm diameter for medial temporal lobe (MTL) activations. L (left), R (right), Inf (inferior), Mid (middle), Sup (superior), G (gyrus), C (cortex), Med (medial), PHG (parahippocampal gyrus), HC (hippocampus), Ant (anterior).

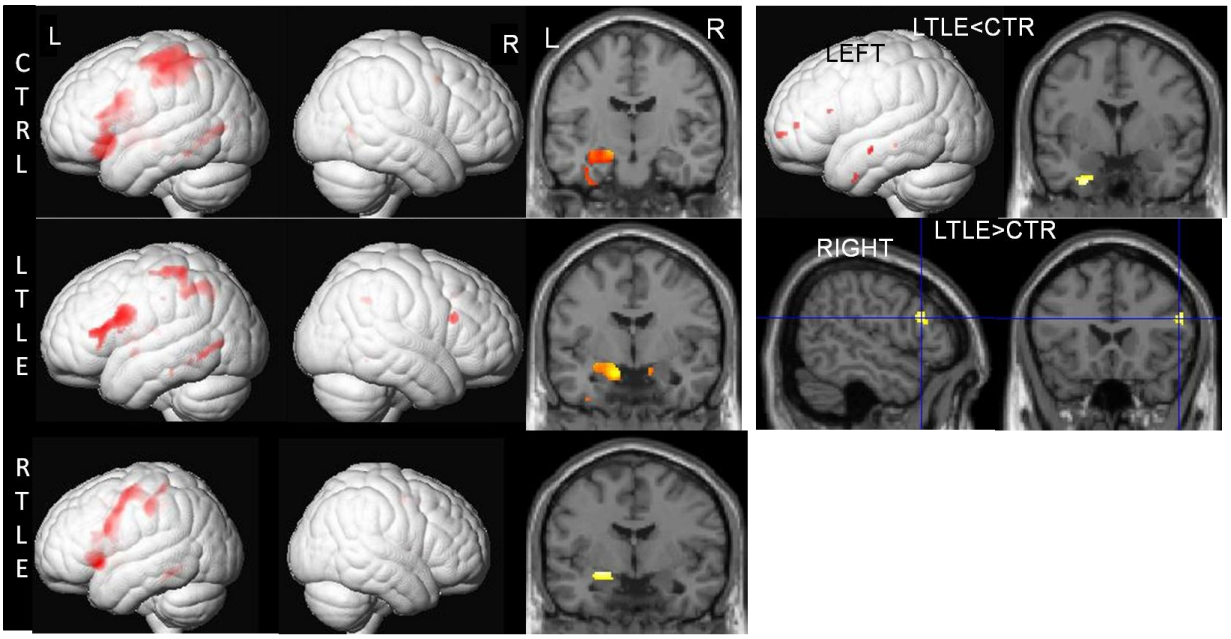


Fig 9.1 Memory encoding activations in controls, left TLE and right TLE patients. Surface rendered whole brain and coronal images showing medial temporal lobe (MTL) words remembered (WR) activations in controls, CTR (upper panel), left TLE patients, LTLE (middle panel) and right TLE patients, RTLE (lower panel). LTLE patients showed less left frontal and MTL activations (LTLE<CTR) and greater right frontal activation compared to controls (LTLE>CTR).

9.3.4 Correlation of fMRI word remembered (WR) activations with list learning

No correlation of WR activations with list learning was seen in controls. In LTLE patients, both MTL (left PHG, body of HC, posterior HC, left amygdala (p=0.01) and right HC (p=0.009)) and extra-temporal activations within the left OFC and anterior cingulum correlated significantly with higher pre-operative list learning scores. This implied successful verbal memory formation was associated with activation of these structures pre-operatively. In RTLE patients, no correlation between WR activations and pre-operative list learning was seen (Table 9.3).

Positive Correlation of WR activations with List Learning in LTLE patients				
Region	**Coordinates**	**T score**	**Z score**	**P value**
L HC	-32 -28 -14	3.41	3.01	*0.024
L PHG	-18 -26 -20	3.07	2.76	*0.044
L Posterior HC	-18 -36 2	2.66	2.44	*0.07
L Orbitofrontal C	-38 42 -14	3.79	3.27	0.001
R Orbitofrontal C	46 32 -14	4.18	3.52	0.000
Ant Cingulum	12 40 0	3.57	3.12	0.001
L amygdala	-22 2 -22	2.56	2.36	0.01
R HC	22 -12 -12	2.56	2.36	0.009
Positive Correlation of WR activations with List Learning in RTLE patients				
Nil significant				

Table 9.3: Coordinates, p-values, T and z-scores of word remembered (WR) activations that correlated positively with list learning in left (LTLE) and right (RTLE) temporal lobe epilepsy patients. * Family wise error corrections using a small volume correction within a sphere of 12mm diameter for MTL activations. L (left), R (right), C (cortex), PHG (parahippocampal gyrus), HC (hippocampus), Ant (anterior).

9.3.5 Prediction of post-operative Verbal Memory

9.3.5.1 Clinical parameters and verbal memory decline

LTLE

Verbal memory decline correlated significantly with language LI (Pearson correlation coefficient R=0.44, p=0.037); implying greater verbal memory decline with greater left sided activations. Pre-operative verbal memory, age at onset of epilepsy and hippocampal volumes did not correlate with post-operative verbal memory change (p> 0.1).

RTLE

Neither pre-operative verbal memory, age at onset of epilepsy, hippocampal volume nor language LI correlated with post-operative verbal memory change (p> 0.1).

9.3.5.2 Correlation of fMRI WR activations with post-operative change in list learning

In LTLE patients, predominantly left sided WR activations within the amygdala, HC, OFC, IFG , MFG and anterior cingulate cortex correlated significantly with verbal memory decline after left ATLR. In RTLE patients, left IFG activations correlated with verbal memory decline after right ATLR (Fig 9.2, Table 9.4).

Less verbal memory decline after left ATLR correlated with posterior MTL activations within the right posterior HC and PHG and less significantly with left posterior HC activation (p=0.038) (Table 9.4).

Activations Predictive of Verbal Memory Decline in LTLE patients				
Region	**Coordinates**	**T score**	**Z score**	**P Value**
L Inf Frontal G	-40 32 12	4.72	3.82	0.000
L Mid Occipital G	-32 -66 38	4.36	3.61	0.000
L Orbitofrontal C	-30 36 -18	3.92	3.34	0.000
L Mid Frontal G	-34 56 20	4.78	3.82	0.000
Ant. Cingulum	8 36 0	3.7	3.19	0.001
L anterior PHG/ Hippocampus	-20 -12 -26	3.12	2.79	*0.041
L PHG	-36 -30 -16	4.06	3.03	*0.008
L Amygdala	-28 0 -28	3.47	3.03	*0.023
R Ant PHG	24 0 -30	2.86	2.59	*0.06
Activations Predictive of Less Verbal Memory Decline in LTLE patients				
R Post Hippocampus and PHG	16 -36 -8	2.77	2.51	*0.06
L Post Hippocampus	-28 -32 -2	1.86	1.77	0.038
Activations Predictive of Verbal Memory Decline in RTLE patients				
L Mid Frontal G	-30 44 26	3.80	3.34	0.000
Activations Predictive of Less Verbal Memory Decline				
Nil significant				

Table 9.4: Coordinates, p-values T and z-scores of brain activations predictive of verbal memory change in left (LTLE) and right (RTLE) temporal lobe epilepsy patients.* Family wise error corrections using a small volume correction within a sphere of 12mm diameter for MTL activations. L (left), R (right), Inf (inferior), Mid (middle), G (gyrus), C (cortex), Med (medial), PHG (parahippocampal gyrus), HC (hippocampus), Ant (anterior), Post (posterior).

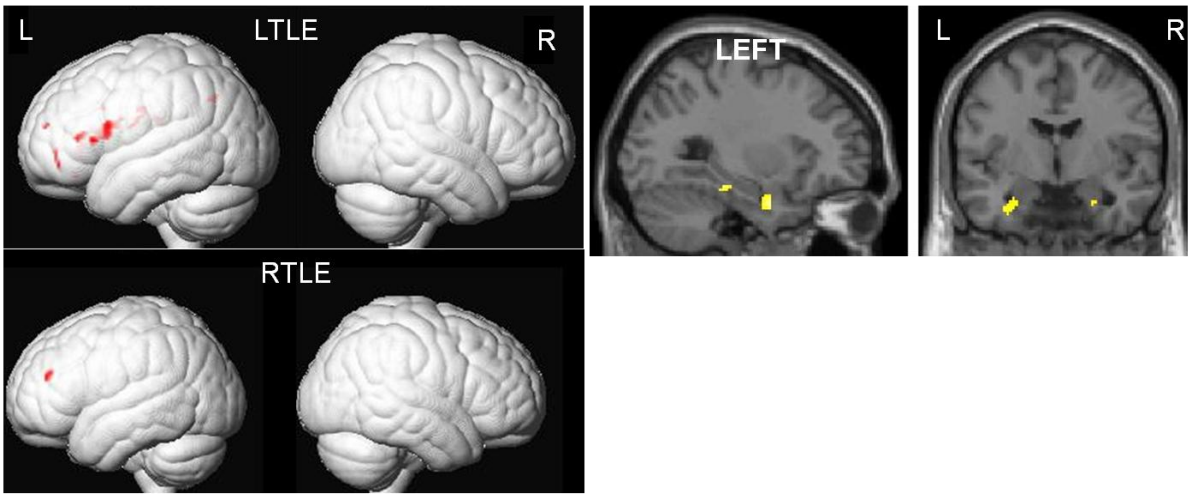


Fig 9.2: Correlation of words remembered activations with post-operative verbal memory decline in left TLE (LTLE (upper panel)) and right TLE patients (RTLE (lower panel)). In both LTLE and RTLE patients, the rendered images show left frontal activations correlated with greater post-operative verbal memory decline. The sliced images showed that predominantly left medial temporal lobe activations correlated with greater post-operative verbal memory decline in LTLE patients. Activations within the medial temporal lobe did not correlate with verbal memory decline in RTLE patients.

9.3.6 Individual memory fMRI parameters predictive of verbal memory decline

The activation LI associated with words remembered in the fronto-temporal mask correlated significantly with change in memory scores, with greater left sided activation predictive of greater verbal memory decline in LTLE patients (Pearson correlation coefficient R=0.66, p=0.001) (Fig 9.3). Memory LI did not correlate with verbal memory change in RTLE patients (Pearson correlation coefficient R=0.14, p>0.1)

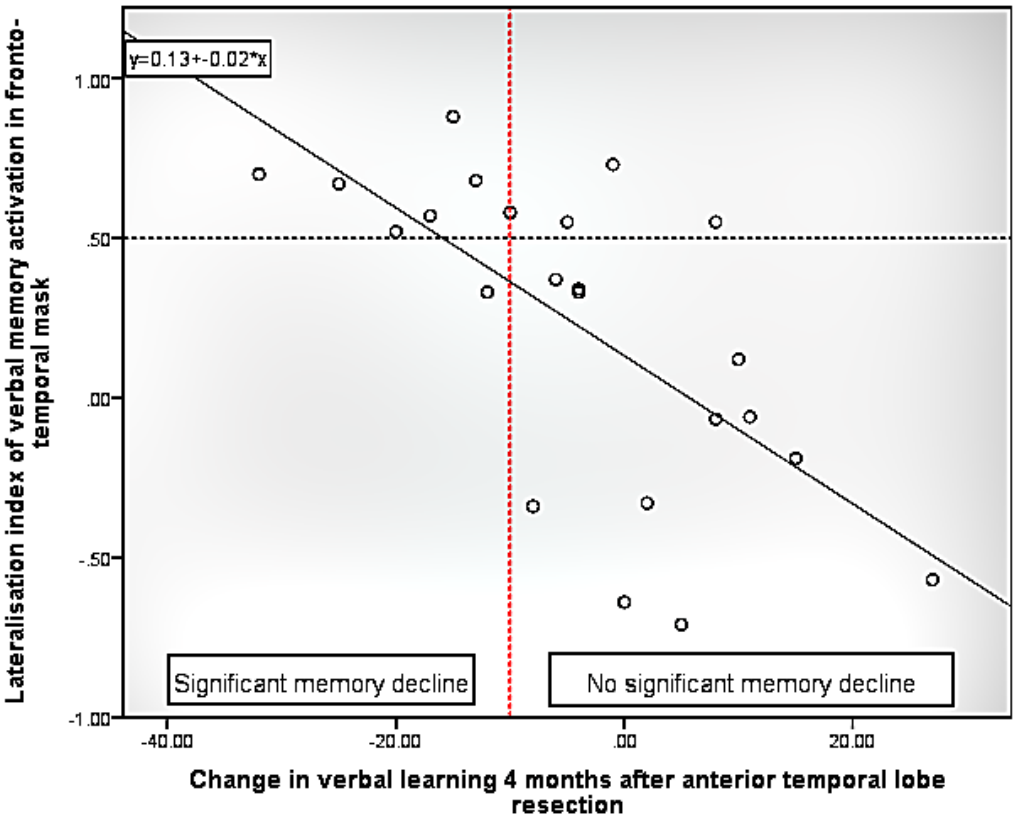


Fig 9.3: Scatter plot of fronto-temporal memory lateralisation index and post-operative change in verbal memory (r^2=0.432). The dotted vertical red line indicates the level of significant decline calculated by reliable change index using control data. The horizontal black dotted line indicates a lateralization index of 0.5 (Left>Right). 7 of 8 patients who experienced a significant verbal memory decline had LI ≥0.5.

9.3.6.1 Linear Regression

Linear regression showed that only language and memory LI predicted post-operative verbal memory decline in LTLE patients. Memory LI was the best predictor of verbal memory outcome compared to all other parameters as shown in the multivariable adjusted analysis (β coefficient -16.1, 95% Confidence Interval -28.4 to -3.9, p = 0.01), (Table 9.5)).

None of the parameters investigated (Language LI, memory LI, age at onset of epilepsy, pre-operative hippocampal volume, pre-operative verbal learning) predicted verbal memory decline in RTLE patients (p>0.1).

LTLE patients	UNADJUSTED		ADJUSTED	
Parameters	**β Coefficient 95% CI**	**p-value**	**β Coefficient 95% CI**	**p-value**
Memory LI	-18.7 -28.4 to -9.0	0.001	-16.1 -28.4 to -3.9	0.01
Language LI	-16.7 -32.3 to -1.2	0.04	-10.3 -26.6 to 5.9	0.2
Age at onset (years)	-0.3 -0.8 to 0.2	0.2	0.1 -0.4 to 0.6	0.8
Hippocampal volume (mm^3)	-2.5 -11.5 to 6.6	0.6	-3.3 -12.1 to 5.4	0.4
Pre-operative Verbal Learning	-0.4 -0.9 to 0.2	0.2	-0.03 -0.6 to 0.5	0.9

Table 9.5: Regression analysis of clinical and fMRI parameters in predicting change after left anterior temporal lobe resection. Memory and language LI had an effect on predicting memory decline after surgery (unadjusted analysis). The multivariate analysis showed that memory LI had an independent effect above all other parameters (adjusted analysis). Confidence interval (CI), Lateralisation index (LI).

9.3.6.2 Memory prediction for individual LTLE patients

Using LI, greater left than right activation within the fronto-temporal mask was the best independent predictor of verbal memory decline above all the other parameters investigated. For use as a clinical predictive tool, an objective measure of LI of ≥ 0.5 was chosen as a predictive threshold. 7 out of 8 significant decliners had a fronto-temporal memory LI of ≥0.5 conferring a test sensitivity of 87.5%. Specificity was 80% (Fig 9.3, Table 9.6). Left lateralised language LI of ≥ 0.5 had 100% sensitivity in predicting verbal memory decline in LTLE patients but specificity was low at 13.3% as 21 of the 23 LTLE patients had a language LI of ≥ 0.5.

Using verbal memory fMRI alone, if a patient had a LI of ≥ 0.5 there was 70% (7/10) risk of significant verbal memory decline after surgery. Should a patient have a LI of <0.5, the risk of significant memory decline was 7.7% (1/13) (Table 9.6).

Fronto-temporal L LI	Significant verbal memory Decline (number of patients)	Non significant decline/improvement in verbal memory (number of patients)	Total
LI ≥ 0.5	7	3	10
LI < 0.5	1	12	13
Total	8	15	23

Table 9.6: Memory fronto-temporal lateralisation index (LI) in relation to changes in verbal memory after left anterior temporal lobe resection.

9.4 Discussion

22 (21 LTLE) patients had dominant and 28 (2 LTLE) patients had non-dominant ATLR. Although the mean change in memory post-operatively in LTLE and RTLE patients did not differ, a greater number of patients with dominant ATLR (9/22) had significant verbal memory decline compared to patients after non dominant resection (6/28), consistent with previous literature (Baxendale and Thompson, 2005; Helmstaedter, 2013).

In the LTLE group, left lateralised activation within the MTL and frontal lobes were involved in successful memory formation and were predictive of significant post-operative verbal memory decline.

Retrospective studies have shown earlier age at onset of epilepsy and better pre-operative memory function to be reliable predictors of post operative verbal memory outcome (Baxendale et al., 2006; Helmstaedter and Elger, 1996). I did not replicate this and suggest this may be due to small numbers. The crucial point is that in the current study, despite small numbers, fronto-temporal memory LI ≥ 0.5 indicating greater left than right activation correlated significantly with post-operative change in

memory and was the strongest independent predictor of post-operative verbal memory decline.

LI within the anatomical fronto-temporal mask rather than a mask created around a group maximum was used to enable the test to be applied to a newly encountered patient. With an LI ≥ 0.5 memory fMRI alone had a positive predictive value (PPV) of 70%, sensitivity of 87.5 % and 80% specificity as a tool for predicting post-surgical significant memory decline after left ATLR. Previous memory fMRI prediction algorithms using asymmetry image analysis alone reported PPV of 35%, 100% sensitivity and 41% specificity based on greater left than right activations within the MTL(Bonelli et al., 2010).

Outcome after surgery may be affected by several factors including age at surgery, age at onset of epilepsy, pre-operative memory, underlying pathology and its extent, surgical variables and post-operative seizure outcome that will all contribute to the scatter seen in figure 9.3. In one left TLE patient memory LI failed to predict significant decline. This patient (patient LTLE 17, Appendix 1) had impaired pre-operative verbal memory, small pre-operative left hippocampal volume, early age at onset of epilepsy and was seizure free one year after surgery, so verbal memory decline was surprising. Three LTLE patients with a memory LI of ≥ 0.5 did not have significant memory decline (LTLE 2, 11, 13, Appendix1). All three had relatively smaller pre-operative hippocampal volumes and younger age at onset of epilepsy; both factors that have been associated with memory preservation post-operatively.

One right TLE patient was right lateralised for language and showed significant decline in verbal memory after right ATLR. Correspondingly, fronto-temporal memory LI was significantly right lateralised in this patient and would have predicted decline

in this patient. Neither memory LI, language LI nor clinical parameters predicted verbal memory decline in RTLE patients.

Epilepsy is recognized to be a network disease and both structural and functional disruption in the contralateral temporal lobe and more remotely has been described in patients with unilateral TLE (Bonilha et al., 2007; Concha et al., 2005; Focke et al., 2008; Keller et al., 2009). We showed that pre-operative left frontal activation also correlated with verbal memory decline in RTLE patients, exemplifying the network disruption that may occur as a consequence of epilepsy and surgery.

Two models have been proposed in the pre-operative risk assessment of post-surgical memory decline. The functional adequacy model suggests that post-surgical memory decline is inversely proportional to the function of the 'to-be-resected' tissue whilst the hippocampal reserve model suggests it is the function of the contralateral hippocampus to sustain memory function after surgery that determines post-surgical memory outcome (Chelune, 1995). Previously, event-related analyses supported the functional adequacy model, with greater activation in the 'to be resected' anterior hippocampus being predictive of verbal memory decline using asymmetry images(Bonelli et al., 2010; Powell et al., 2008; Richardson et al., 2004). Using asymmetry images rather than absolute activations, these studies were unable to comment on the hippocampal reserve model as activations in asymmetry images represent either left>right activations or vice-versa (Richardson et al., 2006). I showed that activations within predominantly the left anterior MTL and frontal lobe that were involved in successful memory formation pre-operatively, were predictive of decline post-operatively. I therefore propose an extension to Chelunes' model to encompass the network approach to cognition whereby functional adequacy is not

just the function of the ‘to-be–resected’ hippocampus but also the pre-operative efficient network that encompasses the ‘to-be-resected’ MTL.

My study has several strengths. First, I used a sensitive verbal memory contrast (words remembered) that showed significant activations both in the MTL and extra-temporally in all patients, a crucial pre-requisite for individual memory prediction paradigms. Of note, this contrast was different to the subtraction contrast used in chapter 6 (words remembered minus words familiar/forgotten). The latter subtraction contrast whilst more specific for successful verbal memory encoding network was less sensitive and not every patient had significant medial temporal activations. For the purpose of prediction in a clinical context for individual patients, a sensitive contrast was required but I acknowledge that the words remembered contrast is less specific and incorporates components of a language network.

Second, I created a prediction algorithm based on an objective LI measure that was calculated within SPM and is applicable to a newly encountered patient. Third, medication was not changed in the interval between the assessments.

This study has limitations. Although reliable change was calculated from the control population at equivalent inter-test time interval to patients, it may have been better to calculate this data using TLE patients who did not have surgery, but this would add further variables such as medication changes.

This algorithm is based on memory outcome 4 months post-operatively. Patients with significant memory decline 4 months remain with this decline at 12 months follow up (Gleissner et al., 2005). Further, 12 months after surgery, other factors such as medication and mood change may complicate interpretation of results.

Asymmetry of verbal memory fMRI activation was the strongest independent predictor of verbal memory outcome after dominant ATLR, compared to language fMRI and clinical parameters. I demonstrate the contribution of extra-temporal areas to memory prediction and that greater pre-operative activation of the memory encoding network that incorporates the ‘to-be-resected’ hippocampus is inversely related to memory outcome.

This memory fMRI prediction algorithm is applicable to temporal lobe surgery and now needs evaluation in larger groups of patients and is applicable at centres that already utilise language fMRI as part of their pre-surgical clinical protocol.

Chapter 10: Memory network plasticity after temporal lobe resection: a longitudinal functional imaging study

Abstract

Aims: ATLR can control seizures in up to 80% of patients with TLE. Memory decrements are the main neurocognitive complication. Pre-operative functional reorganisation has been described in verbal and visual memory networks but less is known of the functional reorganisation that may occur after surgery. I investigated reorganisation of memory encoding networks pre-operatively and four and 12 months after surgery.

Methods: I studied 36 patients with unilateral TLE (19 right) before and four and 12 months after ATLR. 15 healthy controls were studied at three equivalent time-points to patients. All subjects had neuropsychological testing at each of the three time-points. A functional magnetic resonance imaging memory-encoding paradigm of words and faces was performed with subsequent out-of-scanner recognition assessments. Changes in activations across the time-points in each patient group were compared to changes in the control group in a single flexible factorial analysis. Post-operative change in memory across the time-points was correlated with post-operative activations to investigate the efficiency of reorganised networks.

Results: LTLE patients showed increased contralateral right anterior hippocampal and right frontal activation at both four and 12 months after surgery relative to pre-operatively for word and face encoding, with a concomitant reduction in left frontal activation 12 months post-operatively. Right anterior hippocampal activation 12 months post-operatively correlated significantly with improved verbal learning in LTLE patients from pre-operatively to 12 months post-operatively. Pre-operatively,

there was significant left posterior hippocampal activation that was sustained four months post-operatively at word encoding, increased during face encoding. For both word and face encoding this was significantly reduced 12 months post-operatively compared to pre-operatively.

RTLE patients showed increased left anterior hippocampal activation on word encoding from four to 12 months post-operatively compared to pre-operatively. On face encoding, left anterior hippocampal activations were present pre-operatively and 12 months post-operatively. Left anterior hippocampal and orbitofrontal cortex activations correlated with improvements in both design and verbal learning 12 months after surgery. Four months post-operatively, RTLE patients showed increased left posterior hippocampal activations that correlated with a decline in design learning. From four to 12 months post-operatively, there was a significant reduction in this left posterior hippocampal activation on face encoding.

Conclusion: Post-operative changes occur in the memory encoding network in both left and right temporal lobe epilepsy patients across both verbal and visual domains. Four months after surgery, compensatory posterior hippocampal reorganisation that occurs is transient and inefficient. Engagement of the contralateral hippocampus12 months after surgery represented efficient reorganisation in both patient groups, suggesting that the contralateral hippocampus contributes to memory outcome 12 months after surgery.

10.1Introduction

TLE is associated with widespread cognitive deficits with material specific episodic memory impairment being most commonly described; particularly verbal memory loss in LTLE patients and visual in RTLE. More recently, a move away from the material specific model describes task related disruption with both verbal and visual deficits seen across patients with LTLE and RTLE (Flugel et al., 2006; Gleissner et al., 2002; Glikmann-Johnston et al., 2008; Saling, 2009). FMRI studies have shown temporal and extra-temporal reorganisation within memory encoding networks across both verbal and visual domains in individuals with both LTLE and RTLE, as we showed in chapter 6 (Alessio et al., 2013; Bonelli et al., 2010; Dupont et al., 2002; Sidhu et al., 2013).

Although deterioration of both verbal and visual episodic memory has been described as a consequence of surgery, verbal memory decline after dominant ATLR remains the most consistent finding, occurring in up to 30% of patients.

FMRI has been used to predict patients at risk of memory decline after ATLR as described in chapter 9. The greater the activation within the ‘to-be-resected’ anterior MTL, the greater the verbal and visual decline after left and right ATLR respectively, (Binder, 2011; Bonelli et al., 2010; Powell et al., 2008; Richardson et al., 2004) in keeping with the hippocampal adequacy model of memory outcome after ATLR (Chelune, 1995). Recently, activation of the posterior HC pre-operatively was shown to be related to memory preservation post-operatively (Bonelli et al., 2013). We corroborated this finding in chapter 6. Correspondingly, the extent of hippocampal resection is an important determinant of post-operative memory function and has

important implications on surgical planning (Alpherts et al., 2008; Baxendale et al., 2000; Schramm, 2008).

Plasticity in the memory encoding networks within the MTL after ATLR has only been described in a few studies (Bonelli et al., 2013; Cheung et al., 2009; Korsnes et al., 2009) with one reporting extra-temporal post-operative memory network plasticity within a small frontal region (Maccotta et al., 2007). Using a material specific word encoding task Bonelli et al showed that although memory reorganisation to the posterior HC pre-operatively was predictive of preserved verbal memory function after left ATLR, greater post-operative reorganisation to the ipsilateral posterior HC correlated with worse verbal memory four months after resection, indicating that effective reorganisation to the posterior left HC did not occur in the initial post-operative months.

In controls, although memory encoding test-retest studies have shown stable HC activations at least three months after initial scanning (Atri et al., 2011; Putcha et al., 2011), task similarities may incur practice effects and altered memory encoding strategies in healthy controls (Siders et al., 2006), leading to differential engagement of the frontal lobes (Fletcher and Henson, 2001). To date, no studies have described quantitative post-operative network plasticity changes compared to changes in controls imaged across similar time intervals. In this study, I:

1) Investigated dynamic medial temporal and extra-temporal reorganisation of verbal and visual memory encoding networks four and 12 months after ATLR in LTLE and RTLE patients compared to healthy controls.

2) Used a material specific event related analysis to study successful memory encoding with correlations with post-operative changes in neuropsychological performance to determine the efficiency of post-operative changes.

10.2 Methods

10.2.1 Subjects

I studied 36 patients with medically refractory TLE [17 left; median age 32 years, IQR (inter-quartile range) 26-45, 19 right; median age 40,IQR 22-48]. All underwent pre-surgical evaluation and surgery at NHNN, London. All patients had structural MRI at 3T including quantification of hippocampal volumes and T2 relaxation times pre-operatively and at four and 12 months after surgery. In the LTLE group, 11 patients had unilateral HS, two anterior temporal cavernomas, two dysembryoplastic neuroepithelial tumours and in two patients no lesion was identified. In the RTLE group, 10 had unilateral HS, four had dysembryoplastic neuroepithelial tumours, one had non-specific high signal of the PHG and in four patients no structural lesion was seen.

All patients underwent standard en-bloc temporal lobe resections (which involved opening of the temporal horn, followed by resection of the hippocampus with a posterior resection margin at the mid brainstem level), fMRI and detailed neuropsychometry pre-operatively and at four and 12 months after surgery. ILAE post-operative seizure outcome (Wieser et al., 2001) and changes in anti-epileptic medication four and 12 months after surgery were recorded (Table 10.1).

Fifteen healthy native English speaking matched controls [median age 40 (30.5 -49)] underwent memory fMRI and neuropsychometry at three similar time intervals to patients.

	LTLE (n=17)	RTLE (n=19)
Handedness (L/R)	2/15	3/16
Language dominance(R/Left/bilateral)	1/16/0	1/17/1
Median age at onset of epilepsy (IQR), years	14 (7-24)	14 (9-18)
Median duration of epilepsy (IQR), years	14 (7-25)	18 (8.5-32)
Median duration to first post-operative scan, postop1 (IQR), months	3.5 (3.2-3.7)	3.7 (3.1-4.6)
Median duration to second post-operative scan, postop 2 (IQR), months	12.6 (12.1-13.6)	12.9 (12.1-13.3)
AED change at 3 months	Nil	Nil
AED change at 12 months	6/17 one AED reduced or stopped 2/17 off AEDs	7/19 one AED reduced 2/19 off AEDs
ILAE seizure outcome at 3 months	14/17 outcome 1-2 3/17 outcome 3-5	16/19 outcome 1-2 2/19 outcome 3-4 1/19 outcome 5
ILAE seizure outcome at 12 months	15/17 outcome 1-2 2/17 outcome 4	16/19 outcome 1-2 2/19 outcome 4 1/19 outcome 5

Table 10.1: Clinical details of left (LTLE) and right temporal lobe epilepsy (RTLE) patients. IQR (inter-quartile range), AED (anti-epileptic drug).

10.2.2 Neuropsychological testing

All patients and controls underwent standardised cognitive assessments as detailed in chapter 5 at three time points; pre-operatively, four months and 12 months after surgery in patients and 3 equivalent time intervals in controls.

Clinically significant decline in verbal and visual memory was calculated using reliable change indices (Baxendale and Thompson, 2005); defined as decline of 12 points on the verbal learning task and 13 on the design learning task (90 % confidence interval).

Change in verbal and design learning scores between pre-operative and four and 12 months post-operative timepoints were correlated with changes in ipsilesional hippocampal volumes at the corresponding time points in patients. All statistical analyses were performed using PASW Statistics 18.0 (IBM, Armonk, USA).

10.2.3 Pre-processing of post-operative fMRI data

The base-line imaging time series of each patient was realigned using the mean image as a reference. Rigid body co-registration was used to co-register postoperative scans to the preoperative mean image; scans were then spatially normalised into standard space applying each subject's preoperative spatial normalisation parameters to the subject's postoperative realigned and co-registered scans. Preoperatively, a scanner and acquisition specific template created from 30 healthy control subjects, 15 patients with left and 15 patients with right hippocampal sclerosis was used for normalization. All scans were then smoothed with a Gaussian kernel of 8 mm FWHM.

10.2.4 Event-related analysis

Different faces and words were used for the three scanning sessions in all participants. Event-related analyses of words and faces was performed as detailed in chapter 5. Contrast images were created for each subject for word encoding (defined by (WRem)–(WFam+WFo)) and face encoding (defined by (FRem)–(FFam+FFo)). This was performed for each of the three scanning sessions in patients and controls; denoted Preop, Postop1 and Postop2 for word and face encoding. These images were used for the second-level analysis.

Second level

One sample t-test

At the second level, one sample t tests were performed in all controls, LTLE and RTLE patients to model the group effect for the contrasts (WRem)–(WFam+WFo) and (FRem)–(FFam+FFo) at the three scanning time points. For controls, a within subject ANOVA was performed to study longitudinal changes across the three

scanning sessions. Changes in patients relative to changes in controls were investigated in a flexible factorial analysis (Stretton et al., 2014).

10.2.5 Flexible factorial analysis

To investigate the relationship between pre- and post-operative change in memory in the individual patient groups compared to changes in test-retest in controls at the same time intervals, we employed a mixed ANOVA using a flexible factorial design (Glascher and Gitelman, 2008). The difference between controls and LTLE, and controls and RTLE groups were analysed in different flexible factorial sessions as this model only allows two groups to be compared at a time. Faces and words analyses were performed separately. For each flexible factorial, a factor of group with two levels (controls and LTLE or RTLE) and a factor of condition with three levels (Preop, Postop1 and Postop2) was specified. The relevant contrast images for each subject for each of the three conditions were entered allowing the investigation of a Group x Condition interaction for the contrasts of interest. Differences in activations across scanning sessions were compared between TLE patients and controls (for example word encoding LTLE> Controls: Postop1>Preop, Postop2>Preop, Postop2>postop1, Preop>Postop1, Preop>Postop2, Postop1>Postop2).

Thus, I modelled the changes in activations at the three time-points and between the groups, whilst controlling for between subjects and between group variance in a single model.

10.2.6 Correlations with memory performance

A simple regression model of change in verbal learning (VL) and design learning (DL) as continuous regressors in an ANCOVA against verbal and visual subsequent memory activations was employed to assess brain activations corresponding to change in memory scores across the time points in LTLE and RTLE patients.

10.2.7 Statistical thresholds for reporting of all fMRI results

All differences in activations within and between groups and correlations are shown at a threshold of $p<0.001$, uncorrected. Medial temporal lobe activations are shown corrected for multiple comparisons, family wise error using a small volume correction within a sphere diameter of 10 mm (FWE $p<0.05$) unless otherwise stated (Bonelli et al., 2013; Sidhu et al., 2013)**.**

10.2.8 Parameter Estimates

As one of the main aims of this study was to study the dynamic changes of medial temporal activations, I calculated the parameter estimates for word and face encoding pre-operatively and at four and 12 months after surgery within the ipsilateral posterior and contralateral HC where we previously showed pre-operative activations (Sidhu et al., 2013). Parameter estimates were extracted from the activation maps.

10.3 Results

10.3.1 Post-operative Neuropsychometry

LTLE

Controls performed significantly better than LTLE patients at all three time points. As a group, there was a non significant decline in VL from preop to postop1 and preop to postop2 (paired sample t-test, $p>0.05$) and a significant decline in design learning (DL) from preop to postop1 (paired sample t-test, $p< 0.05$), (Table 10. 2).

Four months post-operatively 29.4% (5/17) and 17.6% (3/17) of LTLE patients declined significantly in VL and DL respectively.

12 months post-operatively compared to preop 29.4% (5/17) and 5.9 % (1/17) of LTLE patients declined significantly in VL and DL respectively.

RTLE

Controls performed better than RTLE patients across both VL and DL tasks across all time points. RTLE patients showed a non-significant decline in DL scores from preop to postop1 and preop to postop2 (paired sample t-test, $p>0.05$) and a significant decline in VL between preop and postop1 (paired sample t-test, $p< 0.05$), (Table 10.2).

Four months post-operatively 15.8% (3/19) and 21% (4/19) of RTLE patients declined significantly in DL and VL respectively.

12 months post-operatively 10.5% (2/19) and 21%(4/19) of RTLE patients declined significantly compared to preop in DL and VL respectively. All LTLE and RTLE patients who declined significantly in VL at four and 12 months post-operatively were

left hemisphere dominant for language (LI > 0.5). From postop1 to postop2 there was a non-significant improvement in both VL and DL in both patient groups (paired sample t-test, p>0.05), Table 10.2.

10.3.2 Hippocampal Volumes and correlation with change in memory

There was no significant difference between the ipsilesional and contralesional pre-operative hippocampal volumes in LTLE and RTLE patients (Independent sample t-test p>0.05). Four months post-operatively LTLE patients had significantly larger posterior HC residual volumes compared to RTLE patients (Independent sample t-test p<0.05). LTLE patients showed significant decline in left HC remnant volume from four to 12 months post-operatively, paired sample t-test, p= 0.019 (left hippocampal volume in LTLE patients, mm^3: Preop 1.98 (0.6), Postop1 0.79 (0.7), Postop2 0.70 (0.6), Right hippocampal volume in RTLE patients 2.27 (0.4), Postop1 0.23 (0.1), Postop2 0.20 (0.1)).

There was no correlation of change in the ipsilateral remnant hippocampal volume from 3 to 12 months post-operatively with change in VL and DL at the corresponding time-points in either LTLE or RTLE groups, Pearson correlation coefficient <0.3, 2-tailed t-test p >0.05.

10.3.3 Behavioural: Recognition Accuracy (RA)

Controls performed significantly better than LTLE patients at all three time points (Independent sample t-test p<0.05). LTLE patients showed a significant decline in RA for words from preop to postop1 and preop to postop2, (paired sample t-test p>0.05), (Table 10.2).

In RTLE patients there was a significant decline in RA for faces from preop to postop1 and preop to postop 2 (paired sample t-test $p<0.05$). No significant change in either word or face RA was seen from postop1 to postop2 in LTLE or RTLE patients.

	RA words			RA faces			Verbal learning			Design Learning		
	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
Controls	77.9 (7.8)	82.3 (9.6)	78.6 (11.9)	28.6 (13)	30.8 (11.6)	36.1 (13)	58.6 (7.1)	57.3 (5.5)	61.9 (6.9)	39.4 (5.9)	37.9 (6.5)	38.5 (5.6)
LTLE	60.2* (15.9)	48.7* (20)	45.8* (19.4)	20.2 (10.8)	22.5 (13.5)	22.3* (10.1)	47.5* (10.7)	43.2* (14.5)	44.8* (12.4)	37.2 (4.9)	32.8 (7.5)	34.1* (7.1)
RTLE	63.2 (18.2)	55.4* (21.8)	49.5* (25)	15.3* (8.5)	9.5 * Ω (9.5)	11.6*Ω (12.3)	47.9* (11.2)	43.1* (11.7)	44.6* (14.1)	32.1* (8.7)	28.5* (10)	31.2* (9.4)

Table 10.2 Neuropsychometry and behavioural measures across the three time points in controls and left (LTLE) and right temporal lobe epilepsy (RTLE) patients.*Controls performed significantly better than patient group indicated $p<0.01$. Ω RTLE performed significantly worse than LTLE $p<0.01$. In patients, T1= pre-operative, T2= 3 months post-operatively, T3= 12 months post-operatively.

10.3.4 Functional MRI results

10.3.4.1 Baseline

For details see Table 10.3.

On word encoding, controls activated the left anterior HC, LTLE patients the left posterior HC whilst RTLE patients showed bilateral anterior HC activations. Controls and RTLE patients showed left extra-temporal activations whilst LTLE patients showed bilateral extra-temporal activations.

On face encoding, controls showed right anterior HC activations; LTLE patients showed bilateral posterior HC activations; RTLE patients showed right posterior and left anterior HC activations. LTLE patients showed left extra-temporal whilst RTLE showed bilateral extra-temporal activations. Controls showed right extra-temporal activations only at a lower threshold (p=0.01, uncorrected).

Region	Coordinate	Z Score	P value	Region	Coordinate	Z score	P value
	Word encoding				Face encoding		
Controls							
L Med OFC	-16 62 -4	3.02	0.001	R Mid Temp G	64 -6 -22	3.29	0.000
L Mid Frontal G	-40 12 34	2.99	0.001	R Inf OFC	42 34 -16	2.25	0.01
L Rolandic O	-42 -6 14	3.43	0.000				
Controls_ Medial temporal lobe							
L Ant HC	-24 0 -28	2.71	0.02*	R Ant HC	28 -14 -12	3.79	0.000*
				L Fusiform G	-24 -40 -12	3.37	0.000*
LTLE							
R Mid Frontal G/ Precentral G	54 -10 44	3.82	0.000	L Sup Temp G/ L Post Insula	-44-16 4	3.55	0.000
R Sup Temp G	70-34 2	3.19	0.001	L Med Frontal G	-4 14 -16	2.99	0.001
L Sup Frontal G	-18 2 46	3.18	0.001	L Post cingulum	-6 -42 14	3.1	0.001
L Orbitofrontal G	-8 66 -2	3.18	0.001				
L Fusiform	-22 -42 -16	3.17	0.001				
LTLE_Medial temporal lobe							
L Post HC	-32 -32 -6	2.75	0.02*	R post PHG	22 -44 -2	2.44	0.03*
				L post PHG	-22 -44 -2	2.41	0.05*
RTLE							
L Sup Temp G	-46 6 -14	2.75	0.003	R Rolandic O	52 -16 22	3.78	0.000
L Ant Cingulum	-2 42 -2	2.66	0.004	L Postcentral G	-32 -36 50	3.68	0.000
				R Mid Cingulum	18 -32 48	3.66	0.000
RTLE_Medial Temporal Lobe							
R ant HC	30 -2 -22	3.31	0.01*	L HC body	-22 -20 -16	2.74	0.03*
L ant HC	-34 -22 -16	2.52	0.05*	R post HC	22 -36 6	2.42	0.04*

Table 10.3: Word and face encoding activations pre-operatively in patients, and at the first scanning session in controls. *Medial temporal activations are shown corrected for multiple corrections, FWE (Family wise error) p<0.05 within a 10mm diameter sphere. L (left), R (right), Inf (inferior), Mid (middle), Sup (superior), Med (medial), G (gyrus), Ant (anterior), Post (posterior), HC (hippocampus), O (operculum).

10.3.4.2 Longitudinal changes in controls

Word encoding

Controls showed increased activations in the left IFG at time points two (T2) and three (T3) compared to the first scanning session (T1). No changes in medial temporal activations, or areas of reduced activation were seen (Table 10.3).

Face encoding

Controls showed increased left inferior frontal and orbitofrontal cortex activations at T2 and T3 respectively compared to T1. Reduced activations were noticed within the right hippocampus and orbitofrontal cortex at T2 with reduced activations seen within the right hippocampus at T3 compared to T1 (Table 10.4).

	Coordinate	Z score	P value	Region	Coordinate	Z score	P value
Longitudinal word encoding changes in Controls				**Longitudinal face encoding changes in Controls**			
Time point two > Time point one							
L Inf Frontal G	-60 8 18	4.27	0.000	L Inf Frontal G	-42 10 20	2.64	0.004
L Precentral G	-56 -4 32	3.87	0.000				
Time point three > Time point one							
L Inf Frontal G	-60 6 16	3.17	0.001	N/S			
Time point three > Time point two							
N/S				L OFC	-42 50 4	2.61	0.005
Time point one > Time point two							
N/S				R anterior HC	28 -12 -20	3.43	0.004*
				R OFC	42 22 -18	3.51	0.001
Time point one > Time point three							
N/S				R anterior HC	24 -18 -16	3.33	0.005*
Time point two > Time point three							
N/S				N/S			

Table 10.4: Longitudinal changes in word and face encoding activations in controls. *Medial temporal activations are shown corrected for multiple corrections, FWE (Family wise error), p<0.05 within a 10mm diameter sphere. L (left), R (right), Inf (inferior), Mid G (gyrus), HC (hippocampus), OFC (Orbitofrontal cortex), N/S (no significant activations).

10.3.4.3 LTLE changes compared to changes in controls

See Table 10.5

Word encoding

Four months post-operatively, LTLE patients showed a significant increase in right hemispheric activations within the right anterior HC, PHG and OFC relative to changes in controls.

12 months after surgery, compared to baseline, there were reduced left sided activations within the MFG and posterior HC with an increase in right sided activations within the IFG and right anterior HC relative to changes in controls.

From four to 12 months after surgery, there were significantly increased right MFG activations and reduced left posterior HC and PHG activations relative to changes in controls.

<u>Parameter estimates of word encoding activations within the MTL in LTLE patients</u>

Pre-operative left posterior HC word encoding activations in LTLE patients were sustained four months post-operatively but this significantly declined 12 months after surgery. Increased activation was seen within the right HC four months post-operatively and this was sustained 12 months post-operatively (Fig 10.1).

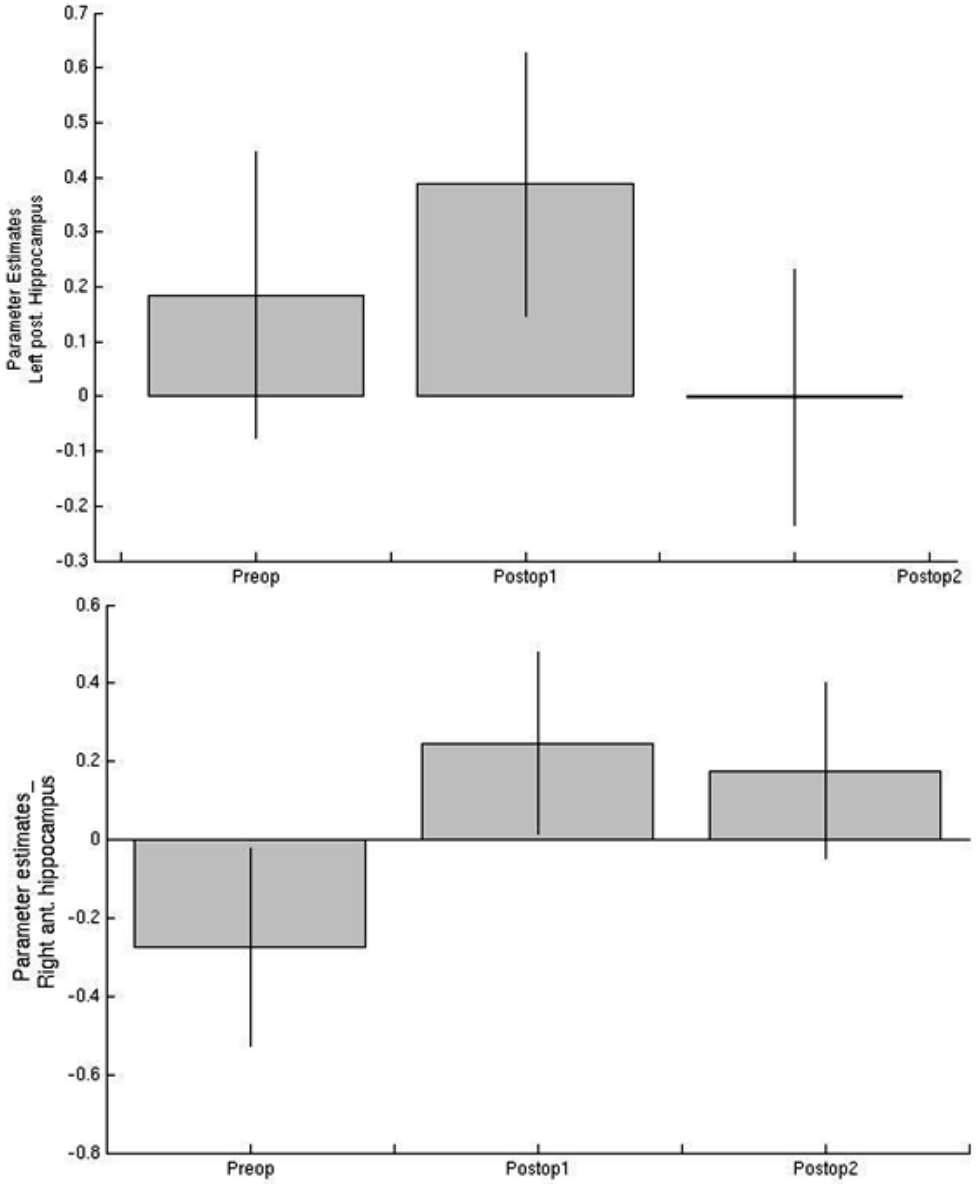


Fig 10.1: Parameter estimates of word encoding medial temporal lobe activations pre-operatively (Preop) and at four (Postop1) and 12 months (Postop2) after anterior temporal lobe resection in left temporal lobe epilepsy patients.

Face Encoding

Four months post-operatively, LTLE patients showed significantly reduced left IFG and MFG activations with increased right sided activations within the anterior HC, MTG, post central gyrus and the left posterior HC relative to changes in controls.

12 months post-operatively, compared to pre-operatively, there were significantly reduced left IFG and MFG activations with increased right MTG activations relative to controls.

From four to 12 months after surgery, there was a significant increase in right IFG activations and reduced activations within the posterior HC bilaterally relative to changes in controls.

Efficiency of 12 month post-operative change in left temporal lobe epilepsy

Improvement in verbal learning 12 months post-operatively compared to pre-operatively correlated significantly with right anterior HC and right extra-temporal activation within the anterior cingulum and parietal lobe (Table 10.6, Fig 10.2).

Region	Coordinate	Z score	P value	Region	Coordinate	Z score	P value
LTLE>Controls_ word encoding				**LTLE>Controls_ face encoding**			
Postop1>preop							
R Orbitofrontal C	36 34 -14	3.79	0.000	R anterior HC	26 -16 -14	3.84	0.001*
R anterior HC/PHG	24 -16 -18	3.43	0.003*	R Mid Temp G	48 -4 -28	4.11	0.000
R anterior PHG	16 -4 -22	2.71	0.026*	L posterior HC	-28 -26 -10	3.4	0.004*
				R Postcentral G	60 -4 18	3.34	0.000
Postop2>preop							
R Inf Frontal G	46 24 6	2.68	0.004	N/S			
R anterior HC	30 -14 -18	1.81	0.035				
Postop2>postop1							
R Mid Frontal G	34 10 34	2.87	0.002	R Inf Frontal G	40 8 16	3.12	0.001
Postop1<preop							
N/S				L Inf Frontal G	-42 10 18	3.09	0.001
Postop2<preop							
L Mid Frontal G	-48 24 28	2.64	0.004	L Inf Frontal G	-50 22 16	3.09	0.001
L anterior HC	-28 -18 -16	1.88	0.03	L Mid Temp G	-56 -66 18	3.07	0.001
L posterior HC	-28 -30 -4	1.71	0.044				
Postop2<postop1							
L posterior PHG	-14 -36 -10	2.06	0.02	R posterior HC	22 -38 4	3.75	0.001*
L posterior HC	-30 -32 -6	1.82	0.03	L posterior HC	-18 -32 -2	3.44	0.004*
				R anterior PHG	26 2 -32	3.92	0.001*

Table 10.5: Longitudinal changes in word and face encoding activations in left temporal lobe epilepsy patients (LTLE) relative to changes in encoding activations in controls. *Medial temporal activations are shown corrected for multiple corrections, FWE (Family wise error), p<0.05 within a 10mm diameter sphere. Preop (pre-operative), Postop1 (3 months post-operatively), postop2 (12 months post-operatively), L (left), R (right), Inf (inferior), Mid (middle), G (gyrus), HC (hippocampus), PHG (parahippocampal gyrus), Temp (Temporal), C (cortex), N/S (no significant activations).

Correlation of change in memory score with fMRI activations						
LTLE						P value
Word Encoding	VL pre to postop1	Improvement	N/S			
		Decline	N/S			
	VL pre to postop2	Improvement	R anterior HC	26 -10 -20	2.78	0.03*
			R postcentral G	56 -8 34	3.2	0.001
			R anterior cingulum	6 16 28	2.97	0.001
		Decline	N/S			
	VL postop1 to postop2	Improvement	N/S			
		Decline	N/S			
Face Encoding	DL pre to postop1	Improvement	Anterior Cingulum	0 36 26	3.65	0.000
		Decline	N/S			
	DL pre to postop2	Improvement	N/S			
		Decline	N/S			
	DL postop1 to postop2	Improvement	N/S			
		Decline	N/S			
RTLE						
Face Encoding	DL pre to postop1	Improvement	N/S			
		Decline	L posterior HC	-30 -32 -10	3.94	0.006*
	DL postop1 to postop2	Improvement	L anterior HC/ amygdala	-30 2 -20	2.43	0.047*
			L insula	-32 2 0	3.08	0.001
			L Inf Frontal G	-60 4 18	3.00	0.001
			L Orbitofrontal C	-44 22 -16	2.99	0.001
		Decline	N/S			
	DL Pre to postop2	Improvement	L Orbitofrontal C	-40 56 -4	2.97	0.001
		Decline	N/S			
Word Encoding	V L pre to postop1	Improvement	N/S			
		Decline	L posterior HC	-32 -22 -10	2.47	0.049*
	VL pre to postop2	Improvement	L anterior HC/PHG	-28 -10 -28	2.55	0.046*
			L Orbitofrontal C	-18 56 -6	3.06	0.001
		Decline	R posterior HC	28 -32 -8	2.42	0.06*
	VL postop1 to postop2	Improvement	N/S			
	VL postop1 to postop2	Decline	R posterior HC	28 -32 -8	3.52	0.000*

Table 10.6: Correlation of change in verbal (VL) and design learning (DL) with word and face encoding activations at the corresponding time points in left (LTLE) and right temporal lobe epilepsy (RTLE) patients. *Medial temporal activations are shown corrected for multiple corrections, FWE (Family wise error), $p<0.05$ within a 10mm diameter sphere. Pre (pre-operative), Postop1 (3 months post-operatively), postop2 (12 months post-operatively), L (left), R (right), Inf (inferior), G (gyrus), HC (hippocampus), PHG (parahippocampal gyrus), C (cortex), N/S (no significant activations).

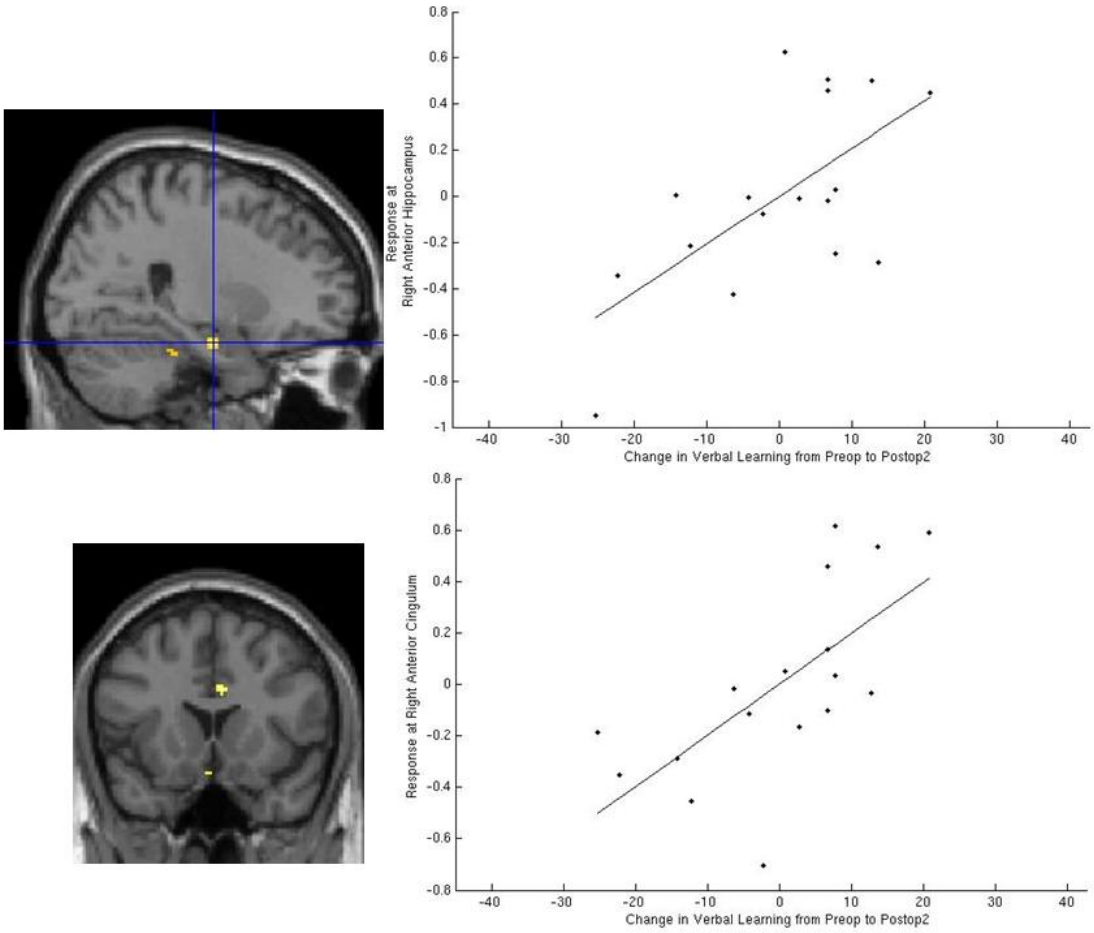


Fig 10.2: Correlation of improvement in verbal learning 12 months post-operatively (postop2) compared to pre-operatively (Preop) in left temporal lobe epilepsy patients. The images show significant correlation of right anterior cingulum and anterior hippocampus activations with improvements in verbal learning 12 months post-operatively.

10.3.4.4 RTLE changes compared to changes in controls

See Table 10.7

Face encoding

Four months post-operatively, RTLE patients showed reduced left inferior parietal lobule and right post-central gyrus activations and increased left posterior HC activations relative to changes in controls.

12 months post-operatively there was a reduction in bilateral anterior HC activations compared to pre-operatively.

From four to 12 months post-operatively, there was a significant decrease in left and right posterior HC activation.

Region	Coordinate	Z score	P value	Region	Coordinate	Z score	P value
RTLE>Controls_ word encoding				RTLE>Controls _face encoding			
Postop1 >preop							
N/S				L posterior HC	-22 -34 -2	2.07	0.069*
				L anterior fusiform gyrus/PHG	-32 -14 -24	2.10	0.018
Postop2>preop							
N/S				N/S			
Postop2>postop1							
L anterior HC	-16 -10 -22	2.35	0.044*	L postcentral G	-38 -34 46	2.97	0.001
R MFG	24 -6 52	2.97	0.001				
Postop1<preop							
R anterior hippocampus	39 -22 -14 (36 -12 -20)	2.61	0.025*	L Inf Parietal L	-38 -38 50	3.54	0.000
R hippocampal body	28 -24 -8	2.26	0.050*	R postcentral G	36 -26 46	3.32	0.001
Postop2<preop							
L med OFC	0 42 -8	3.39	0.000	L anterior HC	-26 -20 -16	2.28	0.048*
L anterior cingulum	-5 18 26	3.21	0.001	R posterior HC	28 -34 0	1.72	0.043
L sup temporal pole	-34 10 -24	3.06	0.001				
Postop2<postop1							
L posterior HC	-24 -36 6	2.73	0.026*	L posterior HC	-20 -34 0	2.77	0.019*
L med OFC	2 32 -14	3.11	0.001	L anterior HC	-22 -22 -16	3.24	0.005*
				R posterior HC	30 -28 -2	2.11	0.060*

Table10.7: Longitudinal changes in word and face encoding activations in right temporal lobe epilepsy patients (RTLE) relative to changes in encoding activations in controls. *Medial temporal activations are shown corrected for multiple corrections, FWE (Family wise error), p<0.05 within a 10mm diameter sphere. Preop (pre-operative), Postop1 (3 months post-operatively), postop2 (12 months post-operatively), L (left), R (right), Inf (inferior), Mid (Middle).

Parameter estimates of face encoding activations within the MTL in RTLE patients

Patients with RTLE showed activation within the left anterior HC and right posterior HC pre-operatively. At postop1, there was a reduction in both activations with a further reduction in activation 12 months after surgery (Figure 10.3).

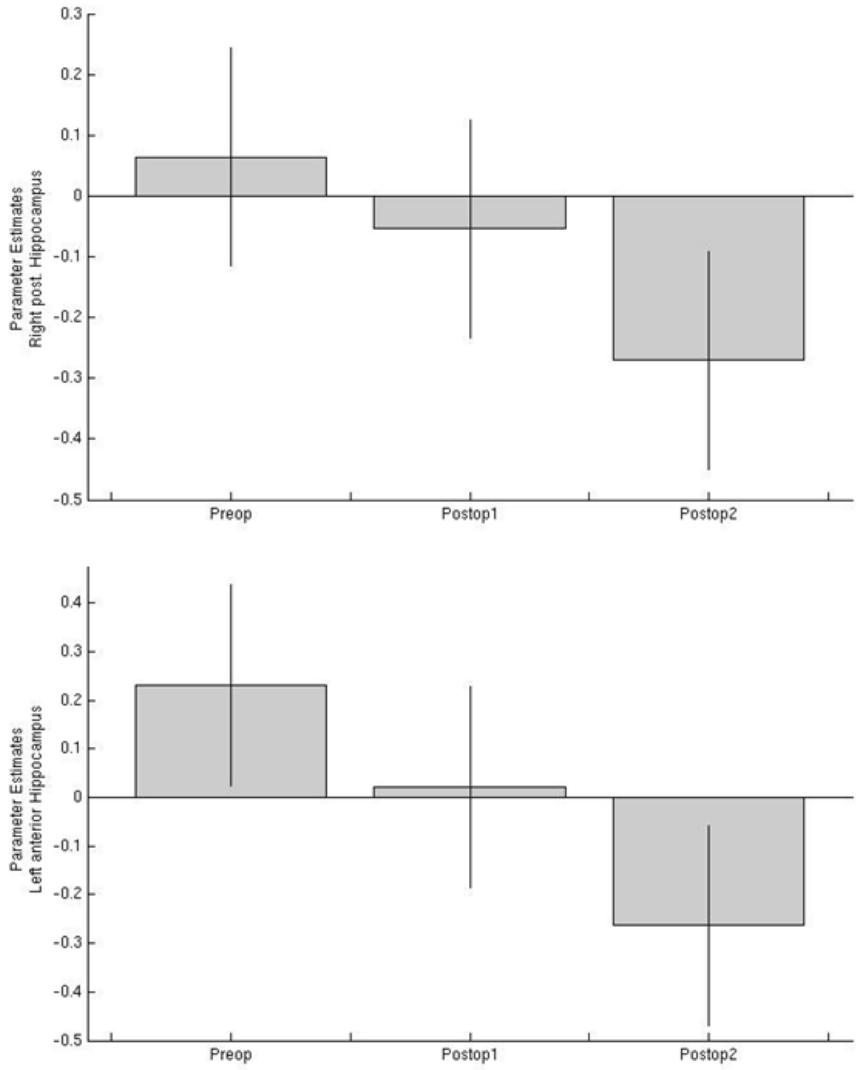


Fig 10.3: Parameter estimates of face encoding medial temporal lobe activations pre-operatively and at four (Postop 1) and 12 months (Postop 2) after anterior temporal lobe resection in right temporal lobe epilepsy patients

Word Encoding

Four months post-operatively, RTLE patients had reduced right anterior HC activations at word encoding relative to changes in controls.

12 months post-operatively, there were reduced left hemispheric activations within the left medial OFC, ACC and superior temporal pole relative to changes in controls.

From four to 12 months post-operatively, there were increased left anterior HC and right MFG activations with reduced activations within the left posterior HC.

Efficiency of 12 month post-operative change in right temporal lobe epilepsy

Improvement in design learning 12 months post-operatively compared to four months post-operatively correlated significantly with left anterior MTL (amygdala and HC) and left extra-temporal activations within the OFC, IFG and insula 12 months post-operatively (Table 10.6, Fig 10.4).

Improvement in verbal learning 12 months post-operatively compared to pre-operatively, correlated significantly with left anterior HC and left OFC activation 12 months post-operatively (Table 10.6).

The increased left posterior HC face encoding activation four months post-operatively compared to pre-operatively correlated significantly with decline in design learning in RTLE patients (Figure 10.5, Table 10.6). Decline in verbal learning from 3 months post-operatively compared to pre-operatively correlated with left posterior hippocampal activation four months post-operatively (Table 10.5).

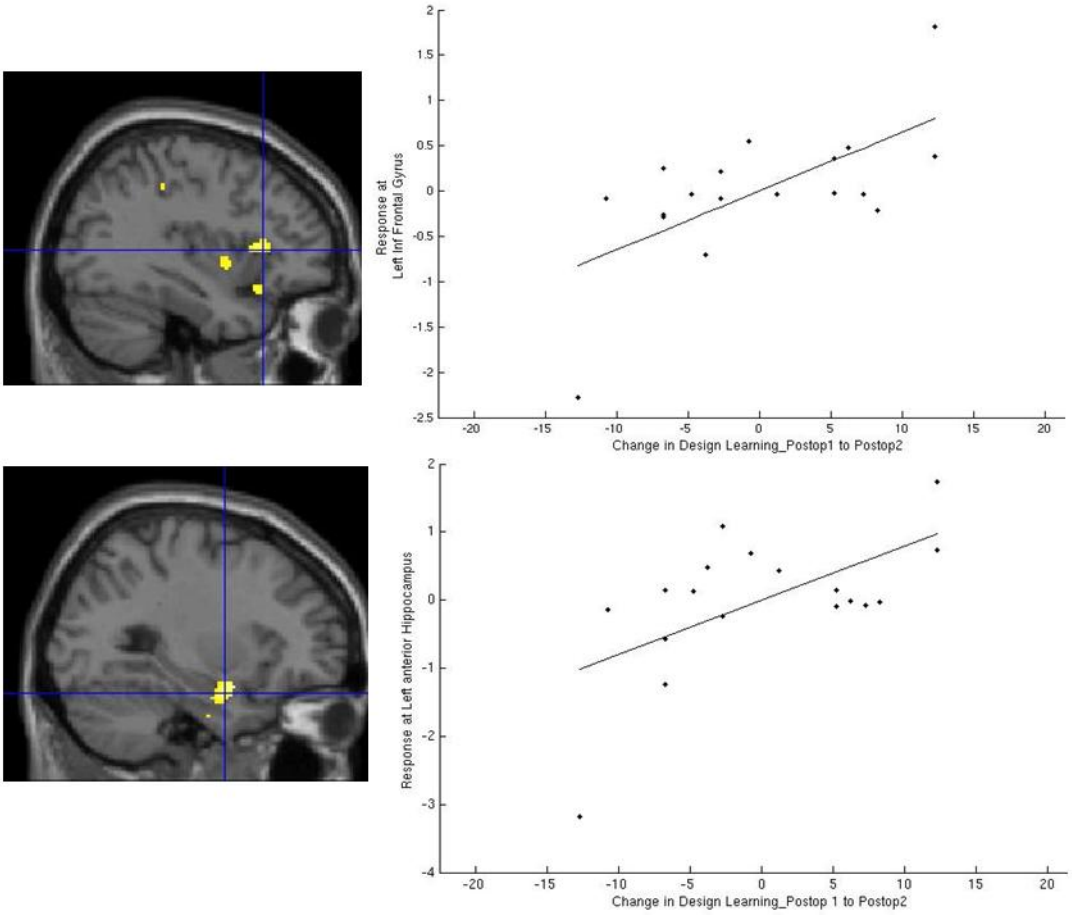


Figure 10.4: Correlation of improvement in design learning 12 months post-operatively in right temporal lobe epilepsy patients. The images show significant correlation of left inferior frontal gyrus, insula, orbitofrontal cortex and anterior medial temporal activations 12 months post-operatively with improvements in design learning 12 months post-operatively. Postop1 (3 months post-operatively), Postop2 (12 months post-operatively).

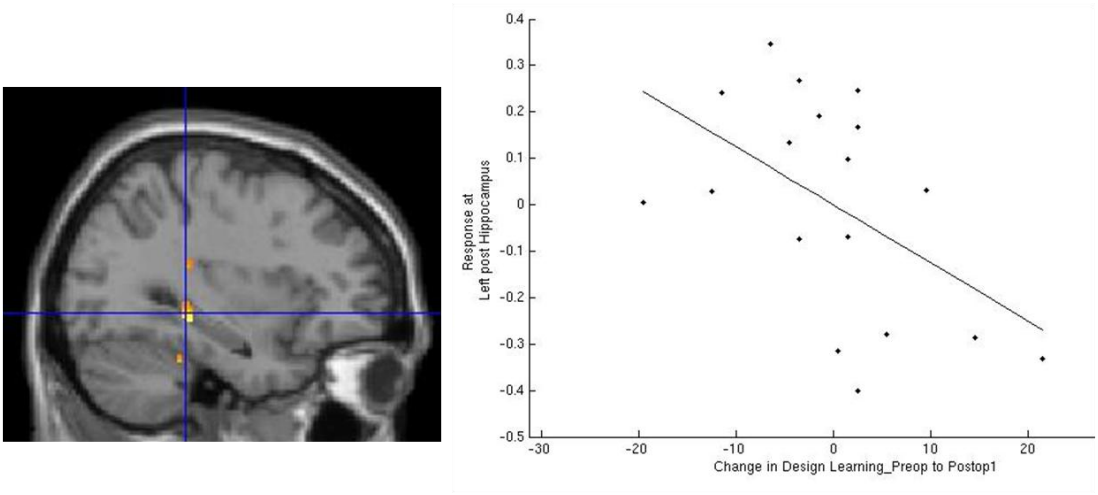


Fig 10.5: Correlation of decline in design learning 3 months post-operatively in right temporal lobe epilepsy patients. The images show significant correlation of left posterior hippocampal activations 3 months post-operatively with decline in design learning 3 months post-operatively compared to pre-operatively. Post (posterior), Preop (pre-operative), Postop1 (3 months post-operatively).

10.4 Discussion

This study examined the effects of temporal lobe resection on verbal and visual memory encoding networks in LTLE and RTLE patients, relative to longitudinal changes in controls, four and 12 months after ATLR. Next, a voxel by voxel whole brain analysis of activations four and 12 months post-operatively were correlated with change in verbal and visual memory to further investigate brain areas involved in improvement or decline in memory functions after ATLR.

Controls showed increased left frontal activations at the second and third scanning sessions compared to the first, on both word and face encoding. No MTL changes were seen on word encoding whilst on face encoding reduced right HC activations were seen at both the second and third scanning sessions.

Pre-operatively, both LTLE and RTLE patients showed ipsilesional posterior HC activation during word and face encoding respectively. Post-operatively, LTLE patients showed increased contralateral right anterior HC and right frontal activation both at four and 12 months after surgery on word and face encoding, with a concomitant reduction in left frontal activation 12 months post-operatively. Right anterior HC activation 12 months post-operatively correlated significantly with improved verbal learning in LTLE patients from preop to 12 months post-operatively, representing efficient plasticity. Extra-temporal activations within the anterior cingulum correlated with improved verbal learning 12 months post-operatively. Four months post-operatively, the pre-operative left posterior HC activation was sustained during word encoding, increased during face encoding but was significantly reduced 12 months post-operatively for both word and face encoding.

RTLE patients showed an increase in left anterior HC activation on word encoding from four to 12 months post-operatively. On face encoding, left anterior HC activations were present pre-operatively and 12 months post-operatively. This left anterior HC and OFC activations correlated with improvements in both design and verbal learning, implying efficient plasticity in these structures 12 months after surgery.

Four months post-operatively, RTLE patients showed increased left posterior HC activations on face encoding. This was not involved in successful memory formation as it correlated with a decline in design learning 3 months post-operatively.

10.4.1 Memory outcome after temporal lobe resection

Behavioural measures showed significant decline in verbal and visual recognition accuracy in LTLE and RTLE patients 12 months after surgery respectively. Although

neuropsychometry showed a non-significant decline in verbal learning and a significant decline in design learning in LTLE patients as a group, a greater proportion of LTLE patients had significant verbal memory decline (29%) compared to visual memory decline (6%) 12 months post-operatively.

RTLE patients showed a non-significant decline in design learning as a group and significant decline in verbal learning. A greater proportion of RTLE (11%) patients showed decline in non-verbal memory compared to LTLE patients (6%). Interestingly, 21 % of RTLE patients also showed significant verbal memory impairment 12 months post-operatively. Historically, material specific deficits with verbal deficits after left temporal resections and visual deficits after right temporal resection (Milner, 1966) had been described. One explanation may be that left and right sided resection patients were compared to each other and not with memory in healthy controls. More recently, verbal memory decline after non-dominant resections has been increasingly described. In a recent study of 124 patients with HS, laterality was not identified as a risk factor (Murphy and Cook, 2010). This is in keeping with the task specific concept proposed by Saling et al in which left and right TLE patients were equally impaired on certain verbal learning measures but not others (Saling et al., 1993; Saling, 2009).

In both patient groups, there was no significant change in either verbal or visual memory from four to12 months after surgery. This is in keeping with longitudinal studies on patients up to five (Baxendale et al., 2012) and 10 years (Engman et al., 2006) after surgery. On an individual level however, several factors such as pre-operative memory, post-operative seizure outcome, mood and medication change play a significant role in memory outcome after surgery.

10.4.2 Longitudinal fMRI changes in controls

Controls showed stable MTL activations on word encoding but reduced right HC activations on face encoding on retesting. This may be explained by the 'novelty encoding' hypothesis which suggests that the encoding of online information into long-term memory is influenced by its novelty and that novelty increases recognition performance (Tulving et al., 1996). We presented black and white faces and although the faces were varied at the second and third scanning sessions the 'novelty' effect may be lost. With word encoding there was less of a novelty effect to begin with as the words were known to subjects. We compared longitudinal changes in encoding activations in patients after ATLR to longitudinal changes seen in controls to ensure changes reported were not simply due to repeat scanning.

10.4.3 Plasticity in LTLE patients

Irrespective of material type LTLE patients showed dynamic changes in both MTL and frontal activations with increased contralateral right anterior HC and right frontal activation both at four and 12 months after surgery on word and face encoding.

Four months post-operatively there was an increase in left posterior HC activation for face encoding and less significantly on word encoding, which correlated with reduced design learning, implying inefficient recruitment of the posterior HC four months after surgery. This is in keeping with a previous study where increased left posterior HC activation in a group of left TLE patients on word encoding 4 months after surgery correlated with a decline in post-operative verbal memory (Bonelli et al., 2013). In this current study, I extend this to show that posterior HC activation four months post-operatively was transitory with significantly reduced posterior HC

activation occurs from four to 12 months post-operatively for both word and face encoding.

One study to date examined extra-temporal memory encoding network plasticity after surgery in TLE patients but in a limited IFG region of interest (Maccotta et al., 2007). Pre and post-operative signal change within this region was compared quantitatively in this word and face classification study. Reduced right frontal activation was found post-operatively during word encoding in LTLE patients suggesting a more left lateralised network post-operatively. No differences were described on visual encoding. No MTL activation changes were reported. Several patient and scanning factors may explain the difference from our results. Firstly, an implicit word and face classification task in which memorisation was not encouraged was employed. Greater activation has been shown with explicit tasks where memorisation is encouraged, as in our paradigm. Second, a blocked design analysis in which subsequent memory was not investigated was used therefore it is not known if activations represent successful memory formation. Third, not all patients underwent ATLR as in our study. Some underwent selective amygdalohippocampectomy or lateral lesionectomy. No change in either word or face recognition was seen post-operatively in this small number of patients (8 LTLE) whilst we showed that LTLE patients declined in the word recognition task. Finally, the post-operative time period varied with patients being scanned between 5 and 9 months after surgery. We showed that frontal changes in LTLE patients were dynamic therefore a varied period of analysis may not capture the true nature of frontal lobe engagement at different stages.

10.4.4 Plasticity in RTLE patients

RTLE patients showed dynamic MTL changes but showed less extra-temporal plasticity effects than LTLE patients. This may be because LTLE patients showed greater decline in both verbal and visual memory than RTLE patients four months post-operatively. No increase in extra-temporal activations were seen four months post-operatively but, as in LTLE, increases in extra-temporal activations were seen four to 12 months post-operatively; left frontal and left parietal on word and face encoding respectively. RTLE patients also showed increased left posterior HC activation four months post-operatively that correlated with decline in visual and verbal memory four months post-operatively compared to preop, implying inefficient early post-operative recruitment. Increments in posterior HC activation were transient, with relative suppression of this activation from four to 12 months post-operatively. Similar to LTLE, contralesional anterior MTL activation reflected efficient plasticity 12 months post-operatively.

Bonelli et al reported no significant change in MTL activation on face encoding in RTLE patients 4 months post-operatively (Bonelli et al., 2013). This could be because no RTLE patients declined significantly in design leaning. Post-operative change in word encoding was not investigated in RTLE patients. In the study by Macotta et al detailed above, no post-operative change within an IFG region of interest in RTLE patients at both word and face encoding was seen (Maccotta et al., 2007). In all these aforementioned longitudinal studies, changes in reported activations were not reported relative to changes in controls.

10.4.5 Efficiency of reorganised networks

In RTLE patients, contralateral hemispheric activations within the left anterior MTL and OFC represented 'efficient' activations irrespective of material type 12 months after ATLR. The role of the OFC in successful memory formation has been described in TLE patients (chapter 6), healthy controls (Frey and Petrides, 2003) and in lesional studies (Meunier et al., 1997). This may be due to its' connections to limbic structures including the amygdala, HC, temporal pole, entorhinal, perirhinal and parahippocampal cortices (Carmichael and Price, 1995; Insausti *et al.*, 1987; Lavenex *et al.*, 2002). Surgery however led to efficient engagement of the hemisphere contralateral to the resection. Similarly, in LTLE patients, contralateral activations within the right MTL and anterior cingulum represented efficient reorganisation 12 months post-operatively. Pre-operative efficient anterior cingulum activations in verbal memory formation in TLE have been previously described (Eliassen et al., 2008; Sidhu et al., 2013) and I corroborated this finding in chapter 6. I showed that this anterior cingulum activation is also efficient 12 months post-operatively.

My research group previously reported dynamic changes in the working memory network in this cohort of patients (Stretton et al., 2014). In healthy controls, the MTL were bilaterally deactivated during working memory tasks whilst LTLE and RTLE patients failed to show ipsilesional MTL deactivation. Four to 12 months after surgery, LTLE patients, showed greater contralesional right HC deactivation that correlated with improved working memory performance. In concert with my findings, the contralesional HC was efficiently engaged 12 months after surgery.

In the only other fMRI study of changes 12 months post-operatively, Cheung et al reported a similar pattern in which the contralateral MTL played an efficient

compensatory role in maintaining verbal and visual episodic memory 12 months after surgery (Cheung et al., 2009). In this study a non-material specific scene encoding task was used and a block design was employed in a small number of TLE patients (9 left, 8 right).

10.4.6 Neurobiological implications

I showed efficient contralateral fronto-temporal recruitment 12 months post-operatively in both patient groups. These changes could represent a 'release' phenomenon with reversal of a functional or metabolic disruption. Functional imaging studies such as FDG-PET showed a normalization of glucose metabolism in the ipsilateral temporal cortex (Gogoleva et al., 1997), inferior frontal lobe, thalamus and parietal lobe (Spanaki et al., 2000; Takaya et al., 2009) following temporal lobe surgery.

Structural imaging studies such as diffusion tensor imaging have also shown ipsilateral and contralateral structural recovery after surgery (Concha et al., 2005; Thivard et al., 2007; Winston et al., 2014; Yogarajah et al., 2008). Pfeuty et al showed that structural recovery in the contralateral anterior HC correlated with improvements in verbal and visual memory post-operatively (Pfeuty et al., 2011), in keeping with our findings of efficient contralateral anterior HC reorganisation, irrespective of material type.

10.4.7 Strengths and Limitations

This is the first longitudinal memory fMRI study to investigate post-operative plasticity at two time points after surgery relative to changes in controls imaged across similar time points. All patients underwent a homogenous surgical procedure as other surgical approaches may cause different cognitive outcomes (Helmstaedter,

2013). I studied LTLE and RTLE patients separately and reported dynamic changes across both verbal and visual memory encoding. I employed a flexible factorial design of analysis that is a quantitative model that allowed the comparison of longitudinal changes in patients against longitudinal changes in controls, which enables controlling for between subject and between group variance in a single model.

This study also has limitations. It is known that factors such as medication (Wandschneider et al., 2014; Yasuda et al., 2013) and mood (Flugel et al., 2006) can impact significantly on cognition. Although no medication changes had been made four months post-operatively, 8/17 LTLE and 9/19 RTLE patients had at least one anti epileptic drug reduced 12 months post-operatively. Drug and mood changes were not accounted for in our analysis 12 months post-operatively. Importantly, there was no significant difference between the patient groups in the number of patients with drug reductions.

Further interval studies between four and 12 months post-operatively are required to ascertain the temporal cadence of change in brain activations more accurately.

In conclusion, dynamic post-operative changes occur in the memory encoding network in both left and right TLE patients across both verbal and visual domains. Four months after surgery, compensatory posterior HC reorganisation that occurs is transient. Engagement of the contralateral HC 12 months after surgery represents efficient reorganisation in both patient groups, suggesting that the contralateral HC influences memory outcome 12 months after surgery. This is compatible with descriptions of functional recovery and structural plasticity in the contralateral MTL after surgery.

Section IV: OVERALL DISCUSSION and CONCLUSIONS

Chapter 11: Discussion

In chapters six to 10, I described the results of pre-operative memory functional imaging using univariate and multivariate event related analyses in LTLE and RTLE patients. Next, I described the use verbal memory fMRI as a tool for predicting verbal memory decline after left ATLR and, finally, I described the plasticity of verbal and visual memory encoding networks four and 12 months after ATLR compared to changes in controls imaged at similar time intervals.

In this chapter, I summarise the findings of this programme of investigations, discuss the neurobiological implications and my perspective on future research and clinical applications of memory fMRI.

11.1 Summary of Main findings

11.1.1 Pre-operative univariate analysis

- Controls showed material-specific memory encoding activations with predominantly left hemispheric activations for word encoding and right for face encoding on both the blocked and subsequent memory (event related) analyses.
- LHS patients showed greater contralateral temporal and extra-temporal activations compared to controls on word and face encoding (blocked design). Contralateral extra-temporal reorganisation was associated with longer duration of epilepsy and greater seizure frequency and was not associated with successful memory formation.

- LHS patients showed predominantly right temporal verbal subsequent memory (verbal event related) activations and no extra-temporal activations on word encoding. MTL activations on word encoding were associated with a shorter duration of epilepsy and fewer seizures. In LHS patients, activations within the left OFC, ACC and left posterior HC correlated positively with verbal learning scores. Greater posterior HC activation was related to an earlier age at onset of epilepsy.
- RHS patients showed increased contralateral temporal activations but bilateral extra-temporal activations on word and face encoding (blocked analysis). Greater extra-temporal frontal reorganisation was associated with longer duration of epilepsy and higher seizure frequency and was not associated with successful memory formation.

- RHS patients showed visual subsequent memory (visual event related) activations within the right anterior and posterior MTL. RHS patients with a better visual memory showed significant correlations with activation within the left amygdala, right anterior PHG and left insula. MTL activations during face encoding were associated with as shorter duration of epilepsy and fewer seizures.
- Extra-temporally, the OFC was involved in successful visual subsequent memory formation in RHS patients and verbal memory in LHS patients. Activations within ACC and insula correlated with better verbal and visual subsequent memory only in LHS and RHS patients respectively, but not in controls.

11.1.2 Pre-operative multivariate analysis

- Using a scene memory task, predictable patterns of activity across voxels associated with specific memories could be detected in MTL structures, including the HC, on the side contralateral to focal unilateral HS in a group of patients with TLE.
- On the sclerotic side, there were no discernible memory representations within the sclerotic HC but adjacent structures such as the parahippocampal cortex and entorhinal/perirhinal cortex contained discernable memory traces.

11.1.3 Prediction of verbal memory decline after ATLR using memory functional imaging

- In LTLE patients, left lateralised activation within the medial temporal and frontal lobes correlated with post-operative verbal memory decline at a group level.
- On an individual patient basis, memory LI of ≥ 0.5 within a fronto-temporal mask indicating greater left than right activation correlated significantly with post-operative decline in verbal memory and was the strongest independent predictor of post-operative verbal memory decline, compared to language LI, age at onset of epilepsy, pre-operative memory function and pre-operative hippocampal volume.
- With an LI ≥ 0.5 memory fMRI alone had a positive predictive value (PPV) of 70%, sensitivity of 87.5 % and 80% specificity as a tool for predicting significant post-surgical significant memory decline after left ATLR.

11.1.4 Plasticity after temporal lobe resection

- Although more LTLE patients declined significantly in verbal memory after left ATLR compared to right, and more RTLE patients declined significantly in visual memory compared to LTLE after ATLR, in both LTLE and RTLE groups, there were patients who declined significantly in visual and verbal memory respectively.
- LTLE patients showed increased contralateral right anterior HC and right frontal activation both at four and 12 months after surgery on word and face encoding, with a concomitant reduction in left frontal activation 12 months post-operatively. Right anterior HC activation 12 months post-operatively correlated significantly with improved verbal learning in LTLE patients from preop to 12 months post-operatively, representing efficient plasticity. Extra-temporal activations within the ACC correlated with improved verbal learning 12 months post-operatively.
- Pre-operative left posterior HC reorganisation in LTLE patients on word encoding was sustained four months post-operatively but was significantly reduced 12 months post-operatively compared to pre-operatively.
- RTLE patients showed an increase in left anterior HC activation on word encoding from four to 12 months post-operatively. On face encoding, left anterior HC activations were present pre-operatively and at 12 months post-operatively. Left anterior HC and OFC activations correlated with improvements in both design and verbal learning, implying efficient plasticity in these structures 12 months after surgery.

- Four months post-operatively, RTLE patients showed increased left posterior HC activations on face encoding. This correlated with a decline in design learning four months post-operatively. Similar to LTLE patients, posterior HC activations were significantly reduced 12 month post-operatively compared to pre-operatively.

11.2 Discussion

11.2.1 Pre-operative memory encoding network

This study investigated whole brain event related material specific memory activations in LTLE and RTLE patients. Pre-operative memory reorganisation is presumed to occur as a 'compensatory' mechanism due to the disruption of cognitive networks by the epileptic network and structural deficits in TLE patients.

fMRI studies in TLE patients have consistently shown atypical material-specific involvement of the MTL in episodic memory encoding, with reorganisation of memory functions to the contralesional side (Golby *et al.*, 2002; Powell *et al.*, 2007; Richardson *et al.*, 2003) and with varied efficiency within the MTL (Bonelli et al., 2010; Guedj et al., 2011; Powell et al., 2007; Richardson et al., 2003). Bonelli et al recently showed that ipsilesional posterior HC reorganisation in LTLE patients was efficient on word encoding (Bonelli et al., 2010). I corroborated this finding. Similarly, in RHS patients, right posterior HC activations were associated with visual subsequent memory. In addition, both LHS and RHS patients who performed better showed effective recruitment of the contralesional MTL during verbal and visual encoding respectively. In a separate experiment, I investigated the factors that may be associated with memory reorganisation and showed that in LHS patients,

reorganisation of the verbal encoding network to involve the posterior HC was associated with an earlier age at onset of epilepsy. This imaging finding may be contributory to the observation that earlier age at onset of epilepsy is associated with a more favourable memory outcome after ATLR. Post-natal brain development continues into adolescence with brain myelination occurring in a posterior to anterior fashion so frontal lobe myelination occurs last. In TLE patients, early age at onset of epilepsy affected white matter maturation with a lag in the frontal and parietal but not the occipital lobes (Hermann et al., 2010). The hemispheric asymmetry of brain maturation suggests that the left hemisphere matures later than the right. Regional cerebral blood flow at rest was maximal in the right hemisphere at 1 year and in the left hemisphere at age 3, in keeping with the cadence of skill acquisition in children namely visuo-spatial (right dominant) skills followed by language acquisition (left dominant) (Chiron et al., 1997). Disruption of this maturation process by early onset epilepsy may therefore preferentially influence 'dominant' functions including verbal memory. Another possible explanation for the modulation of the verbal encoding network only in LHS patients is that structural and morphological changes described in early onset epilepsy may be greater in LTLE than in RTLE patients (Kemmotsu et al., 2011; Riederer et al., 2008). This hemispheric and anterior-posterior maturation asymmetry renders the left hemisphere and frontal lobes more vulnerable to early insults such as that incurred from early seizures which may explain why there appeared to be a selective effect of earlier age at onset of epilepsy in LHS patients.

Using MVPA, I investigated the ability to 'decode' the MTL in patients with unilateral mesial TLE. This is detailed in chapter 8. This was done in collaboration with Professor Maguire at the Wellcome Trust Centre for Neuroimaging, Queen Square. The paradigm we employed involved the cued recall of a set of movies that depicted

everyday events. Memories of naturalistic stimuli have been found to be encoded and represented in the MTL bilaterally, in healthy controls. Recall of these memories could be predicted from patterns of fMRI brain activity across MTL voxels (Chadwick et al., 2010). We showed that there were no discernable memory traces within the sclerotic HC but the contralateral HC and adjacent MTL structures predicted memories accurately. Compared to the univariate material specific study presented in chapter 6 where contralateral activations were not seen in controls but present only in patients, we were unable to comment on memory 'reorganisation' using this bilateral task.

Asymmetric MTL activations in a bilateral task have also been shown in univariate analyses (Detre et al., 1998; Jokeit et al., 2001; Mechanic-Hamilton et al., 2009), with greater activation in the non-lesional MTL. However, without specific event related analyses or correlations with neuropsychological performance it could not be definitively ascertained if contralateral activations were specifically related to successful memory encoding. One of the main advantages of MVPA is that it investigates the representational content or efficacy of brain regions. This was the first study to investigate the use of MVPA in TLE and future studies should employ MVPA in material specific paradigms to investigate the capacity for effective reorganisation in unilateral TLE.

Another novel pre-operative finding of this thesis includes the extra-temporal changes demonstrated as the extra-temporal functional anatomy of episodic memory processes in those with TLE had not been investigated in detail. This is an important consideration for patients who may be candidates for epilepsy surgery.

The OFC with its close anatomical connections to the MTL, (Carmichael and Price, 1995) is thought to be critical to the successful encoding of both verbal (Savage *et al.*, 2001) and visual material (Frey and Petrides, 2002). Both LHS and RHS groups did not activate the ipsilesional OFC as controls did. In an electrical stimulation study, responses in the OFC were detected upon stimulation of the HC positing a role of the OFC in propagation of MTL seizures (Wilson and Engel, 1993). The reduced ipsilesional frontal activation I observed in patients may therefore be a result of either network dysfunction caused by propagation of epileptic activity, be due to concomitant frontal structural deficits (Bonilha *et al.*, 2007), or both. In LHS patients on word encoding, predominantly left extra-temporal activations correlated with successful verbal memory formation.

In LHS patients I also showed that ACC activation similarly represents effective recruitment for verbal subsequent memory in LHS patients but not in controls. ACC activation has been shown to be related to motivation, goal directed behaviour (Devinsky *et al.*, 1995) and is activated particularly in tasks with greater difficulty (Fu *et al.*, 2002). This may explain ACC activation in LHS patients who performed better. Left insula visual subsequent memory activations were seen in both LHS and RHS patients but not in controls. The insula has been functionally implicated in higher order cognition and emotional recognition from facial expression (Calder *et al.*, 2000; Singer *et al.*, 2004) and atrophy in the insula has been associated with a reduced ability to discern facial expression in patients with dementia (Hsieh *et al.*, 2012). Encoding emotional faces has been shown to be associated with better subsequent recognition memory (Nomi *et al.*, 2012). In RHS patients, insula activation was associated with better visual memory implying efficient recruitment. This may be attributed to better emotional recognition in patients who performed better.

11.2.2 Prediction of verbal memory decline using memory functional imaging

One of the main objectives of this thesis was to develop a clinically applicable memory fMRI method of predicting post-surgical memory outcome in individual patients. This study is detailed in chapter 9.

In the univariate pre-operative analysis discussed above and in chapter 7, we used a subtraction paradigm of words remembered - (words familiar + words forgotten). The contrast used for the prediction algorithm was simply words remembered. The latter contrast whilst less specific for subsequent memory was more sensitive with significant activations in the MTL and extra-temporally in all patients, a crucial pre-requisite for individual memory prediction paradigms. Despite a different contrast and different cohort of LTLE patients (mixed pathology rather than just HS patients) to the study in chapter 6, we showed similar areas of verbal effective reorganisation; left posterior HC, right anterior HC, left OFC and ACC. In addition body of the left HC was also involved in successful memory formation. As a group correlation, decline in verbal memory was associated with not just pre-operative left MTL but also left frontal activations.

Using an objective LI value of ≥ 0.5 representing greater left than right activations in an anatomical fronto-temporal mask, we showed that there was 70% (7/10) risk of significant verbal memory decline after surgery. If LI was <0.5, the risk of significant memory decline was 7.7%.

Other non-invasive measures showing predictive value for post-operative memory outcome include severity of hippocampal sclerosis assessed by hippocampal volume, type of pathology, neuropsychological memory measures, and age at onset of epilepsy (Baxendale et al., 2006; Baxendale et al., 2012; Helmstaedter et al.,

2011; Trenerry et al., 1993). We showed that memory fMRI was the only independent predictor of verbal memory decline in LTLE patients when compared to language LI, age at onset of epilepsy, hippocampal volume and pre-operative memory measures with a sensitivity of 87.5 % and 80% specificity as a tool for predicting post-surgical significant memory decline.

Two models have been proposed in the pre-operative risk assessment of post-surgical memory decline. The functional adequacy model suggests that post-surgical memory decline is inversely proportional to the function of the 'to-be-resected' tissue, whilst the hippocampal reserve model suggests it is the ability of the contralateral hippocampus to sustain memory function that determines post-surgical memory outcome (Chelune, 1995). Previously, event-related analyses supported the functional adequacy model, with greater activation in the 'to be resected' anterior hippocampus predicting verbal memory decline (Bonelli et al., 2010; Powell et al., 2008; Richardson et al., 2004). Using asymmetry images, these studies were unable to comment on the hippocampal reserve model as activations in asymmetry images represent either left>right activations or vice-versa (Richardson et al., 2006).

I showed that activations within the left anterior MTL and frontal lobe, involved in successful memory formation pre-operatively, predicted decline post-operatively. I therefore propose extending Chelunes' model whereby functional adequacy is not just the function of the 'to-be–resected' hippocampus but also the pre-operative network, encompassing the 'to-be-resected' MTL.

11.2.3 Plasticity after anterior temporal lobe resection

In fMRI data, the reliability of test-retest has been shown using an intra-class class correlation coefficient (ICC) statistic (Caceres et al., 2009). In all our controls, language and memory LIs were not significantly different between scanning sessions but an ICC was not calculated as this was not a primary aim of this study. This would be a suggestion for future studies.

I scanned controls at similar time intervals to patients as although memory encoding test-retest studies have shown stable HC activations at least three months after initial scanning (Atri et al., 2011; Putcha et al., 2011), task similarities may incur practice effects and altered memory encoding strategies in healthy controls (Siders et al., 2006), leading to differential engagement of the frontal lobes (Fletcher and Henson, 2001). As one of the main aims of this study was to study memory plasticity after surgery, comparing changes in patients quantitatively to changes in controls would control for changes incurred as part of test re-test and practise effects.

Plasticity in the memory encoding networks within the MTL after ATLR has only been described in a few studies (Bonelli et al., 2013; Cheung et al., 2009; Korsnes et al., 2009) with one reporting extra-temporal post-operative memory network plasticity within a small frontal region (Maccotta et al., 2007). Furthermore, there has been no studies to date comparing post-operative changes in patients to changes that may be seen in controls imaged across similar time-points.

I examined the effects of temporal lobe resection on verbal and visual memory encoding networks in LTLE and RTLE patients, relative to longitudinal changes in controls, four and 12 months after ATLR. Next, a voxel by voxel whole brain analysis

of activations four and 12 months post-operatively was correlated with change in verbal and visual memory to further investigate brain areas involved in improvement or decline in memory functions after ATLR (Chapter 10).

Although more LTLE patients declined in verbal memory and RTLE in visual memory 12 months after ATLR, in both patients groups there were patients whose memory declined significantly across both verbal and visual domains. Historically, material specific deficits with verbal deficits after left temporal resections and visual deficits after right temporal resection (Milner, 1966) had been described. One explanation may be that left and right sided resection patients were compared to each other and not with memory in healthy controls. More recently, verbal memory decline after non-dominant resections has been increasingly described. In a recent study of 124 patients with HS, laterality was not identified as a risk factor (Murphy and Cook, 2010). This is in keeping with the task specific concept proposed by Saling et al in which left and right TLE patients were equally impaired on certain verbal learning measures but not others (Saling et al., 1993; Saling, 2009).

In RTLE patients, contralateral hemispheric activations within the left anterior MTL and OFC represented 'efficient' activations irrespective of material type 12 months after ATLR. Similarly, in LTLE patients, contralateral activations within the right MTL and ACC represented efficient reorganisation 12 months post-operatively. Surgery led to efficient engagement of the hemisphere contralateral to the resection. Structural imaging studies such as diffusion tensor imaging have shown ipsilateral and contralateral structural recovery after surgery (Concha et al., 2005; Thivard et al., 2007; Winston et al., 2014; Yogarajah et al., 2008). Pfeuty et al showed that structural recovery in the contralateral anterior HC correlated with improvements in

verbal and visual memory post-operatively (Pfeuty et al., 2011), in keeping with our findings of efficient contralateral anterior HC reorganisation, irrespective of material type.

What is intriguing is that in LTLE patients, the increased left posterior HC activation seen pre-operatively was sustained on word encoding, increased on face encoding and significantly reduced from four to 12 months post-operatively. Four months post-operatively, posterior HC activations did not contribute to efficient memory formation and this represents inefficient reorganisation. Similarly in RTLE patients, increased posterior HC activations four months post-operatively was inefficient and was significantly reduced from four to 12 months post-operatively. One postulation is whether this early compensation occurs as a consequence of disconnection from the anterior MTL and as the contralateral hemisphere 'recovers' as a subsequent phenomenon after surgery this increased activation subsides. Further interval studies between four and 12 months post-operatively are required to ascertain the temporal cadence of changes in brain functional anatomy more accurately.

After surgery, some patients undergo cognitive rehabilitation. It would interesting to see if contralateral 'functional' recover occurs faster in these patients compared to patients who do not undergo cognitive rehabilitation. This may help to identify patients who require and benefit from cognitive rehabilitation and maybe even provide objective endpoints along with neuropsychometry in time to come.

Aside from answering pertinent questions, this thesis has generated questions that I hope future research with methodological advances will address. Functional connectivity (FC) analysis of fMRI data identifies temporally correlated regions to evaluate the network involved. Several studies have investigated resting-state FC

networks in TLE patients (Bettus et al., 2009; Chiang et al.; Laufs et al., 2014; Liao et al., 2010; Liao et al., 2011) but fewer have investigated pre-operative episodic memory FC (Addis et al., 2007; Voets et al., 2009; Wagner et al., 2007). There have been no studies to date investigating changes in memory FC after ATLR.

MVPA is a promising tool to investigate not just memory 'activations' but memory 'representations' and memory FC using MVPA would be the ideal tool to investigate cognitive networks. This has not been performed to date.

Chapter 12: Conclusion

Over the last two decades, experimental studies in memory fMRI have advanced the understating of neural correlates of the memory encoding network tremendously in healthy controls and disease states. In unilateral TLE, reorganisation of encoding networks to the contralateral MTL has been consistently described. With refinements in methodology including MVPA, paradigms and contrasts used, more accurate descriptions of functional efficacy of temporal as well extra-temporal activations were described in this thesis.

The finding that extra-temporal brain regions contribute significantly to successful memory encoding in patients, led to the question of whether these pre-operative activations may be predictive of post-operative memory outcome. I showed that the patterns of both temporal and extra-temporal activations were predictive of verbal memory outcome. Using an objective LI parameter that can be calculated on a relatively simple word encoding paradigm on a single subject basis, memory fMRI can be tested and validated as a clinical tool for predicting verbal memory decline in individual patients. This would be a useful tool for pre-operative risk counselling.

My work on describing the post-operative plasticity of verbal and visual encoding networks in TLE patients has shown that this is not a static process and significant changes in activations as well as efficiency of these changes vary at intervals after surgery. The findings of this thesis suggest that memory fMRI is an evolving research method that also holds promise as a clinical tool.

SECTION V: APPENDICES

APPENDIX 1

Subjects	Age	Age at onset	Duration	HC Vol	NART	Preop VL	Postop VL	Change in VL	Memory LI	Language LI	Pathology	Preop Seizures	Postop Seizures	12 month ILAE Outcome
LTLE 1	26	0.8	25	1.7	95	59	55	-4	0.3	0.6	HS + FCD II b	CPS 4, SGTC every 2 years	None	1
LTLE 2	20	13	7	1.1	100	41	40	1	0.7	0.8	HS	CPS 6 , SGTC 2 per year	None	1
LTLE 3	52	0.3	52	1.6	102	39	39	0	-1	0.6	HS	CPS 2	None	1
LTLE 4	33	20	13	3.6	96	50	30	-20	0.5	0.8	HS	CPS 10, SGTC nil since 2006	None	1
LTLE 5	45	35	10	1.4	70	40	23	-17	0.6	0.6	HS	CPS 3, SGTC nil in 4 years	None	1
LTLE 6	47	11	36	1.2	96	27	37	10	0.1	0.8	HS	SPS 30, CPS 5	SPS 50	2
LTLE 7	28	23	5	2.4	91	48	33	-15	0.9	0.7	Ependymoma	CPS 60, SGTC 2 per year	None	1
LTLE 8	37	34	3	1.6	100	61	57	-4	0.3	0.7	HS	CPS 32	None	1
LTLE 9	32	17	15	2.2	90	44	59	15	-0	0.7	HS	CPS 4	None	1
LTLE 10	40	30	10	2.8	86	46	14	-32	0.7	0.9	Gliosis	CPS 20, SGTC 5	SPS 60 ?NEAD	2
LTLE 11	38	8	30	1.1	100	35	30	-5	0.6	1	HS	CPS 2	None	1
LTLE 12	48	3	45	1.7	97	53	45	-8	-0	0.8	HS	CPS 12	None	1
LTLE 13	26	7	18	1.5	80	46	54	8	0.6	0.9	HS	CPS 4	None	1
LTLE 14	31	24	7	2.5	96	54	62	8	-0	0.8	Gliosis	CPS 15	CPS 3	4
LTLE 15	19	14	5	2	99	56	46	-10	0.6	0.5	HS	CPS 10, SGTC 1 /year	None	1
LTLE 16	28	10	18	2.9	77	58	45	-13	0.7	0.7	HS	CPS 5, GTC 1	SGTC 6 per year	4
LTLE 17	38	2	36	1.6	111	33	21	-12	0.3	0.5	HS	CPS 1, SGTC	None	1

												6 per year		
LTLE 18	27	0.3	27	2	73	35	37	2	-0	0.6	HS	CPS 80	None	1
LTLE 19	46	0.4	46	1.5	89	41	46	5	-1	0.7	HS +WM lesions	CPS 3, SGTC 2 per year	None	1
LTLE 20	44	30	14	2	97	25	36	11	-0	0.7	HS	CPS 5, SGTC 3 per year	None	1
LTLE 21	49	11	38	0.8	101	31	6	-25	0.7	0.9	DNET	CPS 4, SGTC 4 per year	None	1
LTLE 22	29	4.5	25	2.4	106	28	55	27	-1	-1	ITG dysplasia	SPS 4, CPS 1	None	1
LTLE 23	34	26	9	2.7	90	41	35	-6	0.4	0.2	DNET	CPS 30	None	1
RTLE 1	41	31	10	2.6	110	48	45	-3	0.6	0.9	HS	CPS 1	none	1
RTLE 2	43	19	24	2.2	117	43	44	1	0.1	0.9	HS	CPS 120	none	1
RTLE 3	24	6	18	2.5	108	60	58	-2	0.9	0.9	HS	CPS 6, SPS 2	SPS 2	2
RTLE 4	66	44	22	3	105	44	29	-15	0.8	0.7	DNET	CPS 6	CPS 6, SGTC 4	5
RTLE 5	26	22	4	3.2	104	39	61	22	0.4	0.8	Gliosis	CPS 10	none	1
RTLE 6	23	18	5	2.7	96	56	37	-19	0.2	1	MCD II	CPS 8	CPS 12	5
RTLE 7	51	39	12	2.2	120	45	46	1	0.9	1	HS	CPS 1	none	1
RTLE 8	21	14	7	2.4	104	33	28	-5	0.6	0.8	HS	CPS 12	SPS 4 per year, CPS 1	4
RTLE 9	29	7	22	2.1	90	49	50	1	0.1	0.6	DNET	SPS 40, CPS 4, SGTC 2	none	1
RTLE 10	35	23	12	2.9	116	66	67	1	0.4	0.9	Gliosis	SPS 12, CPS 6	SPS 8	2
RTLE 11	38	17	21	2.1	103	62	57	-5	0.2	-0	HS+FCDIIIa	CPS 17, last SGTC 2007	none	1
RTLE 12	20	17	3	2.3	103	60	61	1	0.7	0.8	DNET	SPS 25, CPS 3	none	1
RTLE 13	18	13	5	2.5	97	42	33	-9	0.3	1	Gliosis	CPS 3 SGTC 3	none	1
RTLE 14	50	18	32	1.9	82	36	28	-8	0.6	0.8	HS	SPS 25, CPS 10, SGTC 1 per year	SPS 60, 1 SGTC	3
RTLE 15	47	12	35	1.5	105	47	25	-22	0.6	0.6	HS	CPS 4 per year, SGTC 1 per year	none	1

RTLE 16	19	15	4	2.6	98	43	44	1	-1	0.8	HS	CPS 24	none	1
RTLE 17	46	7	39	1.7	79	40	36	-4	-0	0.5	HS	CPS 15	none	1
RTLE 18	34	18	16	3	84	44	51	7	0.2	0.9	Gliosis	CPS 8, last SGTC 2008	none	1
RTLE 19	29	28	1	3.7	99	38	51	12	0.3	0.5	Cavernoma	SPS 2	none	1
RTLE 20	46	18	28	2.5	109	44	40	-4	0.4	1	Unclear	CPS 2, SGTC 2	SGTC 1	4
RTLE 21	30	18	12	1.6	87	52	39	-13	-1	-1	HS	CPS 1	none	1
RTLE 22	41	1	40	2	112	48	46	-2	0.7	0.8	HS	SPS 7	none	1
RTLE 23	40	10	30	2.9	100	57	54	-3	0.8	0.8	Gliosis	SPS 3, CPS 2	none	1
RTLE 24	31	25	6	3	94	60	48	-12	0.9	0.9	Cavernoma	SPS 5, CPS 6	none	1
RTLE 25	56	11	45	1.9	108	41	25	-16	0.7	0.8	HS	SPS 8, CPS 8	none	1
RTLE 26	41	9	32	1.9	91	52	46	-6	0.7	0.9	HS	SPS 5, CPS 6	none	1
RTLE 27	18	1	17	2.5	84	59	46	-13	1	0.8	FCDIIb	SPS 15, CPS 2	none	1

Appendix 1, Chapter 9: Patient demographics, age, age at onset of epilepsy, duration of epilepsy, pre-operative hippocampal volume (HC Vol), NART IQ, Pre-operative verbal learning (Preop VL), post-operative verbal learning (postop VL), change in verbal learning, memory and language lateralisation indices (LI), post-operative histopathology, pre and post-operative seizure outcome (number of seizures per month unless otherwise stated) and 12 month ILAE seizure outcome. LTLE (left temporal lobe epilepsy), RTLE (right temporal lobe epilepsy), HS (hippocampal sclerosis), FCD (focal cortical dysplasia), WM (white matter), ITG (inferior temporal gyrus), DNET (dysembryoplastic neuroepithelial tumour), MCD (malformation of cortical development), CPS (complex partial seizures), SPS (simple partial seizures), SGTC (secondarily generalised tonic clonic seizures), NEAD (non-epileptic attack disorder).

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