

**Cognitive Functional MRI in
Temporal Lobe Epilepsy**

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DECLARATION

I, Silvia Beatrice Bonelli-Nauer, confirm that the work presented in this thesis is my own.

Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

The work presented in this thesis reflects the contributions of a team of researchers including colleagues from the Department of Clinical and Experimental Epilepsy, Institute of Neurology, However, for the scientific studies included in this thesis I have outlined my individual contribution below.

I was responsible for recruitment and data acquisition on all subjects studied. I performed all data analyses described in the thesis and was responsible for archiving the data. I performed all statistical analyses and was responsible for producing all the figures and graphical presentation of the data. All results and interpretations were presented by myself and developed following discussions with colleagues and at regular supervision meetings.

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ABSTRACT

Anterior temporal lobe resections (ATLR) provide an effective treatment option for patients with medically refractory temporal lobe epilepsy (TLE) rendering up to 70% of them seizure free.

The goal of epilepsy surgery is to remove the brain areas generating the seizures without causing neuropsychological deficits such as language or memory dysfunction. Furthermore up to 60% of patients with TLE suffer from emotional disturbances following surgery.

The principle aim of the work presented in this thesis was to improve presurgical evaluation of patients with TLE by using cognitive functional MRI (fMRI) to non-invasively localise brain areas that are essential for processing cognitive function such as language and memory function and emotional and social behaviour.

150 consecutive patients and 40 healthy controls were included in our experiments. Different fMRI paradigms for the evaluation of cognitive functions have been implemented on a 3 Tesla scanner. All subjects underwent language and memory fMRI and standard neuropsychological assessment; those patients who proceeded to have temporal lobe surgery were reinvestigated 4 months following ATLR.

We studied the efficiency of reorganisation of language and memory function due to the underlying disease and in particular following ATLR. Amygdala fMRI was used to investigate potential implications on emotional and social outcome. A major part of the work included in this thesis has concentrated on the use of fMRI for the exploration and prediction of postoperative complications such as language and memory impairment but also emotional disturbances.

When used in concert with other MR imaging modalities the results of these methods can be used to improve surgical strategies tailored to individual patients with regard to functional outcome, by virtue of definition of epileptic cerebral areas that need to be resected and eloquent areas that need to be spared.

COGNITIVE FMRI IN TEMPORAL LOBE EPILEPSY

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LIST OF ABBREVIATIONS

A	Asymmetry
AED	Antiepileptic drug
AF	Arcuate fasciculus
AI	Asymmetry index
ANOVA	Analysis of variance
ATLR	Anterior temporal lobe resection
BOLD	Blood-oxygen-level-dependent
CA	Cornu Ammonis
CFS	Complex focal seizure
Cho	Choline
CPS	Complex partial seizure
Cr	Creatine
CSF	Cerebrospinal fluid
CT	Computed tomography
DBS	Deep brain stimulation
DNET	Dysembryoplastic neuroepithelial tumour
DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
ECS	Electrocortical stimulation
EEG	Electroencephalography
EPI	Echo planar imaging
ESI	Electrical source imaging
ESM	Electrocortical stimulation mapping
FA	Fractional anisotropy
FC	Functional connectivity
FDG	Fluoro-Desoxyglucose
FLAIR	Fluid attenuated inversion recovery

FLE	Frontal lobe epilepsy
FMRI	Functional magnetic resonance imaging
FWE	Family wise error
FWHM	Full width half maximum
GLM	General linear model
GTCS	Generalised tonic-clonic seizure
HADS	Hospital Anxiety and Depression Scale
HFO	High frequency oscillations
HMPAO	Hexamethylpropyleneamine Oxime
HRF	Haemodynamic response function
HS	Hippocampal sclerosis
IAT	Intracarotid amytal test
ICA	Independent component analysis
IED	Interictal epileptiform discharges
IFG	Inferior frontal gyrus
IGE	Idiopathic generalised epilepsy
ILAE	International League against Epilepsy
IQ	Intelligent quotient
MCD	Malformation of cortical development
MD	Mean diffusivity
MEG	Magnetencephalography
MFG	Middle frontal gyrus
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MTL	Medial temporal lobe
NAA	N-acetylaspartate
NMR	Nuclear magnetic resonance

PaD	Axial diffusivity
PeD	Radial diffusivity
PET	Positron emission tomography
PFC	Prefrontal cortex
PHG	Parahippocampal gyrus
RCI	Reliable change index
RF	Radiofrequency
ROI	Region of interest
sAHE	Selective amygdala-hippocampectomy
SD	Standard deviation
SFS	Simple focal seizure
SLF	Superior longitudinal fasciculus
SMG	Supramarginal gyrus
SNR	Signal-to-noise ratio
SPECT	Single photon emission computed tomography
SPM	Statistical Parametric Mapping
SPS	Simple partial seizure
STG	Superior temporal gyrus
SUDEP	Sudden unexplained death in epilepsy
SVC	Small volume correction
SVI	Small volume of interest
T	Tesla
TE	Echo time
TLE	Temporal lobe epilepsy
TBSS	Tract Based Spatial Statistics
TR	Repetition time
VBM	Voxel based morphometry
VF	Verbal fluency

VG	Verb generation
VNS	Vagal nerve stimulation
WAIS-III	Wechsler Adult Intelligence Scale

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Preoperative verbal and non-verbal memory fMRI in temporal lobe epilepsy (poster presentation).

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SB Bonelli, HWR Powell, M Yogarajah, PJ Thompson, MR Symms, MJ Koepp, JS Duncan.
Language fMRI and tractography pre- and post-surgery: evidence for structural and functional plasticity (invited speaker).

8th European Congress on Epileptology, September 2008/ Berlin

SB Bonelli, HWR Powell, R Samson, M Yogarajah, N Focke, PJ Thompson, MR Symms, MJ Koepp, JS Duncan.

Prediction of postoperative verbal and non-verbal memory decline using preoperative memory fMRI (invited speaker).

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SB Bonelli, R Powell, M Yogarajah, R Samson, PJ Thompson, MR Symms, MJ Koepp, JS Duncan.

Prädiktion von Gedächtnisstörungen nach Temporallappenresektionen (invited speaker).

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SB Bonelli, R Powell, M Yogarajah, R Samson, PJ Thompson, MR Symms, MJ Koepp, JS Duncan.

Functional MRI of memory in temporal lobe epilepsy - Prediction of effects of temporal lobe resection (platform presentation).

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Imaging language networks before and after anterior temporal lobe resection: Evidence of inter- and intrahemispheric functional reorganisation in temporal lobe epilepsy (invited speaker).

10. Österreichisches fMRT Symposium, December 2010/ Graz

SB Bonelli, PJ Thompson, M Yogarajah, C Vollmar, RH Powell, MR Symms, AW McEvoy, C Micallef, MJ Koeppe, JS Duncan.

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9. Jahrestagung der Österreichischen Gesellschaft für Neurology, March 2011/ Vienna

SB Bonelli.

How useful is fMRI in patients with epilepsy: rely or not to rely? – Pro Mapping Language (invited speaker).

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Imaging techniques such as DTI and fMRI should be employed in the routine diagnosis of patients with epilepsy (invited speaker).

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The role of fMRI to predict deficits after epilepsy surgery (invited speaker).

10th European Congress on Epileptology, September 2012/ London

SB Bonelli.

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Material specific memory fMRI in temporal lobe epilepsy (invited speaker).

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Funktionelle Magnetresonanztomographie (invited speaker).

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Verbal and visual memory function in temporal lobe epilepsy: results of a blocked versus event-related analysis (poster presentation).

11th European Congress on Epileptology, June 2014/ Stockholm

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“Preoperative amygdala fMRI in mesial TLE (mTLE) – a predictor for mood disturbances after temporal lobe surgery?”

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“Functional MRI of memory in temporal lobe epilepsy - Prediction of effects of temporal lobe resection.”

Prof. Dr. Herbert Reisner-Preis 2010 for Epileptology/ Bregenz, 2010

“Imaging memory in temporal lobe epilepsy: predicting the effects of temporal lobe resection”

Ernst Niedermeyer-Preis 2013 for Epileptology/ Vienna 2013

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CHAPTER I

1. INTRODUCTION

1.1. EPILEPSY – A COMMON NEUROLOGICAL DISEASE

Epileptic seizures and syndromes have a high prevalence and incidence affecting all ages and all races of both sexes and are highly variable meaning a precise medical diagnosis and accurate classification are crucial for an accurate prognosis and treatment of individual patients.

1.1.1. Definition and epidemiology

Epileptic seizures represent the clinical manifestation of excessive, hypersynchronous, usually self limited activity of neurons of the cerebral cortex (Blume et al., 2001). The clinical symptoms during an epileptic seizure vary greatly from impaired consciousness, motor and sensory-motor symptoms, and psychiatric symptoms to the more widely recognised tonic-clonic symptoms, depending on the origin and the propagation of seizure activity. Suffering from an epileptic seizure does not necessarily result in the diagnosis of “epilepsy” as under certain circumstances such as sleep deprivation, alcohol withdrawal, pyrexia, acute diseases of the brain, toxicity or metabolic derangement individuals with a certain predisposition have a higher risk of generating a seizure. In these cases a seizure would be classified as a “provoked seizure” but not as epilepsy.

In contrast to a single epileptic seizure, **epilepsy** is defined as a chronic neurological disorder characterized by recurrent unprovoked epileptic seizures (Blume et al., 2001). According to the definition of the International League against epilepsy (ILAE) epilepsy is characterized by “an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition” (Fisher et al., 2005). At least two unprovoked seizures or the occurrence of one seizure in individual patients with a functional or structural abnormality of the brain which predisposes them to recurring seizures are needed for the diagnosis of an epileptic disorder. The term “epilepsy” is not attributable to a single disease entity but comprises several diseases. Because of the great variety of underlying etiologies,

epilepsies are a very heterogeneous group of diseases manifesting with repetitive, unprovoked epileptic seizures, emphasizing the need of accurate diagnosis.

With a prevalence of 0.5-0.8% epilepsy is one of the most common neurological diseases (Annegers, 1997; Hauser, 1997). The incidence shows two maxima; the first occurs in the first year of life due to abnormal brain development, perinatal insults or metabolic disorders, while during childhood and adolescence the risk decreases with a minimum during adulthood. The second maximum occurs in the elderly population (>70 years), because of a higher rate of acquired brain lesions such as stroke, degenerative conditions, trauma or tumour (Hauser, 1997; Sander and Shorvon, 1996). The cumulative incidence of epilepsy at the age of 20 is one percent, at the age of 75 three percent. Including individuals who have a single unprovoked seizure or febrile convulsions, at least 5% of the population will have had one seizure at some point in life (Hauser, 1997).

1.1.2. Classification of epileptic seizures and syndromes

While epileptic seizures in general are characterized based on clinical seizure semiology, the classification of an epileptic syndrome is not only based on different seizure types, but also takes epidemiology and electro-encephalographic signs, treatment response and prognosis into account.

There are several overlaps between these two types of classification as one seizure type may occur in various different epilepsy syndromes; on the other hand one epileptic syndrome often manifests more than one type of seizure. In particular, it is important to differentiate between focal and generalised epilepsies as according to the classification of the ILAE in 1981 the differentiation between the two was most relevant with regard to medical treatment.

An accurate diagnosis is first of all based on a detailed patient history including observations and seizure description of relatives or friends which will then be completed by results of other possibly relevant investigations such as electroencephalography (EEG), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) and positron emission tomography (PET).

For successful treatment the most accurate diagnosis and characterization of the underlying epileptic syndrome is crucial, which requires a standardized classification and terminology.

Several classifications have been proposed by the ILAE since 1970 which are not only helpful to optimize medical treatment but also benefit communication between members of different medical professions, carers, relatives but also clinical research.

The Classification of Epileptic Seizures was accepted in 1981 (Commission on Classification and Terminology of the ILAE, 1981) and the Classification of Epilepsies and Epileptic Syndromes in 1989 (Commission on Classification and Terminology of the ILAE, 1989); advances in EEG, functional and structural imaging, other investigative procedures and genetics mandated a new and thorough revision of these classifications which was published in 2001 as “A Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy” by the ILAE Task Force (Engel, 2001) and which was updated and revised in 2006 (Engel, 2006). A glossary of descriptive terminology for ictal semiology has also been published (Blume et al., 2001).

1.1.2.1. Classification of epileptic seizures (ILAE 1981)

The ILAE “Classification of Epileptic Seizures” suggested in 1981 (Commission on Classification and Terminology of the ILAE, 1981) is an updated version of the classification proposed by Gastaut in 1970 (Gastaut, 1970).

Epileptic seizures are divided into “partial (focal or local) seizures”, which are usually generated in circumscribed cortical regions, and “generalised seizures”, which primarily affect both hemispheres.

Focal seizures can be classified as “simple partial seizures” (SPS) in which patients’ awareness is not affected, and “complex partial seizures” (CPS) which are characterized by impaired consciousness.

Classification is based on the clinical signs and symptoms during the seizure (ictal seizure semiology), supported by EEG findings.

In summary, partial (focal) seizures can be separated into simple partial (focal) and complex partial (focal) seizures and further classified as motor (clonic, tonic) and somato-sensory seizures and auras, which are exclusively experienced by the patient and have a high localising value (visual, auditory, olfactory, gustatory, autonomic and psychic seizures). Generalised seizures can be separated into absences, myoclonic, tonic-clonic, clonic, tonic and atonic seizures.

Because of propagation of seizure activity simple partial seizures can evolve into complex partial or generalised tonic-clonic seizures (Commission on Classification and Terminology of the ILAE, 1981).

1.1.2.2. Classification of epilepsy syndromes (ILAE 1989)

The recognition of epileptic syndromes and diseases, most of which are well defined and easy to diagnose, was an important milestone in modern epileptology. It benefits therapeutic decisions and enables natural history, prognosis and treatment efficacy to be studied scientifically in contrast to simple seizure/ symptom diagnosis.

In 1989 the ILAE proposed a classification of epilepsy syndromes, according to the following criteria (Commission on Classification and Terminology of the ILAE, 1989):

- Focal versus generalised epilepsy syndromes
- Idiopathic (with genetic predisposition) versus symptomatic (structural, metabolic or genetic cause) or possibly symptomatic (cryptogenic) epilepsy syndromes
- Syndromes with seizures of uncertain type (nocturnal seizures)
- Conditions with seizures that do not require a diagnosis of epilepsy (fever, drugs, metabolic imbalance) (Engel, 2001).

Important clinical features include the type of seizure, localisation, frequency, circadian distribution, precipitating factors, response to treatment, age at onset, inheritance and physical and mental symptoms. Focal epilepsies are further classified according to the affected hemisphere and lobe (left/ right – temporal, frontal, parietal, occipital, insular). Specific clinical

symptoms together with EEG findings may be helpful to localise the seizure onset zone within these brain areas (i. e. medial/ lateral temporal).

1.1.2.3. The ILAE 5 axis classification

The diagnostic scheme of the ILAE Task Force is divided into five axes, aiming to facilitate a logical clinical approach and diagnostic studies which are necessary to generate appropriate therapeutic strategies for individual patients (Engel, 2001; Engel, 2006).

Axis 1: Ictal semiology – description of ictal events;

Axis 2: Seizure type – localisation and precipitating stimuli should be specified (if available);

Axis 3: Epilepsy Syndrome – may not always be possible;

Axis 4: Etiology (if available) – genetic defects or specific pathologies for symptomatic focal epilepsies;

Axis 5: Impairment.

Over recent decades notable diagnostic tools - in particular epilepsy imaging and genetics - have been developed which have significantly improved our understanding of the underlying mechanisms of epileptic seizures and epilepsy syndromes. In order to take this additional information (EEG manifestations, newly described syndromes, information gained from video-EEG monitoring, functional and structural imaging, invasive procedures and genetics) into account, periodically modifications of this classification with changes in terminology are required. Most recently, the ILAE proposed a new classification system in 2010 (Berg et al., 2010).

The main changes in the 2010 classification concern terminology and classification of generalised seizures. The terms “generalised” and “focal” were redefined as “seizures occurring in and rapidly engaging bilaterally distributed networks (generalised) and within networks limited to one hemisphere and either discretely localised or more widely distributed (focal)”. Focal seizures should be described according to their clinical manifestation (i. e. focal motor,

dyscognitive), while classification of generalised seizures in general has been simplified. In summary, it is suggested that certain terms will no longer be used but replaced as follows:

- “Idiopathic” will be replaced by the term “genetic”, when a genetic cause has been identified.
- “Symptomatic” will be replaced by “structural-metabolic” when imaging or laboratory results reveal an underlying condition.
- “Cryptogenic” will be replaced by “unknown” for all other situations.

Figures 1.1 and 1.2 provide an overview of the revised classification of focal and generalised seizures and how electroclinical syndromes can be organized according to the 2010 classification.

As this new classification was only published in 2010 this thesis and the associated publications are based on the previous classification systems, which are still widely used.

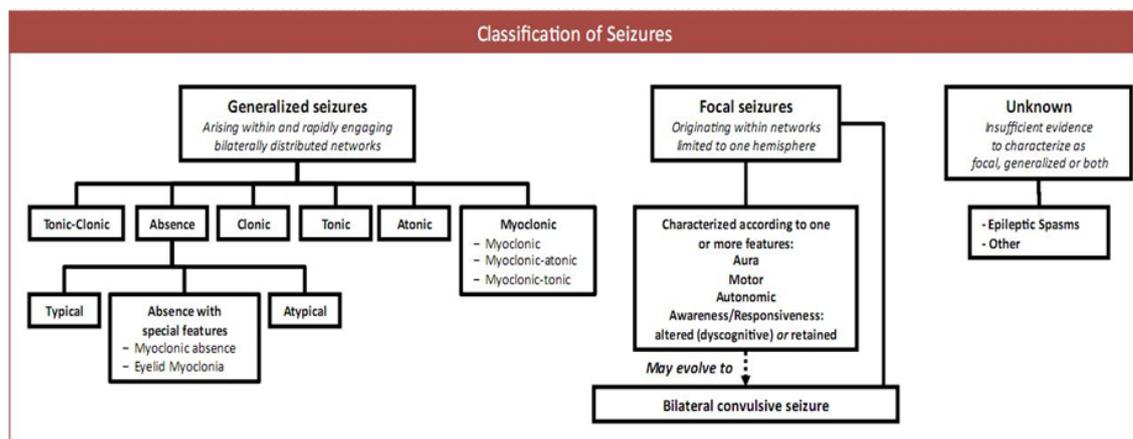


Figure 1.1 Classification of seizures (ILAE 2010)

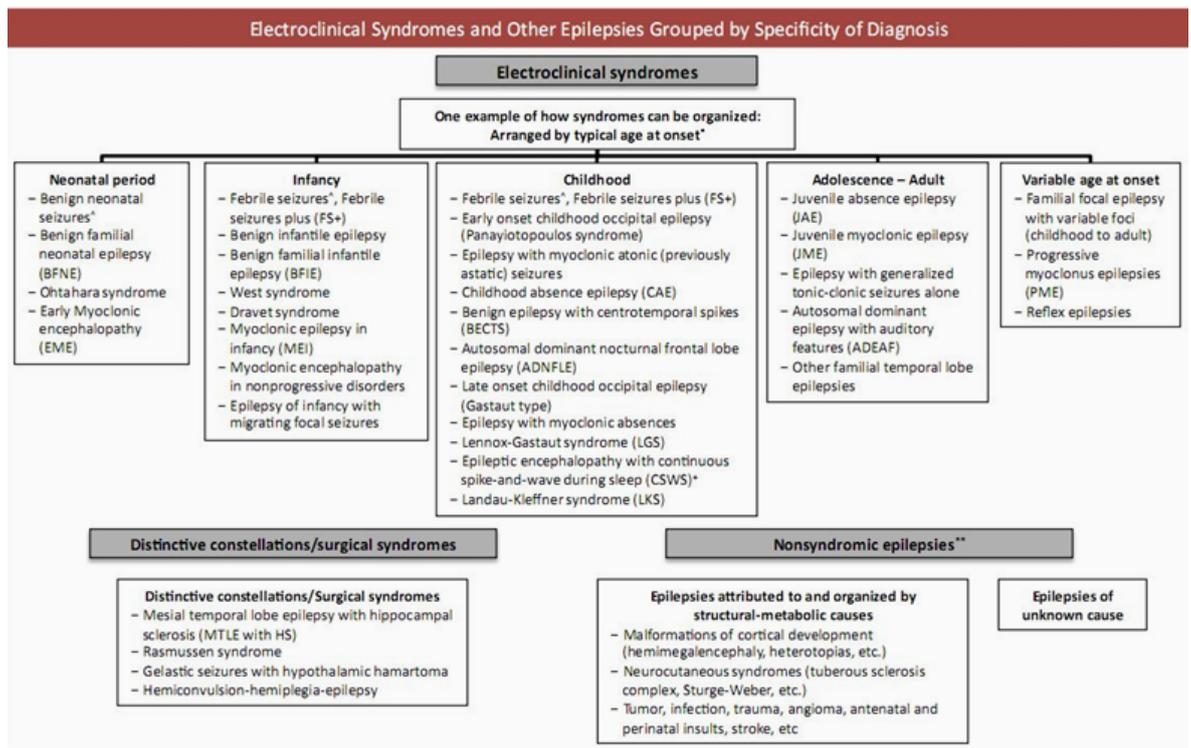


Figure 1.2 Classification of electroclinical syndromes (ILAE 2010)

1.1.3. Natural history

1.1.3.1. Response to treatment

60-80% of all patients suffering from epilepsy will become seizure free with an appropriate antiepileptic medication (Casetta et al., 1997; Cockerell et al., 1997; Sillanpaa et al., 1998); in certain patient populations it is possible to stop medication completely as patients may remain seizure free without it.

Excellent seizure control is very much dependent on the underlying epilepsy syndrome:

- Patients suffering from childhood absence epilepsy or juvenile absence epilepsy have an 80% chance of becoming seizure free with the appropriate medication. The same is also valid for the following syndromes:
- 86-90% of patients with juvenile myoclonic epilepsy;
- 60-80% of patients with idiopathic generalised epilepsy with generalised tonic-clonic seizures only;
- 30-50% of patients with focal epilepsies;
- 98% of patients with benign childhood focal seizures;

- 20-40% of patients suffering from Lennox-Gastaut-syndrome;
- 40-50% of patients with West-syndrome.

In another 15% of patients several attempts of modification of antiepileptic medication will eventually lead to sufficient seizure control. In a significant minority of 15-20% of all patients seizures will not be controlled with any antiepileptic drug. In this patient population alternative treatment strategies such as epilepsy surgery need to be considered.

1.1.3.2. Prognostic factors

Several studies investigated potential prognostic factors for different epileptic syndromes (Berg et al., 1996; Casetta et al., 1999; Kwan and Brodie, 2000). In these studies the following factors have been predictive for an unfavourable outcome of medical treatment:

- Aetiology: symptomatic epileptic syndromes
- Underlying pathology: mesial temporal lobe epilepsy, focal cortical dysplasia
- Neurological or psychiatric comorbidity
- Type of seizures: complex-focal seizures, spasms,
- Early age of epilepsy onset (< one year)
- Status epilepticus before commencement of medical treatment
- High number of seizures before commencement of medical treatment
- No treatment response to initial (mono-) therapy.

1.1.3.3. Mortality

In patients with epilepsy, mortality in general is 2-3 times higher compared to the healthy population. This is mainly valid for the first 10 year after disease onset and even higher in patients with symptomatic epilepsy and therefore most likely associated with the underlying pathology (i.e. brain tumour, stroke, trauma). But also in patients with idiopathic (genetic) generalised epileptic syndromes mortality is increased with patients with less well controlled seizures being at higher risk (Cockerell, 1996).

The following causes of death have been associated with epilepsy (Nilsson et al., 1997):

- Cardiovascular diseases (44.9%)
- Tumours (16.2%)
- Diseases of the respiratory system (8.9%)
- Psychiatric diseases (6.4%)
- Accidents, suicide including seizure-related death such as status epilepticus and sudden unexplained death in epileptic patients (SUDEP) (7.3%).

1.2. TEMPORAL LOBE EPILEPSY

1.2.1. Introduction

In 60-70% of all epilepsies simple and complex focal seizures may occur, with 50% of them originating from the temporal lobe structures (Wiebe, 2000), meaning that with a prevalence of 30-35% temporal lobe epilepsy (TLE) is the commonest type of focal epilepsy (Engel, 1996). Two thirds of all temporal seizures originate from the mesio-basal temporal structures, while the remainders arise from the lateral neocortical temporal structures.

1.2.2. The hippocampus and its connections

The hippocampal formation is located in the medial part of the temporal lobe, lying on the floor of the temporal horn of the lateral ventricle. The hippocampus itself contains the four CA (Cornu Ammonis) subregions, CA 1-4, whereas the hippocampal formation includes the dentate gyrus, the CA subfields and the subiculum. All hippocampal components are composed of simple three layered allocortex, which differentiates them from surrounding six layered medial temporal neocortex. The ventricular surface of the hippocampus is a layer of white matter called the alveus which is continuous with the fornix and which contains afferent and efferent axons. Adjacent to these lies the parahippocampal gyrus (PHG), which includes the entorhinal cortex, both of which are functionally related to the hippocampus (Duvernoy, 1998).

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. The neurotransmitter of these pathways is glutamate. Much of the input from the CA1 field is sent on to the subiculum which projects, amongst other areas to the entorhinal cortex, creating a loop involving the hippocampus (Duvernoy, 1998).

1.2.3. Classification of TLE

As mentioned earlier, this thesis and associated publications are based on the ILAE classification of 2001/ 2006, which classifies TLE according to the following categories (Engel, 2001; Engel, 2006): underlying aetiology, seizure onset zone and bilaterality.

The main changes in terminology and seizure classification in the ILAE classification of 2010 are discussed in chapter 1.1.2.3.

1.2.3.1. Aetiology

This classification differentiates between idiopathic, symptomatic and cryptogenic TLE, and the symptomatic subtype can be classified further into mesial TLE and TLE due to specific lesions such as tumours, vascular malformations, cortical dysplasia etc. (Commission on Classification and Terminology of the ILAE, 1989).

1.2.3.2. Seizure onset zone

- Limbic epilepsy
- 1. Mesial temporal lobe epilepsy with the underlying aetiology – hippocampal sclerosis;
- 2. Mesial temporal lobe epilepsy defined by specific aetiologies;
- Neocortical epilepsy
- 3. Lateral temporal lobe epilepsy.

1.2.3.3. Bilaterality

During presurgical assessment bitemporal changes on interictal and /or ictal EEG, structural or functional imaging and bitemporal dysfunction during neuropsychological assessment can be identified in some cases. It has been postulated that both temporal lobes cannot be considered as separate entities but must be evaluated as a biological entity (Engel, 1994).

1.2.4. Mesial temporal lobe epilepsy with hippocampal sclerosis

1.2.4.1. Aetiology and pathology

The typical underlying pathological substrate in mesial temporal lobe epilepsy (mTLE) is hippocampal sclerosis (HS) – also known as medial temporal sclerosis or Ammon’s Horn sclerosis – which is characterized by a selective loss of pyramidal cells in the CA1 subfield and in the hilar region (including CA4 pyramidal cells) with accompanying astrocytic gliosis (Wieser, 2004) and to a minor degree also in the CA3 compartment, while the CA2 sector is spared. Pyramidal cells of CA2 and dentate granule cells appear more resistant. In severe HS almost total neuronal loss is seen in all hippocampal subfields, including the granule cells of the dentate gyrus. In end folium sclerosis, seen in 3-4% of surgical cases, damage is centered on the hilus and dentate gyrus. This is important as it may be undetectable with neuroimaging and is associated with a later onset of epilepsy and a worse postoperative seizure outcome (Armstrong, 1993). 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 sprouting of mossy fibres, the excitatory, glutamatergic axons of the dentate gyrus (Sutula et al., 1989). More recent experimental findings however, in which mossy fibre sprouting is prevented, suggest that it is not an essential process to the generation of spontaneous recurrent seizures (Longo and Mello, 1999). Other theories involve alterations of neurotransmitter systems and inhibitory interneuronal populations, leading to a shifting of balance between excitation and inhibition towards excitation.

Hippocampal sclerosis accounts for around 65% of cases with mTLE (Babb, 1999). While the typical picture of HS is well established, the question of its aetiology and relationship to the generation of seizures remains a matter of debate. There is a strong association between the development of HS and a history of prolonged, complex childhood febrile convulsions (Falconer et al., 1964; Mathern et al., 1995) or other early injuries of the central nervous systems such as trauma or infection. This has led to the hypothesis that an initial precipitating injury irreversibly damages or alters the hippocampus and acts as a template for the progression to HS following a ‘latent’ interval. Furthermore the severity or degree of HS correlates with an

earlier age of onset of seizures (Davies et al., 1996). On the other hand only a minority of children with complex febrile convulsions finally develop mTLE.

Other evidence suggests that an underlying malformation of the hippocampus predisposes to both HS and febrile convulsions. Evidence from neuroimaging has suggested subtle hippocampal malformations as a cause of familial febrile convulsions and subsequent HS (Davies et al., 1996), and HS has also been reported in patients in association with isolated malformations of the hippocampus (Baulac et al., 1998). Other studies have demonstrated the coexistence of HS with focal cortical dysplasia (Blumcke et al., 2011) or other subtle cytoarchitectural malformations in the neocortex (Hardiman et al., 1988). It is possible that these epileptogenic extra-hippocampal lesions ‘kindle’ the hippocampal neuronal loss, leading to the development of HS. Also a genetic predisposition has been discussed in particular in mTLE patients with a familial history of TLE (Engel, 1996; Wieser et al., 1993).

In summary, the cause of HS is unknown, but the pathological changes lead to a status of increased excitability and increased synchrony of firing thresholds resulting in spontaneous seizures (Engel, 1996; Wieser et al., 1993).

1.2.4.2. Course of the disease

Following a complex febrile convulsion in early childhood in many but not all patients with TLE, afebrile seizures usually commence without any precipitating factors in late childhood or adolescence. Initial seizures are often well controlled with antiepileptic drugs (AEDs), such that a seizure free period may last for several years (sometimes even without any AEDs). Seizures may recur in the third decade or later and at this stage are generally more difficult to control which underpins the progressive nature of mTLE. In the long term 30-50% of all mTLE patients become drug resistant (Engel, 1996; Wieser et al., 1993) and these patients have a predictably good outcome following anterior temporal lobe resections (ATLR).

1.2.4.3. Clinical seizure semiology

Patients with TLE may experience different types of seizures, often starting with auras and other simple partial seizures which may go unrecognised for many years. Subsequently, the appearance of complex partial seizures or generalised tonic-clonic seizures finally attracts medical attention.

A patient suffering from TLE may have some or all of the semiologies and types of seizures described in the following paragraphs (Engel et al., 1997; Gil-Nagel and Risinger, 1997):

1.2.4.3.1. Simple partial seizures

90% of all patients with mTLE suffer from ascending **epigastric or visceral auras**, which therefore are the most common symptoms in mTLE. Such an aura can remain an isolated symptom (simple partial seizure (SPS)) (Wieser et al., 1993) or it can be followed by a complex partial seizure. The sensation is characterized by an arising feeling from the stomach, moving upwards in a slow or fast fashion (within seconds), until it reaches the level of the throat. A sensation moving downwards towards the feet is rarely described.

The other common aura experienced by patients with mTLE is **ictal fear**, although this type of aura is not exclusive to mTLE. Other auras including déjà-vu, jamais-vu, olfactory and gustatory auras etc. are rarer in mTLE while visual or auditory auras are suggestive of a diagnosis other than that of mTLE. In some patients auras can disappear in the course of the disease and this has been described as a negative prognostic factor (Engel et al., 1997).

1.2.4.3.2. Complex partial seizures

Complex partial seizures (CPS) are characterized by an **impairment of consciousness** which is often paralleled by the appearance of other symptoms such as **staring, motor arrest** (“motionless stare” more often than motor restlessness), **oro-alimentary automatisms** and **early head-turning**. The patient may be (partially) responsive during this phase, but will have no recollection of the events. This initial phase may be followed by **gestural or other automatisms, vocalisations** (of identifiable words) and **dystonic posturing** (in 20-30%).

Lateralising signs include unilateral dystonic posturing (contralateral to seizure onset) and early head turning or unilateral gestural automatisms (ipsilateral to seizure onset). **Ictal nausea** and **ictal autonomic** signs such as borborygmi, belching, pallor, flushing, cardiac arrhythmias, respiratory arrest and pupillary dilatation can also be observed (Commission on Classification and Terminology of the ILAE, 1989).

Oro-alimentary automatisms typically include lip-smacking, chewing, swallowing, licking and tooth-grinding while gestural automatisms consist of simple movements such as fiddling, fumbling, picking, tapping, patting or plucking, rubbing or scratching the face and other simple gestural movements.

In mTLE automatisms cannot only be preceded by an epigastric aura or fear but also by **mental or psychic symptoms** (the “dreamy state” of Jackson (Gloor et al., 1982)), alone or in combination.

Ictal mental symptoms usually include elements of perception, memory and affect, which are disturbed in various combinations and to varying degrees. During different seizures one element can be involved more than another, but also occur in isolation. One can differentiate between ideational (impairment of thoughts), dysmnestic (impairment of memory), affective (emotional impairment) and dyscognitive (impairment of perception and cognition) disturbances.

Complex partial seizures in mTLE tend to have a more gradual onset, slower evolution and longer duration (2-10 minutes on average) (Wieser et al., 1993) than extra-temporal complex partial seizures. They occur both in wakefulness and sleep, and may cluster. In some women predominantly catamenial seizures arising from the medial temporal lobe have been reported.

1.2.4.3.3. Secondary generalised tonic-clonic seizures

Complex partial seizures can also evolve into secondary generalised tonic-clonic seizures (GTCS) in 60% of all mTLE patients (Kotagal, 1997).

1.2.4.3.4. *Postictal symptoms*

Following CPSs postictal symptoms are very frequent and include a variable phase of postictal confusion, disorientation and sometimes headache and speech disturbance, which usually lasts up to several minutes and indicates a seizure onset in the dominant hemisphere. Another postictal lateralising sign is postictal nose-wiping which occurs ipsilateral to the seizures focus in 90% of cases (Leutmezer et al., 1998). The duration of postictal dysfunction is longer for seizures originating from the dominant hemisphere (Fakhoury et al., 1994).

1.2.4.4. **Diagnostic procedures**

An accurate clinical **history** (from both the patient, and importantly, someone who has witnessed the patient's seizures) and careful evaluation of the **clinical seizure semiology** are essential for establishing the diagnosis of TLE, together with various investigations.

1.2.4.4.1. *Imaging*

High resolution MRI is the most important diagnostic tool and identifies abnormalities in approximately 75% of patients with focal epilepsy who may benefit from epilepsy surgery (Duncan, 2010). It allows visualization of hippocampal sclerosis and other common abnormalities such as focal cortical dysplasia, vascular malformations, tumours, and acquired cortical damage in most patients.

In two thirds of TLE patients, unilateral or bilateral hippocampal atrophy can be identified on MRI by a decrease in hippocampal volume on coronal T1 weighted images and/or an increase in signal in the hippocampus on T2-weighted MRI scans (Jackson et al., 1990; von Oertzen et al., 2002a). Some patients also show evidence of a so called "dual" pathology, which is characterized by another pathological substrate such as cortical malformation in addition to HS. Von Oertzen and colleagues demonstrated that the sensitivity of standard MRI for the detection of focal lesions reported by non-experts was 39%, but this rose to 91% when an epilepsy MRI protocol was employed and the images were reported by expert neuroradiologists (Von Oertzen et al., 2002b).

The following sequences are recommended for baseline MRI evaluation in epilepsy imaging:

- a) A T1-weighted volume acquisition that is acquired in an oblique coronal orientation, orthogonal to the long axis of the hippocampi, and covers the whole brain in 0.9 mm partitions. This sequence produces approximately cubic voxels, allowing for reformatting in any orientation, subsequent measurement of hippocampal morphology and volumes, and for three-dimensional reconstruction and surface rendering of the brain;
- b) Oblique coronal spin-echo sequence, with proton density (TE = 30), heavily T2-weighted (TE = 90 or 120) and FLAIR acquisitions that are orientated perpendicular to the long axis of the hippocampus, to demonstrate any increase in T2-weighted signal intensity.

Hippocampal sclerosis can reliably be quantified by hippocampal volumetry and T2 relaxometry (Cook et al., 1992; Jackson et al., 1990; Van Paesschen et al., 1997a). Hippocampal atrophy as identified by hippocampal volumetry has been shown to correlate well with neuronal loss, particularly in the CA1 subfield (Van Paesschen et al., 1997b). In addition the severity of hippocampal atrophy on the side of the language dominant hemisphere has been found to be an important predictor of verbal memory impairment following hippocampal resection. The more severe the atrophy preoperatively, the less likely it is that there will be a significant decline of verbal memory after surgery (Trenerry et al., 1993). Regarding seizure outcome studies have shown that ipsilateral hippocampal atrophy was a good prognostic factor for seizure control following ATR (Berkovic et al., 1991). Measuring T2 relaxation times allows a quantitative determination of T2-weighted signal changes, and has been proven useful at identifying hippocampal pathology, with marked elevations being associated with HS and intermediate values being seen in patients without qualitative MRI evidence of HS (Jackson et al., 1993b). Standard MRI sequences enable the visual assessment of unilateral hippocampal atrophy by experienced neuroradiologists with asymmetry of up to 20% between sides. Quantitative assessment can detect differences below this (Bartlett et al., 2007; Farid et al., 2012), although it probably only increases sensitivity to around 90-95%.

The development of new MRI acquisitions such as diffusion tensor imaging (DTI) and advanced MRI sequences such as PROPELLER (periodically rotated overlapping parallel lines with enhanced reconstruction), which compensates for subject movement, may not only be helpful at identifying abnormalities that are not revealed on conventional MRI but may allow more detailed delineation of structures within the hippocampus (Eriksson et al., 2008). High field MRI has also been shown to be a valuable tool in the delineation of hippocampal sub-fields, correlating well with histo-pathological findings (Mueller et al., 2009).

Voxel based morphometry has successfully been used in TLE to identify structural changes outside the mesial temporal structures adding support to the concept that TLE reflects abnormalities not only in the mesial temporal structures, but also in structurally and functionally connected regions in other parts of the brain (Keller and Roberts, 2008). In mTLE more localised changes in the parahippocampal gyri, thalamus and entorhinal cortex have been observed, while more widespread changes were seen in neocortical TLE (Pell et al., 2004).

In TLE **18F FDG-PET** and **interictal SPECT** (with lower sensitivity) show an extensive hypometabolism/ hypoperfusion in the medial and lateral temporal lobe structures, in the thalamus, the basal ganglia and the lateral frontal cortex (Berkovic et al., 1993; Henry and Chugani, 1997). **Ictal SPECT**, in contrast, shows medial and lateral hyperperfusion in the temporal lobes (Berkovic et al., 1993). Therefore these methods may be more sensitive in some patients when MRI is unremarkable, but do not confer specificity of aetiological diagnosis (Duncan, 1997).

The role of functional imaging and other (new) imaging techniques are discussed in more detail in chapters 1.5 to 1.7.

1.2.4.4.2. Routine EEG

In up to 75% of all mTLE patients a single, **routine EEG**, lasting for 20 minutes, will show a normal or unspecific result, with mild and non-specific abnormalities. Only one third of patients will show the classical EEG features of mTLE which are spikes and sharp and slow waves in the anterior temporal electrodes (Williamson et al., 1993). In one third of patients the spikes

appear independently over both temporal lobes (Engel et al., 1997). Interictal regional temporal slowing has been shown to have a lateralising value (Gambardella et al., 1995) and can be observed in about 50% of all patients.

1.2.4.4.3. Video-EEG monitoring

By using **prolonged video-EEG monitoring** (also including sleep EEG) as described in chapter 1.8.3.1.1 the likelihood of registering mTLE specific changes can be increased to 70-80%. During a seizure the ictal EEG usually shows rhythmic activity (Alpha- Theta or Delta), which is observed over the affected temporal lobe, timely correlated with clinical events. The most typical pattern is rhythmic theta-activity of 5-7 HZ over one temporal lobe (Engel et al., 1997). Fast spiking is rare.

1.2.4.4.4. Neuropsychological assessment

Memory impairment

Patients with epilepsy have an increased risk of cognitive impairment. In patients with TLE memory difficulties are the most frequently reported and assessed cognitive problem, as the hippocampus and related medial temporal lobe (MTL) structures have a critical role for the encoding of episodic memory (Squire and Zola-Morgan, 1991). Previous studies have provided evidence for a dissociation in function between the dominant (usually the left) MTL, mediating verbal memory (Frisk and Milner, 1990) and non-dominant (usually the right) MTL mediating visual memory (Smith and Milner, 1981). As a result neuropsychological assessment typically shows material-specific memory impairment (Hermann et al., 1997) with verbal memory deficits in left sided TLE (Hermann et al., 1997) and visuo-spatial memory deficits in right sided TLE (Gleissner et al., 1998). Transient epileptic amnesia is a recently described – most likely – focal medial temporal lobe epilepsy syndrome, characterized by recurrent episodes of isolated memory loss. It is associated with two forms of interictal memory impairment: accelerated long-term forgetting and autobiographical amnesia (Butler et al., 2007; Butler and Zeman, 2008; Kapur, 1990; Milton et al., 2010; Zeman et al., 2013).

A number of factors may contribute to the memory deficits seen in epilepsy. These include the underlying pathological lesion which may be stable or progressive and tend to cause irreversible impairment, and functional changes such as interictal discharges, ongoing seizures and anti-epileptic medications, the effects of which are potentially reversible (Butler et al., 2012; Butler et al., 2013; Elger et al., 2004). Some studies have suggested that cognition is already affected at disease onset, suggesting that the underlying disease causes a baseline cognitive deficit (Aikia et al., 2001) which may then change in the long term course of the disease. When grouped according to age of onset, patients with onset in early childhood had worse memory (Lespinet et al., 2002). A longitudinal study looking at a large number of medically and surgically treated TLE patients found that chronic TLE was associated with progressive memory impairment (Helmstaedter et al., 2003). Surgery, particularly if unsuccessful, accelerated the decline, however memory decline may be stopped if seizures were fully controlled. In another study of a large group of patients with severe epilepsy, the presence of generalised tonic-clonic seizures was the strongest predictor of cognitive decline, while periods of seizure remission were associated with a better cognitive outcome (Thompson and Duncan, 2005).

Early neuropsychological assessment of these patients is advisable, both in aiding diagnosis and to help identify any cognitive difficulties which may exist in order to set realistic employment and educational goals.

1.2.4.4.5. Psychiatric assessment

Psychiatric disorders in mTLE

A number of TLE patients develop psychiatric disorders, most commonly depression, anxiety and psychotic disturbances. These can be classified into ictal, peri-ictal or inter-ictal events.

Ictal psychiatric symptoms

Anxiety, depression and hallucinations can occur as a direct manifestation of a seizure. These are usually brief and stereotyped; treatment is aimed at adequate seizure control.

Peri-ictal psychiatric symptoms

Preictal mood changes can last a few hours up to a few days before a seizure and are usually relieved by the seizure. Postictal psychiatric disturbances are more likely to occur following clusters of seizures, generalised seizures or status epilepticus.

Postictal confusion is characterised by impaired awareness/consciousness and diffuse EEG slowing without ictal discharges. These episodes are usually brief and common after complex partial or generalised tonic-clonic seizures. Aggressive behaviour may occur and is usually undirected; the patient is likely to be amnesic for the event.

Postictal depression can last longer than other postictal states (up to two weeks). Symptoms range from mild to severe and may involve suicidal behaviour. It has been reported to occur more commonly with right-sided temporal or frontal foci (Kanner and Nieto, 1999). Postictal anxiety and mania are less common and shorter in duration.

The prevalence of postictal psychosis has been estimated to be 6-10% in patients with epilepsy, and is usually seen in TLE (Kanner et al., 1996). It typically occurs after a cluster of complex partial seizures and there is usually a period of lucidity (12-72 hours), prior to the onset of psychosis. The psychotic symptoms include delusions, hallucinations, thought disorder or mania, which are usually transient but can last several weeks. It has also been reported that some patients with recurrent episodes of postictal psychosis may develop an inter-ictal psychosis (Logsdail and Toone, 1988). Mechanisms are unknown but may be related to transient neurochemical changes as a result of seizures. Treatment of acute postictal psychosis may require short courses of benzodiazepines or antipsychotics. Improving seizure control would be the long-term goal to prevent such occurrences.

Inter-ictal psychiatric symptoms

Up to 40% of patients with epilepsy, most commonly TLE, suffer from inter-ictal depression (Robertson et al., 1987). Patients usually present with persistent low mood, anhedonia, loss of interest and biological symptoms of sleep or appetite disturbances; however some patients can present with atypical symptoms, referred to as inter-ictal dysphoric disorder (Blumer, 2000).

This is characterised by chronic intermittent dysthymia, irritability and anxiety symptoms. Treatment for depression includes psychological interventions such as counseling, psychotherapy or cognitive/behaviour therapy if appropriate. For more severe depression, antidepressant medications such as selective serotonin reuptake inhibitors are required but should be used cautiously because of the potential risk of lowering seizure threshold.

Inter-ictal anxiety disorders, such as panic disorder, generalised anxiety, agoraphobia, social phobia and obsessive compulsive disorder can also occur in patients with TLE, especially with a left-sided seizure focus.

Inter-ictal psychosis occurs with a prevalence of 4-10% in patients with epilepsy, mainly reported in TLE (Onuma et al., 1995). The onset of the psychosis usually occurs after many years of epilepsy (> 10 years). Early age of disease onset, bilateral temporal foci and a refractory course have been reported as potential risk factors. Inter-ictal psychosis has been associated with left-sided epileptic foci (Sherwin, 1981). Treatment includes antipsychotic medication, psychosocial support and family education. Atypical antipsychotic drugs are potentially less likely to reduce seizure threshold (with the exception of clozapine) or cause extrapyramidal side effects. Lower doses than those used in primary schizophrenia seem to be effective.

1.2.4.5. Management of mTLE

Treatment with antiepileptic drugs is similar to that for any other type of focal epilepsy and is effective in about 80% of all mTLE patients. For the remaining 20% who have to be classified as “drug resistant” epilepsy surgery is an alternative and effective treatment option, which is discussed in detail in chapter 1.8.

1.2.5. Lesional temporal lobe epilepsy other than hippocampal sclerosis

1.2.5.1. Mesial temporal lobe epilepsy defined by specific aetiologies other than hippocampal sclerosis

In mTLE with other underlying pathology clinical seizure semiology and EEG findings do not differ from that observed in seizures due to HS – however the underlying structural lesion may be identified in nearly 100%. Careful examination of the whole brain is necessary, in order to identify multiple lesions (e. g. cavernomas) (Cendes et al., 1995; O'Brien et al., 1997).

Possible underlying pathologies include tumours (malignant or benign), vascular (cavernous and venous angiomas and arteriovenous malformations) and developmental causes (malformations of cortical development), traumas, infectious diseases and cerebrovascular diseases (O'Brien et al., 1997).

1.2.5.2. Lateral temporal lobe epilepsy (LTLE)

Lateral TLE originates from the neocortical structures of the temporal lobe in contrast to mTLE, which arises within the limbic structures and which is more likely to be associated with a prior history of febrile seizures and other initial precipitating incidents (Foldvary et al., 1997).

Clinical seizure semiology differs from that observed in mTLE, reflecting the different anatomical region of seizure onset (although none of the following symptoms reliably differentiates mTLE from LTLE in individual patients): Auras typically include auditory hallucinations, vestibular phenomena, mental illusions and visual misperceptions. Language disturbances can be seen in seizures arising from the dominant hemisphere. Motor symptoms occur early in the course of a seizure and include clonic movements of facial muscles, grimacing, finger and hand automatisms, dystonic posturing, leg automatisms, restlessness and unformed vocalisations. Whole body rotations are frequently observed and can be used for differentiation from mTLE seizures.

Simple partial seizures can progress to CPSs and secondary GTCSs because of spreading to mesial temporal or extratemporal structures. However, impairment of consciousness is not as pronounced as in mTLE (Elger, 2000).

The structural causes for LTLE are the same as for mTLE due to other lesions than HS.

Diagnosis

MRI is the most important diagnostic tool, and allows identification of the underlying pathology in most cases of lesional TLE.

In LTLE surface EEG typically shows unilateral or bilateral midtemporal or posterior temporal spikes (Commission on Classification and Terminology of the ILAE, 1989; Elger, 2000).

Treatment

Drug treatment of lesional TLE is similar to all other types of focal seizures; surgical interventions are often associated with an excellent outcome.

Before surgical intervention careful presurgical evaluation including prolonged video-EEG monitoring is necessary in all types of lesional TLE.

1.2.6. Cryptogenic TLE

(TLE of unidentified cause according to the ILAE 2010 classification)

By definition cryptogenic TLE is characterized by a normal MRI scan and/ or unremarkable histopathological findings after a surgical intervention. However, this definition is not ideal as despite constant improvements in the available neuroimaging methods, some patients with normal MRI still show histopathological abnormalities (most commonly focal cortical dysplasia); in addition a definition based on histological findings is problematic as only a small proportion of all patients will undergo epilepsy surgery, and the diagnosis can only be confirmed retrospectively.

Possible underlying pathophysiological mechanisms remain a matter of debate. Some postulate lesions too small to be identified on MRI as the underlying pathological substrate, but there is also evidence that neuronal loss and synaptic reorganisation similar to that in mTLE (but which cannot be identified using the conventional histopathological methods) may play a significant role also in cryptogenic TLE (Engel, 1996).

Clinical seizure semiology may have features of either/ both mesial and lateral temporal lobe epilepsy as described above (Foldvary et al., 1997; Gil-Nagel and Risinger, 1997). Dupont and colleagues found a highly significant association between contralateral dystonia and ipsilateral automatisms in patients with cryptogenic TLE with a medial seizure onset zone and between ipsilateral dystonia and contralateral automatisms in cryptogenic TLE patients with lateral seizure onset zone (Dupont et al., 1999).

The interictal EEG typically shows temporal spikes; MRI is per definition normal. PET may sometimes show hypometabolism in the lateral temporal region/lobe while the medial temporal structures show normal metabolism (Hajek et al., 1993). In most patients neuropsychological testing does not reveal any material-specific memory deficits (Burgerman et al., 1995).

1.2.7. Bilateral TLE

In patients with TLE, bitemporal changes are common, such that both temporal lobes may be considered a single functional entity. It is still a matter of debate, whether initial bitemporal lesions are the underlying substrate or whether secondary epileptogenesis is responsible for bitemporal changes. Interictal EEG typically shows independent bitemporal spikes in 30% of all patients, which has been identified as an unfavorable prognostic factor after epilepsy surgery (Chung et al., 1991). Also seizures may arise from both temporal lobes independently (So et al., 1989a; So et al., 1989b). It is important to quantify temporal changes in high resolution MRI using volumetric methods in order to accurately identify bilateral abnormalities. Also PET and MR-spectroscopy may show additional bitemporal changes. Disturbances of visuo-spatial and verbal memory during neuropsychological assessment also suggest a bitemporal functional problem (Engel, 1994).

1.3. STRUCTURAL IMAGING

1.3.1. Clinical CT and MRI in epilepsy

Recent advances regarding structural and functional MRI have revolutionized the diagnosis and management of epilepsies (Commission on Neuroimaging of the ILAE, 1997; Commission on Neuroimaging of the ILAE 1998; Commission on Diagnostic Strategies, 2000a), and are particularly relevant in epilepsy surgery. With the different brain imaging techniques, which are currently available, a great amount of anatomical and metabolic information can be provided.

1.3.1.1. Computed Tomography (CT)

Owing to its low sensitivity, particularly in common pathologies underlying focal epilepsy, together with other disadvantages such as radiation exposure and a higher incidence of allergic reaction to contrast, CT has largely been superseded by MRI in the investigation of focal epilepsy with the exception of a few specific indications (e.g. for the detection of areas of cortical calcification (Commission on Neuroimaging of the ILAE, 1997), as an initial emergency investigation when seizures occur in the context of a neurological insult or if MRI is contraindicated).

1.3.1.2. Magnetic Resonance Imaging (MRI)

MRI is now the imaging investigation of choice for patients suffering from epilepsy because of its high sensitivity and specificity for identification of small abnormalities (Commission on Neuroimaging of the ILAE, 1997; Commission on Neuroimaging of the ILAE, 1998). When used in concert with clinical and EEG findings, it may add valuable information and even enable syndrome-classification.

Specific clinical MR-protocols for patients with epilepsy vary from centre to centre; one protocol has been suggested as follows (Commission on Neuroimaging of the ILAE, 1998; Duncan, 2010):

1. Volumetric T1-weighted sequence
2. Proton density, T2-weighted and fluid-attenuated inversion recovery sequences in oblique coronal and axial planes
3. Gradient-echo sequence.

The main role of MRI is the identification of structural abnormalities that underlie seizure disorders. The most common focal abnormality underlying temporal lobe epilepsy (TLE) is hippocampal sclerosis (HS), which may be identified reliably as it usually comes along with hippocampal atrophy on MRI (best seen on T1 weighed images in coronal axis), an increased T2 signal in coronal axis (Jackson et al., 1990) and a decreased T1 signal combined with disruption of the internal structure of the hippocampus as detected with inversion recovery (IR)-sequences (Jackson et al., 1993a) (refer to chapter 1.2.4.4.1 for more detail).

Other focal abnormalities which can be detected with MRI include cavernous angiomas (Farmer et al., 1988), low-grade tumours (Mohamed and Luders, 2000), and a range of malformations of cortical development such as focal cortical dysplasia, heterotopia, polymicrogyria and schizencephaly (Lee et al., 1998; Yagishita et al., 1997). With improvements in MRI hardware, signal acquisition techniques and postprocessing methods the rate of patients with cryptogenic epilepsies has significantly decreased. In particular there are different ways of using a voxel-based analysis of MRI data in order to identify subtle structural changes, such as malformations of cortical development (Focke et al., 2008) that might not be evident during visual inspection of the scans (Focke et al., 2009). In summary between 10 to 30% of patients with a previously unremarkable conventional MRI scan may benefit from such a way of analysis; a cautious interpretation is required because of the possibility of false positive results (Salmenpera et al., 2007).

As suggested by the International League against Epilepsy, structural imaging with MRI is not necessary in case of generalized epilepsy (such as absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy) and in case of benign focal epilepsy of childhood, as scans usually

do not show any abnormalities and the majority of patients becomes seizures free when treated with antiepileptic medication (Commission on Neuroimaging of the ILAE, 1997; Commission on Neuroimaging of the ILAE, 1998). However, using special protocols and advanced imaging techniques it has been shown that even in these patients, structural abnormalities are present suggesting focal abnormalities even in generalized epilepsies, which may be of prognostic or therapeutic relevance (Vollmar et al., 2011; Woermann et al., 1999; Woermann et al., 1998b).

1.3.2. Principles of MR

1.3.2.1. Nuclear magnetic resonance

Magnetic resonance imaging relies on the phenomenon of nuclear magnetic resonance (NMR) which depends on the interaction of nuclei, which under normal conditions spin about themselves and, in the presence of a magnetic field, have a magnetic moment. Nuclei of many atoms with a nuclear “spin” can behave as simple magnetic dipoles.

In the human body hydrogen nuclei, which consist of a single proton, are by far the most common nuclei; and typically it is hydrogen ions which are measured during MRI.

The concept of nuclear magnetic resonance was discovered by Block and Purcell in the 1940s, while Lauterbur and Mansfield described its application in imaging in the early 1970s.

In the absence of a strong magnetic field hydrogen spins within the human body are oriented randomly and their different magnetic moments tend to cancel each other out. When a strong magnetic field, such as occurs in an MRI scanner, is applied, nuclei of atoms with a so called “nuclear spin” can assume two different states: 1. In a high-energy state nuclei are oriented against the applied magnetic field (anti-parallel) while 2. In a low-energy state nuclei behave as if they were aligned with the applied field (parallel) (Jezzard et al., 2001). There will always be more protons in the parallel state than in the anti-parallel state, which results in the so-called net magnetization (M_0).

The net magnetization is represented by a vector with a longitudinal component parallel to the magnetic field and a transverse component perpendicular to the magnetic field. The longitudinal component as a measure of number of spins in the parallel and anti-parallel direction reflects the

strength of the external magnetic field (B). Normally, the transverse components are evenly distributed and tend to cancel out, so that only the longitudinal components are present.

1.3.2.2. Spin excitation

While the main magnet of the MRI scanner is necessary to create the net magnetization (with its static magnetic field), an additional component - an excitation/ reception coil - is needed to measure changes in the net magnetization. Transitions between the low and high energy level are accompanied by absorption or emission of energy, which is proportional to the applied field and which lies within the range of radiofrequency (RF).

During excitation an additional magnetic field is applied via the MRI scanner which oscillates at the precession frequency of the spins of interest (excitation or radiofrequency pulse). As the pulse frequency matches the spin frequency, some spins will absorb energy from the excitation pulse and take a higher energy state. Protons will only change state if the radiofrequency pulse is applied at the specific rotational frequency at which the protons are precessing for any given element (known as Larmor frequency). However, after the excitation ceases, spins at the higher energy state will return to the lower, stable energy level, which is accompanied by a release of the absorbed energy as a radio frequency wave which decays over time. The resulting MR signal can be measured as a change in voltage (reception).

Although an individual proton's energy level is determined by the radiofrequency pulse applied, the signal emitted is dependent on the behaviour of a population of protons. In the case of in vivo MRI, the water content varies between particular tissues providing MR contrast between tissue types.

1.3.2.3. Relaxation times

With the end of the excitation pulse the amplitudes of the longitudinal and transverse components of the net magnetization start to change over time.

1.3.2.3.1. T1 relaxation

The longitudinal component experiences an exponential recovery (as spins return to the parallel state). The rate at which this recovery occurs for a given substance depends on a time constant known as T1, with T1 as the so-called relaxation time. The spin-lattice relaxation process refers to the fact that the spin relaxation depends very much on the interaction of the spins with the surrounding compartment (=lattice). Substances with a very long T1 value such as cerebrospinal fluid (T1=4000 ms at 1.5T) will regain net magnetization very slowly, while substances with a short T1 such as white matter (T1=600 ms at 1.5T) will recover much more rapidly.

1.3.2.3.2. T2 relaxation and T2 sequences*

The transverse component of the net magnetization will experience an exponential decay. This is due to a loss in coherence (synchrony) between spins. This reduction in coherence is caused by two main factors: Firstly, spins affect each other (spin-spin interactions), so that some of them precess more rapidly than others; the time constant which underlies the rate of transverse decay caused by this spin-spin interactions is known as T2. Secondly, local inhomogeneities within the magnetic field additionally contribute to the loss of coherence. Both factors, spin-spin interactions and local magnetic field inhomogeneities, are characterized by the decay constant T2*, which is the basis for functional MRI, while T1 and T2 are crucial for structural MRI. Time to echo (the time from the RF pulse to signal transmitted from the tissue) and TR (repetition of the RF pulse) should be long enough to allow T1 to have completely elapsed in a T2 sequence.

1.3.2.4. Spin and gradient echo pulse sequences

Spin echo

In magnetic resonance, a spin echo is the refocusing of spin magnetization by a pulse of resonant electromagnetic radiation, an effect which was first explained by Erwin Hahn in 1950 (Hahn, 1959). The spin echo sequence is routinely used in MRI and involves the use of a second 180° RF pulse to refocus the dephasing of nuclei which occur due to inhomogeneities in the

magnetic field: In the basic sequence a 90° pulse is used to flip the average magnetic moment into the horizontal (x-y) plane (transverse magnetisation along the x axis). Owing to local magnetic field inhomogeneities, some spins slow down (because of lower local field strength) while others speed up (because of higher local field strength) which in summary causes the signal to decay. At time t ($TE/2$), a 180° pulse is applied which 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° pulse was applied, leading to rephasing of the transverse magnetisation. Complete refocusing has occurred at a time $2t$ to produce a spin echo signal which can be detected. The time $2t$ is called the echo time TE. Although the 180° 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, 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.

Gradient echo

Echoes can also be formed without 180° pulses by using magnetic field gradients to rephase the protons dephased by the initial RF pulse. Again the rephasing leads to a signal which can be detected by the receiver coil, and this is called a gradient echo. The gradient echo sequence differs from the spin echo sequence in regard to 1. the flip angle, which is usually below 90° and 2. the absence of a 180° RF rephasing pulse.

Flip angles lower than 90° decrease the amount of magnetization tipped into the transverse plane leading to faster recovery of longitudinal magnetisation allowing the use of a shorter repetition time, TR (the time between consecutive 90° pulses)/ TE with a decreased scan time.

The advantages of low-flip angle excitations and gradient echo techniques are faster acquisitions, new contrasts between tissues and a stronger MR signal in case of short TR.

The flip angle determines the fraction of magnetization tipped in the transverse plane (which will produce the NMR signal) and the quantity of magnetization left on the longitudinal axis.

If the flip angle decreases, the residual longitudinal magnetization will be higher and the

recovery of magnetization for a given T1 and TR will be more complete. In contrast, the result of a lower flip angle excitation is a lower tipped magnetization.

Gradient echo imaging is therefore frequently used in fast imaging sequences but as single radiofrequency (RF) pulses and no 180° rephasing pulses are used, the relaxation due to fixed causes is not reversed and the loss of signal results from T2* effects. The resulting signal is T2*-weighted rather than T2-weighted which is susceptible to magnetic field inhomogeneities, caused by intrinsic defects in the magnet itself or susceptibility-induced field distortions produced by tissue or haemoglobin.

1.3.3. Image formation

The two main goals of NMR-imaging are spatial localisation and generation of contrasts between different tissues.

1.3.3.1. Spatial localisation

After the MR signal has been generated, that signal now needs to be used to differentiate between tissues with different characteristics. In order to illustrate the spatial distribution of different spin properties, a third component of the MRI scanner, coils for the generation of additional magnetic field gradients, is required. Lauterbur was the first to demonstrate that a superimposed magnetic field which varies linearly across space will cause spins at different locations to precess at different frequencies in a controlled fashion. Resulting changes in magnetization can be measured as a function of precession frequency (Lauterbur, 1989). When small magnetic field gradients are superimposed on the large homogenous static magnetic field of the imaging magnet (typically 1.5 or 3.0 T in clinical use) the positions of molecules along the smaller gradient field can be measured by looking at the differences in the resonance frequency. The resonance frequencies for different nuclei in a specific substance such as water are proportional to the applied field strength which consists of the large static magnetic field and the smaller field of the applied gradients. When applying gradients along two or three dimensions it is then possible to allow multi-slice imaging in two or three dimensions. In this

way imaging of the location of various resonating nuclei is possible. Magnetic field strengths are measured in units of Tesla (T) or Gauss (G).

K-space

The raw data of the MR signal which is collected in such way can be organized into a coordinate system which is the so called k-space. All points in k-space contain data from all locations in an MR image but contribute differently to the resulting image. Points near the centre of k-space contain most of the image intensity but 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, but have little effect on image contrast. In order to convert an MR signal from its frequency expression into its time expression a mathematical manipulation, the Fourier transformation is needed; to convert it back (time to frequency) an inverse Fourier transformation is required. This concept can get extended into two dimensions so that sets of different spatial frequencies can represent an image. The k-space representation follows a sine function, with the greatest intensity in the center and intensity bands of decreasing amplitude at the edges of k-space. Any image can be constructed using a two-dimensional inverse Fourier-transformation.

1.3.3.2. Image contrast

As described above, a nuclear spin, that has been excited to a high-energy level, can return (“relax”) to the low energy state. When this happens radiofrequency energy is emitted that can be detected by MRI. The spin-lattice relaxation process refers to the fact that the spin relaxation depends very much on the interaction of the spins with the surrounding compartment (= lattice). This is an exponential process with a constant rate, $1/T_1$, with T_1 as the so-called relaxation time. Over one T_1 period excited spins can regain 66% of their equilibrium state and 95% within three T_1 periods. If excitation pulses are applied more rapidly than is required for full relaxation, only a smaller proportion of spins can be excited with a concomitant decrease in resonance signal. This effect can be used for generating imaging contrasts, for example T_1 for a

water molecule varies depending on the surrounding compartments and therefore for different parts of the brain. By definition, 'contrast' refers to the degree of differentiation between substances with different properties. A change in contrast is possible either by altering the interval between successive excitations pulses (repetition time, TR) or changing the interval between the excitations pulse and data acquisition (echo time, TE). The amount of MR signal recorded is dependent on these parameters with TR influencing the amount of longitudinal recovery and TE the amount of transverse decay. For anatomical MRI, images are sensitive to contrasts dependent on the type, number and relaxation properties (such as T1/ T2) of atomic nuclei within a voxel. Most functional MR imaging is based on T2* contrasts. As with T2, T2* depends on the change of transverse magnetization, but in addition, inhomogeneities of the local magnetic field which cause changes in spin precession frequency also contribute. Within a brain voxel the homogeneity of the local magnetic field is determined by deoxygenated hemoglobin, so that T2* imaging is most relevant for functional MRI.

1.3.4. Quantitative MRI methods

1.3.4.1. MR-Volumetry

As temporal lobe epilepsy is the most common of the focal epilepsies quantitative methods such as MR-volumetry have mainly been optimized for parts of the limbic system such as the hippocampus (Jack et al., 1990), the amygdala (Cendes et al., 1993; Cook et al., 1992), fornix (Baldwin et al., 1994) and the entorhinal cortex (Bernasconi et al., 1999) or the whole temporal lobe (Lee et al., 1995). It requires side-to side ratios, but also absolute volume corrected for intracranial volume. This is of particular importance to strengthen lateralization of the epileptogenic zone as part of the surgical work-up. By visual inspection only volume asymmetries of 20 per cent or more can be reliably detected while using quantitative methods much smaller asymmetries can be seen (Van Paesschen et al., 1995). Therefore MR-volumetry is an important method for presurgical evaluation; especially in patients with TLE subtle unilateral hippocampal damage can be detected while one can assure that the contralateral hippocampus is intact. The big disadvantage is that it is user dependent and very time

consuming. A great amount of work is currently targeted to a reliable automatised of this quantitative method, results so far seem promising (Bonilha et al., 2009; Winston et al., 2013) (<https://hipposeg.cs.ucl.ac.uk/>).

1.3.4.2. T2-Relaxometry

Using T2-relaxometry it is possible to measure signal changes within a chosen anatomical structure such as the hippocampus or the amygdala, which are associated with hippocampal sclerosis (Bartlett et al., 2007; Jackson et al., 1993b; Woermann et al., 1998a). As T2 is an absolute measure it is a good method for identifying bilateral HS (Commission on Neuroimaging of the ILAE, 1997), and there is no need to correct for intracranial volumes.

1.4. FUNCTIONAL MRI

1.4.1. Introduction

In order to assess changes in brain function it was necessary to find a way to measure neuronal activity. Owing to the obvious disadvantages of directly measuring neuronal activity by implantation of electrodes inside the brain (invasive, costs etc.) and because of the limitations in spatial resolution in electrophysiological studies, in which electrical or electromagnetic activity was measured via detectors outside the scalp, the development of functional imaging (using indirect measures of neuronal activity) was a major milestone in understanding cerebral function.

Positron emission tomography (PET), introduced in the early 1980s was the first imaging technique to allow the measurement of quantities of radioactively labeled glucose, oxygen or other metabolites in normal human subjects. However, it is still considered to be invasive as it requires the injection of radio labeled tracers into the body.

In 1990 Ogawa and colleagues described the so-called blood-oxygenation-level-dependent (BOLD) contrast, which was based on the findings of Linus Pauling and Charles Coryell, who discovered the magnetic properties of oxygenated and deoxygenated hemoglobin, and which would come to be the basis of functional MRI (Ogawa et al., 1990; Pauling and Coryell, 1936).

1.4.2. Principles of functional MRI

1.4.2.1. BOLD contrast

Within red blood cells oxygenated haemoglobin is diamagnetic, so that it does not affect the surrounding magnetic field, while deoxygenated haemoglobin is paramagnetic, so that it causes distortions of the local magnetic field, resulting in reduced $T2^*$ values. As blood oxygenation varies spatially according to brain function, this variability is detectable with MRI (Ogawa et al., 1990).

The BOLD signal consists of several components: the neuronal response to a stimulus, neurovascular coupling, which reflects the relationship between the neuronal activity and the haemodynamic response, the haemodynamic response itself and detection of the MRI scanner.

The BOLD effect mainly represents synaptic activity, referred to as local field potentials (Logothetis, 2003). Normally, oxygenated haemoglobin is converted to deoxygenated haemoglobin at constant rates within the capillaries. With increasing neuronal activity (with increased oxygen and glucose usages in the relevant brain areas), after a short initial decrease in oxygen concentration, an increase in the supply of oxygenated haemoglobin above that needed by the neurons occurs (Villringer and Dirnagl, 1995), resulting in a relative decrease in the amount of deoxygenated haemoglobin, which suppresses the MR signal. Therefore this is paralleled by a decrease in the signal loss due to T2* effects and the fMRI signal increases in areas of neuronal activity. As neuronal activity and the associated metabolic demands end, blood flow decreases more rapidly than blood volume; this results in a greater amount of deoxygenated hemoglobin, which explains the so called “post-stimulus undershoot”, when the overall fMRI signal falls below the baseline (Figure 1.3). The dynamics of the neurovascular coupling mean that the BOLD response takes up several seconds to evolve and the time course of this response must be taken into account in the statistical analysis of fMRI time series. BOLD changes range within the order of only a few percent, which requires sophisticated image processing and analysis techniques to filter activations that actually reflect the correct BOLD signal and not noise.

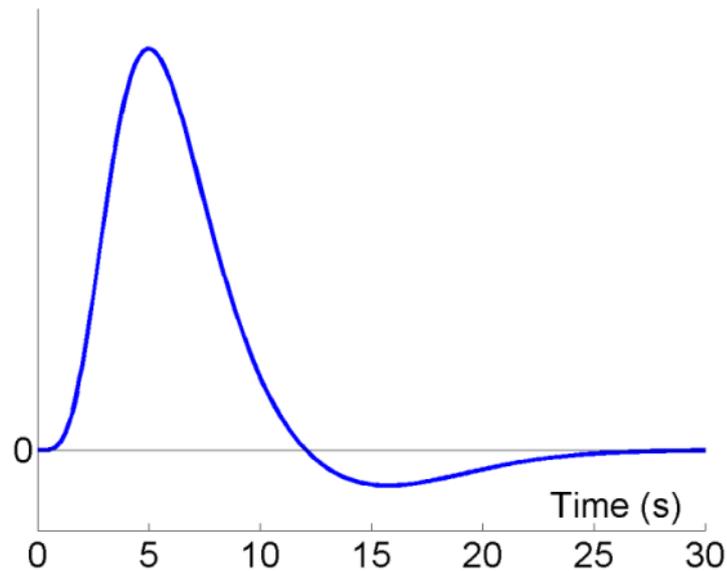


Figure 1.3 BOLD response

This figure shows a typical BOLD response to an impulse of neural activity as a function of peri-stimulus time. The peak response occurs at 4-6s, and is often followed by undershoot from approximately 10-30s. The precise shape of the BOLD response does vary across individuals, and across brain regions within an individual.

1.4.2.2. Echo Planar Imaging

In order to measure $T2^*$ changes efficiently it was necessary to employ pulse sequences which provide whole brain coverage and rapid acquisition. Together with Paul Lauterbur, Peter Mansfield discovered a technique called echo-planar imaging (EPI). 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 k-space after each radiofrequency (RF) pulse whereas a fast sequence such as EPI samples all lines of k-space after a single RF excitation. A single EPI could be acquired within a few milliseconds, so that in fMRI this allowed data from the entire brain to be collected every few seconds. EPI therefore greatly reduces imaging time and makes it an ideal sequence for dynamic MRI techniques (such as fMRI).

1.4.2.3. Spatial and temporal resolution – Technical issues

As the technique of fMRI matures it has become necessary to develop methods to improve its spatial and temporal resolution and to overcome technical limitations of BOLD fMRI.

With advances in hardware it was possible to significantly improve the spatial and temporal resolution by collecting smaller voxels and sampling the MR signal more frequently. Despite this, the spatial resolution of fMRI remains weak when compared to structural MRI. In animal models it has been shown, that by using ultrahigh-resolution MRI (9T or greater) spatial resolution can be increased significantly by collecting images with voxels less than 1/20 of one millimeter, although acquisition times were very long (Johnson et al., 2002) and these experimental conditions cannot easily be adapted for fMRI experiments in humans.

Another effective and less expensive way to increase spatial and temporal resolution besides increases in field strength or imaging time is to collect data more rapidly using a method called **parallel imaging**. With parallel imaging it is possible to increase the amount of data sampled per unit time and improve spatial resolution, or to reduce the amount of data sampled per coil and therefore improve temporal resolution. This can be done by using several detector coils to sample the brain simultaneously.

An important caveat in functional MRI is the problem of **magnetic susceptibility artifacts**, **signal losses** or **spatial distortions**, which can be observed as the result of microscopic gradients or variations in the magnetic field strength in areas near the interfaces of substances of different magnetic susceptibility, so typically in ventral brain regions close to interfaces between air, bone and brain tissue. These gradients cause dephasing of spins and frequency shifts of the surrounding tissues resulting in bright and dark areas with spatial distortion of surrounding anatomy. Susceptibility artifacts are present on every T2* weighted image and are worst with long echo times and gradient echo sequences. They are exacerbated by fast imaging methods and high-field scanning. Within the human brain, susceptibility artifacts are most commonly seen in the ventral frontal lobe (above the sphenoid sinus) and the lateral inferior temporal lobe (above the auditory canals). It is well documented that in particular these areas are crucial for many cognitive tasks including memory, emotion, language, attention and the

olfactory system. Many research groups have therefore made (and still do make) great efforts to develop methods to minimize these artifacts. These include the use of thinner slices (less than 1.5 mm), the use of higher-order gradients to correct for field inhomogeneities (Cho and Ro, 1992) and more recently so-called ‘single shot methods’, which provide much-improved signal recovery (Glover and Law, 2001; Song et al., 2002).

In addition to improvements in scanner hardware, advances in **experimental design** have also proved extremely valuable. For example, in order to improve temporal resolution of fMRI data a method called **interleaved stimulus presentation** (introducing **jitter** into the sampling of the hemodynamic response) is now routinely used for most experimental designs. In summary, jittering refers to the use of variable delays between the start of the sampling of brain volume images relative to the start of the stimulus presentation, a method by which the effective sampling rate can be increased. If all images are collected with the same delay from stimulus presentation all brain regions would be sampled at the same time points at every inter-stimulus interval, with a periodicity rate exactly equal to the TR. On the other hand, if one jitters the stimulus presentation time to image acquisition, then different time points would be sampled at each stimulus presentation. This can be achieved by using an inter-stimulus interval that is not a multiple of the TR (the so called fixed jittering scheme) or varying the inter-stimulus intervals (variable jittering) (Amaro and Barker, 2006). Using this technique, however, the number of trials within each condition is greatly reduced – therefore length of the experiments must be increased considerably.

The different experimental designs that are available and the ways in which they influence both, detection power and estimation efficiency will be discussed later in the chapter (refer to section 1.4.4).

1.4.2.4. Summary

In summary, fMRI provides many advantages compared to invasive methods in order to study changes in brain function, not only for research purposes but also as a clinical tool. It allows non-invasive mapping of brain functions with good spatial resolution; it is reproducible, does

not require radiation and is a universally available technology, with well established and widely-accepted analysis techniques. However, one has to be aware of the following caveats (Duncan, 2010):

1. The area of BOLD activation varies greatly in size, depending on thresholds used for display.
2. Regions of maximal BOLD activation do not always pinpoint the most eloquent cortical regions.
3. Areas that do not surpass the chosen threshold are not necessarily functionally inert.
4. Some areas showing activation might not be crucial to the execution of the task a patient is asked to perform.
5. Tasks/ paradigms may not accurately reflect functional ability.

1.4.3. Statistical analysis of fMRI data

Using fMRI, functionally specialized brain responses can be identified by characterizing functional anatomy and disease-related changes. In fMRI experiments inferences are made about differences in regional brain activity between different conditions or states. A number of different packages exist for carrying out the required statistical steps including statistical parametric mapping (SPM) (Friston et al., 1995). The analysis of fMRI data includes several steps, which can be divided into: 1. Spatial processing; 2. Estimation of the parameters of the statistical model; 3. Drawing inferences about the acquired parameter estimates regarding differences in regional brain activity between different conditions or states with appropriate statistics.

The analysis of fMRI data begins with a series of preprocessing steps, the aims of which include correcting for motion and ensuring that the data conforms to a known anatomical space.

1.4.3.1. Spatial preprocessing

1.4.3.1.1. Realignment

In all fMRI studies, changes in signal intensity over time – from any voxel - can occur from head motion, which is a serious confound, often amounting to several millimeters even in cooperative subjects. Therefore the first preprocessing step involves realigning the imaging time series to a common reference frame (usually the first or an average of all scans in the time series) to correct for subject movement during scanning. This removes variance from the time series which would either be attributable to error or to evoked effects, in the case of stimulus-correlated motion.

1.4.3.1.2. Normalisation

After realignment the data is transformed into standard anatomical space. The first step is to use the functional mean image of the series (produced during the realignment step), or another co-registered image (i.e. T1-weighted image), and estimate some warping parameters to map it onto a template (i.e. SPM EPI template, or a scanner-specific template) which already conforms to the standard anatomical space. Currently the two most important systems are the Talairach atlas (Talairach and Tournoux, 1988) and the Montreal Neurological Institute (MNI) space (Evans et al., 1993). The resulting transformation parameters are then applied to every image in the time course.

This is known as spatial normalisation and allows group analyses to be performed and permits data reporting within a standardized reference co-ordinate system.

3.4.3.1.3 Spatial Smoothing

Spatial smoothing is a process by which data points are averaged with their neighbours' in a series, such as a time series, or image. This has the effect of a low pass filter, so that high frequencies of the signal are removed from the data while low frequencies are enhanced. This results in blurring the sharp "edges" of the "smoothed" images. The approach of spatial smoothing is commonly used in fMRI studies. This can be justified by the fact that fMRI data

show spatial correlations due to functional similarities of neighboring brain regions and the blurring of the vascular system.

The standard procedure is employed by convolving the fMRI signal with a Gaussian function of a specific width. Smoothing in SPM is carried out by applying a Gaussian kernel of known width with the shape of a normal distribution curve to each voxel. The size of the Gaussian kernel defines the "width" of the curve which determines in turn how much the data is smoothed. The width is not expressed in terms of the standard deviation, but with 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. Spatial smoothing is associated with several benefits, such as improvement of the signal to noise ratio leading to increased sensitivity, improving validity of the statistical tests by adjusting the error distribution to a more normal one and finally better accommodation of anatomical and functional variations between the various subjects, which is necessary in order to perform comparisons across subjects so that homologies in functional anatomy that exist over subjects may be detected.

The following disadvantages need to be considered carefully: reduction of spatial resolution of the data, increment of edge artifacts, merging of activations peaks, which are less than twice the FWHM, extinction of smaller activations and finally mislocalisation of activation peaks, because of unavoidable shifts of activation peaks.

1.4.3.2. The general linear model (GLM)

The GLM is a statistical linear model, which is often used to analyse fMRI data. It may be expressed as a matrix:

$$Y = XB + U,$$

where Y describes a data matrix with a series of multivariate measurements; X might be a design matrix (with one row per observation (i.e. each scan) and one column per model parameter), while B is a matrix that contains parameters which are usually to be estimated to best fit the data and U is a matrix containing errors or noise, which usually follow a multivariate normal distribution.

The general linear model incorporates a number of different statistical models: ANOVA, ANCOVA, MANOVA, MANCOVA, ordinary linear regression, t-test and F-test. The general linear model is a generalization of multiple linear regression models to the case of more than one dependent variable. With the GLM, hypotheses can be tested in two different approaches, as multivariate tests or as several independent univariate tests. In multivariate tests the columns of Y are tested together, whereas in univariate tests the columns of Y are tested independently, i.e., as multiple univariate tests with the same design matrix.

An important application of the GLM appears in the analysis of multiple brain scans in scientific experiments, where Y contains data from brain scanners and X contains experimental design variables and confounds. It is usually tested in a mass univariate way as applied to the work presented here, and is often referred to as statistical parametric mapping (SPM) (Friston et al., 1995).

Essentially, 'SPM' is testing for experimentally-induced effects at each voxel independently and simultaneously applying the GLM. The design matrix X is displayed graphically by SPM and consists of a number of columns; each column corresponds to some effect that has been built into the experiment. At first an analysis of variance is performed separately at each voxel. In a next step t-statistics are performed from the results of this analysis and a Z-score equivalent for the t-statistic is calculated, before producing an image of this t-statistic, i.e. a statistical parametric map. The Z-scores are the numbers from the unit normal distribution that would give the same p-value as the t-statistic. Finally, an inference is drawn from this statistical map, so that voxels where an effect is present can be located while guarding against false positives; the significance value takes account of the multiple comparisons in the image (refer to section 1.4.3.3).

The 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.

As the data are correlated from one scan to the next, scans cannot be treated as independent observations. The GLM accounts for these autocorrelations by imposing a temporal smoothing function on the time-series.

1.4.3.3. Random Field Theory

The null hypothesis for a particular statistical comparison assumes that no change in activation can be observed anywhere in the brain. Because each SPM map consists of many statistics (i.e. one for each voxel) even if the null hypothesis is true, one can be sure that some of these will appear to be significant at standard statistical thresholds such as $p < 0.05$ or $p < 0.01$, giving a certain number of false positives. This is the problem of multiple comparisons, which requires a correction for the number of statistical tests that have been performed.

One of the common methods for dealing with this problem is the Bonferroni correction: For the Bonferroni correction the p-value threshold is divided by the number of tests performed. However, in most cases this will be considered as a too conservative method, as for most SPMs, the Z scores at each voxel are highly correlated with their neighbours'. Instead the correction used by SPM is based on the Gaussian field theory, which takes into account the fact that neighbouring voxels are not independent by virtue of the spatial smoothing performed. This correction is similar to a Bonferroni correction for multiple comparisons but less conservative provided that the data are sufficiently smooth.

In cases where activation has been predicted a priori in a particular brain region, an appropriate search volume can be specified and an appropriate correction can be made for this volume (small volume correction).

1.4.4. Experimental designs

Most commonly used fMRI experimental paradigms are blocked designs, where events are concentrated in time or event-related designs, whereby consecutive events are separated by extended or random intervals. More recent work has shown that combining both approaches into one design (with the characteristics of blocked and event-related designs) can provide

substantial improvements in both detection power and estimation efficiency (Liu, 2004; Liu et al., 2001).

1.4.4.1. Block designs

By far the most commonly used fMRI experimental designs are blocked paradigms. During a blocked paradigm a series of trials in one condition is presented for a certain epoch of time (with long continuous periods (10-30 seconds) for each condition). The signal gained during one blocked condition can then be compared to other blocks involving different task conditions. A typical study will consist of activation and rest blocks, to allow the contrast for fMRI signal between task blocks. Each block typically ranges in duration from 15 to 60 seconds. Therefore, during a blocked language production task we are looking for regions of the brain showing greater activation during task blocks compared with rest blocks, when subjects are passively viewing words 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 during the rest condition. The advantage of blocked designs is that they are very efficient in detecting differences between two conditions, however they offer less flexibility in the experimental design required for studying more complex cognitive functions.

1.4.4.2. Event-related designs

In the early 1990s the advent of event-related designs was a major breakthrough in fMRI experimental design. Using event-related designs it was now possible to present individual trial events in an unpredictable, randomized order. This can be arranged in two different ways. In slow event-related designs the trials are widely separated in time (12-14 seconds), which allows the HRF signal to return to baseline between the different events (Bandettini and Cox, 2000). In rapid event-related designs various types of trials can be presented rapidly (every 2 seconds) (Dale and Buckner, 1997). However, analysis of such rapid event-related designs is more complex, requiring careful counterbalancing of trial sequences or deconvolution of the fMRI signal with “jittered” presentations with irregular intervals.

For the development of event-related designs the following characteristics of the BOLD signal/fMRI data were crucial:

1. Technical advances enabled rapid data acquisition, so that the signal of interest can be sampled frequently and repeatedly, and that the data can be acquired over the time course of an individual event.

2. Sensitivity of the signal

Even very brief stimuli followed by brief periods of neural activity elicit measurable signal changes, despite the delayed and prolonged nature of the time course of the haemodynamic response.

3. Linearity of the signal

In their initial study Dale and Bruckner showed that not only could a reliable signal be detected even when successive stimuli were presented rapidly (Dale and Buckner, 1997), but also that the acquired response to this signal summated in a nearly linear fashion, so that the individual responses to sequential events could be estimated.

In summary, although event-related designs are clearly less powerful in detecting activations than block designs and may be more vulnerable to alterations in the HRF (due to pathology for example), they have several valuable advantages. In particular, for example, in evaluation of memory function it is possible to categorize the subject's performance into correct and incorrect responses so that many specific questions can be addressed (a subject's performance during a memory test can be taken into account for example etc.).

1.4.4.3. Voxelwise versus region of interest (ROI) approach

Most neuroimaging experiments can be considered hypothesis-driven, as there are certain expectations as to which kind of differences between different conditions will be observed and which will then be verified (or excluded) with the appropriate statistical tests. More recently data-driven approaches have been implemented that do not require any a priori assumptions about expected results and which require more sophisticated statistical techniques such as independent component analysis (ICA).

For hypothesis-driven analyses there are two different approaches with respect to which specific brain areas will be activated: the voxelwise approach and the region of interest (ROI) approach. In brief, no prior assumptions regarding the location of specific brain activation are needed for the voxelwise approach, as statistical comparisons between various conditions of interest are tested on a voxel-by-voxel basis. Again, this method requires transformation of every subject's data into standard space in order to enable averaging across different brains (refer to section 1.4.3.1). The great advantage of this approach is that it enables the investigation of the whole brain (or a specifically selected volume) without any detailed hypothesis regarding the expected location of activations.

With the ROI approach novel hypotheses can be tested in previously described brain regions, whereby definition of the chosen regions can be based on anatomical criteria (i. e. the hippocampus in memory studies), but may also be activation based.

1.4.4.4. Group analyses

Statistical inferences about groups of subjects may be of two types: fixed or random-effects analyses. Second level fixed-effects and random-effects analyses can be carried out on the first-level statistic maps in order to test for differences in activation between different subject groups. A fixed-effects analysis shows results specific to the particular subjects at the time of scanning and is drawn from the effect size relative to the within subject variability. The effect size is averaged across subjects to provide a representative mean across subjects. This type of analysis is limited by the fact that an effect size may be primarily driven by only a few subjects.

In contrast, 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 kind of analysis is not at risk of being biased by strong effects in a subset of subjects. Therefore, a random-effects analysis allows inferences to be drawn regarding the population from which the sample of subjects was drawn.

Random effects analyses were used for all the second level analyses performed in this thesis.

1.4.5. Functional connectivity

In recent years functional connectivity has been increasingly used to estimate the relationship between different sites of activation in the brain, aiming to illustrate a more sophisticated picture of the functioning networks within the brain. In brief, connectivity analysis is based on either similarities in time courses or relationships between activation levels between different brain regions. It is defined as a statistical dependency or correlation between remote regions of BOLD signal change, x and y ; its relationship can be described by a correlation coefficient (refer to chapter 1.5.3 for clinical application).

Note: Parts of this chapter have been summarized from the textbook “Handbook of Functional Neuroimaging of Cognition”, edited by Roberto Cabeza and Alan Kingstone, published by The MIT Press, 2006.

1.5. FUNCTIONAL MRI APPLIED TO EPILEPSY

1.5.1. Background

Cognitive impairment is a frequent comorbidity in focal epilepsies and has a major impact on quality of life in patients with epilepsy. Cognitive deficits can either result from the underlying disease as a consequence of seizures or interictal epileptic activity, or can be caused by adverse effects of antiepileptic drugs (AED) (Helmstaedter, 2002).

In temporal lobe epilepsy (TLE), typically material-specific memory impairment and naming difficulties have been reported (Helmstaedter, 2004; Hermann et al., 1991) and can be observed in some patients even with epilepsy of recent onset (Witt and Helmstaedter, 2012). This supports the hypothesis that cognitive problems cannot fully be explained by adverse effects of medication. In general, patients who are refractory to AED treatment are at higher risk of suffering from cognitive impairment.

In patients with medically refractory TLE, anterior temporal lobe resection (ATLR) is an effective and safe treatment option, leading to seizure freedom in up to 60-70% of these patients (de Tisi et al., 2011; Wiebe et al., 2001). Unfortunately this procedure may also be complicated by a decline in language and memory abilities as well as emotional disturbances. Therefore an important emphasis during presurgical evaluation is to identify the epileptic brain tissue that has to be removed for the patient to become seizure free (Rosenow and Luders, 2001). At the same time neuropsychological deficits must be avoided which requires accurate localisation of the brain areas that are responsible for motor, language and memory function but also for emotional processing.

In recent years, epilepsy surgery has been carried out earlier in the course of the disease (and therefore in a younger patient population) and so the potential benefits must be carefully weighed against the potential risks of decline. In order to successfully identify eloquent brain areas and guide resection a range of techniques are employed. Important diagnostic tools for presurgical cognitive evaluation are detailed neuropsychological assessment and until recently the intracarotid amytal test (IAT), which has been increasingly replaced by assessment with fMRI over recent years.

The IAT is still routinely used in some epilepsy centres assessing the capacity of the contralateral temporal lobe to maintain useful memory function and to lateralise language function. During the procedure sodium amytal is injected into one carotid artery, inactivating the corresponding hemisphere for 10 minutes mimicking the effects of surgery on the medial temporal structures. During this time the patient's language and memory skills are tested (refer to chapter 1.8.3.1.5 for more detail).

There are considerable disadvantages of this method including costs and the fact that it is an invasive procedure with potentially serious complications such as stroke. There are also doubts regarding its reliability and validity in predicting postoperative amnesia (Baxendale, 2002; Baxendale et al., 2007). In comparison with standardised neuropsychological cognitive tests that are widely used, test protocols, stimuli and administration of amytal are highly variable between institutions, leading to variations in results (Baxendale, 2002). In particular, the IAT provides poor ability to predict verbal memory decline as deactivation of the language dominant hemisphere causes increased errors on verbal memory testing (Kirsch et al., 2005).

In recent years, fMRI has proven a valid and reliable tool to investigate cognitive functions during presurgical assessment of patients with TLE, which has increasingly replaced invasive techniques as it is non-invasive, cheaper and repeatable. Compared to standard neuropsychological assessment, it also has the potential to provide additional information about the lateralisation and localisation of language and memory function and specifically allows evaluation of functional reorganisation processes (over time). There is also an increasing interest in its possible role for identification of the eloquent cortex which needs to be spared during surgery, and prediction of postoperative cognitive changes.

1.5.2. Cognitive fMRI

1.5.2.1. Methodological considerations and limitations

As discussed above invasive methods have been routinely used to identify the eloquent cortex in the past: the IAT was widely used to lateralise function, and electro-cortical stimulation mapping (ESM) is still the gold standard to localise eloquent cortex. In the last years, however,

non-invasive methods, predominantly fMRI, have been established for this purpose (Duncan, 2009; Haag et al., 2008). Obvious advantages of non-invasive methods are patient safety and tolerability. In addition they can be applied in healthy volunteers for research purposes allowing systematic comparison of different study groups. There are, however, some methodological aspects that need to be considered.

Functional MRI, like most other non-invasive imaging tools, is an activation based method. The rationale behind this is that if a certain cognitive function is used, relevant brain areas will be activated. Blood flow will increase in these areas to compensate for the higher demand of oxygen. In fMRI, this is displayed by the BOLD contrast which represents the regional changes in blood flow over time (refer to chapter 1.4.2 for more detail). To be able to get a reasonable temporal resolution echo planar imaging (EPI), a fast MRI sequence, is used. Functional MRI has a high spatial resolution which, in principal, allows very good localisation of areas in the brain that are involved in certain tasks. However, which areas will be activated depends on the fMRI paradigm. It is important to assure sufficient task performance as only then activation can be accurately interpreted in relation to function. A differential pattern of activation between patients and normal subjects is only interpretable if patients are performing the task adequately (Price and Friston, 1999). This needs to be considered in fMRI paradigm design, especially when applying fMRI to patient groups in which cognitive performance can vary considerably. It is mandatory to make sure that participants understand and follow task instructions. However, during fMRI the subject's performance cannot easily be assessed. The majority of fMRI paradigms applied to date uses covert tasks or assesses performance with a joy-stick or button press response. This can restrict the variety of possible responses that can be used in an fMRI paradigm. More recently developed devices such as MRI-compatible microphones can now be used to monitor speech during fMRI. For simple paradigms which only require basic analysis, e.g. as used for clinical language fMRI, scanner implemented software for online data analysis can be employed to show activation patterns during the scan.

In addition, one must be aware of differences in the questions being asked by cognitive neuroscientists and clinicians, which can lead to different approaches to data analysis. By

looking at groups of matched controls, or patients and controls, performing the same task neuroscientists aim to determine which brain regions are commonly activated across the group. The emphasis is on avoiding false positive results (Type I errors) which requires conservative statistical thresholds, which in general may lead to an under representation of brain areas truly involved. Clinicians on the other hand are considering individual patients where the priority is to identify all brain regions involved in a task, and therefore aim to avoid false negatives (Type II errors). Less stringent statistical thresholds are required and thresholds used may need to vary on an individual basis (Thornton et al., 2009).

Most cognitive tasks do not only rely on one particular function. If visual stimuli are presented, activation of visual cortex can be expected. If the subject is asked for a motor response, motor activation can be expected. To differentiate between activation related to a certain function and other activation, neuroanatomical information (e.g. Broca's area, Wernicke's area for language; medial temporal lobe structures for memory) may be used to interpret results. Further, most fMRI paradigms include other tasks with the aim to control for irrelevant activations; only activation in the 'real' task that exceeds activations during the control task is considered.

The specific brain areas which are displayed as 'active' vary substantially with different statistical thresholds. A high threshold reduces the sensitivity in detecting activations as well as the extent of activation clusters while a low threshold increases the risk of false-positive activations.

In the specific case of epilepsy, seizures and interictal epileptic activity as well as AEDs may have an effect on state or interaction between different brain regions and therefore additionally alter fMRI results (Jansen et al., 2006).

In summary, caution is needed in the interpretation of the results. Firstly, areas activated by a particular fMRI paradigm are not necessarily essential for performing a task. Secondly, not necessarily all areas involved in a task will be activated by one particular fMRI paradigm; in addition the region of maximal BOLD activation does not always pinpoint the most eloquent cortical regions and vice versa areas that do not surpass the chosen threshold are not necessarily

functionally inert. Finally areas of BOLD activation vary greatly in size depending on thresholds used for display, while extent and magnitude of activation seen in a task do not necessarily relate to the competence with which the task is performed (Duncan, 2010). One must also bear in mind the limitation of fMRI techniques especially in the temporal lobes, such as lower MRI signal to noise ratio due to susceptibility artifacts and signal loss in areas that are close to larger blood vessels and bone tissue (refer to section 1.5.2.4.3).

1.5.2.2. Motor and sensorimotor functions

The localisation of the primary sensori-motor regions using fMRI is well established in most centres. Simple motor tasks (e. g. foot and finger tapping) usually give us very strong and reliable activation in single subjects and are relatively easy to perform. Unilateral active or passive movements or passive somato-sensory stimulation lead to reliable activation in the contralateral central/ peri-central region (Bittar et al., 1999; Guzzetta et al., 2007; Yetkin et al., 1997). In epilepsy, specifically when an epileptogenic lesion is in close proximity of the primary motor cortex fMRI has proven to be a useful, non-invasive tool and may:

- 1) Estimate the risk of postoperative motor deficits;
- 2) Together with results of other functional and structural imaging methods, provide valuable information prior to invasive recordings including electro-cortical stimulation (De Tiege et al., 2009).

1.5.2.3. Language functions

1.5.2.3.1. Assessing language functions with fMRI

During evaluation for epilepsy surgery, fMRI is the most frequently applied non-invasive method for language imaging (Haag et al., 2008). The primary aims of preoperative language fMRI are lateralisation and localisation of language functions and to use this information to predict postoperative complications and advise patients accordingly. Clinically applied paradigms focus on the classic language areas such as Broca's area (inferior frontal gyrus (IFG)) and Wernicke's area (supramarginal gyrus (SMG), superior temporal gyrus (STG)). Covert

lexical word generation (i.e. thinking of words starting with a given letter) is an expressive language task that reliably activates the IFG (Figure 1.4), corresponding to Brodmann's area 44 and 45. Fluency tasks are usually less reliable at identifying receptive language areas in the dominant temporal lobe. Posterior temporal lobe activation (SMG, STG), corresponding to Brodmann's area 20, 21 and 39 can be achieved by more receptive tasks, e.g. semantic decision tasks (i.e. which word does not match the others: shirt, gloves, shoes, rose?) or story listening tasks. Also reading tasks usually activate the superior temporal cortex extending to the SMG; these "receptive" tasks are less strongly lateralising than verbal fluency tasks.

Most of the time, these tasks are performed without out of scanner performance monitoring (covertly); however, numerous studies have replicated these activations in both, healthy control subjects and patient populations. Within-subject reproducibility has also been demonstrated, although frontal activations have been replicated more reliably compared to temporo-parietal activations (Fernandez et al., 2003).

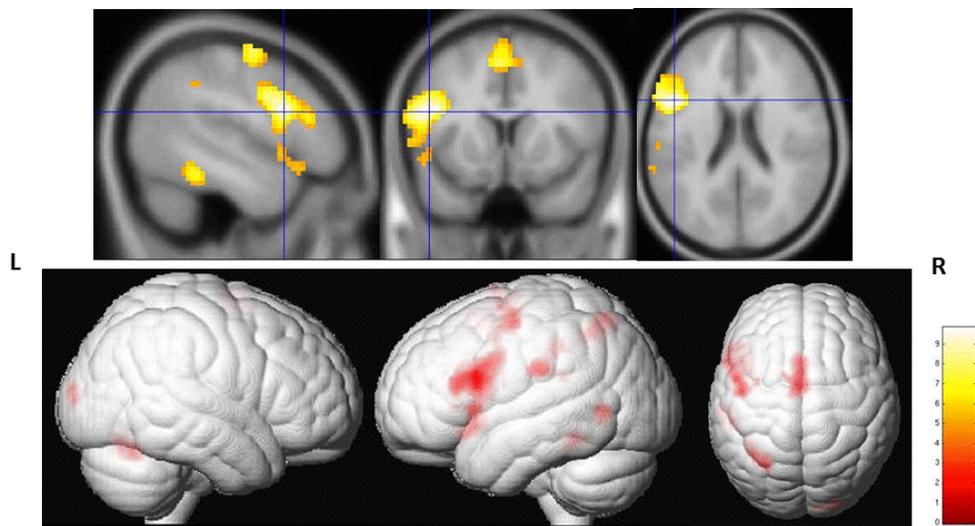


Figure 1.4 Language fMRI activations during covert lexical fluency

Language fMRI activations during covert lexical fluency in a single subject at $p=.05$, family wise error; strong activation can be seen in the left IFG, as well as in the left MFG and SFG.

For the clinical application it is essential that subjects are able to perform the tasks; it has been shown that these language tasks can reliably be applied to patients with a wide range of

cognitive abilities (Weber et al., 2006b). Verbal fluency and verb generation tasks not only provide us with usual language related activations (as they are not pure language tasks), but also require executive processing and involvement of verbal and working memory, resulting in activation patterns seen in the middle frontal gyrus (MFG) corresponding to Brodmann Areas 46 and 49.

Most language paradigms are presented as blocked designs in order to detect regions of the brain showing greater activation during a task compared with rest. The major advantage of blocked designs is that they very reliably detect differences between two conditions (task versus rest); however, they often lack sensitivity in detecting activation when studying more complex cognitive tasks (e. g. memory tasks) (refer to chapter 1.4.4 for more detail).

As a measure of laterality a so called “Laterality index” is calculated by quantifying the degree of asymmetry: $(A) = (L - R) / (L+R)$. L and R represent the strength of activation for the left (L) and right (R) sides respectively, based on the number of activated voxels for the whole hemisphere or using regions of interest (ROIs) targeted to known language areas (Gaillard et al., 2002). As these methods are very much dependent on the various thresholds chosen, more recent methods are based on calculation of an overall weighted bootstrapped lateralisation index, taking thresholds into account (Wilke and Lidzba, 2007; Wilke and Schmithorst, 2006).

1.5.2.3.2. Language fMRI in epilepsy

Numerous different language paradigms have been applied to group studies, which may partly explain some differences in the results between studies (Haag et al., 2008; Woermann and Labudda, 2010). Many studies comparing language fMRI with the classic invasive methods in particular the IAT showed that fMRI is a valid method for identifying the language dominant hemisphere (Dym et al., 2011; Janecek et al., 2013; Woermann and Labudda, 2010) with an overall concordance of 90% between the two techniques. Functional MRI seems more likely to elicit bilateral language representation compared to the IAT; however, the meaning of this finding for language function after surgery is not fully understood (Janecek et al., 2013). Concordance between fMRI and the IAT is the highest for right TLE patients with left language

dominance and for frontal language areas, and the lowest for left TLE patients with left language dominance (Benke et al., 2006). Atypical language dominance on fMRI (Janecek et al., 2013) and inter-hemispheric language dissociation (Lee et al., 2008) is correlated with IAT/fMRI discordance. This suggests that fMRI may be more sensitive than the IAT or cortical stimulation to map the whole network involved in language processing, but is less specific at an individual level as compared to cortical stimulation.

From a clinical perspective in patients with focal epilepsy it is advisable to use a combination of expressive and receptive fMRI tasks (e. g. verbal fluency, reading comprehension, auditory comprehension) to reduce inter-rater variability and help to evaluate language laterality (Gaillard, 2004). 90% of the healthy population have left-sided language representation, while the remaining 10% show atypical (i.e. bilateral, right-hemispheric) language representation. Patients with epilepsy have a significantly higher incidence of atypical language representation (16% bilateral, 6% right-lateralised, 78% left-lateralised) which is additionally influenced by variables such as earlier age of epilepsy onset and the underlying pathology (Springer et al., 1999). It has been speculated that an early insult to the originally language dominant hemisphere may lead to reorganisation of language function to homotopic regions in the contralateral hemisphere. At the same time it is not ultimately necessary that lateralisation for different language functions (i. e. receptive and expressive) within one patient is the same (“crossed” language lateralisation) (Berl et al., 2005; Gaillard et al., 2007). Temporal lobe foci have wide-ranging effects on the distributed language system such as TLE patients are more likely to have atypical language representation in Wernicke’s area compared with a frontal focus, while the effects of a frontal lobe focus appear restricted to anterior rather than posterior language processing areas (Duke et al., 2012). There is an increase and posterior shift of language related activation in the right inferior frontal gyrus after left hemisphere injury. However, activations in left inferior frontal gyrus remain in the same location (Voets et al., 2006). There is also evidence that the hippocampus itself may be an important factor for establishing language dominance as patients with left hippocampal sclerosis compared to patients with left frontal and lateral temporal lesions had a higher incidence of atypical language

representation (Weber et al., 2006a). Language areas activated for abstract and concrete words are also different for TLE patients, with or without HS, suggesting that HS is associated with altered functional organization of cortical networks involved in lexical and semantic processing (Jensen et al., 2011). In pediatric patients with lesions in close proximity to Broca's area, expressive language function could be demonstrated in the peri-lesional cortex (Liegeois et al., 2004). Pahs and colleagues explored whether neuroanatomical asymmetries linked to human language dominance were likely to contribute to atypical language representation. In children with focal epilepsy and left sided underlying pathology they demonstrated that the length of the planum temporale in the right hemisphere was the main predictor of language lateralisation (compared to other epilepsy-related factors) with a longer contra-lesional planum temporale being associated with a greater likelihood of atypical language dominance (Pahs et al., 2013). In summary, apart from age at disease onset, other factors such as an underlying structural lesion, neuroanatomical substrates as well as the underlying pathology of the lesion seem to contribute to the reorganisation process of language functions, which needs to be taken into account for the clinical interpretation of such data (Wellmer et al., 2009). In patients with left TLE, Janszky and colleagues found that atypical language representation was associated with increased interictal epileptic discharges (Janszky et al., 2006) which suggest that fMRI might also be suitable for investigation of dynamic changes in cognitive networks (Monjauze et al., 2011). Also, atypical language lateralization in the right hemisphere may shift back to the left hemisphere in seizure free patients after left selective amygdalo-hippocampectomy (Helmstaedter et al., 2006). There is increasing evidence that pre- and postoperatively reorganisation of language function can occur to the contralateral but also within the ipsilateral hemisphere (Noppeney et al., 2005).

Language fMRI may, however, be useful in patients other than those who are undergoing pre-surgical evaluation. In patients with generalised epilepsy, fMRI showed that language function was impaired as represented by reduced suppression of the default mode network, an inadequate suppression of activation in the left anterior temporal lobe and the posterior cingulate cortex and an aberrant activation in the right hippocampal formation (Gauffin et al., 2013). In primary reading epilepsy, a study combining EEG and fMRI showed specific regions that were involved

in seizure generation during reading (Salek-Haddadi et al., 2009). Language fMRI has also been used to study language networks in different epilepsy syndromes, showing that not only patients with left TLE, but also patients suffering from benign epilepsy, were less likely to have left lateralised language representation compared with healthy controls (Weber et al., 2006a). Children with benign epilepsy with centrotemporal spikes (BECTS) and other epilepsy types also showed bi-hemispheric language networks, which may represent a compensatory response for ongoing epileptic activity in the brain (Datta et al., 2013; Yuan et al., 2006). Also, anterior language networks are affected more in BECTS, resulting in language difficulties for functions dependent on the integrity of anterior language regions e.g., sentence production (Lillywhite et al., 2009). Brain activation patterns can be assessed repeatedly during language development in certain epilepsies which may provide prognostic information regarding potential language achievement in relation to seizures and help finding new rehabilitation strategies (Pal, 2011; Salek-Haddadi et al., 2009).

Antiepileptic drugs can affect cognitive processing (Wang et al., 2011). Topiramate has an effect on activation in the basal ganglia, anterior cingulate and posterior visual cortex and can cause reduced deactivation of the default mode network-related areas during a language task suggesting interference in cognitive processing by Topiramate (Szaflarski and Allendorfer, 2012; Yasuda et al., 2013).

1.5.2.3.3. Localisation of language function and prediction of postoperative language deficits

Aphasia is rare after epilepsy surgery, but more subtle language decline such as word finding and naming difficulties have been reported in up to 50% of patients after ATR of the language dominant hemisphere (Davies et al., 1998). There is evidence that the risk for postoperative naming decline increases both with age of seizure onset and the extent of the resection of the lateral temporal neocortex (Hermann et al., 1999a). A cortical stimulation study suggested that TLE in the dominant hemisphere with an early onset of disease lead to a more widespread or atypical representation of language areas, in particular naming and reading (Devinsky et al., 1993). In a recent fMRI study the impact of focal epilepsy on the developing language system

was investigated. In 21 children with focal epilepsy and left language dominance the authors demonstrated decreased activation of the ventral language network (compared to healthy controls) which was associated with poorer language outcome. The authors concluded that childhood onset epilepsy preferentially alters the maturation of the ventral language system, and that this was related to poorer language ability (Croft et al., 2014). Using a semantic decision paradigm Sabsevitz and colleagues demonstrated that greater left than right-sided activation in particular in the temporal structures was associated with a significantly higher risk for postoperative naming deficits (Sabsevitz et al., 2003). In addition, in left TLE, a predictive value of fMRI language lateralisation for verbal memory decline (Binder et al., 2010; Labudda et al., 2012) could be shown. However, prediction models for specific language tasks on an individual level are not yet sufficient to be applied in clinical routine. Future studies will need to investigate whether specific language paradigms will allow more accurate prediction in individual patients.

Compared to lateralisation accurate localisation of language areas with fMRI is not yet established. First of all, test-retest series have shown that the localisation of areas that were activated during a specific language fMRI task was less reliable than lateralisation (Fernandez et al., 2003). Furthermore, ESM studies showed only imperfect overlap with activation clusters of fMRI: in some cases electric stimulation of fMRI activated brain areas did not result in language disturbances (Kunii et al., 2011), while in others crucial areas were not displayed during fMRI (Roux et al., 2003). The differences may be related either to the applied language paradigms or the statistical thresholds. Rutten and coworkers developed an fMRI imaging protocol which involved four different language tasks for the intraoperative localisation of critical language areas. The authors suggested that retrospectively, regions where no fMRI activation was present during the four different language tasks (verbal fluency, word finding, naming, sentence comprehension), could have safely been removed without performing cortical stimulation mapping (Rutten et al., 2002b). So an important message for the clinical implication of language fMRI is that multiple language tasks are preferable, as also suggested by Gaillard et al. in 2004 (Gaillard et al., 2004).

To date, language fMRI localisation is not suitable for resection decision (Giussani et al., 2010) but may be helpful in planning electrode placement for ESM (Duncan, 2009).

1.5.2.4. Memory functions

Memory impairment is common in patients with epilepsy. Working and long-term memory (autobiographical, verbal, visual memory) may become affected, in a material specific way, based on the site of lesion. Functional MRI can reveal memory networks non-invasively and reliably, and also the effect of surgery on these networks (Centeno et al., 2010; Stretton et al., 2012).

1.5.2.4.1. Autobiographical memory

This network including the hippocampus, the medial prefrontal cortex, temporal poles, the retrosplenial and lateral parietal cortex showed reduced activation in patients with left HS and transient epileptic amnesia (Addis et al., 2007; Milton et al., 2012). The connectivity of a sclerosed left hippocampus was also reduced, whereas connections between extra-hippocampal nodes were increased (Addis et al., 2007). In patients with transient epileptic amnesia, there was reduced activation of the right hemisphere, more specifically of the posterior parahippocampal gyrus, the temporoparietal junction and the cerebellum, for mid-life and recent memories (Milton et al., 2012). In addition, there was reduced effective connectivity between the right posterior parahippocampal gyrus and the right middle temporal gyrus (Milton et al., 2012). These findings suggest that there is functional reorganization of the neural network supporting autobiographical memory retrieval in patients with TLE and transient epileptic amnesia (Addis et al., 2007; Milton et al., 2012).

1.5.2.4.2. Material specificity and episodic memory in TLE

A cognitive process which enables the explicit recollection of unique events and the context in which they occurred (Baddeley, 2001), including the transformation of an experience into an enduring memory trace (memory encoding) and the subsequent recollection of this event at a

later time (memory retrieval), is defined as episodic memory. Several brain regions including the medial temporal lobe (MTL) and prefrontal cortices (PFC) are involved in these processes (Otten et al., 2001). The MTL consists of the hippocampus, the amygdala and the parahippocampal regions and is strongly associated with memory function. TLE and even more though ATRs are associated with reduced memory function. Initial lesion studies have provided evidence that the hippocampi play a crucial role in memory functioning (Squire and Zola-Morgan, 1991). While bilateral injury to these areas leads to a characteristic amnesic syndrome (Scoville and Milner, 2000) patients with unilateral TLE often present with memory impairment which is specific to certain materials (e. g. verbal and visual). After temporal lobe surgery of the language dominant hemisphere more often verbal memory decline can be observed (Ivnik et al., 1987) while temporal lobe surgery in the non-dominant hemisphere is more likely to result in visual-spatial memory decline (Spiers et al., 2001). Sustained anterograde amnesic syndrome after unilateral ATR, however, is rare. In addition, most of these patients have subsequently been found to have evidence of contralateral hippocampal pathology, either on postoperative EEG (Penfield and Milner, 1958), post-mortem pathological findings (Warrington and Duchon, 1992) or postoperative volumetric MRI (Loring et al., 1994a).

Many fMRI studies have demonstrated material-specific lateralisation of memory function in prefrontal but also medial-temporal regions (Detre et al., 1998; Golby et al., 2001; Powell et al., 2005a). For clinical purposes, paradigms are usually applied which show bilateral MTL activation in healthy controls (Jokeit et al., 2001; Powell et al., 2007b). Previous fMRI studies in patients reported reduced activation in the temporal lobe ipsilateral to the seizure onset (Detre et al., 1998; Golby et al., 2001; Janszky et al., 2005; Richardson et al., 2003). These results were comparable with the IAT (Golby et al., 2001). As mentioned above, most of these studies employed blocked analyses and showed more posterior hippocampal activations. More recent studies using event-related analyses showed material-specific lateralisation of memory function in more anterior hippocampal regions during successful memory encoding (Powell et al., 2005a) and therefore in an area which is most likely to be resected during standard ATR. The reduced

activation within the affected temporal lobe but increased contralateral MTL activation during memory fMRI has provided further evidence of reorganisation of memory function in TLE (Powell et al., 2007b; Richardson et al., 2003). It is a matter of debate if reorganisation towards the healthy hemisphere is effective, and whether it may be protective for memory decline after surgery. By correlation of fMRI activation and performance on standard neuropsychological memory tests it has been shown that higher MTL activation ipsilateral to the pathology was associated with better memory performance while contralateral, compensatory activation correlated with poorer performance (Powell et al., 2007b). In one study that investigated patients with left and right TLE, higher MTL activation was observed in the healthy temporal lobe. However, better verbal memory was still related to left MTL activation (Vannest et al., 2008). This explains why good verbal memory is a risk factor for postoperative decline (Helmstaedter and Elger, 1996; Jokeit et al., 1997).

1.5.2.4.3. Working memory

Working memory is also affected in TLE patients with HS, showing variable connectivity between brain regions (Doucet et al., 2013). Compared to healthy controls there was reduced right superior parietal lobe activity in patients with TLE and hippocampal activity from the healthy hippocampus was progressively suppressed as the working memory load increased, with maintenance of good performance in patients with TLE (Stretton et al., 2012). Stronger functional connectivity between the superior parietal lobe (BOLD activation) and the sclerosed hippocampus (BOLD deactivation) was associated with worse performance, suggesting that the segregation of the task-positive and task-negative functional network was disrupted resulting in working memory dysfunction in TLE (Stretton et al., 2013). Patients with FLE recruited more widely distributed networks for working memory encoding as compared to controls; particularly activation of the frontal lobe contralateral to the seizure focus was associated with better performance, suggesting an effective compensatory response of the brain to maintain memory function (Centeno et al., 2012). Moreover, pediatric patients with FLE showed decreased frontal lobe connectivity which was associated with cognitive impairment, despite intact fMRI

activation patterns for working memory. This decreased frontal lobe connectivity may explain the cognitive problems encountered in children with FLE (Braakman et al., 2013). In addition, high numbers of secondary generalized seizures may induce functional reorganization of working memory related networks e.g., increased activation and reduced functional connectivity of the prefrontal cortex explaining working memory dysfunction in patients with focal epilepsy (Vlooswijk et al., 2011; Vlooswijk et al., 2008).

1.5.2.4.4. Prediction of postoperative memory changes

In up to 70% of patients with medically refractory TLE, an ATRR leads to seizure freedom (Wiebe et al., 2001), but this may be complicated by memory impairment, typically verbal memory decline following left ATRR (Chelune et al., 1991; Helmstaedter and Elger, 1996; Hermann et al., 1995; Loring et al., 1995; Sabsevitz et al., 2001) and visual memory decline following right ATRR (Lee et al., 2002). Investigation of patients' ability to sustain memory is critical for planning an ATRR as memory decline is not an inevitable consequence of temporal lobe surgery. One of the ultimate goals of clinical neuroimaging is to accurately predict likelihood and severity of postoperative memory decline in order to make an informed decision regarding surgical treatment.

Two different models of hippocampal function have been proposed to explain memory deficits following unilateral ATRR, the hippocampal reserve model and the functional adequacy theory (Chelune, 1995). According to the hippocampal reserve model, postoperative memory decline depends on the capacity or reserve of the contralateral hippocampus to support memory following surgery, while the functional adequacy model suggests that it is the capacity of the hippocampus that is to be resected that determines whether changes in memory function will be observed. Evidence from baseline neuropsychology (Chelune et al., 1991), the IAT (Kneebone et al., 1995), histological studies of hippocampal cell density (Sass et al., 1990) and MRI volumetry (Trenerry et al., 1993) has suggested that of the two, it is the functional adequacy of the ipsilateral MTL, rather than the functional reserve of the contralateral MTL that is most closely related to the typical material specific memory deficits seen following ATRR.

Over recent years many studies focused on the identification of prognostic indicators for risk of memory loss after ATR. The severity of hippocampal sclerosis (HS) on MRI turned out to be an important predictor, being inversely correlated with a decline in verbal memory following left ATR, with less severe HS increasing the risk of memory decline (Trenerry et al., 1993). Another recognised prognostic factor for memory decline after ATR was preoperative performance on neuropsychological tests, with higher preoperative scores indicating a greater risk for postoperative decline (Baxendale et al., 2006; Chelune et al., 1991; Helmstaedter and Elger, 1996; Jokeit et al., 1997; Lineweaver et al., 2006). Language lateralisation assessed by the IAT or more recently language fMRI has been found helpful to predict memory outcome (Baxendale, 2002; Binder et al., 2008; Lineweaver et al., 2006; Loring et al., 1990; Rabin et al., 2004). These risk factors reflect the functional integrity of the resected temporal lobe and suggest that patients with residual memory function in the pathological hippocampus are at greater risk of memory impairment after ATR. Other epilepsy related factors such as age of epilepsy onset and duration of epilepsy have also been identified as useful predictors of postoperative outcome (Baxendale et al., 2008).

Recently, memory fMRI has also shown to be a potential predictor of postoperative memory decline after ATR (Figure 1.5).

Prediction of memory decline with fMRI- Literature		
Functional MRI predicts postsurgical memory following temporal lobectomy.	Rabin ML et al.	Brain 2004
Preoperative verbal memory fMRI predicts postoperative memory decline after left temporal lobe resection.	Richardson MP et al.	Brain 2004
Functional MRI Predicts Memory Performance after Right Mesiotemporal Epilepsy Surgery.	Janszky J et al.	Epilepsia 2005
Memory fMRI in left hippocampal sclerosis: Optimizing the approach to predicting postsurgical memory.	Richardson MP et al.	Neurology 2006
Use of preoperative functional MRI to predict verbal memory decline after temporal lobe epilepsy surgery	Binder JR et al.	Epilepsia 2008
Preoperative fMRI predicts memory decline following anterior temporal lobe resection.	Powell HWR et al.	JNNP 2008
A comparison of two fMRI methods for predicting verbal memory decline after left temporal lobectomy: language lateralization versus hippocampal activation asymmetry	Binder JR et al.	Epilepsia 2010
Imaging memory in temporal lobe epilepsy: predicting the effects of temporal lobe resection	Bonelli SB et al.	Brain 2010
Functional MR imaging or Wada test: which is the better predictor of individual postoperative memory outcome?	Dupont S et al.	Radiology 2010

Figure 1.5 Literature overview on prediction of postoperative memory decline using fMRI

Several small studies have investigated the predictive value of fMRI for verbal memory decline (Binder et al., 2008; Powell et al., 2008b; Richardson et al., 2006; Richardson et al., 2004b). Only a few fMRI studies have investigated visual memory after ATLR (Janszky et al., 2005; Powell et al., 2008b; Rabin et al., 2004). In patients with left HS, greater verbal memory encoding activity in the left hippocampus prior to surgery predicted the extent of verbal memory decline following left ATLR (Powell et al., 2008b; Richardson et al., 2003). In a further analysis of the same patients, it was demonstrated that greater activation within the left hippocampus predicted a greater postoperative decline in verbal memory (Richardson et al., 2006). These findings have since been replicated and extended to patients undergoing right ATLR (Powell et al., 2008b). A recent study in patients with left and right TLE demonstrated that preoperative recruitment of more extensive networks, mainly in extra-temporal regions, during memory encoding was associated with better memory outcomes (Sidhu et al., 2013). Other groups employed asymmetry-indices to account for contralateral hippocampal activation and demonstrated that relatively higher activation in the ipsilateral hippocampus was associated with

greater memory decline (Janszky et al., 2005; Rabin et al., 2004). Using a complex visual scene-encoding paradigm Binder and colleagues also demonstrated asymmetric MTL activation in TLE patients, which was not predictive for postoperative verbal memory decline (Binder et al., 2010). A recent fMRI study combined medio-temporal activation asymmetry during a memory task with preoperative verbal memory scores and the information regarding the laterality of the epileptogenic focus. Greater ipsi- than contralateral fMRI activation was associated with a greater decline of verbal memory function. Using all the variables provided postoperative verbal memory deficits could be predicted in 90% of all patients in this study (Dupont et al., 2010). Studies using asymmetry indices are unable to address the important issue of hippocampal reserve versus functional adequacy to sustain memory function. Despite this, the findings of some previously mentioned studies showing that greater preoperative activation within the ipsilateral, diseased hippocampus, correlated with greater postoperative decline in memory also support the functional adequacy theory (Powell et al., 2008b; Richardson et al., 2006).

1.5.2.4.5. Functional MRI in the temporal lobes – Technical challenges

Echo planar imaging is the sequence most commonly used for fMRI studies, as these require images to be acquired at high speed. Memory fMRI in the medial temporal lobe is in particular challenging due to limits on resolution and the possibility of geometric distortions and signal drop out caused by susceptibility effects associated with the use of EPI (Robinson et al., 2004). Inhomogeneities in the magnetic field occur due to the different magnetic properties of bone, tissue and air, as soon as the head is introduced into the scanner. Brain regions close to borders between sinuses and brain or bone and brain are most affected and therefore most likely to suffer geometric distortions or loss of BOLD signal (Jezzard and Clare, 1999). Geometric distortions of the EPI data cause difficulties overlaying fMRI activation on co-registered high-resolution scans. Alternative acquisition sequences that do not experience geometric distortions are a way around this problem, although they rarely have the temporal resolution or high signal-to-noise ratio (SNR) per unit time of EPI.

The occurrence of material specific (verbal and visual) memory impairment after ATLRe indicates the major relevance of these areas for successful memory function. Intracranial electrophysiological recordings during verbal encoding tasks have shown greater responses in anterior hippocampal and parahippocampal regions for words remembered than those forgotten (Fernandez et al., 1999). At first, these results could not be replicated with functional imaging studies, with many showing encoding related activations in posterior hippocampal and parahippocampal regions, which would be left intact following ATLRe. One possible explanation for this apparent conflict is that anterior temporal regions are subject to signal loss during fMRI sequences, which is most prominent in the inferior frontal and inferior lateral temporal regions (Ojemann et al., 1997). Signal loss leading to sensitivity loss is unrecoverable by image-processing techniques and therefore more serious (Thornton et al., 2009). The anatomical position of the hippocampus which rises from anterior to posterior may explain greater susceptibility-induced signal loss in the anterior (inferior) relative to the posterior (superior) hippocampus which may have been one reason for the relative lack of anterior hippocampal activation in early fMRI studies of memory. One study demonstrated that there was a differential effect of susceptibility artefacts on the activation in the anterior versus the posterior hippocampus. They showed that the averaged resting voxel intensity in an anterior hippocampal region of interest (ROI) was significantly less than in a posterior hippocampal ROI; intensity decreases were substantial enough to leave many voxels below the threshold at which BOLD effects could be detected (Greicius et al., 2003). Even more though in a different study it could be demonstrated that the sensitivity to BOLD changes was proportional to signal intensity at rest so that voxels with a lower baseline signal (such as those in anterior hippocampal regions) would be more difficult to activate than those with higher baseline signals (Lipschutz et al., 2001). Shimming, which is a process whereby the static magnetic field is made more homogeneous over the ROI (Jezzard and Clare, 1999), has been shown to be a useful method to correct some of these artefacts.

Paradigm design may be an alternative explanation for the lack of anterior hippocampal activation seen in many early memory fMRI experiments. Most of the paradigms used were not

optimized for detecting subsequent memory effects as for example most of these early studies used blocked experimental designs. Studying memory function in general is much more challenging than examining motor or language function and therefore requires more complex paradigms and tasks and ways of analysis. There are several possible reasons:

- 1) Several different components are involved in memory processing, such as encoding and retrieval;
- 2) The nature of the material being encoded or retrieved influences which brain areas are activated;
- 3) A further difficulty is how to separate brain activity related specifically to memory from that related to other cognitive processes.

By using blocked design paradigms we are looking for regions of the brain showing greater activation during task blocks compared with rest blocks, which makes it difficult to separate brain activity due specifically to memory from that due to other cognitive processes involved in the task. To account for differing memory performance early fMRI studies of memory encoding employed blocked experimental designs using the “depth of encoding” principle (Craik and Lockhart, 1972), which states that if you manipulate material in a deep way (e.g. make a semantic decision about a word) then it is more likely to be recalled successfully than material manipulated in a “shallow” way (e. g. make a decision of whether the first letter of a word is alphabetically before the last letter). With this method consistent activation was usually seen in left prefrontal cortical regions and less reliable activation in the MTL (Kelley et al., 1998). Golby and colleagues employed so called “Novelty paradigms”, which consist of alternating blocks of novel and repeated stimuli, based on the hypothesis that stronger memory encoding takes place while viewing a block of novel stimuli than when viewing repeated stimuli (Golby et al., 2001).

As already discussed, most early memory fMRI studies employed blocked experimental designs which have the advantage that they are generally most efficient in detecting differences between two conditions. However, the interpretation of these contrasts remains problematic as it is not straight forward to assume that effects shown by these contrasts reflect differences in memory

encoding, rather than any other differences between the two conditions, based on additional cognitive tasks which are involved (semantic processing etc.) and which are independent from differences in memory encoding. To overcome this problem parametric block designs were introduced initially, but were soon replaced by the advent of event-related designs (as summarized by Thornton et al. (Thornton et al., 2009))

In brief, the detection of transient haemodynamic responses to brief stimuli or tasks is defined as event-related fMRI. With this technique, which was derived from techniques used by electrophysiologists to study event-related potentials, trial-based rather than block-based experiments can be carried out. These trial-based designs have a number of methodological advantages, but also some draw-backs: A subject's individual performance on a subsequent cognitive test can be taken into account so that trials can be categorised post-hoc according to each subject's performance. When for example studying memory encoding, activations for the different items can be contrasted according to whether they are subsequently remembered or forgotten in a subsequent memory test in each individual. In this way we can identify brain regions with greater activation during encoding of different (material specific) items that are subsequently remembered compared to items that are subsequently forgotten (subsequent memory effects) representing the neural correlates of memory encoding (Wagner et al., 1999).

A previous study compared results from a blocked and event-related analysis of memory fMRI of words, pictures and faces: only the event-related analysis of successfully encoded stimuli showed significant activations in the anterior MTL whereas simply viewing the different stimuli (using a blocked analysis without taking into account whether items were subsequently remembered or not) revealed predominant activation in the posterior hippocampus (Powell et al., 2005a). This study provided evidence for a functional dissociation between anterior and posterior hippocampal regions.

In summary, although event-related designs are less powerful than blocked designs at detecting activation and are also more vulnerable to alterations in the haemodynamic response function, they have the big advantage of permitting specifically the detection of subsequent memory effects due to successful encoding.

1.5.2.5. Emotion

The amygdala has long been implicated in the semiology of temporal lobe epilepsy. In John Hughlings Jackson's first description of the "dreamy-state" in *Brain* in 1880 he stressed sensations of terror and anger as well as epigastric sensations, olfactory hallucinations and automatic behaviours as features of complex focal seizures arising from the temporal lobe (Hughlings Jackson, 1880; Kullmann, 2011). Up to 60% of patients with TLE suffer from emotional disturbances such as anxiety or depression which may only start or even be aggravated following epilepsy surgery.

It is well known, that the amygdalae are involved in fear conditioning, face perception, emotional processing and social behaviour. Together with the hippocampi they play a crucial role in emotional memory encoding. Gloor and co-workers demonstrated that stimulation of the amygdala could elicit a full spectrum of experiential symptoms in patients with TLE (Gloor et al., 1982).

Richardson and colleagues first of all looked into the interaction between the hippocampus and the amygdala during encoding of emotional words in patients with temporal lobe epilepsy. By integration of functional imaging and structural imaging parameters they showed that emotional word encoding strongly depended on the structural integrity of the amygdala and vice versa (Richardson et al., 2004a). There was converging evidence from behaviour and imaging data that hippocampal pathology correlated with encoding success for neutral items; amygdala pathology correlated with encoding success for emotional items more than for neutral items. Functional MRI results showed that emotional stimuli produced greater hippocampal but also greater amygdala encoding-related activity than neutral stimuli, an effect which was lost in case of amygdala and/ or hippocampal pathology. The authors postulated that this interaction between amygdala and hippocampus served to enhance memory for emotional events (Richardson et al., 2004a). Schacher and colleagues were the first to show that amygdala fMRI was feasible in controls and patients with epilepsy. Using a dynamic paradigm, which provided asymmetric activations contralateral to the seizure onset in single subjects, they demonstrated that it was possible to lateralise TLE using amygdala fMRI (Schacher et al., 2006).

Further studies will be needed to replicate these results and to investigate a potential role of amygdala fMRI as a predictor of postoperative emotional disturbances.

1.5.3. Functional connectivity

The possibility to analyse functional connectivity in patients with epilepsy has significantly improved our understanding of seizure generation and propagation. The analysis of functional connectivity during cognitive tasks allows studying the neuronal networks that subserve these tasks (Axmacher et al., 2007).

During the last few years several studies have demonstrated altered connectivity within the epileptic network but also in networks of cognitive function such as language and memory. In patients with left TLE compared to healthy controls the functional connectivity within the expressive language network was reduced, most likely due to the underlying disease (Waites et al., 2006). More specifically, functional connectivity was decreased in the left hemisphere irrespective of the epileptogenic focus (Pravata et al., 2011) and within the prefrontal and frontotemporal networks (Vlooswijk et al., 2010) which was associated with impaired performance on language assessment (Vlooswijk et al., 2010).

Other studies evaluating memory function showed that functional connectivity was reduced between the posterior cingulate and the epileptogenic hippocampus and increased between the posterior cingulate and the contralateral hippocampus (McCormick et al., 2013; Pereira et al., 2010). Functional reorganization of networks involving extra-temporal and temporal structures for verbal, visual and non-material specific memory suggests compensatory mechanisms to mitigate the failure of the sclerosed hippocampus (Alessio et al., 2013; Guedj et al., 2011; Sidhu et al., 2013).

A recent study used a visual scene encoding task to evaluate memory function in healthy controls compared to patients with TLE. In this study, patients with left TLE demonstrated a significant decrease in functional connectivity to the inferior temporal, occipital, cingulate and parietal cortices and the thalamus. In addition the authors showed that orbital frontal activity correlated with structural measures of tract coherence in the fornix, which led to the suggestion,

that this might be the structural correlate of reduced functional connectivity (Voets et al., 2009). Vollmar and colleagues reported similar observations of increased connectivity of motor and cognitive networks in patients with juvenile myoclonic epilepsy (Vollmar et al., 2011). However, whether functional connectivity studies may prove clinically useful still needs to be established. A potential application is the use as a clinical predictor of postoperative outcome following surgery and studies are just beginning to emerge which address this possibility. In one such study, epileptic networks were investigated in patients who underwent surgery for different types of epilepsy. By comparing connectivity measures, the authors found that patients with a less lateralised epileptic network had a less good postsurgical outcome than those patients in whom the network was more lateralised (Negishi et al., 2011).

1.5.4. Functional MRI applied to epilepsy - Conclusion

Functional MRI is increasingly used to image cognitive functions such as language and memory. Language fMRI is well established in many centers and is often applied to identify the language dominant hemisphere on an individual level. However, the localisation of language areas is much more complicated and still requires invasive electro-cortical stimulation mapping. Regarding memory function, it still needs to be established whether memory fMRI has the potential to predict postoperative memory decline but also emotional disturbances after surgery which are so commonly observed in these patients.

Up to date, invasive methods have not been fully replaced by non-invasive techniques but the latter may help planning invasive procedures. Non-invasive methods allow us to investigate healthy volunteers and to systematically compare different study groups and changes in activation over time to assess mechanisms of cognitive development and functional reorganisation. This may help to improve the individual prognosis of even subtle cognitive deficits and may stimulate the development of new therapeutic strategies for cognitive rehabilitation.

In summary, there are three main areas where fMRI is relevant in patients undergoing surgery for epilepsy.

1. As a clinical tool to localise/lateralise the eloquent cortex, which needs to be spared during epilepsy surgery;
2. In the exploration and prediction of post-operative complications, leading to reduction of surgical morbidity by changes in techniques, which is one of the ultimate goals of clinical neuroimaging;
3. To understand more about how chronic seizures contribute to cognitive impairment in patients with epilepsy. As an important research tool it can further increase our understanding of functional reorganisation/plasticity in patients with epilepsy.

It was the aim of this PhD thesis to further explore the utility of cognitive functional MRI during presurgical evaluation of patients with TLE, and to contribute to its implementation and translation from a research tool to clinical use.

Parts of this chapter have been included in the reviews “Clinical application of Language and Memory fMRI in Epilepsy”, by Anja Haag and Silvia B. Bonelli, *Epileptologie* 2013, 30:101-108 and “Functional MRI and Tractography in the Diagnosis of Patients with Epilepsy: Recent Advances and Clinical Relevance” by Silvia B. Bonelli, *Klinische Neurophysiologie*, 2012; 43(02): 151-157.

1.6. OTHER FUNCTIONAL IMAGING METHODS

1.6.1. Background

In about 25% of patients who are surgical candidates, currently available in vivo structural MRI does not show any abnormalities, and other techniques are needed to determine the probable cause of the epilepsy (Duncan, 2010). Especially in those patients, whose standard MRI proves unremarkable or who show discordances between results from MRI and video-EEG telemetry, other functional imaging methods such as discussed below may be helpful in identifying the epileptogenic zone (Dupont et al., 2006; O'Brien et al., 1999).

1.6.2. Magnetic resonance spectroscopy (MRS)

With the help of MRS it is possible to recognize interictal metabolic changes which typically arise within the epileptogenic zone (Cendes et al., 1994b; Connelly et al., 1994; Hugg et al., 1993). The use of MRS has primarily been evaluated in patients with TLE. Proton MRS usually measures the signal of N-acetylaspartat (NAA), creatine and phosphocreatine (Cr), choline (Cho) and lactate and provides a useful lateralization of metabolic dysfunction, with a sensitivity of about 90% (in TLE); caution is needed as bilateral temporal abnormalities are common and also may be reversible. In clinical practice MRS may be useful as part of presurgical evaluation in patients with otherwise normal MRI studies.

Phosphate (^{31}P) MRS on the contrary has only moderate sensitivity for lateralization based on abnormal elevations of inorganic phosphate.

Finally MRS has been reported to be useful in extratemporal epilepsies but the present limitation of spatial coverage limits clinical utility (Commission on Diagnostic Strategies, 2000a; Panayiotopoulos, 2004).

1.6.3. Positron emission tomography (PET)

For PET imaging tracers labeled with positron-emitting isotopes are used to visualize and quantify the cerebral metabolism of the brain. In the diagnosis of epilepsy PET can be performed with 2-(^{18}F) Fluoro-Desoxyglucose (FDG) and ^{15}O -water (H_2^{15}O). Usually PET is

obtained interictally to identify the epileptogenic zone, which typically shows an extensive reduced glucose uptake (cerebral hypometabolism) including the area where the seizures are generated from. Typically the seizure onset zone is not located in the area of most severe hypometabolism but at its margin (Vinton et al., 2007).

Currently this method can be used for lateralization purposes in patients with bilateral TLE, or in TLE patients with discordant results of MRI, EEG and other data; it may also be useful for detection of extratemporal epileptogenic foci (in particular in patients with unremarkable structural MRI) as an area of hypometabolism can indicate the location of subtle abnormalities such as focal cortical dysplasia (Salamon et al., 2008). In TLE patients a focal hypometabolism ipsilateral to the temporal lobe which was subsequently resected was found to be predictive of a favorable surgical outcome (Willmann et al., 2007). In TLE sensitivity ranges from 60-90% (Engel et al., 1982a; Engel et al., 1982b; Engel et al., 1982c; Theodore et al., 1983), in frontal lobe epilepsy sensitivity is about 60% (Duncan, 1997). Over the last years the role of PET during presurgical evaluation has decreased with greater availability of high-quality MRI. However, in patients with unremarkable MRI or discordant results provided by other presurgical investigations FDG-PET may be a useful, cost-effective method in order to aid placement of intracranial electrodes for recording ictal onsets in patients with temporal and extratemporal epilepsies (O'Brien et al., 2008). The clinical role of H2150 PET for mapping areas of cerebral activation has widely been replaced by fMRI (Commission on Diagnostic Strategies, 2000a). In presurgical evaluation of patients with medically refractory focal epilepsy the use of PET with specific ligands such as ¹¹C-flumazenil, which binds to the γ -aminobutyric acid A receptor complex, may be superior to FDG-PET offering more precise localisation of the epileptogenic zone (Richardson et al., 1998; Ryvlin et al., 1998); however, this is not the case for lateralization. Again in MRI negative patients with neocortical seizures flumazenil PET may be useful to guide placement of intracranial EEG electrodes (Commission on Diagnostic Strategies, 2000a).

In summary, PET is not readily available in many hospitals, although ¹⁸F-labeled tracers can be transported, while ¹¹C tracers have a short half-life and need to be manufactured on site, which comes along with great costs, restricting it to a few research-oriented sites only.

1.6.4. Single photon emission computed tomography (SPECT)

SPECT is another useful imaging tool, especially for presurgical evaluation. In addition to interictal PET the great value of this method is that it can be performed ictally. In principle, a radio labeled tracer (stable isotopes e. g. HMPAO) is applied intravenously, the cerebral uptake of which reflects cerebral blood flow during a seizure. Especially during focal seizures transient focal cerebral hyperperfusion can be observed in the area in which the seizures are generated. When SPECT is performed ictally or in the early post-ictal phase, ictal-interictal subtraction of SPECT scans and coregistration with MRI can be performed which makes it possible to visualize areas of ictal blood-flow change for several hours following a seizure. Therefore ictal SPECT studies – although technically demanding - can provide valuable information regarding the localization of the seizure onset zone in focal epilepsy. In TLE the seizure onset zone can be correctly localized in about 90% using ictal SPECT (Newton et al., 1995), while in extratemporal focal epilepsies (e. g. frontal lobe epilepsy) this is possible in only 68% (Biraben et al., 1998). In patients who will need intracranial recordings SPECT results may also help guiding the placement of the intracranial electrodes if other data including structural imaging are not concordant. When an area of ictal hyperperfusion is detected using SPECT, a review of MRI scans might reveal a previously occult abnormality. If this area is not in close vicinity to the eloquent cortex, theoretically, a resection can be recommended without intracranial EEG (Duncan, 2009). However, as discussed above in most patients information gained from SPECT will aid intracranial EEG electrode placement, providing information on the possible secondary spread of ictal activity and postictal suppression of cerebral blood flow (Van Paesschen et al., 2003). In apparently generalized epilepsies, ictal SPECT may be helpful to identify a focal component (Commission on Diagnostic Strategies, 2000a).

1.7. DIFFUSION MR IMAGING

1.7.1. Background

Diffusion tensor tractography is an advanced MRI technique that for the first time, allows us to image in-vivo white matter tract anatomy. Before the development of this MRI technique the only feasible ways to study white matter was with post-mortem human and animal specimens, using either gross dissection or histological tract tracing techniques. For this reason it is only now that scientists are rediscovering the role of white matter in the brain, and starting to understand, that white matter is as important as the eloquent cortex, to the adequate functioning of the brain. Therefore it is increasingly appreciated that we need to frame the functioning of the brain not only in terms of cortical and subcortical activation but also white matter tracts connecting these regions (Catani et al., 2002; Guye et al., 2003).

1.7.2. Diffusion weighted imaging

Diffusion weighted imaging (DWI) is based on the fundamental biological principle of Brownian motion. In a free medium the molecular diffusion of water refers to the random translational or 'Brownian' motion of molecules resulting from the thermal energy carried by them. In the brain diffusion is restricted by intra- and extra cellular boundaries such as membranes, macromolecules, and intra- and extra cellular microcirculatory effects (Hansen, 1971; Le Bihan and Turner, 1992). This restriction to their diffusion differs in different parts of the brain. Within cerebrospinal fluid (CSF) and, to a lesser extent, grey matter, water molecules are essentially unrestricted in their diffusion. It is essentially directionless or random, also known as isotropic diffusion. Within white matter the restriction to diffusion is much greater due to structures such as myelin, axonal membranes, microtubules etc. (Beaulieu, 2002). In other words, this diffusion has direction and is known as anisotropic diffusion (Basser, 1995); it tends to be greatest in the direction of white matter pathways.

Image acquisition can be sensitized to the diffusional properties of water if one incorporates pulsed magnetic field gradients into a standard spin echo sequence and takes measurements in at least six directions (Taylor and Bushell, 1985). One can then use a variety of mathematical

models to understand the nature of the diffusion of these water molecules. One such model is the tensor model.

1.7.3. Diffusion tensor imaging (DTI)

Using this model it is possible to calculate, for each voxel or pixel element, a tensor (i.e. a symmetric positive definite 3×3 matrix) that describes the 3-dimensional shape of diffusion within every voxel (or pixel) of one's MR image and use this to describe diffusion within each voxel rather than a single scalar quantity (Le Bihan et al., 2001).

In a voxel within CSF or grey matter the extent of diffusion of the water molecules is the same in every direction. In three dimensions therefore, the diffusion tensor describes a sphere. In white matter the diffusion is anisotropic, which means that it has direction which tends to be parallel to the tracts as diffusion perpendicular to the tracts is restricted by biological substrates; therefore the diffusion tensor describes an ellipsoid and diffusion tends to be greatest in the direction of the white matter.

In summary, the tensor is a mathematical description of the magnitude and directionality (anisotropy) of the movement of water molecules in a 3 dimensional space. From this information a number of quantitative measures in each voxel or pixel element in an image can be derived such as mean diffusivity (MD) or the average diffusion of water molecules within a voxel, and fractional anisotropy (FA) which represents the degree of directionality of diffusion of water molecules in white matter, axial diffusivity (PaD) which represents diffusion along the length of an axon and radial diffusivity (PeD) which represents diffusion perpendicular to it. Patterns of change of both provide information about the microstructural changes occurring in white matter in given pathological states. So, for example studies suggest that a decrease in myelination will primarily lead to an increase in PeD (as there is less of a barrier to the diffusion of water molecules in a perpendicular direction) and a reduction in FA as there is less directionality to the diffusion.

1.7.3.1. Analysis of DTI data

There are two ways of analysing DTI data:

1.7.3.1.1. Whole brain analysis

This method allows to compare two groups of data – for example TLE patients versus controls – by looking for differences in diffusion parameters such as FA, PaD, PeD or MD between groups; in a subsequent step these differences can be anatomically located. There are various packages including Tract Based Spatial Statistics (TBSS) and Statistical Parametric Mapping (SPM), which allow the manipulation of data in such a way that all subject data is well aligned and in the same space, so that statistical analyses can be carried out whilst allowing for multiple comparisons, which is a significant issue in imaging analyses because of the great number of voxels studied.

1.7.3.1.2. Tractography

With standard clinical MRI such as T1 weighted images, white matter is essentially homogenous in signal intensity, and it is not possible to parcellate out neighbouring white matter tracts, so that one cannot visualise the white matter network. With tractography this is now a possibility, and in particular valuable as it can be done non-invasively and (in vivo) repeatedly.

Tractography is an extension of DTI. First of all directional information of the diffusion tensor is obtained in every voxel with the aid of post-processing. Using a mathematical algorithm and computer processing outside the scanner, three-dimensional white matter maps can be produced. These maps are based on similarities between the diffusion properties of neighboring voxels in terms of shape and orientation, or in terms of magnitude of diffusion anisotropy and orientation of maximum diffusion. In order to start the algorithm one typically has to place a “start” region in whichever area of the brain one is interested in.

Tractography is therefore capable of creating virtual white matter maps which are thought to represent the underlying anatomy. Once the white matter tract of interest has been parcellated out it is possible to derive tract specific qualitative and quantitative information including

volume, and fractional anisotropy from which biological inferences as well as group comparisons can be made (Ciccarelli et al., 2003a). Tracts can also be normalized to some standard space and combined to generate group maps which indicate how reproducible a given tract or connection is across a group of subjects (Ciccarelli et al., 2003b).

In summary, measurement of water diffusion by tractography provides a means of probing integrity and pathology of white matter tracts in the brain (Catani et al., 2002), which helps preoperative planning and may prevent damage to the eloquent cortex, particularly when combined with functional activation studies (Guye et al., 2003).

1.7.4. Clinical applications of DWI

1.7.4.1. Localisation of the seizure onset zone

Much of the early work with diffusion imaging aimed to explore its utility in the localisation of structural causes of seizures in patients who were MRI negative on standard clinical acquisitions (Mori and van Zijl, 2002).

Using diffusion data in MRI negative patients with epilepsy, Rugg-Gunn and colleagues found diffusion imaging abnormalities in a significant proportion which co-localised with the areas identified on ictal EEG and clinical semiology (Rugg-Gunn et al., 2001). One paediatric study and one study in adult patients with temporal lobe epilepsy (TLE) showed that in the ipsilateral hippocampus MD was increased while FA was lower than in healthy controls and in the contralateral hemisphere (Kimiwada et al., 2006; Salmenpera et al., 2006). Applying similar principles, the use of this technique in aiding detection of subtle focal cortical dysplasias (FCD) is being developed (Widjaja et al., 2007), and there is the potential to use other diffusion contrasts to increase its utility. Attempts to correlate diffusion parameters with results of intracranial EEG have not been successful thus far (Guye et al., 2007; Thivard et al., 2006).

To summarise, DTI may be useful to lateralise/ localize the epileptogenic zone in MRI negative patients, but should be used in concert with clinical and EEG data.

1.7.4.2. Prediction of postoperative complications

More recent applications of diffusion data in epilepsy patients have included the exploration and prediction of postoperative complications. In the context of epilepsy this is perhaps most relevant to TLE as anterior temporal lobe resection (ATLR) is an effective and well-established method of treatment. However, this procedure may be complicated, by the removal of eloquent brain tissue with a resulting impact on function. One of the specific complications that can arise after temporal lobe surgery is the occurrence of a visual field deficit, which occurs in up to 40% of patients following ATLR and which may be severe enough to prevent them from driving even if they were seizure free.

The reason for the occurrence of visual field deficits after temporal lobe surgery and the variation in its severity from patient to patient is dependent on an anatomical peculiarity concerning the optic radiation and in particular the part of it in the temporal lobe which is known as Meyer's loop. Temporal lobe resections can cut into the optic radiation, therefore causing visual field deficits. The problem is that there is inter-subject variability in the extent to which the optic radiation extends anteriorly and inferiorly, so that one cannot predict which patients will or will not get visual field deficits. With standard T1 weighted imaging, specific white matter tracts cannot be differentiated from surrounding white matter. Using tractography it was possible to visualise the optic radiation and Meyer's loop (Kikuta et al., 2006; Yamamoto et al., 2005). Powell and colleagues also assessed how this white matter tract related to the zone of resection and how this may have given rise to postoperative visual field deficits (Powell et al., 2005b). Taking this further Yogarajah et al. investigated whether it was possible to use this method to predict postoperative deficits. In their study from 2009 the authors showed that substantial visual field defects were only seen in patients for whom the anterior part of Meyer's loop was less than 35 mm from the temporal pole. In other words: a smaller distance between the tip of the loop and the temporal pole correlated with bigger visual field deficits postoperatively for a given size of temporal lobe resection (Yogarajah et al., 2009). Winston et al. systematically examined 20 patients who underwent an ATLR pre- and postoperatively with structural MRI, tractography and perimetry. In patients who suffered a visual field defect after

surgery (60% of these patients) Meyer's loop was 4.4 to 18.7 mm anterior to the resection margin, but 0.0 to 17.6 mm behind the resection margin in those patients without a visual field defect. The extent of damage to Meyer's loop significantly correlated with the degree of the visual field defect and explained 65% of the variance in this measure (Winston et al., 2012). Therefore it can be postulated that by mapping out the important connections between functional brain tissue tractography can predict postoperative complications, and - when display of tracts is incorporated into interventional MRI to guide surgery - ultimately may help to prevent them (Winston et al., 2012; Winston et al., 2011; Yogarajah et al., 2009).

1.7.4.3. Effects of chronic epilepsy on cognitive impairment

Tractography can also be used to understand more about how chronic seizures contribute to cognitive impairment in patients with epilepsy. This has been particularly explored in TLE with regard to memory and language function. One can understand these cognitive deficits in patients with TLE not only in terms of dysfunction in discrete cortical or sub-cortical structures, but partly also through disruption of white matter connections between cortical areas. Concha et al. showed that TLE was associated with white matter abnormalities that were extensive and bilateral in particular in patients with mesial temporal sclerosis and which remained on the contralateral side after epilepsy surgery (Concha et al., 2005; Concha et al., 2007). McDonald et al. carried out one of the first studies that showed that white matter tract integrity correlated with a variety of different cognitive measures (i. e. episodic memory performance, naming performance etc.) (McDonald et al., 2008). These findings have since been replicated and extended by several other groups working on the question which white matter structures were particularly important for memory and language functions. Tractography allows parcellation of these tracts of interest, which include the fornix, uncinate fasciculus and parahippocampal gyrus, in order to assess how they relate to memory impairment (Diehl et al., 2008; Yogarajah et al., 2008). Looking at specific tracts similar correlations were seen for language functions (Yogarajah et al., 2010).

1.7.4.4. Reorganisation and plasticity of cognitive networks

Not only can we use diffusion imaging to understand part of the structural basis of cognitive dysfunction in TLE, we can also use it to further increase our understanding of the structural basis of functional language reorganisation/plasticity in TLE.

According to the classical 19th century language model language function depends upon two important functional “zones” - Broca’s area at the inferior-frontal part of the brain, and Wernicke’s area in the temporo-parietal part of the brain - and the white matter tracts connecting these. Until recently the most important tracts have been thought to be the dorsal pathways otherwise known as the superior longitudinal fasciculus (SLF)/ arcuate fasciculus (AF).

Powell and colleagues were among the first to demonstrate that in addition to functional reorganisation there is also structural reorganisation in TLE, such that the arcuate fasciculus is bigger and better connected in the right hemisphere in left TLE patients than in controls, and that the degree of structural reorganisation correlates with the degree of functional reorganisation (Powell et al., 2007a). They also showed that greater tract volumes of the expressive language networks in the dominant hemisphere correlated with greater postoperative naming deficits (Powell et al., 2008a).

Following this seminal piece of work by Powell et al. there have been a number of similar studies with larger numbers but with mixed findings.

Matsumoto et al. studied 24 patients (with TLE and extra TLE and a mixture of underlying pathologies) using WADA testing and deterministic tractography in order to find out whether lateralisation derived from their tractography measures, agreed with the lateralisation classification derived from WADA testing (Matsumoto et al., 2008). Overall, in this study tractography as a lateralisation tool falsely categorised language lateralisation in only 5% of patients with language dominance in the left hemisphere, but in 67% patients with dominance in the right hemisphere. As a result, and in view of the fact that they had actually excluded patients with bilateral WADA results, the authors concluded that DTI should at best be used in combination with fMRI for language lateralisation (Matsumoto et al., 2008).

A similar study by Rodrigo compared tractography findings in 12 right TLE and 8 left TLE patients, all of whom were right handed, to the results of language fMRI lateralisation. As in the previous study in patients with epilepsy of left temporal origin, who were more likely to have atypical language lateralisation, there appeared to be a breakdown of the coupling between structural and functional based-lateralisation indices, not seen in right TLE (Rodrigo et al., 2008).

Finally, Ellmore et al. investigated 23 mainly TLE patients who not only had fMRI testing for language lateralisation but also WADA testing. In addition, the authors of this study used tractography to parcellate out the AF/SLF in all subjects. They defined the lateralisation of this tract on the basis of asymmetry in numbers of streamlines or tract volume. In this study DTI derived lateralisation indices correctly classified 19/23 patients, whereas fMRI derived lateralisation indices correctly classified 20/23 patients. Of the 3 patients misclassified by fMRI 2 had left WADA outcome, and of the 4 misclassified by DTI 1 had right WADA and 3 left WADA outcome (Ellmore et al., 2010). The authors of this study concluded that DTI could prove useful in lateralising language in TLE patients, though it was perhaps not quite as good as fMRI. However where fMRI was difficult to obtain (e. g. in patients unable to cope with fMRI tasks) DTI may be useful to lateralise language, particularly if used in combination with handedness (Ellmore et al., 2010).

More recent studies demonstrated that diffusion imaging was also a tool that was able to increase our understanding of plasticity in epilepsy and following epilepsy surgery and therefore had significant implications for our understanding of brain injury and plasticity in general.

A large longitudinal study evaluated the structural changes that may take place in white matter after temporal lobe surgery. Patients were scanned using diffusion tensor imaging before and after undergoing an ATR for the treatment of refractory seizures. In this study the authors first of all found an early postoperative increase of the FA in the ipsilateral external capsule in patients with left TLE, a location which corresponded to the ventromedial language stream. Secondly, patients with higher FA-increases had less postoperative language decline. Given the

short postoperative interval the authors discussed that this effect could be explained by an additional activation of the ventro-medial language network (Yogarajah et al., 2010).

1.7.4.5. Limitations and future directions

Ultimately, given results of recent studies it is likely to see the use of tractography as a tool not just to predict postoperative complications, but also to prevent them. However, there are some technical issues and limitations to overcome:

As a first step accurate registration of the images into stereo-navigational space needs to be achieved. Different MRI modalities have differing geometric distortions, and EPI sequences are particularly sensitive to magnetic susceptibility differences, and have a tendency towards anatomic distortion and blur. This can hinder accurate co-registration between EPI based tractography images and T1 images which have differing geometric distortions. These errors due to distortion are greatest in the temporal lobes and can be of order of at least several millimetres. Another limiting factor related to this, is the fact that images usually consist of voxel sizes at the smallest 3 mm cubed. This is many orders of magnitude greater than the nerve fibres in question. More work is required to get better resolution images. Another hurdle of preoperative tractography is the problem of brain shift. Even when we have accurately co-registered, high-resolution images in stereo-navigational space these images may not be accurate as surgery proceeds. Before tractography can be used as a tool to prevent complications, peri-operative acquisitions will be needed, which in turn means faster acquisition times, and the implementation of quick and robust algorithms.

In summary, clinical applications are currently limited by the fact that in order to infer information about networks one basically needs good spatial resolution and much better diffusion models, in order to solve the problem that a single voxel in a diffusion image is likely to contain multiple white matter tracts, some of which may be crossing. These better diffusion models will inevitably require larger numbers of diffusion directions, together with the huge amount of computer processing power needed to process this data.

1.8. EPILEPSY SURGERY

1.8.1. Introduction

In the late nineteenth century the first successful surgical procedures for lesions underlying epilepsy were performed by Victor Horsley following the work of Hughlings Jackson, who had previously demonstrated that specific brain areas were associated with certain seizure characteristics. In the late 1930s, Penfield became one of the first surgeons who undertook resections for epilepsy on the basis of EEG evidence alone (Penfield and Flanigin, 1950). Victor Horsley had already stressed that converging evidence from the careful examination of diagnosis, surgical procedure and outcome was necessary, so that progress could be made, principles which remain relevant today.

There is now a wide range of surgical procedures which may be offered to patients with epilepsy in a large number of centers. The most commonly used surgical procedures can be divided into resective procedures, which are considered potentially curative, and disconnection procedures, which are for palliative use only. About 35% of patients with focal epilepsy suffer from medically refractory seizures (Kwan et al., 2010; Kwan and Brodie, 2000). For many of these patients epilepsy surgery represents a highly effective and safe treatment option. In particular anterior temporal lobe resections (ATLR) benefit patients with intractable mesial temporal lobe epilepsy (mTLE) rendering up to 60-70% of them seizure free in the medium term (de Tisi et al., 2011; Wiebe et al., 2001).

The goals of epilepsy surgery are to remove the brain areas generating the seizures without causing cognitive or other functional impairment to minimize side-effects and to improve overall quality of life (European Federation of Neurological Societies Task Force, 2000b).

1.8.2. Requirements for epilepsy surgery

Before a surgical intervention can be offered to a patient two main requirements have to be fulfilled:

1. The patient should have a pharmaco-resistant epilepsy syndrome;

2. Surgical treatment would be a reasonable therapeutic option, likely to result in cessation or a significant reduction of seizures.

1.8.2.1. Pharmaco-resistant epilepsy

To improve patient care and facilitate clinical research, the International League against epilepsy (ILAE) has recently formulated a consensus definition of drug resistant epilepsy (Kwan et al., 2010). Two hierarchical levels have to be considered:

Level 1

At the first level the response (outcome) to an appropriate and adequate therapeutic intervention is categorized according to control of seizures (Category 1: no seizures, Category 2: (continued) seizures, Category 3: undetermined) and side effects (Category A: no side effects, Category B: side effects, Category C: undetermined).

An intervention can be defined as being “appropriate” if an appropriate drug (ideally its efficacy was tested and approved in a randomized, controlled trial) for a present epilepsy syndrome is available. An intervention is “adequate” if the appropriate antiepileptic drug was administered in an efficiently high dose for an appropriate period of time.

Level 2

At level 2 a core definition of “drug resistant epilepsy” using a set of essential criteria based on the categorization of responses (from Level 1) to trials of antiepileptic drugs is proposed. In summary, drug resistant epilepsy is defined as the failure of adequate trials of two tolerated, appropriately chosen antiepileptic drugs (whether as monotherapies or in combination) to achieve sustained seizure freedom.

It is important to verify whether a patient’s epilepsy syndrome should be classified as drug resistant as quickly as possible, at least within two years (in children with a high seizure frequency shorter intervals need to be considered, owing to the potential impact of uncontrolled

seizures on neurodevelopment). However, in reality the latency from onset of disease until a patient is referred for epilepsy surgery can still take up to 20 years (Wiebe and Jette, 2012).

1.8.2.2. Epilepsy syndromes that can be treated by epilepsy surgery

The second requirement is that the patient is suffering from an epilepsy syndrome which in principle can be treated by epilepsy surgery.

One can differentiate between three different groups of epilepsy syndromes, for which a surgical intervention may be possible and useful:

1. Epilepsies with focal pathologies, for which a circumscribed, tailored resection can be carried out, including mesial temporal lobe epilepsy, malformations of cortical development, benign/ low-grade tumours, vascular malformations, posttraumatic/ post-encephalic alterations but also focal epilepsies with unremarkable MR scan (MRI negative epilepsies);
2. Epilepsies associated with multiple or extensive underlying lesions, which require extensive, sometimes even multilobular resections, such as it might be necessary for the Sturge-Weber-Syndrome, Rasmussen's Encephalitis or extensive malformations of cortical development;
3. Epilepsies, for which only disconnection surgery as a palliative treatment can be offered, such as for drop attacks as part of the Lennox-Gastaut-Syndrome or the Landau-Kleffner-Syndrome.

1.8.3. Presurgical evaluation

Prior to safe surgical resection, careful presurgical evaluation is necessary. The aim of this is to localise the brain areas from which seizures are generated ('seizure onset zone'), as well as areas responsible for motor, language and memory function but also for emotional processing ('essential brain regions') (refer to chapter 1.5).

Two different phases can be differentiated during the preoperative evaluation for epilepsy surgery: a non-invasive (phase I) and an invasive phase (phase II).

In the majority of epilepsy patients indications for a surgical intervention can be established after phase I; however, if the findings are inconclusive or contradictory, further investigation with intracranial electrodes can be considered in phase II. Despite the continuous introduction of new antiepileptic drugs the results of (early) epilepsy surgery after careful patient selection are substantially better than continuation of pharmacotherapy alone (Engel et al., 2012; Wiebe et al., 2001).

The following terminology has been established for the description of various brain regions identified during presurgical evaluation in focal epilepsy (Rosenow and Luders, 2001):

- **Irritative zone:** The cortical area that generates interictal epileptiform activity. It is estimated by interictal scalp EEG, magnetoencephalography, or intracranial EEG.

- **Ictal/ seizure onset zone:** The brain region capable to generate ictal epileptiform discharges and therefore spontaneous seizures. It is a subset of the irritative zone. In principle it can be estimated with the same tools as the irritative zone (ictal EEG) plus ictal SPECT.

- **Ictal symptomatogenic zone:** The cortical area that produces the first ictal symptoms in individual patients when it is activated by an epileptic discharge. It can be identical with the ictal onset zone, but it is also possible that it is only activated by propagation in the course of a seizure. It is characterized by clinical seizure semiology (defined by history and video-EEG semiology).

- **Functional deficit zone:** The resection of the functional cortex would result in deficit, the so called functional deficit zone (Rosenow and Luders, 2001). It is defined as a brain region, which shows non-epileptic functional deficits and which can be identified by neurological examination, neuropsychological examination, inter-ictal EEG or PET, interictal SPECT and functional MRI.

- **Eloquent cortex:** The cortical region that is identified as crucial for neurological or cognitive functions (i.e. motor, sensory, visual, language cortex).

- **Epileptogenic lesion:** Structural brain abnormalities which are responsible for the generation of interictal and ictal epileptic activity. It can be identified by neuroimaging methods or by postoperative histological examination.

- **Epileptogenic zone:** Area of brain tissue that is necessary to generate the seizures and which needs to be surgically removed to obtain seizure freedom. It is defined by virtue of a combination of all the above zones estimated during presurgical evaluation.

In order to reliably estimate the epileptogenic zone converging evidence from the different diagnostic modalities is needed.

1.8.3.1. The non-invasive phase (phase I)

During phase I there are diagnostic methods which are obligatory for every patient who undergoes presurgical evaluation, namely video-EEG-Monitoring, high-resolution MRI, neuropsychological evaluation and most recently fMRI. Optional diagnostic tools (interictal PET, ictal SPECT, MR-Spectroscopy, MEG) are only used in case of incongruent or contradictory results. Finally, several new, promising diagnostic tools have been developed during the last years such as electrical source imaging (ESI) with high resolution EEG, high frequency oscillations during EEG, EEG-fMRI, resting state-fMRI and tractography; however, the clinical utility and relevance of these additional methods still needs to be established.

1.8.3.1.1. Prolonged Video-EEG-Monitoring

The documentation of the clinical seizure semiology together with registration of ictal and interictal changes on surface-EEG during prolonged video-EEG-monitoring is arguably the most important investigation for accurate seizure localisation for presurgical evaluation. The video-EEG-documentation can last from 24 hours/ day up to 5-7 days. With the help of the interictal EEG, non-specific changes (regional slowing) but also epileptic discharges (interictal spikes) can be identified and quantified. It is essential that several seizures are registered during the time of the monitoring in order to make sure that all seizures are generated within the same

brain region and it may be necessary to reduce/ withdraw the antiepileptic medication in order to achieve this. Careful documentation of clinical seizure semiology can provide valuable localising and lateralising information, in particular if an appropriate ictal and postictal examination is performed. One major advantage of this method is the possibility to retrospectively correlate registered ictal EEG changes with clinical seizure semiology (Dworetzky and Reinsberger, 2011; Loddenkemper and Kotagal, 2005; Miller and Cole, 2011).

1.8.3.1.2. Structural Imaging – MRI

The recent advances in neuroimaging, in particular the advent of structural MRI has revolutionized the diagnostic possibilities and therefore also epilepsy surgery. Patients with a structural lesion identified on MRI have a chance of 70% to become seizure free after appropriate epilepsy surgery, while only 46% of MRI-negative patients will become seizure free (Tellez-Zenteno et al., 2010). Over the past decade technical advances in image acquisition as well as image processing and image analysis (FLAIR, DWI, T2-relaxometry, hippocampal volumetry, voxel-based morphometry etc.) which are described in detail in chapters 1.3 and 1.7 have additionally confirmed the central role of MRI during presurgical evaluation. Using these novel methods it is now possible to identify structural changes in up to 20% of patients with a previously unremarkable MRI scan, which of course has a great impact on planning surgical strategies (Duncan, 2010).

1.8.3.1.3. Neuropsychological examination

In all patients an extensive and careful neuropsychological examination is necessary in order to create an individualized preoperative neuropsychological profile. While for localisation purposes the functional imaging methods – in particular fMRI – have generally replaced neuropsychological testing, it still has an important role in predicting postoperative neuropsychological decline. Additionally it is possible to initiate preoperative rehabilitation programs which might help preventing postoperative cognitive decline (Baxendale and Thompson, 2010; Helmstaedter, 2004).

1.8.3.1.4. Functional MRI

The role of fMRI in epilepsy imaging and in particular its role in localising the eloquent cortex in the course of presurgical evaluation is discussed in detail in chapter 1.5.

1.8.3.1.5. Intracarotid amygdala test

Today the intracarotid amygdala test (IAT) plays only a minor role in the presurgical assessment of only a small and selected number of TLE patients in some centres. Over the last years it has widely been replaced by fMRI. It was mainly used for assessing the capacity of the contralateral temporal lobe to maintain memory functions, thus guarding against a severe post-operative amnesic syndrome, and as a means of lateralising language function. During the procedure sodium amygdala is injected into one carotid artery via a catheter in the femoral artery. This inactivates the corresponding hemisphere for around 10 minutes, mimicking the effects of surgery on the MTL structures. The activity of the sodium amygdala is monitored by the presence of a contralateral hemiplegia and unilateral slow wave activity on the EEG. During this period the patient is tested with a series of items to name and remember. When the side ipsilateral to the pathology is injected, normal memory function is expected but injection of the contralateral side is expected to result in impaired memory function due to the combined disruptive effects of the pathology and the amygdala. Therefore if poor IAT memory performance is obtained after injection ipsilateral to the seizure focus, the patient may be at risk of postoperative amnesia, given the implication of additional contralateral temporal lobe impairment.

Since the introduction of the IAT and even more though since cognitive fMRI came into use for presurgical evaluation of epilepsy patients numerous studies have (re-)evaluated the role of the IAT in memory testing (Kirsch et al., 2005; Sabsevitz et al., 2001). In summary, the IAT has considerable disadvantages, as it is an expensive, invasive procedure with potentially serious complications. In contrast to the traditional neuropsychological assessment, which relies on standardized tests of cognitive abilities with results that can be easily validated, the IAT differs significantly among the various centers. Differences exist for example in the testing protocols that are used, choice of behavioural stimuli, dosage and administration of amygdala, which can all

lead to variations in the results (Baxendale, 2002; Baxendale et al., 2007). The IAT has also been shown to be a poor predictor of verbal memory decline as deactivation of the language dominant hemisphere will cause increased errors on verbal memory testing (Kirsch et al., 2005). And finally doubts also exist about its reliability and validity in predicting postoperative amnesia.

1.8.3.1.6. PET and SPECT

The basic principles of PET and SPECT and how it is used during presurgical evaluation is discussed in chapter 1.6.

1.8.3.1.7. Magnetoencephalography (MEG)

Using MEG field potentials related to neuronal activity can be registered similar to EEG. The great advantage of MEG compared to EEG is a higher sensitivity for detecting superficial neuronal sources orientated perpendicular to the scalp and a faster registration with a high number of sensors. However, its use is limited by technical requirements, as highly specialized scanning systems are needed and by the time the patients need to spend in the scanner. It can provide additional information which may be helpful in localising the seizure onset zone in MRI-negative patients (Baumgartner and Patariaia, 2006; Stefan et al., 2003; Stefan et al., 2011) and also in improving implantation strategies in patients who are undergoing intracranial recordings; there is evidence that the resection of the irritative zone as defined by MEG correlates with good postoperative seizure control (Schneider et al., 2013).

1.8.3.1.8. Electroencephalographic (EEG) source imaging (ESI) with high resolution EEG

EEG source imaging has made tremendous progress in recent years. With this approach it is possible to consider the temporal and spatial dimension of brain activity simultaneously using increasingly high numbers of EEG sensors. In brief, the source imaging procedure includes the application of a source localisation algorithm to EEG data, resulting in reconstructed maps of

electrical activity in the brain which are then coregistered with the patient's MRI to aid localisation of epileptic activity.

Using ESI in 8 out of 10 MRI-negative patients (5 with an extratemporal seizure onset) it was possible to correctly localise the seizure onset zone (Brodbeck et al., 2010). Similar results have since been replicated in both adults (Kaiboriboon et al., 2012; Wang et al., 2011) and children (Elshoff et al., 2012). Therefore in patients with unremarkable MRI, ESI with high resolution EEG may provide valuable information for presurgical evaluation.

1.8.3.1.9. High frequency oscillations (HFO) during surface-EEG

During the last years the analysis of so-called "high frequency oscillations" on intracranial EEG with a spectrum of more than 80 Hz (compared to the routine EEG which typically considers frequencies below 70 Hz) has shown some promising results: Several studies demonstrated that HFOs seem to be a good indicator for localising the seizure onset zone and complete resection of the cortical area from which HFOs were recorded was associated with a better postsurgical outcome (Jacobs et al., 2012; Zijlmans et al., 2012). Most recently Andrade-Valenca and colleagues registered HFOs (γ -oscillations 40-80 Hz and "ripples" with > 80 Hz) even with surface-EEG. In this study HFOs had a lower sensitivity, but a higher specificity and better accuracy for the localisation of the seizure onset zone compared to the usual interictal spikes (Andrade-Valenca et al., 2011).

1.8.3.1.10. EEG-fMRI

Another relatively new promising tool for the presurgical workup is simultaneous EEG-fMRI which can reveal regions of haemodynamic fluctuations related to epileptic activity and help localising its generators. The original idea behind this method was that interictal epileptiform discharges (IED) such as spikes were related to BOLD signal changes (Gotman and Pittau, 2011) and these were sometimes colocalised with regions giving rise to seizures. Applied to epilepsy, it has been shown that in particular in patients with multifocal or contradictory results from conventional examinations, EEG-fMRI provided an additional source of information

regarding the possible seizure onset zone (Al-Asmi et al., 2003; Salek-Haddadi et al., 2006). Good concordance between results from EEG-fMRI and intracranial EEG as the current gold standard has been shown (Zijlmans et al., 2007). In another study Thornton and colleagues not only demonstrated an excellent correlation between the localisation of the epileptogenic zone with the help of EEG-fMRI and intracranial EEG, but were also able to predict postoperative seizure control in a cohort of patients with focal cortical dysplasia (Thornton et al., 2011).

One draw-back of using EEG-fMRI is that in 40-70% of all patients no conclusions can be drawn due to the absence of interictal epileptiform discharges during simultaneous recordings, or the lack of haemodynamic changes correlated to interictal epileptiform discharges. To address this, Grouiller and colleagues investigated whether epilepsy-specific voltage maps on scalp-EEG correlated with haemodynamic changes in the absence of IEDs recorded during scanning. By building epilepsy-specific EEG voltage maps using averaged interictal epileptiform discharges recorded during long-term video-EEG monitoring outside the scanner they calculated the correlation of this map with the EEG findings in the scanner for each time frame. The time course of this correlation coefficient was used as a regressor for functional magnetic resonance imaging analysis to map haemodynamic changes related to these epilepsy-specific maps (topography-related haemodynamic changes). Using this method it was possible to localise the epileptogenic zone in 78% of patients with previously inconclusive EEG-fMRI findings (validated by the spatial correlation with intracranial EEG findings or with the resection area). Better concordance was seen in patients with lateral temporal and extratemporal neocortical epilepsy compared to medial or polar temporal lobe epilepsy (Grouiller et al., 2011).

More recently, the first ictal studies were published (Donaire et al., 2009). In a group of patients with frequent seizures Chaudhary and coworkers found that ictal BOLD changes showed a concordance with the seizure onset zone in 85%; in 65% of the patients even a sub lobar localisation was possible and most interestingly in 75% changes that were concordant with the seizure onset zone could be registered already 98-14 seconds before the electro-clinical seizure onset (Chaudhary et al., 2012).

1.8.3.1.11. Resting-state fMRI

The aim of this method is to use studies of connectivity to make inferences about the epileptic network. One group, studying the functional connectivity of the right hippocampus with the nucleus ventralis lateralis of the thalamus showed that it was possible to differentiate between left and right sided TLE with a high sensitivity and specificity: right TLE patients showed a low functional connectivity while in left TLE patients the right hippocampus showed a strong functional connectivity with the thalamus. In addition a significant correlation between functional connectivity and postoperative seizure control was shown (Morgan et al., 2012). Resting state fMRI was also useful for predicting postoperative seizure control, as in patients with postoperative seizure recurrence functional connectivity was significantly less lateralised than in patients who were seizure free after surgery (Negishi et al., 2011).

1.8.3.1.12. Tractography

The methodological principles of diffusion weighted imaging and tractography and how they are applied to epilepsy are discussed in detail in chapter 1.7.

1.8.3.2. The invasive phase (phase II):

If the findings of phase I are inconclusive or contradictory, intracranial electrodes must be brought into use in phase II.

Invasive EEG recording is carried out by using temporarily implanted electrodes to register interictal epileptiform discharges and spontaneous seizures over a prolonged period of time, usually one to two weeks, as well as allowing stimulation studies. Two types of electrodes are commonly used, depth electrodes and sub-dural electrodes (in strip or grid configurations). Sometimes a combination of both types is used.

If the presumed epileptogenic zone which needs to be resected is located in close vicinity to the eloquent cortex, intracranial functional mapping (electrocorticography) can be performed at the same time as invasive recording.

Placement of electrodes is performed in each individual patient based on results of the non-invasive investigations.

1.8.3.2.1. Stereotactic implanted depth electrodes (stereotactic EEG)

Depth electrodes are semiflexible, multi-contact electrodes (4-12 contacts), that are usually implanted under stereotactic guidance using navigations systems, allowing registration from within the cortical substance as well as deep structures, which normally cannot be detected using surface EEG.

1.8.3.2.2. Sub-dural grid electrodes

Sub-dural grid electrodes include strips (single row) or grid (several interlinked rows) electrodes, which typically consist of conductive metal disc electrodes constructed in flexible plastic layers which are directly placed on the surface of the brain following a craniotomy or insertion via small “burr-holes” and stripping of the dura. Electrodes can be inserted in the inter-hemispheric fissure if seizures are assumed to have a medial onset, but can also be placed over the convexity of the cerebral cortex.

The electrodes remain implanted for a variable period of time until spontaneous seizures can be registered; it is also possible to carry out stimulations to delineate the eloquent cortex if necessary but also to record seizures following stimulation (Kahane and Spencer, 2012; Lesser et al., 2011).

In clinical practice, the choice between using depth electrodes or sub-dural grids and strips depends on the pathology and the patient’s seizure semiology and has to be made for each individual patient.

1.8.3.2.3. Safety and Efficacy

A large retrospective study investigated efficacy and safety of invasive recordings in a cohort of 242 patients with medically refractory epilepsy and 18 tumour patients. In this study invasive

electrodes remained implanted between 3 to 40 days; any kind of (minor) complication occurred in 23% of all patients, while in only 9% major complications which required a neurosurgical intervention were noted. There was no case of permanent disability or death and in general complications were more often associated with subdural grids than with depth electrodes. In 99.2% of all patients seizures could be registered; only in 6.3% of all cases no resective surgical intervention could be performed (Wellmer et al., 2012).

1.8.4. Surgery for specific epileptic syndromes

1.8.4.1. Surgery for temporal lobe epilepsy

Surgical treatment of TLE and in particular of patients with mesial TLE quantitatively represents the biggest group of surgical procedures carried out for epilepsy. At first so-called *en bloc* temporal lobe resections were typically carried out. With advances in surgical techniques, new surgical procedures have been developed which allow more tailored resections; during an anterior temporal lobe resection (ATLR) surgery is restricted to the temporal pole and the mesial temporal structures while lateral temporal structures are spared, but surgery may even be restricted to the mesial temporal lobe structures only (selective amygdala-hippocampectomy (sAHE)) (Spencer and Inserni, 1992; Wieser and Yasargil, 1982). It has been shown, that for optimal seizure control resection of the mesial temporal lobe structures should be carried out from the pes hippocampi 2-3 cm posteriorly to the lateral sulcus, so that also the entorhinal cortex is removed. There has been an ongoing discussion with partly contradictory results about the significance of removal of more posterior regions of the temporal lobe regarding postoperative seizure control but also regarding cognitive outcome (Okonma et al., 2011). A major part of this thesis has been dedicated to further explore this interesting aspect. A review of 53 studies showed that the neuropsychological outcome after sAHE was significantly better than after ATLR while there was no difference in surgical outcome between the two procedures (Schramm, 2008). In a more recent meta-analysis with 1203 patients it could be shown, that cessation of seizures (Engel class I outcome) was significantly more often achieved in patients who underwent an ATLR instead of sAHE; this results remained even significant during

subgroup-analysis looking at patients with hippocampal sclerosis only (Josephson et al., 2013). The authors therefore postulated that better seizure control after ATR needs to be weighted versus better postoperative neuropsychological outcome. Similarly in children, surgery for temporal lobe epilepsy results in excellent long-term seizure control with good cognitive outcome and improved brain development (Skirrow et al., 2011).

1.8.4.2. Surgery for lateral temporal and extratemporal lobe epilepsy

For surgical treatment of extra-temporal and neocortical temporal lobe epilepsies cortical resections are carried out. Planning of surgical strategies is mainly dependent on the existence of a structural lesion, removal of which together with electrophysiological parameters is crucial for postoperative seizure control (Okonma et al., 2011), although good outcomes are also reported in the absence of a lesion on MRI (McGonigal et al., 2007).

In case of extensive lesions (Rasmussen's encephalitis, Sturge-Weber-Syndrome etc.) which often cause difficult-to-treat epilepsies in early childhood, generous multilobar resections or functional hemispherectomies/ hemispherotomies might be necessary. In particular children with frequent seizures often show a significant improvement not only regarding seizure control but also regarding psychomotor development after an early surgical intervention (Obeid et al., 2009; Schramm and Clusmann, 2008).

1.8.4.3. Palliative procedures

A callosotomy is indicated for treatment of drug-refractory seizures which occur in context of the Lennox-Gastaut-Syndrome. During this palliative procedure the first two thirds of the corpus callosum are severed, so that the interhemispheric propagation of epileptic activity between both frontal and parietal lobes is disrupted (Obeid et al., 2009).

If a surgical resection is not possible because of the risk of major postoperative neurological or neuropsychological deficits, an alternative treatment option is a technique called multiple subpial transections (Morrell et al., 1989); this surgical approach requires severing of the tangential intracortical fibers while preserving the vertical fiber connections, and therefore

inhibits horizontal propagation of seizures. However, long-term results of multiple subpial resections alone were disappointing.

If a surgical resection is not appropriate vagal nerve stimulation (VNS) has been established as an alternative treatment option for many years with an estimated median seizure reduction rate in certain epilepsy syndromes of 30%. Lately also promising attempts have been reported to use deep brain stimulation (DBS) for medically refractory focal epilepsy, with the stimulation targeted at the sub-thalamic nucleus and the centro-median thalamic nucleus. Detailed discussion of these methods is beyond the scope of this thesis.

1.8.5. Postoperative seizure control

1.8.5.1. Postoperative outcome-scales

The two most important classification systems to measure postoperative seizure outcome are Engel's classification (Engel et al., 1993) and the ILAE classification proposed by Wieser et al. (Wieser et al., 2001). According to Engel's classification postoperative outcomes are divided into 4 categories. However, in clinical practice the use of this scale is associated with several methodological problems; it does not account for the fact that seizures might change over time postoperatively and therefore does not allow longitudinal assessment of seizure frequency. During the postoperative clinical course considerable variability in the frequency of seizures occurs within the various patient populations. It is important therefore to differentiate between

1. Immediate cessation of symptoms;
2. Reduction of seizure frequency over the time with a late cure ("running down phenomenon");
3. Relapse of seizures after a seizure-free period of time;
4. Continued seizures (Salanova et al., 1996).

Another drawback of Engel's classification is the fact that it does not take into account preoperative seizure frequency so that it is not possible to precisely quantify seizure frequency. Also the definition of being "seizure free" is somehow imprecise as there is no differentiation between being "complete seizure free" and the occurrence of auras. For these reasons Wieser's

classification was proposed in 2001, trying to address these issues (Table 8.1). Postoperative results in this thesis are reported according to Wieser's classification.

Table 8.1 ILAE Classification of seizure outcome following surgery for focal epilepsy (from ILAE Commission Report, 2001)

Outcome classification	Definition
Class	
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

1.8.5.2. Prediction of postoperative seizure outcome

Recently several comprehensive studies have systematically investigated long term outcome after epilepsy surgery. De Tisi et al reported follow-up data in one centre over a median of 8 years and showed seizure freedom rates of 52% at 5 years and 47% at 10 years across all patients, while reiterating the findings of previous studies that the best outcomes were in those with mesial temporal lobe epilepsy compared to patients with extratemporal lobe epilepsy. Within the TLE group patients with hippocampal sclerosis had a better outcome compared to those with focal cortical dysplasia or unremarkable histopathological findings. In addition they also reported that relapse became less likely with longer periods of remission, while remission was much less likely if there was a long period in which seizures were refractory to treatment following surgery. In common with other studies of postoperative surgical outcome, there was a decline in seizure freedom with longer follow up periods (de Tisi et al., 2011). One study investigating the long-term outcome after extra-temporal resection in 81 patients showed that

only 23.5% of all patients were free from disabling seizures after one year and 14.7% after 5 years (McIntosh et al., 2012). An 80% reduction of seizures could be achieved in 57% of all patients after 5 years. Predictors of an unfavorable seizure outcome included focal cortical dysplasia type I, incomplete resection of a lesion and early seizures after a surgical intervention. The most significant predictor of postoperative seizure outcome was the identification of a structural lesion. On average postoperative seizure freedom can be achieved in 70% of all patients with a structural lesion on MRI, but in only 46% of MRI-negative patients (Tellez-Zenteno et al., 2010). Subgroup analysis showed that 75% of all TLE patients with a structural lesion and 51% of MRI-negative TLE patients remained seizure free; in patients who underwent an extra-temporal resection 51% with a structural lesion and 35% with unremarkable MRI scan became seizure free (Tellez-Zenteno et al., 2010).

In MRI negative patients it is also crucial to differentiate between patients with a normal histopathological (histology-negative) result and patients with a positive histopathological examination (histology-positive). In 190 MRI-negative patients who underwent presurgical evaluation 29 patients (15%) finally had a surgical intervention. 38% of these patients were completely seizure free, another 45% were seizure free with persisting auras. In 9 patients histopathological examination showed a focal histopathological lesion, which – retrospectively – could also be identified on previous MRI scans in 8 of these patients. 7 out of 9 MRI-negative, histology-positive patients (78%) became seizure free, compared to 4 out of 20 MRI-negative, histology-negative patients (20%), ($p=0.003$) (Bien et al., 2009). This underpins the importance of re-evaluation of MRI findings with all information obtained from additional non-invasive investigations during phase I of the presurgical evaluation before proceeding to phase II.

1.8.6. Complications following epilepsy surgery

The positive effect of seizure reduction or termination by surgical intervention on the quality of life of patients has been indicated in several studies (Hermann et al., 2000; McLachlan et al., 1997). However, unfortunately epilepsy surgery can be complicated by unwanted side effects, which can be divided into neurological, psychological and psychiatric complications.

How fMRI can further add to our understanding of cognitive and in particular memory and language impairment so often seen in temporal lobe epilepsy patients is one major topic of this thesis. Much of the work in this thesis has been dedicated to further explore the role of fMRI as a potential predictor of postoperative complications, and how it ultimately may help us to prevent them.

1.8.6.1. Neurological complications

In approximately 10% of patients following ATR visual field defects can occur and in 5% these are severe enough to render the patient ineligible for a driving license, despite being seizure free. Typically visual field defects take the form of a superior homonymous quadrantanopia and are due to the disruption of Meyer's loop, the anterior part of the optic radiation (refer to chapter 1.7.4 for more detail). More serious complications such as intracranial infection, haemorrhages, severe neurological deficits, e.g. hemiparesis, and occasionally death occur less frequently, with most studies reporting a risk between 1 and 5%.

1.8.6.2. Psychological complications

The most famous case of postoperative memory impairment is that of the devastating amnesia suffered by the patient HM after an extensive bilateral temporal lobe resection. Although his ability to retrieve information learnt prior to surgery was unaffected and general intellectual function and personality remained intact, HM was unable to learn any new information. In the following Scoville and Milner reported the results of memory tests of 10 patients who had undergone bilateral temporal lobe resections, which confirmed that those patients in whom resections were extensive enough to damage the hippocampus demonstrated a clear and persistent disturbance of recent memory, and that the extent of the resection was related to the memory disturbance (Scoville and Milner, 2000). These findings led to the end of practicing bilateral temporal lobe resections for the relief of focal epilepsy.

However, positive changes in neuropsychological functions may occur after unilateral temporal lobe surgery. This may be due, in part, to cessation of seizures but also to reduction in doses of

antiepileptic drugs. It has been shown, that improvements are greatest in cognitive functions subserved by the hemisphere contralateral to the site of resection and are typically observed in patients who become seizure-free (Rausch and Crandall, 1982).

The careful and individualized documentation of cognitive risk factors associated with epilepsy surgery is of ultimate importance and will help counseling patients regarding the attendant risks with more confidence.

1.8.6.3. Psychiatric complications

The prevalence of psychiatric conditions, such as affective disorders, anxiety disorders and psychosis is high in patients with medically refractory TLE both before and after surgical treatment. Therefore, psychiatric assessment prior to surgery is mandatory in order to document evidence of psychiatric conditions which may require separate interventions and to identify patients who may need additional psychiatric support postoperatively. However, it has been shown that while pre-existing psychiatric conditions may be resolved or diminished following ATR, new psychiatric problems can occur in up to one third of patients (Glosser et al., 2000).

Many of these psychiatric problems were transitory mood disorders which had usually resolved when patients were re-evaluated one year after surgery. Theories regarding the underlying anatomical mechanisms include disruption of the functional network within the temporal lobe structures involved in emotional processing (Ring et al., 1998), so-called ‘forced normalisation’ which is responsible for the occurrence of “new” affective disorders through the suppression of the antidepressant effects of seizures, or because patients respond negatively to increased expectations once seizures have been abolished or reduced (burden of normality). Having said this, seizure free status has been recognized as the most powerful predictor of improved psychiatric and psychosocial outcome later in the postoperative course (Bladin, 1992; Hermann et al., 1992a).

Psychotic disorders are less likely to change after surgery (Trimble, 1992), so that in clinical practice surgical treatment is not offered to patients with epilepsy and psychotic disorders (with the exception of isolated postictal psychosis). Psychosis may however present for the first time

after temporal lobe surgery and it has been suggested that it is more common following right-sided surgery and which typically follows a chronic interictal course. There are also some reports of the de novo occurrence of postoperative postictal psychosis after ATR, associated with seizure recurrence contralateral to the resection (Christodoulou et al., 2002). Episodes of postictal psychosis preoperatively are not a contraindication for temporal lobe surgery.

Considering long term psychosocial outcomes of patients who undergo ATR compared with medically managed patients, surgery has been shown to have a significant positive impact in terms of employment, independent living, driving and financial independence (Jones et al., 2002).

As the relation between seizure control and psychiatric symptoms shortly after surgery is still an open question and as psychiatric problems are still underreported in TLE, parts of this thesis have been dedicated to the investigation of the role of functional MRI for evaluation of emotional disturbances in TLE and how they may be predicted (chapter 1.5.2.5 and chapter 7).

1.9. MODERN EPILEPSY SURGERY - SUMMARY

These days a wide range of surgical procedures including lesionectomies, *en bloc* temporal lobe resection, anterior temporal lobe resection, hemispherectomy and extra-temporal cortical resection can be carried out in a large number of centres. Selection of patients is based on the principles that they have drug resistant seizures of a frequency and severity to cause social and/or medical disability, that the risk-benefit of surgery is acceptable, and that there is convergent data from different investigative modalities localising the seizure onset zone, and that this can be removed without causing serious new morbidity.

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.

CHAPTER II

2. COMMON METHODOLOGY

This chapter describes common experimental methods which were used for more than one of the studies described in subsequent chapters. Information is provided on subject recruitment, MR data acquisition and analysis, cognitive paradigms that were used for the fMRI studies and the neuropsychological tasks that were routinely used during presurgical evaluation and which provided the basis for correlational analyses between fMRI results and out-of-scanner performance. The following chapters refer back to this section; in those studies, where a specific analysis was used only in one particular study it is included in the relevant chapter.

All of the subsequent research studies were approved by the Research Ethics Committee of the UCL Institute of Neurology and UCL Hospitals. Written informed consent was obtained from all patients and healthy controls.

2.1. SUBJECT RECRUITMENT

All patients were recruited from the National Hospital for Neurology and Neurosurgery, London, United Kingdom, and the Epilepsy Society, Chalfont St Peter, United Kingdom. All patients suffered from medically refractory unilateral TLE and underwent presurgical 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.

The control subjects were all right-handed native English-speaking healthy volunteers with no history of neurological or psychiatric disease.

2.2. ACQUISITION OF CLINICAL DATA AND NEUROPSYCHOLOGICAL EVALUATION

2.2.1. Clinical data

2.2.1.1. Electro-clinical characteristics

Electro-clinical assessment was carried out in all patients with prolonged interictal and ictal video-EEG monitoring at the National Hospital for Neurology and Neurosurgery, which confirmed seizure onset in one temporal lobe, ipsilateral to the side of the lesion. In addition, all patients had structural MRI at 3T (Duncan, 1997), including qualitative assessment by expert neuroradiologists and quantification of hippocampal volumes and T2 relaxation times according to previously published protocols (Bartlett et al., 2007; Van Paesschen et al., 1995; Woermann et al., 1998a) as well as psychological and psychiatric assessments. On qualitative and quantitative assessment all patients had normal MTL structures (in particular a normal hippocampus) on the contralateral side to their epilepsy. All patients' first language was English and all were treated with antiepileptic medication at the time of their assessment. Handedness was determined using the Edinburgh Hand Preference Inventory (Oldfield, 1971).

2.2.1.2. Surgical resection

In those patients on whom surgery was performed left or right ATLRL was carried out by the same neurosurgeon, Mr AW McEvoy. The standard neurosurgical procedure was removal of the temporal pole and opening of the temporal horn, followed by en bloc resection of the hippocampus with a posterior resection margin at the mid-brainstem level. The same neocortical resection was performed to 3–3.5 cm on both the left and the right sides including the superior temporal gyrus to this length on both left and right sides. The International League Against Epilepsy (ILAE) classification of postoperative seizure outcome following epilepsy surgery was used (Wieser et al., 2001). Seizure outcomes are given at one year after surgery for all patients if not stated otherwise.

2.2.2. Neuropsychological and psychiatric evaluation

All patients underwent preoperative language and memory fMRI and standard neuropsychological and psychiatric assessment. In those patients undergoing epilepsy surgery this was repeated four months postoperatively. Neuropsychological and psychiatric evaluation was carried out according to the standard presurgical assessment at the National Hospital for Neurology and Neurosurgery. All tests were performed at least 24 hours after a secondarily generalized and at least 6 hours after a complex partial seizure.

2.2.2.1. Intelligent quotient (IQ)

IQ was measured using the Wechsler Adult Intelligence Scale (WAIS-III). In the subsequent experiments assessing language function verbal IQ was used as a covariate to control for the effect of ability level on fMRI activation.

In controls, IQ was estimated using the Nelson Adult Reading Test (Nelson and Willison, 1991).

We used two language tests, phonemic verbal fluency and the McKenna Graded Naming Test (McKenna&Warrington,1983), as patients with TLE are at particular risk of developing naming deficits after ATR (Davies et al., 1998) (refer to chapter 1.5.2.3 for more detail).

2.2.2.2. Phonemic verbal fluency (VF)

All subjects completed a VF test outside the scanner. The subject is given 60 s to produce as many words starting with a given letter (“S”). This is a non-standardised test used commonly in our clinical practice. The total number of words correctly produced is the performance indicator.

In the subsequent language experiments performance during the out of scanner VF task was used as a proxy measure of motivation and adherence to the in scanner tasks, which could not be ascertained during scanning due to the covert nature of the responses.

2.2.2.3. Naming

All subjects completed the McKenna Graded Naming Test. This is a well-established confrontation naming test commonly used to assess expressive language functions in the United Kingdom. The subject is required to name 30 black and white line drawings of increasing difficulty. The total number of items correctly named is the performance indicator (McKenna & Warrington, 1983).

We selected two learning tests, one verbal and one visual, from the memory tests employed that have been demonstrated to be good indicators of postoperative memory decline (Baxendale et al., 2006). The verbal learning test was chosen as it has less semantic content than other verbal memory tests (i.e. verbal recall) so that it is a better test for hippocampal function.

For both tests, verbal learning and design learning, reliable change indices (RCIs) were available, so that patients with a clinically significant memory change after surgery could be identified.

2.2.2.4. Verbal learning

In the verbal learning task, subjects are read a list of 15 words five times and following each presentation they are asked to recall as many words as possible. The total number of correct words, expressed as a percentage, was used as the indicator of verbal memory performance.

2.2.2.5. Design learning

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 measure of visual memory performance.

2.2.2.6. Anxiety and depression

As cognitive functions, in particular memory, may be affected by anxiety and depression, all patients (and controls) were tested for comorbid anxiety and depression preoperatively and

again at the time of their postoperative assessment (4 months after ATR) using the Hospital Anxiety and Depression Scale (HADS) as a measure of self-reported symptoms of anxiety and depression (Zigmond and Snaith, 1983).

The scale is a user-friendly, concise questionnaire comprising 14 items that assess current levels of anxiety and depression. The score is derived from responses on a four-point Likert-type scale. A score of 7 or above is considered positive and scores classify the severity of symptoms as follows: normal (0–6), mild (7–10), moderate (11–13), severe (14 and above).

2.2.2.7. Comparison of pre- and postoperative results

In those patients who underwent an ATR, measures of language and verbal and visual memory changes following surgery were calculated as postoperative – preoperative scores and recorded. A clinically meaningful postoperative naming change was defined as a change of >3 points, which represented a decline of at least 15 centiles. A clinically significant VF decline was defined as change of >1 standard deviation (SD). A clinically significant postoperative memory change was defined using reliable change indices (Baxendale and Thompson, 2005). The reliable change indices (90% confidence interval) were 16% for verbal learning and 28% for design learning.

Pre- and postoperative scores as well as changes in language and verbal and visual memory scores from baseline following left/right ATR were correlated with pre- and postoperative fMRI activation patterns, to assess the ability of language/ memory fMRI to predict postoperative language/memory deficits as detailed below (refer to section 2.3.3).

A clinically significant change in anxiety and depression scores was defined by a change in category.

2.3. FUNCTIONAL MRI

2.3.1. Acquisition details

The acquisition of imaging data was the same for all pre- and postoperative fMRI studies. All fMRI studies were performed on a 3T General Electric Excite HDx scanner (General Electric,

Milwaukee, WI, U.S.A.). Standard imaging gradients with a maximum strength of 40 mT/m and slew rate 150 T/m/s were used. All data were acquired using an eight-channel array head coil for reception and the body coil for transmission. In addition to the fMRI data, for each subject we acquired a high resolution echo planar image covering the whole brain with the following parameters: two shots, echo time = 30 ms, repetition time = 4500 ms, matrix 256x256, 88 contiguous 1.5 mm slices. The geometric distortions were matched by introducing an additional delay to increase the echo spacing (Boulby et al., 2005).

For both, the memory encoding task and the two language tasks, gradient-echo planar T2*-weighted images were acquired, providing BOLD contrast.

2.3.1.1. Language fMRI

Each volume comprised 58 contiguous 2.5 mm oblique axial slices, through the temporal and frontal lobes with a 24 cm field of view, 96x96 matrix, reconstructed to 128x128 for an in-plane resolution of 1.88x1.88 mm. TE was 30 ms and TR 4.5 s. The field of view was positioned to maximize coverage of the frontal and temporal lobes.

2.3.1.2. Memory fMRI

Each volume comprised 44 contiguous 1.5 mm oblique axial slices through the temporal and frontal lobes, with a 24 cm field of view, 128x128 matrix and in-plane resolution of 1.88x1.88 mm; echo time = 30 ms and repetition time = 4.5 s. The field of view was positioned to cover the temporal lobe with the anterior–posterior axis aligned with the long axis of the hippocampus on sagittal views, and with the body of the hippocampus in the centre.

2.3.2. Cognitive fMRI paradigms

2.3.2.1. Language paradigms

Subjects performed two language fMRI experiments, verbal fluency (VF) and verb generation (VG) preoperatively and, in those patients who underwent surgery, postoperatively. Both

paradigms consisted of a blocked experimental design with 30-s activation blocks alternating with 30-s of cross-hair fixation over 5.5 min. During the **VF task block** subjects were asked during the activation phase to covertly generate different words beginning with a visually presented letter (A, S, W, D, and E) contrasted by crosshair fixation as rest condition.

During the **VG task block**, concrete nouns were presented visually every 3 s in blocks of 10 contrasted by 30 s of crosshair fixation as rest. Subjects were instructed to either covertly generate verbs associated with these nouns (indicated by the letter “G” preceding the noun) or silently repeat the nouns presented (indicated by the letter “R” preceding the noun) during the activation time.

Both paradigms were used to identify anterior language regions in the inferior and middle frontal gyri (Liegeois et al., 2004; Woermann et al., 2003).

We assessed language dominance using a range of fMRI tasks (Powell et al., 2006). For quantification, we calculated pre- (and postoperative) lateralisation indices using the Bootstrap method of the SPM (statistical parametric mapping (<http://www.fil.ion.ucl.ac.uk/spm/>)) (Friston et al., 1995) toolbox (Wilke and Lidzba, 2007) for the contrast ‘verbal fluency’ for each subject in the middle and inferior frontal gyri using anatomical masks (Hammers et al., 2003). The verb generation task was additionally used to define language dominance in patients with a LI between -0.2 and -0.4 on the VF task.

In all memory studies these lateralisation indices were used as covariates for the second level analysis.

2.3.2.2. Memory paradigm

The following paradigm was designed to investigate verbal and visual memory encoding (Powell et al., 2007). Stimuli of three different material types [Pictures (P), Words (W) and Faces (F)] were visually presented to the subjects during a single scanning session. Stimuli were presented on a black background using Cogent 2000 (www.fil.ion.ucl.ac.uk/cogent2000). A total of 210 stimuli were presented, one every 4 s, in 7 cycles. Each cycle consisted of a block of

10 pictures (black and white nameable line drawn objects), 10 words (single concrete nouns) and 10 faces (partly black and white, partly coloured photographs unfamiliar to the subjects), followed by 20 s of crosshair fixation. During scanning, subjects were instructed to perform a deep encoding task which involved making a judgment on whether each stimulus was pleasant or unpleasant, and to indicate this using a button press. This task was employed in order to encourage stimulus encoding, but was not used in any subsequent parts of the fMRI analysis. Sixty minutes after scanning, subjects performed a recognition test outside the scanner; this comprised three separate blocks (one for pictures, one for words and one for faces). For the recognition task each of the 70 stimuli of each material type presented during scanning were randomly mixed with 35 foils and presented in an identical way to that used during scanning. Subjects were instructed to indicate whether they could remember seeing the stimulus during scanning or whether it was new to them. The 210 encoding stimuli presented during scanning were classified according to the responses made during the recognition test. A correctly remembered (R) response indicated the stimulus was subsequently remembered. An incorrect response indicated the stimulus was subsequently forgotten (F). Thus, for each of the three stimulus types (P, W and F) R and F responses were identified, giving a total of six event types: PR, WR, FR and PF, WF and FF. These were then entered as regressors in the design matrix. Recognition accuracy for each event type was calculated in our subjects as follows: Stimuli seen in the recognition test were classified as ‘hits’ (stimuli correctly remembered) and ‘false alarms’ (foils incorrectly tagged as remembered). Recognition accuracy was then calculated for each stimulus type as: hit rate minus false alarm rate. All subjects with rates of <20% or >80% for the two possible responses ‘remembered’ and ‘forgotten’ were not included in this study as there were not enough responses in the different categories to ensure sufficient contrast.

2.3.3. Data analysis

2.3.3.1. Preprocessing

The images were transferred to a Linux workstation and converted to ANALYZE format for analysis. All imaging data were analysed using Statistical Parametric Mapping (SPM5) (using

SPM5 software from the Wellcome Trust Centre for Imaging Neuroscience (<http://www.fil.ion.ucl.ac.uk/spm/>) (Friston et al., 1995).

The preoperative imaging time series of each subject was realigned using the mean image as a reference, spatially normalised into standard anatomical space (using a scanner specific template from 30 healthy controls, 15 patients with left HS and 15 patients with right HS) (including the individual coregistered high resolution whole brain EPIs in all memory studies, to give anatomical reference), and smoothed with a Gaussian kernel of 10 mm FWHM (full width at half maximum).

Postoperative scans were 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. All scans were then smoothed with a Gaussian kernel of 10 mm FWHM. Co-registration of postoperative scans was checked visually for each subject.

In order to remove low frequency noise (e.g. due to scanner drift) the time-series in each voxel was high pass filtered with a cutoff of 1/128 Hz.

2.3.3.2. Analysis of language data

A two-level random-effects analysis was employed for all preoperative and postoperative imaging data. At the first level, condition-specific effects were estimated according to the GLM (Friston et al., 1995) for each subject. Regressors of interest were formed by creating boxcar functions of task against rest. Parameter estimates for regressors were calculated for each voxel. One contrast image was produced for each subject preoperatively (and postoperatively) within the groups (controls, left and right TLE patients), corresponding to the main effects of verbal fluency against fixation. This contrast image was used for the second-level analysis.

At the second level, individual subject's contrast images were combined and used

1. To examine the main effects of verbal fluency across the whole group;
2. To test for correlations between areas of VF fMRI activation and both, preoperative and postoperative performance on VF/ naming outside the scanner.

Verbal IQ was entered as an additional covariate to control for performance.

Unless otherwise stated, I report activations at a threshold of $P < 0.05$, corrected for multiple comparisons (family wise error rate [FWE]) across the whole brain. For correlation analyses with neuropsychological data I report all medial temporal and frontal activations at a threshold of $P < 0.01$, corrected for multiple comparisons in small volumes of interest (SVI). MTL activations were labeled with reference to Duvernoy's the Human Hippocampus (Duvernoy, 1998).

2.3.3.3. Analysis of memory data

Event-related analysis

In order to test for subsequent memory effects, an event-related analysis was used to compare encoding-related responses to individual stimuli that were subsequently remembered versus stimuli that were forgotten (Friston et al., 1998; Mechelli et al., 2003; Powell et al., 2005a; Richardson et al., 2004b; Seghier et al., 2012). A two-level, event-related, random-effects analysis was employed.

At the first level, for each subject trial specific responses were modeled by convolving a delta function that indicated each event onset with the canonical haemodynamic response function to create regressors of interest, one regressor for each of the six event types (PR, PF, WR, WF, FR and FF). Each subject's movement parameters were included as confounds and parameter estimates pertaining to the height of the haemodynamic response function for each regressor of interest were calculated for each voxel. Three contrast images were created for each subject corresponding to the subsequent memory effect for each material type (picture encoding defined by PR–PF, word encoding defined by WR–WF and face encoding defined by FR–FF). All these images were then used for the second-level analysis.

Second level analyses were performed

1. To examine group effects for the controls and the left and right TLE groups (pre- and postoperatively). Each subject's contrast images were entered into a second level one sample t-test, which modeled the group effect (i.e. control subjects or patients pre- and postoperatively) on the various contrasts of interest; two sample t-tests were used to highlight brain regions demonstrating more or less activation in one group compared with another.
2. In order to test for correlations between areas of fMRI activation and subject's performance on verbal learning and design learning pre- and postoperatively, simple and multiple regression analyses were performed over the whole brain. The verbal learning score and the design learning score were entered as covariates for each subject, separately for controls, left and right TLE patients.
3. The measures of change of verbal learning and design learning scores were used to test for correlations between preoperative fMRI activation and change in verbal and visual memory test scores, from before to four months after epilepsy surgery in those patients who had an ATR and postoperative neuropsychological assessment.

Unless otherwise stated, we report all MTL activations at a threshold of $P < 0.01$, corrected for multiple comparisons (FWE in a small volume of interest). In view of our a priori hypothesis we performed the small volume correction using a sphere of 10 mm diameter for the left and right hippocampi based on the group peak activation. MTL regions of activation were labeled with reference to Duvernoy's *The Human Hippocampus* (Duvernoy, 1998).

In chapters III and IV we used functional MRI (fMRI) to study basic language function and how this is impaired in a group of healthy volunteers and patients with temporal lobe epilepsy (TLE); secondly, we investigated the role of functional MRI as a potential predictor of language decline following anterior temporal lobe resection (ATLR); third, we aimed to investigate potential reorganisation processes of basic language function which may take place 1) preoperatively - due to the underlying disease; and 2) postoperatively - due to disruption of the functional language network as a result of ATLR.

CHAPTER III

3. HIPPOCAMPAL INVOLVEMENT IN BASIC LANGUAGE FUNCTIONS: FMRI FINDINGS IN HEALTHY CONTROLS AND PATIENTS WITH TEMPORAL LOBE EPILEPSY

In the work presented in this chapter we investigated the use of fMRI to study basic language networks (i. e. verbal fluency and naming) in healthy control subjects; we then aimed to investigate how the integrity of these networks was disrupted in a group of patients with left and right temporal lobe epilepsy (TLE).

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3.1. OBJECTIVE

In patients with left TLE due to hippocampal sclerosis (HS) decreased naming ability is common, suggesting a critical role for the medial left temporal lobe and in particular the hippocampus in this task. The underlying mechanisms for the high incidence of clinically relevant naming difficulties in particular after ATLR in the speech-dominant hemisphere remain a matter of debate.

In this study, we used language fMRI to retrospectively investigate the relationship between naming ability and the integrity of language networks in healthy controls and patients with left and right TLE.

3.2. INTRODUCTION

The impairment of episodic memory in TLE is well recognised and the medial temporal lobe and in particular the hippocampus has been shown to be crucial for memory encoding and retrieval (Squire and Zola-Morgan, 1991). The impairment of language function in patients with TLE, in contrast, is less well understood. Up to 40 % of patients with TLE and a speech dominant focus have a clinically significant deficit in naming abilities (Bell et al., 2003; Loring et al., 1994b) which is often aggravated following ATLR in the language dominant hemisphere (Davies et al., 1998).

Functional MRI is an attractive clinical tool to evaluate cognitive function as it is non-invasive and highly reproducible in particular for localising the parts of the brain involved in processing language function (Rutten et al., 2002a; Rutten et al., 2002c) (refer to chapter 1.5.2.3 for more detail).

Functional MRI studies using simple phonemic verbal fluency paradigms reliably lateralise language dominance in healthy controls and TLE patients by showing left frontal lobe activation corresponding to Broca's area and less prominent activation in the medial temporal lobes (Friedman et al., 1998; Phelps et al., 1997).

It is well established that naming function is mediated by the perisylvian cortex in the language dominant hemisphere. More recently, there is accumulating evidence from cortical stimulation studies (Hamberger et al., 2007) as well as fMRI studies (Tomaszewski Farias et al., 2005) that the hippocampus is directly involved in naming functions.

ATLR in the language dominant hemisphere, a well established and effective treatment for patients with medically refractory TLE (Wiebe et al., 2001) carries the risk of postoperative naming deficits. About 25% of patients with TLE due to hippocampal sclerosis suffer a clinically significant naming decline after left ATLR (Davies et al., 1998; Saykin et al., 1995).

Baseline naming has been reported to be poorer in patients with hippocampal sclerosis compared to patients without hippocampal sclerosis (Bell and Davies, 1998). However, the underlying mechanisms are still poorly understood. Bell and colleagues for example suggested that naming deficits in patients with left TLE were more attributable to a related semantic memory impairment rather than simply to retrieval deficits (Bell et al., 2001). Other studies discussed that naming difficulties in TLE are more likely to be due to lexical retrieval problems associated with the temporal lobe network (Trebuchon-Da Fonseca et al., 2009).

In this experiment we used fMRI and a simple verbal fluency task to specifically test the hypotheses

1. That stronger fMRI activations in the lateral frontal and medial temporal lobes were associated with better verbal fluency and naming ability in healthy controls and patients with TLE;
2. That reorganisation of language functions within the speech-dominant hemisphere would take place in TLE patients due to the underlying disease.

3.3. METHODS

3.3.1. Subjects

We studied 22 healthy controls (median age 42.50 years, range 22-70, 11 females) with no history of neurological or psychiatric disease and 66 patients undergoing presurgical evaluation for medically refractory TLE. Thirty-seven patients had left hippocampal sclerosis (median age 42 years, range 17-63, median age of epilepsy onset 7 years, range 0.50-44, 20 females) and 29 right hippocampal sclerosis (median age 37 years, range 22-54, median age of epilepsy onset 10 years, range 0.75-25, 17 females). All patients were on antiepileptic medication at the time of their assessment with five left TLE and three right TLE patients receiving Topiramate, which has been associated with neuropsychological impairment such as slowed processing speed, especially in tests requiring verbal processing (Lee et al., 2003; Loring et al., 2011; Thompson et al., 2000). English was the first language of all subjects, handedness was assessed using the Edinburgh Hand Preference Inventory (Oldfield, 1971) standardised questionnaire. Language

dominance was assessed calculating a lateralisation index (LI) using the Bootstrap method of the SPM toolbox (Wilke and Lidzba, 2007) as described in detail in the common methodology section (chapter 2.3.2.1). Left language dominance was defined by a LI of ≤ -0.2 . All patients and controls were left hemisphere dominant for language. IQ was measured using WAIS-III. The mean verbal IQ in controls was 105.1 (SD 12.16), 97.07 (SD 16.72) in right TLE and 93.30 (SD 12.95) in left TLE patients; there was a significant difference in verbal IQ between controls and left TLE patients (ANOVA $p < 0.01$); the mean performance IQ in controls was 106.4 (SD 13.46), 95.59 (SD 15.66) in right TLE and 93.38 (SD 13.41) in left TLE patients (ANOVA $p < 0.05$). The full details of the presurgical evaluation are presented in the common methodologies (chapter II).

3.3.2. Neuropsychological assessment

All patients and controls in this study completed the Mc Kenna Graded Naming Test and a phonemic verbal fluency test outside the scanner. These tests are described in the common methodology section (refer to chapters 2.2.2.2 and 2.2.2.3).

3.3.3. MR acquisition

The MRI acquisition was performed according to the common protocol as described previously (refer to chapters 2.3.1 and 2.3.1.1).

3.3.4. Language fMRI paradigm

Each subject in this experiment performed a simple verbal fluency fMRI task, which is known to reliably lateralise language (Powell et al., 2006) and which is described in the common methodology section (refer to chapter 2.3.2.1).

3.3.5. Data analysis

The first level of the fMRI data analysis including preprocessing and blocked analysis is described in the common methodology section (refer to chapters 2.3.3.1 and 2.3.3.2).

At the second level, we tested for

1. Verbal fluency effects in control subjects
2. Verbal fluency effects in patients
3. Verbal fluency effects that differed between controls and patients
4. Verbal fluency effects that increased with naming and verbal fluency in controls
5. Verbal fluency effects that increased with naming and verbal fluency in patients.

The contrast image (verbal fluency relative to baseline) for each subject was entered into a second level ANOVA, which modeled the group effect (i.e. control subjects or patients) on the contrast of interest. Naming and verbal fluency scores were entered as covariates separately for control subjects and patients. Inferences were made at the second level to emulate a random effects analysis and enable inferences at the population level (Friston et al., 1999). Given that our design was balanced, this two- stage procedure is mathematically identical to a random/mixed effects analysis. Verbal IQ was entered as an additional covariate of no interest to control for effect of variation in this measure.

In view of our hypothesis we performed the small volume correction using a sphere of 10 mm diameter for the left (and right) hippocampi and a sphere of 20 mm diameter for the middle and inferior frontal gyri based on the peak activation.

3.4. RESULTS

3.4.1. Naming Test scores

There was a significant difference in naming scores between controls (mean 22.59, SD 3.45), left (mean 15.05, SD 3.94) and right TLE patients (mean 17.93, SD 4.94), with patients showing significantly lower scores than controls (ANOVA left: $p < 0.001$; right: $p < 0.001$, Bonferroni corrected for multiple comparisons) and left TLE patients demonstrating significantly lower naming scores than right TLE patients (ANOVA $p < 0.01$, Bonferroni corrected for multiple comparisons).

There was no significant correlation between age of epilepsy onset and naming test scores in left or right TLE patients.

3.4.2. Verbal fluency Test scores

Left TLE patients (mean 13.32, SD 5.57) demonstrated significantly lower scores for verbal fluency than controls (mean 18.41, SD 5.69) (ANOVA $p < 0.01$, Bonferroni corrected for multiple comparisons); there was no significant difference in verbal fluency scores between controls and right TLE patients (mean 15.00, SD 6.71) or left and right TLE patients.

There was no significant correlation between naming and verbal fluency scores outside the scanner.

3.4.3. Hippocampal volumes

Left and right hippocampal volumes were significantly different in both left and right TLE patients:

left TLE group: mean (SD) right hippocampal volume, 2.78 (0.28) cm^3 ; mean left hippocampal volume, 1.72 (0.44) cm^3 , (paired t-test $p < 0.0001$, 2-tailed);

right TLE group: mean (SD) right hippocampal volume, 1.75 (0.43) cm^3 ; mean left hippocampal volume, 2.66 (0.33) cm^3 , (paired t-test $p < 0.0001$, 2-tailed).

There was no significant difference between left hippocampal volume in the left TLE group and right hippocampal volume in the right TLE group or between left and right hippocampal volume in controls. Controls' hippocampal volumes did not differ significantly from contralateral hippocampal volumes in right and left TLE patients. No significant correlation was seen between left hippocampal volumes and naming scores in healthy controls and patients with left or right hippocampal sclerosis.

3.4.4. Functional MRI results

3.4.4.1. Main effects of verbal fluency within each and across the three groups

Left lateralised activation was demonstrated in the left middle ($p < 0.0001$, FWE corrected) and inferior ($p < 0.0001$, FWE corrected) frontal gyri for healthy controls (Fig 3.1A) and patients with left and right hippocampal sclerosis. Group comparison revealed greater left frontal activation in controls compared to left (Z score=4.19, $p < 0.0001$, uncorrected) and right TLE patients (Z score=4.48, $p < 0.0001$, uncorrected). There was no significant difference between left and right TLE patients in left frontal activation (Table 3.1).

Table 3.1 FMRI activation peaks for the main effects of verbal fluency

Subjects	Z-score	Cluster size	Df, corrected p-value (FWE)	Coordinates (x,y,z) in MNI space	Anatomical locations of maxima
Controls	infinity	12258	85, p<0.0001	-44, 22, 24	left middle frontal gyrus
	infinity	12258	p<0.0001	-30, 24, 0	left inferior frontal gyrus
	6.37	499	p<0.0001	32, 22, 0	right inferior frontal gyrus
	3.88	75	-	-28, -20, -10	left hippocampus
Left TLE	infinity	13124	85, p<0.0001	-50, 8, 20	left middle frontal gyrus
	infinity	13124	p<0.0001	-32, 22, 0	left inferior frontal gyrus
	6.45	593	p<0.0001	32, 24, 0	right inferior frontal gyrus
	5.20	59	-	-30, -24, -8	left hippocampus
Right TLE	infinity	8320	85, p<0.0001	-50, 10, 22	left middle frontal gyrus
	7.28	8320	p<0.0001	-32, 22, 0	left inferior frontal gyrus
	5.8	772	p<0.0001	32, 22, 2	right inferior frontal gyrus
	2.43	22	-	-30, -26, -6	left hippocampus
Group comparisons between patients and controls for the main effects of verbal fluency					
Left TLE < controls	4.19	47	85, p<0.0001 (uncorrected)	-44, 26, 26	left middle frontal gyrus
Right TLE < controls	4.48	127	85, p<0.0001 (uncorrected)	-44, 24, 26	left middle frontal gyrus
Left TLE vs. right TLE	ns	-	ns	-	-

Legend: FWE, family wise error corrected for multiple comparisons; MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); ns, not significant; TLE, temporal lobe epilepsy.

3.4.4.2. Correlation of naming ability with verbal fluency fMRI activation

Voxel-wise correlational analysis (Table 3.2)

a) Healthy controls

McKenna Graded Naming Test Scores were significantly related to fMRI activation for verbal fluency in the left hippocampus in healthy controls ($p=0.014$, FWE corrected in SVI), characterised by greater hippocampal fMRI activation being correlated with better naming scores (Fig 3.1B and C).

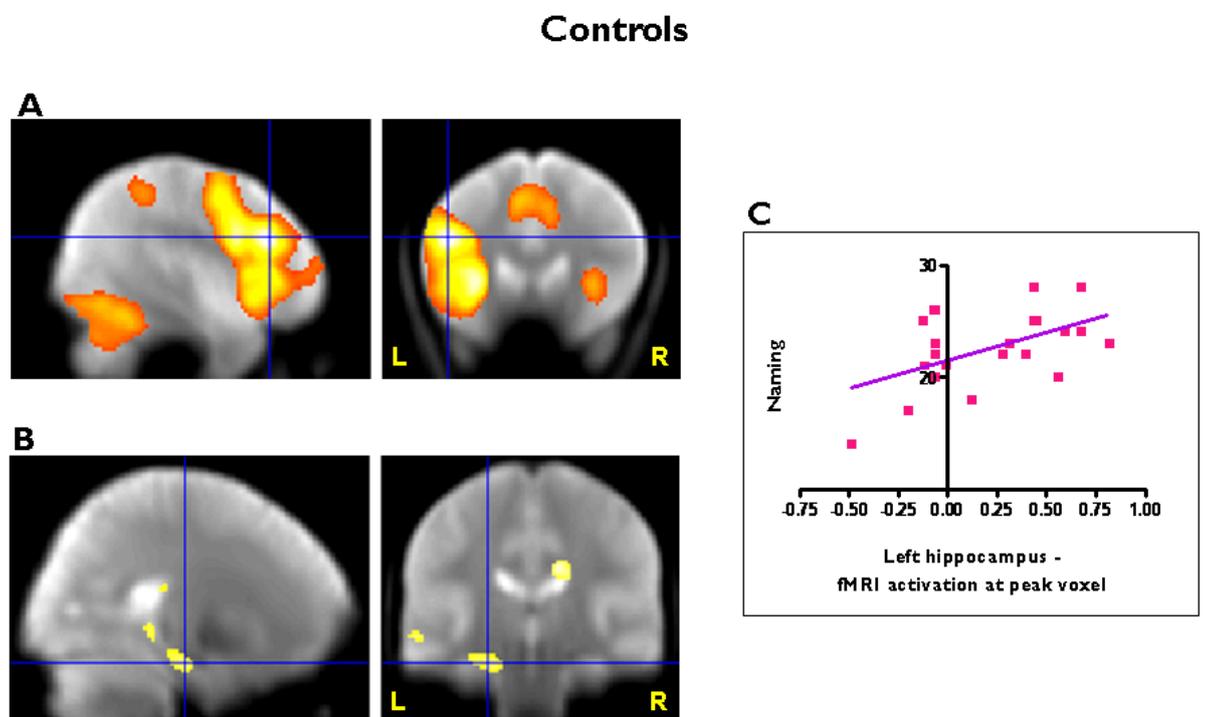


Figure 3.1 Language fMRI results in controls

A: Main effect for verbal fluency

Left middle and inferior frontal activation (Threshold $p<0.05$, FWE correction).

B: Correlational analysis

Left hippocampal activation for verbal fluency correlates with naming scores, characterised by better naming scores in subjects with greater fMRI activation (Threshold $p<0.01$, uncorrected).

C: Correlation of fMRI activation for verbal fluency and naming scores at the peak voxel in the left hippocampus.

Significant regions are superimposed onto an averaged normalised mean EPI from 30 healthy controls, 15 patients with left and 15 patients with right hippocampal sclerosis.

b) Right TLE

In right TLE patients, naming scores co-varied significantly with left hippocampal fMRI activation for verbal fluency ($p=0.049$, FWE corrected in SVI) (Fig 3.2A).

In controls or right TLE patients voxel-wise analysis over the whole brain did not show a significant correlation in any other brain areas other than the hippocampus.

c) Left TLE

In left TLE patients there was no significant correlation between naming scores and left hippocampal fMRI activation for verbal fluency. There was, however, a significant positive correlation in the left middle ($p=0.008$) and inferior frontal gyri ($p=0.024$, FWE corrected in a SVI using a sphere of 20 mm diameter centred on the peak activation in the middle (-46/4/54) and inferior (-60/18/18) frontal gyri) (Fig 3.2B). There was also a positive correlation in the right middle and inferior frontal gyri, which did not reach statistical significance.

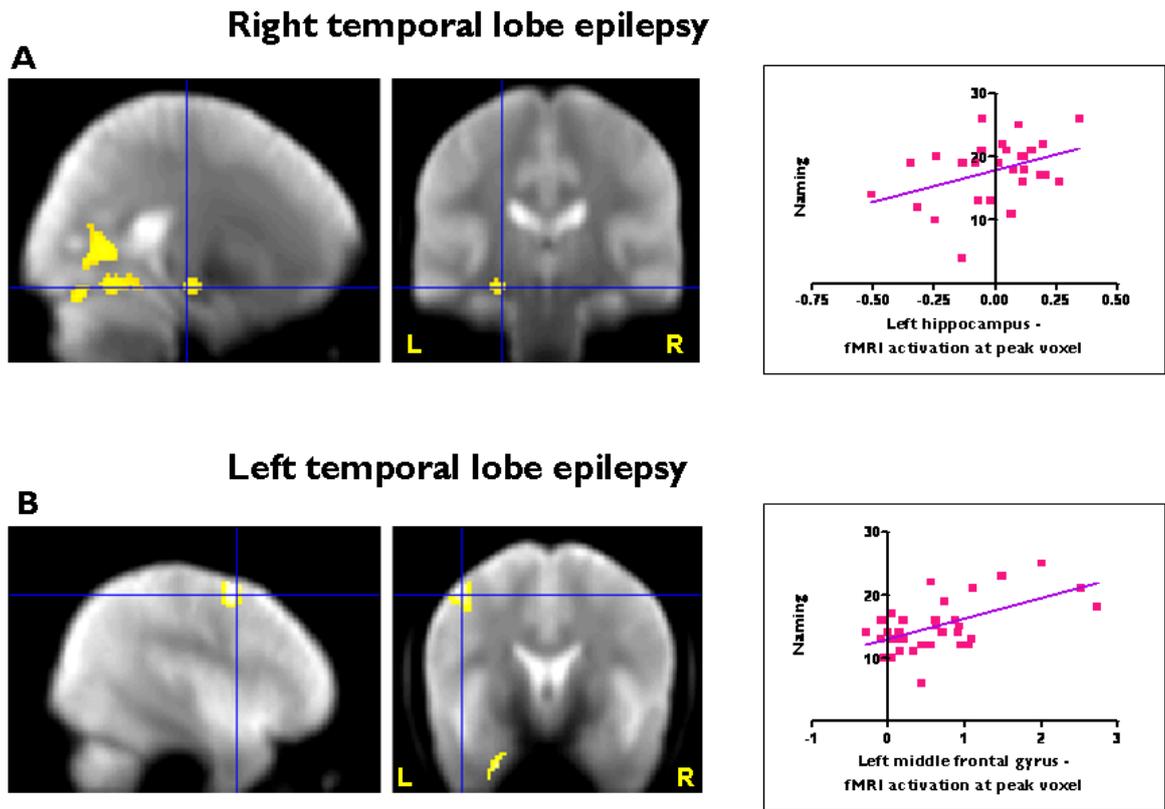


Figure 3.2 Language fMRI results in TLE patients

A: Right TLE patients: Correlational analysis

Left hippocampal activation for verbal fluency correlates with naming scores, characterised by better naming scores in subjects with greater fMRI activation (Display at threshold $p < 0.01$, uncorrected).

B: Left TLE patients: Correlational analysis

Left middle and inferior frontal activation for verbal fluency correlates with naming scores, characterised by better naming scores in subjects with greater fMRI activation (Display at threshold $p < 0.001$, uncorrected).

The correlations at the peak voxel are illustrated on the right.

Significant regions are superimposed onto an averaged normalised mean EPI from 30 healthy controls, 15 patients with left and 15 patients with right hippocampal sclerosis.

Table 3.2 Correlation of McKenna graded naming scores with verbal fluency fMRI activation

Subjects	Z-score	Cluster size	Df, corrected p-value (FWE corrected in SVI)	Coordinates (x,y,z) in MNI space	Anatomical region
Controls	2.90	76	78, p=0.014	-24, -20, -18	left hippocampus
Right TLE	2.38	62	78, p=0.049	-26, -22, -14	left hippocampus
Left TLE	-	-	ns	-	left hippocampus
Left TLE	3.54	134	78, p=0.008	-46, 4, 54	left middle frontal gyrus
Left TLE	3.17	80	p=0.024	-60, 18, 10	left inferior frontal gyrus

Legend: MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); ns, not significant; SVI, small volume of interest; TLE, temporal lobe epilepsy.

3.4.4.3. Correlation of verbal fluency performance outside the scanner with verbal fluency fMRI activation

Voxel-wise correlational analysis

Using the same correlational analysis and the same thresholds as for the correlations with naming, verbal fluency outside the scanner was significantly related to fMRI activation for verbal fluency in the left inferior frontal gyrus ($p=0.002$, FWE corrected in a SVI using a sphere of 20 mm diameter centred on the peak activation in the inferior frontal gyri (-60/ 12/ 24) in left TLE patients, while there was no significant correlation for controls and right TLE patients. In controls, left and right TLE patients no significant correlation was seen in the hippocampi.

3.5. DISCUSSION

3.5.1. Summary of results

In this experiment we assessed the integrity of a fronto-temporal language network by including naming and verbal fluency scores as regressors in a between subjects (random effects) analysis of verbal fluency activation. By correlating activation obtained during a verbal fluency fMRI task with out of scanner naming ability we identified brain areas where activation increased in association with improved verbal fluency performance, which is dependent, in part, on recall of

names of items. In this way we showed that left hippocampal fMRI activation in a verbal fluency task was associated with object naming proficiency in healthy controls and right TLE patients, highlighting the role of the hippocampus in naming ability, while verbal fluency was shown to be more dependent on frontal structures.

We included a group of age and gender matched control subjects to identify brain areas activated by the task in patients, but not controls. In this way we demonstrated recruitment of specific language areas required for naming involving the left middle and inferior frontal gyri in patients with left TLE.

3.5.2. Organisation of functional language networks

Verbal fluency tasks usually activate frontal areas, but are very dependent on the functional integrity of a network of language areas, including the dominant inferior frontal lobe, dorsolateral prefrontal cortex, mesio-temporal and parietal lobe (Friedman et al., 1998; Phelps et al., 1997; Pihlajamaki et al., 2000). In keeping with previous studies, in healthy controls our fMRI group results demonstrated activation in these areas while the main effect of verbal fluency relative to fixation was less prominent in the mesio-temporal structures. However, by introducing the covariate of naming ability, we found exclusive hippocampal activation in subjects with a presumed normally functioning hippocampus. Whilst we found a similar, albeit less significant correlation in the left hippocampus in right TLE patients, left TLE patients showed a different pattern, with weaker performance on the graded naming test, and which was associated with significant activation in the left middle and inferior frontal gyri, but not in the mesio-temporal structures.

3.5.3. Left hippocampal dysfunction and naming impairment in TLE

Clinical evidence for hippocampal involvement in language function is provided by patients with circumscribed focal lesions in the speech-dominant hippocampus showing impaired naming abilities and also by TLE patients, who frequently develop specific language

impairment such as difficulties with naming rather than verbal fluency after dominant anterior temporal lobe resections (Powell et al., 2008a; Sabsevitz et al., 2003).

The specific role of the hippocampus in episodic memory is well documented (Detre et al., 1998; Dupont et al., 2000; Gaillard, 2004; Powell et al., 2005a; Richardson et al., 2004a; Squire and Zola-Morgan, 1991). An important aspect highlighting the relationship between memory and language functioning was demonstrated by Binder et al. who found that evaluation of preoperative language dominance as assessed by fMRI was useful in identifying patients at high risk of verbal memory impairment after temporal lobe epilepsy surgery (Binder et al., 2008). Earlier studies also emphasized the importance of the hippocampus in associative processing (Vandenberghe et al., 1996). Our findings suggest that the left hippocampus is engaged in effective word retrieval in healthy subjects and right TLE patients providing further support for the hypothesis that the hippocampus plays a role in retrieving lexically and semantically associated words (Bartha et al., 2003; Bartha et al., 2005; Pihlajamaki et al., 2000). In patients with left TLE and hippocampal sclerosis object naming weakness was paralleled by left hippocampal dis-engagement. A positive correlation in the left and to a lesser extent also in the right middle and inferior frontal gyri suggests compensatory strategies using less functionally developed regions in the frontal lobe supporting naming function. These areas are recruited when the dominant hippocampus is disabled as is the case in hippocampal sclerosis. Naming performance difficulties in left TLE patients might then be explained by the need to rely on a functionally less specialised, compensatory network in the frontal lobe. A similar process has previously been reported for episodic memory in left TLE (Dupont et al., 2000). The underlying mechanisms may either be the pathology (hippocampal sclerosis) or the ongoing epileptic activity and propagation involving temporal and frontal regions, disrupting normal functioning of this part of the expressive language network.

3.5.4. Limitations of the study

(1) Our results may be influenced by the effect of volume averaging on the extent and magnitude of hippocampal signal, given that the left TLE patients all had hippocampal sclerosis.

(2) The verbal fluency task during fMRI was carried out covertly, so that performance was not directly measured in the scanner. We used performance during out of scanner neuropsychological testing as an approximate measure of general motivation and task adherence. In addition all patients underwent one practice run outside the scanner with a different letter than the ones used during the scanning process in order to ensure adequate understanding of the task. Performance differences between controls and patients can simply explain differences in fMRI activations. We have overcome this confound by correlating fMRI activations on a verbal fluency task with a behavioural measure of interest, naming ability. Performance on letter fluency outside the scanner did not correlate with hippocampal activation on verbal fluency inside the scanner suggesting that hippocampal activation predicts naming more than verbal fluency. The Graded Naming test is a more pure measure of naming while the out of scanner verbal fluency task in addition draws upon strategy formation and other executive processes.

(3) We only looked at indicators of expressive language skills by combining a verbal fluency fMRI task which was part of our standard presurgical language fMRI assessment with out of scanner verbal fluency and naming performance, which is of great clinical relevance in patients with TLE especially following ATR. The verbal fluency task used required recollection of words and was associated with hippocampal activation. However, for future studies it will be favourable to design suitable fMRI paradigms to assess naming function directly in the scanner and to examine receptive language function in more detail.

(4) Early age of epilepsy onset is known to influence reorganisation of language function in TLE. As our patient sample for this study was restricted to patients with left language dominance in order to study language reorganisation in a “methodologically idealized” patient population and as atypical dominance is highly related to an early seizure onset we were not able to study effects of age of seizure onset in this particular study. Within our restricted patient sample there was no relationship between age of epilepsy onset and naming performance. It would be interesting to compare the extent of hippocampal activation/ correlation in patients with pure left language dominance versus those with atypical language representation.

3.6. CONCLUSION

In conclusion, our results demonstrate the importance of the dominant hippocampus for naming function in healthy controls and patients with TLE. Additionally in left TLE patients we demonstrated that decreased naming ability was most likely due to disruption of the hippocampal system either via pathology or epileptic activity and the reliance on functionally less developed frontal lobe networks. Further studies using activation protocols which reliably provoke fMRI activation in these areas will be needed to evaluate the neural pathways in more detail which will then lead to a better understanding of the underlying neurobiological substrate.

CHAPTER IV

4. IMAGING LANGUAGE IN TEMPORAL LOBE EPILEPSY: INTER- AND INTRAHEMISPHERIC FUNCTIONAL REORGANISATION OF LANGUAGE FUNCTION AFTER ANTERIOR TEMPORAL LOBE RESECTION

In the previous experiment we used simple language functional MRI (fMRI) tasks to demonstrate how the integrity of the hippocampal-frontal language network was essential for basic language functions such as naming and phonemic verbal fluency (VF) in healthy controls and patients with left and right temporal lobe epilepsy (TLE). For the work presented in this chapter we used the same language tasks to study the effects of temporal lobe surgery on language function in a group of patients with medically refractory left and right TLE and to evaluate a potential use of fMRI as a clinical predictor of postoperative naming decline.

The material in this chapter has been published in: Bonelli SB et al. Imaging language networks before and after anterior temporal lobe resection – results of a longitudinal fMRI study. *Epilepsia*. 2012 Apr; 53(4):639-50. doi: 10.1111/j.1528-1167.2012.03433.x. Epub 2012 Mar 16.

4.1. OBJECTIVE

Anterior temporal lobe resection controls seizures in up to 70% of patients with intractable TLE but, in the language dominant hemisphere, may impair language function, particularly naming. Functional reorganisation can occur within the ipsilateral and contralateral hemispheres.

In this chapter we systematically investigated 1. reorganisation of language function in left-hemisphere dominant patients with TLE before and after anterior temporal lobe resection (ATLR) using a simple VF fMRI task and functional connectivity analysis; 2. whether preoperative fMRI predicts postoperative naming decline; 3. efficiency of postoperative language networks.

4.2. INTRODUCTION

Anterior temporal lobe resection for refractory TLE (Wiebe et al., 2001) may be complicated by impairment of verbal memory (Bonelli et al., 2010; Helmstaedter and Elger, 1996; Hermann et al., 1995) and language, especially naming, after ATR in the language dominant hemisphere (Davies et al., 1998).

We have already discussed that many typical language areas can be identified in healthy controls and in patients with TLE using fMRI. In brief, verbal fluency and verb generation tasks reliably activate the left inferior frontal gyrus (IFG) (Binder et al., 1996; Gaillard et al., 2004; Woermann et al., 2003), whereas the lateral temporal neocortex is activated by sentence comprehension tasks (Gaillard et al., 2002) (refer to chapter 1.5.2.3 and the previous chapters 3.2 and 3.4-3.5 for more detail). On the other hand very few studies have reported activation in the medial temporal structures. Naming typically involves the perisylvian cortex, and basal temporal regions which may be affected in TLE (DeLeon et al., 2007; Trebuchon-Da Fonseca et al., 2009). Twenty-five per cent of patients with hippocampal sclerosis (and TLE) suffer a clinically significant naming decline after left ATR (Davies et al., 1998; Saykin et al., 1995) and there is evidence for direct involvement of the dominant hippocampus in naming demonstrated in this work, as well as in previous studies (Hamberger et al., 2007). Relatively few fMRI studies have systematically investigated functional reorganisation of language after ATR. Postoperatively, language activation may shift to the contralateral hemisphere in patients with seizures in the language dominant hemisphere (Hertz-Pannier et al., 2002) and there is evidence for both intra- and interhemispheric reorganisation of language function after ATR (Noppeney et al., 2005). One longitudinal fMRI study showed that the language network was affected differently by left and right TLE and was reorganised after ATR (Wong et al., 2009). In addition, there is still very little work assessing the role of fMRI to predict postoperative language outcome. Preoperative language fMRI with a semantic decision task has been used to predict language decline in TLE patients (Sabsevitz et al., 2003) (refer to chapter 1.5.2.3.3 for more detail).

Therefore, in this experiment we used longitudinal data to specifically test the hypotheses that:

1. Reorganisation of language function will be different for patients undergoing left or right ATR.
2. There is a relationship between preoperative language fMRI activation and language test proficiency in TLE patients.
3. The relationship between language function and VF activation is affected by ATR and differs between the dominant or non-dominant hemispheres.
4. Preoperative language fMRI can predict postoperative language deficits, particularly naming decline, after left ATR.

4.3. METHODS

4.3.1. Subjects

We studied 44 patients with medically refractory TLE (24 left) due to unilateral hippocampal sclerosis (Table 4.1). All patients underwent ATR for hippocampal sclerosis at the National Hospital for Neurology and Neurosurgery, London, UK. All underwent detailed pre-surgical evaluation including structural MRI at 3T and electroclinical assessment as previously described in chapters 2.1-2.2 All patients' first language was English and all were left language dominant on fMRI. We calculated pre- and postoperative lateralisation indices (LI) using the Bootstrap method of the SPM toolbox (Wilke and Lidzba, 2007) as described in the common methodology section (refer to chapter 2.3.2.1). Left language dominance was defined by a preoperative LI of ≤ -0.4 on the VF task. This threshold was chosen to ensure clear left language dominance. For patients showing a LI between -0.2 and -0.4, activation maps on a verb generation task were additionally used to decide language laterality (Bonelli et al., 2011; Gaillard et al., 2004; Sabsevitz et al., 2003). Nine patients (five left) showed atypical, bilateral language representation and were not included in this study.

All patients underwent language fMRI and standard neuropsychological assessment preoperatively and again four months after ATR. Verbal IQ, measured using WAIS-III and

performance during an out of scanner VF task were used as covariates of no interest (refer to the common methodology chapter 2.2.2 for more detail).

Medication remained unchanged in 34 patients, in 10 patients the doses had been slightly reduced by the time of postoperative assessment.

All patients underwent left or right ATR by the same neurosurgeon. The standard neurosurgical procedure is described in the common methodology section (refer to chapter 2.2.1.2). The ILAE classification of post-operative seizure outcome following epilepsy surgery was used (Wieser et al., 2001).

For full details of the presurgical evaluation please refer to the common methodology chapter 2.

Table 4.1 Demographic data

Subjects	Gender	Median age (range), y	Median age at onset (range), y	Handedness (Oldfield, 1971)	Mean verbal IQ (SD) (WAIS-III)	ILAE postoperative seizure outcome 1 year follow up	Mean HV cm ³ (SD); paired t-test, 2 tailed
24 left TLE	12 female	37 (17-63)	6 (0.25-44)	22 right, 2 left	93.50 (15.74)	Grade 1-2: 19 Grade 3-5: 5	Right HV: 2.83 (0.27) Left HV: 1.87 (0.67); p<0.0001
20 right TLE	13 female	35 (22-52)	12 (0.92-55)	18 right, 2 left	95.60 (16.72)	Grade 1-2: 14 Grade 3-5: 6	Right HV: 1.81 (0.44) Left HV: 2.69 (0.38); p<0.0001

Legend: HV, hippocampal volumes; TLE, temporal lobe epilepsy; y, year;

4.3.2. Neuropsychological assessment

As in the previous chapter we used two language tasks outside the scanner, phonemic VF and the McKenna Graded Naming Test (McKenna and Warrington, 1983), which are described in the common methodology chapters 2.2.2.2 and 2.2.2.3.

Neuropsychological testing occurred before and four months after ATR. Postoperative and preoperative scores were correlated with pre- and postoperative fMRI activation patterns. Changes in language scores from baseline following left or right ATR were correlated with preoperative fMRI activation patterns to assess language fMRI ability to predict postoperative language deficits. A clinically meaningful postoperative naming change was defined as a change of >3 points, which represented a decline of at least 15 centiles. A clinically significant VF decline was defined as change of > 1 SD (refer to section 2.2.2.7 in the common methodologies for more detail).

4.3.3. MR acquisition

MR data acquisition was performed according to our common protocol as illustrated in the common methodology section (refer to chapters 2.3.1 and 2.3.1.1).

4.3.4. Language fMRI paradigm

Verbal fluency and verb generation tasks were used in this study as described in the common methodology section 2.3.2.1.

4.3.5. Data analysis

The first level of analysis including preprocessing steps and the blocked analysis of the pre- and postoperative imaging time series was carried out using SPM 5 and is described in the common methodology sections 2.3.3.1 and 2.3.3.2.

4 patients had to be excluded from further analysis because of coregistration problems.

Functional connectivity analysis

To assess functional connectivity (FC) between activated areas, each subject's individual peak response to the VF task was located within a region of interest (ROI) in the left IFG and middle frontal gyrus (MFG), defined from combined (preoperative left and right TLE) group activation maps. This peak voxel's time series was extracted from the normalised, smoothed EPI images and used as regressors of interest for a new general linear model fMRI analysis for each subject. Areas functionally coupled to the left frontal seed region were compared across groups and time.

At the second level, the subjects were divided into four groups: left TLE and right TLE patients, pre- and postoperatively. Each subject's contrast images were entered into a one sample t-test, modelling the group effect (i.e. patients pre- and postoperatively) on the various contrasts of interest.

Correlations between areas of VF fMRI activation and pre- and postoperative performance on VF and naming outside the scanner were tested using multiple regression analyses over the whole brain with verbal IQ as an additional covariate to control for performance. Changes in VF and naming scores were used to test for correlations between preoperative fMRI activation and change in language scores from before to after ATR (refer to chapter 2.3.3.2 for more detail).

We defined regions of interest (ROIs) in the left and right MFG, and the left and right IFG using anatomical masks (Hammers et al., 2003). In the medial temporal lobe these regions were geometric spherical ROIs (10 mm diameter) in the left and right anterior and posterior medial temporal lobe centred on the coordinates of the peak group-activation for VF. We extracted the parameter estimates in these regions and tested for correlations between subjects' fMRI activation within these ROIs and their performance on naming and VF tests outside the scanner, pre- and postoperatively.

At the second level we tested for:

1. Evidence of reorganisation of language networks after ATLR by group comparison of pre- versus postoperative main effects;
2. Postoperative change in functional connectivity between typical language areas;
3. Efficiency of (re)organisation of language function by correlating pre- and postoperative activations for VF with pre- and postoperative language scores;
4. A relationship between preoperative fMRI activation for VF and change in language scores to evaluate whether preoperative language fMRI was a useful predictor of postoperative language deficits.

4.4. RESULTS

4.4.1. Neuropsychological test results

4.4.1.1. Naming

The left TLE group had significantly lower naming scores preoperatively (mean=14.7, SD=4.3; $p=0.03$, t-test) and postoperatively (mean=11.3, SD=5.90; $p=0.0001$, t-test) than the right TLE group (preoperative, mean=17.9, SD=4.7; postoperative, mean=18.1, SD=4.5). There was a significant reduction of pre- versus postoperative naming scores in left TLE ($p=0.004$, t-test).

4.4.1.2. Verbal fluency

There was no significant difference in mean VF scores between left and right TLE patients pre- and postoperatively and no significant change of pre- versus postoperative mean VF scores in both groups.

4.4.1.3. Postoperative language change

Fourteen /24 patients had a decline in naming scores after left ATLR (12 patients were classified as clinically significant, which was also reflected by clinical neuropsychological reports highlighting increased word finding difficulties elicited during the naming test and in daily life as rated by patients); mean change between pre – and postoperative naming scores was

-3, (range -18 to +5), 5/24 patients naming scores remained unchanged, 5/24 had a postoperative improvement in naming (of which 1 was classified as clinical significant).

Nine/24 patients had a postoperative decline in VF scores (3 classified as clinically significant), 13/24 patients had a postoperative improvement (5 classified as clinically significant), and 2/24 patients' scores remained unchanged; mean change between pre – and postoperative VF scores +1.5, (range -12 to +19).

Seven/20 patients had a decline in naming after right ATR (not clinical significant), 5/20 had a postoperative improvement (2 classified as clinically significant), 8 patients' scores unchanged; mean change between pre – and postoperative naming scores +0.2, (range -3 to +5).

Ten/20 patients had reduced VF scores after right ATR (with 2 being clinically significant), 8/20 a postoperative improvement (2 clinically significant), 1 patient's score unchanged. One patient did not complete postoperative VF testing. Mean change between pre– and postoperative VF scores +0.5, (range -7 to +10).

4.4.2. Organisation of language networks before and after ATR

4.4.2.1. Preoperative main effects on fMRI activation for VF

In patients with both left and right TLE there was significant activation in the left IFG and MFG ($p < 0.0001$)

(Fig 4.1A and 4.1B, Table 4.2).

4.4.2.2. Postoperative main effects on fMRI activation for VF

Left TLE: bilateral activation in the IFG and MFG ($p < 0.0001$).

Right TLE: left middle and inferior frontal activation ($p < 0.0001$) (Fig 4.1A and 4.1B, Table 4.2).

Table 4.2 FMRI activation peaks for pre- and postoperative main effects of VF

Subjects	Z-score	Corrected p-value (FWE)	Coordinates (x,y,z) in MNI space	Anatomical region
Left TLE Preoperative	6.96	p<0.0001	-54, 10, 20	left IFG
	6.69	p<0.0001	-48, 20, 26	left MFG
	6.69	p<0.0001	-32, 30, -2	left IFG
Left TLE Postoperative	5.77	p<0.0001	-42, 2, 26	left IFG
	5.74	p<0.0001	-40, 18, -6	left IFG
	4.88	p<0.0001	40, 20, -6	right IFG
Right TLE Preoperative	5.89	p<0.0001	-46, 30, 22	left MFG
Right TLE Postoperative	5.81	p<0.0001	-52, 8, 22	left IFG
	5.88	p<0.0001	-46, 16, 10	left IFG
	5.79	p<0.0001	-50, 14, 30	left MFG

Legend: HC, hippocampus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); TLE, temporal lobe epilepsy.

Main effects – verbal fluency

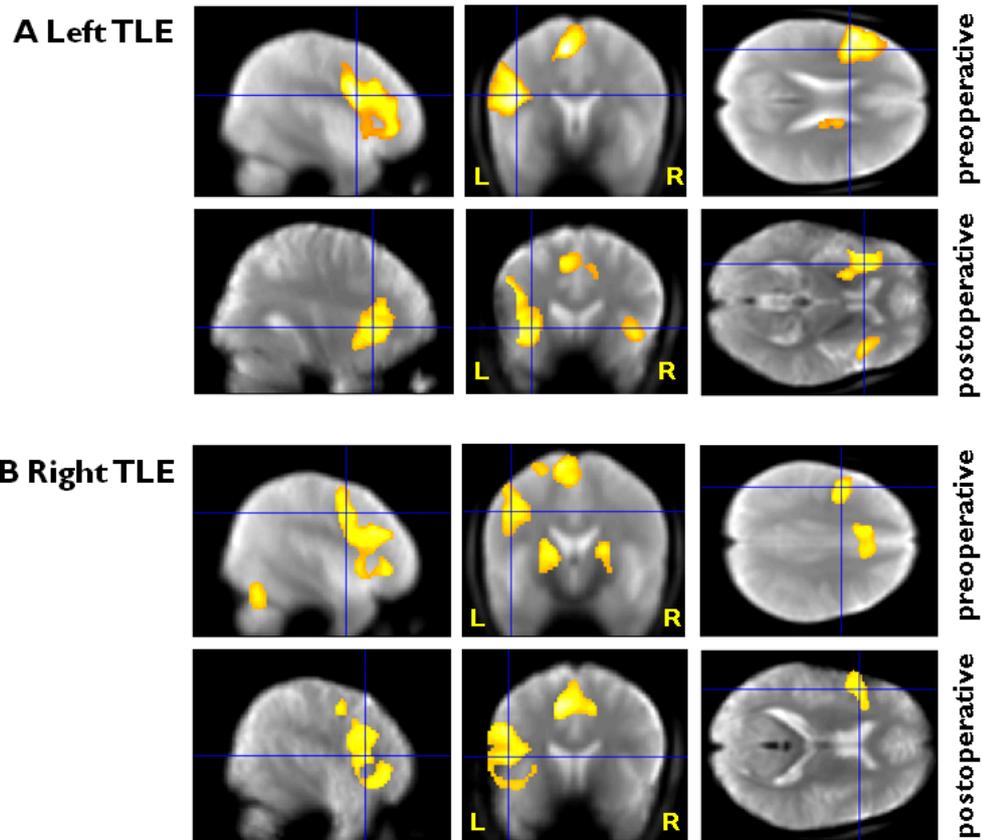


Figure 4.1 Pre- and postoperative language fMRI results in patients with left and right TLE

Pre- and postoperative main effects for verbal fluency in

A: Left TLE: preoperative – left inferior and middle frontal activation;
 postoperative – bilateral inferior and middle frontal activation;

B: Right TLE: pre- and postoperative – left inferior and middle frontal activation.

(Threshold $p < 0.05$, FWE corrected)

Preoperative: Significant regions are superimposed onto an averaged normalised mean EPI from 30 healthy controls, 15 patients with left and 15 patients with right hippocampal sclerosis.

Postoperative: Significant regions are superimposed onto an averaged normalised mean EPI from all patients who underwent left ATLR and one for all patients who underwent right ATLR.

The crosshair points to the peak maximum activation for the group.

4.4.2.3. Group comparisons for pre- versus postoperative main effects of VF in left and right TLE patients

Left TLE patients demonstrated significantly less postoperative than preoperative activation in the left inferior and middle frontal gyri ($p=0.02$) and in the left posterior hippocampus ($p=0.009$).

There were no areas of significantly greater postoperative than preoperative activation in left or right TLE patients.

4.4.2.4. Functional connectivity analysis

Preoperatively, left TLE had activation in the left IFG (main activation for VF) highly correlated with the response in the left MFG ($p<0.0001$) and the left precentral gyrus ($p=0.016$). Postoperatively, there was greater functional connectivity to the homotopic contralateral regions in the right IFG and MFG ($p=0.001$) (Fig 4.2A).

Preoperatively, the right TLE group showed similar findings to the left TLE group, with the left IFG being functionally connected to the left middle frontal and left precentral gyri ($p=0.001$). There was no postoperative increase in functional connectivity to the contralateral hemisphere (Fig 4.2B).

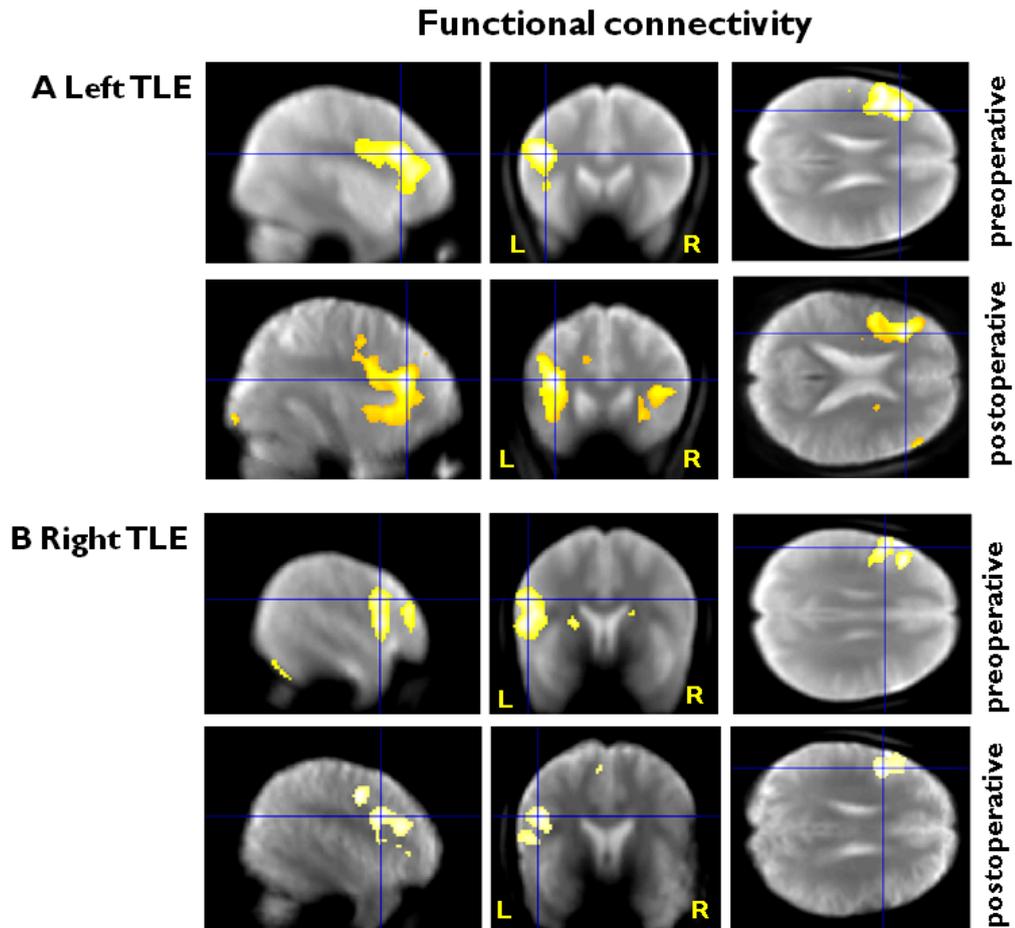


Figure 4.2 Functional connectivity: Pre- and postoperative results in left and right TLE patients

Seed region: in the left middle and inferior frontal gyri

A: Left TLE: preoperative – functional connectivity within ipsilateral middle and inferior frontal gyri; postoperative – functional connectivity within the ipsilateral and to the contralateral middle and inferior frontal gyri;

B: Right TLE: pre- and postoperative – functional connectivity within left inferior and middle frontal gyri; in contrast to left TLE no increased functional connectivity to the contralateral frontal lobe postoperatively.

(Threshold $p < 0.05$, FWE corrected)

Preoperative: Significant regions are superimposed onto an averaged normalised mean EPI from 30 healthy controls, 15 patients with left and 15 patients with right hippocampal sclerosis.

Postoperative: Significant regions are superimposed onto an averaged normalised mean EPI from all patients who underwent left ATLR and one for all patients who underwent right ATLR.

The crosshair points to the peak maximum activation for the group.

4.4.3. Efficiency of pre- and postoperative language networks

4.4.3.1. Results of the voxel by voxel analysis

A multiple regression analysis was performed to assess the relationship between pre- and postoperative fMRI activations for VF and performance on pre- and postoperative language tests (Table 4.3a and b).

Correlation between preoperative fMRI activations for verbal fluency and preoperative neuropsychological performance

a. Left TLE

In left TLE there was a significant correlation between VF activation and performance on **verbal fluency** outside the scanner in the left middle frontal gyrus ($p=0.002$), the left inferior frontal gyrus ($p=0.003$), the left hippocampus ($p=0.033$) and the right middle frontal gyrus ($p=0.043$), characterised by higher fMRI activation being associated with better VF scores.

There was also a significant positive correlation between preoperative VF activation and preoperative **naming** scores in the left hippocampus/parahippocampal gyrus ($p=0.016$) characterised by greater fMRI activation being correlated with better naming performance. There was also a trend for a positive correlation in the left middle frontal gyrus ($p=0.08$) (Table 4.3a).

b. Right TLE

There was a significant positive correlation between preoperative VF fMRI activation and preoperative **verbal fluency** scores outside the scanner in the left middle ($p=0.021$) and left inferior frontal gyri ($p=0.07$) and the left hippocampus ($p=0.023$).

There was no significant correlation between preoperative VF activation and preoperative **naming** scores over the whole brain in right TLE patients (Table 4.3b).

There were no significant correlations for the inverse contrasts.

Correlation between postoperative fMRI activations for verbal fluency and postoperative neuropsychological performance

a. Left TLE

Patients with left TLE demonstrated a significant positive correlation between postoperative VF activation and postoperative **verbal fluency** scores outside the scanner in the right middle frontal gyrus ($p=0.017$) and the left inferior frontal gyrus ($p=0.041$), characterised by higher fMRI activation being associated with higher verbal fluency scores. There was no significant correlation between postoperative fMRI activation and postoperative **naming** scores over the whole brain (Table 4.3a).

b. Right TLE

In patients with right TLE there was a significant positive correlation between postoperative VF fMRI activation and postoperative **verbal fluency** scores in the right middle frontal gyrus ($p=0.021$); correlations within the left middle/ inferior frontal gyri did not reach statistical significance. There was no significant correlation with postoperative **naming** scores.

For both left and right TLE patients there were no significant correlations for the inverse contrasts (Table 4.3b).

Table 4.3 Association of pre- and postoperative VF/ naming scores with pre- and postoperative VF fMRI activation

a)

Subjects	fMRI contrast – neuropsychology task	Z-score	Corrected p-value (FWE)	Coordinates (x,y,z) in MNI space	Anatomical region
Left TLE	preoperative VF fMRI –	4.06	p=0.002	-46, -6, 38	left MFG
		3.97	p=0.003	-58, 10, 18	left IFG
Preoperative	preoperative VF	3.09	p=0.043	56, 0, 44	right MFG
		2.65	p=0.033	-26, -20, -12	left HC
Left TLE	preoperative VF fMRI –	2.79	p=0.084	-48, 4, 52	left MFG
		2.95	p=0.016	-34, -26, -18	left PHG
Left TLE	postoperative VF fMRI –	3.37	p=0.017	46, 42, 26	right MFG
		3.03	p=0.041	-36, 32, 12	left IFG
Left TLE	postoperative VF fMRI –	-	ns	-	-
		Postoperative	postoperative naming		

b)

Subjects	fMRI contrast – neuropsychology task	Z-score	Corrected p-value (FWE)	Coordinates (x,y,z) in MNI space	Anatomical region
Right TLE	preoperative VF fMRI –	3.44	p=0.021	-44, 14, 54	left MFG
		2.95	p=0.070	-32, 14, -18	left IFG
Preoperative	preoperative VF	2.85	p=0.023	-22, -10, -14	left HC
		Right TLE	preoperative VF fMRI –	-	ns
Preoperative	preoperative naming				
		Right TLE	postoperative VF fMRI –	3.29	p=0.021
Postoperative	postoperative VF				
		Right TLE	postoperative VF fMRI –	-	ns
Postoperative	postoperative naming				

Legend: HC, hippocampus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); ns, not significant; PHG, parahippocampal gyrus; TLE, temporal lobe epilepsy; VF, verbal fluency.

4.4.3.2. Results of the ROI analysis

We quantified activation in predefined ROIs in the left and right IFG, MFG and the left and right medial temporal lobe including the hippocampi (refer to section 4.3.5) and correlated this with naming performance, as the most relevant clinical language parameter in TLE patients.

a. Left TLE

Preoperatively, the left TLE group showed significant correlations of VF activation in the left hippocampus with preoperative naming ($p=0.02$, $R^2=0.24$). After left ATR, naming scores were positively correlated with activation in the left MFG ($p=0.02$, $R^2=0.23$) and in the remnant of the left posterior hippocampus ($p=0.03$, $R^2=0.20$).

b. Right TLE

In right TLE there were significant correlations of VF activation with preoperative naming scores in the left MFG ($p=0.046$, $R^2=0.20$) and IFG ($p=0.049$, $R^2=0.21$), and the left hippocampus ($p=0.05$, $R^2=0.19$). Postoperatively, there were significant correlations between naming and VF activation in the left MFG ($p=0.039$, $R^2=0.22$) and IFG ($p=0.042$, $R^2=0.21$) and also in the right MFG ($p=0.049$, $R^2=0.2$). There was no significant correlation with activation in the left hippocampus after right ATR.

4.4.3.3. Efficiency of postoperative reorganisation – comparison of patients with and without clinically significant naming decline after left ATR

Twelve/ 24 left TLE patients suffered clinically significant naming decline and 12/24 did not, or had improved naming scores after left ATR.

Those with a clinically significant naming decline had a significant positive correlation between postoperative VF activation and postoperative naming scores in the right MFG ($p=0.02$). Left TLE patients with stable or improved naming demonstrated a significant positive correlation in the posterior remnant of the left hippocampus ($p=0.034$), with greater fMRI activation being correlated with better naming scores (Fig 4.3, Table 4.4). Patients with positive naming

outcomes had greater activation in the left MFG ($p=0.031$) suggesting reorganisation within the ipsilateral hemisphere underpins more robust word retrieval. Patients with significant naming decline demonstrated greater activation in the right MFG ($p=0.002$) than patients with no decline, inferring that recruitment of contralateral frontal lobe networks does not confer proficiency.

There were no significant correlations between preoperative hippocampal volumes or postoperative volumes of the residual hippocampi and pre- or postoperative naming scores in patients with left or right hippocampal sclerosis.

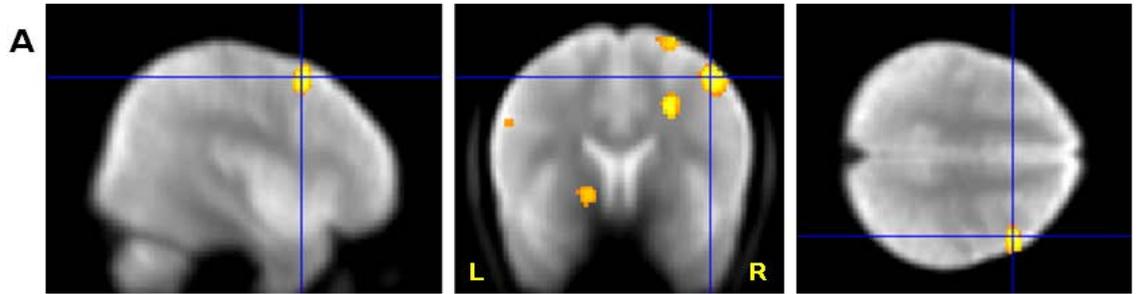
Table 4.4 Association of postoperative naming and postoperative VF fMRI activation after left ATR in patients with, and without a clinically significant naming decline

Subjects	Postoperative fMRI activation – neuropsychology score	Z-score	Corrected p-value (FWE)	Coordinates (x,y,z) in MNI space	Anatomical region
Left TLE with clinically significant decline	postoperative VF activation – naming	3.27	$p=0.022$	24, 6, 38	right MFG
Left TLE with no significant decline	postoperative VF activation – naming	2.58	$p=0.034$	-36, -20, -30	left HC/ PHG
Left TLE with decline > left TLE without decline	postoperative VF activation – naming	2.86	$p=0.002$	44, 12, 52	right MFG
Left TLE without decline > left TLE with decline	postoperative VF activation – naming	3.14	$p=0.031$	-36, 16, 6	left MFG

Legend: HC, hippocampus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); PHG, parahippocampal gyrus; TLE, temporal lobe epilepsy; VF, verbal fluency.

Left temporal lobe epilepsy

Clinically significant naming decline



No significant naming decline

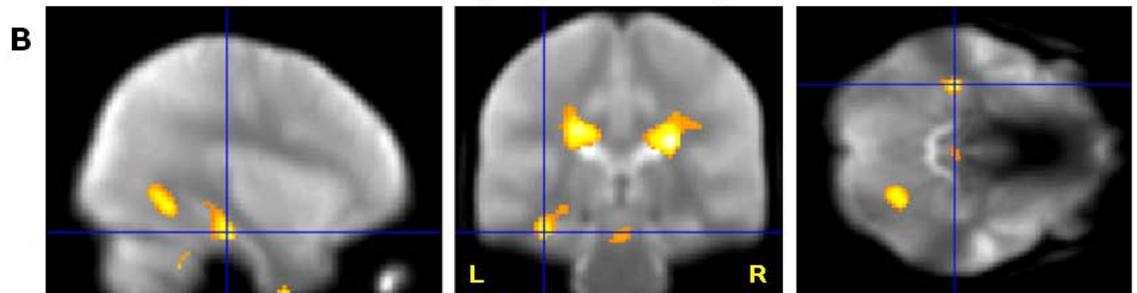


Figure 4.3 Efficiency of postoperative language networks

A: Left TLE with clinically significant decline in naming

Greater postoperative right middle frontal gyrus fMRI activation for verbal fluency correlates with better postoperative naming scores, characterised by greater, but inefficient recruitment of the contralateral frontal lobe.

B: Left TLE without clinically significant naming decline

Greater postoperative left posterior hippocampal fMRI activation for verbal fluency correlates with better postoperative naming scores, characterised by efficient recruitment of the remaining ipsilateral posterior hippocampal structures.

Threshold $p < 0.01$, uncorrected. Significant regions are superimposed onto an averaged normalised mean EPI from all patients who underwent left ATR. The crosshair points to the peak maximum activation.

4.4.4. Prediction of naming decline

4.4.4.1. Preoperative language fMRI and change in naming scores – voxel by voxel analysis

12/24 left TLE patients had a clinically significant naming decline after left ATLR and no patient had a clinically significant naming decline after right ATLR.

In left TLE there was a significant correlation between preoperative fMRI activation in the left MFG and postoperative decline in naming scores ($p=0.003$), characterised by greater preoperative fMRI activation being correlated with greater postoperative decline (Table 4.5, Fig 4.4A).

There was a significant correlation between preoperative fMRI activation for VF and change in VF scores outside the scanner in the left MFG ($p=0.001$), characterised by greater fMRI activation being associated with greater decline in VF. From a clinical perspective a decline in VF scores was less relevant than a decline in naming scores and therefore VF was not considered further (as an out of scanner correlate).

Table 4.5 Association of change of naming scores with preoperative VF fMRI activation in patients with left temporal lobe epilepsy

Subjects	fMRI contrast – change in neuropsychology task	Z-score	Corrected p-value (FWE)	Coordinates (x,y,z) in MNI space	Anatomical region
Left TLE	VF fMRI – 1/naming	3.95	$p=0.003$	-42, 6, 56	left MFG
		2.34	$p=0.064$	-20, -8, -18	left HC

Legend: HC, hippocampus; MFG, middle frontal gyrus; MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); TLE, temporal lobe epilepsy; VF, verbal fluency.

4.4.4.2. Prediction of naming decline in individual subjects – positive predictive value (PPV), sensitivity and specificity of language fMRI and preoperative naming performance

A clinically significant naming decline was defined as a decline of >3 on the McKenna Graded Naming Test. Two of the 24 left TLE patients, performed in the impaired range (i.e. $<1^{\text{st}}$ centile) preoperatively and therefore were excluded from further analysis as floor effects prevented identification of a postoperative decline.

Having identified that fMRI activation in the left MFG was significantly related to a decline in naming scores we correlated each individual patient's lateralisation index for VF in the MFG with each patient's change in naming scores.

There was a significant correlation between the lateralisation index for VF in the MFG and change in naming scores ($p=0.03$, $R^2=0.21$), characterised by patients with greater left lateralised language in this area being at higher risk for postoperative naming decline after left ATR (Fig 4.4B). A lateralisation index of <-0.65 in the MFG was defined as a cut-off – representing strongly left lateralised language representation for VF - which identified all patients with a clinically significant naming decline with a PPV of 60% with 100% sensitivity and 33.33% specificity because of a relatively high number of false positives. Preoperative naming scores alone identified all, but 2 patients with a clinical significant naming decline (PPV of 54.54 %, 100% sensitivity, 16.67% specificity). Considering both independent predictors to calculate the risk for the individual patients all left TLE patients with a clinically significant naming decline were identified with a PPV of 66.67%, 100% sensitivity and 40% specificity.

There was no significant correlation between preoperative naming scores or left hippocampal volume and naming change in patients with left TLE.

Left temporal lobe epilepsy

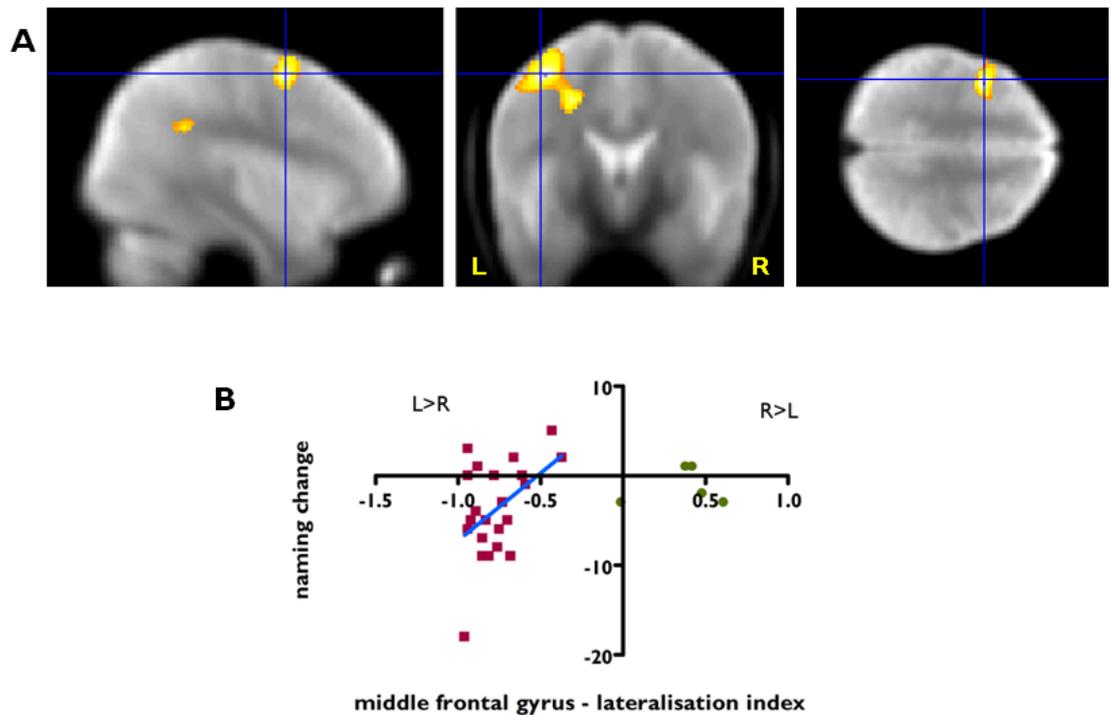


Figure 4.4 Prediction of naming decline using preoperative verbal fluency fMRI in patients with left TLE

A: Whole brain voxel by voxel analysis. Left middle frontal gyrus activation for verbal fluency correlates with change in naming scores after left ATR, characterised by greater naming decline in subjects with greater preoperative fMRI activation.

Threshold $p < 0.01$, uncorrected. Significant regions are superimposed onto an averaged normalised mean EPI from 30 healthy controls, 15 patients with left and 15 patients with right hippocampal sclerosis.

The crosshair points to the peak maximum activation.

B: Prediction of naming decline in individual subjects -

Language lateralisation index for verbal fluency in the middle frontal gyrus

Strongly left lateralised middle frontal gyrus activation for verbal fluency correlates with clinical significant naming decline after left ATR ($r^2 = 0.21$, $p = 0.03$). For comparison, five patients with left TLE and atypical language representation are indicated by green circles; these patients were not included in this study.

4.5. DISCUSSION

4.5.1. Summary of main findings

In this longitudinal study we performed language fMRI in TLE patients preoperatively and four months after left/ right ATR to assess reorganisation and efficiency of pre- and postoperative language networks.

We demonstrated reorganisation to the contralateral hemisphere within 4 months of left ATR, which was not observed after right ATR, suggesting that multiple systems support language. These findings were corroborated by functional connectivity analysis showing greater postoperative than preoperative connectivity to the contralateral frontal lobe in left TLE patients.

Preoperatively, a significant correlation between naming function and fMRI VF activation in the left hippocampus and the left frontal lobe in left and right TLE highlighted the role of the dominant hippocampus for word retrieval. After left ATR, the posterior remnant of the left hippocampus and the left frontal system had a continued role in successful naming, and reorganisation to the contralateral frontal lobe network was less productive.

Preoperatively, greater left middle frontal activation was predictive of greater postoperative naming decline after left ATR.

4.5.2. Language fMRI in temporal lobe epilepsy - reorganisation of language function after ATR

Several small studies have investigated postoperative reorganisation and plasticity of language function (Backes et al., 2005; Helmstaedter et al., 2006; Hertz-Pannier et al., 2002; Pataria et al., 2005; Wong et al., 2009). A postoperative fMRI study showed more bilateral language representation after left ATR than right ATR, and healthy controls (Backes et al., 2005). Without preoperative data, no conclusion on the effects of surgery can be drawn.

One fMRI study found evidence for reallocation of language processing to other regions than typical language areas in left TLE, compared to right TLE patients whose activation patterns remained unchanged postoperatively (Wong et al., 2009). This study was limited by small

numbers, heterogeneous pathologies and region of interest analysis restricted to typical language areas, so that possible compensatory mechanisms in other brain areas were not assessed.

In our longitudinal study we used VF and neuropsychological assessment pre- and postoperatively to show reorganisation/ recruitment of the contralateral frontal lobe network within four months of left ATLR in a large cohort of patients with hippocampal sclerosis, who were all left dominant for language. Most likely these findings reflect multiple systems supporting language, which come into action once the main system in the speech dominant hemisphere is disrupted. A similar dynamic was described in stroke patients (Saur et al., 2006). We are carrying out long term follow-up studies at one year to investigate subsequent reorganisation after ATLR.

Earlier age of epilepsy onset is associated with a higher incidence for atypical language representation (Gaillard et al., 2007) but also early intrahemispheric reorganisation (Bell et al., 2002). Postoperative interhemispheric reorganisation of language function is more likely in patients with pre-existing atypical language representation (Pataria et al., 2005) . We did not observe an effect of age of epilepsy onset, but our sample was purposefully restricted to patients with preoperative left language dominance in order to study inter- and intrahemispheric postoperative reorganisation and its functional capacity. Within our sample there was no relationship between age of onset and naming performance.

4.5.3. Neurobiological implications

Naming deficits have been reported after language dominant hemisphere ATLR (Davies et al., 1998; Davies et al., 2005; Hermann et al., 1999b; Seidenberg et al., 1998). The underlying mechanisms are not fully understood.

The hippocampus has a key role in verbal learning and memory (Squire, 1992) and there is evidence that the hippocampus is essential for naming. In line with several other studies we demonstrated increased hippocampal activity during naming tasks in the previous chapter (Bonelli et al., 2011; Tomaszewski Farias et al., 2005). Further, prior to surgery, naming was

poorer in patients with hippocampal sclerosis and the risk of naming decline after ATR was lower in patients with hippocampal sclerosis than in those without hippocampal sclerosis (Davies et al., 1998; Hamberger et al., 2007) suggesting a key role for the hippocampus. A paediatric study concluded that reorganisation of language function occurred when there was a hippocampal lesion (Liegeois et al., 2004). Patients with left hippocampal sclerosis had a higher chance of atypical language representation than TLE patients with other pathologies (Weber et al., 2006a), suggesting that the speech-dominant hemisphere's hippocampus has an important role in language function, particularly naming and that this function is impaired in hippocampal sclerosis, and if it is resected. Language lateralisation in TLE patients is not straightforward and there may be complex findings such as crossed lateralisation for anterior and posterior language areas (Gaillard et al., 2004), which could partly explain preoperative naming deficits in some patients with right TLE.

As we have demonstrated in the previous chapter functional MRI activates a network of cerebral regions. A requirement for naming and VF tasks is the retrieval of semantically or lexically associated words from long-term memory. Given the role of the dominant hippocampus in verbal learning and memory, it most likely has an essential role in the acquisition of phonemic, lexical and conceptual information, which are crucial for naming and word retrieval.

Language functions, particularly naming and reading, can be transferred to the contralateral hemisphere after injuries to the language dominant hemisphere in early life, or the development of TLE (Devinsky et al., 1993; Liegeois et al., 2004). Preservation of naming in patients with hippocampal sclerosis after ATR has been attributed to intrahemispheric reorganisation, in particular to the posterior and inferior temporal regions (Hamberger et al., 2007). In the subsequent section on assessing memory function I will discuss results from fMRI studies of memory which also suggest that it is the capacity of the remaining posterior ipsilateral hippocampus which preserves verbal and visual memory encoding function after ATR (refer to chapters 4 and 5).

In the current study we showed that, preoperatively, in left TLE with left-hemisphere speech dominance the left hippocampus and frontal lobe supported efficient naming function.

Postoperatively, left TLE patients with no significant naming decline relied on the recruitment of the residual left posterior hippocampus for word retrieval, while patients demonstrating a decline showed greater reliance on the contralateral frontal lobe. The implication is that reorganisation within 4 months of speech dominant ATR to the contralateral hemisphere is less effective, while reorganisation involving the ipsilateral posterior hippocampus underpins good naming functions postoperatively. The circumstances that determine whether language function is reorganised to the contralateral hemisphere and/or the ipsilateral hemisphere and temporal lobe still need to be established. Possible factors are age of onset, preoperative lateralisation index for language, genetic factors, severity of sclerosis, electroclinical findings (Helmstaedter et al., 1997b; Janszky et al., 2003) and extent of hippocampal resection.

4.5.4. Clinical implications - Prediction of postoperative naming decline

Identifying who is at risk of language impairment postoperatively improves the advice that is given to patients considering surgery. Sabsevitz et al. previously highlighted the role of temporal lobe regions compared to frontal regions in predicting postoperative naming deficits after temporal lobe surgery as assessed by a semantic decision fMRI task (Sabsevitz et al., 2003). In contrast to these findings, using the VF paradigm in left TLE patients who were left dominant for language (and therefore at risk of suffering a postoperative naming decline), those with greater VF activation in the left MFG were at greater risk of a postoperative naming decline implying an important interaction between MFG and anterior temporal lobe. We have shown in the previous chapter, that in patients with left TLE due to hippocampal sclerosis left hippocampal disengagement during language tasks was paralleled by greater frontal activation suggesting compensatory strategies in less functionally developed regions in the frontal lobe (Bonelli et al., 2011). A similar process has previously been described for episodic memory in left TLE (Dupont et al., 2000).

In order to establish a robust method to predict postoperative decline in individual subjects we calculated a lateralisation index in the anatomically defined MFG, which would be easy to apply in a clinical setting. Patients with strongly left lateralised VF in this area ($LI < -0.65$) were at risk

of suffering a clinically significant naming decline after left ATR. Combining preoperative performance on the naming test and language lateralisation indices we were able to predict a clinically significant naming decline in all our patients with a positive predictive value of 67%. Further, none of the 5 left TLE patients with preoperative atypical language representation (who were not included in this study) suffered a clinically significant naming decline after ATR (Fig 4B).

4.5.5. Methodological strengths and limitations

4.5.5.1. Strengths

1. This study has the advantage of comparing fMRI data and neuropsychological assessment before and 4 months after left or right ATR in a large cohort of TLE patients, all left language dominant with the same pathology. This allowed explicit study of the effects of surgery with respect to cortical reorganisation of language function.
2. We confined this study to a homogenous group of left hemisphere dominant patients, to determine the effects of left ATR.

4.5.5.2. Limitations

1. The VF task had to be carried out covertly, so that performance was not directly measured in the scanner.
2. Our results may be influenced by the effect of volume averaging on the extent and magnitude of hippocampal signal, given that all TLE patients had hippocampal sclerosis.
3. Postoperatively, language was assessed 4 months after ATR, and reorganisation may continue over a longer time. Also, we did not include healthy controls for repeat measures effects in this study. At present we are undertaking longitudinal follow-up studies of language organisation over 12 months after ATR, and in healthy controls to address these issues.
4. We examined expressive language skills by combining a VF fMRI task with out of scanner VF and naming performance, which is of great clinical concern in TLE patients and following ATR. The VF task does not primarily elicit temporal activation but requires word

retrieval and was associated with hippocampal activation. Future studies will benefit from fMRI paradigms that evaluate receptive language functions and explore the network sustaining naming processes, particularly posterior and basal temporal areas. We are currently implementing and validating a library of such tasks.

5. Early age of onset is associated with a higher incidence of atypical language dominance. We considered a selected population of left language dominant patients with hippocampal sclerosis, so the effects of age of onset were not investigated. It is necessary to establish patterns of change in typical language dominance before assessing the input of preoperative atypical language representation.

4.6. CONCLUSION

In this chapter we extended the preoperative findings of the previous chapter and showed an early postoperative activation in the contralateral frontal lobe for basic language functions in patients with left TLE who underwent left ATR. The capacity of the remaining ipsilateral posterior hippocampus was important to maintain naming function postoperatively, while involvement of the contralateral frontal lobe was less proficient.

VF-fMRI was predictive of postoperative naming decline in individual patients, with good sensitivity, but with less specificity.

In chapters V and VI, I describe the application of an fMRI paradigm, which was previously developed by our group and allows testing of verbal and visual memory encoding in a single session, to a group of healthy volunteers and patients with left and right TLE with the aim to study material-specific memory function and its impairment in TLE. From a clinical perspective, prediction of postoperative memory decline and effectiveness of reorganisation of memory function, either due to the underlying disease or following surgical intervention, is very important. In chapters V and VI we investigated how fMRI may contribute to answer some of these clinically significant questions.

CHAPTER V

5. (RE-)ORGANISATION OF MATERIAL-SPECIFIC MEMORY FUNCTION AND PREDICTING THE EFFECTS OF TEMPORAL LOBE RESECTION

In this chapter I will describe the use of fMRI to study material-specific memory function and how memory function is reorganized in a group of left and right TLE patients compared to a group of healthy control subjects; the second part of this chapter describes the role of fMRI as a potential predictor of clinically significant verbal and visual memory decline.

The material in this chapter has been published in: Bonelli SB et al. Imaging memory in TLE: predicting the effects of temporal lobe resection. *Brain*. 2010 Apr;133:1186-99. doi: 10.1093/brain/awq006. Epub 2010 Feb 15.

5.1. OBJECTIVE

There is evidence of material specific lateralisation of memory encoding in controls and patients with TLE from previous studies. In this experiment we studied 72 patients with unilateral medial TLE and 20 healthy controls using a memory fMRI paradigm that allowed testing of verbal and visual memory in a single scanning session. Fifty-four patients subsequently underwent ATLR. We aimed to test the hypothesis that there would be reorganisation of material-specific memory encoding in patients with TLE compared with controls, due to the

underlying pathology or ongoing epilepsy. We also assumed that there would be a relationship between activations on a memory fMRI task and neuropsychological scores for verbal and visual memory in controls and patients with TLE with increased activation being associated with better verbal or visual memory competence.

Subsequently, in patients who underwent left or right ATRR we wanted to determine whether preoperative memory fMRI was able to predict postoperative verbal and visual memory decline.

5.2. INTRODUCTION

(refer to chapter 1.5.2.4 for more details)

Anterior temporal lobe resection (ATLR) leads to seizure freedom in up to 70% of patients with medically refractory TLE (Wiebe et al., 2001) but this may be complicated by material-specific memory impairment (Chelune et al., 1991; Helmstaedter and Elger, 1996; Hermann et al., 1995; Lee et al., 2002; Loring et al., 1995; Sabsevitz et al., 2001).

To date several prognostic factors for memory decline after ATRR such as preoperative performance on neuropsychological tests (Baxendale et al., 2006; Chelune et al., 1991; Helmstaedter and Elger, 1996; Lineweaver et al., 2006), language lateralisation (Baxendale, 2002; Binder et al., 2008; Lineweaver et al., 2006; Loring et al., 1990; Rabin et al., 2004), severity of hippocampal sclerosis (Hermann et al., 1992b; Trenerry et al., 1993) and other epilepsy related factors such as age of epilepsy onset and duration of epilepsy (Baxendale et al., 2008) have been identified.

Functional MRI is an attractive clinical tool to evaluate cognitive function as it is non-invasive and repeatable. Most previous fMRI studies have focused on the prediction of verbal memory decline, only a few have investigated visual memory decline after non-dominant ATRR (Binder et al., 2008; Janszky et al., 2005; Powell et al., 2008b; Rabin et al., 2004; Richardson et al., 2006; Richardson et al., 2004b).

Memory fMRI in the medial temporal lobe is challenging due to limits on resolution and the possibility of geometric distortions and signal drop out caused by susceptibility effects associated with the use of Echo Planar (EP) Imaging (Robinson et al., 2004).

We previously developed a material specific memory encoding paradigm which allowed testing of verbal and visual memory in one scanning session (Powell et al., 2005a).

In the current experiment, we applied a similar paradigm to a large number of patients with medial TLE, who were candidates for either right or left ATR. We also studied a group of age and gender matched healthy controls to answer the main questions addressed in this chapter, reorganisation of memory functions in TLE and evaluation of the predictive value of preoperative memory fMRI in order to predict material-specific memory changes following ATR.

From a clinical perspective, the predictive power of a diagnostic method for individual patients is most relevant. We therefore used a stepwise linear regression model to test the predictive power of memory encoding fMRI compared to other epilepsy related predictors. Finally, we established an algorithm to predict postoperative verbal and visual memory outcome on an individual subject level.

5.3. METHODS

5.3.1. Subjects

We studied 72 patients with medically refractory TLE (41 left (21 female); median age 43 years, range 17-63; 31 right (20 female); median age 37 years, range 23-52) who underwent pre-surgical evaluation at the National Hospital for Neurology and Neurosurgery, London. All patients had undergone structural MRI at 3T, showing unilateral hippocampal sclerosis in 40 left TLE and 28 right TLE patients; of the remaining patients, one had a left, one a right anterior temporal cavernoma, one right anterior temporal focal cortical dysplasia and one patient showed a right medial temporal dysembryoplastic neuroepithelial tumour. All patients had normal contralateral medial temporal lobe structures on qualitative and quantitative MRI. Prolonged interictal and ictal video-EEG confirmed that seizures arose from the ipsilateral temporal lobe in all 72 patients. All patients' first language was English. Assessment of language dominance using fMRI revealed left hemisphere dominance in 39 patients, atypical, bilateral language representation in 31 patients and 2 patients with atypical, right hemisphere dominance. As

described in the common methodology section 2.3.2.1, we calculated a lateralisation index (LI) using the Bootstrap method of the SPM toolbox (Wilke and Lidzba, 2007) for the contrast “verbal fluency” for each subject in the middle and inferior frontal gyri. A lateralisation index of < -0.65 or > 0.65 was considered as strongly lateralised to the left/ right hemisphere. These LI were used as covariates for the second level analysis. In patients IQ was measured using WAIS-III. The mean verbal IQ was 98.72 (SD 17.66) in right TLE and 92.03 (SD 12.59) in left TLE patients; the mean performance IQ was 95.91 (SD 15.51) in right TLE and 95.78 (SD 19.41) in left TLE patients.

All patients were treated with anti-epileptic medication at the time of their assessment which mostly remained unchanged at the time of postoperative neuropsychological testing.

Twenty-nine of 41 left and 25 of 31 right TLE patients underwent an ATR. The standard neurosurgical procedure is described in section 2.2.1.2. The ILAE classification of postoperative seizure outcome following epilepsy surgery was used (Wieser et al., 2001), revealing a seizure outcome grade of 1 or 2 in 25 left and 17 right TLE patients and a seizure outcome grade of 3 to 5 in 4 left and 8 right TLE patients. For the 54 operated patients seizure outcome is given at one year following surgery for 42 subjects and 6-12 months for 12 subjects.

We also studied 20 right-handed native English-speaking healthy volunteers (median age 50 years, range 22 - 70; 10 female) with no history of neurological and psychiatric disease. Seventeen controls were left language dominant, 3 showed atypical, bilateral language representation as assessed by the fMRI language tasks. In controls IQ was estimated using the Nelson Adult Reading Test (NART) (Nelson and Willison, 1991). The mean NART in controls was 106.3 (SD 14.12).

For full details of the presurgical evaluation please refer to the common methodology chapter II.

5.3.2. Neuropsychological tests

Neuropsychological testing is an integral part of the standard presurgical assessment at the National Hospital for Neurology and Neurosurgery. We selected two learning tests, one verbal and one visual, from the memory tests employed that have been demonstrated to be good

indicators of postoperative memory decline (Baxendale et al., 2006). The verbal learning and the design learning test are described in chapters 2.2.2.4 and 2.2.2.5.

Patients completed these tests before and four months after ATR. In those patients who underwent an ATR, measures of verbal and visual memory change following surgery were calculated as postoperative - preoperative scores. Preoperative scores as well as changes in verbal and visual memory scores from baseline following left or right ATR were then correlated with preoperative fMRI activation patterns. A clinically significant postoperative change was defined using reliable change indices (RCI) (Baxendale and Thompson, 2005). The reliable change indices (90% confidence interval) were 16% for verbal learning and 28% for design learning.

5.3.3. MR data acquisition

MR data acquisition was performed according to our common protocol (refer to chapters 2.3.1 and 2.3.1.2).

5.3.4. Memory fMRI paradigm

The memory paradigm including the subsequent recognition test which we used in our memory experiments are described in the common methodology section 2.3.2.2.

5.3.5. Data analysis

The initial analyses of the fMRI dataset are described in the common methodology chapter. This includes preprocessing steps (section 2.3.3.1) and the event-related analysis (section 2.3.3.3).

Second level analysis

At the second level of the random effects analysis, we divided the subjects into three groups: healthy volunteers, left TLE and right TLE patients. Each subject's contrast images were entered into a second level one sample t-test, which modelled the group effect (i.e. control

subjects or patients) on the various contrasts of interest; two sample t-tests were used to highlight brain regions demonstrating more or less activation in one group compared to another. In order to test for correlations between areas of fMRI activation and subject's performance on verbal learning and design learning pre- and postoperatively, simple and multiple regression analyses were performed over the whole brain. For each subject the verbal learning score and the design learning score were entered as covariates separately for control subjects and left and right TLE patients. The measures of change of verbal learning and design learning scores were used to test for correlations between preoperative fMRI activation and change in verbal memory and visual memory test scores from before to four months after epilepsy surgery in those patients who had an ATR and postoperative neuropsychological assessment.

The language lateralisation index derived from language fMRI as described above, the ratio of hippocampal volumes and duration of epilepsy (in years) were entered as additional covariates.

“Asymmetry image” analysis

In order to investigate the relationship between the asymmetry of medial temporal encoding activation and memory change after ATR, we created “asymmetry images” by rotating the normalised contrast images by 180 degrees in the x-axis and subtracting these flipped images from the original contrast image (Richardson et al., 2004b). The created images represent encoding asymmetry for each stimulus type showing left minus right activation in the left and right minus left activation in the right hemisphere. At the second level of the random effects analysis, we used a simple regression model for each group to look for brain regions showing correlations between preoperative encoding asymmetry and verbal and visual memory change following ATR.

Small volume correction

Unless otherwise stated, we report all medial temporal lobe activations at a threshold of $P < 0.01$, corrected for multiple comparisons (FWE in a small volume of interest) (refer to the general methodology section 2.3.3.3). In view of our a-priori hypothesis we performed the small volume

correction using a sphere of 10 mm diameter for the left and right hippocampi based on the peak activation.

5.3.6. Hypotheses

We tested for:

1. Main effects of verbal and visual memory encoding in patients and controls.
2. Evidence of material specific lateralisation of memory function by group comparison of subsequent verbal and visual memory effects in patients versus controls.
3. Efficiency of (re)organisation of verbal memory functions by correlating effects for encoding pictures and words with verbal learning in controls and TLE patients.
4. Efficiency of (re)organisation of visual memory functions by correlating effects for encoding pictures and faces with design learning in controls and TLE patients.

In order to evaluate whether preoperative memory fMRI is a useful predictor of postoperative verbal and visual memory deficits we then tested whether:

1. Change in verbal learning scores was related to fMRI activation for encoding words in left and right TLE patients.
2. Change in design learning scores was related to fMRI activation for encoding faces in right and left TLE patients.
3. Encoding asymmetry for words predicted change in verbal learning scores in left TLE patients.
4. Encoding asymmetry for faces predicted change in design learning scores in right TLE patients.

5.3.7. Prediction of verbal and visual memory outcome in individual subjects

In order to identify a robust fMRI method which would be useful in a clinical setting to predict verbal and visual memory decline in individual subjects we applied the following method:

5.3.7.1. Region of interest analysis: memory asymmetry index

Based on the “Asymmetry image analysis” we defined two spherical regions of interest of 6 mm diameter centred on the coordinates of the peak activation for encoding words or faces in the left (representing left minus right activation) and right (representing right minus left activation) anterior and posterior medial temporal lobes, in order to quantify this activation in the single subjects. In this way we obtained a memory asymmetry index within these regions for each subject. We then tested for correlations between each subject’s memory asymmetry index within these regions and their change in performance on the verbal learning and design learning tests (after left or right ATR) outside the scanner.

5.3.7.2. Stepwise linear regression

To identify the most important predictive variable(s) for postoperative verbal and visual memory decline, memory asymmetry indices were then entered into a stepwise linear regression together with variables that have been found to be predictive in previous studies.

We tested the following hypotheses:

Preoperative neuropsychology: We tested whether preoperative verbal learning and design learning scores would correlate with and therefore be predictive of change in verbal and visual memory.

Pathology: We looked for correlations between severity of pathology and change in verbal learning and design learning scores. We used left hippocampal volume as covariate for the left TLE group and right hippocampal volume as covariate for the right TLE group.

Language lateralisation: We tested whether language lateralisation to the left hemisphere would predict postoperative change in verbal memory after left and visual memory after right ATR.

Lastly, we considered whether memory asymmetry indices, language lateralisation and preoperative learning test performance were predictive of postoperative decline in individual subjects.

5.4. RESULTS

5.4.1. Neuropsychological performance

Left TLE patients had significantly lower scores (mean 55.83, SD 11.34) than controls (mean 66.53, SD 10.85) on the verbal learning test ($p=0.004$, ANOVA). There was no significant difference between controls and right TLE patients (mean 59.26, SD 12.12) or between left and right TLE patients on the verbal learning test.

Right TLE patients (mean 62.23, SD 17.54) demonstrated significantly lower scores for design learning than controls (mean 77.42, SD 16.60) ($p<0.013$, ANOVA). There was no significant difference in design learning scores between controls and left TLE patients (mean 71.49, SD 18.53) or between left and right TLE patients.

5.4.1.1. Postoperative memory change

Twenty-five out of 29 patients undergoing a left ATR had a postoperative decline in verbal learning scores, and for 7 this was classified as clinically significant; three patients showed a non-significant improvement in verbal learning scores and one patient's score remained unchanged. The mean change between pre- and postoperative verbal learning scores was -12, ranging from -48 to +10. In patients with right TLE, the mean change score for verbal learning after right ATR was -3, ranging from -45 to +12.

Twelve out of 25 patients undergoing a right ATR had a postoperative decline in design learning scores (2 clinically significant), 13 patients showed a clinically non-significant postoperative improvement in design learning. The mean change between pre- and postoperative design learning scores was -2, ranging from -61 to +26. In patients with left TLE, the mean change score for design learning after left ATR was -3, ranging from -54 to +36.

5.4.2. Hippocampal volumes

Left and right hippocampal volumes were significantly different in both left and right TLE patients. In the left TLE group: mean (SD) right hippocampal volume 2.78 (0.30) cm³, mean left hippocampal volume 1.80 (0.54) cm³ (paired t-test $p<0.0001$, 2-tailed). In the right TLE group:

mean (SD) right hippocampal volume 1.78 (0.47) cm³, mean left hippocampal volume 2.60 (0.34) cm³ (paired t-test $p < 0.0001$, 2-tailed).

There was no significant difference between left hippocampal volume in the left TLE group and right hippocampal volume in the right TLE group or between left and right hippocampal volume in controls. Controls' hippocampal volumes did not differ significantly from contralateral hippocampal volumes in right and left TLE patients.

5.4.3. Preoperative functional MRI activations and material-specific memory lateralisation

5.4.3.1. Main effects on fMRI activation for encoding words, faces and pictures

Controls demonstrated significant left hippocampal activation for encoding words ($p < 0.0001$, FWE (FWE) corrected). For encoding faces there was a significant activation in the right hippocampus ($p = 0.050$, FWE corrected) (Fig 5.1A-B). There was no significant hippocampal activation for encoding pictures in controls.

In left TLE patients, there was significant left hippocampal activation for encoding words ($p = 0.031$, FWE corrected) and significant right hippocampal activation for encoding faces ($p = 0.005$, FWE corrected), while there was no significant hippocampal activation for encoding pictures.

Right TLE patients did not reveal any significant hippocampal activation for encoding pictures, words or faces at the group level (Table 5.1).

5.4.3.2. Group comparisons for main effects

Left TLE patients demonstrated significantly less left hippocampal activation for encoding words ($p = 0.010$, FWE corrected) than controls (Fig 5.1C).

Right TLE patients revealed significantly less left hippocampal activation for encoding words ($p = 0.022$, FWE corrected) than controls. There was a trend for right TLE patients to have less right hippocampal activation for encoding faces ($p = 0.058$, FWE corrected) than controls (Fig 5.1D).

There was no significant difference in fMRI activation for encoding pictures between left or right TLE patients and controls.

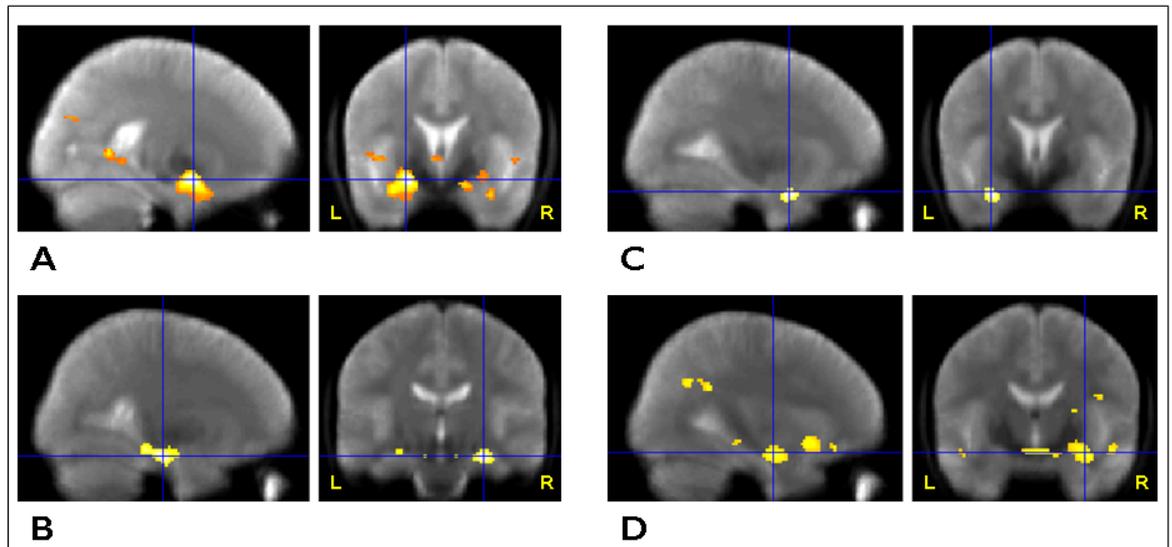


Figure 5.1 Group results of memory fMRI in controls, left and right TLE patients

A and B: Main effect in controls

A: word encoding – left hippocampal activation

B: face encoding – right hippocampal activation

C and D: Group comparison between controls, left and right TLE patients

C: Less left hippocampal activation for encoding words in left TLE compared to controls

D: Less right hippocampal activation for encoding faces in right TLE compared to controls

Threshold $p < 0.01$, uncorrected.

Significant regions are superimposed onto an averaged normalised mean EP image from 30 healthy controls, 15 patients with left and 15 patients with right hippocampal sclerosis.

Table 5.1 fMRI activation peaks in the hippocampus for the main effects of encoding words and faces

Subjects	fMRI contrast	Z-score	Corrected p-value (family-wise error)	Coordinates (x,y,z) in MNI space	Lateralisation of hippocampal activation
Controls	word encoding	4.49	p<0.0001	-22, 2, -16	left
	face encoding	2.47	p=0.050	28, -18, -20	right
Left TLE	word encoding	2.63	p=0.031	-12, -8, -18	left
	face encoding	3.33	p=0.005	26, -20, -8	right
Right TLE	word encoding	-	ns	-	-
	face encoding	-	ns	-	-

Group comparisons between patients and controls for the main effects of encoding words and faces

Left TLE < controls	word encoding	3.05	p=0.010	-28, 4, -24	left
Right TLE < controls	word encoding	2.82	p=0.022	-22, -2, -22	left
Right TLE < controls	face encoding	2.34	p=0.058	32, -6, -18	right

Legend: MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); ns, not significant; TLE, temporal lobe epilepsy.

5.4.3.3. Correlation between fMRI activations and neuropsychological performance

A multiple regression analysis was performed to assess the relationship between left and right hippocampal fMRI activation for encoding pictures, words and faces and performance on preoperative tests for verbal and visual memory (Table 5.2).

In controls, there was no significant correlation between memory fMRI for encoding pictures or words and verbal learning or between memory fMRI for encoding pictures or faces and design learning.

In left TLE patients, there was a significant correlation in the left hippocampus ($p=0.008$, FWE corrected), characterised by greater fMRI activation for encoding words being correlated with better verbal learning scores. There was no correlation in the contralateral hippocampus.

There was a significant positive correlation between left hippocampal fMRI activation for encoding pictures and verbal learning scores ($p=0.017$, FWE corrected).

We also found a significant positive correlation in the left hippocampus between preoperative fMRI activation for encoding faces and design learning scores ($p=0.011$, FWE corrected). At a lower threshold, there was also a positive correlation in the right hippocampus, but this was not significant.

In right TLE patients, there was a significant positive correlation in the left hippocampus ($p=0.042$, FWE corrected), with greater fMRI activation for encoding words being correlated with better verbal learning scores. The inverse contrast revealed a significant negative correlation in the right hippocampus ($p=0.036$, FWE corrected), with greater fMRI activation for encoding words in the right hippocampus being correlated with worse verbal learning scores. There was also a significant positive correlation in the right hippocampus characterised by greater fMRI activation for encoding faces being correlated with better design learning scores ($p=0.003$, FWE corrected). There was no correlation in the contralateral hippocampus.

There was no significant correlation in the medial temporal structures between fMRI activation for encoding pictures and design learning scores.

5.4.3.4. Relation of hippocampal fMRI activation to hippocampal volumes

There was no significant correlation between hippocampal volume and fMRI activation for encoding words in left TLE patients and no significant correlation between hippocampal volume and fMRI activation for encoding faces in right TLE patients.

Table 5.2 Association of verbal learning/ design learning scores with memory fMRI activation

Subjects	fMRI contrast – neuropsychology task	Z-score	Corrected p-value (family-wise error)	Coordinates (x,y,z) in MNI space	Lateralisation of hippocampal activation
Controls	word encoding - VL	-	ns	-	-
	face encoding - DL	-	ns	-	-
Left TLE	word encoding - VL	3.15	p=0.008	-18, -6, -18	left
Left TLE	face encoding - DL	3.02	p=0.011	-24, -8 -10	left
Right TLE	word encoding - VL	2.60	p=0.042	-22, -28, -6	left
Right TLE	word encoding – 1/VL	2.68	p=0.036	22, -8, -14	right
Right TLE	face encoding - DL	3.53	p=0.003	34, -16, -14	right

Legend: DL, design learning; MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); ns, not significant; TLE, temporal lobe epilepsy; VL, verbal learning.

5.4.4. Preoperative functional MRI and prediction of memory decline

5.4.4.1. Results of the “whole brain”analysis

A multiple regression analysis was performed to assess the relationship between preoperative fMRI activation for encoding words and faces and changes in performance on tests for verbal and visual memory after left and right ATLR (Table 5.3).

Encoding pictures with more bilateral activations provided weaker correlations with neuropsychological performance on tests for verbal and visual memory and so was not considered further.

There was a significant correlation in the left anterior hippocampus between preoperative fMRI activation for encoding words and change in verbal learning scores after left ATR (p=0.028, FWE corrected), characterised by greater preoperative fMRI activation for encoding words being correlated with greater postoperative decline in verbal learning (Fig 5.2A). No correlations were seen between preoperative memory fMRI for encoding faces and change in design learning scores after left ATR.

There was no significant correlation between preoperative fMRI activation for encoding words and postoperative change in verbal learning scores in right TLE patients. There was a significant correlation between change in design learning after right ATR and preoperative fMRI activation for encoding faces in the right anterior hippocampus (p=0.05, FWE corrected), characterised by greater preoperative fMRI activation for encoding faces being correlated with greater postoperative decline in design learning (Fig 5.2B).

Table 5.3 Association of change of verbal learning/ design learning scores with preoperative memory fMRI activation

Subjects	fMRI contrast – change in neuropsychology task	Z-score	Corrected p-value (family-wise error)	Coordinates (x,y,z) in MNI space	Lateralisation of hippocampal activation
Left TLE	word encoding - 1/VL	2.72	p=0.028	-24, -20, -6	left
Left TLE	face encoding - DL	-	ns	-	-
Right TLE	word encoding - VL	-	ns	-	-
Right TLE	face encoding - 1/DL	2.60	p=0.050	16, -14, -16	right

Legend: DL, design learning; MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); ns, not significant; TLE, temporal lobe epilepsy; VL, verbal learning.

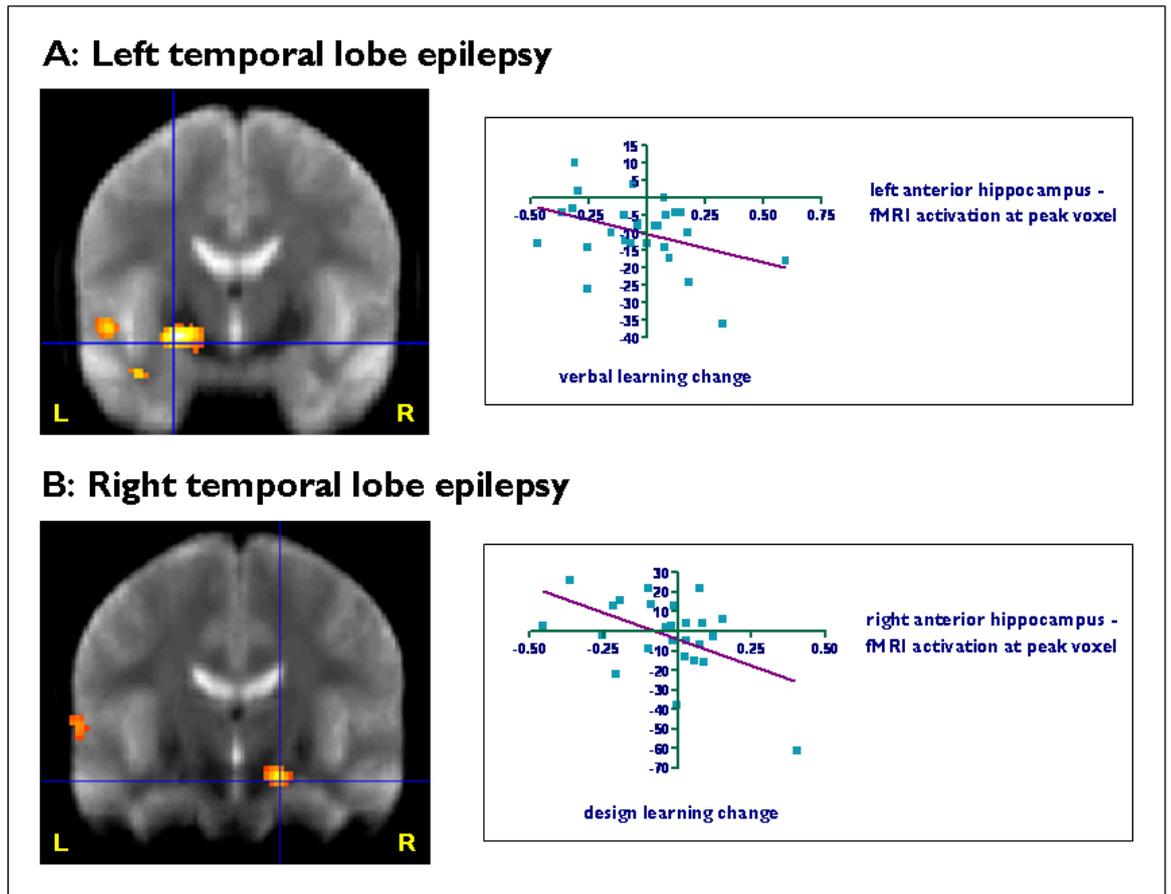


Figure 5.2 Prediction of verbal and visual memory decline using memory fMRI

A: Left anterior hippocampal activation for encoding words correlates with change in verbal learning scores after left ATLR, characterised by greater verbal memory decline in subjects with greater fMRI activation.

B: Right anterior hippocampal activation for encoding faces correlates with change in design learning scores after right ATLR, characterised by greater visual memory decline in subjects with greater fMRI activation.

Threshold $p < 0.01$, uncorrected. The correlations at the peak voxel are illustrated on the right. Significant regions are superimposed onto an averaged normalised mean EP image from 30 healthy controls, 15 patients with left and 15 patients with right hippocampal sclerosis.

5.4.4.2. Asymmetry of encoding-related fMRI activations and correlation with postoperative change in neuropsychological performance.

Having identified that hippocampal activation particularly for word and face encoding was related to changes in material specific memory after ATLR, a simple regression analysis was performed to assess the relationship between preoperative fMRI encoding asymmetry for words

and faces and change in performance on tests for verbal and visual memory after ATR (Table 5.4).

Table 5.4 Preoperative memory encoding asymmetry for words and faces and changes of verbal learning and design learning scores

Subjects	fMRI encoding asymmetry - change in neuropsychology task	Z-score	Corrected p-value (family-wise error)	Coordinates (x,y,z) in MNI space	Anatomical region
Left TLE	encoding words – 1/VL	2.96	p=0.028	-16, -4, -4	left anterior HC
Left TLE	encoding words – VL	2.70	p=0.076	-34, -38, -10	left posterior HC
Right TLE	encoding faces – 1/DL	2.63	p=0.063	32, -6, -10	right anterior HC
Right TLE	encoding faces – DL	2.12	ns	38, -26, -8	right posterior HC

Legend: DL, design learning; HC, hippocampus; MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); ns, not significant; TLE, temporal lobe epilepsy; VL, verbal learning.

Preoperatively, greater left than right anterior hippocampal activation asymmetry for encoding words was correlated with greater verbal memory decline after left ATR (p=0.028, FWE corrected). There was a positive correlation in the left posterior hippocampus, that did not reach statistical significance for the voxel wise analysis (p=0.076, FWE corrected) with greater left than right posterior hippocampal activation being associated with better verbal memory outcome after left ATR.

Greater right than left anterior hippocampal activation asymmetry for encoding faces was correlated with greater visual memory decline after right ATR (p=0.063, FWE corrected).

Region of interest analysis: Memory asymmetry index in individual subjects

In order to determine whether memory fMRI may be applied as a robust clinical tool for predicting effects of ATR on memory we calculated a memory asymmetry index in the

anterior and posterior medial temporal lobe for encoding words and faces for each individual subject for correlation with each patient's change in verbal and visual memory scores.

There was a significant negative correlation between memory asymmetry indices for encoding words and change in verbal learning scores, characterised by greater left than right anterior medial temporal lobe fMRI activation for encoding words being correlated with greater verbal memory decline after left ATR (R²= 0.23, p=0.008).

In the posterior medial temporal lobe there was a significant positive correlation, characterised by greater left than right posterior medial temporal lobe activation being correlated with better verbal memory outcome after left ATR (R²= 0.14, p=0.04) (Fig 5.3).

Greater right than left fMRI activation for encoding faces in the right anterior medial temporal lobe was correlated with greater visual memory decline (R²= 0.22, p=0.02) after right ATR.

In the posterior medial temporal lobe there was a significant positive correlation between memory asymmetry indices for encoding faces and change in design learning scores after right ATR, characterised by greater right than left posterior medial temporal lobe activation being correlated with better visual memory outcome (R²= 0.16, p=0.05) (Fig 5.4).

Left temporal lobe epilepsy

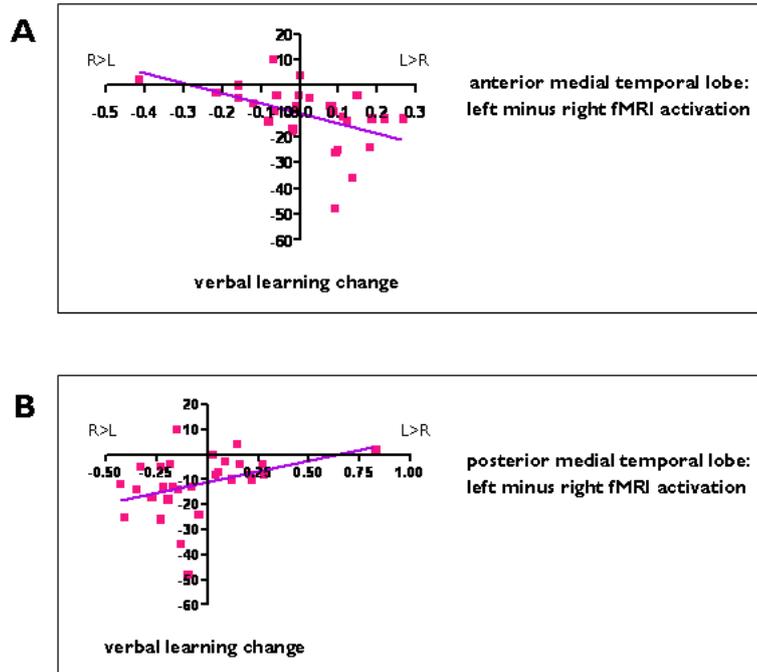


Figure 5.3 Prediction of verbal memory decline in individual subjects

Asymmetry of activation with encoding words in regions of interest in the anterior and posterior medial temporal lobe in left temporal lobe epilepsy patients.

A: Greater left anterior medial temporal lobe activation for encoding words correlates with greater verbal memory decline after left ATR ($r^2= 0.23$, $p=0.008$).

B: Greater left posterior medial temporal lobe activation for encoding words correlates with better verbal memory outcome ($r^2= 0.14$, $p=0.04$).

Right temporal lobe epilepsy

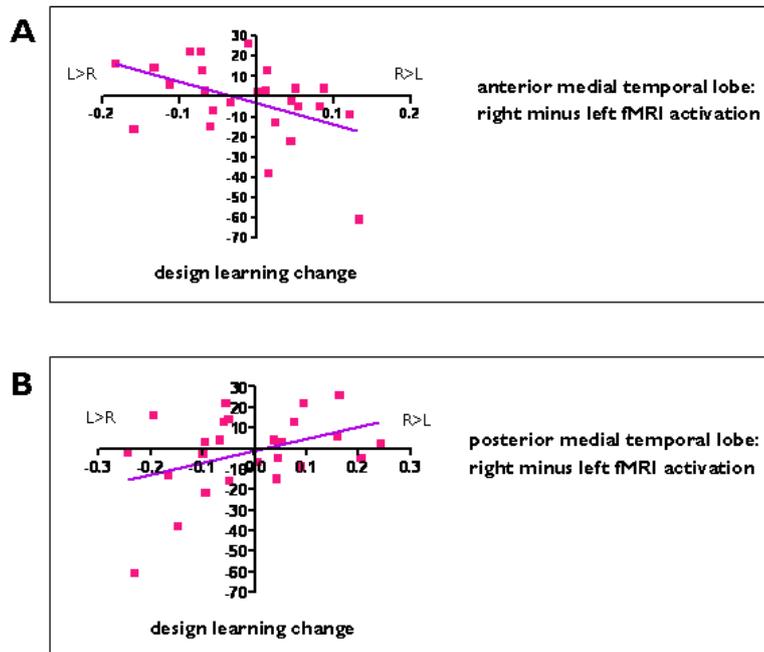


Figure 5.4 Prediction of visual memory decline in individual subjects

Asymmetry of activation with encoding faces in regions of interest in the anterior and posterior medial temporal lobe in right temporal lobe epilepsy patients.

A: Greater right anterior medial temporal lobe activation for encoding faces correlates with greater visual memory decline after right ATLR ($r^2=0.22$, $p=0.02$).

B: Greater right posterior medial temporal lobe activation for encoding faces correlates with better visual memory outcome after right ATLR ($r^2=0.16$, $p=0.05$).

5.4.5. Epilepsy related factors and memory decline

There were no statistically significant correlations between left hippocampal volume and postoperative verbal memory decline in left TLE patients or between right hippocampal volume and postoperative visual memory decline in right TLE patients.

In left TLE patients there was no significant correlation between preoperative verbal learning scores and verbal memory decline after left ATLR (Pearson's correlation coefficient (r)=-0.037; $p=0.42$ (1-tailed)). In right TLE patients there was a significant correlation between preoperative design learning scores and visual memory decline after right ATLR, characterised by a greater decline in patients with better preoperative performance (Pearson's correlation coefficient (r)=-0.381; $p=0.03$ (1-tailed)).

There was a significant correlation between language lateralisation index and verbal memory decline (Pearson's correlation coefficient (r)=0.331; p =0.04 (1-tailed)), characterised by greater language lateralisation to the left being correlated with greater verbal memory decline after left ATR. There was no significant correlation between language lateralisation index and visual memory decline after right ATR.

No significant correlations were seen between duration of epilepsy and verbal or visual memory decline in left or right TLE patients.

0.1% (R^2 =0.001) of the variance of verbal memory decline were explained by preoperative verbal learning scores, 0.1% (R^2 =0.001) by left hippocampal volumes and 11% (R^2 =0.109) by language lateralisation.

14.5% (R^2 =0.145) of the variance of visual memory decline were explained by preoperative design learning scores, 7.2% (R^2 =0.072) by right hippocampal volumes and 4.1% (R^2 =0.041) by language lateralisation.

5.4.6. Stepwise linear regression to identify variables predictive of memory decline

Four variables were entered into stepwise linear regression models with postoperative verbal and visual memory change as the dependent variables in order to test for the strongest predictor.

These were:

For verbal memory: preoperative verbal learning scores, left hippocampal volume, language lateralisation index, memory asymmetry index for encoding words (in the left anterior medial temporal lobe).

For visual memory: preoperative design learning scores, right hippocampal volume, language lateralisation index, memory asymmetry index for encoding faces (in the right anterior medial temporal lobe).

Verbal memory: In this model which was predictive of postoperative verbal memory change (R^2 =0.23, p <0.008) memory asymmetry for encoding words in the anterior medial temporal

lobe was the only and strongest predictor; no other variables made a significant contribution ($p > 0.1$) to the model.

Visual memory: This model predicted postoperative visual memory change ($R^2 = 0.395$, $p < 0.004$). Stepwise linear regression demonstrated that memory asymmetry for encoding faces in the anterior medial temporal lobe (Beta weights: -0.502) and preoperative design learning scores (Beta weights: -0.425) made a significant contribution to this model with memory asymmetry for encoding faces being the strongest predictor.

5.4.7. Prediction of memory decline in individual subjects

From a clinical perspective the sensitivity, specificity and positive predictive value of a diagnostic method are the most important measures, with the latter reflecting the probability that a positive test reflects the underlying condition being tested for. Being able to advise patients on the possible risk for a clinically significant verbal or visual memory decline is most relevant.

A clinical significant verbal memory change was defined as a decline of $> 16\%$ and a significant visual memory change as a decline of $> 28\%$. We first calculated the positive predictive value, sensitivity and specificity of memory fMRI alone (Table 5.5):

Greater activation on word encoding in the left, than the right anterior medial temporal lobe identified all 7 patients who subsequently experienced a clinically significant decline of verbal memory after left ATR. Of the two who experienced a clinically significant decline of visual memory after right ATR one had greater activation during face encoding in the right, than the left anterior medial temporal lobe.

With a relatively large number of false positives memory fMRI alone provides only average power to predict postoperative decline (positive predictive value for verbal memory change: 35%; positive predictive value for visual memory change: 20%). We therefore also considered language lateralisation (< -0.65 = strongly left lateralised) and performance on preoperative psychology tests ($> 50\%$ = high preoperative verbal learning score; $> 65\%$ = high preoperative design learning score) in addition to the memory asymmetry index (either predominantly left or

right anterior medial temporal lobe activation) to calculate the risk on an individual subject level (positive predictive value of all three tests) as these variables have been previously reported to be predictive (Baxendale et al., 2006; Binder et al., 2008; Saling, 2009). In this way anterior medial temporal lobe encoding asymmetry for words with greater left than right activation, combined with higher preoperative verbal memory scores on neuropsychological testing and language lateralisation to the left hemisphere identified all left TLE cases with a clinically significant verbal memory decline after left ATR with 100% sensitivity and with 86% specificity.

In the same way, visual memory decline after right ATR was predicted with 50% sensitivity and 100% specificity in right TLE, but only 2 patients had a clinically significant visual memory decline (Table 5.6). When used without the fMRI data, preoperative verbal learning and hippocampal volumes did not discriminate between the 7 who did, and the 22 patients who did not have a significant decline in verbal memory.

Table 5.5 Positive predictive value, sensitivity and specificity of memory fMRI in a region of interest in the anterior medial temporal lobe

Verbal memory change (left TLE)	Sensitivity	Specificity	PPV
	100%	40.91%	35%
Visual memory change (right TLE)	Sensitivity	Specificity	PPV
	50%	82.61%	20%

Legend: PPV, positive predictive value.

Table 5.6 Positive predictive value, sensitivity and specificity of memory asymmetry indices, language lateralisation and preoperative verbal learning/ design learning scores

Verbal memory change (left TLE)	Sensitivity	Specificity	PPV
	100%	86.36%	70%
Visual memory change (right TLE)	Sensitivity	Specificity	PPV
	50%	100%	100%

Legend: PPV, positive predictive value.

5.5. DISCUSSION

5.5.1. Summary of main findings

In this chapter we report a series of investigations of memory fMRI in TLE, and the ability of the method to predict memory decline after ATR. First, we demonstrated that left hippocampal activation in a verbal memory task was associated with out of scanner verbal learning proficiency in left TLE patients, while right hippocampal activation in a visual memory task was associated with performance on design learning in right TLE patients, highlighting the role of the hippocampus during material specific memory encoding. Secondly, we demonstrated that memory fMRI activation in the hippocampal regions was predictive of both verbal and visual memory outcome after left or right ATR. We showed that memory fMRI was the strongest predictor for postoperative verbal and visual memory decline compared to other related factors such as language lateralisation, preoperative performance on neuropsychological tasks and duration of epilepsy. Finally, we devised an algorithm to predict a clinically significant postoperative decline in individual patients.

5.5.2. Memory fMRI in TLE

A number of studies have used fMRI for prediction purposes (Binder et al., 2008; Janszky et al., 2005; Powell et al., 2008b; Rabin et al., 2004; Richardson et al., 2006; Richardson et al., 2004b); however, nearly all of these studies are based on small patient numbers mostly reporting group results or are limited by imaging techniques. Most studies used block designs

which have the advantage of greater sensitivity detecting activation in individual subjects and of being less vulnerable to alterations in the haemodynamic response function than event-related analyses. Rabin et al. for example used a complex visual scene-encoding task to show symmetrical medial temporal lobe activation in controls while TLE patients showed greater asymmetry. This was also related to postsurgical memory outcome with greater ipsilateral activation correlating with greater memory decline using change in recognition performance during the tasks rather than out of scanner tests of verbal and visual memory as a covariate (Rabin et al., 2004). Using Roland's Hometown Walking task (Roland et al., 1987) Janszky et al. found that reduced activation of the medial temporal lobe region ipsilateral to the seizure focus correlated with a favourable memory outcome after right ATLR (Janszky et al., 2005). Binder and co-workers found that left language dominance assessed by preoperative language fMRI was useful in addition to other factors such as late age of epilepsy onset and preoperative neuropsychological performance to predict postoperative memory decline in patients with left TLE compared to intracarotid amytal testing for both language and memory lateralisation (Binder et al., 2008).

Previous studies by our group have demonstrated the advantages of an event-related analysis for evaluating verbal and/ or visual memory decline after ATLR (Powell et al., 2008b; Richardson et al., 2004b), which are also discussed in chapter 1.5.2.4.3. In brief, event-related designs allow detection of activations that arise specifically during successful encoding although being less powerful than blocked designs. Another advantage is the possibility of capturing anterior hippocampal activation during an encoding task, which is therefore in an area that will be removed by ATLR, while studies based on blocked designs are more likely to show areas of activation in more posterior hippocampal and parahippocampal regions, which occur during cognitive processes other than memory encoding. Richardson et al. used an event-related design to assess verbal memory encoding in 10 TLE patients who subsequently underwent left ATLR demonstrating that greater left than right hippocampal activation was strongly related to greater postoperative verbal memory decline (Richardson et al., 2003; Richardson et al., 2004b).

Powell et al. used a material specific memory encoding paradigm that tested verbal and visual memory in one scanning session (Powell et al., 2005a). They demonstrated that patients with relatively greater ipsilateral compared to contralateral medial temporal lobe activation suffered greater verbal or visual memory decline after dominant/ non-dominant ATLR in an initial pilot study of 15 TLE patients (Powell et al., 2008b). Using a similar paradigm with a 3T rather than a 1.5T MRI scanner, our study assessed the predictive power of memory fMRI in a large cohort of patients that resulted in the development of an algorithm to predict clinical significant verbal and visual memory decline in individual subjects. We demonstrated that relatively greater ipsilateral than contralateral preoperative anterior hippocampal activation for word or face encoding predicted greater verbal or visual memory decline in a large series of TLE patients who underwent left or right ATLR. In addition absolute activation within the left or right anterior hippocampus was also predictive of both postoperative verbal and visual memory decline.

5.5.3. Neurobiological implication

To explain memory deficits following ATLR two different models of hippocampal function have been put forward (Chelune et al., 1991), which we have discussed in chapter 1.5.2.4.2. Briefly summarised, the hippocampal reserve theory suggests that it is the reserve or capacity of the contralateral hippocampus that supports memory function after surgery and therefore determines the decline in memory function. The functional adequacy model on the other hand suggests that it is the capacity of the ipsilateral hippocampus, which is to be resected that determines whether changes in memory function will be observed. Other studies assessing baseline neuropsychology (Chelune et al., 1991; Helmstaedter and Elger, 1996), intracarotid amytal testing (Kneebone et al., 1995) and MRI volumetry (Trenerry et al., 1993) have provided support for the functional adequacy model of the ipsilateral hippocampus rather than the functional reserve of the contralateral hippocampus supporting memory function. Our findings that greater left/ right anterior hippocampal activation was associated with greater verbal/ visual memory decline after ATLR while no significant correlations were observed in

the contralateral hippocampus strongly support the functional adequacy theory in keeping with findings of other studies that employed regions of interest in the medial temporal lobe to evaluate the risk of postoperative memory decline (Rabin et al., 2004; Richardson et al., 2006). The fact that there was some bitemporal involvement of some verbal and visual memory function with the paradigms used suggests that the paradigms were not “pure” in terms of being material specific or that there may have been some bilaterality of specific memory encoding functions. This may provide some evidence for the hippocampal reserve model. Several post-resection studies challenge the model of pure material specificity as summarised by Saling suggesting that cerebral organisation of verbal and visual memory are neither opposites nor fully lateralised (Saling, 2009). Recent functional MRI studies also concluded that contralateral reorganisation was not efficient but rather a marker of network disruption due to underlying pathology (Powell et al., 2007b) and which is also in line with our findings reported in the previous chapter on efficiency of language reorganisation after ATLR (Bonelli et al., 2012).

A novel finding of this study was that while ipsilateral anterior hippocampal activation was associated with greater verbal and visual memory decline following left and right ATLR respectively, relatively greater activation in the posterior part of the ipsilateral hippocampus (which is likely to be spared during an ATLR) was correlated with better verbal or visual memory outcome. Together with the results of the voxel-based analysis these findings provide strong support for the functional adequacy model suggesting that ipsilateral recruitment of posterior hippocampal networks is more efficient than recruitment of the contralateral hippocampus supporting memory function after surgery.

5.5.4. Clinical implications

Prediction of postoperative neuropsychological deficits is the ultimate goal of clinical neuroimaging as part of presurgical investigations in TLE patients. We demonstrated that the prediction of both verbal and visual memory decline was possible using memory fMRI in left and right TLE patients.

From a clinical perspective it is the prediction of verbal memory decline in individual subjects which is most relevant, particularly in those individuals who are high functioning preoperatively and therefore have most to lose. We devised an algorithm using asymmetry indices of preoperative memory encoding activation in the anterior medial temporal lobe, language lateralisation and performance on preoperative neuropsychological assessment to predict clinically significant postoperative verbal and visual memory outcome in individual subjects. We identified a region of interest in individual patients, in the anterior medial temporal lobe and calculated an asymmetry index of fMRI activation for memory encoding for each subject. Individuals with greater left than right activation in this region were at greater risk of suffering a clinically significant verbal memory decline after left ATR, while those with greater right than left activation were found to be at risk of suffering a clinically significant visual memory decline following right ATR. This methodology is straight forward to apply and robust and could be readily adopted in clinical practice. Using memory asymmetry indices, language lateralisation indices and preoperative performance on neuropsychological tests we were then able to predict a clinically significant postoperative verbal decline in all of our patients who underwent left ATR. The algorithm was less predictive of visual memory decline but this was much less common and is usually of less clinical importance but may be relevant for some roles, such as remembering routes and architectural designs. Having devised this algorithm, it now needs to be tested prospectively in a further large series of patients.

5.5.5. Methodological aspects and limitations

This experiment has several strengths and limitations:

1. Using an event-related memory design is time consuming and demanding on patients and personnel. In patients and controls with excellent performance on the post-scanning memory test the contrast “items remembered” versus “items forgotten” might not result in strong activation. Introducing a third contrast such as “familiar” and therefore more variety, could be a solution for this problem. On the other hand the event-related analysis has the great advantage of showing activation in the anterior hippocampus, which is the part of the

hippocampus that will be removed during an ATR. By using an event-related design one only takes into account successfully encoded items. Localising the part of the brain at which fMRI activation correlates with out of scanner performance on neuropsychological tests provides the biological basis for (postoperative) neuropsychological findings. In 10 further patients with TLE scanned over the time frame of this study, there was no activation seen in the single subjects, or the subjects could not manage to carry out the scanning protocol, which is therefore not universally applicable.

2. In this study imaging parameters were optimized for capturing activation in the temporal lobes and nearby structures. Accordingly our field of view was limited to coverage of the temporal lobes so that we cannot comment on any possible compensatory mechanisms involving other brain areas such as the orbito-frontal cortex as for example described by Dupont et al. (Dupont et al., 2000). Furthermore, our results may be influenced by the effect of volume averaging on the extent and magnitude of hippocampal signal, given that most of the patients had hippocampal sclerosis. We also experienced the usual technical difficulties of fMRI studies tailored to the temporal lobes such as low resolution, distortions and signal dropout. Future studies will benefit from improved fMRI techniques with whole brain coverage and improved fMRI paradigms to obtain strong and reliable activations in each subject.

3. Finally memory was tested only 4 months after surgery, which might be too early for any contralateral hippocampal reserve to become fully functional; prospective follow-up studies are underway evaluating memory outcome after one year.

5.6. CONCLUSION

In this chapter we have shown that memory fMRI is the strongest predictor for postoperative verbal and visual memory decline in individual subjects using a material specific memory encoding paradigm compared to other previously suggested predictors. Our results support the functional adequacy theory, suggesting that it is the capacity of the ipsilateral hippocampus, most likely the remaining posterior part that preserves verbal and visual memory encoding function after ATR. This finding may lead to a re-evaluation of the role of tailored

hippocampal resections to minimise the risk of memory impairment. The algorithm we devised to predict memory decline in individual patients now needs to be tested in a further prospective cohort. For comparison with preoperative activation patterns and to elucidate the nature of postoperative recovery and plasticity we have carried out postoperative fMRI memory studies correlating postoperative fMRI activation with postoperative performance on neuropsychological tests. I will discuss the findings in the subsequent chapter.

CHAPTER VI

6. REORGANISATION OF MATERIAL-SPECIFIC MEMORY

FUNCTION FOLLOWING ANTERIOR TEMPORAL LOBE

RESECTION

In chapter VI we report longitudinal fMRI results in patients with temporal lobe epilepsy (TLE) whose preoperative findings were discussed in the previous chapter and who subsequently underwent left or right anterior temporal lobe resection (ATLR). We applied the same material-specific memory encoding paradigm used in the previous experiment but used a parallel set of stimuli to evaluate reorganisation of postoperative verbal and visual memory function in a sub-cohort of our patient sample with left and right TLE.

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6.1. OBJECTIVE

Anterior temporal lobe resection controls seizures in 50-60% of patients with intractable temporal lobe epilepsy but may result in material-specific memory function, typically verbal memory decline following left, and visual memory decline following right ATLR. After surgery functional reorganisation can occur within the ipsilateral and contralateral hemispheres. In this longitudinal experiment we used memory fMRI and neuropsychological assessment to 1. investigate postoperative recovery and reorganisation of successful verbal and visual memory encoding in patients with left and right TLE before and four months after ATLR; 2. to investigate the efficiency of postoperative memory networks. With the help of this postoperative dataset we aimed to verify important findings in our preoperative experiment which led to the hypothesis that reorganisation of memory function to posterior parts of the ipsilateral medial temporal lobes was necessary to avoid postoperative memory decline and therefore was in keeping with the functional adequacy theory of hippocampal function.

6.2. INTRODUCTION

(refer to chapter 1.5.2.4 for more details)

Anterior temporal lobe resection (ATLR) has proven a successful treatment for patients with medically intractable TLE (Wiebe et al., 2001) rendering 50-60% seizure free at 10 years (de Tisi et al.). Neuropsychological follow-up studies, however, have shown that this procedure can be complicated by cognitive decline which is usually material specific to the side of resection (Gleissner et al., 2002; Gleissner et al., 2004; Hermann et al., 1995; Sabsevitz et al., 2001) (Gleissner et al., 1998; Lee et al., 2002). Decline in verbal memory function has a greater impact on everyday memory functioning for individual patients, while a decline in visual memory is usually less relevant (Gleissner et al., 2004).

Functional MRI allows evaluation of cognitive function non-invasively and has proven to be a useful tool to investigate underlying neural mechanisms. We have already discussed that many fMRI studies in the past concentrated on preoperative memory processing and how this changes in the course of the underlying disease and in particular the prediction of postoperative deficits (Binder et al., 2008; Bonelli et al., 2010; Janszky et al., 2005; Rabin et al., 2004; Richardson et al., 2004b) (refer to the previous chapter V).

However, fMRI may also be used to investigate the extent to which the brain may functionally reorganize following epilepsy surgery. Functional reorganisation – both pre- and post surgery – can occur within the unaffected ipsilateral or contralateral hemisphere but under which circumstances reorganisation becomes effective is poorly understood.

There is increasing evidence that in TLE patients, memory outcome depends on the extent of the removal of non-lesional functional tissues (Alpherts et al., 2008; Helmstaedter et al., 2003; Helmstaedter et al., 2008; Schramm, 2008). In the previous experiment we demonstrated that greater ipsilateral anterior medial temporal activation was associated with greater decline of verbal or visual memory function and that activation in the ipsilateral posterior medial temporal lobe, which is usually preserved during ATLR, was associated with better preservation of memory function after surgery (Bonelli et al., 2010). Postoperative fMRI follow-up studies are now needed to determine the role of the posterior hippocampal remnant in memory function.

This could lead to re-evaluation of more selective surgery in order to optimize risks of postoperative memory impairment in addition to seizure control. To date, there is only one fMRI study apart from a few case studies (Korsnes et al., 2009), in which memory function was systematically investigated before and after surgery. Postoperative memory function was assessed using a complex visual scene encoding task and was significantly associated with functional activation contralateral to the side of resection in nine left and eight right TLE patients and therefore suggested a role for the contralateral medial temporal lobe in supporting postoperative memory (Cheung et al., 2009).

6.3. METHODS

6.3.1. Subjects

We studied 46 patients with medically refractory TLE (26 left (14 females); median age 41.5, range 17-63; 20 right (13 females); median age 34.5, range 23-52). All underwent left or right ATR at the National Hospital for Neurology and Neurosurgery, London. Preoperatively, all patients had undergone detailed presurgical evaluation including structural MRI at 3T with qualitative and quantitative assessment (Bartlett et al., 2007; Woermann et al., 1998a), prolonged interictal and ictal video-EEG monitoring and standardized neuropsychological and psychiatric assessment as described in full detail in the common methodology chapter II. Structural MRI showed unilateral HS in 25 patients with left TLE and 16 patients with right TLE; one patient had a left and one patient a right medial dysembryoplastic neuroepithelial tumour, one had a right anterior temporal cavernoma, one had right anterior temporal focal cortical dysplasia and one patient showed a right anterior temporal ganglioglioma.

All patients underwent language and memory fMRI and standard neuropsychological assessment preoperatively and again four months after ATR. Language dominance was assessed using a range of fMRI tasks (Bonelli et al., 2011) revealing left hemisphere dominance in 20 left TLE and 13 right TLE patients, and atypical (bilateral or right) language representation in six left and seven right TLE patients. As described previously (Bonelli et al., 2010), chapters 2.3.2.1 and V), we also calculated pre- and postoperative lateralisation indices

for the contrast “verbal fluency” for each subject, which were used as covariates for the second level analysis. Mean verbal IQ as measured using the Wechsler Adult Intelligence Scale - III was 91.62 (SD 13.4) in left TLE and 93.7 (SD 14.7) in right TLE. Mean performance IQ was 97.9 (SD 13.4) in left and 92.0 (SD 13.0) in right TLE.

As memory may be affected by anxiety and depression, all patients in this study were tested for co-morbid anxiety and depression preoperatively and again at the time of their postoperative assessment (4 months after ATR) using the Hospital Anxiety and Depression Scale (HADS) as a measure of self-reported symptoms of anxiety and depression (Zigmond and Snaith, 1983), which is described in the common methodology section 2.2.2.6.

Preoperatively (data missing in two cases), there was no significant difference in anxiety scores between left and right TLE patients, but a significant difference in depression scores with left TLE patients showing higher scores (anxiety—median: left TLE, 7; range, 1–18; right TLE, 7.5; range, 4–15; depression—median: left TLE, 5.5; range, 0–10; right TLE, 4.5; range, 0–15; $p=0.03$). In right TLE scores were within the pathological range in 11 patients for anxiety (8 mild, 2 moderate, 1 severe), and in 2 patients for depression (1 mild, 1 moderate); in left TLE scores were considered as positive in 13 patients for anxiety (5 mild, 5 moderate, 3 severe) and 8 patients for depression (8 mild).

Postoperatively, there was no significant difference in anxiety and depression scores between left and right TLE patients (anxiety—median: left TLE, 6; range, 0–19; right TLE, 6.5; range, 0–16; depression—median: left TLE, 3; range, 0–15; right TLE, 3; range, 0–13). In right TLE postoperative scores were within the pathological range in 10 patients for anxiety (5 mild, 1 moderate, 4 severe) and in 5 patients for depression (4 mild, 1 severe); in left TLE scores were considered as positive in 10 patients for anxiety (5 mild, 2 moderate, 3 severe) and 6 patients for depression (5 mild, 1 severe).

In right TLE there was no significant difference between pre- and postoperative anxiety or depression scores; in left TLE depression scores improved significantly after left ATR

compared to preoperatively (paired t-test; $p=0.0023$), while there was no significant difference between pre- and postoperative anxiety scores.

There were no statistically significant correlations between pre- and postoperative anxiety or depression ratings and pre- and postoperative performance on verbal and visual memory tests (verbal learning and design learning) in left or right TLE patients and therefore pre- and postoperative anxiety and depression scores were not considered a factor in performance of verbal and visual memory tests in our patients and therefore not included as additional covariates.

All patients were treated with anti-epileptic medication, which mostly remained unchanged at the time of their postoperative assessment. The standard neurosurgical procedure is described in chapter 2.2.1.2. Postoperative seizure outcome was classified according to the International League Against Epilepsy classification (Wieser et al., 2001) showing a seizure outcome grade one or two in 21 left and 14 right TLE and a seizure outcome grade 3 to 5 in 5 left and 6 right TLE patients. Seizure outcome is given at one year following surgery for all subjects.

6.3.2. Neuropsychological tests

We used the same neuropsychological tests as applied in the previous experiment and as described in the common methodology sections 2.2.2.4 and 2.2.2.5 for this follow-up experiment: verbal learning as a measure of verbal memory and design learning as a measure of visual memory. Patients completed these neuropsychological tests before and four months after ATR. Measures of change in verbal and design learning following surgery were calculated as postoperative – preoperative scores. Changes in scores and postoperative scores alone were correlated with pre- versus postoperative change in/ postoperative fMRI activation patterns for left and right TLE patients. At the second level of analysis, patients were additionally divided into groups who suffered a clinical significant decline in verbal or visual memory using reliable change indices (Baxendale and Thompson, 2005). These were defined as a change of 16% for verbal learning and 28% change for design learning (90% confidence interval).

6.3.3. MR data acquisition

MR data acquisition was the same for all pre- and postoperative MRI studies and performed according to our common protocol (refer to sections 2.3.1 and 2.3.1.2).

6.3.4. Memory fMRI paradigm

In this postoperative follow-up study we applied the same memory paradigm as for the preoperative series in the previous experiment using a parallel set of stimuli containing three different material types (pictures, words and faces) in order to investigate postoperative verbal and visual memory encoding. The memory paradigm and the subsequent recognition test are described in the common methodology section 2.3.2.2.

6.3.5. Data analysis

The basic analyses of the postoperative fMRI dataset and in particular the preprocessing steps including coregistration to the preoperative dataset are described in the common methodology chapters 2.3.3.1 and 2.3.3.3. In brief, the postoperative imaging time series of each subject was realigned using the mean image as a reference. Rigid body coregistration was used to coregister 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 coregistered scans. Preoperatively, a scanner specific template created from 30 healthy controls, 15 patients with left and 15 patients with right hippocampal sclerosis was used for normalisation. All scans were then smoothed with a Gaussian kernel of 10 mm full-width at half maximum. Coregistration of postoperative scans was checked visually for each subject, 3 patients with unsatisfactory coregistration were excluded from further analysis.

Event-related analysis

In order to test for subsequent memory effects, an event-related analysis was used to compare encoding-related responses to individual stimuli that were subsequently remembered versus

stimuli that were forgotten (Friston et al., 1998; Mechelli et al., 2003; Powell et al., 2005a; Richardson et al., 2003; Seghier et al., 2012). The analysis of the memory data (event-related analysis) is described in the common methodology section 2.3.3.3.

Recognition accuracy for each event type was calculated in all our patients as follows: Stimuli seen in the recognition test were classified as “hits” (stimuli correctly remembered) and “false alarms” (foils incorrectly tagged as remembered). Recognition accuracy was then calculated for each stimulus type as: hit rate minus false alarm rate. All subjects with rates of <20% or >80% for the two possible responses “remembered” and “forgotten” were not included in this study as there were not enough responses in the different categories to ensure sufficient contrast.

Second-level analysis

At the second level of the random effects analysis, subjects were divided into two groups, patients with left and right TLE. Each subject’s contrast images were entered into a second level one sample t-test, which modelled the group effect (left and right TLE patients, pre- and postoperatively) on the various contrasts. In order to test for correlations between areas of postoperative fMRI activation and subjects’ performance on postoperative verbal learning and design learning, simple and multiple regression analyses were performed over the whole brain. For each subject verbal learning and design learning scores were entered as covariates separately for left and right TLE patients. Encoding pictures usually gave more bilateral activations and was not considered for further postoperative correlational analyses. The language lateralisation index derived from postoperative language fMRI (refer to section 2.3.2.1) was used as an additional covariate.

“Difference image” analysis

In order to investigate the relationship between pre- and postoperative change in memory fMRI activation and change in scores for verbal and visual memory from before to four months after ATR, we created “difference images” by subtracting the coregistered, normalised postoperative contrast images from the original preoperative contrast images and vice versa.

The created images represent activation changes for each contrast, highlighting areas of greater/ lesser pre- than postoperative activation for the contrasts “word and face encoding” over the whole brain. At the second level of the random effects analysis, we looked for brain regions showing correlations between greater/ lesser pre- than postoperative or post- than preoperative activation and change (post- minus preoperative) scores for verbal and visual memory after ATR.

Small volume correction

Unless otherwise stated we report all medial temporal lobe activations at a threshold of $P < 0.01$, corrected for multiple comparisons (FWE in a small volume of interest). In view of our a priori hypothesis we performed the small volume correction using a sphere of 10 mm diameter for the left and right hippocampi based on the group peak activation.

6.3.6. Hypothesis

At the second level we investigated:

1. Effects of ATR on the functional anatomy of verbal and visual memory encoding by comparing pre- versus postoperative main effects in left and right TLE patients.
2. Efficiency of reorganisation of postoperative verbal and visual memory functions by correlating postoperative activations on encoding words and faces with postoperative verbal learning and design learning scores in patients with left and right TLE.

6.4. RESULTS

6.4.1. Memory test results

6.4.1.1. Verbal learning

The left TLE group had a significant reduction in verbal learning scores post- (mean=44.8, SD=16.4) compared to preoperatively (mean=56.4, SD=10.3; $p < 0.0001$). No significant changes for verbal learning were observed for the right TLE group.

6.4.1.2. Design learning

There was no significant difference between pre- and postoperative design learning scores in right or left TLE patients.

6.4.1.3. Postoperative memory change

22/ 26 left TLE patients had a decline in verbal learning scores after left ATR, in seven this was classified as clinically significant; 3/26 patients had a postoperative improvement in verbal learning, one patient's score remained unchanged; the mean change between pre- and postoperative verbal learning scores was -9, ranging from -48 to +10.

10/20 right TLE patients showed a decline in design learning scores after right ATR, in one patient this was classified as clinically significant; 10/20 patients' design learning scores improved; the mean change between pre- and postoperative design learning scores was +0.5, ranging from -38 to +26.

6.4.2. Hippocampal volumes

Preoperatively, left and right hippocampal volumes were significantly different in both left and right TLE patients. Left TLE group: mean (SD) right hippocampal volume was 2.82 (0.28) cm³, mean left hippocampal volume 1.93 (0.63) cm³ (paired t-test p<0.0001, 2-tailed). Right TLE group: mean (SD) right hippocampal volume was 1.77 (0.44) cm³, mean left hippocampal volume 2.53 (0.28) cm³ (paired t-test p<0.0001, 2-tailed). There was no significant difference between left hippocampal volume in the left TLE group and right hippocampal volume in the right TLE group.

Postoperatively there was no significant difference between postoperative volumes of the residual left or right hippocampi. Left TLE group: mean (SD) residual of left hippocampus 0.57 (0.56), range 0.07-2.9 cm³. Right TLE group: mean (SD) residual of right hippocampus was 0.62 (0.71), range 0.12-2.64 cm³. In 3 left and 2 right TLE patients it was not possible to

measure postoperative hippocampal volumes because of technical problems or because remnants were too small.

6.4.3. Functional MRI results – verbal and visual memory

In left TLE patients the mean recognition rates for “pictures” were 0.7 preoperatively and 0.6 postoperatively, for “words”, 0.5 preoperatively and 0.45 postoperatively, and 0.3 for “faces” pre- and postoperatively. There was no significant difference between pre- and postoperative recognition rates for “pictures” and “faces”. Words were less well remembered postoperatively in the left TLE group (paired t-test: $p=0.02$).

In right TLE patients the mean recognition rates were 0.7 for “pictures” pre- and postoperatively, 0.5 for “words” pre- and postoperatively and 0.2 for “faces” preoperatively and 0.1 for “faces” postoperatively. There was no significant difference between pre- and postoperative recognition accuracy for “pictures” or “words” but a trend for “faces” to be less well remembered in right TLE postoperatively (paired t-test: $p=0.07$).

6.4.3.1. Main effects for encoding pictures, words and faces

Preoperatively, in the left TLE group there was weak right hippocampal activation for encoding faces ($p=0.07$, FWE corrected in small volume of interest) but no significant hippocampal activation for encoding pictures or words.

In right TLE, there was significant left hippocampal activation for encoding words ($p=0.029$, FWE corrected in small volume of interest), but no significant activation for encoding pictures or faces.

Postoperatively, left TLE patients had significant left posterior hippocampal activation for encoding words ($p=0.001$, FWE corrected in small volume of interest) and significant right ($p=0.033$, FWE corrected in small volume of interest) hippocampal activation for encoding faces at the group level (Fig 6.1).

In right TLE, there was weak left hippocampal activation for encoding words ($p=0.073$, FWE corrected in small volume of interest) postoperatively, and no effect was seen for encoding pictures or faces (Table 6.1).

Table 6.1 Pre – and postoperative fMRI activation peaks in the hippocampus for the main effects of encoding words and faces

Subjects	fMRI contrast	Z-score	Corrected p-value (family-wise error)	Coordinates (x,y,z) in MNI space	Hippocampal activation
Left TLE Preoperative	word encoding	-	ns	-	-
	face encoding	2.28	0.070		right
Left TLE Postoperative	word encoding	3.86	0.001	-32, -22, -12	left posterior
	face encoding	2.61	0.033	34, -14, -22	right
Right TLE Preoperative	word encoding	2.86	0.029	-34, -20, -22	left
	face encoding	-	ns	-	-
Right TLE Postoperative	word encoding	2.30	0.073	-34, -12, -18	left
	face encoding	-	ns	-	-

Legend: MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); ns, not significant; TLE, temporal lobe epilepsy.

Postoperative main effects for word and face encoding in left temporal lobe epilepsy

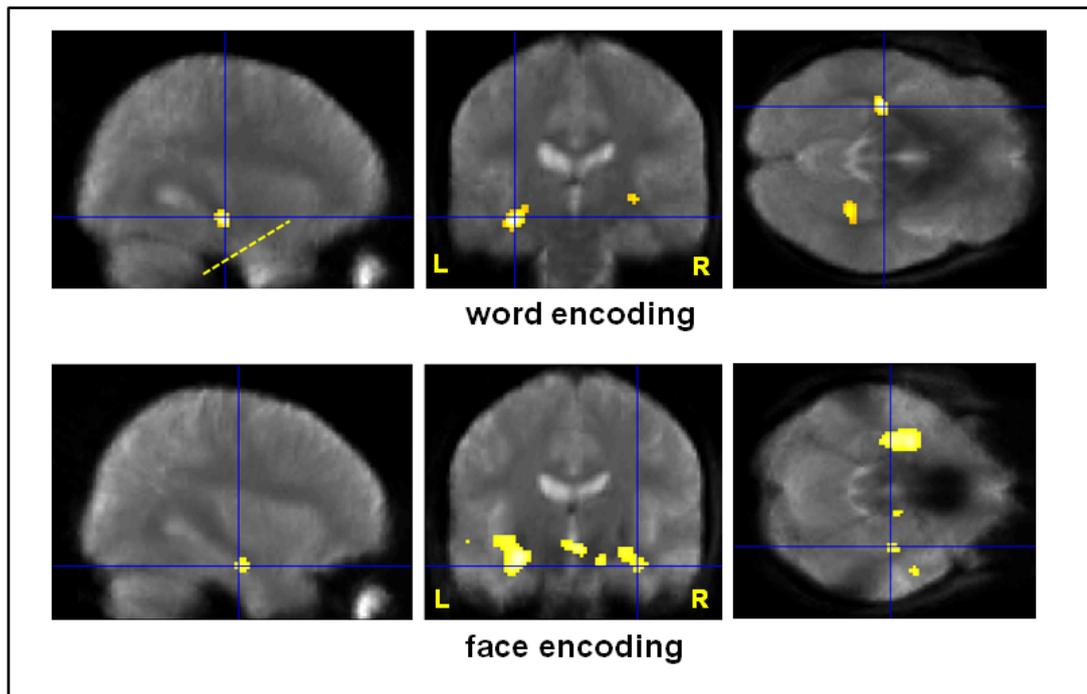


Figure 6.1 Postoperative group results of memory fMRI in left TLE patients

Postoperative main effects for:

word encoding: left posterior hippocampal activation;

face encoding: right hippocampal activation.

The yellow line indicates the estimated hippocampal resection margin for the left TLE group.

Threshold $p < 0.01$, uncorrected.

Significant regions are superimposed onto averaged normalised mean EP images from all patients who underwent left ATLR.

6.4.3.2. Comparison of pre- and postoperative main effects for encoding words and faces:

Difference - image analysis

We determined significant activation changes following ATLR using difference images representing greater pre- than postoperative activation and vice versa for the single subjects for the contrasts of interests (word encoding for left TLE, face encoding for right TLE) (Table 6.2).

Left TLE patients showed significantly greater postoperative than preoperative activation in the posterior remnant of the left hippocampus for encoding words ($p=0.042$, FWE corrected in small volume of interest), while no areas showed greater pre- than postoperative activation (Fig

6.2 and Fig 6.3). There was no significant main effect (either greater pre- than postoperative activation or vice versa) for face encoding in right TLE.

Table 6.2 Difference image analysis: Main effects of greater pre- than postoperative and greater post- than preoperative memory fMRI activation for encoding words and faces

Subjects	Change in fMRI contrast	Z-score	Corrected p-value (family-wise error)	Coordinates (x,y,z) in MNI space	Hippocampal activation
Left TLE	word encoding (pre->postoperative)	-	ns	-	-
Left TLE	word encoding (post->preoperative)	2.52	0.042	-34, -24, -12	left posterior
Right TLE	face encoding (pre->postoperative)	-	ns	-	-
Right TLE	face encoding (post->preoperative)	-	ns	-	-

Legend: MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); ns, not significant; TLE, temporal lobe epilepsy.

Comparison of post- and preoperative main effects for word encoding in left temporal lobe epilepsy

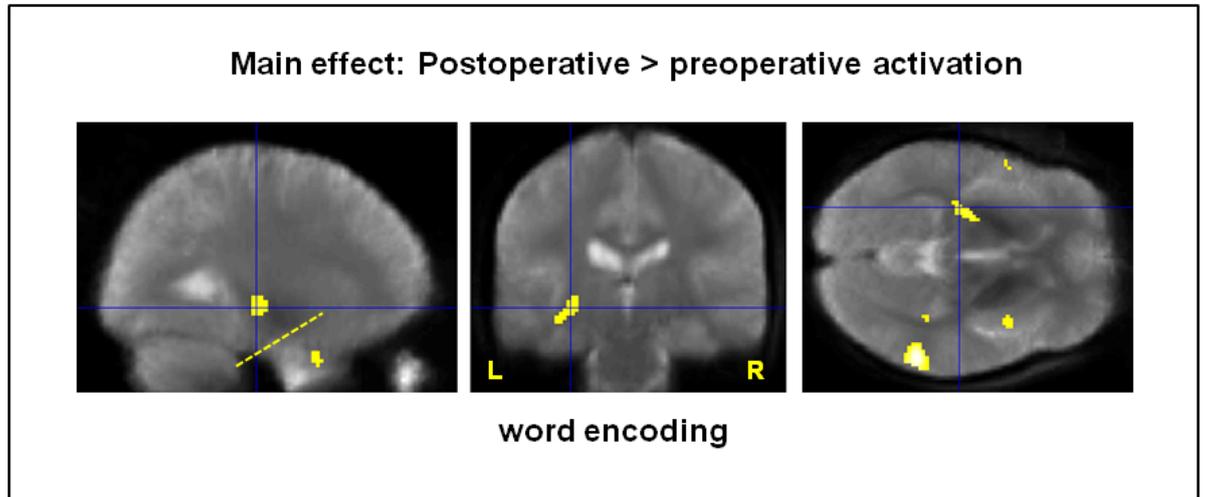


Figure 6.2 Comparison of post- and preoperative fMRI activation for verbal memory function in left TLE

Main effects:

Greater postoperative than preoperative activation for encoding words in the left posterior medial temporal lobe four months after left ATLR.

The yellow line indicates the estimated hippocampal resection margin for the left TLE group.

Threshold $p < 0.01$, uncorrected.

Significant regions are superimposed onto an averaged normalised mean EPI from all patients who underwent left ATLR.

Change in mean BOLD percent signal change in the left posterior hippocampus after ATR

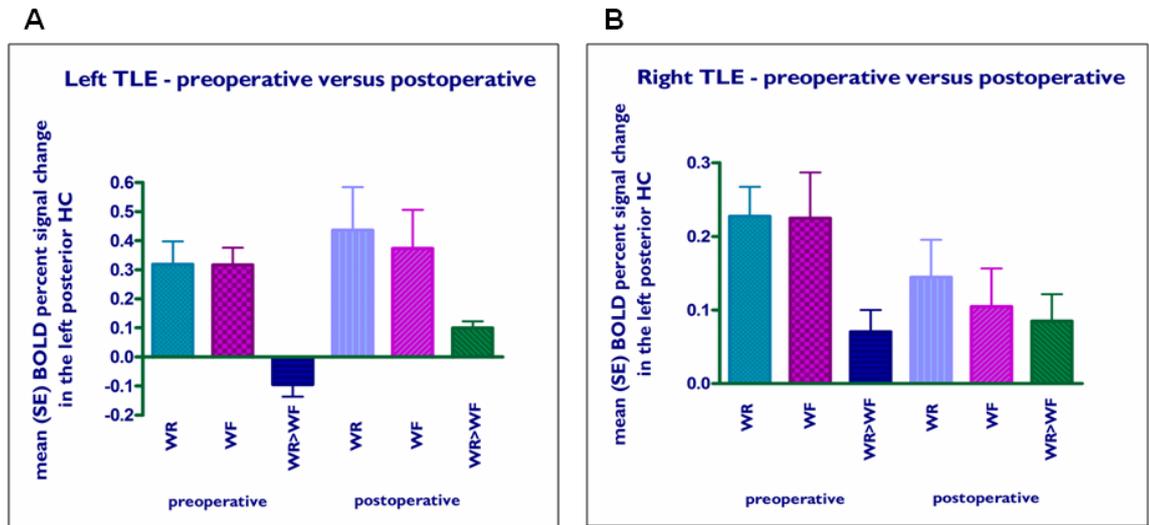


Figure 6.3 Mean BOLD percent signal change pre- versus postoperatively in left and right TLE

Mean percent signal change and standard error (SE) for words in a region of interest (sphere with 3 mm radius based on the peak activation) in the left posterior hippocampus in left (A) and right (B) TLE patients for the three contrasts “words remembered (WR)”, “words forgotten (WF)” and “words remembered minus words forgotten (WR>WF)”.

HC – hippocampus; SE – standard error; TLE – temporal lobe epilepsy.

6.4.3.3. Efficiency of preoperative reorganisation of verbal and visual memory

One aim of this postoperative follow-up study was to test the functional integrity of the ipsilateral posterior hippocampus after ATR.

We examined subgroups of left TLE patients according to whether they suffered a clinically significant decline in verbal learning (n=7) or whether their postoperative verbal learning scores were improved/ remained stable (n=19). A similar subgroup analysis was not possible in right TLE patients as only one suffered a clinically significant decline in design learning scores.

Correlation between change in fMRI activation for encoding words and faces (pre- minus postoperative) and change in verbal and visual memory scores

In order to evaluate in which areas of the brain, change in fMRI activation for encoding words or faces from pre- to postoperative were correlated with change in memory scores, we performed a voxel by voxel analysis over the entire temporal lobe field of view (Table 6.3).

Left TLE: There was a significant positive correlation in the left posterior hippocampus ($p=0.05$ corrected in small volume of interest), characterised by greater pre- than postoperative activation for encoding words in this area being correlated with better postoperative verbal memory (Fig 6.4). Subgroup analysis showed that this result was mainly driven by patients with no significant verbal memory decline: Left TLE patients with stable or improved verbal memory test scores had a significant positive correlation between change in fMRI activation for word encoding and change in verbal learning scores in the left posterior hippocampus ($p=0.002$ corrected in small volume of interest), characterised by greater pre- than postoperative activation being associated with better postoperative verbal memory outcome. No correlation was observed for patients with a clinically significant memory decline.

Right TLE: There was no significant correlation between change in fMRI activation for encoding faces and change in visual memory scores.

Table 6.3 Association of change of memory fMRI activation for encoding words and faces (preoperative minus postoperative) with change of verbal learning/ design learning scores

Subjects	Change in fMRI contrast – change in neuropsychology task	Z-score	Corrected p-value (family-wise error)	Coordinates (x,y,z) in MNI space	Hippocampal activation
Left TLE	word encoding – VL	2.47	0.047	-30, -28, -12	left posterior
Left TLE	word encoding – 1/VL	-	ns		-
Left TLE with decline	word encoding – VL	-	ns	-	-
	word encoding – 1/VL				
Left TLE without decline	word encoding – VL	3.60	0.002	-30, -20, -16	left posterior
Left TLE without decline	word encoding – 1/VL	-	ns	-	-
Left TLE	face encoding – DL	-	ns	-	-
	face encoding – 1/DL				
Right TLE	face encoding – DL	-	ns	-	-
	face encoding – 1/DL				
Right TLE	word encoding – VL	-	ns	-	-
	word encoding – 1/VL				

Legend: DL, design learning; MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); ns, not significant; TLE, temporal lobe epilepsy VL, verbal learning.

Left temporal lobe epilepsy – verbal memory Efficiency of preoperative reorganisation

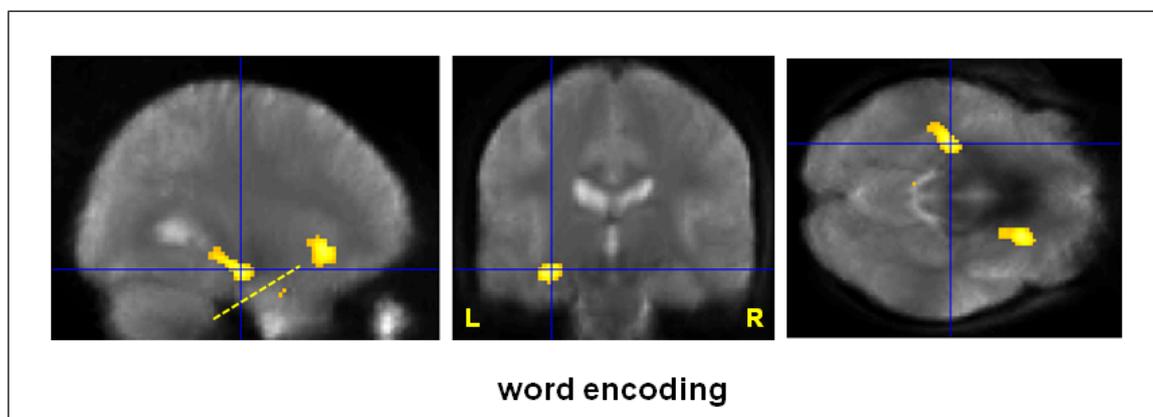


Figure 6.4 Efficiency of preoperative reorganisation of verbal memory function in left TLE

Correlational analysis:

Greater pre- than postoperative activation on encoding words in the left posterior medial temporal lobe is associated with better verbal learning outcome.

The yellow line indicates the estimated hippocampal resection margin for the left TLE group.

Threshold $p < 0.01$, uncorrected.

Significant regions are superimposed onto an averaged normalised mean EPI from all patients who underwent left ATR.

6.4.3.4. Efficiency of postoperative reorganisation of verbal and visual memory

Data for the correlation between postoperative fMRI activation for word or face encoding and postoperative neuropsychological performance is presented in Table 6.4.

In the left TLE group, there was a significant negative correlation between postoperative fMRI activation for encoding words and postoperative verbal learning scores ($p = 0.014$, FWE corrected in small volume of interest) in the left posterior hippocampus. This was characterised by greater postoperative fMRI activation being associated with worse postoperative verbal memory performance. Subgroup analysis showed that this negative correlation in the left posterior hippocampus ($p = 0.001$) was driven by left TLE patients with no clinically significant decline and this negative correlation was also seen in the right hippocampus ($p < 0.001$) and the

right superior temporal gyrus ($p=0.03$, all FWE corrected in SVI). There was no significant correlation for left TLE with clinically significant decline.

In the right TLE group there was a negative correlation in the right posterior hippocampus ($Z=2.42$, $p=0.047$, FWE corrected in small volume of interest, TH 0.05), characterised by greater postoperative fMRI activation for face encoding being correlated with worse postoperative design learning scores.

Table 6.4 Association of postoperative verbal learning/ design learning scores with postoperative memory fMRI activation

Subjects	fMRI contrast – neuropsychology task	Z-score	Corrected p-value (family-wise error)	Coordinates (x,y,z) in MNI space	Hippocampal activation
Left TLE	word encoding – VL	-	ns	-	-
Left TLE	word encoding–1/VL	2.99	0.014	-30, -30, -14	left posterior
Left TLE with decline	word encoding–VL word encoding–1/VL	-	ns	-	-
Left TLE without decline	word encoding-VL	-	ns	-	-
Left TLE without decline	word encoding–1/VL	3.95 4.16	0.001 $p<0.001$	-26, -30, -14 32, 2 -32	left posterior right
Right TLE	face encoding – DL face encoding–1/DL	-	ns	-	-

Legend: DL, design learning; ns, not significant; MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); TLE, temporal lobe epilepsy; VL, verbal learning.

Data for the correlation between change in fMRI activation for word or face encoding (postoperative minus preoperative) and postoperative neuropsychological performance is presented in Table 6.5.

To further characterise these results and to investigate the efficiency of early postoperative reorganisation/ compensation we correlated postoperative minus preoperative fMRI activations with postoperative memory scores.

In left TLE we found a significant negative correlation with postoperative verbal learning scores in the left posterior hippocampus ($p=0.02$), characterised by greater post- than preoperative fMRI activation in this area being correlated with worse verbal memory performance (Fig 6.5).

There was no significant correlation between postoperative volumes of the residual hippocampi and postoperative memory scores.

Table 6.5 Association of change in memory fMRI activation (postoperative minus preoperative) for words and faces with postoperative verbal learning and design learning scores

Subjects	Change in fMRI contrast - postoperative neuropsychology task	Z-score	Corrected p-value (family-wise error)	Coordinates (x,y,z) in MNI space	Hippocampal activation
Left TLE	encoding words – VL	-	ns	-	-
Left TLE	encoding words – 1/VL	2.82	0.021	-32, -32, -12	left posterior
Right TLE	face encoding – DL	-	ns	-	-
	face encoding – 1/DL				

Legend: DL, design learning; ns, not significant; MNI space, coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); TLE, temporal lobe epilepsy; VL, verbal learning.

Left temporal lobe epilepsy – verbal memory Efficiency of postoperative reorganisation

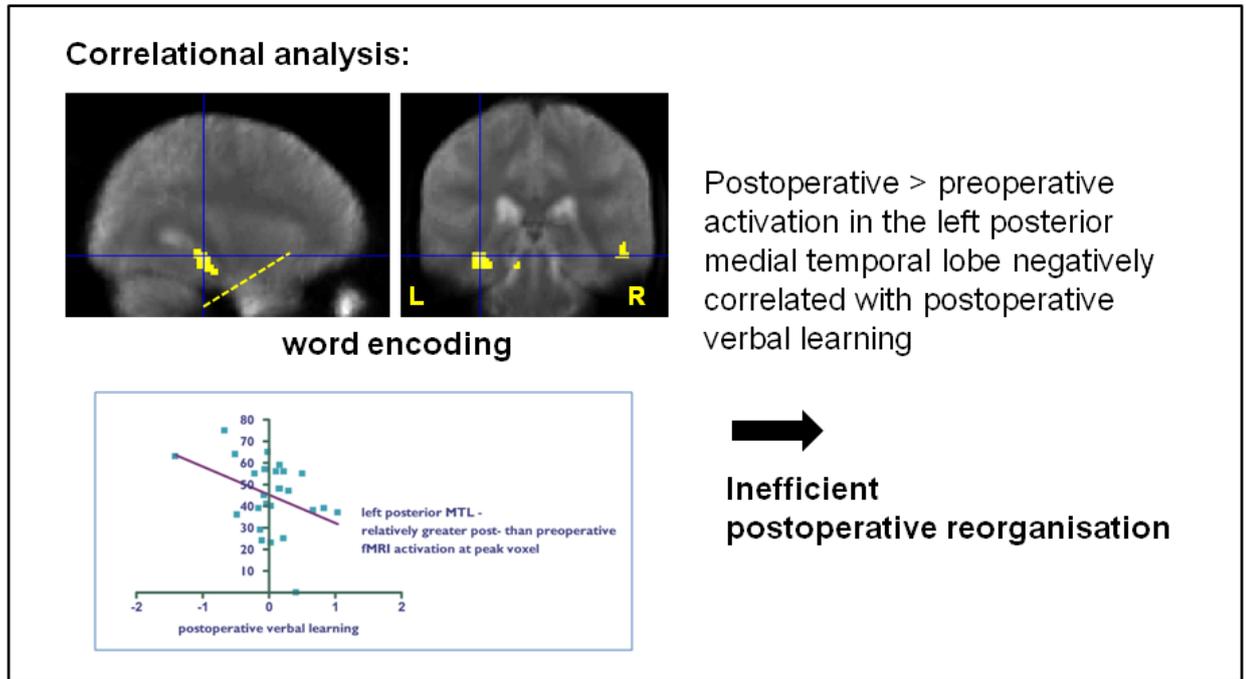


Figure 6.5 Efficiency of postoperative reorganisation of verbal memory function in left TLE

Correlational analysis:

Greater post- than preoperative left posterior medial temporal lobe fMRI activation for word encoding correlates with worse postoperative verbal learning scores, characterised by an inefficient postoperative response within the remaining ipsilateral posterior medial temporal lobe structures. The correlation at the peak voxel in the left posterior medial temporal lobe (MTL) is illustrated.

“Functional MRI activation” is given in “postoperative > preoperative percent signal change”; scores for “verbal learning” are given as z-scores.

The yellow line indicates the estimated resection margin for the left TLE group

Threshold $p < 0.01$, uncorrected.

Significant regions are superimposed onto an averaged normalised mean EPI from all patients who underwent left ATLR.

6.5. DISCUSSION

6.5.1. Summary of results

In this longitudinal fMRI experiment we examined how material specific memory function is reorganised in patients with TLE after left or right ATR and explored the effectiveness of these postoperative memory networks. In the preoperative experiment described in the previous chapter we demonstrated that preoperative ipsilateral activation within the anterior medial temporal lobe predicted greater verbal and visual memory decline while greater ipsilateral posterior medial temporal lobe activation was predictive of better verbal and visual memory outcome after ATR (Bonelli et al., 2010). This postoperative follow-up experiment was concordant with these findings as greater pre- than postoperative activation within the ipsilateral posterior hippocampus correlated with better verbal memory outcome in left TLE patients. In contrast, early postoperative reorganisation within the ipsilateral hippocampus or to homologous areas in the contralateral hemisphere was not efficient. Only one right TLE patient suffered a clinically significant decline in visual memory. Therefore it was not surprising that we found a similar, albeit weaker activation pattern for visual memory in right TLE patients.

6.5.2. Postoperative memory processing

Previous neuropsychological and functional MRI studies have shown that left and right TLE patients may have impaired memory function, which is usually material specific, due to the underlying pathology and ongoing disease (Gleissner et al., 1998; Golby et al., 2002; Helmstaedter et al., 1997a; Helmstaedter et al., 2003; Powell et al., 2005a). More recently this model of material-specificity has been challenged by several post-resection studies (Helmstaedter et al., 2011b; Saling, 2009). Memory impairment may be worse following ATR (Gleissner et al., 2002; Gleissner et al., 2004; Helmstaedter et al., 2003) and there is evidence that postoperative verbal memory processing in left TLE is affected differently by temporal lobe surgery than visual memory processing in right TLE. This was also true in the current experiment in which preoperatively both left and right TLE patients showed impairment in verbal and visual memory function which was correlated to left/ right medial temporal lobe

memory fMRI activation. Postoperatively, only one right TLE patient suffered a clinically significant decline in visual memory compared to seven left TLE patients with significant verbal memory decline after left ATR. This finding parallels several previous studies suggesting a differential effect of temporal lobe resection on verbal and visual memory function (Helmstaedter et al., 2008; Lee et al., 2002) in left and right TLE patients (Wong et al., 2009) with verbal memory being more vulnerable (Cheung et al., 2009). Previous studies also suggest that visual-spatial memory is a more bilateral task than verbal memory and for which verbalisation may play a significant role (van Asselen et al., 2006). This would be compatible with our results in right TLE.

Many fMRI studies focused on the evaluation of preoperative memory processing and the prediction of postoperative memory decline (Binder et al., 2008; Janszky et al., 2005; Powell et al., 2008b; Rabin et al., 2004; Richardson et al., 2004b) as did our previous preoperative experiment (refer to chapter V), in which we demonstrated that stronger ipsilateral memory encoding activation within the anterior medial temporal lobe was associated with greater postoperative verbal or visual memory decline, while greater ipsilateral posterior fMRI activation in the medial temporal lobe before surgery was predictive of better verbal and visual memory outcome. The underlying mechanism of postoperative reorganisation and processing of memory function is poorly understood. Apart from a few case studies there is only one fMRI study in which patients with TLE were systematically followed up one year after surgery (Cheung et al., 2009). In this study a complex visual scene-encoding task was used to show that postoperative memory performance at 12 months after surgery was significantly associated with functional activation contralateral to the side of resection and therefore suggested that memory function in the contralateral medial temporal lobe might be necessary for supporting memory after ATR. This study, however, was limited by including only nine left and eight right patients with TLE, and heterogeneous pathologies. In contrast, we used a material specific memory encoding paradigm for words and faces in a large and homogenous group of patients with medial TLE and showed that postoperative verbal memory function was still clearly lateralised with the main activation in the posterior remnant of the left medial temporal lobe,

which is usually spared during ATR. Comparison with preoperative data showed that postoperatively there was no significant reduction in posterior medial temporal lobe activation for word or face encoding in left or right TLE patients, but a significant increase in activation for word encoding in the posterior remnant of the left medial temporal lobe.

Postoperative correlational analysis showed a significant but negative correlation between this activation and postoperative verbal learning scores in left TLE patients, who did not have a significant postoperative verbal memory decline, characterised by greater postoperative activation being associated with worse performance on neuropsychological tests. We believe that the absence of a significant correlation between ipsilateral posterior medial temporal lobe activation and postoperative memory performance in left TLE patients with clinically significant decline is because patients without decline have already reorganized memory function to their ipsilateral posterior medial temporal lobe over years before surgery, which protects them from declining significantly after ATR, while patients with significant verbal memory decline had failed to effectively reorganize memory function to the posterior medial temporal lobe before surgery, but showed stronger activation in the anterior part of the ipsilateral medial temporal lobe, which was shown to be predictive of greater postoperative decline in our preoperative experiment. At an early postoperative stage, left TLE patients without decline activated this posterior part of the hippocampal remnant more strongly (probably as a compensatory response) but this additional activation did not result in any further memory improvement. Those who had a decline, on the other hand, still did not show any activation in this part of the hippocampal remnant.

We interpret this result as reflecting an inefficient additional compensatory response within structures of the ipsi- and partly contralateral medial temporal lobe involved in postoperative memory processing in the early postoperative phase. These findings are consistent with the suggestion that preoperative reorganisation within the ipsilateral medial temporal lobe and engagement of the posterior hippocampus in memory encoding prior to surgery is efficient and helps to maintain verbal memory postoperatively, while early postoperative reorganisation is an inefficient process.

As for the right TLE patients, there is evidence that memory function is affected differently in left and right TLE patients (Helmstaedter et al., 2008; Lee et al., 2002). There is an ongoing discussion regarding possible reasons for this: From a clinical perspective verbal memory seems much more vulnerable to surgery compared to visual memory – which was also the case in our patient sample with seven patients showing a clinically significant verbal memory decline, while only one patient had a significant visual memory decline.

Another reason might be that visual memory is less material-specific than verbal memory as patients tend to use verbal strategies in order to memorize visual-(spatial) material. Finally, the weaker correlation in our right TLE patients might also be due to the smaller sample size of 20 patients.

6.5.3. Neurobiological and clinical implications

In section 1.5.2.4.2 we have discussed the two models that have been put forward to explain memory deficits after ATLR: the hippocampal reserve theory suggests that it is the capacity of the contralateral hippocampus which preserves postoperative memory function while the functional adequacy model suggests the functional reserve of the ipsilateral hippocampus as the key structure to support memory function after surgery (Chelune et al., 1991). In their pre- and postoperative follow up study, Cheung et al. provided support for the hippocampal reserve theory by suggesting that it was the function of the contralateral medial temporal lobe that supports ipsilateral memory function after surgery (Cheung et al., 2009).

The findings of the current experiment support the functional adequacy model, in concordance with other neuropsychological and functional imaging studies, in particular for verbal memory (Baxendale et al., 2000; Bonelli et al., 2010; Helmstaedter et al., 2011a; Helmstaedter et al., 2011b). By directly comparing pre- and postoperative fMRI data sets we demonstrated that functional reorganisation to the ipsilateral posterior medial temporal lobe earlier in the epileptic history - prior to surgery - and to structures spared during ATLR was essential for better postoperative verbal memory outcome.

More selective compared to extended temporal resections do not necessarily result in poor seizure outcome and may carry less risk of clinically significant deterioration of memory (Alpherts et al., 2008; Helmstaedter et al., 2008; Morino et al., 2006). Recently Helmstaedter and co-workers confirmed the negative impact of the resection of non-lesional functional tissue for cognitive surgical outcome in a cohort of MRI and histopathologically negative TLE patients while selective versus extended surgery appeared to result in similar seizure outcomes (Helmstaedter et al., 2011a). The same authors postulated, that neither medial resection length nor resected hippocampal volumes influenced postoperative seizure outcome while resection of larger hippocampal volumes resulted in poorer verbal memory outcome in TLE patients who underwent selective amygdalo-hippocampectomy (Helmstaedter et al., 2011b).

Our finding that functional tissue within the to be resected area is crucial to preserve verbal and visual memory encoding function after ATLR emphasizes the need to re-evaluate the role of more restricted hippocampal surgery in order to minimize clinically relevant memory impairment in patients with TLE. We infer that the posterior hippocampus has an important role in the maintenance of verbal memory, and that tailored hippocampal resection, taking this into account, with the extent of hippocampal sclerosis, may optimize seizure and memory outcomes.

6.5.4. Methodology and future work

This study has the advantage of comparing memory fMRI data and neuropsychological assessment before and 4 months after left or right ATLR in a large and homogenous cohort of TLE patients. Language dominance, which is in turn affected by age of disease onset, may influence results of material specific memory lateralisation (Griffin and Tranel, 2007). A language lateralisation index, as assessed by language fMRI pre- and postoperatively, was used as a covariate to control for this possibility. This allowed to explicitly study the effects of ATLR with respect to pre- and postoperative reorganisation of material specific memory function.

Similar to the previous experiment, there are several strengths and limitations regarding methodology such as the advantages and disadvantages of using an event-related design, as well as the technical difficulties in the temporal lobes such as signal dropout and low resolution,

common to all experiments presented. Imaging parameters were optimized for capturing activation within the temporal lobes and adjacent structures (refer to the previous chapter 5.5.5 for more detail). More work is needed to optimize these parameters including the field of view so that activation in other areas of the brain than the medial temporal lobe can be identified (e.g. the orbito-frontal cortex), in order to be able to comment on possible compensatory mechanisms. Furthermore, our results may be influenced by the effect of volume averaging on the extent and magnitude of hippocampal (remnant) signal, given that a) most of the patients had hippocampal sclerosis and b) all patients underwent left or right ATR.

Postoperatively, memory was reassessed at an early postoperative stage of four months after ATR. Four months might be too early for compensatory responses (such as in the contralateral medial temporal lobe) to become fully functional, which could account for our divergence from Cheung's results (Cheung et al., 2009). Memory function (decline and recovery) has been found to stabilize within 2 years after surgery (Alpherts et al., 2006). We are now carrying out further longitudinal follow-up studies of memory organisation at three months and 12 months after surgery to further investigate how this activation changes over a longer period of time in patients with temporal lobe epilepsy, having temporal lobe resection, and with a healthy control group also studied longitudinally, which will give us important further insights into postoperative recovery and plasticity.

6.6. CONCLUSION

In conclusion, engagement of the posterior left medial temporal lobe in verbal memory encoding prior to surgery was efficient and preserved verbal memory function after surgery. In contrast, early postoperative reorganisation within the ipsilateral or to the contralateral medial temporal lobe was inefficient. Our results strengthen the view that functional tissue needs to be preserved by more selective and restricted surgical approaches with the ultimate goal of achieving maximum seizure control at a minimum of cognitive costs. Future work is needed to optimize imaging parameters in order to obtain whole brain coverage to gain information on possible reorganisation in brain areas other than the temporal lobe. Development of additional

cognitive fMRI tasks will be required in order to assess other aspects of memory function that might be impaired in TLE patients in addition to verbal and visual memory encoding (i.e. working memory).

CHAPTER VII

7. IMAGING AMYGDALA FUNCTION IN TEMPORAL LOBE

EPILEPSY

Temporal lobe epilepsy (TLE) is often associated with emotional disturbances which are still underreported but have a great impact on quality of life. Emotional disturbances can be particularly aggravated after anterior temporal lobe resection (ATLR).

In this chapter we applied fMRI to healthy controls and patients with TLE to investigate the role of the amygdala in processing emotions and whether this may be a potential preoperative predictive marker for emotional disturbances following epilepsy surgery in TLE.

The material in this chapter has been published in: Bonelli SB et al. Preoperative amygdala fMRI in temporal lobe epilepsy. *Epilepsia* 2009 Feb;50(2):217-27. doi: 10.1111/j.1528-1167.2008.01739.x. Epub 2008 Aug 19.

7.1. OBJECTIVE

In this experiment we used a fearful face paradigm to visualize amygdala activation in 21 healthy controls compared to 54 patients with unilateral TLE of which 21 subsequently underwent an ATLR.

We specifically hypothesized that 1) in patients with TLE stronger fMRI activation in the amygdala would be associated with higher anxiety and depression ratings; 2) greater amygdala fMRI activations preoperatively would be associated with a greater risk of mood disturbances after ATLR. If confirmed, preoperative amygdala fMRI might then be used as an additional preoperative predictor for emotional disturbances following ATLR.

7.2. INTRODUCTION

(refer to chapter 1.5.2.5 for more detail)

Temporal lobe epilepsy and ATLR are associated with both cognitive and emotional disturbances. The amygdalae are involved in emotional and social behaviour, fear conditioning, face perception and facial expression processing (Cahill et al., 1995; Morris et al., 1998a;

Morris et al., 1996). In humans, amygdala lesions can lead to deficits in the recognition of, especially, fearful facial expression (Morris et al., 1996) and impaired fear conditioning (LaBar et al., 1995).

In patients with TLE, mesial temporal sclerosis affects the hippocampus, the entorhinal cortex and the amygdala complex (Williamson et al., 1993), which may underlie emotional symptoms and changes that are present before and develop following ATR. Isolated amygdala damage is observed in 10% of patients with TLE (Bartlett et al., 2002) and often accompanies hippocampal sclerosis (HS) (Van Paesschen et al., 1996). Functional MRI has been used to study language and memory function in patients with refractory TLE and HS as I have outlined in the previous chapters. We have already discussed that hippocampal and parahippocampal activation may help the prediction of postoperative neuropsychological deficits (Bonelli et al., 2010; Bonelli et al., 2012; Janszky et al., 2005; Rabin et al., 2004; Richardson et al., 2006; Richardson et al., 2004b) (chapters IV and V).

Few studies have used fMRI paradigms capable of lateralizing amygdala activation during presurgical assessment of patients with TLE (Richardson et al., 2004a; Schacher et al., 2006) and the utility as a clinical tool remains uncertain. An animated fearful face paradigm resulted in bilateral amygdala activation in healthy volunteers, while in patients with mesial TLE amygdala activation was clearly lateralized to the contralateral side (Schacher et al., 2006). Amygdala-hippocampal co-dependence was shown during emotional-memory encoding. Severity of amygdala pathology was a predictive factor for memory for emotional items, and severity of hippocampal pathology predicted memory performance for neutral and emotional items (Richardson et al., 2004a).

Several psychiatric studies have shown atypical amygdala responsiveness, mostly hyperactivity, being associated with anxiety disorders (Killgore and Yurgelun-Todd, 2005; Thomas et al., 2001) and major depressive disorder (Abercrombie et al., 1998; Roberson-Nay et al., 2006).

Between 20 to 50% of all patients with TLE suffer from comorbid psychiatric symptoms, most commonly anxiety and depression (Boylan et al., 2004; Kanner, 2003; Ring et al., 1998). Up to 50% of patients with no psychiatric history may develop symptoms of anxiety and depression

shortly after ATR (Blumer et al., 1998; Ring et al., 1998), but postoperative emotional disturbances have received less attention than cognitive changes, and the underlying mechanisms are poorly understood. So far only a few prognostic indicators for emotional disturbances after ATR (preoperative anxiety and depression, right ATR, postoperative surgical outcome, structural MRI changes) have been described.

7.3. METHODS

7.3.1. Subjects

We studied 54 consecutive patients with medically refractory TLE due to unilateral HS (26 left (15 female); median age: 42, range 18-62 years; 28 right (12 female); median age: 37, range 21-52 years). All patients underwent presurgical evaluation at the National Hospital for Neurology and Neurosurgery, London. Hippocampal volumetry demonstrated a normal contralateral hippocampus in all subjects. Video-EEG confirmed seizures arising from the ipsilateral mesial temporal lobe in all 54 patients. All patients' first language was English, handedness was determined using a standardised questionnaire (Oldfield, 1971); assessment of language dominance revealed left hemisphere dominance in 39 patients, bilateral language representation in 10 patients and atypical, right hemisphere dominance in 5 patients. Left TLE patients had on average 2.33 simple partial seizures (SPS), 6.77 complex partial seizures (CPS) and 0.21 generalized tonic clonic seizures (GTCS) per month; right TLE patients had 5.85 SPS, 8.38 CPS and 0.65 GTCS on average per month. All patients were treated with anti-epileptic drugs, without changes made to medication between the preoperative fMRI scan and four month postoperative follow up. Ten of 26 left and 11 of 28 right TLE patients had an ATR. There was no difference in the size of the temporal lobe resection between the left and right TLE groups; the standard surgical procedure is described in section 2.2.1.2.

We also studied 21 right-handed native English-speaking healthy volunteers (median age 47, range 22-62 years; 10 female) with no history of neurological and psychiatric disease. 20 controls were right handed, one was left handed, and all were left language dominant as assessed by the fMRI language tasks.

For full details of the presurgical evaluation please refer to the common methodology chapter II.

7.3.2. Neuropsychological Test

The Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) was used as a measure of self-reported symptoms of anxiety and depression; it is described in the common methodology chapter 2.2.2.6. Patients completed this scale before and four months after ATR. Changes in anxiety and depression scores from baseline following ATR were correlated with preoperative fMRI activation patterns.

7.3.3. MR data acquisition

MRI studies were performed on a 3T General Electric Excite HD scanner according to our standard protocol as described in sections 2.3.1 and 2.3.1.2.

7.3.4. Functional MRI paradigm

For this experiment we used our memory encoding paradigm which is described in the common methodology section 2.3.2.2 and which was also used in our memory experiments in the previous chapters V and VI. This paradigm also includes viewing fearful and neutral faces. In brief, a total of 210 stimuli of three different material types (Pictures (P), Words (W) and Faces (F)) were visually presented, one every 4 s, in 7 cycles. Each cycle consisted of a block of 10 pictures (black and white nameable line drawn objects), 10 words (single concrete nouns) and 10 faces (partly black and white, partly coloured photographs unfamiliar to the subjects), followed by 20 s of crosshair fixation. The faces used consisted of 23 fearful, 23 happy and 24 neutral faces. Each block of faces contained a balanced mixture of the three expression types.

7.3.5. Data analysis

Imaging data were analysed with Statistical Parametric Mapping (SPM2) (Friston et al., 1995). The preprocessing steps of the fMRI dataset are described in the common methodology chapter 2.3.3.1.

A two-level event-related random-effects analysis was employed.

At the first level, for each subject trial specific responses were modelled by convolving a delta function that indicated each event onset with the canonical haemodynamic response function (HRF) to create regressors of interest, one regressor for each of the three event types (neutral, fearful and happy faces). Each subject's movement parameters were included as confounds and parameter estimates pertaining to the height of the HRF for each regressor of interest were calculated for each voxel. One contrast image for the main effect of viewing fearful compared to neutral faces and one for the main effect of viewing happy compared to neutral faces was created for each subject. These images were then used for the second-level analysis.

At the second level of the random effects analysis, we divided the subjects into three groups: healthy volunteers, left TLE and right TLE patients. Within each group, each subject's contrast images were entered into a one-sample *t*-test to examine the main effects of viewing fearful and happy faces compared with neutral faces. Two-sample *t*-tests were performed to highlight brain regions demonstrating more or less activation in one group compared to another.

In order to test for correlations between areas of fMRI activation and subject's performance on the anxiety and depression questionnaires pre- and postoperatively multiple regression analyses were performed for each voxel over the whole brain. For each subject we used the anxiety and depression scores as covariates for fMRI activation during the fearful face paradigm. Furthermore, the measures of change of anxiety and depression scores were used to test for correlations between preoperative fMRI activation and change in anxiety and depression scores from before to four months after ATR in those patients who had an ATR and postoperative neuropsychological assessment.

We report all MTL activations at a threshold of $P < 0.001$, uncorrected for multiple comparisons, if not stated otherwise. This uncorrected threshold was adopted because of the low signal-to-noise ratio in the anterior temporal lobe and as we were testing a specific hypothesis regarding MTL activation.

7.4. RESULTS

7.4.1. HADS – scores

Preoperatively, there was no significant difference in anxiety and depression scores between left and right TLE patients (anxiety - median: left TLE 7, range 1 - 18; right TLE 9, range 3 - 15; depression – median: left TLE 5.5, range 0 - 10; right TLE 4.5, range 0 - 15). The median scores in our controls' data were 5.5 for anxiety, range 0 - 13) and 1.5 for depression, range 0 - 5.

Five out of ten patients undergoing left ATR had a postoperative decline in anxiety scores, three had an increase in anxiety scores and two remained unchanged. The mean change between pre- and postoperative anxiety score was -0.5 (range -8 to +3). Seven left TLE patients had a postoperative decline in depression scores, one an increase, two remained unchanged. The mean change between pre- and postoperative depression score was -1.5 (range -6 to +1).

Four out of 11 patients undergoing right ATR had a postoperative decline in anxiety scores, six an increase and one patient's score remained unchanged. The mean change between pre- and postoperative anxiety score was +1.0 (range -5 to +7). Four right TLE patients had a postoperative decline in depression scores, six an increase and one patient remained unchanged. The mean change between pre- and postoperative depression score was +1.0 (range -7 to +6).

A clinically significant change in anxiety was observed in four out of 10 left TLE patients (three patients with an improvement, one with worsening of anxiety) and a clinically significant change in depression in two out of 10 left TLE patients (two patients with an improvement in depression).

In right TLE patients we found a clinically significant change in anxiety in seven out of 11 patients (three patients with an improvement and four with worsening of anxiety) and a clinically significant change in depression in four out of 11 patients (two patients with an improvement and two with worsening of depression).

There were no statistically significant correlations between preoperative anxiety or depression ratings and postoperative change in anxiety or depression.

There was no significant correlation between postoperative seizure outcome as measured by Wieser et al. (Wieser et al., 2001) and change in anxiety or depression scores at four months and

therefore postoperative seizure control was not a factor in changes of anxiety or depression after ATR.

7.4.2. Hippocampal Volumes and Amygdala T2 maps:

Left and right hippocampal volumes were significantly different in both left and right TLE patients; left TLE group: mean (SD) right hippocampal volume 2.79 (0.30) cm³, mean left hippocampal volume 1.81 (0.46) cm³ (paired *t*-test $p < 0.0001$, 2-tailed); right TLE group: mean right hippocampal volume 2.00 (0.58) cm³, mean left hippocampal volume 2.62 (0.35) cm³ (paired *t*-test $p < 0.0001$, 2-tailed). There was no significant difference between left hippocampal volume in the left TLE group and right hippocampal volume in the right TLE group. There was no significant difference of amygdala T2 values between right and left TLE patients within each group.

7.4.3. Functional MRI activations

We report all significant activations within the amygdala, the hippocampus and the parahippocampal structures for the contrast of viewing fearful compared to neutral faces.

Activation peaks in the medial temporal lobe for the main effects and their interactions across each group are given in Tables 7.1 and 7.2.

7.4.3.1. Main effects

Controls:

There was left-sided amygdala activation on viewing fearful faces ($p = 0.003$) (Fig 7.1A). Activation was also seen in the right amygdala; however, this did not reach statistical significance ($p = 0.011$).

Right TLE:

Both, left and right amygdala ($p = 0.001$) activations were observed on viewing fearful faces (Fig 7.1B).

Left TLE:

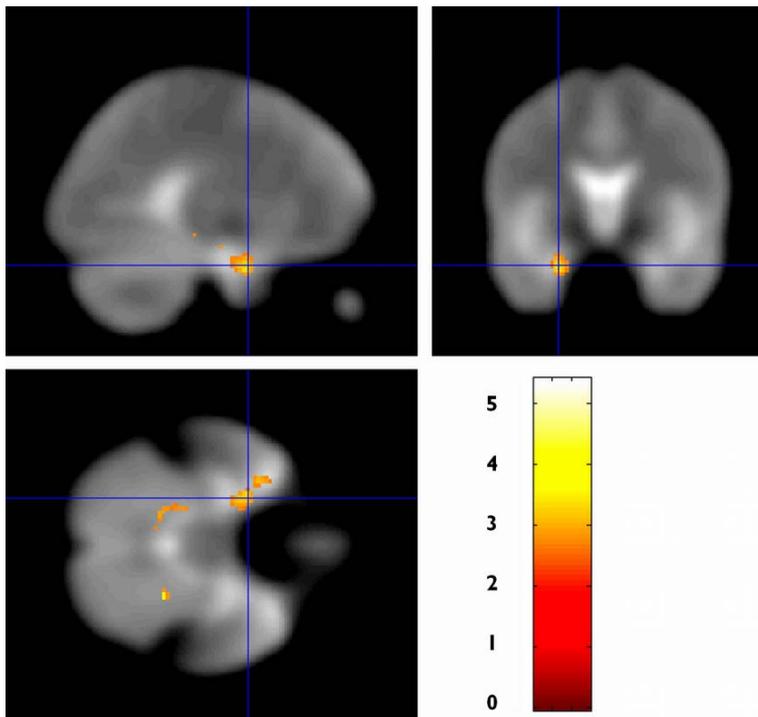
No significant MTL activation was seen for viewing fearful faces.

Table 7.1 One sample t-test showing fMRI activation peaks for the main effects of viewing fearful faces contrasted by neutral faces in the MTL for each group (TH 0.001)

Subjects	Z-score	Uncorrected p-value	Coordinates (x y z) in MNI space	Anatomical region
Controls	2.80	0.003	-24 2 -26	left amygdala
	2.31	0.011	14 2 -22	right amygdala
	4.07	0.000	50 -20 -2	right superior temporal gyrus
	3.09	0.001	52 -40 -18	right fusiform gyrus
	3.09	0.001	-52 -20 -10	left superior temporal gyrus
	3.10	0.001	-40 -46 -22	left fusiform gyrus
Left TLE patients	ns	ns
Right TLE patients	3.21	0.001	-24 2 -30	left amygdala
	3.13	0.001	26 0 -26	right amygdala

Legend: MNI space – coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); ns – not significant; TLE - temporal lobe epilepsy.

A



B

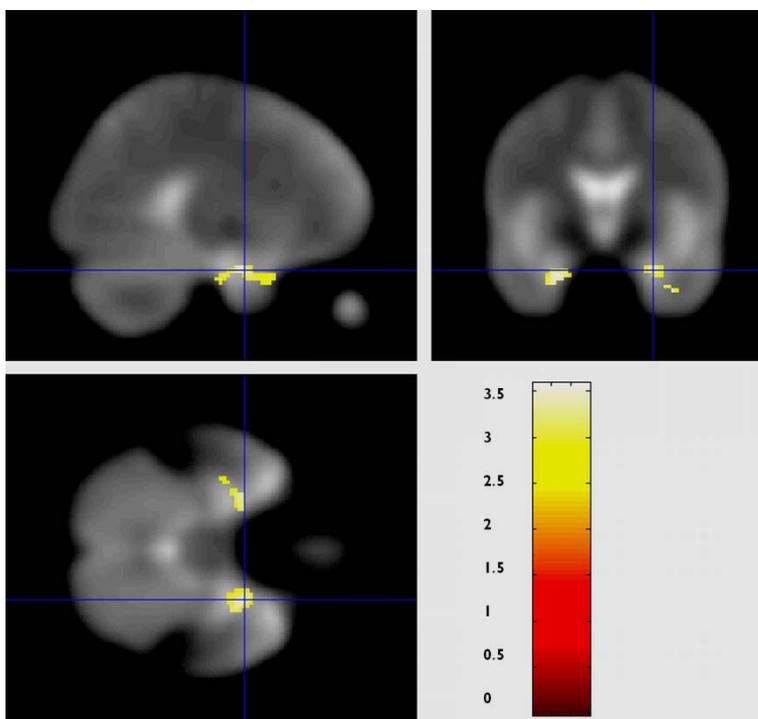


Figure 7.1 Main effects of viewing fearful contrasted by neutral faces

(A) in controls: left amygdala activation,

(B) in patients with right temporal lobe epilepsy: bilateral amygdala activation.

Colour scale indicating increasing Z-scores.

7.4.3.2. Group comparisons

For group comparisons please see Table 7.2.

Left TLE versus controls:

Left TLE patients activated significantly less in the left ($p=0.000$) and right amygdala ($p=0.001$) compared to controls. Left TLE patients also demonstrated significantly less activation than controls in the right hippocampus ($p=0.000$).

Right TLE versus controls:

Right TLE patients showed less activation in the left ($p=0.011$, uncorrected) and right ($p=0.025$, uncorrected) amygdala than controls; however this did not reach statistical significance.

Left TLE versus right TLE:

Compared to right TLE patients, left TLE patients activated significantly less in the left and right amygdala ($p=0.000$) and left and right hippocampus ($p=0.000$) (Fig 7.2).

For the contrast “happy compared to neutral faces” we did not find any significant activations within the temporal lobe at the group levels. Therefore we did not perform correlations between this contrast and scores of anxiety and depression.

Table 7.2 Two sample t-tests showing two way interactions between patients and controls for the main effects of viewing fearful faces contrasted by neutral faces in the medial temporal lobe

Subjects	Z- score	Uncorrected p-value	Coordinates (x y z) in MNI space	Anatomical region
Left TLE<controls	3.75	0.000	50 -20 -2	right superior temporal gyrus
	3.63	0.000	22 -8 -12	right hippocampus/amygdala
	3.17	0.001	32 -4 -28	right amygdala
	3.22	0.001	-26 -8 -8	left insula
	3.29	0.000	-20 -10 -20	left amygdala
	2.90	0.002	52 -4 -6	right insula/
Left TLE >controls	ns	ns
Right TLE<controls	3.38	0.001	48 -22 -2	right superior temporal gyrus
	2.28-ns	0.011-ns	-16 0 -14	left amygdala
	1.69-ns	0.025-ns	20 -2 -14	right amygdala
Right TLE > controls	ns	ns
Left TLE > right TLE	ns	ns
Right TLE > left TLE	3.77	0.000	32 -4 -26	right amygdala
	3.48	0.000	10 -12 -20	right hippocampus
	3.39	0.000	22 -8 -16	right amygdala/hippocampus
	3.67	0.000	-18 -12 -20	left hippocampus
	3.40	0.000	-28 -6 -28	left amygdala

Legend: ns – not significant; TLE - temporal lobe epilepsy.

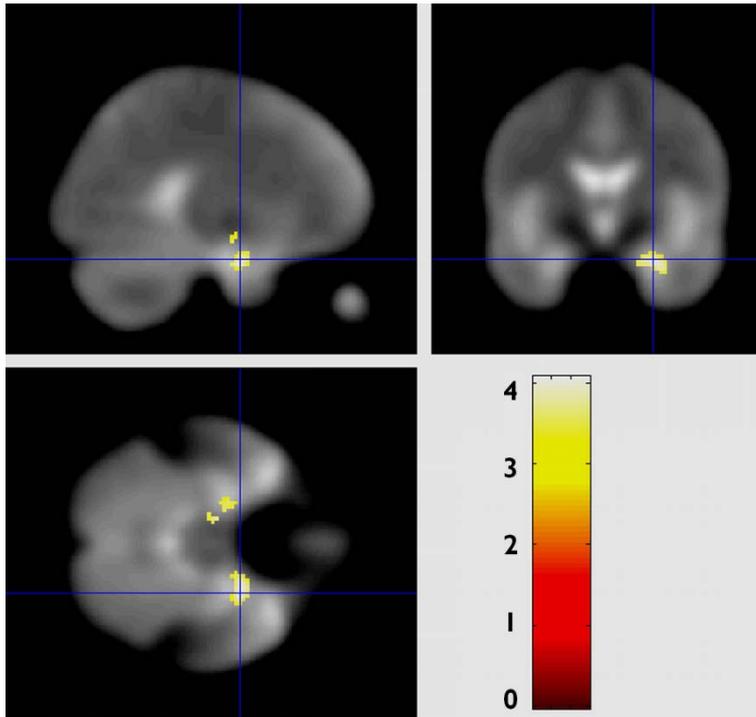


Figure 7.2 Amygdala activation in patients with right TLE compared to patients with left TLE

Significantly greater fMRI activation on viewing fearful contrasted by neutral faces in both, left and right amygdala in patients with right temporal lobe epilepsy compared to patients with left temporal lobe epilepsy.

7.4.3.3. Correlational analysis

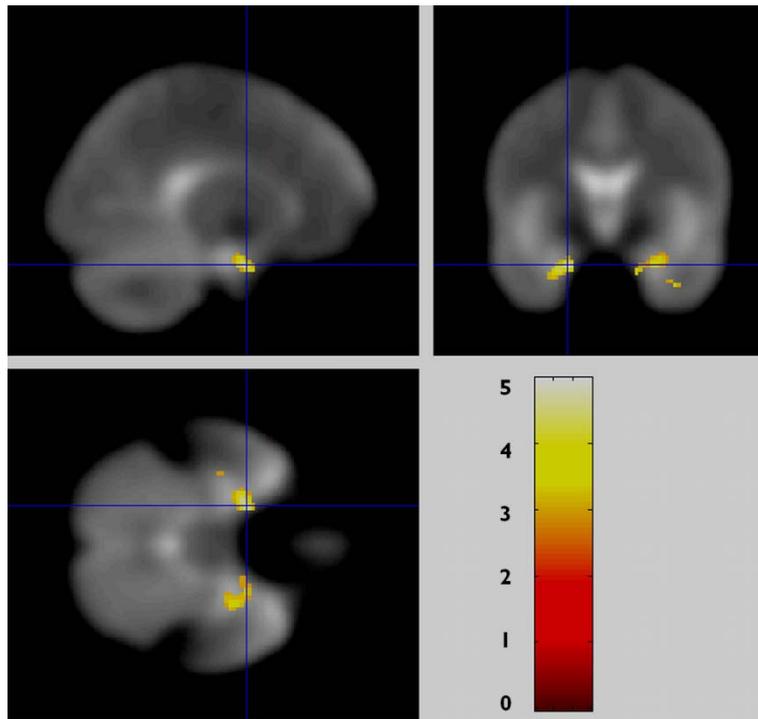
Correlation of fMRI activation (viewing fearful contrasted by neutral faces) with preoperative anxiety/ depression scores:

In right TLE patients there was a significant correlation between preoperative anxiety scores and fMRI activation associated with viewing fearful faces in left ($p=0.001$) and right amygdala ($p=0.000$) (Fig 7.3A, Table 7.3).

Right TLE patients also showed a significant correlation between preoperative depression scores and fMRI activation associated with viewing fearful faces in left and right amygdala ($p=0.000$) (Fig 7.3B).

No significant correlations were demonstrated for left TLE patients or healthy controls.

A



B

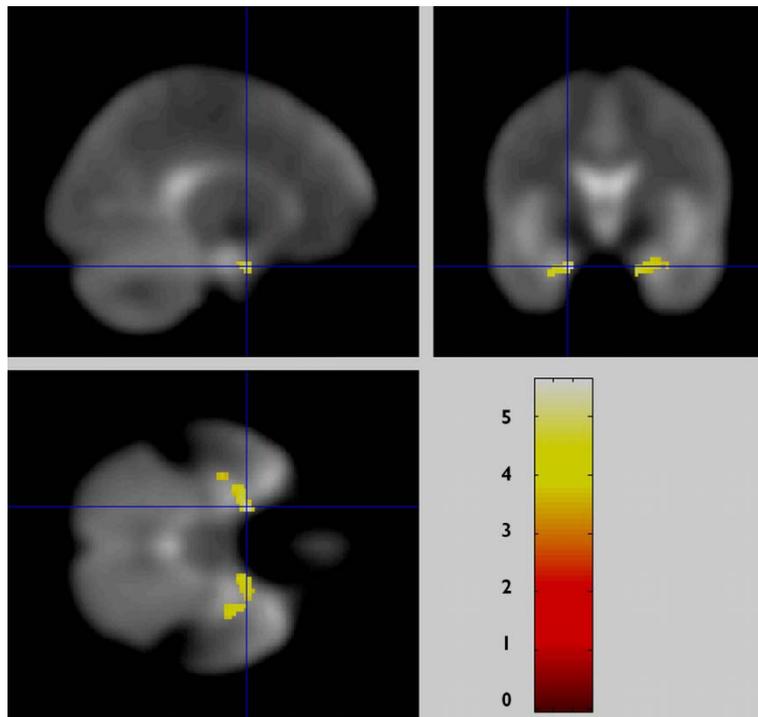


Figure 7.3 Correlation between preoperative fMRI activation on viewing fearful faces and preoperative levels of anxiety and depression in patients with right TLE

Multiple regression analysis calculated for each voxel over the whole brain

Positive correlation between preoperative fMRI activation on viewing fearful contrasted by neutral faces and preoperative anxiety (A) and preoperative depression (B) scores in left and right amygdala

Table 7.3 Correlations of preoperative fMRI activation on viewing fearful faces contrasted by neutral faces and preoperative anxiety and depression scores over the whole brain

	Subjects	Z- score	Uncorrected p-value	Coordinates (x y z) in MNI space	Anatomical region
Correlation of preoperative fMRI activation versus preoperative anxiety scores	controls	ns	ns
	left TLE	ns	ns
	right TLE	4.00	0.001	-20 0 -26	left amygdala
Correlation of preoperative fMRI activation versus preoperative depression scores	controls	ns	ns
	left TLE	ns	ns
	right TLE	3.29	0.000	30 -4 -24	right amygdala
Correlation of preoperative fMRI activation versus preoperative anxiety scores	controls	ns	ns
	left TLE	ns	ns
	right TLE	3.17	0.001	16 0 -28	right amygdala
Correlation of preoperative fMRI activation versus preoperative depression scores	controls	ns	ns
	left TLE	ns	ns
	right TLE	4.34	0.000	-20 0 -26	left amygdala
Correlation of preoperative fMRI activation versus preoperative anxiety scores	controls	ns	ns
	left TLE	ns	ns
	right TLE	3.95	0.000	16 0 -28	right amygdala

Legend: ns – not significant; TLE - temporal lobe epilepsy.

Correlation of fMRI activation (viewing fearful contrasted by neutral faces) with change in anxiety/ depression scores postoperatively:

Twenty-one patients (11 right and 10 left TLE) underwent ATLR and completed mood ratings four months following surgery (Table 7.4).

In right TLE patients there was a significant correlation between fMRI activation and postoperative change in anxiety scores in the right amygdala (p=0.000), characterised by a greater increase in anxiety scores in patients with greater preoperative fMRI activation (Fig 7.4A and B).

In right TLE patients there was also a significant correlation between fMRI activation and postoperative change in depression scores in the right amygdala (p=0.000), characterised by a

greater increase in depression scores in patients with greater preoperative fMRI activation (Fig 7.4C).

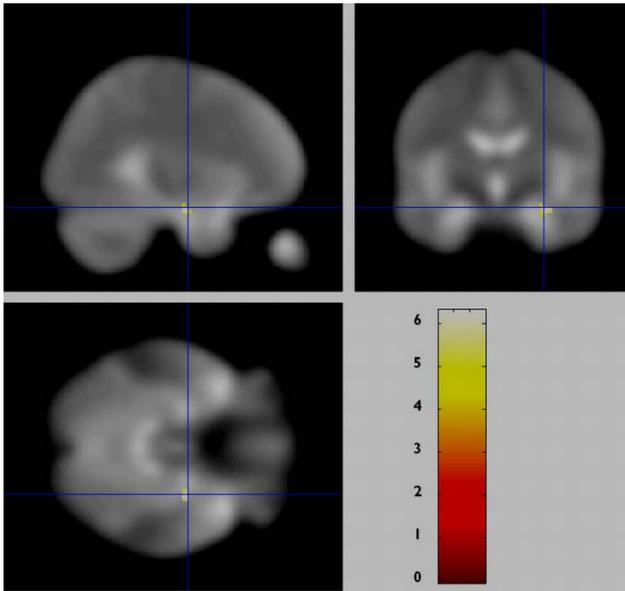
In left TLE patients we did not observe any significant correlations between preoperative fMRI activations on viewing fearful faces and postoperative changes in anxiety or depression scores.

Table 7.4 Correlations of preoperative fMRI activation on viewing fearful contrasted by neutral faces and postoperative change in anxiety and depression scores over the whole brain

	Subjects	Z- score	Uncorrected p-value	Coordinates (x y z) in MNI space	Anatomical region
Correlation of preoperative fMRI activation versus postoperative change in anxiety scores	right TLE (11 subjects)	3.91	0.000	30 -8 -20	right amygdala
	left TLE (10 subjects)	ns	ns
Correlation of preoperative fMRI activation versus postoperative change in depression scores	right TLE	3.37	0.000	20 -2 -10	right amygdala
		3.20	0.001	18 2 -10	right amygdala
		4.09	0.000	-66 -30 -12	left middle temporal gyrus
		3.98	0.000	52 -10 -20	right middle temporal gyrus
	left TLE	ns	ns

Legend: ns – not significant; TLE - temporal lobe epilepsy.

A



B

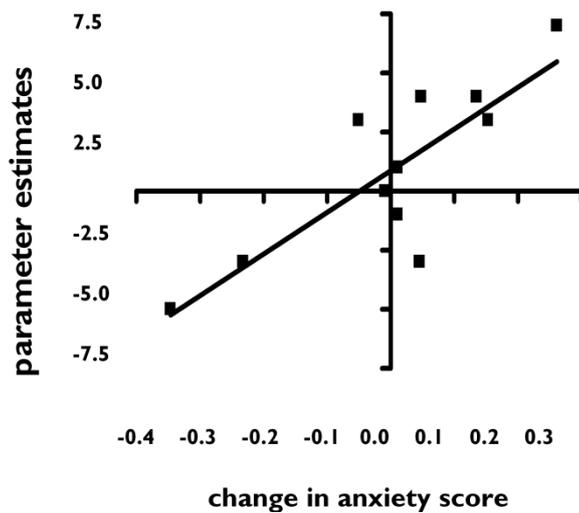
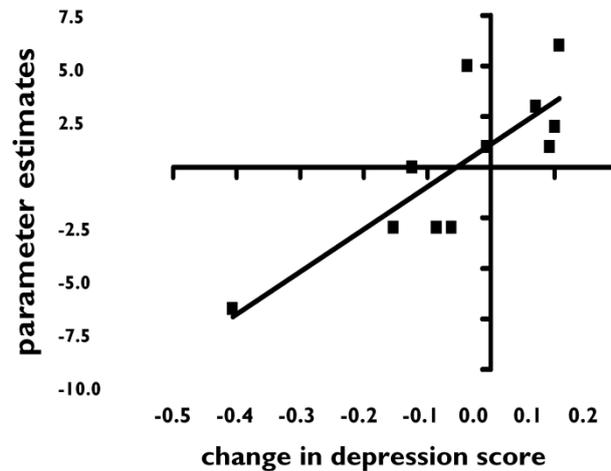


Figure 7.4 Correlation between preoperative fMRI activation on viewing fearful faces and postoperative change in anxiety (A and B) and depression (C) scores in patients with right TLE
Right TLE group: Multiple regression analysis – parameter estimates calculated for each voxel over the whole brain: Preoperative right amygdala activation with fearful contrasted by neutral faces correlates with postoperative change in anxiety scores, characterised by a greater increase in anxiety scores in patients with greater preoperative activation

C



Correlation between preoperative fMRI activation on viewing fearful faces and change in depression scores in patients with right TLE

Right TLE group: Multiple regression analysis – parameter estimates calculated for each voxel over the whole brain: Preoperative right amygdala activation with fearful contrasted by neutral faces correlates with postoperative change in depression scores, characterised by a greater increase in depression scores in patients with greater preoperative activation

7.5. DISCUSSION

7.5.1. Summary of main findings

In this experiment we demonstrated the feasibility of amygdala fMRI and compared the role of the amygdala in processing emotion in healthy controls and in patients with medically refractory TLE using a fearful face paradigm. Furthermore we demonstrated that in these patients, atypical amygdala responsiveness was significantly related to pre- and postoperative levels of anxiety and depression.

The paradigm proved to be easy to perform due to its low cognitive demands and allowed evaluation of hippocampal and amygdala functional integrity in a single session.

Controls demonstrated a left lateralized pattern of amygdala activation, whilst patients showed reduced amygdala activation compared to controls.

Significant correlations were seen in right TLE patients between amygdala activation and levels of preoperative anxiety and depression, characterised by higher preoperative fMRI activation correlating with higher anxiety and depression scores. Finally, those right TLE patients who had

undergone surgery also demonstrated correlations between preoperative right amygdala activation on viewing fearful faces, and postoperative change in anxiety and depression levels, with greater preoperative activation being associated with worsening of anxiety and depression scores following ATR.

7.5.2. Amygdala involvement in processing emotions

Our findings corroborate previous studies showing asymmetric activations in response to viewing fearful stimuli in normal subjects and extend these findings to patients with refractory epilepsy. Using PET Morris et al. observed a significantly greater neural response to fearful as opposed to happy faces in the left amygdala and therefore provided evidence of a differential neural response to facial expressions of fear and happiness (Morris et al., 1996). Schacher et al. reported symmetric bilateral amygdala activation on presentation of fearful faces in controls, whereas 12 patients with either right or left mTLE had an activation pattern that was lateralized to the contralateral side (Schacher et al., 2006). A possible explanation for the apparent discrepancy between the current findings and those of Schacher in 2006 might be that, in contrast to our experiment, the paradigm used in the latter study combined the dynamic perception of motion with the presentation of fearful facial expressions to maximize signal change mainly within the amygdalae, while we used static stimuli. In patients, the severity and extent of the underlying pathology may also contribute to the functional dissociation in the various patient groups as amygdala and hippocampal sclerosis may be combined, but the sclerotic process may be restricted to the hippocampus or the amygdala. A recent cortical stimulation study suggested a functional lateralization of the amygdalae for different types of stimuli. Electrical stimulation of the right amygdala induced negative emotions, especially fear and sadness, whereas stimulation of the left amygdala led to either pleasant (happiness) or unpleasant (fear, anxiety, sadness) emotions (Lanteaume et al., 2007). Other studies have suggested a specific role for the right amygdala in automatic stimuli processing, while more detailed decoding of the importance of stimuli might be associated with activity of the left amygdala (Morris et al., 1998b; Wright et al., 2003). This functional dissociation might be a

reason for the differing results in our left TLE and right TLE patients. Left TLE patients demonstrated less left amygdala activation, most likely due to pathology. We also observed less activation in the right amygdala, possibly because left and right amygdalae do not function as independently as has been suggested by the “functional dissociation hypothesis” (Lanteaume et al., 2007; Morris et al., 1998b).

7.5.3. Amygdala (dys-)function in TLE

Medically refractory TLE is associated with an increased prevalence of emotional disorders, in particular mood and anxiety disorders (Boylan et al., 2004; Gilliam et al., 2003) which may be related to dysfunction of the limbic system, in particular the amygdala and the hippocampus. In patients with TLE the amygdala is often affected by sclerosis, together with the hippocampus (Van Paesschen et al., 1996; Williamson et al., 1993). The hippocampus is critical for memory encoding and hippocampus and amygdalae are responsible for emotional memory encoding (Richardson et al., 2004a). As the amygdala is one of the key structures for emotional processing (Morris et al., 1998a; Morris et al., 1996) and social perception, surgical trauma to a normal amygdala may result not only in impairment of emotional memory (Cahill et al., 1995) but also in emotional and social disturbances (Adolphs, 2003).

In the current study we found a correlation between preoperative bilateral amygdala activation and anxiety and depression levels preoperatively in right TLE patients, characterised by greater anxiety and depression scores with greater fMRI activation. In contrast, left TLE patients did not show a correlation between amygdala activation and anxiety and depression scores. This suggests that the right amygdala has a key role in feelings of anxiety and depression, and that dysfunction in this structure is associated with increased anxiety and depression, the degree of which is associated with increased activation.

Our results are in keeping with psychiatric studies in which a positive correlation was found between amygdala activation and measures of anxiety and depression using fMRI as a predictor for treatment outcome in anxiety disorders (McClure et al., 2007). Amygdala involvement has also been linked with fear auras at the onset of seizures (Cendes et al., 1994a) and with

aggressive outbursts in patients with TLE (van Elst et al., 2000). Abnormally high resting activity of the amygdala has been described in patients with major depression (Abercrombie et al., 1998).

7.5.4. Neurobiological and clinical implications

Several studies have evaluated potential predictive factors for postoperative psychiatric disorders, such as preoperative depression or anxiety disorder (Devinsky et al., 2005; Quigg et al., 2003), right ATR (Quigg et al., 2003) and postoperative seizure control (Devinsky et al., 2005), but prediction of postoperative psychiatric symptoms remains a challenge. Irrespective of seizure outcome, patients are at risk of either developing de novo mood disorders or continuing to suffer from anxiety or depression after ATR (Blumer, 2002; Blumer et al., 2002).

We observed a clinically significant improvement in depression only in two out of ten patients with left TLE and two out of 11 patients with right TLE following surgery, whilst only two patients with right TLE significantly deteriorated.

In three out of ten left TLE and three out of 11 right TLE patients we found a clinically significant improvement in anxiety after surgery, while one left TLE patient and four right TLE patients significantly worsened. The analysis used the actual change scores. Reducing the data to increased /decreased scores would not be appropriate for a study with this number of subjects and would result in loss of sensitivity.

We found a positive correlation in right TLE patients between preoperative right amygdala activation on viewing fearful faces and postoperative increase in anxiety and depression scores. As with previous studies there was no relation between seizure outcome and mood disturbances after ATR (Wrench et al., 2004). We conclude from our findings that resection of a right amygdala that is reacting strongly to emotional stimuli, albeit less than controls, results in increased risk of emotional disturbances, at least at four months following ATR. The inference is that a dysfunctional right amygdala has a modulating role on emotion and mood. There are, of course, no data to determine the effects of removal of a normal right amygdala on anxiety and depression.

Occasionally, a significant improvement of pre-existing mood disturbances after epilepsy surgery is reported (Devinsky et al., 2005; Reuber et al., 2004; Spencer et al., 2003). Results are contradictory with regard to laterality. Some studies suggested a higher risk of (de novo) psychiatric symptoms after right ATR (Glosser et al., 2000; Quigg et al., 2003), others for left ATR (Piazzini et al., 2001) whilst others found no effect of laterality (Devinsky et al., 2005). Multiple mechanisms are likely to contribute to the evolution of postoperative mood symptoms. The higher rate of anxiety and depression in TLE patients in the early postoperative stage suggests that neurobiological mechanisms play a part (Kanner and Balabanov, 2002; Krishnamoorthy et al., 2002). Disruption, removal or deafferentation of the limbic system structure after ATR is most obvious.

In the longer term, psychosocial factors such as the “burden of normality” are likely to be contributory (Wilson et al., 2001).

7.5.5. Strengths and limitations

There are several methodological limitations of the study. First, our study focused on activations within the medial temporal lobe and therefore our imaging parameters were not optimal for studying neocortical regions outside the temporal lobe. We cannot, therefore, report on other extratemporal/ limbic systems that are likely to be involved in emotional processing, such as the orbito-frontal regions.

Secondly, our postoperative results are based on a follow-up of only four months, with a relatively small sample of 21 patients. Several studies have shown that there is a temporal pattern to psychiatric morbidity after surgery with up to 50% of the patients developing psychiatric symptoms within six weeks, but symptoms of depression tend to improve or resolve by one year follow up, which seems less true for comorbid anxiety disorders (Ring et al., 1998). Third, the HADS is a scale of self-reported symptoms of anxiety and depression. The results, based on these scores, are preliminary and merit further evaluation using more detailed diagnostic instruments.

7.6. CONCLUSION

In conclusion, fMRI with emotional stimuli activates the amygdalae in controls and to a lesser extent in those with right TLE, and even less in left TLE. The correlation of amygdala activation with anxiety and depression in those with right TLE suggests a modulatory role for the right amygdala on mood. Of potential clinical relevance, the degree of activation of the right amygdala in those with right TLE was predictive of postoperative mood disturbances, and this may be a useful tool to identify those at risk of this morbidity.

CHAPTER VIII

8. OVERALL DISCUSSION

8.1. INTRODUCTION

With a prevalence of 0.8% Epilepsy is one of the most frequent neurological diseases. 60-70 % of all epilepsy patients suffer from focal epilepsies, 35% of these patients will be classified as “medically refractory” in the course of their disease. For these patients epilepsy surgery, such as anterior temporal lobe resection (ATLR) in patients with intractable mesial temporal lobe epilepsy (TLE), provides an effective and safe treatment option rendering up to 50-60% of them seizure free (de Tisi et al., 2011; Spencer and Huh, 2008; Wiebe et al., 2001).

The goal of epilepsy surgery is to remove the epileptogenic brain tissue which ideally will lead to seizure-freedom. At the same time neuropsychological deficits, such as memory and language dysfunction have to be avoided (Davies et al., 1998; Helmstaedter and Elger, 1996; Hermann et al., 1995; Sabsevitz et al., 2001). This in turn, requires accurate localisation of the brain areas generating the seizures as well as the areas responsible for motor, language and memory function and also for emotional processing during presurgical evaluation. Up to 50% of all patients with TLE suffer from psychiatric symptoms such as emotional disturbances including anxiety and depression, which can be particularly aggravated following epilepsy surgery in the temporal lobe (Blumer et al., 1998; Kanner, 2003; Ring et al., 1998).

The indications for surgical interventions have significantly increased in the last 20 years. It is most likely due to technical advances, in particular the advent of MRI and other imaging methods, as well as improved surgical techniques, that epilepsy surgery is nowadays carried out earlier in the course of the disease and is also offered to patients with less severe epileptic syndromes with little or no preoperative cognitive impairment and who are therefore at high risk for a significant postoperative cognitive decline (Wiebe et al., 2001). A comprehensive presurgical work-up is essential to estimate the risk for postoperative cognitive, psychiatric and social changes and therefore allow better preoperative counseling of individual patients.

Over the last few years fMRI has been increasingly used for mapping of eloquent functions as it is non-invasive, repeatable and much cheaper than i.e. the IAT.

The main goal of the work presented in this thesis was to apply different cognitive fMRI paradigms on a 3 T scanner to a group of healthy controls and patients with medically refractory left or right TLE to gain additional patient-specific information with two main aims:

1. Functional MRI can be applied to understand more about how focal epilepsy contributes to cognitive impairment. I have used fMRI to investigate how cognitive functions are reorganised in patients with medically refractory TLE, compared to healthy controls due to the underlying pathology and ongoing epileptic activity or after ATR. This will further increase our understanding of functional reorganisation/plasticity in patients with epilepsy.

2. From a clinical perspective we need to identify the likely cause of the epilepsy and define the epileptogenic zone, removal of which will ideally cure the epilepsy. At the same time it is essential to localise the eloquent cortex. A major part of the work included in this thesis has concentrated on the use of fMRI for the exploration and prediction of postoperative complications such as language and memory impairment but also emotional disturbances. This is one of the ultimate goals of clinical neuroimaging.

8.2. SUMMARY OF MAIN FINDINGS

8.2.1. Language

1. In controls there was a significant correlation between fMRI activation in the left hippocampus during a verbal fluency (VF) task, and out of scanner naming performance. This finding underpins the fact that naming ability depends on the integrity of the hippocampus and connecting fronto-temporal networks. It also supports the observations that surgical removal of the dominant hippocampus in patients with left TLE may cause language alterations, mainly naming deficits.

2. Similarly to controls, fMRI activation in the dominant hippocampus during VF was associated with naming function in patients with right TLE.

3. In patients with left TLE, there was a significant correlation between fMRI activation during VF and out of scanner naming performance in the left middle frontal gyrus, providing

evidence of reallocation of naming function to the connected left frontal lobe, trying to compensate for the diseased left hippocampal system.

4. Four months following ATR, left TLE patients already demonstrated greater bilateral fMRI activation for VF compared to preoperatively. This finding suggests an early postoperative reorganisation/reallocation of language function to the contralateral hemisphere with evidence of multiple systems supporting language function.

5. Postoperatively, right TLE patients showed no change in activation patterns for VF compared to preoperative findings, with significant, persistent activation in the left middle and inferior frontal gyri.

6. These findings were corroborated by functional connectivity analysis showing greater postoperative than preoperative connectivity to the contralateral frontal lobe in patients with left TLE while there was no postoperative change in functional connectivity compared to preoperatively in patients with right TLE.

7. In left TLE patients we found a significant correlation between preoperative fMRI activation for VF and change in naming scores in the left middle frontal gyrus (MFG) with greater left middle frontal activation being correlated with greater decline. In left TLE patients preoperative left middle frontal activation for VF was predictive of postoperative naming decline, with high sensitivity and relatively lower specificity.

8. In left TLE patients without a significant naming decline following surgery we found the strongest correlation between postoperative fMRI activation for VF and postoperative out of scanner naming performance in the posterior remnant of the left hippocampus (HC). In patients with a significant naming decline the correlation was on the contralateral side in the right MFG. This finding strengthens the hypothesis that ipsilateral reorganisation even within the damaged hippocampus is crucial for maintaining naming function while reorganisation to the contralateral side works inefficiently.

8.2.2. Memory

1. In controls it was possible to lateralise medial temporal lobe (MTL) memory function using a material specific memory encoding paradigm with word encoding lateralised to the left and face encoding lateralised to the right MTL structures respectively. Picture encoding resulted in bilateral MTL activation.
2. Compared to healthy controls there was significantly less activation for encoding of words in the left MTL in left TLE patients and significantly less activation for face encoding in the right MTL in right TLE patients.
3. Functional MRI activation during an event-related analysis of the memory fMRI data correlated with out of scanner memory performance.
4. Preoperatively, greater ipsilateral than contralateral activation for word/ face encoding within the anterior MTL predicted greater verbal/ visual memory decline.
5. Preoperatively, greater ipsilateral than contralateral activation for word/ face encoding within the posterior hippocampus correlated with better verbal/ visual memory outcome.
6. Compared to other epilepsy related variables, preoperative memory fMRI was the strongest predictor of postoperative verbal and visual memory decline following ATLR.
7. The asymmetry of MTL-fMRI activation with verbal memory encoding, language lateralisation and performance on preoperative verbal learning tests predicted a clinically significant verbal memory decline in all patients who underwent left ATLR.
8. The same algorithm (MTL-fMRI activation asymmetry with visual memory encoding, language lateralisation and performance on preoperative design learning tests) was less able to predict visual memory decline in patients who underwent right ATLR.
9. We found greater post- than preoperative activation for verbal memory encoding in the posterior remnant of the left hippocampus in patients who underwent left ATLR, providing evidence for early postoperative reorganisation/ compensation to the left posterior MTL structures.
10. In patients with right TLE there was no significant difference between pre- and postoperative patterns of activation for encoding faces.

11. Results from the correlational analysis between greater pre- than postoperative fMRI activation for word encoding and change in verbal learning scores provided a strong positive correlation in the left posterior MTL. This was characterized by greater pre- than postoperative left posterior MTL fMRI activation being correlated with better postoperative verbal memory outcome.

12. Postoperatively, we found a negative correlation between a greater post- than preoperative fMRI activation and postoperative verbal learning scores in the left posterior and right anterior MTL. In other words, additional postoperative activation in the left posterior and the right anterior MTL was not associated with better postoperative verbal memory performance, which provided evidence for an inefficient early postoperative reorganisation to ipsilateral/ contralateral posterior MTL structures.

13. Visual memory function in right TLE was affected differently by right ATR than verbal memory in left TLE.

8.2.3. Emotion

1. Amygdala fMRI was feasible demonstrating greater left than right amygdala activation during a fearful face paradigm in controls.

2. Right TLE patients demonstrated bilateral amygdala activation while left TLE patients did not show any significant amygdala activation at all during the fearful face paradigm.

3. In patients with right TLE, left and right amygdala activation was related to preoperative anxiety and depression levels.

4. Postoperatively, greater preoperative right amygdala activation was associated with worsened anxiety and depression scores in patients with right TLE suggesting a role for amygdala fMRI in evaluating the risk of emotional disturbances following right ATR.

8.3. NEUROBIOLOGICAL AND CLINICAL IMPLICATIONS

The studies presented in this thesis aimed to address the following questions:

1. Is there evidence of reorganisation of pre- and postoperative cognitive function due to the underlying pathology, ongoing disease or following epilepsy surgery?
2. How efficient are pre- and postoperative networks in terms of out of scanner performance on cognitive tasks?
3. Can we use fMRI to predict a clinically significant cognitive decline?

Most interestingly, results of all the experiments provided support for the functional adequacy theory which postulates that it is the capacity of the ipsilateral (posterior) hippocampus and not reorganisation to homotopic contralateral structures which is crucial for maintaining postoperative cognitive function (Chelune et al., 1991). This was particularly evident in the studies of memory, which first of all demonstrated a functional dissociation between the anterior and posterior part of the MTL structures and in particular the hippocampus: Greater preoperative anterior MTL activation was correlated with greater verbal and visual memory decline, while greater preoperative posterior MTL activation was correlated with better postoperative verbal and visual memory outcome. These findings were confirmed in the postoperative follow-up experiment in which we demonstrated that preoperative reorganisation to ipsilateral posterior MTL structures was necessary to maintain good memory function postoperatively, while increased postoperative activation during verbal memory encoding in the posterior remnant of the MTL was associated with less good performance, indicating that this early postoperative reorganisation was inefficient.

In addition longitudinal pre- and postoperative language experiments demonstrated that patients without a clinical significant decline in naming function relied on the posterior remnant of the dominant hippocampus (which was spared during surgery), while activation in the contralateral hemisphere was associated with poorer performance (= a clinically significant decline in naming function), similar to the findings in the memory experiments. Therefore none of the results of my experiments provided support for the hippocampal reserve theory.

In general, the circumstances which determine whether cognitive function is reorganised to the contralateral hemisphere or remains within the ipsilateral hemisphere still need to be established. In a recent memory study we aimed to extend the previous findings presented in this thesis and investigated not only temporal but also extra-temporal reorganization of memory encoding networks in refractory TLE and the neural correlates of successful subsequent memory formation. This study, in line with growing evidence from the literature suggests that there might be multiple patterns of resting and task driven fMRI activation and functional connectivity in patients with otherwise similar mesial TLE, with some patterns being correlated with better baseline function and some with better postoperative cognitive function (Sidhu et al., 2013). This in turn might be influenced by various factors such as genetic predisposition, and learning strategies employed.

It is also of paramount importance to consider how these research findings may be translated into clinical practice, which is particularly relevant for the prediction of postoperative cognitive decline. First of all, for all cognitive tasks which have been evaluated in this thesis, a potential use of fMRI as a clinical predictor of postoperative cognitive outcome has been demonstrated. Results of our memory studies, in particular, suggested that an fMRI derived memory asymmetry index in the MTL was the strongest predictor of postoperative memory outcome compared to other clinically established, epilepsy related predictors such as the preoperative level of function during neuropsychological assessment, preoperative language lateralisation, hippocampal volume and duration of disease. We have also derived an algorithm which included memory asymmetry measured with fMRI, language lateralisation and preoperative neuropsychological test results and with this algorithm it was possible to predict clinically relevant verbal memory decline in all our individual patients. This memory algorithm now needs to be tested prospectively in a large cohort of patients, ideally with different pathologies in the MTL before we can safely adopt fMRI as reliable predictor of memory outcome in clinical practice.

For language function, in patients with left TLE, an asymmetry index in individual subjects which indicated strongly left lateralised language representation in the medial frontal lobe during a verbal fluency task was predictive of greater clinical decline of specific naming functions, with high sensitivity and relatively less specificity.

Finally, our results also suggested that amygdala fMRI was a promising tool for the reliable prediction of postoperative emotional disturbances, which are extremely common in TLE, particularly after ATR, but are frequently not identified in preoperative counseling or noticed in postoperative assessment.

For both, language and emotional disturbances more effort will be needed to establish ideal fMRI protocols which, for example, directly assess naming function, or which provide strong and reliable amygdala activation in single subjects.

All results presented in this thesis are in line with those recent studies which increasingly emphasize the need to consider selective as opposed to extended temporal resections (and in particular to spare as much as possible of the posterior part of the MTL) to minimize the risk of cognitive impairment, but at the same time provide the same chance of good seizure control (Alpherts et al., 2008; Helmstaedter et al., 2011a; Helmstaedter et al., 2008; Helmstaedter et al., 2011b; Morino et al., 2006).

It is hoped that, in the near future, functional MRI may be able to provide reliable results in individual patients which when used in concert with other clinical, electrophysiological and imaging results will not only predict postoperative cognitive decline in single patients but ultimately help prevent them.

8.4. LIMITATIONS

8.4.1. Subject selection

- Most experiments included in this thesis were carried out in relatively homogenous groups of patients, as most of them suffered from unilateral TLE with hippocampal sclerosis. This is a great advantage for drawing conclusions about changes at the group level, but it also

has some methodological and clinical draw backs: First of all our results may be influenced by the effect of volume averaging on the extent and magnitude of the hippocampal (remnant) signal. Before a diagnostic tool can be reliably implemented in a clinical setting, it is necessary to establish patterns of activation in a large and homogenous group of patients. However, it has been shown, that localisation and type of pathology play an important role in how cognitive function is reorganised. Therefore our findings will need to be validated in a large group of patients with different pathologies and in particular in patients with non-lesional TLE, who are at the greatest risk of postoperative cognitive decline.

- As we considered a selected population of patients with mesial TLE who were in most cases left dominant for language, other effects such as age of disease onset, duration of disease, effects of medication, seizure frequency and interictal epileptic discharges, which might all contribute to the degree and way cognitive function is reorganised, were not investigated in these experiments.

8.4.2. fMRI paradigm design/ Data acquisition

- Many of the fMRI results presented in this work are still based on group findings, while clinically it is what happens to the individual patient that is most relevant. As we have shown in our memory experiments future work should focus on improving fMRI paradigm design and on developing methods to obtain strong and reliable fMRI activation in individual patients which we can then quantify (for example with ROIs or asymmetry indices).

- Development of additional cognitive fMRI tasks will be required in order to assess other aspects of memory function that might be impaired in patients with TLE in addition to verbal and visual memory (i.e. working memory). Auditory and visual naming paradigms may give more specific prediction of naming difficulties after anterior temporal lobe resection (Rosazza et al., 2013) than the simple verbal fluency task we used in our experiments.

- Postoperatively, memory and language functions were reassessed at an early postoperative stage of four months after ATR. Four months might be too early for compensatory responses (such as in the contralateral medial temporal lobe) to become fully functional. Memory function

(decline and recovery) has been found to stabilize within 2 years after surgery (Alpherts et al., 2006). Our group is currently carrying out further longitudinal follow-up studies of memory and language organisation at three months and 12 months after surgery to further investigate how this activation changes over a longer period of time in patients with TLE, having temporal lobe resection, and with a healthy control group also studied longitudinally, which will give us important further insights into postoperative recovery and plasticity.

- All our language tasks have been carried out covertly. Overt tasks have been shown to be advantageous for presurgical fMRI assessment in several aspects (higher quality scans, higher sensitivity for detecting activation on an individual level) (Croft et al., 2013). Therefore, in an ideal setting performance during the in-scanner tasks can be measured.

8.4.3. Technical limitations

- In most of the experiments presented in this thesis technical difficulties common to all functional imaging studies of the temporal lobe occurred; signal dropout, distortions, movement artefacts and low resolution are particularly relevant. It is now necessary to optimize imaging parameters including fields of view so that activation in areas of the brain other than the MTL and the adjacent structures such as the orbito-frontal cortex can be identified, in order to be able to comment on possible compensatory mechanisms.

8.4.4. Analysis

- In our memory fMRI experiments we used event-related designs, which have the great advantage that it is possible to investigate memory encoding function elegantly by adding performance during out of scanner memory testing to the model. However, this method has some disadvantages which I have discussed in detail in section 1.5.2.4.3. In particular it should be borne in mind, when considering the potential use of memory fMRI in clinical practice, that event-related designs are time-consuming and demanding for both subjects and clinicians. Stronger paradigms (see above) and improvements in data analysis such as automated processing would improve this aspect.

8.5. FUTURE PERSPECTIVES

In conclusion, we have shown that fMRI is an excellent, non-invasive tool to study the effects of epilepsy surgery on the brain and factors that are associated with effective functional reorganisation after surgery (Bonelli et al., 2013; Bonelli et al., 2012; Salek-Haddadi et al., 2009).

One of the aims of future work is now to integrate fMRI data with structural MRI into neuronavigation systems, including interventional MRI, and to repeat fMRI studies intraoperatively in order to enable image guided resections (Duncan, 2010). Hurdles to overcome include the different anatomical distortions of T1-weighted MR and EPI fMR images but also physical distortions such as brain shift which may be as much as 2 cm after surgery (Nimsky et al., 2006).

There is hope that constant improvements in hardware and software and in particular functional MR imaging at higher magnetic fields will lead to improved signal-to-noise. A recent fMRI study compared the presurgical localisation of the primary motor hand area on a 3 T and 7 T Siemens scanner with identical investigational procedures and comparable system specific sequences. Results showed significantly higher functional sensitivity of the 7 T system (measured via percent signal change, mean t-values, number of suprathreshold voxels and contrast to noise ratio) although 7 T data suffered from a significant increase of artifacts such as ghosting and head motion (Beisteiner et al., 2011). However, results are promising that ultra high field systems provide a clinically relevant increase of functional sensitivity for patients also in the MTL, which might lead to strong and reliable hippocampal activation at an individual level and which might even allow to delineate fMRI activation in hippocampal subfields during memory experiments.

Another exciting area is the use of fMRI to study brain network dynamics. Functional connectivity can elicit neuronal networks that contribute to various cognitive tasks. It has been shown that cognitive impairment is often accompanied by reduced functional connectivity. Whether these methods may add to the prediction of postoperative cognitive outcome remains a topic of current research (Axmacher et al., 2007; Voets et al., 2009). Together with tractography

which can provide a means to understand the distributed and inter-related structural networks of the brain, functional connectivity can be useful to understand seizure propagation and spread and how this may be related to impaired function. Perhaps ultimately this information can be used to disconnect seizure foci from the rest of the network. To be able to derive this kind of information one will need to combine the structural information derived from tractography with other modalities such as fMRI or MEG which provide functional information and EEG or ESI which provide directional information.

Finally, fMRI may help to improve the individual prognosis of even subtle cognitive deficits, but also stimulate the development of new therapeutic strategies for cognitive rehabilitation. An exciting possibility for future work could therefore be to evaluate whether it is possible to modify dysfunctional networks prior to surgery i. e. by applying specific learning strategies to the patients in order to optimize or even improve the chances of a good cognitive outcome following epilepsy surgery. Ultimately, it is likely that fMRI will be used as a tool not only to predict postoperative complications, but also to prevent them.

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