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Leena Jutila

Surgical Treatment of Refractory Temporal Lobe Epilepsy

Predictors of Long-term Outcome

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LEENA JUTILA

Surgical Treatment of Refractory Temporal Lobe Epilepsy:

Predictors of Long-term Outcome

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ABSTRACT

Temporal lobe epilepsy (TLE) is the most common focal epilepsy in adults. In drug-resistant TLE, surgery is superior to prolonged medical treatment. The main objective of this study was to evaluate long-term seizure and cognitive outcome after surgical treatment of TLE and to identify preoperative markers and predictive factors for the outcome.

This series of studies is based on the preoperative evaluation, surgical treatment and follow-up of adult TLE patients treated at Kuopio University Hospital between 1988 and 2006. The occurrence of damage in the medial temporal cortical structures in unilateral drug-refractory TLE was evaluated with magnetic resonance imaging (MRI) volumetry.

After a mean follow-up of 5.4 years, 46% of patients with unilateral TLE had become completely seizure-free, 10% had only postoperative auras, and 15% had rare seizures. Seizure outcome one year after the operation was predictive of long-term seizure outcome. The introduction of a standardised MRI protocol from 1993 onwards enhanced the detection of focal MRI abnormalities and improved postoperative seizure outcome (52% of patients with unilateral TLE had become completely seizure-free and 7% had only postoperative auras). Surgery was beneficial also in those TLE patients who had no focal abnormality in the preoperative MRI, even though the outcome was not as favourable as in those patients with focal pathological MRI findings. Palliative surgery was beneficial in a subgroup of TLE patients, who did not have a restricted unilateral seizure focus.

Hippocampal atrophy with or without temporal cortical atrophy, other unilateral structural lesions of the temporal lobe, seizure type predominance, and early onset of epilepsy predicted good seizure outcome during long-term follow-up. After TLE surgery a decline in verbal learning and memory was observed in the long-term follow-up. Both patients with left and right TLE were affected. Left side of surgery and better baseline performance were identified as risk factors for significant individual decline in delayed verbal memory. Volumes of the entorhinal and temporopolar cortices were reduced in a subpopulation of patients with unilateral TLE ipsilateral to the seizure focus.

The seizure outcome after TLE surgery in a Finnish national referral centre for epilepsy surgery is comparable to the outcomes reported from epilepsy surgery centres elsewhere. Good seizure outcome is retained also over the long-term. Selected patients undergoing surgery for drug-resistant TLE are at risk of having a significant postoperative memory decline especially after left temporal lobe surgery. This implies, that long-term cognitive performance needs to be followed also in clinical practice and better individual predictors of memory decline should be developed. Finally, it was possible to demonstrate that the medial temporal cortical structures are damaged in TLE, indicative of a disturbance in a larger structural network in TLE.

National Library of Medicine Classification: WL 385, WL 368, WN 185
Medical Subject Headings: Epilepsy, Temporal Lobe/surgery; Follow-Up Studies; Humans; Magnetic Resonance Imaging; Treatment Outcome; Hippocampus/pathology; Memory; Seizures

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TIIVISTELMÄ

Vaikean lääkehoidolle reagoimattoman ohimolohkoepilepsian tehokkain hoitovaihtoehto on leikkaushoito. Tämän väitöskirjatyön tarkoituksena oli selvittää ohimolohkoepilepsian leikkaushoidon pitkäaikaisseurannan tuloksia kiinnittäen erityistä huomiota leikkauksen jälkeiseen kohtaustasapainoon ja kognitiiviseen suoriutumiseen. Tavoitteena oli myös tunnistaa tekijöitä, jotka ennustavat kirurgisen hoidon pitkäaikaistulosta.

Tutkimuksen osatyöt perustuvat Kuopion yliopistollisessa sairaalassa vuosina 1988–2006 leikattujen vaikeaa ohimolohkoepilepsiaa sairastavien aikuispotilaiden leikkausta edeltäviin tutkimuksiin, kirurgiseen hoitoon ja pitkäaikaisseurantaan. Selvitimme myös esiintyykö ohimolohkoepilepsiassa magneettikuvauksella (MK) havaittavia tilavuusmuutoksia ohimolohkon sisäosien aivokuorella.

Toispuoleista ohimolohkoepilepsiaa sairastavista potilaista 46% oli leikkauksen jälkeen pitkäaikaisseurannassa kohtauksettomia (seuranta 5,4 vuotta), 10% sai lyhyitä kohtauksen alkuoireita ilman tajunnan häiriötä (auroja) ja 15%:lla potilaista todettiin vain harvoin kohtauksia. Kohtaustilanne vuoden kuluttua leikkauksesta ennusti pitkäaikaistulosta. Vuonna 1993 käyttöön otetun erityisen MK-käytännön seurauksena aiempaa suuremmalla osalla potilaista voitiin havaita leikkausta edeltävässä MK:ssa paikallinen poikkeavuus. Tämä vaikutti myös leikkaushoidon tuloksiin (52% oli kohtauksettomia ja 7%:lla oli auroja). Kirurginen hoito oli tuloksekasta myös niillä potilailla, joilla aivojen MK:ssa ei havaittu paikallista häiriötä. Lisäksi palliatiiviset leikkaukset, joiden tavoitteena oli lievittää vaikeaa kohtaustilannetta, olivat hyödyllisiä. Hyvää kohtaustasapainoa leikkauksen jälkeen ennustivat hippokampuksen tilavuuden pieneneminen, muut toisen ohimolohkon rakenteelliset poikkeavuudet, pääasiallinen kohtaustyyppi ja varhainen sairastumisikä. Leikkauksen jälkeen potilailla todettiin heikkenemistä kielellisen materiaalin oppimisessa ja muistamisessa leikkauksen puolesta riippumatta. Leikkauksen kohdistuminen vasempaan ohimolohkoon ja hyvä muistisuoriutuminen ennen leikkausta ennustivat leikkauksen jälkeistä muistin heikkenemistä yksittäisillä potilailla. Entorhinaalisen ja temporopolaarisen aivokuoren tilavuus pieneni osalla toispuoleista ohimolohkoepilepsiaa sairastavista potilaista epilepsiapesäkkeen puolella.

Ohimolohkoepilepsian leikkaushoidon tulokset Kuopion Epilepsiakeskuksessa vastaavat kansainvälistä tasoa. Hyvä hoitotulos säilyy myös pitkäaikaisseurannassa. Osalla potilaista leikkaushoitoon liittyy kielellisen muistin heikkenemisen riski erityisesti vasemman ohimolohkon leikkauksen jälkeen. Tämän vuoksi tarvitaan parempia tapoja mahdollisen yksilöllisen muistin heikkenemisen ennustamiseen. Ohimolohkon sisäosien aivokuoren rakenteet vaurioituvat ohimolohkoepilepsiassa, mikä viittaa näiden rakenteiden muodostaman laajemman hermoverkon häiriöön sisemmän ohimolohkon epilepsiassa.

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This study was carried out in the Department of Neurology, Epilepsy Center/ NeuroCenter, Kuopio University Hospital in collaboration with the Departments of Neurosurgery, Clinical Radiology, Clinical Neurophysiology, Clinical Physiology and Nuclear medicine, as well as Pathology during the years 1999–2012.

Combining research and clinical work during this thesis project has been interesting, but also a challenge. Therefore, it is appropriate to acknowledge that this work would never have been possible without the contribution of a large network of people, to whom I want to express my sincere appreciation and respect.

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Leena Jutila

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IV Jutila L, Äikiä M, Immonen A, Mervaala E, Alafuzoff I and Kälviäinen R. Long-term memory performance after surgical treatment of unilateral temporal lobe epilepsy (TLE). *Submitted.*

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Abbreviations

AED	Antiepileptic drug
ATR	Anterior temporal lobe resection
CA	Cornu Ammonis
CI	Confidence interval
CT	Computer tomography
3D	Three-dimensional
D2/D3	Dopamine receptor subtypes
DNET	Dysembryoplastic neuroepithelial tumour
EC	Entorhinal cortex
99mTc-ECD	99mTc-ethyl cysteinate dimer
ECoG	Electrocorticography
EEG	Electroencephalography
FCD	Focal cortical dysplasia
[18F]FDG	[18F]-fluorodeoxyglucose
FLAIR	Fluid attenuated inversion recovery sequence
fMRI	Functional magnetic resonance imaging
FOV	Field of view
FSIQ	Full scale intelligence quotient
GABA	Gamma-aminobutyric acid
99mTc-HMPAO	99mTc-hexamethylpropyleneamine oxime
HRQOL	Health related quality of life
HS	Hippocampal sclerosis
5-HT1A	Subtype of 5-hydroxytryptamine receptor that binds serotonin
IED	Interictal epileptiform discharge
ILAE	International League Against Epilepsy
IPI	Initial precipitating incident

ISAS	Subtraction of ictal and interictal SPECT scans analysed by statistical parametric mapping
IQ	Intelligence quotient
MP-RAGE	Magnetisation prepared rapid acquisition gradient echo
MRI	Magnetic resonance imaging
MRI-negative	There is no focal structural abnormality in MRI
MRI-positive	There is a focal structural abnormality in MRI
MTLE	Mesial temporal lobe epilepsy
MTS	Mesial temporal sclerosis
[123I] NNC-13-8241	[123I]-labelled specific benzodiazepine receptor radioligand
NTLE	Neocortical temporal lobe epilepsy
OR	Odds ratio
PET	Positron emission tomography
PIQ	Performance intelligence quotient
PRh	Perirhinal cortex
QOL	Quality of life
RCI	Reliable change index
ROI	Region of interest
SAH	Selective amygdalohippocampectomy
SD	Standard deviation
SISCOM	Subtraction of ictal and interictal SPECT co-registered with MRI
SPECT	Single photon emission computed tomography
STATISCOM	Statistical ictal SPECT coregistered to MRI
SUDEP	Sudden unexpected death in epilepsy
T	Tesla
TE	Echo time
TLE	Temporal lobe epilepsy
TP	Temporopolar cortex
TR	Repetition time
VIQ	Verbal intelligence quotient
WMS	Wechsler Memory Scale

1 Introduction

Epilepsies are one of the most common chronic neurological diseases. They affect people of all ages, races, and socioeconomic backgrounds. According to the World Health Organisation, around 50 million people in the world have epilepsy and an estimated 2.4 million new cases occur each year globally. Epilepsy accounts for 0.5% of the global burden of disease, a measure that combines years of life lost due to premature mortality and time spent in states of less than full health.

The goal of antiepileptic treatment is complete long-term seizure control without significant adverse effects. The first line treatment of epilepsy is antiepileptic medication, which can be used either in monotherapy or as polytherapy. Despite the increase in the numbers of antiepileptic drugs (AED) available, approximately one-third of patients with epilepsy continue to have seizures (Brodie et al. 2012). Therefore also other treatment modalities such as epilepsy surgery, neurostimulation and ketogenic diet are needed.

In adults, the most common focal epilepsy is temporal lobe epilepsy (TLE). Studies assessing the prognosis of TLE indicate that from 20 to 40% (Semah et al. 1998, Stephen et al. 2001) of patients become seizure-free with the AEDs. In addition to refractory seizures, patients with chronic TLE are prone to significant cognitive and psychiatric comorbidity. Epilepsy is also associated with increased mortality, particularly due to status epilepticus and sudden unexpected death in epilepsy (SUDEP). SUDEP is rare in community based studies and among patients in remission. However, the risk increases with the severity of epilepsy, with the highest SUDEP rates being reported in candidates for epilepsy surgery (Dasheiff 1991). Refractory epilepsy may additionally lead to changes in the cardiovascular autonomic function (Mukherjee et al. 2009) and seizure related injuries (Friedman & Gilliam 2010, Kwon et al. 2010).

Epilepsy surgery is a treatment alternative for patients with drug-resistant focal epilepsy. The aim of epilepsy surgery is seizure freedom or at least a significant reduction in the number and severity of seizures, without significant morbidity or mortality. The secondary aims of surgery include reduction of antiepileptic medication and drug induced side effects, prevention of cognitive sequelae of severe epilepsy, and improvements in the quality of life (QOL). Successful epilepsy surgery may also reduce mortality when compared to nonsurgical patients (Bell et al. 2010) or to patients with persistent postoperative seizures (Sperling et al. 2005). In particular, surgery is an effective treatment for drug-resistant TLE (Wiebe et al. 2001).

Kuopio University Hospital serves as a national centre for epilepsy surgery with a catchment area of 4 million inhabitants. The systematic evaluation of patients for epilepsy surgery and surgical treatment began already in 1988. Especially during the early years, the work concentrated mainly on surgery for drug-resistant TLE. The main objective of this study was to evaluate the long-term seizure and cognitive outcome after surgical treatment of TLE in patients from a defined geographical area and to assess the possible predictive factors influencing the outcome.

2 Review of the Literature

2.1 DEFINITION AND CLASSIFICATION OF EPILEPSY

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Fisher et al. 2005). Epileptic seizures are diverse in their presentation, pathophysiology, syndromic relationship, prevalence and triggering factors. The clinical features of the seizures are determined by the normal functions of that area of the cortex in which the abnormal neuronal firing occurs. The signs and symptoms may include stereotypical alteration of consciousness, behaviour, emotion; and motor, sensory or autonomic functions.

Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological and social consequences of this disorder (Fisher et al. 2005). The definition of epilepsy requires the occurrence of at least one unprovoked epileptic seizure. Epilepsy is best described as a variety of disorders reflecting the underlying brain dysfunction that may result from many different causes.

The report of the International League Against Epilepsy (ILAE) Commission on Classification and Terminology (Berg et al. 2010) classifies epileptic seizures into three main types; focal, generalised or unknown. Generalised epileptic seizures originate at some point within bilaterally distributed networks and rapidly engage these networks which can include both cortical and subcortical structures. Focal epileptic seizures originate within networks limited to one hemisphere. They may be discretely localised or more widely distributed, and may also originate in the subcortical structures.

The same report also acknowledges three groups for causes of epilepsy (Berg et al. 2010). Genetic epilepsies are a direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder. Structural and/or metabolic causes include e.g. structural lesions that can be either acquired or of genetic origin. The unknown cause of epilepsy means that the nature of the underlying defect has not yet been identified. It may be caused by a genetic defect or it may be the consequence of some separate unrecognised disorder. It is recommended that the unknown aetiology of epilepsy should be regularly re-evaluated in the clinic.

The epilepsy syndrome (Berg et al. 2010) is a complex of clinical features, signs and symptoms that together define a distinctive, recognizable clinical disorder. These may include the type of seizures, age of onset, precipitating factors, aetiology, or prognosis. However, certain syndromes may also have multiple different causes or they may differ in prognosis. The identification of a specific epileptic syndrome helps in diagnosis and management of the individual patient. In adults, the most common epilepsy syndrome is TLE.

2.2 EPIDEMIOLOGY OF EPILEPSY

In the classical study from Rochester (Minnesota, USA), the prevalence of active epilepsy was estimated at 2.7–6.8 per 1000 (Hauser et al. 1991). In Europe, population-based epidemiological studies on epilepsy are available mainly from the UK and the Nordic, Baltic and Western Mediterranean countries (Forsgren et al. 2005). According to a systematic review, the age specific prevalence of active epilepsy in European children and

adolescents ranges from 4.5 to 5.0 per 1000, in adults 6 per 1000, and in the elderly it is estimated as 7 per 1000 (Forsgren et al. 2005). In individual studies from the Nordic countries and Estonia, the prevalence of active epilepsy in adults has varied between 5.3 and 6.3 per 1000 (Keränen et al. 1989, Forsgren 1992, Oun et al. 2003b) with 56–83% of patients having focal seizures or focal epilepsy (Keränen et al. 1989, Forsgren 1992, Oun et al. 2003b).

In Rochester (Minnesota, USA) the mean annual incidence of epilepsy was assessed as 44 per 100 000 (Hauser et al. 1993). In the Nordic countries and Estonia, the mean annual incidence rates of unprovoked seizures and epilepsy in adults range between 24 and 56 per 100 000 (Keränen et al. 1989, Forsgren et al. 1996, Oun et al. 2003a) with the highest age specific incidence rates being observed in the elderly. Accordingly, the age specific incidence of epilepsy in European countries is 70 per 100 000 in children and adolescents, 30 per 100 000 in adults and 100 per 100 000 in the elderly (Forsgren et al. 2005).

2.3 TEMPORAL LOBE STRUCTURES

The human medial temporal lobe is composed of the hippocampus, the amygdala, and the surrounding cortex, including the entorhinal, perirhinal, and parahippocampal cortices.

The hippocampus is a prominent bulging structure in the floor of the temporal horn of the lateral ventricle. It consists of two interlinked C-shaped structures, the hippocampus proper (Cornu Ammonis, CA) and the dentate gyrus. Hippocampus has a laminar structure and the pyramidal cell layer of the various hippocampal subfields is microscopically differentiated into distinct CA areas. The classification system of different hippocampal subregions that is predominantly used in human epilepsy research describes four sectors from CA1 to CA4 (Lorente de No 1933).

The majority of the cortical inputs to the hippocampus originate in layers II and III of the entorhinal cortex (EC). The most important excitatory glutaminergic pathway (i.e. the polysynaptic intrahippocampal pathway) to the hippocampus originates from layer II of the EC and projects to the granule cells of the dentate gyrus (Duvernoy 2005). It then continues via the axons of granule cells (i.e. mossy fibers) to CA4 and CA3 pyramidal cells, via their Schaffer collateral axons to CA1 and subicular neurons, after which the main hippocampal output fibers pass through the alveus (Duvernoy 2005, Malmgren & Thom 2012). The direct hippocampal pathway originates from layer III of the EC and projects directly to the pyramidal neurons of the CA1 subfield (Duvernoy 2005). Figure 1 displays the cortical connections and inter-connectivity of different medial temporal lobe structures.

The amygdala or rather the "amygdala complex" is located in the medial temporal lobe rostral to the hippocampus. It is composed of more than 10 nuclei and their subdivisions, each of which has a distinct cytoarchitectonic, chemoarchitectonic, and connectional characteristics. There are plentiful efferent and afferent connections between the amygdala, the hippocampus, and the surrounding medial temporal cortex (Pitkänen et al. 2000). The amygdala also receives numerous projections from all sensory modalities.

The parahippocampal region comprises of several cortical regions grouped together on the basis of their laminar organisation and connections (Scharfman et al. 2000). These include the entorhinal, perirhinal and posterior parahippocampal cortices. The EC lies in the anterior parahippocampal gyrus and comprises Brodmann's area 28 (Amaral et al. 1987). Functionally, it serves as an interface between the hippocampus and the surrounding unimodal and multimodal sensory cortices (Insausti et al. 1987). The perirhinal cortex (PRh) is located along the collateral sulcus in the ventromedial aspect of the temporal lobe. It borders the EC laterally and comprises Brodmann's areas 35 and 36 (Insausti et al. 1987, Ding & Van Hoesen 2010). The rostromedial continuation of area 36 of the PRh (area 36p) forms the temporopolar cortex (TP) as defined by Insausti and colleagues (Insausti et al. 1987). The PRh is the major input area to the EC and has many connections with the unimodal and polymodal cortical association areas as well as with the amygdala (Suzuki &

Amaral 1994a, Suzuki & Amaral 1994b). It has been proposed that the anterior parahippocampal structures may be important in spatial memory (Bohbot et al. 1998, O'Brien et al. 2003), recognition memory (Guedj et al. 2010), verbal episodic memory (O'Brien et al. 2003) and verbal learning (Lillywhite et al. 2007, Weintrob et al. 2007). In patients with mesial temporal lobe epilepsy (MTLE), EC and PRh may also contribute to individual's scores in tests of immediate and delayed verbal memory, immediate visual memory and verbal fluency (Alessio et al. 2006, Bonilha et al. 2007a).

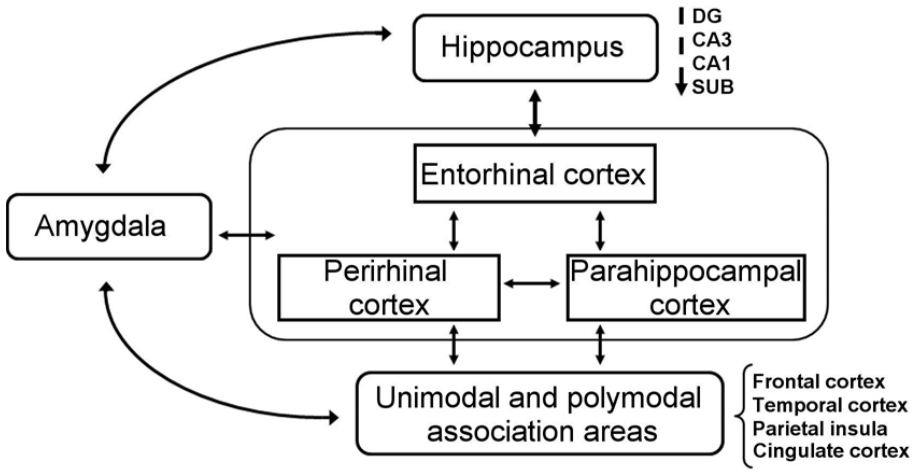

Figure 1. Schematic view of the inter-connectivity and cortical connections of different medial temporal lobe structures. All connections are reciprocal. Abbreviations: DG, dentate gyrus; CA, Cornu Ammonis; SUB, subicular complex. Adapted from Suzuki, 1996; and Simons & Spiers, 2003.

2.4 TEMPORAL LOBE PATHOLOGY

The most common pathological finding in MTLE is hippocampal sclerosis (HS). It was originally described in the late 19th century in autopsies of epilepsy patients. In a series of 956 patients obtained from two European epilepsy centers, HS was identified in 64% of patients with TLE (Blumcke et al. 2002). The classical HS (or mesial temporal sclerosis, MTS, type 1a) consists of neuronal loss and gliosis in the CA1 and CA4 subfields, together with variable degrees of neuronal loss in the CA3 subfield. Severe HS (or MTS type 1b) refers to extensive neuronal loss and gliosis in all hippocampal subfields. Two atypical variants have been characterized since they exhibit severe neuronal loss and gliosis restricted to subfield CA1 (CA1 hippocampal sclerosis or MTS type 2) or to CA4 (endfolium sclerosis or MTS type 3) (Blumcke et al. 2007, Blumcke 2011, Malmgren & Thom 2012). Granule cell dispersion in the dentate gyrus is found in 40–50% of patients with HS (Wieser & ILAE Commission on Neurosurgery of Epilepsy 2004, Blumcke et al. 2009). Other HS associated pathological features include mossy fiber sprouting of granule cells (El Bahh et al. 1999, Proper et al. 2000) and changes in the hippocampal interneurons (Magloczky 2010). There may also be variability in the HS along the longitudinal axis of the hippocampus (Thom et al. 2012).

The term "Dual pathology" has been used variably in the literature. It can either refer to those cases in which HS is associated with another temporal or extratemporal epileptogenic

abnormality (Malmgren & Thom 2012) or more strictly to the presence of HS associated with an another lesion (i.e. tumour or vascular lesion) in the ipsilateral temporal lobe (Blumcke 2011). HS in combination with temporal focal cortical dysplasia (FCD) can also be classified as a FCD type IIIa according to the new classification of FCDs (Blumcke et al. 2011).

In addition to HS, MTLE can be caused by other mesial pathologies such as cavernomas, benign tumours such as dysembryoplastic neuroepithelial tumour (DNET) or ganglioglioma, low-grade tumours of glial origin and gliosis. Microdysgenesis, a microscopic cortical malformation, is also known to involve the temporal lobe in some patients with MTLE, but the incidence of this abnormality, its relationship to HS, as well as its relationship to epileptogenesis or postoperative outcome remain poorly understood (Thom et al. 2001).

Observations in animal models have demonstrated neuronal loss, particularly in layer III of the EC (Du et al. 1995, Schwarcz et al. 2000). A similar finding has been confirmed in patients with TLE (Du et al. 1993). Later studies have indicated a more variable pattern of neuronal loss and gliosis in the EC. For example Yilmazer-Hanke et al. (2000) found cell loss and gliosis in all layers of the EC but with considerable interindividual variability. In another study (Dawodu & Thom 2005), gliosis was a common finding in the EC of patients with TLE, but only the most severe gliosis was associated with lower neuronal densities in the EC. There are no systematic studies of the neuropathology of the human PRh in TLE, probably due to the surgical techniques used.

2.5 TEMPORAL LOBE EPILEPSY (TLE)

2.5.1 Mesial temporal lobe epilepsy (MTLE)

MTLE is the most common focal epilepsy in adults and it is often associated with HS. In MTLE, the seizures begin from the mesial temporal lobe structures, especially from the hippocampus.

Retrospective studies from surgical series have demonstrated that in particular, those patients with MTLE and HS exhibit a high incidence of initial precipitating incidents (IPI) (Wieser & ILAE Commission on Neurosurgery of Epilepsy 2004). These include complex febrile seizures, trauma, hypoxia and intracranial infections. However, no prospective studies have demonstrated the relation of an IPI to the development of MTLE and HS. Also in a Finnish prospective study, 24 children with a prolonged first febrile seizure and 32 matched controls with a single simple febrile seizure (selected from 329 febrile seizure patients) were followed up for a mean of 12.3 years. During this long-term follow-up period, none of the patients developed HS as defined by magnetic resonance imaging (MRI) volumetry (Tarkka et al., 2003). In addition to IPI, there have been other possible theories postulated to explain the pathogenesis of MTLE e.g. glutamate neurotoxicity, mitochondrial dysfunction, immune factors, developmental factors and genetic predisposition (Wieser & ILAE Commission on Neurosurgery of Epilepsy 2004). It is possible that several different acquired factors are needed before the patient will develope MTLE.

The typical clinical features of mesial temporal seizures have been summarized by the ILAE Commission on Neurosurgery of Epilepsy (Wieser & ILAE Commission on Neurosurgery of Epilepsy 2004). Habitual seizures begin in the majority of patients with MTLE and HS between 4–16 years of age, often after a latent period. The typical clinical symptoms of mesial temporal lobe seizures include aura, behavioural arrest, alteration of consciousness, amnesia, and oroalimentary automatisms. The typical auras consist of an epigastric sensation, a non-specific aura that is difficult to describe, fear or anxiety, autonomic symptoms, an illusion of familiarity or strangeness including déjà vu, and a olfactory–gustarory aura. Auras can occur in isolation or as an initial symptom of a more widespread seizure. The positive motor symptoms are associated with seizure spread to extratemporal brain areas and can help as lateralising signs (contralateral facial and

brachial clonic or tonic motor symptoms, clonic version of the head and eyes, dystonic posturing of the contralateral upper extremity, and the figure of four sign). Generalisation into a bilateral convulsive seizure can also occur in some of the patients, but this is relatively infrequent. Postictal deficits most frequently affect cognition, memory, mood and language. Atypical extratemporal clinical features can also occur (Borelli et al. 2008, Staack et al. 2011) and they should not exclude patients from undergoing a thorough preoperative evaluation. In a minority of patients with MTLE, an independent bitemporal seizure onset may be observed (Holmes et al. 2003, Boling et al. 2009, Cukiert et al. 2009b).

2.5.2 Neocortical temporal lobe epilepsy (NTLE)

Neocortical temporal lobe epilepsy (NTLE) probably accounts for at least 10% of temporal lobe epilepsies (Schramm et al. 2001). It is a more heterogeneous disorder when compared to MTLE as the seizures may arise from more widespread and variable neocortical areas. The onset of NTLE typically occurs after the age of 16 and the patients do not seem to have any particular early risk factors (Foldvary et al. 1997, Gil-Nagel & Risinger 1997).

The clinical symptomatology of seizures arising from the NTLE often includes initial auditory, visual or vestibular hallucinations or illusions, or experiential auras (Gil-Nagel & Risinger 1997, Maillard et al. 2004). The initial loss of contact and early motor involvement of upper extremity reflecting the spread of seizure activity to the frontoparietal convexity are the typical early ictal signs (Gil-Nagel & Risinger 1997, Maillard et al. 2004). Many of the features commonly seen in MTLE, including automatisms, contralateral dystonia, searching head movements, body shifting, hyperventilation, and postictal cough or sigh are less frequently seen or lacking in NTLE seizures (Foldvary et al. 1997). However, if present, a dystonic posturing of the contralateral upper extremity may also occur earlier in NTLE when compared to MTLE (Holl et al. 2005). The seizures tend to be shorter in duration and generalisation into a bilateral convulsive seizure occurs more frequently than in MTLE (Foldvary et al. 1997, Maillard et al. 2004).

The aetiology of NTLE is thought to be related to various different pathological substrates including malformations of cortical development, cavernomas and other vascular lesions, benign tumours (DNET or ganglioglioma), as well as low-grade tumours of glial origin (pilocytic astrocytoma, grade I–II astrocytoma or oligodendroglioma) (Schramm et al. 2001).

NTLE is a potentially surgically remediable epilepsy syndrome (O'Brien et al. 1996, Schramm et al. 2001, Janszky et al. 2006) and lesional cases with complete removal have especially good postoperative outcomes (O'Brien et al. 1996). FCDs are associated with a poorer outcome when compared to tumours (Janszky et al. 2006). Nonlesional patients require intracranial recordings in order to delineate the epileptogenic zone and to exclude seizure onset from adjacent neocortical regions.

2.6 PROGNOSIS OF TLE

Our understanding of the natural prognosis of TLE is mainly based on the information acquired from large epidemiological studies of patients with focal epilepsies, hospital-based observational studies of TLE, and information gathered from tertiary epilepsy surgery centres.

In the epidemiological studies, approximately one-third of patients with focal epilepsy have intractable seizures. A hospital-based cohort study from France demonstrated that TLE was the most refractory focal epilepsy with only 20% of the patients remaining seizure-free. In addition, only 11% of patients with HS were seizure-free (Semah et al. 1998). In a smaller but more recent study, 21% of TLE patients remained seizure-free for at least two years (Pittau et al. 2009). In two hospital-based studies assessing the prognosis of TLE associated with HS 23–25% of patients were completely controlled with AED therapy (Kim

et al. 1999, Kumlien et al. 2002). Stephen et al. (2001) reported that 42% of patients with HS were seizure-free for at least one year.

The possible prognostic factors associated with poor seizure control in TLE include a history of febrile seizures, early age of seizure onset, HS, interictal epileptiform discharges (IED), response to the first AED, mental retardation and female sex (Kim et al. 1999, Dlugos et al. 2001, Pittau et al. 2009, Varoglu et al. 2009). However, in patients with MTLE and HS, the volume of the atrophic hippocampus does not differentiate patients with good or poor seizure outcome and detection of HS does not always indicate intractability (Andrade-Valenca et al. 2003, Briellmann et al. 2007). In studies using T2-relaxometry or proton magnetic spectroscopy, refractory TLE has also been associated with white matter changes and metabolic disturbances, e.g. reduced concentration of N-acetyl aspartate, in the ipsilateral temporal lobe (Briellmann et al. 2007).

Spooner et al. (2006) followed prospectively a community-based cohort of 77 children with new-onset TLE for up to 14 years. Altogether, 25% of the patients were seizure-free and off treatment, 56% were not seizure-free and had ongoing seizures or had undergone epilepsy surgery. Detection of a lesion by MRI was a strong predictor of intractable seizures and the potential need for epilepsy surgery, i.e. none of the children with lesions observed by MRI were seizure-free. In contrast, infantile onset of epilepsy, family history of seizures, initial seizure frequency, presence or absence of IPI, and early seizure remission were not predictive of seizure outcome.

There is both clinical and experimental evidence that TLE may be a progressive neurological disorder that requires early and effective treatment (Pitkänen & Sutula 2002). The transition from the latent period to onset of the seizure disorder represents a disease process. Persisting seizures (Salmenperä et al. 2001, Coan et al. 2009) and longer duration of TLE (Bonilha et al. 2006, Bernhardt et al. 2009) have been associated with neuronal damage. Unfortunately, the duration of epilepsy in patients undergoing surgical treatment is often measured in decades, not in years. This prolonged period of intractability may be associated with progressive psychosocial problems, cognitive impairment, as well as adverse effects of AEDs. Therefore, the patients should be evaluated for resective surgical treatment as soon as drug-resistancy (Kwan et al. 2010) is observed. In particular, in TLE associated with HS or some other MRI lesion, early surgery should be considered (Semah et al. 1998, Janszky et al. 2005, Spooner et al. 2006).

2.7 HISTORY OF EPILEPSY SURGERY

The history of epilepsy surgery probably began in the 19th century, when Benjamin Winslow Dudley (Dudley 1826) in the USA and Victor Horsley (Horsley 1886) in the UK operated the first patients with posttraumatic epilepsy. Thereafter, there was significant interest in surgical treatment of possible epileptogenic lesions (Feindel et al. 2009), probably due to the fact that no effective AEDs were available before the introduction of phenobarbital in 1912. At first surgery was targeted mainly to the convexity of the cerebral hemispheres and most often towards traumatic scars and tumours. After the first human electroencephalography (EEG) was introduced (Berger 1929), the understanding and diagnostics of epilepsy became revolutionised and the temporal lobe was identified as an important target for surgical treatment of focal drug-resistant epilepsy.

The pioneering works of Jasper, Penfield and Flanigin (Penfield & Flanigin 1950) in Montreal; Bailey and Gibbs (Bailey & Gibbs 1951) in Chicago; and Falconer and Serafetinides (Falconer & Serafetinides 1963) in London initiated the period of modern TLE surgery. Murray Falconer also described the role of HS and focal lesions in the pathogenesis of MTLE (Falconer & Cavanagh 1959, Falconer & Taylor 1968). By the late 20th century, the progress of epilepsy surgery had continued and it was facilitated by the development of computerised neuroimaging techniques, particularly MRI. Researchers also started to classify the seizure outcome and to evaluate the pooled outcome of TLE surgery in larger

international series in order to demonstrate the efficacy and safety of surgical treatment in TLE (Engel 1993, Feindel et al. 2009).

In Finland, the history of epilepsy surgery began in Oulu University Hospital, where the first patients with drug-resistant epilepsy were operated between 1979 and 1988 by two neurosurgeons, Stig Nyström and Esa Heikkinen. The first comprehensive epilepsy surgery center including a multidisciplinary team was initiated at Kuopio University Hospital in 1988 under the leadership of Professor Matti Vapalahti. The second Finnish multidisciplinary epilepsy surgery center for pediatric patients was established at Helsinki University Hospital in 1991 by pediatric neurologist Marja-Liisa Granström and neurosurgeon Göran Blomstedt. Adult patients with epilepsy have been operated in Helsinki since 1998. Currently the Finnish government has issued a decree stating that preoperative invasive epilepsy recordings and epilepsy surgery should be performed only in these two specialised centers at Helsinki and Kuopio University Hospitals.

2.8 CANDIDACY FOR EPILEPSY SURGERY

2.8.1 Patient selection

Epilepsy surgery represents a treatment alternative for patients with drug-resistant focal epilepsy. Currently, drug-resistant epilepsy is defined as a failure of adequate trials of two tolerated, appropriately chosen and used AED schedules to achieve sustained seizure freedom (Kwan et al. 2010). Drug-resistancy may develop early in the course of the epilepsy, or the patient may have a fluctuating course of the disease with a delayed onset of prolonged drug-refractoriness (Berg et al. 2003, Berg et al. 2006b, Brodie et al. 2012). It is important to identify those patients with drug-resistant epilepsy as early as possible.

The indications of epilepsy surgery have changed over time and the spectrum of patients who might benefit from surgery has gradually expanded. The absence of a lesion in MRI, older age, lower intelligence quotient (IQ) or chronic psychiatric diseases should not exclude patients from the presurgical evaluation.

Some reports have suggested that seizure outcome may be more favourable in younger patients in comparison to older ones (over 50 years of age) (Sirven et al. 2000, Srikijvilaikul et al. 2011). However, several studies have demonstrated equally good postoperative seizure outcomes in younger and older patients (Boling et al. 2001, Grivas et al. 2006, Acosta et al. 2008, Murphy et al. 2010). In older patients, the risks for surgical and neurological complications may be somewhat higher than in series of younger patients (Grivas et al. 2006, Srikijvilaikul et al. 2011). Cardiorespiratory diseases, coagulopathies and other systemic diseases may require further preoperative consultation, particularly in older patients, and these may sometimes preclude surgery.

Patients with low IQ are under-represented in surgical series probably for several reasons (Davies et al. 2009). Previously the benefits of TLE surgery have been questioned in patients with a low IQ since a poor cognitive level has been associated with a more widespread disturbance of cerebral functioning and the increased risk of unfavourable postoperative outcome (Malmgren et al. 2008). However, also patients with low IQ can benefit from epilepsy surgery (Bjørnaes et al. 2004, Malmgren et al. 2008, Davies et al. 2009), especially if the lesional aetiology of epilepsy is identified (Malmgren et al. 2008). Therefore patients with impaired general intellectual ability should not be excluded from resective epilepsy surgery, although this is an important prognostic factor that needs to be discussed preoperatively with the patient.

For patients with chronic psychiatric diseases, preoperative assessment with a psychiatrist familiar with epilepsy surgery is recommended. However, patients with an active and/or untreated psychiatric disorder (psychosis, depression or a significant personality disorder) should be excluded from surgery because of the inability of the patient to cooperate in the evaluation and the possibility of difficulties in post-operative recuperation (Matsuura 2000).

In general epilepsy care should take into account individual needs and preferences of the patient. This is particularly important when any invasive treatment including epilepsy surgery is being considered. Although the primary goal of epilepsy surgery should always be seizure freedom, it has to be accepted that curative surgery is not possible in every patient. Therefore, significant seizure reduction or elimination of the most disabling seizure type may also represent a valid goal for palliative surgery (Perry & Duchowny 2011). Patients who have been referred to presurgical evaluation should have the opportunity to make informed decisions about their treatment in partnership with the epilepsy surgery team. They should be advised about their probability of being seizure-free after surgery, and the risks of surgery to ensure realistic expectations of the outcome. The individual characteristics of the patient including age, cognition, or culture must be taken into account during preoperative counseling.

2.8.2 Need for epilepsy surgery

About 25% of patients with newly diagnosed epilepsy will not become seizure-free with medication (Brodie et al. 2012). According to the treatment guidelines, patients with refractory epilepsy willing to undergo presurgical evaluation should be referred to specialised multidisciplinary epilepsy centres for a comprehensive presurgical evaluation (European Federation of Neurological Societies Task Force 2000, Engel et al. 2003). However, it is important to acknowledge that considerably more patients need to be evaluated for surgery that will be eventually operated. It has been estimated that from 30 to 50% of patients who are evaluated specifically for epilepsy surgery do not proceed to resective epilepsy surgery (Duncan 2011a). In Kuopio University Hospital Epilepsy Center only one out of every five referred patients with intractable epilepsy will proceed to surgery.

In a prospective community based cohort of children with newly diagnosed epilepsy, 5% of the imaged cohort and 8% of non-idiopathic epilepsy patients had undergone surgery to treat their epilepsy or a tumour during follow-up (Berg et al. 2009). Using an annual incidence rate of 500 per 1 000 000, the authors estimated that there will be approximately 127 per 1 000 000 new cases of childhood onset pharmacoresistant epilepsy per year and 52 per 1 000 000 children will undergo comprehensive epilepsy evaluations. A total of 21 per 1 000 000 from this age group alone will undergo surgical procedures for the treatment of seizures and 6 per 1 000 000 for lesion resection only (Berg et al. 2009). In another study, the population-based use rate of anterior temporal resection (ATR) alone was 1.2 per 100 000 person-years of follow-up during a 17-year study period (Van Gompel et al. 2012). However, population-based use rates of the procedure declined significantly, from 1.9 (between 1993 and 2000) to 0.7 per 100 000 person-years (between 2001 and 2009) for some unknown reason.

Surgical treatment of focal epilepsy is currently still under-utilised across the world. The delay to referral is long (Haneef et al. 2010) and the number of operated patients has not increased despite the current evidence based recommendations for referral (Englot et al. 2012, Schiltz et al. 2013). Significant differences in the availability of surgical treatment due to race and insurance coverage have also been observed in some countries (Englot et al. 2012). It has been estimated that in Finland at least 90 operations should be performed each year (3 % of newly diagnosed patients; 1.7 operations per 100 000 inhabitants). However, between 1991 and 2005 altogether only 0.57 operations/ 100 000 were performed (Immonen et al. 2008) highlighting the under-utilisation of epilepsy surgery.

2.9 PREOPERATIVE EVALUATION

2.9.1 General principles of preoperative evaluation

The presurgical evaluation in patients with intractable epilepsy aims at identification of the cortical areas indispensable for generating seizures i.e. the epileptogenic zone (Rosenow & Luders 2001). A complete removal or disconnection of the epileptogenic zone results in seizure freedom (Figure 2).

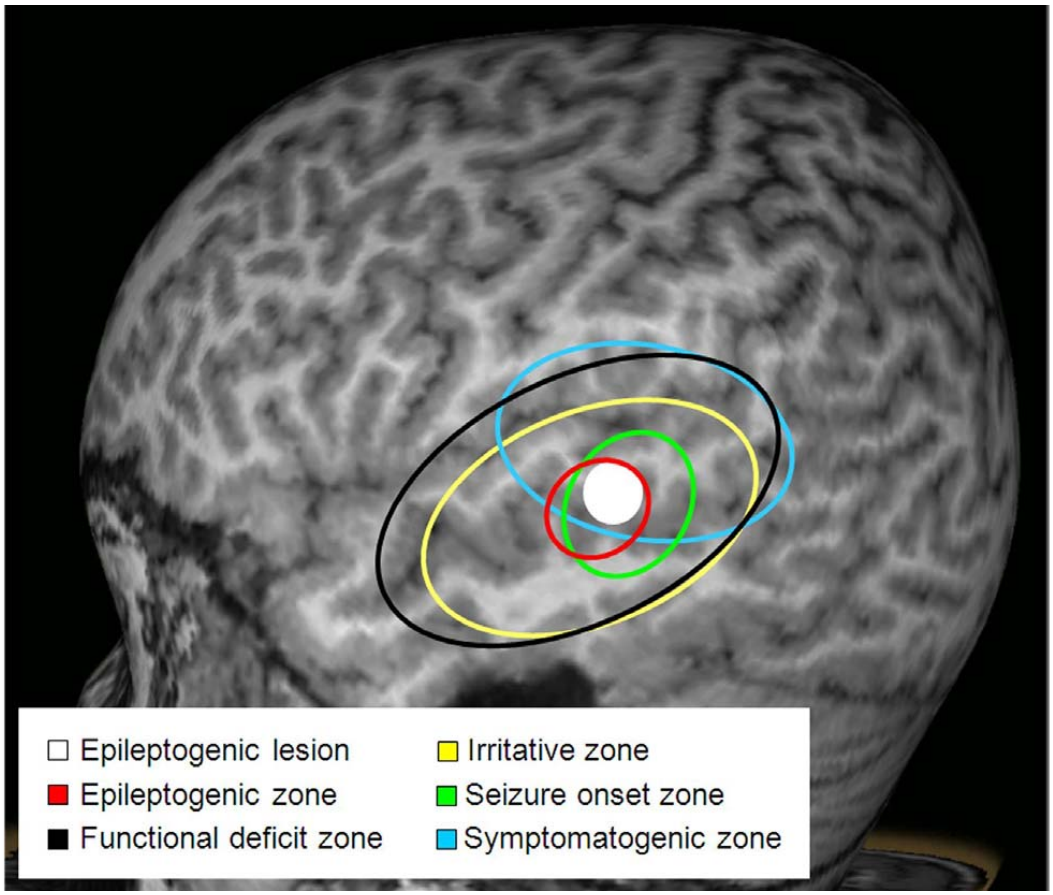

Figure 2. A schematic view of six cortical zones that have been defined in the presurgical evaluation of candidates for epilepsy surgery. Modified from Rosenow and Luders (2001).

Seizure semiology reflects the symptomatogenic zone, which is the cortical area that generates the typical ictal symptoms when it is electrically activated during a seizure (Rosenow & Luders 2001). In particular, evaluation of the initial symptoms and objective signs of the seizure are important in localisation of the symptomatogenic zone. However, the epileptogenic zone and the symptomatogenic zone do not necessarily overlap as the cortex includes areas that are silent when they are electrically stimulated and the semiology also reflects the spread of the seizure. Electrophysiological studies provide information on the irritative zone, which is the area of cortex capable of generating interictal spikes measured by EEG or magnetoencephalography (Rosenow & Luders 2001). The irritative zone is usually larger than the epileptogenic zone. The seizure onset zone is the cortical

region from which the onset of a seizure during ictal video-EEG recording can be demonstrated (Rosenow & Luders 2001). Even the seizure onset and the epileptogenic zones do not necessarily overlap with the epileptogenic zone perhaps being more widespread or less extensive. An epileptogenic lesion is a structural lesion visible in the MRI that is responsible for the generation of seizures (Rosenow & Luders 2001). Usually incomplete resection of an epileptogenic lesion leads to a poor postoperative outcome. Finally, the functional deficit zone is the area that is functionally abnormal during the interictal period (Rosenow & Luders 2001). This can be investigated with routine neurological physical examination, neuropsychological evaluation, the Wada test, psychiatric assessment, EEG or molecular imaging. The functional deficit zone is usually substantially larger than the epileptogenic zone, but it provides additional supportive information about the epileptogenic zone.

The presurgical evaluation generally includes careful analyses of clinical history and the evolution of epilepsy, general and neurological physical examination, analysis of detailed seizure semiology, noninvasive electrophysiological studies (routine interictal EEG and long-term video-EEG), structural neuroimaging, as well as neuropsychological and psychiatric assessments. In patients with normal MRI or discordant preliminary data, further information of the epileptogenic cortex may be acquired with molecular imaging, functional imaging or magnetoencephalography. Finally, in selected patients, invasive intracranial EEG may be necessary to delineate the epileptogenic zone and its relationship to the eloquent cortex (Duncan 2010).

2.9.2 Magnetic resonance imaging, MRI

2.9.2.1 Structural imaging

The main purpose of conducting MRI in patients with epilepsy is to identify the underlying structural abnormalities. These abnormalities may require specific treatment, aid in aetiologic or syndromic diagnosis, or contribute to the localisation of the epileptic focus during the presurgical evaluation. High resolution MRI [i.e. from 1.5 Tesla (T) to 3T or more] in patients with epilepsy should be performed according to a specific imaging protocol, which takes into consideration the pathological abnormalities commonly seen in drug-resistant patients e.g. HS, malformations of cortical development, neoplasms, vascular abnormalities, gliosis and other miscellaneous abnormalities (Vattipally & Bronen 2004, Duncan 2010).

Recommendations for specific MRI protocols have been proposed to enhance the yield of MRI in patients with refractory epilepsy (Commission on Neuroimaging of the International League Against Epilepsy 1998, Vattipally & Bronen 2004, Duncan 2010). The recommended sequences should include a volumetric T1-weighted sequence, a gradient-echo sequence; and proton density, T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences in oblique coronal and axial planes. Coronal sequences should be oriented perpendicular to the long axis of the hippocampus. The routine use of intravenous contrasts (gadolinium) is not recommended.

MRI is highly sensitive and specific in detecting HS, which is the most frequent structural abnormality observed in TLE (Jackson et al. 1993, Lehericy et al. 1997, Watson et al. 1997). The typical features of HS revealed by MRI are hippocampal atrophy, increased signal in T2-weighted images, loss of internal structure and decreased signal in T1-weighted images (Jackson et al. 1993, Wieser & ILAE Commission on Neurosurgery of Epilepsy 2004) (Figure 3). The typical extrahippocampal abnormalities associated with HS are atrophy and signal alterations of the ipsilateral amygdala, temporal neocortex, temporal lobe white matter, fornix, mamillary body, insula, thalamus, basal frontal cortex and rarely the entire ipsilateral hemisphere (Wieser & ILAE Commission on Neurosurgery of Epilepsy 2004). Atrophy and signal alterations can also be found in the contralateral hippocampus (Wieser & ILAE Commission on Neurosurgery of Epilepsy 2004).

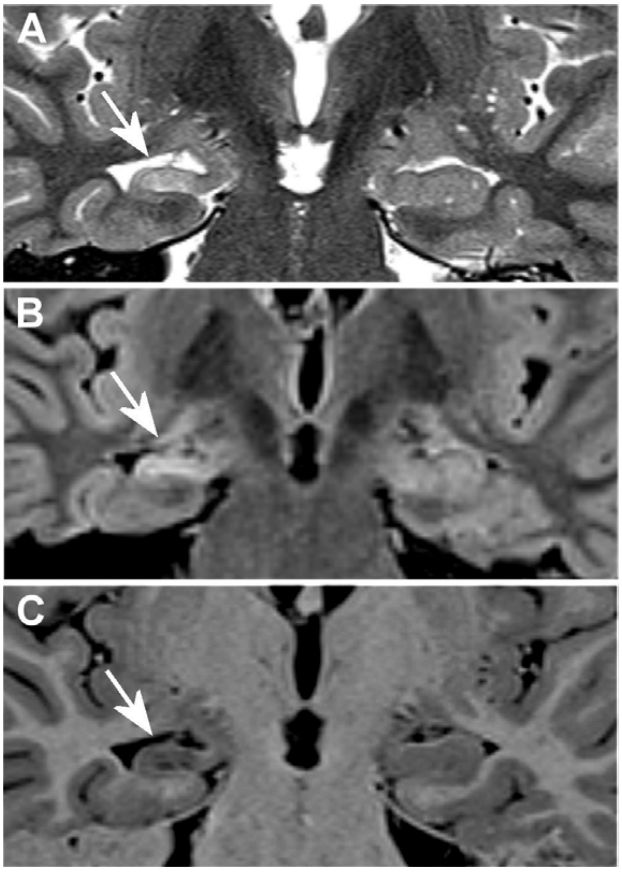

Figure 3. Oblique coronal three Tesla MRI images showing hippocampal sclerosis in the right temporal lobe. Increased signal intensity is observed in T2-weighted (A) and FLAIR-sequences (B), whereas reduced volume is best observed in T1-weighted images (C).

Twenty percent of patients with refractory focal epilepsy have an unknown aetiology despite extensive investigations, including optimal MRI (Duncan 2010). These patients, including TLE patients with no evident lesion in the MRI, remain a challenging subgroup for epilepsy surgery. Invasive preoperative investigations are often needed in preoperative evaluation and the surgical outcome may be less beneficial when compared to patients with unitemporal MRI abnormalities. However, by using a modern 3T MRI scanner and sequences focal abnormalities, mainly malformations of cortical development, can be identified in 20% of patients with previously unremarkable MRI (Strandberg et al. 2008). In the diagnosis of HS, no substantial difference has been noted between 1.5T and 3T MRI, although hippocampal border definition is claimed to be more straightforward and easier with 3T because of the improved signal-to-noise characteristics (Jeukens et al. 2009, Hashiguchi et al. 2010). However, recently a high-field MRI with 4T or 7T scanner has been able to demonstrate subregional hippocampal abnormalities on the epileptogenic side in patients with TLE (Mueller et al. 2009, Breyer et al. 2010, Henry et al. 2011).

Volumetric MRI has become a widely used tool for the quantitative identification of structural temporal lobe damage in TLE during the last twenty years (Jack et al. 1988, Watson et al. 1992, Insausti et al. 1998). Soon after the introduction of the method of hippocampal volumetry, it was observed that hippocampal atrophy was a powerful indicator of a mesiotemporal seizure onset in EEG (Spencer et al. 1993, Adam et al. 1994, Baulac et al. 1994). However, HS in MRI can also be a falsely localising sign, and MRI should always be evaluated together with all available preoperative clinical data (Spencer et al. 1993). Hippocampal volumetry was also reported to be highly sensitive in lateralising the side of seizure focus (Jack et al. 1990, Cascino et al. 1991, Jack et al. 1992, Cendes et al. 1993b) in patients with TLE. Additionally, hippocampal volumetry has been found to be an

important preoperative prognostic tool for surgical treatment and it also provided information of the expected surgical outcome (Jack et al. 1992, Arruda et al. 1996) in accordance with qualitative MRI studies (Kuzniecky et al. 1993, Garcia et al. 1994). Finally, hippocampal volumetric measurements displayed a correlation with histopathological cell loss of the hippocampus (Bronen et al. 1991, Cascino et al. 1991, Lencz et al. 1992), history of prolonged febrile convulsions in early childhood (Cendes et al. 1993a, Salmenperä et al. 2001), preoperative memory performance (Lencz et al. 1992), memory asymmetry in the Wada test (Loring et al. 1993), postoperative change in memory performance (Trenerry et al. 1993) and number of seizures during the lifetime (Van Paesschen et al. 1997, Salmenperä et al. 2001).

Saukkonen et al. (1994) first reported that the rostral portion of the ipsilateral parahippocampal gyrus (which is mostly composed of the EC) was 12% smaller in patients with TLE of unknown aetiology when they were compared to controls. Subsequent volumetric studies have shown that patients with TLE may exhibit an EC volume reduction either ipsilateral to the seizure focus (Bernasconi et al. 2003a, Bernasconi et al. 2003b, Bonilha et al. 2003, Bartolomei et al. 2005, Meade et al. 2008) or bilaterally (Bernasconi et al. 1999, Meade et al. 2008). In the cases where there is a bilateral entorhinal volume reduction, it may be greater ipsilaterally (Bernasconi et al. 1999). In the early study of Salmenperä et al. (2000b) the authors found no EC volume reduction at the group level, but individual analyses revealed > 25% volume loss in 31% of patients with TLE and in 64% of patients, this was ipsilateral. There was also a correlation between the hippocampal and the entorhinal volumes, but later studies have not been able to confirm this association (Bonilha et al. 2003, Meade et al. 2008) and EC volume loss has been found also in patients with normal hippocampal volumes (Bernasconi et al. 2001). The duration of epilepsy has been related to the degree of entorhinal atrophy in two different studies (Salmenperä et al. 2000b, Bernasconi et al. 2005). There is also evidence that the degree of EC atrophy may correlate with the involvement of the EC in the electrical seizure onset (Bartolomei et al. 2005). With regards to epilepsy surgery, EC atrophy has correctly lateralised the seizure focus in 64% TLE patients with normal hippocampal volumes (Bernasconi et al. 2001). It is still unclear whether the resection of the EC (Bonilha et al. 2007b) or stereotactic radiofrequency treatment of the EC (Malikova et al. 2011) in addition to the hippocampus improves the postoperative outcome in TLE. Atrophy of EC seems to be specific to TLE, since it is not detected in extratemporal focal epilepsy or in genetic generalised epilepsies (Bernasconi et al. 2003a).

Fewer studies have assessed the volumes of the PRh or TP in TLE. Bernasconi et al. (2000) analysed the volumes of the parahippocampal region with voxel based morphometry in a small group of TLE patients, but at least a two standard deviation (SD) volume reduction of PRh was observed only in two out of six patients and the volume of the posterior parahippocampal cortex was unaffected. In their second study (Bernasconi et al. 2003b) the authors could confirm that the volumes of the hippocampus, EC and PRh ipsilateral to the seizure focus were reduced when compared to controls. EC was more severely affected than the PRh, but the volumes of the posterior parahippocampal region did not differ from controls at the group level. Two other studies have also demonstrated ipsilateral PRh volume reduction in patients with TLE (Bonilha et al. 2003, Meade et al. 2008). The volumes of the temporopolar grey and white matter were also decreased ipsilateral to the seizure focus (Coste et al. 2002, Sankar et al. 2008) but these changes were not related to surgical outcome (Sankar et al. 2008). However, the participation of TP in the seizure onset may be related to surgical outcome (Chabardes et al. 2005).

Volumetric analyses have mainly been performed manually or semi-manually by outlining the predefined regions of interest (ROI). Alternatively, stereology with the Cavalieri-method (Salmenperä et al. 2005) or voxel based morphometry (Keller et al. 2002, Li et al. 2012) has been used. Manual segmentation is especially time consuming and may suffer from inter- and intra-observer variability, which can potentially affect the

reproducibility of the findings. Currently hippocampal volumetry is not routinely used in the preoperative evaluation of individual patients, but rather for research purposes. Protocols for automated hippocampal volumetry are under development (Bonilha et al. 2009, Farid et al. 2012, Kim et al. 2012) to allow volumetric studies to become part of clinical practice.

2.9.2.2 Functional MRI

Functional MRI (fMRI) is a non-invasive imaging method, which is based on measuring cerebrovascular changes associated with neuronal activation triggered by certain stimuli. These hemodynamic responses result in changing ratios of oxyhemoglobin and deoxyhemoglobin; and in MRI, these cause contrast differences which can be measured by exploiting the blood oxygenation level dependent (i.e. BOLD) effect (Labudda & Woermann 2011).

In TLE, fMRI is most often used for the lateralisation of the hemispheric language dominance. Language lateralisation with fMRI shows a relatively high concordance with the Wada test in most studies which have included patients with TLE (Gaillard et al. 2002, Rutten et al. 2002, Adcock et al. 2003) or with different focal epilepsies (Woermann et al. 2003). Preoperative language mapping with fMRI was also predictive of a naming decline after left ATR in two studies (Sabsevitz et al. 2003, Bonelli et al. 2012).

FMRI studies evaluating lateralisation of memory functions indicate that epileptic activity can influence the lateralisation of mesiotemporal fMRI activity. Patients with unilateral TLE display asymmetrically stronger fMRI responses in the temporal lobe contralateral to the side of seizure focus (Jokeit et al. 2001, Janszky et al. 2004, Frings et al. 2008), but independent bilateral epileptiform activity decreases the extent of the asymmetry (Janszky et al. 2004).

A growing number of fMRI studies have tried to predict postsurgical memory changes in patients undergoing surgery for TLE. In these studies, a greater ipsilateral mesiotemporal fMRI activation was associated with a higher risk of postoperative memory decline (Richardson et al. 2004, Koylu et al. 2008, Powell et al. 2008, Bonelli et al. 2010, Dupont et al. 2010). However, before fMRI can be used in everyday clinical practice in the prediction of postsurgical memory changes in patients undergoing surgery for TLE, larger patient groups, results in individual patients, and probably also new test paradigms will need to be further investigated.

2.9.3 Molecular imaging

2.9.3.1 Positron emission tomography, PET

Interictal positron emission tomography (PET) can be used in the preoperative evaluation to explore the localisation and extent of the epileptic focus. In epilepsy, a glucose analog [18F]-fluorodeoxyglucose ([18F]FDG), which reflects the glucose utilisation in the brain is most commonly used. The epileptic focus usually appears as hypometabolic in interictal [18F]FDG-PET, but the hypometabolic area can be substantially more extensive than the actual seizure onset zone (la Fougere et al. 2009, Richardson 2010). The degree of hypometabolism of the epileptogenic temporal lobe and other neighbouring cortical regions may increase with longer epilepsy duration in TLE (Akman et al. 2010). However, the degree of temporal hypometabolism does not seem to be related to the degree of hippocampal damage as assessed either by histology or volumetric MRI (Foldvary et al. 1999, Lamusuo et al. 2001).

In the early studies [18F]FDG-PET displayed excellent sensitivity and specificity in TLE and these could be linked both with neurophysiology and pathology (Swartz et al. 1992). It is now well established that [18F]FDG-PET correctly lateralises the epileptic temporal lobe (Ho et al. 1995, Ohta et al. 2008) and predicts postoperative seizure outcome (Dupont et al. 2000, Choi et al. 2003, Vinton et al. 2007, Struck et al. 2011). [18F]FDG-PET is most useful

and cost-effective in patients with TLE when MRI or video-EEG monitoring are nonlocalising or nonconcordant (Uijl et al. 2007, O'Brien et al. 2008). In patients who have seizure focus localised by ictal scalp-EEG and MRI (Willmann et al. 2007), or in patients with a unilateral temporal lobe MRI lesion and either concordant or non-lateralising EEG (Kilpatrick et al. 2003), [18F]FDG-PET provides little additional prognostic information.

Other PET tracers have also been developed in attempts to image different receptor systems in the brain (la Fougere et al. 2009, Richardson 2010), including $GABA_A$ -receptors ([11C]Flumazenil), opioid receptors, serotonin receptors (selective 5-HT1A receptor antagonists) and dopamine receptors (D2/D3-receptor antagonist [18F]Fallypride). Additionally, serotonin metabolism can be imaged with α-[11C]methyl-L-tryptophan particularly in patients with tuberous sclerosis. The clinical utility of all these ligands is restricted by their limited availability and they are mainly used for clinical research purposes. However, the new serotonin receptor ligands have shown promising results in TLE by detecting reduced binding in patients in whom the MRI appears normal (Liew et al. 2009), correctly lateralising the seizure focus (Didelot et al. 2008, Liew et al. 2009, Theodore et al. 2012), and predicting the postoperative outcome (Theodore et al. 2012).

2.9.3.2 Single photon emission computed tomography, SPECT

Single photon emission computed tomography (SPECT) is an adjunctive noninvasive method in the presurgical evaluation of patients with drug-resistant focal epilepsy. It can be used interictally and ictally to measure the regional flow of blood in the brain (Bonte et al. 1983). In epilepsy, the two most commonly used perfusion tracers have been 99mTc-hexamethylpropyleneamine oxime (99mTc-HMPAO) and 99mTc-ethyl cysteinate dimer (99mTc-ECD) (Oku et al. 1997, Lee et al. 2002a). Benzodiazepine receptor SPECT studies in epilepsy have been performed mainly with [123I]Iomazenil (Umeoka et al. 2007).

The usefulness of interictal SPECT in the preoperative evaluation is limited because of the technique's low sensitivity (Siegel et al. 2002). In current practice, both interictal and ictal SPECT studies are usually performed, and the digital subtraction of ictal and interictal SPECT scans is then co-registered to MRI (SISCOM) (Zubal et al. 1995). Composite SISCOM studies in patients with well-localised MTLE most commonly detect a region of hyperperfusion in the ipsilateral anterior temporal region, which often also involves the basal ganglia and insula (Kaiboriboon et al. 2005). However, the anterior temporal hyperperfusion may also be bilateral (Huberfeld et al. 2006). Since peri-ictal perfusion patterns reflect the evolution of the seizure, ictal SPECT should always be analysed in combination with ictal EEG to avoid false localisation due to seizure propagation (Cho et al. 2010) or postictal switch to hypoperfusion.

The use of SISCOM improves the visualization of regional hyperperfusion and predicts the postoperative outcome (O'Brien et al. 1998, Matsuda et al. 2009). More recently, statistical ictal SPECT coregistered to MRI (STATISCOM) was shown to be superior to SISCOM for seizure localisation and identification of TLE subtypes (MTLE and NTLE) before TLE surgery (Kazemi et al. 2010). Additionally, the subtraction of ictal and interictal SPECT scans have been analysed with statistical parametric mapping (ISAS) (McNally et al. 2005).

It has been reported that ictal perfusion SPECT could correctly differentiate patients with TLE and extratemporal focal epilepsy (sensitivity 86% and 66%, respectively) (Weil et al. 2001). In a prospective multicenter study comparing different noninvasive preoperative investigations in TLE, the sensitivity for seizure localisation was 86% for MRI, 84% for ictal SPECT, 70% for ictal EEG, 55% for interictal SPECT, and 40% for interictal EEG (Zaknun et al. 2008). In another study, SPECT provided localising information in 77% and influenced the final decision-making for surgery in 45% of patients with MTLE (Rathore et al. 2011a). It seems that SPECT may be particularly useful in patients with lesional TLE and nonlocalising ictal data, and those with dual pathologies (Rathore et al. 2011a). However, in a randomised trial, ictal SPECT gave neither additional localising information nor

improved the postoperative seizure outcome after surgery in patients with MTLE and hippocampal atrophy in MRI, in fact it was found to increase the length of hospital stay, cost of presurgical evaluation and risk of generalised seizures during video-EEG monitoring (Velasco et al. 2011).

2.9.4 Long-term video-EEG

2.9.4.1 Surface (scalp) EEG

The long-term video-EEG aims to record the habitual seizures of the patient. If necessary, seizures can be provoked by gradual tapering of the antiepileptic medication and partial sleep deprivation.

In MTLE, relatively typical scalp-EEG findings can be observed interictally, at seizure onset, during the course of a seizure and postictally. Interictal temporal intermittent rhythmic delta activity is a typical finding in TLE (Gambardella et al. 1995) and can be seen in up to 28% of patients evaluated for temporal lobe surgery (Geyer et al. 1999). IEDs are typically located in the anterior temporal region, particularly in patients with HS (Hamer et al. 1999). Anterior temporal IEDs provide lateralising information of the seizure onset and are prognostic for a good postoperative outcome in most studies (McIntosh et al. 2001). Bitemporal interictal epileptiform discharges increase the risk of independent bitemporal seizure onset, but do not preclude a good postoperative outcome if other data is indicative of unitemporal seizure onset (Williamson et al. 1993).

With the scalp-EEG, the ictal EEG findings are typically seen only after the clinical onset of the seizure. Ictal scalp-EEG in MTLE may show initially an attenuation of EEG rhythms, followed by progressive theta activity with decreasing frequency and increased amplitude (Wieser & ILAE Commission on Neurosurgery of Epilepsy 2004). Alternatively a waxing and waning type of theta activity can be observed. The ictal activity may be regional with a maximum over the temporal areas, lateralised or nonlateralised (bilateral). The ictal scalp EEG may also appear as normal, particularly during seizures that do not impair consciousness. The presence of postictal lateralised slowing may provide lateralising information (Williamson et al. 1993, Jan et al. 2001). In the majority of adult patients with TLE, surface ictal EEG combined with other non-invasive methods can provide an accurate estimation of the epileptogenic zone (Kilpatrick et al. 1997, Foldvary et al. 2001, Uijl et al. 2008a).

2.9.4.2 Intracranial recordings

The main advantages of intracranial EEG electrodes are improved spatial resolution and ability to record higher EEG frequencies, which are attenuated in scalp-EEG. With intracranial electrodes, it is possible to detect at first the ictal EEG onset, followed by the subjective or objective clinical symptoms of a seizure. In TLE, the need for intracranial electrodes has decreased during the last decades mainly due to improvements in the structural and functional imaging modalities.

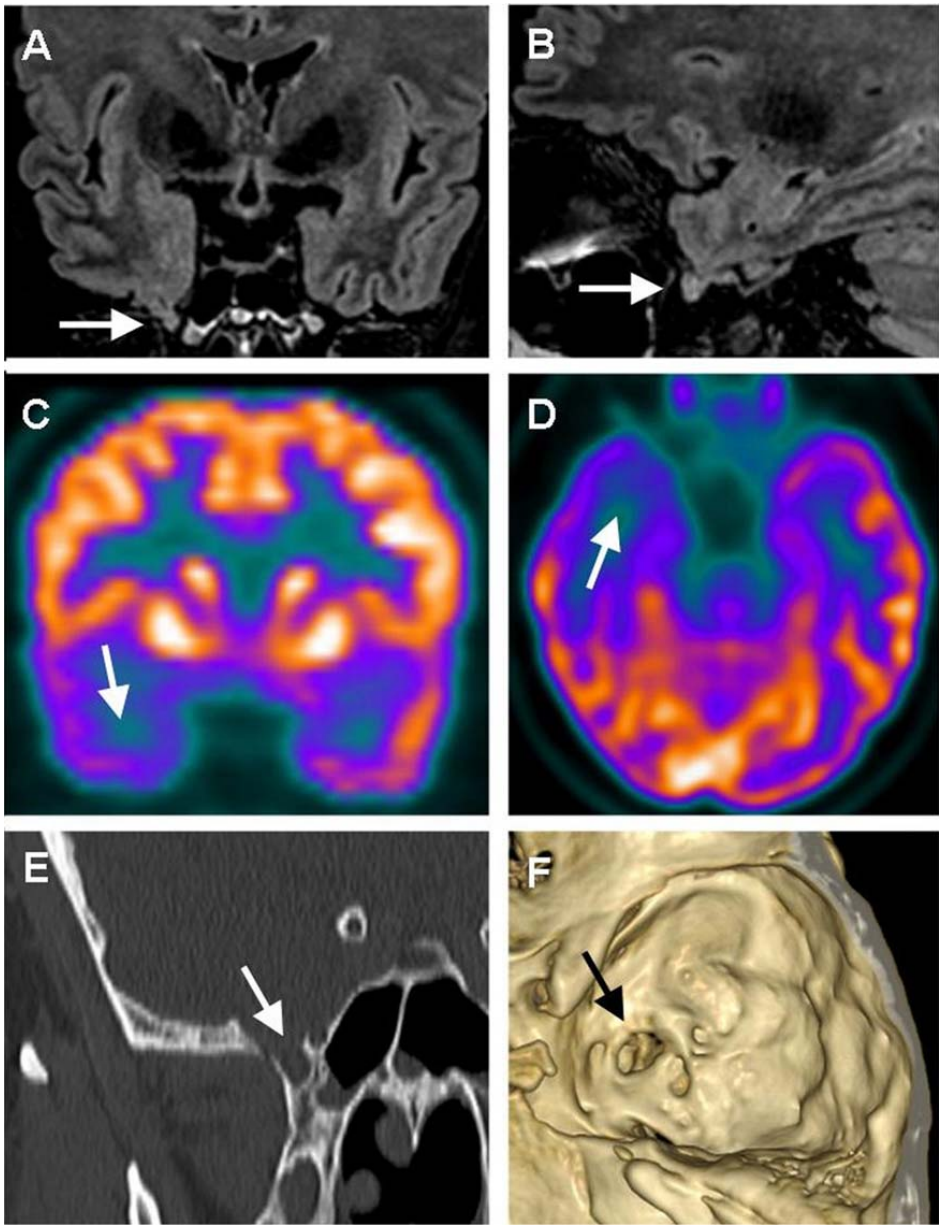

Figure 4. Preoperative multimodal imaging. A 40 year old male was referred to presurgical evaluation due to an adult onset drug-resistant TLE. Preoperative MRI with 3T scanner revealed an occult anteroinferior temporal encephalocele in the right middle fossa (A and B). A small part of the inferior temporal gyrus (arrow) is protruding to the bony defect. [18F]FDG-PET showed a concordant hypometabolism in the right anterior, medial and lateral temporal lobe (C and D). Thin-slice CT (E) with 3D reconstruction images (F) revealed an 8 x 7 x 5 mm bony defect in the sphenoidal bone (arrows). Ictal and interictal EEG were concordant with the multimodal imaging. The patient was diagnosed with neocortical TLE and anterior temporal neocortical resection was performed sparing the mesial structures.

Intracranial recordings in general are indicated if a patient is a potential surgical candidate, but in whom the initial noninvasive investigations have revealed inconclusive or discordant information of the seizure onset (Duncan 2011b). In TLE, the most common indications for intracranial evaluation are normal structural imaging, discordant or inconclusive non-invasive studies in lesional patients, and difficulties in bitemporal or frontotemporal differential diagnostics (Diehl & Luders 2000).

Subdural strip electrodes can be used in patients with suspected MTLE. The advantages of subdural strip electrodes over the intracerebral depth electrodes include easier implantation, coverage of larger cortical areas, delineation of epileptogenic zone within one temporal lobe, and a lower risk of complications (Diehl & Luders 2000). In order to minimize the risk of false localisation, the subtemporal subdural electrode should cover the parahippocampal area medially to the collateral sulcus (Eisenschenk et al. 2001). The exact location of the subdural electrodes can be obtained by using three-dimensional (3D) MRI and computer tomography (CT) based reconstruction of the electrodes (Schulze-Bonhage et al. 2002, LaViolette et al. 2011). Bitemporal depth electrodes may be useful in cases of MTLE, e.g. bilateral HS, to define the side of seizure origin. Subdural grid electrodes or stereo-EEG may be beneficial when it is not clear whether the seizure onset occurs from the mesial or lateral aspect of the temporal lobe, particularly in nonlesional patients. Subdural grid electrodes may also be advantageous if it is necessary to define the relationship between a structural lesion and the epileptogenic zone in the lateral temporal neocortex, or if the delineation of eloquent cortex (Wernicke area) by cortical stimulation is needed. Each intracranial evaluation should be individually planned according to the presumed seizure onset area indicated by non-invasive evaluation. The final surgery is planned only if the epileptogenic zone is defined and the resection is feasible with tolerable risks (Duncan 2011b).

2.9.5 Neuropsychological evaluation

A preoperative neuropsychological assessment is indicated in all patients who are being evaluated for epilepsy surgery. Furthermore all operated patients should also be followed postoperatively to track possible impairment and recovery of cognitive functions. The neuropsychological evaluation assists in the localisation of the seizure focus by identifying the area(s) of cognitive dysfunction and in evaluation of possible cognitive risks of epilepsy surgery in an individual patient. The assessment should be targeted towards different cognitive functions such as intelligence, executive functions, memory, language and attention (Jones-Gotman et al. 2010).

The cognitive functioning among patients with chronic TLE is typically characterised by significant impairment in episodic memory i.e. impairment of the long term memory consolidation and retrieval of newly acquired information (Wieser & ILAE Commission on Neurosurgery of Epilepsy 2004). Left or language dominant TLE is associated with material specific verbal memory deficits, especially with regards to delayed recall of verbal material (Hermann et al. 1997). An association between right TLE and visual memory deficits has also been detected in some patients with HS (Gleissner et al. 1998) but this relationship is less consistent (Alessio et al. 2004). There is also association between right TLE and deficits in spatial memory (Abrahams et al. 1999), identification of famous faces (Drane et al. 2013) and recognition of emotional facial expressions (Meletti et al. 2003). In addition to memory impairment, patients with TLE may perform poorly in measures of intelligence, language, executive functions and motor speed (Oyegbile et al. 2004, Hermann et al. 2007).

It has been postulated that patients with chronic TLE fail to achieve adequate learning and memory performance already during childhood and adolescence (Helmstaedter & Elger 2009). Furthermore, the profile of cognitive deficits associated with MTLE and HS may already be established when children with TLE enter adulthood (Baxendale et al. 2010). The cognitive profile appears to remain stable in adults, at least until 60 years of age (Baxendale et al. 2010). However, patients with chronic TLE may be more vulnerable to the

effects of ageing, as the negative interaction of the initial cognitive deficit and ageing reduces the patient's cognitive reserve capacities and thus these individuals may have decreased cognitive performance earlier than would be the case in normal ageing (Helmstaedter & Elger 2009).

2.9.6 The Wada test

The classical Wada test was originally introduced to lateralise language dominance (Wada & Rasmussen 1960). Later it was expanded to test memory lateralisation and to prevent risk of global amnesia prior to temporal lobe resection (Milner et al. 1962). Other indications have historically been preoperative lateralisation of seizure focus and prediction of seizure outcome in TLE (Baxendale et al. 2008c).

Currently the validity, reliability, and predictive value of the Wada test results are being re-evaluated, especially with regard to the prediction of postoperative global amnesia or memory decline after ATR (Baxendale et al. 2007, Loddenkemper et al. 2007, Baxendale et al. 2008c, Kemp et al. 2008). These questions, together with the development of structural and functional imaging techniques, information on the Wada complications (Haag et al. 2008, Loddenkemper et al. 2008), as well as recent worldwide shortage on sodium amytal, have led to changes in the role of Wada test in the presurgical evaluation.

Haag et al. (2008) examined 1421 Wada procedures conducted in 16 European centres between 2000 and 2005. During this period, the ratio of Wada tests to surgical treatment declined from 56% to 35%, revealing the gradual loss of favour of the Wada test. The overall complication rate was 1%. In another international survey (Baxendale et al. 2008b) only 12% of epilepsy surgery centers were using the Wada test in the surgical evaluation for all TLE patients, whereas 13% of centers never used the Wada test. There were significant regional variations in the employment of the Wada test. The number of Wada tests declined also in a large single center study, and the Wada test was most likely performed on patients with left TLE or on patients being evaluated with subdural electrodes (Das et al. 2010).

The clinical indications for a Wada test need to be determined on an individual basis to ensure that the risk–benefit ratio is appropriate for every patient (Baxendale 2009). First all information from the available non-invasive studies should be assessed. Future studies should be focused on the identification of those patients in whom the Wada test may still reveal unique information helpful in the preoperative decision-making.

2.9.7 Psychiatric evaluation

Patients with epilepsy are prone to significant psychiatric comorbidity (Tellez-Zenteno et al. 2007), and according to more recent studies, both patients with temporal and extratemporal focal epilepsy are equally affected (Swinkels et al. 2006, Adams et al. 2008). However, major depression may be particularly associated with HS (Sanchez-Gistau et al. 2012). Patients with epilepsy in general have also an increased risk of suicide (Christensen et al. 2007, Bell et al. 2009a), the risk is higher in some patient subgroups e.g. in patients seen in tertiary clinics, in patients with TLE and in surgical TLE patients (Bell et al. 2009a). In a controlled prospective study on psychiatric comorbidity in chronic TLE, a significantly higher risk of all Axis I psychiatric disorders and mood disorders was observed when the subjects were compared to healthy controls (Jones et al. 2007). Furthermore, in a study from a tertiary epilepsy centre, 60% of patients with mainly drug-resistant TLE had a current psychiatric disorder (de Oliveira et al. 2010), which was often underdiagnosed and undertreated. Consequently, all epilepsy surgery candidates should be evaluated by a psychiatrist who is familiar with epilepsy surgery, and if necessary treated adequately before surgery.

2.10 POSTOPERATIVE OUTCOMES AFTER TLE SURGERY

2.10.1 Outcome with respect to seizures

2.10.1.1 Classification of seizure outcome

The most extensively used classification for postoperative seizure outcome was originally described by Engel (Table 1) (Engel et al. 1993) and it has subsequently been applied with modifications. However, the category of patients free of disabling seizures (Class I) may also include patients with postoperative auras (i.e. seizures not impairing awareness), and the outcome measure '≥ 50% seizure reduction' typically used in AED trials is missing from the main classification. Therefore, ILAE has proposed a new outcome classification (Table 2), which identifies the completely seizure-free patients (ILAE class 1) and also counts seizure days rather than the total number of postoperative seizures (Wieser et al. 2001).

Table 1. Engel's classification of postoperative seizure outcome (Engel et al. 1993)

Class I: Free of disabling seizures [a]	
A	Completely seizure-free since surgery
B	Nondisabling simple partial seizures only since surgery
C	Some disabling seizures after surgery, but free of disabling seizures for at least two years
D	Generalized convulsion with antiepileptic drug withdrawal only
Class II: Rare disabling seizures	
A	Initially free of disabling seizures, but has rare seizures now
B	Rare disabling seizures since surgery
C	More than rare disabling seizures after surgery, but rare seizures for at least two years
D	Nocturnal seizures only
Class III: Worthwhile improvement [b]	
A	Worthwhile seizure reduction
B	Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than two years
Class IV: No worthwhile improvement [b]	
A	Significant seizure reduction
B	No appreciable change
C	Seizures worse

[a] Excludes early postoperative seizures (first few weeks)

[b] Determination of "worthwhile improvement" will require quantitative analyses of additional data such as percent seizure reduction, cognitive function, and quality of life

Table 2. Classification of outcome with respect to seizures according to the International League Against Epilepsy (ILAE) (Wieser et al. 2001)

Outcome Class	Definition
1	Completely seizure-free; no auras
1a	Completely seizure-free since surgery; 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

2.10.1.2 Randomised controlled trials

The only successful randomised controlled trial comparing surgical treatment of TLE to optimal AED treatment was conducted between 1996 and 2000 by Wiebe et al. (2001). The primary outcome measure in the study was freedom from seizures that impair awareness of self and surroundings. One year after the operation, the proportion of these seizure-free patients was 58% in the surgical group versus 8% in the medically treated group. Additionally, 38% of patients in the surgical but only 3% in the medically treated group were free of all seizures, including auras. Two patients needed to undergo surgery (i.e. number needed to treat) to render one additional patient free of seizures impairing awareness at one year. The study clearly demonstrated that epilepsy surgery was superior to prolonged medical treatment in patients with drug-refractory TLE.

A multicenter, randomised, controlled, parallel group clinical trial tried to assess whether early surgery after failure of two AED trials is superior to continued medical treatment in controlling seizures and improving QOL in TLE (Engel et al. 2012). Only 38 patients were recruited and the trial had to be stopped prematurely. None of the patients (0/23) in the medical group became seizure-free whereas 73% (11/15) of operated patients were seizure-free during year two of the follow-up.

Randomised controlled trial comparing the efficacy of 2.5 cm versus 3.5 cm mesial (hippocampal and parahippocampal) temporal resection in TLE did not show different seizure-freedom rate between the more anterior and more posterior resection group (Schramm et al. 2011).

2.10.1.3 Nonrandomized studies comparing surgical and medical treatment

The results from nonrandomised studies comparing surgical and medical treatment in TLE are in line with the first randomised controlled study of TLE surgery. In a systematic review which included a meta-analysis (Schmidt & Stavem 2009) in all 20 studies comparing surgical and medical treatment published between 1947 and 2007 were identified. These studies included altogether 1621 patients with a follow-up ranging from one to thirteen years. The majority of patients had TLE and only three studies included some patients with extratemporal focal epilepsy. The proportion of patients who were seizure-free in the original articles differed greatly, i.e. between 7–85%, as defined by original authors. After the heterogeneity of the studies was statistically corrected, it was estimated that 44% of operated patients compared to 12% of the nonsurgical controls were

seizure-free at long-term. No particular explanatory factors for outcome were identified. In a more recent prospective controlled study comparing surgical and medical treatment in patients with TLE, it was found that 73% of the surgical patients and 12% of the medically treated patients were free of all seizures including auras during a one-year follow-up (Yasuda et al. 2006).

2.10.1.4 Long-term outcome

TLE affects the whole course of the patient's life. It is therefore important to assess whether the good postoperative seizure outcome observed in short-term follow-up studies is retained during long-term follow-up and which factors predict the postoperative outcome.

A prospective observational multicenter study of epilepsy surgery was performed in seven different epilepsy surgery centers in USA between 1996 and 2001. Altogether 396 patients over 12 years of age were operated with 88% of them undergoing mesial temporal lobe resections (n=312) (Spencer et al. 2003). In the initial report, 77% of the patients followed for at least a year after surgery achieved a one-year remission at some point during the follow-up (Spencer et al. 2003). During the long-term follow-up (median 4.6 years, range from 2 to 7.3 years) 68% of operated MTLE patients had experienced a two-year remission (Spencer et al. 2005). However, after achieving a two-year remission, 25% of patients with mesial temporal resection relapsed. Only the delay to remission predicted relapse in the patients undergoing mesial temporal resections (Spencer et al. 2005). As in many earlier studies, the duration of epilepsy before entering the study was long (mean 22 years) (Spencer et al. 2003).

In a meta-analysis of 40 long-term follow-up studies (follow-up at least five years) of TLE surgery published between 1991 and 2003, the median proportion of seizure-free patients was 66% (Tellez-Zenteno et al. 2005). Higher seizure-free rates were observed in more recent studies and in studies using the Engel´s classification as the outcome measure. The authors concluded that the long-term seizure outcome was similar to that reported in short-term controlled studies.

Eleven studies describing the percentage of seizure-free patients at different time intervals during long-term follow-up are displayed in Table 3. The percentage of patients who were seizure-free in these studies was in the range 53–89% at 1 year, 50–89% at 2 years, 54–91% at 5 years, and 41–86% at 10 years (Elwes et al. 1991, Salanova et al. 1999, Paglioli et al. 2004, Jeong et al. 2005, Dupont et al. 2006, Kelemen et al. 2006, Asztely et al. 2007, Aull-Watschinger et al. 2008, Tanriverdi et al. 2008b, Tezer et al. 2008, Özkara et al. 2008). These numbers indicate, that the proportion of seizure-free patients after TLE surgery remains relatively stable also over the long-term. However, different classifications for determination for seizure-free outcome have been used, and this needs to be considered when different studies are being compared. There has also been a considerable loss of patients during the follow-up in some studies and the number of patients remaining in the study has not always been reported. This may bias the results as patients with good postoperative seizure outcome are more likely to remain in the study. The outcomes are also affected by the aetiology of epilepsy as the study describing by far the best results included only patients with HS (Paglioli et al. 2004).

Table 4 describes the probability of remaining seizure-free in eight studies published between 2000 and 2011. In these studies the probability of remaining seizure-free after surgery was in the range 61–98% at 1 year, 55–86% at 2 years, 48–83% at 5 years, and 41–81% at 10 years (Foldvary et al. 2000, McIntosh et al. 2004, Paglioli et al. 2004, Cohen-Gadol et al. 2006, Dupont et al. 2006, Jeha et al. 2006, Elsharkawy et al. 2009a, de Tisi et al. 2011). In this group of studies the best prognosis was also observed in a group of patients with HS (Paglioli et al. 2004).

Table 3. Long-term seizure outcome after the surgical treatment of TLE

Study	Number of patients (n)	Duration of follow-up in years	Determination of seizure-freedom	Percentage of seizure-free patients (the number of remaining patients) at different time intervals
Elwes et al. 1991	n = 102	mean 5.1 (range 0.7–12)	Seizure free ± auras for a year	1 year 56% (101), 2 years 60% (100), 3 years 57% (94), 4 years 61% (77), 5 years 67%(69), 6 years 57% (52)
Salanova et al. 1999	n = 145	mean 5.6 (range 2–12)	Engel's class I	1 year 66% (145), 2 years 63% (144), 5 years 60% (94), 10 years 55% (22)
Paglioli et al. 2004	n = 135	mean 5.5 (range 2–11)	Engel's class I	1 year 89% (134), 2 years 89% (134), 5 years 91% (68), 10 years 86% (6)
Jeong et al. 2005	n = 227	mean 4.6 ± 2.0 (at least a year)	Engel's class I	1 year 81% (227), 2 years 79% (193), 3 years 79% (174), 4 years 77% (150), 5 years 75% (121)
Dupont et al. 2006	n = 110	mean 7 ± 4 (range 1–17)	Engel's class IA	1 year 75% (83), 2 years 66% (73), 5 years 54% (34), 10 years 41% (11)
Kelemen et al. 2006	n = 94	mean 6.1 (range 2–17)	Engel's class I	1 year 72% (-), 2 years 66% (-), 5 years 59% (-)
Asztely et al. 2007	n = 70 (TLE 54)	mean 12.4 (range 8.6–16.2)	ILAE class 1–2	2 years 59% (51), long-term follow-up 65% (51) for TLE
Aull-Watschinger et al. 2008	n = 135	not reported	Engel's class I A–B ILAE Ia	1 year 70% (135), 2 years 71% (111), 5 years 79% (72) 1 year 64% (135), 2 years 56% (111), 5 years 46% (72)
Tanriverdi et al. 2008b	n = 63	mean 12.3 ± 0.6	Engel's class IA	2 years 76% (63), 12 years 71% (63)
Tezer et al. 2008	n = 109	mean 4.8 ± 2.6 (range 1–11)	Engel's class I ILAE Ia	1 year 83% (109), 3 years 72% (82), 7 years 69% (26), 10 years 86% (7) 1 year 59% (109), 3 years 40% (82), 7 years 39% (26), 10 years 43% (7)
Özkara et al. 2008	n = 165	mean 5.0 ± 2.7 (range 1–11)	ILAE 1	1 year 53% (165), 2 years 50% (149), 3 years 47% (131), 5 years 54%(101), 8 years 57% (35), 10 years 56% (6)

Abbreviations: Engel's class I, free of disabling seizures; Engel's class 1A, completely seizure-free since surgery; Engel's class 1B, nondisabling simple partial seizures (auras) only since surgery; ILAE class 1, completely seizure-free; ILAE class 1a, completely seizure-free since surgery; ILAE 2, only auras, no other seizures; n, number of patients; TLE, temporal lobe epilepsy.

Table 4. Probability of remaining seizure-free after surgical treatment of TLE

Study	Number of patients (n)	Duration of follow-up in years	Determination of seizure-freedom	Probability in percentage (95% CI) of remaining seizure-free at different time intervals
Foldvary et al. 2000	n = 79	mean 14 (range 2.1–33.6)	Engel class I	5 years 52% (41–63), 7 years 50% (39–61), 10 years 45% (33–56)
Mc Intosh et al. 2004	n = 325	mean 9.6 ± 4.2 (range 0.7–23)	Engel class I A–B, D	1 year 61% (55–66), 2 years 55% (50–61), 5 years 48% (42–53), 10 years 41% (36–48), 15 years 37% (30–44)
Paglioli et al. 2004	n = 134	mean 5.5 (range 2–11)	Engel class I	1 year 89%, 2 years 86%, 5 years 83%, 10 years 81%
Cohen-Galdol et al. 2006	n = 399 (TLE 372)	mean 6.2 ± 4.5 (range 0.6–15.7)	Engel class I	1 year 80% (76–85), 2 years 78% (74–83), 5 years 76% (71–81), 10 years 74% (69–79) for TLE
Dupont et al. 2006	n = 110	mean 7 ± 4 (range 1–17)	Engel class IA	1 year 98%, 2 years 85%, 5 years 60%, 10 years 43%
Jeha et al. 2006	n = 371	mean 5.5 (range 1–14)	ILAE class 1	2 years 78% (75–81), 5 years 66% (62–70), 8 years 58% (52–63), 10 years 53% (47–58)
Elsharkawy et al. 2009a	n = 434	mean 9 ± 3.1 (range 2–16)	Engel class I	2 years 72% (68–76), 5 years 71% (67–75), 10 years 71% (65–75), 16 years 69% (64–74)
de Tisi et al. 2011	n= 615 (TLE 497)	median 8 (range 1–19)	ILAE class 1–2	2 years 63% (59–67), 5 years 52% (48–56), 10 years 47% (42–51) for all patients 5 years 55% (51–60), 10 years 49% (44–54) for TLE patients

Abbreviations: CI, confidence interval; Engel's class I, free of disabling seizures; Engel's class 1A, completely seizure-free since surgery; Engel's class 1B, nondisabling simple partial seizures only since surgery; Engel's class 1D, generalized convulsions with antiepileptic drug withdrawal only; ILAE class 1, completely seizure-free; ILAE 2, only auras, no other seizures; n, number of patients; TLE, temporal lobe epilepsy.

The seizure outcome at one (Salanova et al. 1999, Cohen-Gadol et al. 2006) or two years (Elwes et al. 1991, Foldvary et al. 2000, McIntosh et al. 2004, Asztely et al. 2007) after surgery is predictive of the long-term seizure outcome. In addition, latency to first seizure predicts the long-term outcome after surgery (Buckingham et al. 2010). Relapse is less likely the longer that the patient remains postoperatively seizure-free (de Tisi et al. 2011,) and for those patients who are seizure-free for at least two years, the probability of remaining seizure-free at five years has been approximately 86–93% (Salanova et al. 1999, McIntosh et al. 2004). Late recurrences have been associated with different conditions e.g. HS (Salanova et al. 1999), temporal lobe gliosis (Salanova et al. 1999), head trauma (Tezer et al. 2008) or reduction of AEDs (Lowe et al. 2004, Özkara et al. 2008). Additionally late worsening of postoperative seizures was related to ipsilateral EEG spikes over the resected side, preoperative bilateral IEDs, Taylor type FCD and ictal contralateral seizure propagation in one study (Kelemen et al. 2006). On the other hand, no particular risk factors (including HS and reduction of AEDs) for late recurrence were identified in one large study (McIntosh et al. 2004). Late relapses do not necessarily lead to medical intractability (Foldvary et al. 2000). However, remission is rare if seizures continue initially and the likelihood of subsequent remission is less likely the longer seizures continue postoperatively (de Tisi et al. 2011). Late remission after surgery may be associated with the introduction of some previously untried AED (de Tisi et al. 2011).

In most studies, similar seizure outcomes have been reported after selective amygdalohippocampectomy (SAH) when compared to standard ATR. The long-term (median follow-up time 7.2 years) seizure outcome following SAH in 369 patients reported by Wieser et al. indicated that 67% of patients were postoperatively seizure-free as defined by Engel's class I (Wieser et al. 2003). Comparative studies have also achieved similar seizure outcomes (Tanriverdi et al. 2008a), particularly in patients with HS (Paglioli et al. 2006, Wendling et al. 2013).

2.10.1.5 Prognostic factors for the seizure outcome

In a meta-analysis which evaluated the predictors of epilepsy surgery outcomes in 47 studies published between 1984 and 2001, the strongest positive predictive factors for seizure remission were HS, tumours, abnormal MRI, concordance of MRI and EEG, febrile seizures and more extensive resections (Tonini et al. 2004). Predictors of unfavourable outcome were the need for intracranial EEG evaluation and postoperative EEG discharges. Seizure remission was defined as freedom from disabling seizures (Engel's class I) for one year with the minimum duration of follow-up also of one year. Patients with extratemporal surgery were included in 18 out of 47 studies. In a multicenter study of epilepsy surgery, the presence of hippocampal atrophy and the absence of focal onset generalised tonic clonic seizures preoperatively predicted the two-year remission for medial temporal resections (Spencer et al. 2005).

Factors associated with better or unfavourable outcome after TLE surgery in individual long-term outcome studies are displayed in Table 5. Only studies with a mean or median follow-up of at least five years have been included in the table. The most consistently reported group of predictors are those related to the aetiology of epilepsy. HS, low grade tumours or foreign tissue lesions (Salanova et al. 1999, McIntosh et al. 2004, Elsharkawy et al. 2009a, de Tisi et al. 2011) are associated with a better prospect of postoperative long-term seizure-freedom, whereas distant lesions and absence of abnormality in preoperative MRI are associated with poorer seizure outcome (McIntosh et al. 2004). The duration of epilepsy has shown relevance only in specific subgroups such as in patients with HS (Janszky et al. 2005) and patients with tumours (Elsharkawy et al. 2009a). Seizure related negative predictive factors include focal onset generalised tonic clonic seizures, versive seizures and higher preoperative seizure-frequency (Foldvary et al. 2000, Hennessy et al. 2001, McIntosh et al. 2004, Elsharkawy et al. 2009a). Localised unilateral interictal EEG abnormalities have been related to good outcome (Walczak et al. 1990, Hennessy et al. 2001), whereas bilateral

interictal IEDs, contralateral ictal propagation and the need for intracranial EEG predicted poor outcome (Kelley & Theodore 2005, Kelemen et al. 2006, Elsharkawy et al. 2009a). Postoperatively an important risk factor for poor outcome is normal histopathology in the resected tissue (Cohen-Gadol et al. 2006, Jeha et al. 2006, de Tisi et al. 2011). As multiple predictive factors may be needed, models which combine different prognostic factors have been developed (Berg et al. 1998, Uijl et al. 2008b). It has also been highlighted that the prognostic factors may be different in the short-term and the long-term outcome studies (Janszky et al. 2005, Jeha et al. 2006, Aull-Watschinger et al. 2008). In a large long-term outcome study including 171 patients with MRI defined HS, the duration of epilepsy was the most important predictor of surgical outcome from three to five years postoperatively highlighting the need for early surgery (Janszky et al. 2005). Those variables that predicted two-year outcome (focal onset generalised tonic clonic seizures and ictal dystonia) lost their independent predictive status at longer follow-up.

The most frequently reported positive predictive factor for good postoperative seizure-outcome both in short-term and long-term outcome studies is unilateral HS. Studies with MRI defined or pathologically proven HS have reported good seizure-free rates i.e. between 67% and 88% (Hennessy et al. 2001, Lowe et al. 2004, Lee et al. 2006, Paglioli et al. 2006, Özkara et al. 2008, Wendling et al. 2013) over the long-term. Comparable results have been described in longitudinal follow-up studies (Salanova et al. 1999, Paglioli et al. 2004, Elsharkawy et al. 2009a) and when different pathologies have been compared (York et al. 2003, Sindou et al. 2006). However, it is still poorly understood why all patients with HS do not become seizure-free.

The seizure outcome in patients without any focal MRI abnormalities has been reported to be significantly worse than in patients with HS or in those with a foreign tissue lesion detected in preoperative MRI. An early study of Berkovic et al. revealed that only 21% of patients with normal MRI had no postoperative seizures (follow-up sixty months) (Berkovic et al. 1995). However, more recently, a growing number of studies have shown that surgery in patients without any evident focal abnormalities in neuroimaging can be beneficial. Unfortunately, the different series are heterogeneous in terms of patient selection, preoperative evaluations and follow-up. The rate of seizure-free patients in current studies has varied from 31% to 77% (Holmes et al. 2000, Sylaja et al. 2004, Chapman et al. 2005, Alarcon et al. 2006, Bell et al. 2009b, Cukiert et al. 2010, Fong et al. 2011, Smith et al. 2011). The good seizure outcome is also retained in the long-term (Bell et al. 2009b, Fong et al. 2011, Smith et al. 2011). The outcome in patients with MRI negative and PET positive TLE has been exceptionally good, i.e. as many as 71–80% of these patients have become seizure-free as defined by Engel's class I outcome (Carne et al. 2004, Kuba et al. 2011, LoPinto-Khoury et al. 2012). Other positive predictive factors in patients with normal MRI include localising unilateral anterior/basal temporal interictal or ictal EEG patterns, absence of contralateral or extratemporal IEDs, concordant SPECT abnormality, concordant subtle non-specific MRI lesions, absence of prior risk factors for epilepsy, and a history of febrile seizures (Holmes et al. 2000, Sylaja et al. 2004, Tatum et al. 2008, Bell et al. 2009b, Smith et al. 2011,). Negative predictive factors include higher preoperative seizure frequency and preoperative generalised tonic-clonic seizures (Fong et al. 2011).

Studies assessing the long-term outcome of bitemporal epilepsy are rare. Holmes et al. (2003) reported that 71% of patients with bitemporal epilepsy (when defined by intracranial EEG) had ≥ 75% seizure reduction postoperatively. In one smaller and more recent study, 55% of patients with bitemporal epilepsy achieved Engel's class I outcome (Boling et al. 2009). In long-term outcome studies of bitemporal epilepsy with independent bitemporal seizure onsets, the main factor related to seizure freedom or significant reduction of seizures has been seizures originating predominantly (≥ 80%) in one temporal lobe (Holmes et al. 2003, Cukiert et al. 2009b). However, Boling et al. (2009) reported that the proportion of seizures arising from one temporal lobe was not reliable as a single indicator for predicting the postoperative seizure outcome. Furthermore, ictal EEG laterality, duration of

Table 5. Prognostic factors for the seizure outcome after temporal lobe epilepsy surgery (mean or median follow-up of at least five years in individual studies)

Factors associated with better postoperative outcome	
Hippocampal sclerosis	McIntosh et al. 2004, Elsharkawy et al. 2009a, de Tisi et al. 2011[1]
Tumour or foreign tissue lesion	Salanova et al. 1999, McIntosh et al. 2004, de Tisi et al. 2011[1]
Unilateral localised IEDs	Walzak et al. 1990
Ipsilateral localised interictal EEG	Hennessy et al. 2001
Use of intraoperative electrocortigography	Jeha et al. 2006
Short duration of epilepsy	Elsharkawy et al. 2009a[2]
Family history of epilepsy	Elsharkawy et al. 2009a
Factors associated with less favourable postoperative outcome	
Lack of obvious abnormality in MRI	McIntosh et al. 2004
Distant lesion in MRI	McIntosh et al. 2004
Focal cortical dysplasia in MRI / histology	Kelemen et al. 2006, Elsharkawy et al. 2009a, de Tisi et al. 2011[1]
Normal pathological findings / gliosis	Cohen-Galdol et al. 2006[1], Jeha et al. 2006, de Tisi et al. 2011[1]
Bilateral interictal sharp waves or IEDs	Kelemen et al. 2006, Elsharkawy et al. 2009a
Ictal contralateral seizure propagation	Kelemen et al. 2006
Need for intracranial EEG	Kelley and Theodore 2005
Longer duration of epilepsy	Janszky et al. 2005
Preoperative generalised tonic-clonic seizures	Hennessy et al. 2001, McIntosh et al. 2004
Preoperative versive seizures	Elsharkawy et al. 2009a
Higher preoperative seizure-frequency	Foldvary et. al. 2000
Preoperative psychiatric history or symptoms	Guarnieri et al. 2009, Kanner et al. 2009
Male gender	Cohen-Galdol et al. 2006[1]
Postoperative IEDs or ipsilateral spikes in EEG	Kelemen et al. 2006, Elsharkawy et al. 2009a[3]
Postoperative seizures not impairing awareness	De Tisi et al. 2011[1]
Previous surgery	Cohen-Galdol et al. 2006[1]

Numbers 1- 3 refer to studies with mixed patient population or to a selected subgroup of patients: [1] studies including both temporal and extratemporal patients, [2] patients with tumours and gliosis and [3] patients with focal cortical dysplasia.

epilepsy, age at surgery, age at seizure onset and mesial temporal atrophy were not able to differentiate patients with good or unfavourable postoperative outcome.

In earlier studies with a shorter follow-up, an association has been reported between febrile seizures (Tonini et al. 2004) or complex febrile seizures (Janszky et al. 2003) and good postoperative outcome. However, long-term outcome studies have not been able to confirm this finding (Hennessy et al. 2001).

There are some studies suggesting that psychiatric history or active preoperative psychiatric disorders can also affect the postoperative seizure outcome after temporal lobe resection. A preoperative psychiatric history has been claimed to increase the risk of postoperative seizures (Kanner et al. 2009, Cleary et al. 2012). In particular, this has been observed for anxiety and personality disorders (Guarnieri et al. 2009). However, the results are conflicting as two recent studies have demonstrated a lack of any association between psychiatric history (Adams et al. 2012) or depression (Lackmayer et al. 2013) and seizure outcome.

2.10.2 Cognitive outcome

2.10.2.1 Studies with short-term follow-up

It is generally agreed that epilepsy surgery usually evokes no general deterioration of cognitive functioning because primarily it is dysfunctional tissue that is being removed. Thus, it may even result in improved cognitive performance, as the adverse effects of seizures are eliminated and AED treatment can be reduced. However, neurocognitive morbidity, especially a decline in the material specific memory performance, has been reported as a significant and relatively frequent side effect of epilepsy surgery.

The knowledge of the cognitive sequelae of TLE surgery is still somewhat concentrated to those occurring during the first postoperative year. Although numerous short-term follow-up studies have addressed the postoperative cognitive performance both at the group level and based on the analyses of individual change scores, the maximum duration of follow-up in these studies has usually extended only up to one year. At the group level, the most consistent finding has been a decline in verbal memory performance after dominant temporal lobe resection; whereas the pattern of visual memory change after non-dominant temporal lobe resection has been more variable (Bell & Davies 1998, Lee et al. 2002b, Vaz 2004). However, the impact of surgery on cognitive functions is multifaceted and between 10 and 20% of patients may experience a postoperative improvement in their cognitive function (Baxendale et al. 2008a).

If one evaluates the short-term follow-up studies, then it seems that the most important risk factors for postoperative cognitive decline are language dominant temporal lobe surgery (Bell & Davies 1998, Lee et al. 2002b) and factors indicating structural or functional state of the ipsilateral temporal lobe. These factors include better baseline performance (Hermann et al. 1995, Helmstaedter & Elger 1996, Stroup et al. 2003, Gleissner et al. 2004, Baxendale et al. 2006), relatively intact hippocampal structures in the preoperative MRI (Trenerry et al. 1993, Stroup et al. 2003), absence of or mild HS in the pathological analyses (Sass et al. 1994, Baxendale et al. 1998) and better Wada memory performance after contralateral injection (Kneebone et al. 1995, Stroup et al. 2003). In some studies older age at the time of surgery (Hermann et al. 1995, Helmstaedter & Elger 1996, Baxendale et al. 2006), later age at onset of epilepsy (Wolf et al. 1993, Hermann et al. 1995), male gender (Trenerry et al. 1995, White et al. 2002), larger extent of resection (Helmstaedter & Elger 1996, Joo et al. 2005), and poor seizure outcome (Novelly et al. 1984, Sanyal et al. 2005) have also been identified as potential risk factors for the postoperative memory decline. On the other hand, a shorter duration of epilepsy and a better cognitive capacity to allow the development of compensatory strategies were identified as predictive factors for postoperative memory improvement following TLE surgery (Baxendale et al. 2008a).

Two recent studies have also assessed whether cognitive rehabilitation could counteract the verbal memory decline that can be seen after temporal lobe resection, but its usefulness as well as timing is unclear and further investigations are clearly needed (Helmstaedter et al. 2008, Koorenhof et al. 2012).

2.10.2.2 Long-term follow-up studies

The initial attempts to assess the long-term cognitive performance after TLE surgery were conducted already in the 1960`s. These early studies pointed to a decline in performance intelligence quotient (PIQ) after right temporal lobe resection (Meier & French 1966) or auditory verbal learning difficulties after dominant temporal lobe resection (Blakemore & Falconer 1967). Later Selwa and coworkers (Selwa et al. 1994) described a reduction in several measures of verbal memory after left temporal lobe resection, as well as an improvement in full scale intelligence quotient (FSIQ) and logical memory after right temporal lobe resection. Although the duration of the follow-up in these studies sometimes extended up to several years in some patients, many of them were included with short-term follow-up data only.

More recently a growing number of studies have evaluated the long-term postoperative cognitive outcome of TLE surgery with a follow-up of at least two years (Engman et al. 2001, Helmstaedter et al. 2003, Rausch et al. 2003, Alpherts et al. 2004, Engman et al. 2004, Bjørnaes et al. 2005, Alpherts et al. 2006, Engman et al. 2006, Grammaldo et al. 2009, Andersson-Roswall et al. 2010, Andersson-Roswall et al. 2012, Baxendale et al. 2012). The number of patients in these studies has ranged between 25 and 147, with a mean follow-up between 2 and 13 years.

When general intellectual ability has been evaluated before and after surgery, most authors have detected small increases in IQ (Engman et al. 2001, Alpherts et al. 2004, Engman et al. 2006). This finding might in part be related to the so-called practice effect due to repeated testing. Studies assessing long-term memory performance after TLE surgery at group level have shown variable results. Although some studies claim that there is cognitive stability (Engman et al. 2001, Engman et al. 2006, Grammaldo et al. 2009, Baxendale et al. 2012) a decline in verbal memory during long-term follow-up has been reported, particularly after left or dominant ATR (Helmstaedter et al. 2003, Rausch et al. 2003, Engman et al. 2004, Bjørnaes et al. 2005, Alpherts et al. 2006, Andersson-Roswall et al. 2010).

Rausch and co-workers (Rausch et al. 2003) reported selective early decreases in verbal memory one year after the operation in patients with left TLE surgery. However, further late decreases in verbal and visual memory scores were detected in both left and right TLE groups at long-term follow-up of at least nine years. In another six-year follow-up study assessing verbal memory after TLE surgery, only patients with left TLE had an ongoing memory decline in learning and delayed recall of verbal material for up to two years after surgery (Alpherts et al. 2006). Similarly, in a Swedish study, verbal memory decline was reported in patients with left TLE two years after the operation (Engman et al. 2004). However, more recent studies have not supported the concept of an ongoing progressive verbal memory decline after temporal lobe resection (Alpherts et al. 2006, Andersson-Roswall et al. 2010), but instead they seem to indicate that memory performance stabilizes during long-term follow-up after an initial decline.

There is evidence that surgical patients who continue to have seizures may be especially vulnerable to the postoperative memory decline. The association between postoperative seizure control and memory performance was demonstrated in the study of Helmstaedter et al. (2003). These investigators detected a significant memory decline during long-term follow-up both in medically (50%) and surgically (60%) treated patients. However, surgical patients had more pronounced memory impairment when compared to the medically treated group, if surgery had been performed on the left temporal lobe or if seizures continued postoperatively. Additionally, the seizure-free surgical patients showed recovery

of memory functions at the long-term follow-up. In a more recent study (Baxendale et al. 2012) a progressive decline in memory function at the individual level was associated with poor postoperative seizure control. However, it has been claimed that becoming and remaining seizure-free after surgery is not necessarily associated with better memory performance in the long term (Alpherts et al. 2006, Andersson-Roswall et al. 2010).

2.10.2.3 Assessment of cognitive change at individual level

Analysis of individual performance within the test–retest setting can suffer from methodological problems, such as regression towards the mean and the practice effect in repeated assessments. Therefore several methods have been used to define a meaningful change in the postoperative cognitive performance.

The reliable change index (RCI) was originally introduced (Jacobson & Truax 1991), because it takes into account the test–retest paradigm and corrects for the practice effect. Subsequently RCI and standardized regression based norms have been developed and applied (Chelune et al. 1993, Hermann et al. 1996, Sawrie et al. 1996). If necessary, a nonparametric method analogous to RCI can be used (Engman et al. 2001, Engman et al. 2004, Engman et al. 2006). However, also other methods for defining significant change in the pre- versus postoperative test performance have been devised. One alternative cut-off point which has been utilized is a pre- versus post-surgical difference greater than one SD for a given neuropsychological test, which has either been derived from the published normative data (Lendt et al. 2002, Rausch et al. 2003) or calculated from the preoperative baseline performance (Phillips & McGlone 1995, Paglioli et al. 2004, Cukiert et al. 2009a). Other available options include the determination of the magnitude of change by calculating individual effect sizes (i.e. standardized difference scores) or the assessment of possible category change from being in an unimpaired to an impaired range (or vice versa) (Witt & Helmstaedter 2013). However, whether the changes in the cognitive test performance are relevant compared to the everyday memory performance is still uncertain. It has been pointed out that while RCIs may have statistical validity, they do not necessarily reflect everyday memory performance, because the relationship between subjective ratings of postoperative memory function and objective indices of change are lacking (Sawrie et al. 1999, Baxendale & Thompson 2005).

Depending on the side on surgery Helmstaedter and co-workers (Helmstaedter et al. 2003) reported verbal memory losses in 24–47% and verbal memory gains in 11–12% of surgically treated TLE patients during long-term follow-up. Similarly, visual memory losses were observed in 28–34% and visual memory gains in 12–13% of surgically treated TLE patients. In another study assessing longitudinal cognitive outcome after TLE surgery (Engman et al. 2006), decrements in verbal memory were observed in 12–20% of the patients, increments in verbal memory in 16–20%, decrements in visual memory in 24%, and increments in visual memory in 8% of the patients (median follow-up of 2.7 years). In the long-term follow-up (median 9.8 years), these proportions diminished and residual impairments in memory performance were only seen in 0–12% whereas none of the patients had a residual improvement in memory performance after TLE surgery. Most recently, Andersson-Roswall et al. (2012) reported a decline in verbal memory performance in 7–44% of patients and an improvement in verbal memory performance in 4–22% of patients two years after temporal lobe resection. The decline in verbal memory was more common after dominant temporal lobe resections than after nondominant temporal lobe resections. The authors were able to demonstrate that many patients underwent a partial recovery of memory functions during prolonged follow-up of ten years and the memory impairment was not progressive in nature. Although slightly different methods for assessing meaningful change in the postoperative test performance were used in these studies, all seem to indicate that there is complex variability in the individual performance, which is not always associated with the changes seen at group level.

2.10.2.4 Predictive factors in long-term follow-up studies

Rausch and co-workers (Rausch et al. 2003) analysed predictive factors for early and late verbal memory decline in surgically treated TLE patients by applying individual change scores. They found that the early verbal memory decline was predicted by left side of surgery and higher initial verbal memory scores, whereas the late verbal memory decline was predicted only by higher initial verbal memory scores. Left TLE surgery was an additional predictor of late decline on a verbal memory task which was sensitive to the integrity of the left hippocampus. In another study (Andersson-Roswall et al. 2012) the only risk factor detected for both long and short term verbal memory decline was resection of the language dominant temporal lobe. Additionally, better baseline performance in verbal memory predicted a decline in delayed recall two years postoperatively, but not ten years after ATR.

Two other long-term follow-up studies have used absolute performance, not change or difference scores, as dependent variables in the logistic regression analysis. Better postoperative verbal memory performance was predicted by better baseline performance, right side of surgery, and younger age at surgery (Alpherts et al. 2006). Helmstadter et al. (2003) also identified a better mental reserve capacity together with a shorter retest interval and better seizure control as predictors of better postoperative cognitive performance. In other words, patients with better baseline performance retained long-term cognitive performance due to their ability to compensate for the changes associated with the possible cerebral damage. Finally, right side of surgery, younger age and male gender have been associated with greater postoperative improvement in memory performance (Grammaldo et al. 2009).

2.10.3 Complications

When defining the surgical success, the improved seizure control must be weighed against the possible risks associated with surgery. There is no universal definition for a complication after epilepsy surgery, but some authors have defined a complication as an unwanted, unexpected, and uncommon event after a diagnostic or therapeutic procedure (Rydenhag & Silander 2001). Accordingly, symptoms that are unavoidable or preoperatively acknowledged as frequent postoperative phenomena should be classified as side effects rather than complications. The overall rate of complications associated with epilepsy surgery has been claimed to be between 9.3 and 19%; including 8.8–12% minor or transient complications and 0.5–7% major or permanent complications (Behrens et al. 1997, Rydenhag & Silander 2001, Salanova et al. 2002, Sindou et al. 2006, Tanriverdi et al. 2009). The observed differences are in part associated with differences in the classification of complications used and the type of surgery being examined. In most cases mainly surgical and neurological complications have been assessed. Furthermore, some postoperative disturbances related to the postoperative edema may be considered as acceptable side effects instead of complications if they have resolved themselves completely within a few days.

The surgical and neurological complications related to epilepsy surgery were evaluated in a large Swedish multicentre study (Rydenhag & Silander 2001). A complication was defined as minor if it resolved within three months, and major if it affected activities of daily living and lasted for longer than three months. When a total of 449 therapeutic procedures including reoperations were evaluated, then minor complications were reported in 8.9% and major complications in 3.1% of cases. The complication rate for ATRs (168 out of 368 resective procedures) was 9.5% and 2.9%, respectively.

Another large single-centre study reported surgical complications in 8.4% of 429 therapeutic procedures (65% temporal lobe resections). A permanent shunt needed to be inserted in three patients but otherwise no permanent surgical morbidity was observed (Behrens et al. 1997). The total rate of neurological complications was 5.4%, with 3.0% causing transient morbidity and 2.3% causing permanent morbidity. After temporal lobe

resections, surgical complications were observed in 7.5% and neurological in 4.7% of patients.

One study evaluated morbidity in a single institution in Montreal, Canada, involving 1905 epilepsy surgery patients who had undergone 2449 therapeutic procedures performed by single neurosurgeon (Tanriverdi et al. 2009). There were no major surgical complications, and the overall surgical complication rate was 2.9%. The rate of overall neurological morbidity was 3.3% (minor 2.7% and major 0.5%).

In a study examining only patients undergoing surgery for TLE, surgical and neurological complications were observed in 21 out of 215 (9.8%) cases (Salanova et al. 2002). In addition, verbal memory problems were reported in 8.8% and postoperative psychiatric problems in 7.9% of patients. Sindou and co-workers (Sindou et al. 2006) reported complications in a consecutive series of 100 adult patients with medically refractory MTLE using the classification described by Rydenhag and Silander (Rydenhag & Silander 2001). Major complications were observed in 7% of patients and minor complications in 12% of patients.

The most commonly reported surgical complications after epilepsy surgery include infection, haematoma, hydrocephalus, cerebrospinal fluid leakage, deep vein thrombosis and pulmonary embolism. The typical neurological complications include dysphasia, language difficulties, cranial nerve dysfunction, hemianopia, hemiparesis and spasticity (Behrens et al. 1997, Rydenhag & Silander 2001, Salanova et al. 2002, Sindou et al. 2006, Tanriverdi et al. 2009). The factors associated with increased risk of complications include higher age of the patients (Rydenhag & Silander 2001, Tanriverdi et al. 2009) and the number of reoperations (Tanriverdi et al. 2009).

Mortality related directly to epilepsy surgery is rare. Most studies have reported no mortality (Behrens et al. 1997, Salanova et al. 2002, Sindou et al. 2006, Tanriverdi et al. 2009). In the Swedish multicentre study (Rydenhag & Silander 2001) one patient died from a postoperative haematoma after a temporal lobe resection. Therefore, the overall mortality was 0.3% and the mortality rate was 0.45% for the temporal lobe resections.

Partial visual field defects (contralateral upper quadrantanopsia), are very common both after ATR and SAH (Egan et al. 2000, Mengesha et al. 2009, Jeelani et al. 2010). These deficits are caused by damage to Meyer's loop of the optic radiation, which displays considerable heterogeneity in its anterior extent (Barton et al. 2005, Nilsson et al. 2007, Taoka et al. 2008, Yogarajah et al. 2009). The risk of a postoperative visual field defect is probably for the most part due to this individual anatomical variability and therefore contralateral upper quadrantanopsia is generally classified as a surgical side effect rather than a complication. Since most patients are asymptomatic (Egan et al. 2000), routine postoperative assessment of the visual fields is not needed and clinically significant defects can also be identified with clinical assessment (Manji & Plant 2000). In a small minority of patients, the severity of the defect prevents driving and therefore preoperative counseling of the patients is important (Manji & Plant 2000, Jeelani et al. 2010). In the future, diffusion tensor tractography of the optic radiation may be a potentially useful preoperative method for assessing the risk of postoperative visual field defects in individual patients (Nilsson et al. 2007, Taoka et al. 2008, Yogarajah et al. 2009).

In summary, epilepsy surgery can be performed with an acceptably low rate of morbidity, and furthermore, mortality related to surgery is rare.

2.10.4 Reduction of antiepileptic medication after surgery

The majority of patients undergoing surgery for TLE are using polytherapy of at least two drugs prior to surgery (Asztely et al. 2007). Therefore a reduction in AED therapy may be a beneficial effect of epilepsy surgery. However, conflicting opinions exist regarding the indications for continued AED therapy and the appropriate timing for medication withdrawal in postoperatively seizure-free patients.

In a survey of 62 Canadian epileptologists (Tellez-Zenteno et al. 2012), the minimum seizure-free period required after epilepsy surgery before withdrawing AEDs was found to vary substantially among responders. The majority (50%) however felt that a seizure-freedom of at least one year should be necessary before medication could be reduced. The most important factors influencing the decision to completely withdraw AEDs were patient preferences, HS on histopathology, unilateral HS on preoperative MRI and normal EEG before discontinuation. The most important factors against a reduction were generalised or focal epileptiform activity in the EEG, any seizures after surgery, presurgical multifocal, bilateral, or diffuse EEG abnormalities, persistent isolated auras, and patient`s desire to resume driving. There were several determinants of an ideal candidate for stopping AEDs e.g. unilateral HS, a well-defined lesion on MRI before surgery, seizure-freedom and normal EEG after surgery. However, 9% of physicians never recommended complete withdrawal of AEDs postoperatively.

Six retrospective observational studies published between 1983 and 2003 were reviewed by Schmidt and coworkers (Schmidt et al. 2004). After planned discontinuation of AEDs in postoperatively seizure-free patients, the mean recurrence rate in adults in four studies was 34%. These four studies included mainly different types of temporal lobe surgery with a maximum follow-up from one to five years. Seizure recurrence increased during the follow-up of one to three years and occurred within three years of AED discontinuation. More than 90% of adult patients with seizure recurrence regained seizure control after the previous antiepileptic medication was reinstated. Seizure recurrence was unaffected by the duration of postoperative AED treatment; and the authors suggested that delaying discontinuation beyond one to two years of complete postoperative seizure control seemed to confer no added benefit. The occurrence of rare seizures or auras after surgery did not eliminate the possibility of successful AED discontinuation.

More recent studies have reported that between 22% and 53% of patients discontinue AED treatment after TLE epilepsy surgery (Kim et al. 2005, Al-Kaylani et al. 2007, Asztely et al. 2007, Lee et al. 2008, Tanriverdi et al. 2008b, Elsharkawy et al. 2009a, Rathore et al. 2011b). The proportion of postoperatively seizure-free patients, who have seizure recurrence after AED reduction has been in a range between 25 and 40% (Griffin et al. 2004, Kim et al. 2005, Berg et al. 2006a, Al-Kaylani et al. 2007, Lee et al. 2008, Rathore et al. 2011b). Usually the antiepileptic medication is restarted or reinstituted if seizure relapse occurs (Berg et al. 2007). However, between 3 and 18% of patients have recurrent seizures after attempted withdrawal of antiepileptic medication (Griffin et al. 2004, Kim et al. 2005, Al-Kaylani et al. 2007, Rathore et al. 2011b).

There is some information regarding the prognostic factors for seizure outcomes after cessation of AEDs in post-surgical patients. Factors that have been associated with successful AED reduction include immediate remission after hospital discharge (Berg et al. 2006a), younger age at surgery (Kim et al. 2005, Al-Kaylani et al. 2007, Lee et al. 2008), shorter duration of epilepsy (Kim et al. 2005) and AED reduction later than 10 months after surgery (Lee et al. 2008). Seizures may also recur more often in patients with normal preoperative MRI (Schiller et al. 2000) or in patients with continued auras (Berg et al. 2006a). It has also been claimed that seizures that recur after complete AED withdrawal seem to have a better prognosis than seizures that recur during AED reduction (Kim et al. 2005).

Reports concerning the reduction of AEDs after surgery are often observational, retrospective or secondary analyses of larger studies. Therefore, those patients who are currently selected to taper AEDs may differ in their risk profiles from those who continue AEDs postoperatively. Based on the data available, it can be also asked whether it is worthwhile to pursue complete discontinuation of AEDs after epilepsy surgery and a prior long history of drug-refractoriness. An acceptable alternative is to continue an AED monotherapy that is well tolerated in order to minimize the risk of seizure recurrence.

2.10.5 Quality of life after TLE surgery

Health-related quality of life (HRQOL) is impaired by seizures (Birbeck et al. 2002) and by intractable TLE (Aydemir et al. 2004, Mikati et al. 2006). After resective surgery for TLE, HRQOL will improve if good seizure control, especially seizure freedom, can be achieved (Malmgren et al. 1997, McLachlan et al. 1997, Markand et al. 2000, Wiebe et al. 2001, Aydemir et al. 2004, Lowe et al. 2004, von Lehe et al. 2006, Elsharkawy et al. 2009b). In individual studies, HRQOL levels similar to those of matched healthy individuals have been observed during a long-term follow-up (Mikati et al. 2006). However, there is also evidence that HRQOL may improve postoperatively irrespective of seizure outcome (Gilliam et al. 1999). This could be due to the fact, that quality of life in TLE is also affected by the presence and severity of depressive symptoms and, to a lesser degree, of anxiety symptoms (Boylan et al. 2004, Meldolesi et al. 2006).

Most available data regarding the HRQOL after TLE surgery comes from studies with limited follow-up periods, usually only one to two years. In the prospective multicenter study of epilepsy surgery (Spencer et al. 2007) 313 patients were followed-up for 6.5 years after resective epilepsy surgery, with 262 (84%) being followed for at least five years. The majority of the patients were operated on for TLE. The HRQOL improved within six months after surgery, regardless of seizure outcome. However, subsequent changes paralleled the length of time seizure-free or aura-free and stabilised after two years. HRQOL was unrelated to duration of epilepsy, duration of intractable epilepsy, or continuation of medications. When the association of seizure control, memory change, and HRQOL was further analysed in 138 patients (Langfitt et al. 2007b) from the same study, HRQOL improved in patients who were in remission at the two-year or five-year follow-up, regardless of memory outcome. If seizures persisted at both two and five years, but there was no memory decline, then HRQOL remained stable. However, in the patients who experienced both persistent seizures and memory decline the HRQOL also declined. The declines were most apparent on HRQOL subscales assessing memory, role limitations, and limitations in work, driving, and social activities.

In another smaller prospective study (Cunha & Oliveira 2010) QOL after surgery for TLE during five-year follow-up was described. As in the multicenter study of epilepsy surgery (Spencer et al. 2007), the overall QOL increased steadily after surgery until the second year of follow-up. In addition seizure-related worry decreased significantly up to four years. Enhancement of social function was observed 6 months after the operation, and beyond this point, the improvement in social function continued more gradually. Neither the duration of epilepsy or age at surgery influenced the QOL.

2.10.6 Psychosocial outcomes after TLE surgery

Jalava et al. assessed the social adjustment and competence 35 years after the onset of childhood epilepsy in a prospective controlled cohort study (Jalava et al. 1997). Even though the patients in the study had no associated initial neurological impairment or disability, epilepsy was associated with a lower educational level, a lower employment status, a reduced marital rate and an impairment in perceived life management. Epilepsy is also associated with experience of stigma (MacLeod & Austin 2003, de Boer et al. 2008); and particularly patients with drug-resistant epilepsy have to deal with longstanding restrictions in driving (Berg et al. 2000, No et al. 2011).

The process of adjustment after any life changing medical intervention involves four main domains i.e. special and general physical, psychological and socio-behavioral domains (Bladin et al. 1999). Problems in the adjustment process in any of these domains may be related either to unsuccessful treatment i.e. ineffective treatment or adverse reactions; or the treatment success itself, i.e. the "burden of normality" (Bladin et al. 1999). The "burden of normality" is an important factor also in the recovery process after TLE surgery and it is encountered particularly in seizure-free patients (Wilson et al. 2001b). It can be measured by assessing postoperative psychological changes (increased internal and

external expectations, grieving for epilepsy and for the lost years), behavioral changes (excessive or avoidance behavior), affective changes or sociological changes (altered family dynamics, new skills, changed vocational possibilities) (Wilson et al. 2001a, Wilson et al. 2005).

During the first postoperative year, a variety of physical, psychological, and social adaptation skills are needed (Koch-Stoecker et al. 2013). The adaptation process after surgery can be divided in three phases (Koch-Stoecker et al. 2013). In the early postoperative period, the patients experience mainly physical problems and after discharge from hospital, psychiatric problems may appear. Only in the third phase does reorientation occur, although this is dependent on the postoperative outcome.

The type of expectations that patients have preoperatively can affect the patient satisfaction after TLE surgery (Wilson et al. 1998). Postoperative satisfaction with surgery is associated with better psychosocial functioning (Wheelock et al. 1998). Accordingly, the preoperative expectations of surgery are strongly related to seizure-free outcome (Wheelock et al. 1998) and particularly seizure-free patients exhibit improvements in the psychosocial measures after surgery. Additionally, patients with more practical expectations such as being allowed to drive or gaining new employment may have better postoperative psychosocial functioning when compared to patients with psychological or social expectations (Wilson et al. 1998). Since unmet expectations are related to adverse psychosocial outcomes, it is important that the patient has a realistic view of the expected outcome before surgery.

Jones et al. (2002) examined the long-term psychosocial outcomes in a consecutive series of patients who underwent ATR. When compared with medical management, surgery had a positive impact on psychosocial outcomes in terms of employment, independent living, driving, and financial independence. Positive changes in psychosocial outcomes were observed even although the patient did not achieve a seizure-free state (Jones et al. 2002). In another long-term outcome study, a substantial overall improvement in psychosocial condition was also observed regarding driving, employment status, and familial or social relationships (Dupont et al. 2006). The long-term psychosocial outcome (mean seven years) was similar to the short-term outcome. However, the long-term psychosocial outcome did not depend on seizure freedom or postoperative seizure frequency. According to one study, early postoperative anxiety may serve as a marker of poor psychosocial outcome after surgery, whereas the resolution of early anxiety and a vocational change one year after the operation may be predictive of a good long-term outcome (Wilson et al. 2005).

2.10.7 Cost-effectiveness of TLE surgery

Epilepsy is an economic burden on individuals and society because of increased health care cost, as well as losses in employment, wages, and domestic work. Indirect costs account for 85% of the total costs and, in addition to the direct costs, they are concentrated in those individuals with intractable epilepsy (Begley et al. 2000).

The costs and cost-effectiveness of epilepsy surgery are related to the preoperative diagnostic investigations being used, surgical facilities, and the outcome of surgery. For surgery to be cost-effective, the long-term cost savings from reduced health care use should provide some compensation to the initial costs of preoperative evaluation and surgery. At present there is still rather limited data concerning the cost-effectiveness of temporal lobe resections. However, the available studies already indicate that surgical treatment of intractable TLE is cost-effective use of medical resources (Malmgren et al. 1996, King et al. 1997, Langfitt et al. 2007a) and comparable to other accepted medical or surgical interventions, such as total knee arthroplasty or coronary artery balloon angioplasty (King et al. 1997). In an early Swedish study (Malmgren et al. 1996) the mean total cost for epilepsy surgery evaluation and surgery was 46 778 US $. The mean total cost of rendering one patient seizure-free with surgery was 110 000 US $, which was comparable to the cost of a new AED vigabatrin if it were used over lifetime. In the multicenter observational

study of epilepsy surgery health care costs for the two years prior to surgical evaluation and for two years afterwards were calculated in a sample of 68 TLE patients (Langfitt et al. 2007a). Total costs for seizure-free patients declined by 32% in the two years following surgery, due to reduced use of AEDs and inpatient care. The costs did not change in patients with persisting seizures, whether or not they had surgery. Further cost savings in seizure-free patients would be expected if AEDs would be successfully reduced.

3 Aims of the Study

The general aim of this study was to evaluate the long-term outcome after surgical treatment of MTLE, with a special emphasis on long-term seizure and cognitive outcomes. The main purpose was to identify preoperative markers and prognostic factors for the outcome.

The more specific aims were:

I To evaluate the occurrence of damage in the entorhinal, perirhinal, and temporopolar cortices in unilateral drug-refractory MTLE as a MRI-marker for a more widespread damage of temporal lobe structures.

II To evaluate the predictive factors for the long-term seizure outcome after MTLE surgery.

III To evaluate the predictive factors for seizure outcome after MTLE surgery in patients with normal MRI.

IV To evaluate cognitive performance after surgical treatment of unilateral MTLE during long-term follow-up, and to identify the predictive factors for a possible postoperative decline in cognitive performance.

4 Subjects and methods

4.1 PATIENTS

The Kuopio Epilepsy Center in Kuopio University Hospital is a comprehensive centre for epilepsy surgery. It serves an adult population of 4 million inhabitants in Finland as well as children from its own catchment area (approximately 900 000 inhabitants). Between 1988 and 2006, 229 adult patients underwent temporal lobe resection including amygdalohippocampectomy due to drug-resistant TLE. These patients have been postoperatively followed-up according to a specified protocol including neurological and neuropsychological outcome data.

4.1.1 Study I

In study I, the MTLE group consisted of 27 patients operated for unilateral drug-refractory MTLE between 1993 and 1997. On the basis of video-EEG recordings, 12 patients had unilateral seizure focus on the left and 15 patients had seizure focus on the right. Only patients with good postoperative outcome (defined as Engel's classes I and II) were included. The extratemporal epilepsy group included ten patients with well-localized intractable extratemporal focal epilepsy and the control group 20 healthy individuals. All patients with MTLE in study I were also included in study II.

4.1.2 Study II

In study II, 140 consecutive adult patients operated for MTLE between 1988 and 1999 were included. Patients with temporal lesionectomies without amygdalohippocampectomy and patients for whom any extra-temporal cortical excisions had been carried out were excluded from the study.

4.1.3 Study III

In study III, 146 patients with suspected MTLE were evaluated with intracranial EEG-electrodes between January 1990 and December 2006. Of these patients, 70 initially had MRIs that were interpreted as normal. After re-evaluation, 64 patients with normal high-resolution MRI were included in the study, and after invasive video-EEG evaluation resective surgery was performed on 38 patients. Twenty patients in study III were also included in study II and thirteen patients in study IV.

4.1.4 Study IV

The patients in study IV were retrieved from a series of 172 consecutive adult patients, who were operated for drug resistant MTLE between December 1988 and November 2002. Among these altogether 128 patients with unilateral MTLE were identified. Complete neuropsychological evaluation (preoperatively, one year postoperatively, and two or three years postoperatively) was available for 107 patients. Twenty-one patients were not included in the study because they were either lost from follow-up or had no preoperative neuropsychological assessment available. We also excluded six patients (5%) due to right hemisphere speech dominance in the Wada test and three patients (2%) due to a general intellectual ability in the defective range (FSIQ < 70). Taken together, we identified 98 patients with unilateral MTLE who were eligible for the study (Figure 5). Seventy-six out of 98 (78%) patients in study IV were also included in study II.

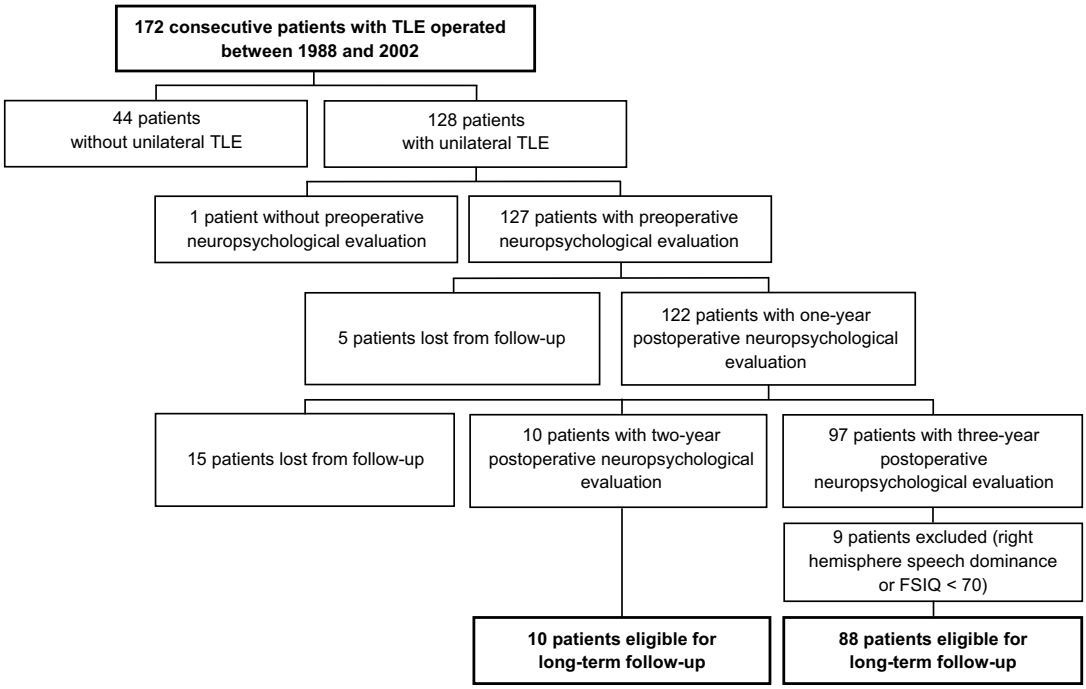

Figure 5. Description of the patient population in study IV

4.2 METHODS

4.2.1 Preoperative evaluation

The presurgical evaluation during the study period in general included a neurological evaluation, MRI, ictal video-EEG recording with scalp and sphenoidal electrodes, neuropsychological assessment, psychiatric evaluation and the Wada test for the assessment of speech lateralization and memory. If considered necessary in clinical assessment, molecular imaging (PET or SPECT) and/or invasive video-EEG recording was performed for selected patients.

In Study I, a neurological evaluation, MRI, ictal video-EEG recording with scalp and sphenoidal electrodes, neuropsychological evaluation and the Wada test were performed in all patients. A psychiatric evaluation was also carried out in the majority of patients (n = 22). Eight patients underwent invasive recordings with subdural strip electrodes.

In study II, all patients underwent a neurological evaluation, MRI and the Wada test. Ictal video-EEG recording was performed with scalp and sphenoidal electrodes in 136 patients and additionally 50 intracranial recordings with subdural strip electrodes were carried out. The neuropsychological evaluation (n = 135), and psychiatric evaluation (n = 118) were also completed by the majority of patients. The surgical procedure was classified as "curative", if preoperative assessment indicated unilateral TLE. However, if the patient had bitemporal or multifocal epilepsy, or if the epileptic focus could not otherwise be completely removed, the aim of surgery was classified as "palliative". Patients with dual pathology (hippocampal atrophy in combination with an extrahippocampal structural lesion in the MRI), combined temporal and extratemporal abnormality (other temporal lobe lesion than hippocampal atrophy in association with an extratemporal lesion in the MRI), bitemporal MRI abnormality, or temporal foreign tissue lesion without ictal EEG, were also

classified as palliative. In palliative patients, only considerable postoperative seizure reduction, rather than seizure-freedom, was probable.

In Study III, all patients were evaluated with ictal scalp- and intracranial video-EEG, high Tesla MRI, neuropsychological assessment and psychiatric evaluation. In the case of bitemporal seizure onsets in invasive EEG, patients with strong unilateral predominance (80% or more of the seizures originating from one temporal lobe) and very difficult symptoms were, however, considered to benefit from resective surgery.

In study IV, the pre-surgical evaluation included neurological evaluation, MRI, neuropsychological assessment and the Wada test. Ictal video-EEG recording was performed with scalp and sphenoidal electrodes in 97 patients and additionally 32 intracranial recordings with subdural strip electrodes were carried out. Eighty-four patients completed the preoperative psychiatric evaluation.

4.2.2 MRI

Between 1988 and 1993, preoperative MRI was performed with different kinds of imagers and a variety of imaging protocols. High-resolution MRI with a standardised protocol became available for presurgical evaluation at Kuopio University Hospital in 1993. Since then, all epilepsy surgery candidates were systematically scanned with a 1.5T Magnetom (Magnetom Vision, Siemens Medical Systems, Erlangen, Germany) using a circular polarized head coil. The brain was imaged with transverse T2- and intermediate-weighted and coronal T2-weighted sequences (repetition time msec/echo time msec, 2,400/80/20; matrix, 192 x 256; and section thickness, 4 mm, interslice gap 0.4 mm). The temporal lobes were imaged with a tilted coronal 3D magnetisation-prepared rapid acquisition gradient-echo (MP-RAGE) sequence with parameters 10/4/1 (TR/TE/excitations), inversion time 250 ms, flip angle 12°; FOV 250 mm, matrix 256×192. This resulted in 128 contiguous T1-weighted images with a 1.5- to 2.0-mm section thickness oriented perpendicular to the long axis of the hippocampus. Experienced neuroradiologists blinded to the epileptic focus evaluated the images qualitatively.

The hippocampal and amygdaloid volumes were measured for investigational purposes (all patients in Study I and 67 patients in Study II) as previously described (Soininen et al. 1994). The intraobserver variability for hippocampal volumes was 6.8%.

The volumes of the EC, PRh, and TP cortices were measured (Study I) using a histology-based volumetric method (Insausti et al. 1998) from the T1-weighted MP-RAGE images. The cases were analysed in a random order without exact knowledge of the focus. The images throughout the entire rostrocaudal extent of the TP, EC, and PRh cortices were reconstructed into 2-mm-thick contiguous sections oriented perpendicular to a line drawn between the anterior and posterior commissures at the midsagittal level. Then, the following landmarks were identified from the images: the temporal pole, appearance and depth of the collateral sulcus, the limen insulae, and the last sections containing the EC or PRh. Thereafter, boundaries of the TP, EC, and PRh were determined. In an attempt to reduce the error in tracing the boundaries, images were magnified and interpolated fourfold, which resulted in an effective pixel size of 0.25 mm. Finally, the outlines of each area were traced with a trackball driven cursor on successive MRI images from the rostral to caudal ends. The volumes were calculated with software developed in-house for a standard work console.

In Study III, all MRI studies were carried out using a high Tesla scanner (four patients with a 1T scanner, 60 patients with a 1.5T scanner, and two patients with a 3T scanner). For the purpose of the study, all MRIs were independently re-evaluated by two experienced neuroradiologists unaware of the clinical details. Between 1990 and 1998, the position of the intracranial electrodes was estimated according to skull X-ray imaging. Since 1999, the 3D reconstructed MRI technique (Curry; Compumedics NeuroScan, Charlotte, U.S.A) has been adopted in order to visualize the intracranial electrodes more precisely in relation to the superficial cortical anatomy after implantation (Immonen et al. 2003).

4.2.3 Molecular imaging

Interictal [18F]FDG-PET studies were performed in Turku PET Centre in 30 of 64 patients (17 of 38 operated patients) in the study III according to previously published methods (Lamusuo et al. 2001). Interictal and/or ictal SPECT studies were performed in Kuopio University Hospital in 28 of 64 patients in study III, of whom the data from 22 of 64 patients (13 of 38 operated patients) were available for re-evaluation. Ictal and/or interictal SPECT-perfusion or benzodiazepine receptor studies were performed using a Siemens MultiSPECT3 gamma camera with fan-beam collimators (Kuikka et al. 1993). [99mTC]ECD was used as a tracer for perfusion studies (Kuikka & Berkovic 1994) and [123I]Iomazenil or [123I] NNC-13-8241 for benzodiazepine receptor studies (Kuikka et al. 1996). The PET and SPECT studies were re-evaluated and graded as either unilateral temporal or other, as well as ipsilateral to the operated side or other.

4.2.4 Neuropsychological evaluation

Neuropsychological assessment was performed with a comprehensive test battery according to the clinical diagnostic requirements. In general, the assessment was performed preoperatively, three months postoperatively, one year postoperatively; and two or three years postoperatively.

Intellectual ability was assessed with the Wechsler Adult Intelligence Scale (Wechsler 1955) or the Wechsler Adult Intelligence Scale–Revised (Wechsler 1981); Verbal and Performance Intelligence Quotients (VIQ, PIQ) were estimated. Verbal memory was evaluated with Logical Prose and Associative Learning (learning of word pairs) subtests of the Wechsler Memory Scale (WMS, Wechsler 1945). Visual memory was assessed with the Visual Reproduction subtest of the WMS. Immediate and delayed recall scores of the memory measures were evaluated. Delayed recall of the Rey-Osterrieth Complex Figure (Rey 1941, Osterrieth 1944) was also used as a measure of the visual memory. Verbal ability was evaluated with the Object Naming Test (Newcombe et al. 1971), the Token Test (Boller & Vignolo 1966) and the Verbal Fluency Test (Milner 1964). The Wada test was performed for each patient to determine the hemispheric dominance for language and to evaluate the risk for severe postoperative memory decline (Wada & Rasmussen 1960).

In study II, only preoperative tests measuring delayed verbal and visual memory were used for logistic regression analysis. In study III, a neuropsychological evaluation of intellectual ability, memory, and language was performed prior to surgery and one year postoperatively. The immediate postoperative neuropsychological assessment (three months postoperatively) was excluded from the analyses. In study IV, neuropsychological evaluation was performed preoperatively (median 6.4 months); one year postoperatively (n = 94, median 12.3 months); and two (the first ten patients) or three years (n = 88) postoperatively (median 37.0 months). The immediate postoperative neuropsychological assessment (two weeks or three months postoperatively) was excluded from the analyses since there was a change in the postoperative follow-up scheme during the study period.

4.2.5 Invasive video-EEG

In the majority of MRI-negative patients the indications for invasive EEG evaluation were bitemporal or unilateral frontotemporal differential diagnosis. Therefore, the electrodes were implanted according to a prejudged, individual plan to cover the frontal and temporal neocortical, and temporal and orbitofrontal basal areas. The strip electrodes (ranging from four to eight contact electrodes) were introduced into the subdural space through two frontal and two temporal burr holes under general anaesthesia. Intracerebral depth electrodes were later introduced in two patients, in whom there was a failure in localisation of the ictal onset zone with subdural strip electrodes. In one of these patients, two electrodes were stereotactically (Leksell Stereotactic System, Elekta Corporate, Stockholm, Sweden) implanted on both sides, with target points on the hippocampus and the amygdala, using the lateral temporal approach. In the other patient, the occipital route was

used and one electrode was implanted into the hippocampus and the amygdala on each side.

Two experienced specialists in clinical neurophysiology re-evaluated the ictal subdural EEG data. When the first ictal electrographic onset appeared only on the mesial electrode strip contacts, the seizure onsets were classified as ”unitemporal mesial”. Accordingly, if the ictal onset occurred in the temporal neocortical strips, or was seen simultaneously in mesial and neocortical temporal contacts, but not in other strips, then the seizures were judged as ”unitemporal neocortical +/- mesial”. ”Bitemporal onset” refers to definite independent ictal onsets from both temporal lobes (either mesial or neocortical). In these seizures, a unilateral predominance in seizure onsets was also evaluated by using the 80% cut-off point. Based on ictal onsets outside the temporal lobe strips, all other seizures were judged to be ”fronto-temporal”, ”extratemporal” or ”multifocal” onset. The temporal EEG findings were further evaluated as being ipsilateral or contralateral to the operation side.

4.2.6 Analyses of postoperative seizure outcome

Preoperative seizure frequency was calculated for the year preceding the operation, excluding seizures occurring during the video-EEG recording. Typical temporal lobe auras were not included in the seizure frequency; however, unclassified seizures (possibly including auras) were included.

Postoperative outcome was assessed according to a modified classification adapted from Engel (Engel et al. 1993) using the complete classification with different subclasses (Table 6). Neighbourhood seizures (seizures occurring one month postoperatively) were excluded from the analyses. Routine postoperative follow-up visits were scheduled for all patients at three months, one year and three years after the operation. Thereafter, the patients were either followed-up at the center as outpatients or contacted by telephone for additional historical details and up-to-date follow-up. In problematic cases, medical records were obtained from other hospitals or community health centres. Whenever possible, the original prospectively collected seizure calendars were obtained.

In Studies I and II, seizure freedom was determined using the different Engel’s subclasses. Seizure freedom refers to Engel’s subclass IA (patients who have been completely seizure-free since surgery) at three months, one year and two years postoperatively. However, during the long-term follow-up (from three years onwards) seizure freedom refers to Engel’s subclasses IA, IC and ID. In Engel’s subclass IC patients may have had some seizures after surgery, but they must have been free of disabling seizures for at least two years at the time of assessment. In Engel’s subclass ID, patients may have had atypical generalized convulsions after AED withdrawal, but no other seizures. Patients with postoperative auras only (Engel’s subclass IB) were displayed separately at all time points, following the suggestions of the new ILAE classification (Wieser et al. 2001). In the subgroup analyses, patients who did not have seizures at the three-month follow-up (Engel IA) were considered as initially seizure-free. In the subgroup analyses of seizure-relapses, patients with Engel’s subclasses IC and ID were not re-considered to be seizure-free after the first postoperative seizure.

In Studies III and IV, Engel’s main class I (including Engel’s subclasses IA–D) was used to describe postoperative freedom from disabling seizures.

In Studies II–IV, Engel’s class II refers to all patients who have rare seizures (fewer than three seizures per year) postoperatively (Engel’s subclasses IIA–C). In subclass IIA patients were originally seizure-free, but have rare seizures at the time of the assessment. In subclass IIB patients have rare seizures after surgery. In subclass IIC patients may originally have had more than rare postoperative seizures, but they must have had only rare seizures for at least two years at the time of assessment. Engel’s class III refers to a reduction in seizure frequency of at least 80% postoperatively (worthwhile seizure reduction). Engel’s class IV refers to a less than 80% seizure reduction postoperatively (no worthwhile improvement in seizure frequency, Engel’s subclasses IVA–C). This includes

patients with a seizure reduction of at least 50% (subclass IVA), patients with no change from preoperative seizure frequency and severity of seizures (subclass IVB), or patients with more frequent (an increase in seizure frequency of at least 50% postoperatively) or more severe seizures than preoperatively (subclass IVC). According to the Engel's classification during long-term follow-up, the seizure outcome data from the preceding last two years is used for the assessment.

Engel's classes I and II were considered to be "good or favourable outcome" and Engel's classes III and IV "poor outcome" in Studies I–III. In Study IV, a stricter criterion was chosen and only Engel's class I was considered as "good outcome".

Table 6. The modified Engel's classification of postoperative seizure outcome (Engel et al. 1993)

Class I: Free of disabling seizures [a]	
A	Completely seizure-free since surgery
B	Nondisabling seizures without impairment of consciousness (auras) only since surgery
C	Some disabling seizures after surgery, but free of disabling seizures for at least two years
D	Atypical generalized convulsions with antiepileptic drug withdrawal only
Class II: Rare seizures	
A	Initially free of disabling seizures, but has rare seizures (fewer than three seizures per year) now
B	Rare disabling seizures since surgery (fewer than three seizures per year)
C	More than rare disabling seizures after surgery, but now rare seizures for at least two years
Class III: Worthwhile improvement	
A	Worthwhile seizure reduction (reduction in seizure frequency of at least 80% postoperatively)
Class IV: No worthwhile improvement	
A	Significant seizure reduction (a seizure reduction of at least 50% postoperatively)
B	No appreciable change (no change from preoperative seizure frequency and severity of seizures)
C	Seizures worse (an increase in seizure frequency of at least 50% postoperatively or more severe seizures than preoperatively)

[a] Excludes early postoperative seizures (seizures occurring one month postoperatively)

4.2.7 Resective surgery and complications

The surgical procedure was performed with controlled respiration under general inhalation anaesthesia. The anterior temporal area was exposed from a large fronto-temporal skin flap removing temporal bone lambeau. After the dura was opened, electrocorticography (ECoG) with neocortical and acute mesial intracerebral depth electrodes was performed to measure epileptic activity in the hippocampus and the amygdala, and to tailor the possible neocortical resection. Intravenous methohexital or propofol (since 2005) were used to enhance the occurrence of focal epileptiform EEG abnormalities in ECoG. Depending on the earlier video-EEG findings and acute ECoG information, the anterior hippocampus and the amygdala with or without neocortical area were removed using a microneurosurgical technique. The extent of anterior temporal neocortical resection never exceeded 3.5 cm on the dominant and 4.0 cm on the nondominant side measured from the tip of the temporal

pole. Since 2001, the temporal neocortical resection was modified according to Spencer, leaving the upper temporal gyrus intact (Kim & Spencer 2000).

Data regarding the complications were retrospectively collected from the medical records. Complications were defined and classified according to Rydenhag and Silander (Rydenhag & Silander 2001). A complication was considered as an unwanted, unexpected, and uncommon event after a diagnostic or therapeutic procedure. A complication was classified as major if it affected activities of daily living, lasted more than three months, or involved any significant neurologic deficit. Minor complications were resolved within three months. In study II, possible adverse postoperative psychiatric reactions were excluded from the analyses of complications. Information on causes of death was acquired from the Finnish national registry of mortality (Statistics Finland) in order to determine whether death was related to epilepsy. We considered that mortality was related to surgery if the death was caused by a clinically or pathologically identified major surgical complication and occurred within 30 days after surgery.

4.2.8 Histopathology

The histopathological diagnosis was collected retrospectively from the medical records, and the interpretation of surgical specimens was re-evaluated by an experienced neuropathologist. The surgical specimens were taken from three defined neuroanatomical regions, i.e. hippocampal formation, amygdala and temporal pole. Each tissue sample was grossly inspected, measured and cut into coronal slices. A selection of these slices were fixed in buffered formalin and embedded in paraffin for histological examination. Seven-micron thick sections were prepared and stained with a hematoxylin-eosin stain. Each section was evaluated under light microscopy for its representativeness. Lesions, such as gliosis in the molecular layer, satellitosis, gliosis in white matter, developmental alterations related to migration of neurons, HS or other pathological lesions, were searched for and recorded.

4.3 STATISTICAL ANALYSES

The data were analysed with several versions of the SPSS software for Windows (SPSS Inc, Chicago, IL, USA). Specifically SPSS versions 9.0 (Studies I and II), 16.0 (Study III) and 17.0 (Study IV) were used. The level of statistical significance was set at $p < 0.05$.

4.3.1 Study I

A ratio was used to correct volumetric data for individual variance in head size (Cendes et al. 1993b) with modifications (Kälviänen et al. 1998). Instead of brain volume, the mean brain area (obtained from the coronal image at the level of the anterior commissure; correlation with the brain volume: $r = 0.67$, $p<0.001$, $n = 20$) of the control subjects was divided by the corresponding brain area of the patient. Each measured cortical volume was then multiplied by this ratio for each patient.

The intraobserver variability of repeated measurements was analysed according to the criteria of Bland and Altman (Bland & Altman 1986) by performing repeated volumetric measurements for ten control subjects. The limits of agreement between the first and second measurements were defined as the mean difference in volume (first - second measurement) ± 2 SD of this mean difference. The clinical significance of the intraobserver variability was assessed by comparing the limits of agreement with the total volume of each measured area, the mean volume reductions, and the volume considered to be a marked volume reduction in individual analyses (± 2 SD from the mean of controls). If the mean difference in volume was near to zero, the limits of agreement were not considered as being clinically significant.

In the statistical analyses, the patients were divided into three groups according to localization of the seizure focus: TLE patients with the focus on the left, TLE patients with the focus on the right, and patients with extratemporal focal epilepsy. As the variances in most volumetric parameters were unequal in the different subgroups but nonetheless normally distributed; then the mean volumes of the EC, PRh, and TP cortices in different patient groups were compared with those in the control group by using the independent samples t- test with Bonferroni adjustment (3x). The combined volumes of the PRh and TP (referred to as the total perirhinal cortex) were subjected to similar analyses.

To assess the degree of asymmetry in the volumes, an asymmetry ratio was calculated according to Bernasconi and colleagues (Bernasconi et al. 1999): Asymmetry (%) = [100 x (R-L)] / [(R + L)/ 2] where R referred to the volume on the right and L that on the left. Asymmetry ratios in different patient groups were compared with those of the control group, and between left and right TLE groups, using the independent samples t- test with Bonferroni adjustment (4x).

The presence of cortical damage ipsilateral and contralateral to the side of seizure focus in individual patients was analysed by using the volume considered to be a marked volume reduction (≥ 2 SD from the mean of controls) as a cut-off point. After the initial analyses, both TLE groups were divided into two subgroups according to the degree of hippocampal damage: patients with a reduction of at least 2 SD from the mean of control subjects in the ipsilateral hippocampal volume, and patients with a reduction of less than 2 SD in the ipsilateral hippocampal volume. Each subgroup was compared with the control group, and, additionally, subgroups of patients with left TLE and subgroups of patients with right TLE were compared with each other (within the TLE group). The comparisons were performed using nonparametric Kruskal-Wallis and Mann-Whitney tests with Bonferroni adjustment (6x).

In control subjects, right–left asymmetry in the volumes was analysed by paired samples t- test, and the effect of sex was assessed with independent samples t- test. The effect of age at the time of MRI, age at onset of epilepsy, and duration of epilepsy between groups were assessed with a one-way analysis of variance with Tukey's post hoc test. Differences in seizure frequency between groups were evaluated using nonparametric Kruskal-Wallis and Mann-Whitney tests with Bonferroni adjustment. The contribution of cause and complex febrile seizures to the damage was evaluated with the nonparametric Mann-Whitney test. The correlations were calculated with the two-tailed Pearson's correlation test.

4.3.2 Study II

The postoperative outcome was analysed using the chi-square test for comparisons between patient groups, and with life tables. The predictive value of different preoperative factors with respect to outcome was analysed with logistic regression analysis. The demographic variables included a history of (complex) febrile seizures, age at onset of epilepsy, duration of epilepsy, clinical aetiology of epilepsy, preoperative seizure frequency (divided into subgroups by quartiles), seizure type predominance, and type of operation. Subgroups of qualitative MRI consisted of (1) hippocampal atrophy with or without temporal cortical atrophy; (2) other unilateral structural abnormality in the temporal lobe; and (3) other. Preoperative ictal EEG was reclassified for the regression analysis and subgroups consisted of (1) unilateral mesial or temporal ictal onset, (2) other. A subset of neuropsychological tests evaluating the delayed visual or verbal memory was additionally chosen for analysis. Additionally, patients with quantitative MRI data were analysed separately. In the logistic regression analyses, a p value of less than 0.05 was used to enter variable into the model and a p value greater than 0.1 was used to delete a variable from the model.

4.3.3 Study III

The potential predictors of seizure outcome were compared between the favourable and the poor outcome group using the two-tailed Fisher's exact test. The differences in preoperative cognitive performance of right and left TLE patients, as well as the change in neuropsychometric scores from preoperative to one-year postoperative assessment, were analyzed using the t- test for independent samples. The groups were compared in terms of change from the preoperative to postoperative assessment using the paired samples t- test. Patients were considered to have had a postoperative performance decline if they performed below one SD of the preoperative baseline findings of the whole patient group (Cukiert et al. 2009a).

4.3.4 Study IV

The univariate comparisons between the groups were performed using chi-square test, independent samples t- test or Mann-Whitney test. Bonferroni-adjustment was used in case of multiple comparisons. A linear mixed model for repeated measures (covariance pattern model with unstructured covariances within subjects) was used to analyse possible changes in the cognitive performance at group level between preoperative assessment (T1), one-year follow-up (T2) and three-year follow-up (T3). As the previous literature has indicated the side of surgery to be one of the explanatory factors for the postoperative cognitive outcome, neuropsychological follow-up data of the left and right TLE groups were analysed separately. Two fixed effects were included into each linear mixed model: Time (T1, T2 and T3) and postoperative seizure outcome three years after the operation (determined as Engel's class I or other). Additionally, the interaction between time and seizure outcome (time x outcome) was evaluated. Missing data were not replaced. Comparisons between estimated means were adjusted for multiple comparisons (Sidak). A significant change in the individual postoperative test performance was defined as greater than one SD change calculated from the preoperative baseline performance of the whole patient group (Cukiert et al. 2009a).

5 Results

5.1 DEMOGRAPHIC AND CLINICAL DATA OF PATIENTS AND CONTROLS

5.1.1 Study I

The mean age and gender did not differ between the controls and patients with left TLE, right TLE, or extratemporal focal epilepsy. Additionally, the mean age at onset of epilepsy, the mean duration of epilepsy, and the preoperative seizure frequency were similar between the different epilepsy groups.

Surgical outcome one year after the operation was excellent in 24 patients, i.e. 19 patients had become completely seizure-free (Engel's class IA), four had only nondisabling seizures (auras) after surgery (Engel's class IB), and one patient experienced a seizure during an inappropriate drug withdrawal (Engel's class ID). One patient had a good outcome with rare seizures (Engel's class IIA). Additionally, two patients initially had a worthwhile seizure reduction (Engel's class IIIA) after surgery. At the three-year follow-up, one of these patients had become seizure-free (Engel's class IC, some seizures after surgery but seizure-free for at least 2 years) and the other had a good outcome (Engel's class IIC, more than rare seizures after surgery but rare seizures for at least 2 years). Thus, these patients were also included in the study.

There was no significant right–left asymmetry in the mean volumes of the entorhinal, perirhinal and temporopolar cortices in control subjects. Additionally, the volumes were not affected by gender or age. In patients with left TLE, the mean hippocampal volume was reduced by 32% ipsilaterally ($p<0.001$) but not contralaterally. The asymmetry ratio of the hippocampus was higher than that in control subjects ($p<0.01$) or in patients with right TLE ($p<0.001$). Similarly, in patients with right TLE, the volume of the hippocampus was reduced by 31% ipsilaterally ($p<0.01$) but not contralaterally when compared with control subjects. The asymmetry ratio of the hippocampus was lower in the right TLE group than in the control group ($p<0.01$) or the left TLE group.

5.1.2 Study II

The median age of the patients at the time of the operation was 32 years (range 14–54). The median age at onset of epilepsy was 12 years (range 0.1–43) and median duration of epilepsy at the time of operation 19 years (range 2–47). Preoperative seizure frequency varied from 10 to 1655 seizures a year (median 78) during the year preceding the operation. In the majority of patients (82%, n = 115), most of the seizures were focal, with ictal impairment of consciousness and focal ictal EEG (median 75, range 7–916).

Based on the preoperative assessment, 103 patients (74%) had concurrent evidence of unilateral TLE. Their operation was preoperatively classified as curative. Additionally, 37 patients were operated on palliatively. These patients had bitemporal seizure onset (n = 18), unitemporal but extratemporally extending seizure focus (n = 6), multifocal epilepsy (n = 2), dual pathology (n = 2), combined temporal and extratemporal abnormality (n = 2), bitemporal MRI abnormality (n = 2), or posterior neocortical seizure onset in the dominant temporal lobe together with ipsilateral speech dominance (n = 2). In addition, three patients with temporal foreign tissue lesions without ictal EEG documentation were also classified in the palliative group.

5.1.3 Study III

Seventy of the 146 surgical candidates had normal MRI. After a re-evaluation of images, three patients were assessed to be MRI-positive and two patients were excluded due to the suboptimal quality of MRI (only low field MRI was available). In addition to temporal resection, one patient had also had extratemporal surgery and was, therefore, excluded from the study. Therefore, after re-evaluation, 64 patients with normal high-resolution MRI findings were included in the study (37 female, 27 male). The mean age at the time of electrode implantation was 31 years (range 15–51 years). The mean age at seizure onset was 16 years (range 1–40 years) and the mean duration of epilepsy was 15 years (range 2–43 years).

A total of 66 intracranial EEG evaluations were performed on 64 patients. Two patients of 64 had a combination of subdural and intracerebral depth electrodes, and in two patients the second recording was performed solely with depth electrodes. Resective surgery was performed on 38 patients but in 26 patients it was not possible to proceed to resective surgery. There were several reasons for not proceeding to operation i.e. probable frontotemporal or multifocal seizure onset (n = 16), seizure onset near Wernicke's area (n = 2), bitemporal onset of seizures (n = 4), inability to record seizures during intracranial video-EEG (n = 2) and subsequent seizure-freedom after invasive monitoring (n = 2, unitemporal seizure onset verified). During the same period, 229 adult TLE patients were operated in our center and the MRI-negative operated group (n = 38) constitutes 17% of all operated TLE patients.

5.1.4 Study IV

The left and right TLE groups were comparable in terms of age at onset of epilepsy, duration of epilepsy, aetiology of epilepsy, seizure frequency, age at surgery and postoperative seizure outcome. There were more female patients in the right TLE group (65%) than in the left TLE group (39%) ($p<0.05$). Fifty-eight patients (59%) achieved Engel's class I (free of disabling seizures) outcome during the three-year follow-up. Additionally 12 patients (12%) had rare seizures (Engel's class II), 11 (11%) achieved a worthwhile seizure reduction (Engel's class III), whereas 17 (17%) of patients gained no benefit from surgery (Engel's class IV).

Preoperatively patients with right TLE had higher VIQ than patients with left TLE ($p<0.05$). Right TLE patients also performed better in both the learning ($p<0.01$) and delayed recall ($p<0.001$) of word pairs, as well as in the Object Naming ($p<0.05$). There were no differences between the left and right TLE groups in other cognitive tests at baseline.

5.2 MRI VOLUMETRY OF THE ENTORHINAL, PERIRHINAL AND TEMPOROPOLAR CORTICES

5.2.1 Volumetry of the entorhinal, perirhinal and temporopolar cortices

In left TLE, the mean volumes of the entorhinal and temporopolar cortices were both ipsilaterally reduced by 17% compared with control subjects ($p<0.001$ and $p<0.05$, respectively). The mean volumes of the perirhinal and total perirhinal cortices did not differ from those in control subjects. All contralateral cortical mean volumes were also normal. The asymmetry ratios of the entorhinal, perirhinal, and total perirhinal cortices were higher in the left TLE group than in the control group ($p<0.05$, in all) or in the right TLE group ($p<0.001$ in all), indicating smaller volumes ipsilateral to the seizure focus. The presence of cortical damage ipsilateral and contralateral to the side of seizure focus in individual patients is summarized in Figure 6.

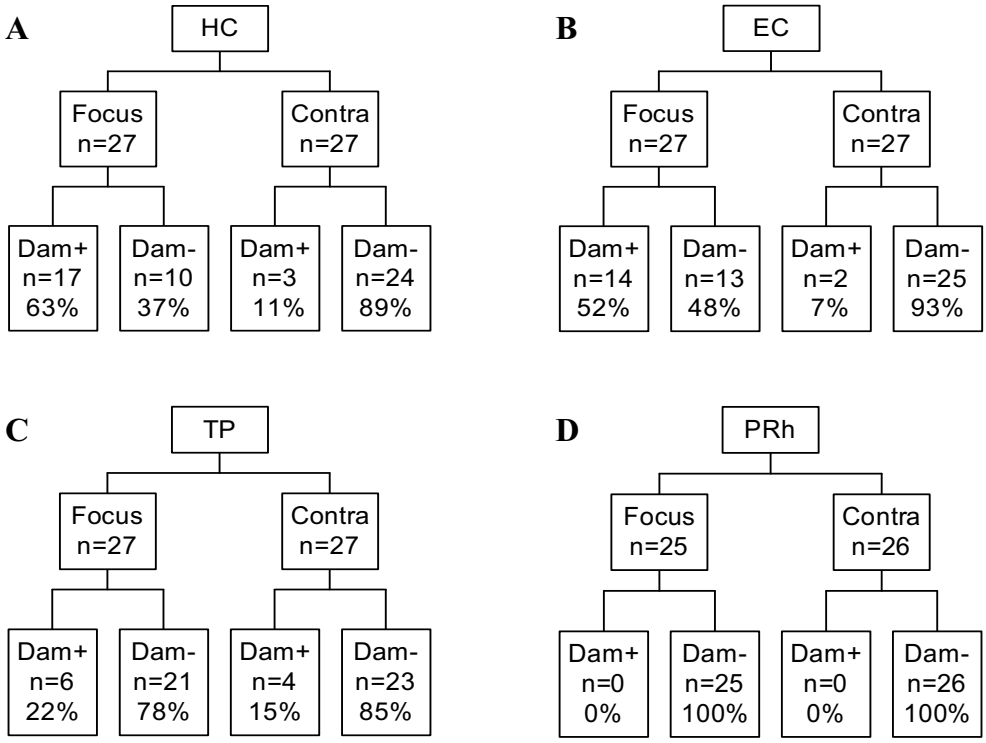

Figure 6. Percentage of TLE patients with damage to the hippocampus (A), entorhinal cortex (B), temporopolar cortex (C), or perirhinal cortex (D) in study I. Contra indicates the side contralateral to the seizure focus; Dam+, a volume reduction of at least 2 SD from the control mean; Dam-, a volume reduction of less than 2 SD from the control mean; EC, entorhinal cortex; Focus, side of the seizure focus; HC, hippocampus; n, number of patients; PRh, perirhinal cortex; TP, temporopolar cortex.

There were no differences in the volumes of the ipsilateral entorhinal, perirhinal, temporopolar, or total perirhinal cortices in the right TLE group when compared with those in the control subjects. Furthermore, all contralateral cortical mean volumes were unaffected. The asymmetry ratios of the entorhinal, perirhinal, and total perirhinal cortices, however, were lower in the right TLE group than in control subjects ($p<0.01$, $p<0.001$, and $p<0.01$, respectively) or the left TLE group, indicating smaller volumes ipsilateral to the side of seizure focus.

The mean volumes of the entorhinal, perirhinal, temporopolar, or total perirhinal cortices, as well as the mean hippocampal volumes in patients with extratemporal focal epilepsy did not differ from those in control subjects. The corresponding asymmetry ratios also did not differ from those of the control group.

5.2.2 Correlation analyses of hippocampal and cortical volumes

There was no correlation between the hippocampal volume and the volume of the ipsilateral or contralateral entorhinal, perirhinal, and temporopolar cortices in control subjects or patients with extratemporal focal epilepsy. In all patients with TLE, the volume of the left hippocampus correlated with the volume of left entorhinal ($r = 0.625$, $p<0.001$), perirhinal ($r = 0.471$, $p<0.05$), and total perirhinal cortices ($r = 0.604$, $p<0.01$). The volume of the right hippocampus correlated with the volume of the right entorhinal ($r = 0.524$, $p<0.01$),

temporopolar (r = 0.556, p<0.01), and total perirhinal cortices (r = 0.511, p<0.05). There was no correlation between the left or right hippocampal volumes and the contralateral cortical volumes.

5.2.3 Comparison between patients with more substantial and milder hippocampal volume reduction

To assess whether TLE patients with a hippocampal volume reduction of at least 2 SD on the side of the seizure focus have more substantial cortical damage than patients with milder hippocampal atrophy, the cortical volumes in these TLE subgroups were evaluated. Seven patients with left TLE had a volume reduction of at least 2 SD from the mean of control subjects (at least a 23% volume reduction) in the ipsilateral hippocampus, and the mean hippocampal volume was reduced by 49% on average compared with the control group (p<0.001). Similarly, ten patients in the right TLE group had a volume reduction of at least 2 SD from the mean of control subjects (at least a 21% volume reduction) in the ipsilateral hippocampus (mean volume reduction of 48% compared with control subjects, p<0.001).

In left TLE patients with a hippocampal volume reduction of at least 2 SD on the side of the seizure focus, the mean volume of the ipsilateral left EC was reduced by 23% (p<0.001) and the total perirhinal cortex by 22% (p<0.05) compared with control subjects. The ipsilateral mean volume of left temporopolar and perirhinal cortices as well as all contralateral cortical mean volumes were unaffected. In right TLE patients with a hippocampal volume reduction of at least 2 SD on the side of the seizure focus, the mean volume of the right EC was reduced by 13% (p<0.01) compared with the control group. The ipsilateral mean volumes of the right perirhinal, temporopolar, and total perirhinal cortices, as well as all contralateral cortical mean volumes, did not differ from those estimated in the control subjects.

The ipsilateral or contralateral cortical mean volumes in patients with milder hippocampal volume reduction did not differ from those found in the control subjects or from those in patients with more substantial hippocampal damage.

5.2.4 The impact of other candidate factors contributing to damage

There were no differences in the ipsilateral or contralateral cortical volumes between patients with clinically determined known or unknown aetiology of TLE. When the pathologic examination of the resected tissue was evaluated, no differences were found in the ipsilateral or contralateral cortical volumes between patients with HS (or gliosis) and normal temporal cortex (n = 8) and patients with HS (or gliosis) and cortical microdysgenesis in the temporal cortex (n = 12). There was also no difference detected in cortical volumes on the side of the focus between TLE patients with (n = 5) or without (n = 22) complex febrile seizures. Finally, there was no correlation between the duration of epilepsy or age at onset of epilepsy and the cortical volumes.

5.3 PREOPERATIVE QUALITATIVE MRI

5.3.1 Unilateral TLE (Study II)

Qualitative MRI demonstrated a unilateral structural abnormality in the temporal lobe in 53% (n = 55) of patients with unilateral TLE (Table 7). This included hippocampal atrophy with (n = 9), or without (n = 24) temporal cortical atrophy, and other unilateral structural lesions of the temporal lobe (n = 22). MRI was normal in 34% of patients with unilateral TLE (n = 35). The MRI data were also evaluated in subgroups of patients imaged before or after the introduction of a standardised MRI protocol (operated on between 1988 and 1993 or 1993 and 1999, respectively). Between 1988 and 1993, a unilateral structural abnormality of the temporal lobe was found in 35% (n = 17) of patients and MRI was normal in 53% (n = 26). After the introduction of a standardised MRI protocol, the proportion of patients with

unitemporal structural abnormality increased to 70% (n = 38, p<0.001), and those with normal MRI were reduced to 17% (n = 9).

5.3.2 Patients with palliative operations (Study II)

The largest subgroup among patients with palliative operations consisted of those with normal qualitative MRI (n = 13) (Table 7). When the MRI data was evaluated in subgroups of patients imaged before (n = 13) or after (n = 24) the introduction of a standardised MRI protocol, the changes were identical to those observed in unilateral TLE (p<0.05). Between 1988 and 1993, a unilateral structural abnormality of the temporal lobe was found in 8% (n = 1) whereas in 62% (n = 8) of palliative patients, the MRI was normal. A total of 31% (n = 4) had dual pathology or a concomitant temporal and extratemporal abnormality. Between 1993 and 1999, the proportion of patients with unitemporal structural abnormality increased to 38% (n = 9) and those with normal MRI became reduced to 21% (n = 5). Additionally, 25% (n = 6) of patients had dual pathology, a concomitant temporal and extratemporal abnormality, or extratemporal pathology leaving 17% (n = 4) with other aetiologies.

Table 7. Results of the preoperative qualitative MR imaging

Preoperative MRI	**Unilateral TLE (n)**	**Palliative operations (n)**
Normal	35	13
Unilateral hippocampal atrophy	24	6
Unilateral hippocampal and temporal cortical atrophy	9	1
Other unitemporal structural lesion	22	3
Bilateral temporal cortical abnormality	2	0
Bilateral hippocampal atrophy	0	1
Dual pathology[1]	2	3
Combined temporal and extratemporal abnormality	0	6
Extratemporal abnormality	3	1
General brain atrophy, cerebellar atrophy, or minor vascular lesions in the watershed area	6	3
Total	**103**	**37**

1 Dual pathology other than unilateral hippocampal and temporal cortical atrophy.

Abbreviations: n, number of patients.

5.4 INTRACRANIAL EEG (STUDY III)

Among the 38 operated patients, according to the invasive ictal video-EEG monitoring, the onset of the seizure could be defined in the unilateral temporal mesial area in 25 patients (66%). The ictal onset was unilateral neocortical +/- mesial in 29 patients (76%), bitemporal in six patients (16%) and frontotemporal or multifocal in three patients (8%). Unilateral predominance of 80% or more was found in all patients with bitemporal seizure onset.

5.5 MOLECULAR IMAGING (STUDY III)

PET showed an area of ipsilateral temporal hypometabolism in ten patients, which was in concordance with ictal onset in invasive EEG recording. Extratemporal changes were seen in seven patients. Interictal or ictal SPECT showed an ipsilateral temporal finding in four patients and other extratemporal locations in nine patients.

5.6 SURGICAL PROCEDURES

In Study II, the operative procedures included anterior temporal resection and amygdalohippocampectomy, alone (n = 113) or combined with lesionectomy (n = 9), and SAH (n = 18). Sixty-four patients (46%) were operated on the left and 76 (54%) on the right.

In Study III, anterior temporal resection and with amygdalohippocampectomy was performed in 30 patients and SAH in eight patients (21%). Twenty-three patients (61%) were operated on the left and 15 (39%) patients on the right.

In Study IV, the operative procedures included anterior temporal resection and amygdalohippocampectomy, alone (n = 70) or combined with lesionectomy (n = 5), and SAH (n = 23). Forty-four (45%) patients were operated on the left and 54 (55%) on the right.

5.7 OUTCOME WITH RESPECT TO SEIZURES

5.7.1 One-year outcome (Study II)

Figure 6 displays the outcome of surgery with respect to postoperative seizures in different patient groups. All patients were followed-up for a minimum of one year, except for one patient who died after a prolonged epileptic seizure three months after the operation.

One year after the operation, 45% (n = 46) of the patients with unilateral TLE were completely seizure-free and 12% (n = 12) had only postoperative nondisabling seizures (i.e. auras) (Figure 7A). Rare seizures (Engel's class II) were identified in 12% of patients (n = 12). Engel's class I outcome was thus observed in 56% of patients and Engel's class I–II outcome in 68% of patients. Additionally, 13% of patients (n = 13) had a worthwhile seizure reduction (Engel's class III), while 19% (n= 19) did not benefit from surgery (Engel's class IV).

As expected, the outcome was better in patients with unilateral TLE than in the palliatively operated patients ($p<0.05$). One year after the operation, 27% (n = 10) of palliative patients were free of seizures, 3% (n = 1) had only postoperative nondisabling seizures, and 8% (n = 3) rare seizures. Additionally, 24% (n = 9) achieved a worthwhile seizure reduction. A minimum of 80% seizure reduction was therefore achieved by 62% of the subjects (Figure 7D).

5.7.2 Long-term outcome (Study II)

In unilateral TLE, the results of the long-term follow-up did not differ from those of one-year follow-up ($p>0.05$ between groups). On the latest available follow-up date [mean follow-up 5.4 ± 2.6 (SD) years, range 3 months–10.5 years], 46% (n = 47) of the patients were seizure-free, 10% (n = 10) had only postoperative nondisabling seizures, and 15% (n = 15) had rare seizures. Additionally, 14% of patients (n = 14) achieved a worthwhile seizure reduction and 17% (n = 17) did not benefit from surgery (Engel's class IV) (Figure 7A).

Similarly, on the latest available follow-up date, 35% (n = 13) of palliative patients became seizure-free, 5% (n = 2) had rare seizures and 22% (n = 8) achieved a worthwhile seizure reduction. The mean follow-up was 4.4 ± 2.2 years (range 1.0–9.0 years). Thus in palliative patients, the results of long-term follow-up did not differ from those of one-year follow-up ($p>0.05$ between groups, Figure 7D).

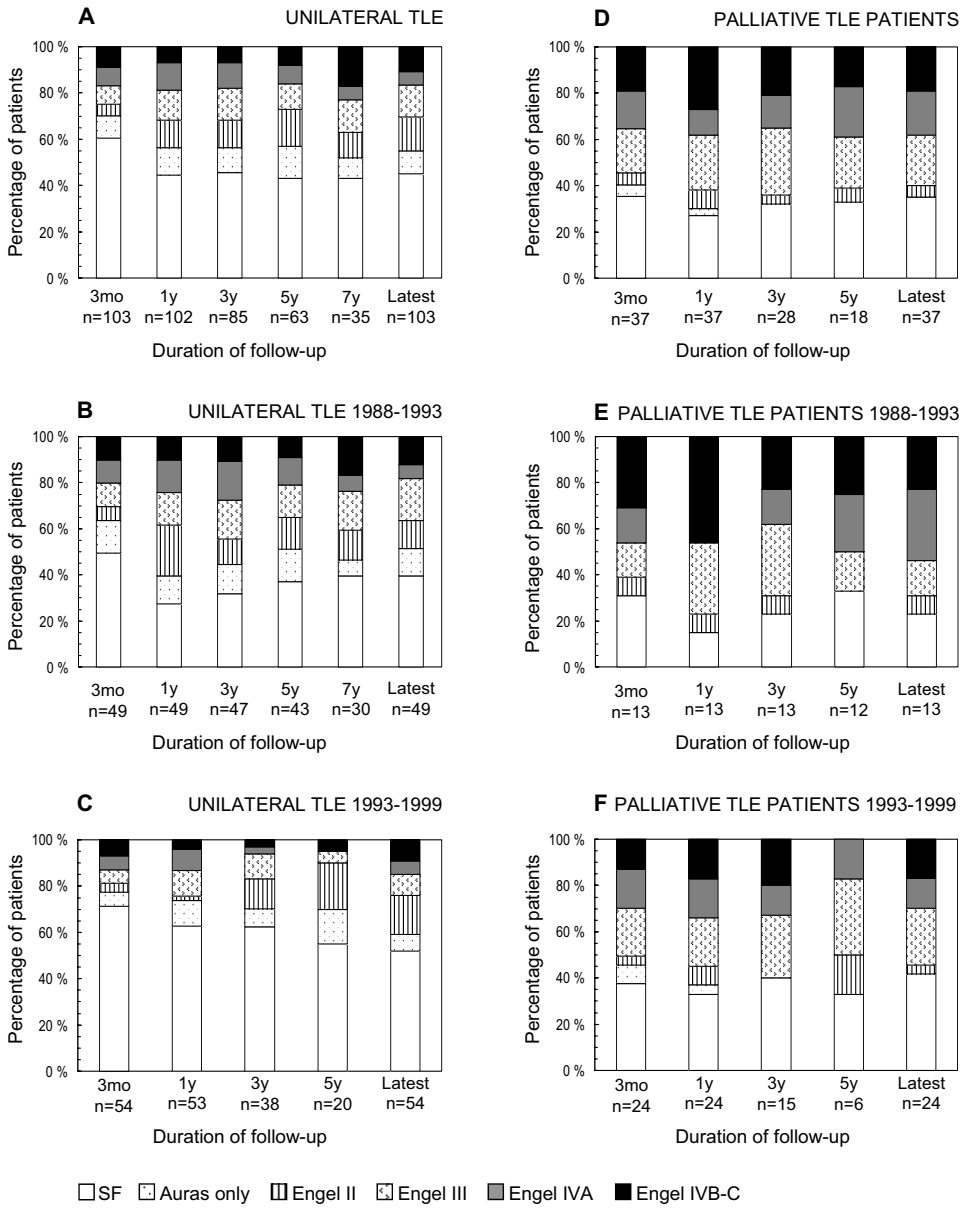

Figure 7. Outcome with respect to seizures as a percentage of patients in different Engel's classes at different time intervals (study II). (A) All patients with unilateral TLE (mean follow-up 5.4 years). (B) Patients with unilateral TLE imaged without a standardised MRI protocol (1988–1993; median follow-up 7.7 years). (C) Patients with unilateral TLE imaged with a standardised MRI protocol (1993–1999; median follow-up 3.8 years). (D) All palliatively operated TLE patients (mean follow-up 4.4 years). (E) Palliatively operated TLE patients imaged without a standardised MRI protocol (1988–1993; median follow-up 5.9 years). (F) Palliatively operated TLE patients imaged with a standardised MRI protocol (1993–1999; median follow-up 3.1 years). Abbreviations: Auras only, seizure-free patients with postoperative auras only; Engel II, rare seizures (fewer than three seizures a year); Engel III, worthwhile seizure reduction (a reduction in seizure frequency of at least 80%); Engel IVA, patients with a seizure reduction of at least 50%; Engel IVB–C, no change in seizure frequency, or more frequent seizures (n = 1); latest, latest available follow up data; mo, months; SF, completely seizure-free patients; y, years.

5.7.3 Outcome in patients operated on with or without a standardised preoperative MRI protocol (Study II)

The surgical results were then evaluated independently in patients operated on with or without a standardised preoperative MRI protocol. There was a significant difference in the postoperative outcome between these two groups ($p \leq 0.001$ for one year outcome).

Altogether 49 patients with unilateral TLE were operated on before the introduction of a standardised MRI protocol (between 1988 and 1993). One year after the operation, 61% (n = 30) of the patients achieved Engel's class I–II outcome, with only 27% (n = 13) being seizure-free (Figure 7B). In the long-term follow-up (latest available follow-up data, median 7.7 years, range 1.0–10.5 years) 39% (n = 19) of the patients became seizure-free, 12% (n = 6) had only postoperative nondisabling seizures, and 12% (n = 6) rare seizures. Additionally, 18% (n = 9) of the patients achieved a worthwhile seizure reduction, while 18% (n = 9) had no worthwhile seizure reduction.

A total of 54 patients with unilateral TLE were operated on after the introduction of a standardised MRI protocol (between 1993 and 1999). One year after the operation 61% (n = 33) of them were free of seizures, 11% (n = 6) had only postoperative nondisabling seizures, and 2% (n = 1) rare seizures. Moreover, 11% (n = 6) achieved a worthwhile seizure-reduction. Furthermore, at the latest available follow-up date (median follow-up 3.8 years, range 3 months – 6.5 years) 52% (n = 28) of the patients were seizure-free, 7% (n = 4) had only postoperative nondisabling seizures, and 17 % (n = 9) rare seizures. Nine percent (n = 5) of the patients achieved a worthwhile seizure reduction. In summary, after the introduction of a standardised MRI protocol, 74% of patients with unilateral TLE achieved Engel's class I–II outcome in the one-year follow-up and 76 % of patients in the long-term follow-up (Figure 7C).

When the outcome was analysed in subgroups of palliative patients operated on before or after the introduction of a standardised preoperative MRI protocol, similar trends of improved outcome as in patients with unilateral TLE were observed ($p > 0.05$) (Figure 7E–F). Twenty-four patients were operated on after the introduction of the standardised MRI protocol (between 1993 and 1999). On the latest available follow-up date (median follow-up 3.1 years, range 1.1–6.8 years) 42% (n = 10) of these patients were free of seizures, 4 % (n = 1) had rare seizures, and 25% (n = 6) achieved a worthwhile seizure reduction. Furthermore, at least an 80% seizure reduction (Engel's class I–III outcome) was therefore achieved by 71% (n = 17) of palliative patients operated on after the introduction of a standardised MRI protocol in the long-term follow-up.

5.7.4 Patients with normal MRI (Study III)

One year after the operation, 45% (17 of 38) of the patients had good seizure outcome; 40% (n = 15) had Engel's class I outcome [26% (10 of 38) patients were seizure-free, Engel's class IA] and 5% (n = 2) had Engel's class II outcome. Altogether, 55% (21 of 38) of the patients had an unfavourable outcome one year after the operation: 21% (n = 8) had Engel's class III and 34% (n = 13) had Engel's class IV outcome.

The latest mean follow-up was 5.8 years (median 4.8 years, range 1.1–14.3 years). At the latest follow-up, 40% (15 of 38) of the patients were free of disabling seizures (Engel class I) and 16% (n = 6) were seizure-free (Engel's class IA). Forty-five percent (17 of 38) of the patients had good outcomes as defined by Engel's class I and II. Fifty-five percent (21 of 38) of the patients had poor outcomes (10 Engel's class III and 11 Engel's class IV). The outcomes did not change between the one-year and the long-term follow-up.

5.7.5 Long-term outcome in patients with initial successful outcome (Study II)

The long-term outcome in all patients (n = 140) was first analysed via life tables. Altogether 86% (71 out of 83) of all seizure relapses occurred within one year after the operation. Late seizure relapses (> 2 years from the operation) were observed in only 5% of all patients (n = 7), and 8% of all relapses were late relapses. The majority of patients with late relapses had

unilateral TLE with known aetiology (n = 6), and pathological examination displayed HS (n = 5) or cortical microdysgenesis (n = 1). Late relapses were often preceded by some specific explanatory factor such as withdrawal of antiepileptic medication (n = 3) or hyponatremia (n = 1), and these did not lead to subsequent intractability during the follow-up in any of the patients.

Initially 63% (n = 88) of all patients were seizure-free or had only postoperative nondisabling seizures at the first postoperative control visit (three months postoperatively). Fifty-three percent of them remained completely free of seizures in the long-term follow-up (mean 5.2 ± 2.6 years, range 1.0–10.5 years) whereas 5% experienced some seizures but became again seizure-free (seizure-free for at least two years). Additionally, 11% had only postoperative nondisabling seizures and 15% had rare seizures.

5.7.6 Prognostic factors for the seizure outcome

Hippocampal atrophy with or without temporal cortical atrophy [$p<0.001$, odds ratio (OR) 5.2, 95% confidence interval (CI) 2.0–13.7] and other unilateral structural lesions of the temporal lobe ($p\leq0.001$, OR 6.9, 95% CI 2.2–21.5) in qualitative MRI predicted Engel's class I–II outcome in the long-term follow-up (using the latest available follow-up data). Additional predictive factors were onset of epilepsy before the age of five ($p<0.05$, OR 2.9, 95% CI 1.2–7.2; n = 43) and focal seizures with ictal impairment of consciousness and focal ictal EEG as a predominant seizure type ($p<0.05$, OR 3.4, 95% CI 1.2–9.1; n = 115). When patients with quantitative MRI data (n = 67) were analysed separately, a volume reduction of at least one SD (10% for both left TLE and right TLE) from the mean of controls on the side of the seizure onset was also predictor of Engel's class I–II outcome ($p<0.05$, OR 3.1, 95% CI 1.1–9.2). History of febrile seizures or complex febrile seizures, clinical aetiology of epilepsy, duration of epilepsy, seizure frequency, localisation of ictal onset by video-EEG, neuropsychological data, and type of operation did not predict Engel class I–II postoperative outcome in study II.

In surgical MRI-negative patients (study III), the only predictive factor for postoperative outcome was PET-imaging. Patients with noncongruent PET results had worse outcomes ($p = 0.044$) than patients with congruent PET results. Gender, duration of epilepsy, invasive ictal EEG onset, SPECT, type of surgery, side of surgery and histopathology did not achieve statistical significance.

5.8 HISTOPATHOLOGY

In Study II, the histopathological examination of resected tissue identified three different entities: patients with hippocampal sclerosis or gliosis (n = 60); patients with tumours or cystic lesions (n = 18); and patients with a microscopic cortical malformation (i.e. cortical microdysgenesis, n = 17). In all, HS was confirmed in 41 of 46 patients with hippocampal atrophy on the preoperative MRI. FCD was observed in one patient, and a microscopically identifiable benign or low grade tumour (DNET, ganglioglioma, hamartoma, or oligodendroglioma) in six patients with preoperative unknown aetiology of epilepsy. HS (n = 10), hippocampal gliosis (n = 3), or hippocampal microdysgenesis (n = 7) were identified in 40% of patients with a preoperative unknown aetiology of epilepsy (n = 20).

In study III, material for histology was available from 38 patients. Twenty-six subjects (68%) did not display any pathologic alteration in any of their surgical specimens in the areas available and examined. In two subjects (also included in study II), only a microscopically identifiable tumour was observed; one was defined as an oligodendroglioma and one was a DNET. In two patients, cortical microdysgenesis was observed. Two cases displayed HS and in six patients there was prominent gliosis without neuronal loss.

In study IV, the histopathology of the resected tissue revealed hippocampal sclerosis or gliosis in 50 out of 98 patients (51%).

5.9 COMPLICATIONS AND MORTALITY

5.9.1 Study II

Altogether three (2.1%) major and 15 (10.7%) minor complications were identified among sixteen patients (11.4%). Two patients had two different minor complications. The major complications included subarachnoidal haemorrhage caused by the intraoperative depth electrode, prolonged aphasia and homonymous hemianopia. Minor surgical complications included aseptic meningitis (n = 5), chronic subdural haematoma (n = 3), subdural effusion (n = 1), hydrocephalus (n = 1), bone lambeau infection (n = 1) and deep vein thrombosis (n = 1). The minor neurological complications included three patients with transient dysphasia. No mortality was attributable to the surgical procedures.

A total of six out of 140 patients (4.3%) died during the follow-up. Two of these patients had been completely free of seizures postoperatively (14 and 27 months), and four had an unfavourable surgical outcome. The causes of death related to epilepsy (four of the six) were SUDEP, suicide (depression related to poor seizure control), and prolonged epileptic seizure (n = 2). Three out of four epilepsy related deaths occurred in patients with recurrent postoperative seizures.

5.9.2 Study III

Nine out of 38 patients with resective surgery (24%) had transient postoperative complications. These included transient dysphasia (n = 6, resolved completely within one year), the need for a second operation due to cerebrospinal fluid leakage through the mastoid cell (n = 1), transient depression (n = 1) and aseptic meningitis (n = 1). Two patients (5%) had permanent hemianopia postoperatively.

Among the 64 patients in whom an intracranial EEG evaluation was conducted, 15 (23%) showed transient complications related directly to the procedure. Eight patients experienced cerebrospinal fluid leakage from the wound, four patients had suspected meningitis with fever without bacteriologic verification, and one patient had asymptomatic subdural haematoma as revealed by the postoperative CT imaging that was used to localize the electrodes. One patient experienced a middle ear infection and one had transient hyponatremia. Despite the complications described, the registration was finished as planned with all patients, and no serious or permanent complications were noted.

5.10 COGNITIVE OUTCOME IN OPERATED PATIENTS WITH NORMAL MRI (STUDY III)

There was no difference in the preoperative cognitive performance between the left and right TLE patients. One year after the operation, patients with left TLE were impaired in both immediate and delayed recall of logical prose compared to their preoperative performance ($p<0.01$ and $p<0.05$, respectively). In patients with right TLE, the cognitive performance did not change significantly from the preoperative to postoperative evaluation. When the left and right TLE groups were compared, the performance was significantly different in immediate recall of logical prose; the patients after left TLE surgery showed impaired verbal immediate memory ($p<0.05$), whereas other tests did not reveal any difference. Up to 26% (6 of 23) of left TLE patients and 27% (4 of 15) of right TLE patients exhibited a memory decline postoperatively in individual tests. Eleven (48%) of 23 of the left TLE patients had decline in one or more verbal tests and 7 (46%) of 15 of the right TLE patients displayed a decline in one or more visual tests.

5.11 LONG-TERM COGNITIVE OUTCOME (STUDY IV)

5.11.1 Cognitive outcome in left and right TLE groups

In the left TLE group, four cognitive variables changed significantly during the follow-up: Learning and delayed recall of word pairs ($p<0.001$ in both), immediate recall of WMS figures ($p<0.05$) and PIQ ($p<0.001$). The effect of seizure outcome alone was not significant for any of the cognitive variables ($p\geq0.05$ in all). However, there was a significant interaction between time and postoperative seizure outcome (time x outcome) for immediate recall of logical prose ($p\leq0.001$) and verbal fluency ($p<0.05$). The intraclass correlation was significant in all models, indicating that the test performance in repeated measurements correlated in the individual patients.

In the left TLE group the learning and delayed recall of word pairs declined from the preoperative to three-year follow-up assessment ($p<0.001$ in both) when the estimated means from the mixed model were compared. In addition, delayed recall of word pairs declined from the one-year to three-year postoperative assessment ($p<0.05$). In patients with left TLE and ongoing postoperative seizures, the immediate recall of logical prose declined from the preoperative to one-year assessment ($p<0.05$) as well as from the preoperative to three-year assessment ($p\leq0.001$). The immediate recall of logical prose remained stable in seizure-free patients. In visual memory tasks, the immediate recall of WMS figures improved from the preoperative to three-year assessment ($p<0.01$). PIQ was also better both at one-year and three-year assessments compared to the preoperative evaluation ($p<0.001$ in both). Three years after the operation, seizure-free patients performed better in the verbal fluency task, than patients with postoperative seizures ($p<0.01$). This was due to an improvement in performance from the preoperative to three-year follow-up assessment ($p\leq0.01$) in the seizure-free patients.

In the right TLE group, five cognitive variables changed significantly during the follow-up: Learning and delayed recall of word pairs ($p\leq 0.001$ and $p\leq 0.01$, respectively), delayed recall of logical prose ($p<0.05$), PIQ ($p\leq0.01$) and verbal fluency ($p<0.05$). The cognitive performance was not related to the seizure outcome in the right TLE group, as the effect of seizure outcome and the interaction between time and outcome (time x outcome) were not significant for any of the cognitive variables. The repeated cognitive measures correlated significantly also in all models for right TLE.

The learning and delayed recall of word pairs declined from the preoperative to the three-year assessments ($p<0.001$ and $p<0.05$, respectively), as well as from the one-year to three-year assessments ($p<0.05$ in both) when the estimated means from the mixed model were compared. On the other hand, the delayed recall of logical prose improved from the preoperative to three-year assessment ($p< 0.05$). PIQ increased and verbal fluency improved from the preoperative to three-year assessments ($p<0.01$ and $p<0.05$, respectively).

5.11.2 Memory change at individual level

Overall, the individual cognitive performance either remained stable or improved after surgery in the majority of patients. However, significant changes in the individual test performance were seen relatively frequently, particularly across memory measures. Depending on the test, 19–38% of patients showed some kind of significant change (either improvement or decline) in their memory performance at the one-year follow-up, and 26-51% at the three-year follow-up. At three years, a decline in the individual memory performance was most frequently seen in the learning (43%) and delayed (38%) recall of word pairs, and in the delayed recall of WMS figures (20%).

The percentage of patients with significant change in the individual memory performance was similar in the left and right TLE groups. Depending on the test 22–44% of patients with left TLE exhibited a significant change in their memory performance at the one-year follow-up, and 17–61% in the three-year follow-up. The respective values in the right TLE group were 13–40% and 22–44%.

5.11.3 Prognostic factors for the memory decline

Postoperative delayed verbal memory was impaired in both left TLE and right TLE groups. Therefore the explanatory factors for the delayed verbal memory decline were further evaluated by comparing those patients who experienced a significant decline in the delayed recall of word pairs three years postoperatively (n = 37) to those without a significant decline in the same test (n = 61). The patients operated on the left temporal lobe ($p<0.01$) and patients with better baseline performance ($p<0.05$) in the delayed recall of word pairs were more likely to have a significant decline in the delayed verbal memory three years postoperatively. No difference was found in seizure outcome at the three-year follow-up (Engel's class I or other), gender, age at surgery, duration of epilepsy, preoperative MRI (HS or other), pathological analyses of resected tissue (HS or other) or preoperative seizure frequency between patients with and without any significant decline in delayed verbal memory.

6 Discussion

The first comprehensive epilepsy surgery programme in Finland was established at Kuopio University Hospital in 1988. The majority of the patients operated in the Kuopio Epilepsy Center have been adults with refractory TLE from a defined geographical area in Finland having a population of 4 million inhabitants. The present series of studies were based on a preoperative evaluation, a surgical treatment and then a systematic follow-up of adult TLE patients treated in Kuopio University Hospital between the years 1988 and 2006. Postoperative long-term seizure outcome, long-term cognitive outcome, and prognostic factors for the outcome were assessed. Furthermore, the occurrence of damage in the medial temporal cortex, including the entorhinal, perirhinal and temporopolar cortices, in patients with drug-resistant TLE was investigated with a histology based MRI volumetric method.

6.1 METHODOLOGIC CONSIDERATIONS

6.1.1 Patient population

The aim of study I was to analyse whether the medial temporal cortical structures are damaged in MTLE. In order to verify correct localization of the operated seizure focus, the patient population in the study was selective and only those MTLE patients with a good postoperative outcome were included.

Study II describes the longitudinal postoperative outcome in a series of consecutive adult patients who were operated between 1988 and 1999 due to drug-resistant MTLE. The patients were referred to presurgical evaluation from an area of 4 million inhabitants. The strength of the study therefore is that it describes long-term postoperative outcome in an unselective group of operated TLE patients from a well-defined geographical area and population.

In study II, patients with unilateral MTLE were analysed separately from patients with palliative aim of resective surgery. In the palliative group, seizure-freedom was not regarded as a realistic goal of surgery, but a significant (≥ 80%) reduction of seizure-frequency was considered worth pursuing. Currently, the most common palliative surgical procedures include corpus callosotomy, multiple subpial transections and neurostimulation. However, significant seizure reduction or elimination of the most disabling seizure type may also be the goal of palliative resective surgery in selected patients (Perry & Duchowny 2011). Accordingly, it was found that a significant seizure-free rate could be achieved also when there is less convincing evidence for a unilateral confined epileptogenic zone, or undeniable evidence of bitemporal epilepsy is identified.

The aim of the current study was to assess patients with MTLE and therefore patients with lateral temporal neocortical lesions undergoing lesionectomy or temporal neocortical resection without amygdalohippocampectomy were excluded from the study population in studies I–IV. However, patients with MRI-negative NTLE may have been included in the study. This is due to the fact that the differential diagnostics between MRI-negative mesial and neocortical TLE was mainly based on evaluations with intracranial bilateral frontotemporal subdural strip electrodes, which do not always indicate the exact localisation of the seizure initiation in TLE, although successful surgery is possible. Thus, it is preferable to refer to the whole patient population as patients with TLE and not as patients with MTLE, although the majority of the patients did have MTLE.

The median duration of epilepsy until the time of operation was 19 years in study II and 16 years in study III. The long duration of epilepsy is in part explained by the fact that study II describes the long-term outcome of the first 140 TLE patients who were operated on at Kuopio Epilepsy Center. Similar results have been reported from other newly established epilepsy surgery centres (Asztely et al. 2007). However, the preoperative duration of epilepsy has been equally long in more recently published long-term outcome studies (de Tisi et al. 2011) or before referral to presurgical assessment (Haneef et al. 2010). As many patients with newly diagnosed epilepsy never become seizure-free with AEDs (Brodie et al. 2012), it must be acknowledged that there is still a considerable delay in providing access to epilepsy surgery evaluation. In the future, willing patients should be referred as soon as drug-resistancy is observed. Early surgery should be considered especially if TLE is associated with HS or some other MRI lesion (Semah et al. 1998, Janszky et al. 2005, Spooner et al. 2006).

In study III, all patients without any focal abnormalities in high resolution MRI were systematically evaluated with intracranial EEG electrodes. During the study, the MRI methods developed considerably, and therefore some MRI-negative patients would probably now be classified as MRI-positive if they were scanned with the current MRI devices. Additionally, molecular imaging studies (SPECT and PET) were not applied systematically, and therefore no firm conclusions can be made regarding their individual value in the preoperative decision-making.

Analyses of postoperative long-term neuropsychological outcome are subject to several confounding factors related to patient selection, repeated testing, and the neuropsychological tests that are being used. Therefore only patients with unilateral TLE were included in study IV. Additionally, it was decided to exclude some patients due to atypical language dominance or defective general intellectual ability. However, altogether 77% of all patients with unilateral TLE were included in the study and therefore the patient cohort can be considered representative of the TLE surgery population in Finland.

6.1.2 Assessment of postoperative seizure outcome

After surgery, routine postoperative follow-up visits were offered for all patients at three months, one year and three years after the operation. Thereafter the patients were either followed-up at Kuopio Epilepsy Center as outpatients or contacted by telephone to obtain additional historical details and up-to-date follow-up. In problematic cases, additional information was obtained from other hospitals, community health centres, or from original seizure calendars. Consequently, it was relatively easy to identify seizure-free patients and patients with rare seizures during the long-term follow-up. Classification of patients between Engel´s classes III and IV was more challenging, and is therefore more likely to be subjected to error.

6.1.3 Quantitative MRI

When comparing the absolute volumes across different groups of subjects, the measured volume needs to be scaled according to the measure of the individual head size. The most commonly used normalisation variables in the literature include intracranial and intracerebral volumes. Since manual volumetry with a trackball-driven cursor is extremely time consuming, alternative methods for normalisation have been developed. It has been demonstrated that in normal individuals the brain volume correlates with the brain area that is measured from a coronal image at the level of the anterior commissure (Kälviäinen et al. 1998). Therefore in study I hippocampal volumes as well as all temporal cortical volumes were normalized according to the mean brain area of the controls. This has been done also in previous studies from our center (Salmenperä et al. 2000a).

6.1.4 Statistical analyses

In study IV, the linear mixed model for repeated measures was used to analyse possible changes in the cognitive performance at group level during long-term postoperative follow-up. As the previous literature had indicated the side of surgery to be one of the explanatory factors for the postoperative cognitive outcome, it was decided to conduct the analyses of neuropsychological follow-up data for the left and right TLE groups separately. This helped in focusing the analyses to the impact of postoperative seizure outcome on cognition, and in avoiding possible complex three-way interactions between different effects. The neuropsychological follow-up data were not corrected by using the baseline performance as a covariate in contrast to some other studies (Andersson-Roswall et al. 2010).

The absence of a control group in study IV can be considered a weakness of the study. Due to the lack of controls with a comparable neuropsychological re-test interval, it was not possible to use RCIs and CIs of regression-based test–retest norms (Jacobson & Truax 1991, Chelune et al. 1993, Hermann et al. 1996) for the determination of significant individual change in the postoperative cognitive performance. Instead, a significant change in the individual postoperative test performance was defined as a change greater than one SD calculated from the preoperative baseline performance of the whole patient group (Cukiert et al. 2009a). However, this method allowed only comparison against the preoperative performance, and did not enable assessment of individual change between the one-year and three-year assessments.

6.2 MRI VOLUMETRY OF THE ENTORHINAL, PERIRHINAL AND TEMPOROPOLAR CORTICES

It was possible to demonstrate that volumes of entorhinal and temporopolar cortices were reduced ipsilateral to the seizure focus in a subpopulation of patients with unilateral TLE. Other authors have also demonstrated that patients with TLE may have an EC volume reduction particularly ipsilateral to the seizure focus (Bernasconi et al. 2003a, Bernasconi et al. 2003b, Bonilha et al. 2003, Bartolomei et al. 2005, Meade et al. 2008). Less commonly, a bilateral entorhinal volume reduction has been observed (Bernasconi et al. 1999, Meade et al. 2008). But even in cases with bilateral entorhinal volume reduction, it seems that the loss has been greater ipsilaterally (Bernasconi et al. 1999). Additionally, the volume of the temporopolar grey and white matter may be decreased ipsilateral to the seizure focus in TLE (Sankar et al. 2008, Özkara et al. 2008).

The mean volumes of PRh were unaffected in all patient groups when compared to controls. However, other studies have demonstrated that the volume of the PRh may also be reduced ipsilateral to the seizure focus in patients with TLE (Bernasconi et al. 2003b, Bonilha et al. 2003, Meade et al. 2008). The volume reduction in the PRh appears to be less severe than in the EC (Bernasconi et al. 2003b).

The volume reduction of the medial temporal cortical structures was a typical characteristics of TLE, and was not observed in extratemporal focal epilepsy. Normal entorhinal volumes have later been observed both in extratemporal focal and in genetic generalised epilepsy (Bernasconi et al. 2003a).

Based on the available information, it would seem that the association between hippocampal and medial temporal cortical volumes is complex in nature and will need to be re-evaluated further in the future. In this study, the medial temporal cortical volume reduction was associated with a hippocampal volume reduction. Salmenperä et al. (Salmenperä et al. 2000b) also demonstrated a correlation between the hippocampal and the entorhinal volumes, but two later studies have not been able to confirm this association (Bonilha et al. 2003, Meade et al. 2008). More importantly, a significant EC volume loss has also been found in patients with normal hippocampal volumes (Bernasconi et al. 2001).

In contrast to the present results, an association between the duration of epilepsy and degree of entorhinal atrophy has been found in some studies (Salmenperä et al. 2000b, Bernasconi et al. 2005). This might be related to differences in the patient population. All patients in study I had been operated on due to drug-resistant unilateral TLE and had good postoperative outcome, whereas in other studies, TLE patients referred for presurgical evaluation (Bernasconi et al. 2005) or TLE patients from an outpatient clinic (Salmenperä et al. 2000b) were included. The duration of epilepsy at the time of imaging was comparable between these studies.

The individual analyses revealed a significant volume reduction from the mean of controls in the ipsilateral hippocampus in 63% of patients; in the EC in 52% of patients; and in the TP in 22% of patients. Due to the study plan it was not possible to evaluate whether the entorhinal volumetry could provide additional information in the preoperative evaluation of patients with drug-resistant TLE. According to one later study, EC atrophy could correctly lateralize the seizure focus in 64% of TLE patients with normal hippocampal volumes (Bernasconi et al. 2001). However, if it were to become a useful tool in preoperative evaluation of individual patients, then an automated volumetric method for EC volumetry would need to be developed. This may prove difficult as there is significant individual variability in the anatomy of collateral sulcus.

There is accumulating evidence that MTLE affects also other brain structures in addition to the hippocampus (Wieser & ILAE Commission on Neurosurgery of Epilepsy 2004, Bernhardt et al. 2009, Bonilha et al. 2010). In a recent study, medial temporal lobe, occipitotemporal areas, the cerebellum, the cingulate cortex, the ipsilateral insula, and thalamus were more likely to be atrophied in randomly selected patients with MTLE (Bonilha et al. 2010). Structures such as the orbitofrontal cortex, the contralateral medial temporal areas and insula, the putamen, and the caudate may also undergo atrophy, but not as consistently (Bonilha et al. 2010). The MTLE may also be associated with a reorganisation of the limbic system connections (Bonilha et al. 2012b). Interestingly, it has been postulated that subtypes of MTLE patients could be identified according to the degree of extrahippocampal damage and epileptogenicity of the medial temporal cortex (Bonilha et al. 2012a). The identification of such subtypes could potentially improve surgical results and e.g. this could help to explain why all patients with HS do not become seizure-free.

6.3 THE IMPACT OF PREOPERATIVE QUALITATIVE MRI

It has been reported that standard MRI fails to detect up to 57% of focal epileptogenic lesions in patients with refractory focal epilepsy (Von Oertzen et al. 2002). Therefore, epilepsy surgery candidates should be evaluated according to a specific MRI protocol, which aims at identifying the pathological abnormalities commonly seen in drug- resistant patients (Vattipally & Bronen 2004, Duncan 2010). In addition, the best results are probably achieved when a MRI is first performed with a specific protocol, and then analysed by an expert neuroradiologist working in a specialised epilepsy centre (Von Oertzen et al. 2002).

In the present study the accuracy of qualitative preoperative MRI increased significantly after the standardised MRI protocol was introduced into our centre in February 1993. In study II, the percentage of structural abnormalities detected by preoperative MRI increased from 35% to 70% in patients with unilateral TLE. Analogous changes were observed in the palliatively operated group of patients. The higher accuracy of preoperative MRI had also a significant impact on the postoperative seizure outcome. In addition to the standardised MRI protocol, the development of MRI techniques in general and the increasing expertise of the neuroradiologists were likely to facilitate the detection of focal MRI abnormalities during the study period.

Twenty percent of patients with refractory focal epilepsy have an unknown aetiology despite e.g. of optimal MRI (Duncan 2010). Although nonlesional MRI is not a contraindication to surgery, patients with nonlesional MRI may be less likely to be referred

for presurgical evaluation. TLE patients with nonlesional MRI most often require assessment with intracranial electrodes, and may be less likely to be operated on. By using a modern 3T MRI scanner and sequences, focal abnormalities, mainly malformations of cortical development, can be identified in 20% of patients with previously unremarkable MRI (Strandberg et al. 2008). In the future, novel MRI techniques may further improve the accuracy of MRI in epilepsy surgery candidates. However, no presurgical technique will consistently provide all the relevant data for the localisation of seizure focus and a hypothesis regarding the epileptogenic zone must be formulated based on all preoperative data available.

6.4 SEIZURE OUTCOME

In study II, 56% of the patients with unilateral TLE achieved Engel's class I outcome one year after the operation, and 55% during long-term follow-up (mean 5.4 years). Similarly, 45% and 46% of patients were seizure-free and had no auras. The results of the long-term follow-up did not differ from those of the one-year follow-up assessment. In a meta-analysis of 40 long-term (mean or median follow-up ≥ 5 years) follow-up studies of TLE surgery published between 1991 and 2003, the median percentage of seizure-free patients was 66% (Tellez-Zenteno et al. 2005). Study II was also included in that meta-analysis. Higher seizure-free rates were observed in more recent studies and in studies using the Engel´s classification as an outcome measure. The authors also concluded that the long-term seizure outcome was similar to that reported in short-term controlled studies (Wiebe et al. 2001).

The seizure outcome was expectedly better in patients with unilateral TLE than in palliatively operated subgroup of TLE patients. In the palliative group, 35% of patients achieved Engel's class I outcome during long-term follow-up (mean 4.4 years). However, a minimum of 80% seizure reduction was achieved by 62% of patients. The largest subgroup among palliatively operated patients was the one with an independent bitemporal seizure onset. Holmes et al. (2003) reported that 71% of patients with bitemporal epilepsy (when defined by intracranial EEG) had ≥ 75% seizure reduction postoperatively. In one smaller and more recent study, 55% of patients with bitemporal epilepsy achieved Engel's class I outcome (Boling et al. 2009), which is comparable to unilateral TLE. An improvement in QOL has also been reported in some patients who achieved only palliation via reduced seizure frequency, severity of seizures or medication (Boling et al. 2009).

In study II, 86% of all seizure relapses occurred within one year of the operation. In most studies, seizure-outcome at one (Salanova et al. 1999, Cohen-Gadol et al. 2006) or two years (Elwes et al. 1991, Foldvary et al. 2000, McIntosh et al. 2004, Asztely et al. 2007) after surgery has been predictive of the long-term seizure outcome. Late seizure relapses were observed in only 5% of all patients and often they were preceded by a specific explanatory factor. Other authors have also shown that a relapse is less likely the longer the patient is postoperatively seizure-free (de Tisi et al. 2011). For those patients who are seizure-free for at least two years, the probability of remaining seizure-free at five years is approximately 86–93% (Salanova et al. 1999, McIntosh et al. 2004). In the present study, late relapses did not lead to subsequent intractability in any of the patients, as reported before (Foldvary et al. 2000).

It was also found that 53% of those patients who were seizure-free or had only postoperative auras at the three-month follow-up visit remained completely free of all seizures throughout the long-term follow-up. On the other hand, 17% of patients with initial Engel's class II–IV outcome became seizure-free. In a large study assessing long-term outcome after epilepsy surgery (81% anterior temporal resections), different patterns of postoperative remission and relapse were identified (de Tisi et al. 2011). The authors found that 40% of all surgical patients were entirely seizure-free (Engel's class IA) after surgery and 11% had only postoperative focal seizures without any impairment of consciousness

(Engel's class IB). Alternating patterns with seizure-freedom and relapse were observed in 15% of patients and 3–15% of patients changed between outcome groups each year. Eighteen percent of patients never became seizure-free postoperatively. Late remissions were often associated with the introduction of a new AED, indicating that adjustment of antiepileptic medication is important if seizures continue postoperatively.

Epilepsy surgery can be beneficial for patients with TLE and nonlesional MRI, although preoperative evaluation with intracranial electrodes is needed. At the latest follow-up (mean 5.8 years) 40% of the present patients achieved Engel's class I outcome, and the outcome did not change between the one-year and the latest follow-up. Currently the reported outcome rates in nonlesional TLE patients (as determined by MRI) demonstrate significant variability (Chapman et al. 2005, Cukiert et al. 2010) in the postoperative seizure-free outcome. This is probably related to the quality of preoperative MRI, patient selection, and the method of intracranial evaluation that is being used in different studies.

6.5 PROGNOSTIC FACTORS FOR THE SEIZURE OUTCOME

In the present study (Study II) unilateral hippocampal atrophy with or without temporal cortical atrophy on qualitative MRI, other unitemporal structural lesions on qualitative MRI, and a hippocampal volume reduction of at least one SD from the mean of controls on the side of the seizure focus predicted good long-term seizure outcome. The importance of HS (McIntosh et al. 2004, Elsharkawy et al. 2009a, de Tisi et al. 2011) and of foreign tissue lesions (Salanova et al. 1999, McIntosh et al. 2004, de Tisi et al. 2011) has been demonstrated previously in the majority of studies assessing prognostic factors for the outcome after ATR. Similarly, lack of any obvious structural abnormality has been identified as a negative prognostic factor (McIntosh et al. 2004).

Early onset of epilepsy and preoperative seizure type predominance were also independent predictive factors for good surgical outcome. The most typical seizure type in MTLE is the focal seizures with impairment of consciousness, whereas focal onset generalised seizures are usually less common. Accordingly, less frequent seizure types such as focal onset generalised seizures (Hennessy et al. 2001, McIntosh et al. 2004,) or versive seizures (Elsharkawy et al. 2009a) have been identified as negative prognostic factors and their absence has been considered as a positive prognostic factor (Jeong et al. 2005) for the good postoperative seizure outcome. The importance of early onset of epilepsy as a prognostic factor may be secondary and related to HS, as early onset of epilepsy has been recognised as a significant risk factor for hippocampal volume loss in several studies (Salmenperä et al. 2001).

In surgical MRI-negative patients (study III), the only predictive factor for postoperative outcome was PET-imaging, as patients with noncongruent PET results had worse outcomes than patients with congruent PET results. This is in line with studies indicating that outcome in patients with MRI-negative and PET-positive TLE would have exceptionally good prognoses (Carne et al. 2004, Kuba et al. 2011, LoPinto-Khoury et al. 2012).

Engel's classes I and II were used as a measure for the favourable outcome when the prognostic factors were analysed (studies II and III). In the future, more information will be needed to try to identify the prognostic factors in those patients who will be completely seizure-free since surgery (defined as Engel's class IA or ILAE class 1a). There is already evidence that absolute freedom of seizures and auras cannot be predicted by conventional preoperative variables (Aull-Watschinger et al. 2008). Patients with postoperative auras are likely to have a more widespread epileptogenic network in the ipsilateral temporal lobe when compared to those who are entirely seizure-free.

6.6 COGNITIVE OUTCOME

It was found that verbal learning and memory declined in the long-term follow-up both in the left and the right TLE groups, whereas visual memory performance remained stable. In most previous long-term outcome studies the verbal memory decline in the group analyses has been restricted to patients with left temporal lobe surgery (Engman et al. 2004, Bjørnaes et al. 2005, Alpherts et al. 2006, Andersson-Roswall et al. 2010). Rausch and co-workers (Rausch et al. 2003) claimed that patients with left temporal lobe surgery have decreased verbal memory scores at one-year, and there are declines in both verbal and visual memory irrespective of the side of temporal lobe resection at the nine-year follow-up. These authors used the same memory tests in their study as applied here, but in the present study it was not possible to verify the postoperative decline in visual memory.

The postoperative improvement in PIQ could be confirmed at the group level in agreement with others (Engman et al. 2001, Alpherts et al. 2004, Engman et al. 2006, Andersson-Roswall et al. 2010). This improvement is likely to be related to a practice effect. However, the ability to benefit from practice in repeated assessments may also reflect improved capacity to develop compensatory and more effective cognitive strategies during the postoperative period.

One of the most intriguing aspects of postoperative cognitive outcome has been the possible association between seizure control and long-term cognitive outcome, especially as the published studies have yielded mixed results. Helmstaedter et al. (2003) observed a significant memory decline during the long-term follow-up in both medically (50%) and surgically (60%) treated patients. In fact, their surgically treated patients had more pronounced memory impairment when compared to the medically treated group, if surgery was performed on the left or if seizures continued postoperatively. However, seizure-free surgical patients showed a recovery of memory functions during the long-term follow-up. Here no association was found between the long-term cognitive outcome and long-term seizure control for majority of the neuropsychological measures, as in some previous studies (Alpherts et al. 2006, Andersson-Roswall et al. 2010). However, it was possible to demonstrate that ongoing seizures were related to a decline in the immediate recall of logical prose, and seizure-freedom was associated with an improvement in verbal fluency in patients with left TLE.

In line with previous studies (Andersson-Roswall et al. 2012) significant variability was detected in the individual memory performance in long-term follow-up although a different cut-off for the determination of a significant change in the postoperative memory performance was used. These results support previous research showing decline in memory function within the first postoperative years, but studies with even longer follow-up indicate that a plateau or partial recovery can be achieved in longer time intervals (Alpherts et al. 2006, Andersson-Roswall et al. 2012). A progressive memory decline after surgery is not common and it has been encountered only in a minority of patients who continue to experience seizures postoperatively (Baxendale et al. 2012).

In the present study, left side of surgery and better baseline memory performance were identified as risk factors for the patients to experience a significant decline in delayed verbal memory. Based on the available long-term follow-up data, it seems quite evident that patients with left or dominant side of surgery are at greater risk for postoperative verbal memory decline (Helmstaedter et al. 2003, Rausch et al. 2003, Alpherts et al. 2006, Andersson-Roswall et al. 2010). Better baseline performance can be associated with better postoperative memory performance (Helmstaedter et al. 2003, Alpherts et al. 2006), but also with a greater decline in postoperative memory (Rausch et al. 2003). However, patients with better baseline cognitive performance and thus better mental reserve capacity may retain long-term cognitive performance due to their ability to compensate for the adverse changes associated with surgery. It is also noteworthy, that in many operated patients memory performance remains unchanged or even slightly improves in the long-term.

Therefore, more accurate preoperative predictors of individual postoperative memory performance would be needed.

It is currently poorly understood how postoperative memory performance in neuropsychological tests relates to everyday memory in individual patients, i.e. whether a statistically significant cognitive change is clinically meaningful and important in the everyday functioning of the patient. Studies investigating postoperative memory performance have observed no significant relationship between subjective ratings and objective indices of memory change (Baxendale et al. 2010). It has been postulated that a statistically significant cognitive change should be accompanied by a meaningful change in a relevant external criterion such as everyday functioning (Witt & Helmstaedter 2013). Furthermore, it has been proposed that standardized assessment of activities of daily living by assessing frequencies of activities, could serve as a surrogate marker for everyday functioning (Helmstaedter et al. 2011).

Neuropsychological rehabilitation might also counteract the adverse cognitive effects of epilepsy surgery, particularly the decline in verbal learning and memory (Helmstaedter et al. 2008, Koorenhof et al. 2012). However, it is not yet known whether rehabilitation should be available pre- or postoperatively and if so, in which patients it would be beneficial.

6.7 COMPLICATIONS AND MORTALITY

In study II, the total rate of complications related to resective surgery was 2.1% for major and 10.7% for minor complications. Results which are in line with the previously published data where 0.5–7% major or permanent complications and 8.8–12% minor or transient complications have been described (Behrens et al. 1997, Rydenhag & Silander 2001, Salanova et al. 2002, Sindou et al. 2006, Tanriverdi et al. 2009).

The definition and classification introduced by Rydenhag and Silander (Rydenhag & Silander 2001) was used to analyse the complications. In their original study, the complication rate was 2.9% for major and 9.5% for minor complications if only patients with ATRs were included. Similarly, in a consecutive series of 100 adult patients with medically refractory MTLE, major complications were observed in 7% and minor complications in 12% of patients using this same classification (Sindou et al. 2006).

In the present work, mortality was related to surgery if the death was caused by a clinically or pathologically identified major surgical complication and occurred within 30 days after the surgery. As in most previous series (Behrens et al. 1997, Rydenhag & Silander 2001, Sindou et al. 2006, Özkara et al. 2008, Tanriverdi et al. 2009) there was no surgical mortality in the present study. However, in the Swedish epilepsy surgery series the mortality rate for the temporal lobe resections was 0.45% (Rydenhag & Silander 2001). Nonetheless, the rare possibility of an unexpected life-threatening complication of surgery needs to be discussed in advance with the patient or the family. However, this information must be balanced with the risks of continuing seizures and drug-refractory epilepsy.

The causes of late mortality were also analysed during the postoperative long-term follow-up. In study II, a total of six patients (4.3%) died during the postoperative follow-up. In four patients, the cause of death was related to epilepsy, and three out of the four epilepsy related deaths occurred in patients with recurrent postoperative seizures. Salanova et al. reported late mortality after TLE surgery as 5.1% (Salanova et al. 2002). Late mortality occurred predominantly in those patients with persistent seizures, whereas in the seizure-free patients the mortality rate was similar to that of the general population (Salanova et al. 2002). In addition, in a prospectively followed cohort of 583 epilepsy surgery patients, the mortality was strongly related to ongoing postoperative seizures (Sperling et al. 2005). There is also evidence that successful epilepsy surgery can be associated with reduced mortality when compared to nonsurgical patients (Bell et al. 2010). However, these authors could not demonstrate any relationship between the yearly seizure outcome and changes in mortality.

In study III, twenty-three percent of the evaluated patients had transient complications related to intracranial EEG. Nonetheless, the EEG evaluation could be completed as planned in all patients. The overall rate of major complications related to invasive EEG evaluation has been reported to be low (Behrens et al. 1997, Rydenhag & Silander 2001) particularly if subdural strip electrodes have been used.

6.8 CLINICAL RELEVANCE AND FUTURE ASPECTS

In the present study, novel information regarding the role of the entorhinal and temporopolar cortices in drug-resistant TLE was gained. It has been postulated that the observed pattern of atrophy in the mesial temporal cortical structures might be related to disruption of connectivity particularly between the hippocampus and the EC; or to the distribution of neurotransmitters within the medial temporal cortex (Bernasconi et al. 2003b). However, the clinical significance of the medial temporal cortical atrophy in TLE remains inadequately understood, and should be evaluated further. This might eventually help to improve the outcome of those MTLE patients who currently dot not become seizure-free after surgery or have a relapse after surgery.

Our findings regarding the different aspects of long-term outcome after TLE surgery were partly confirmatory by nature and ascertained the results described by previous authors. However, the findings of the present study are clearly relevant in the everyday clinical practise; and can be used in the preoperative assessment of patients, selection of individual patient to earlier surgical treatment, as well as in the counseling of individual patients before surgery.

Despite considerable progress in the surgical treatment of TLE, there are many issues that still need to be clarified. In the future, the association between duration of epilepsy and postoperative outcome should be further evaluated in order to confirm the optimal timing of surgery. With regards to cognitive outcome, the postoperative memory performance on individual level is highly variable and relation to the everyday memory is lacking. Therefore more accurate and clinically relevant predictors of individual postoperative memory change would be needed. On the other hand, we need prospective controlled information regarding both the need of postoperative antiepileptic medication, and the risks related to complete cessation of AEDs.

7 Conclusions

1. Volumes of entorhinal and temporopolar cortices are reduced in a subpopulation of patients with unilateral TLE ipsilateral to the seizure focus. The medial temporal cortical volume reduction is associated with a reduction in the hippocampal volume. In individual patients, the EC is affected more often than the TP. A volume reduction in the medial temporal cortical structures is typical for TLE and is not observed in patients with extratemporal focal epilepsy.

2. The postoperative long-term seizure outcome in adult patients with TLE in a Finnish national referral centre for epilepsy surgery is comparable to results reported from established epilepsy centres elsewhere. Seizure outcome one year after the operation predicts long-term seizure outcome. Although the best seizure outcome is observed in patients with unilateral TLE, palliative surgical treatment is beneficial in a subgroup of TLE patients, who do not have a restricted unilateral seizure focus in the preoperative evaluation. The use of a standardised MRI imaging protocol enhances detection of focal MRI abnormalities in epilepsy patients and improves postoperative seizure outcome. Hippocampal atrophy with or without temporal cortical atrophy, other unilateral structural lesions of the temporal lobe, seizure type predominance, and early onset of epilepsy predict good seizure outcome in the long-term follow-up.

3. In patients with no focal abnormality in the preoperative MRI, intracranial EEG evaluation is usually needed to define the epileptogenic zone. Epilepsy surgery is beneficial also in these MRI-negative TLE patients even though the outcome is not as favourable as in patients with focal pathological MRI findings.

4. After TLE surgery, a decline in verbal learning and memory is observed in the long-term follow-up. Both patients with left and right TLE are affected. The left side of surgery and better baseline memory performance are risk factors for a significant individual decline in delayed verbal memory during the long-term follow-up. In some cognitive tests an improvement is observed, this being related in part to the practice effect, but part of the improvement in cognitive performance may be related to seizure outcome. Significant variability in the individual test performance is relatively common and the cognitive performance of epilepsy surgery patients may also improve postoperatively.

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Leena Jutila

Surgical Treatment of Refractory Temporal Lobe Epilepsy

Predictors of Long-term Outcome

Temporal lobe epilepsy (TLE) is the most common type of focal drug-resistant epilepsy. The purpose of this study was to evaluate long-term seizure and cognitive outcome after surgical treatment of TLE and to identify predictive factors for the outcome. The outcomes after TLE surgery in a Finnish national referral centre for epilepsy surgery are comparable to the outcomes reported from epilepsy surgery centres internationally.

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