DEPARTMENT OF NEUROLOGY

SERIES OF REPORTS NO 55, 2001

Tuuli Salmenperä

DAMAGE IN THE HIPPOCAMPUS, AMYGDALA, ENTORHINAL AND PERIRHINAL CORTEX OF ADULTS WITH PARTIAL EPILEPSY

Doctoral dissertation

To be presented with assent of the Medical Faculty of the University of Kuopio for public examination in Auditorium L1, Canthia, University of Kuopio on Saturday 16th June 2001, at noon.

Department of Neurology, University of Kuopio

A.I.Virtanen Institute, University of Kuopio

Department of Neurology, Kuopio University Hospital

Department of Clinical Radiology, Kuopio University Hospital

Kuopio, 2001

Distributor: Kuopio University Library
P.O. Box 1627
FIN-70211 KUOPIO
FINLAND

Tel.: +358 17 163 430
Fax: +358 17 163 410

Email: tuuli.salmenpera@uku.fi
URL: http://www.uku.fi/neuro/

Author's address: Department of Neurology
University of Kuopio
P.O. Box 1627
FIN-70211 KUOPIO
FINLAND
Tel.: +358 17 173 311
Fax: +358 17 173 031

Supervisors: Professor Asla Pitkänen, MD, PhD
A.I.Virtanen Institute, University of Kuopio

Docent Reetta Kälviäinen, MD, PhD
Department of Neurology, Kuopio University Hospital

Professor Hilkka Soininen, MD, PhD
Department of Neurology, University of Kuopio

Reviewers: Docent Jouko Isojärvi, MD, PhD
Department of Neurology, University of Oulu

Professor Ricardo Insausti, MD, PhD
School of Medicine, University of Castilla-La Mancha, Spain

Opponent: Docent Tapani Keränen, MD, PhD
Department of Neurology, University of Turku

ISBN 951-781-747-9
ISSN 0357-6043

Kuopio University Printing Office
Kuopio 2001
Finland

SALMENPERÄ, TUULI. Damage in the hippocampus, amygdala, entorhinal and perirhinal cortex of adults with partial epilepsy. Series of Reports, No 55, Department of Neurology, University of Kuopio 2001, 124 p (*Note:the page count applies to the hard copy of this thesis*).
ISBN 951-781-747-9
ISSN 0357-6043

ABSTRACT

Epilepsy refers to a common group of neurologic conditions characterized by recurrent unprovoked seizures. Although the prognosis of epilepsy is usually favorable, up to 30% of patients continue to have seizures despite intensive treatment with antiepileptic drugs. Hippocampal sclerosis is found in 60 to 70% of patients with intractable temporal lobe epilepsy (TLE). However, it is not known whether the damage in the hippocampus is the cause or the consequence of TLE. The purpose of the present series of studies (I-V) was to investigate with magnetic resonance imaging (MRI) the appearance of medial temporal lobe damage during the course of partial epilepsy, and, particularly, to determine whether recurrent or prolonged seizures contribute to the damage.

Altogether 259 partial epilepsy patients were investigated with quantitative MRI in studies I-IV. The patients were divided into two groups according to the localization of the seizure focus: patients with TLE (n=167), and patients with extratemporal/unclassified partial epilepsy (ETE/UC) (n=92). Study V comprised nine patients with status epilepticus requiring intravenous antiepileptic medication.

High lifetime seizure number, complex febrile convulsions in the medical history, and early age at the onset of spontaneous seizures contributed to hippocampal damage in patients with TLE. The risk factors that predicted amygdaloid volume reduction were intracranial infection and complex febrile convulsions. Damage in the hippocampus or in the amygdala was rare at the time of first spontaneous seizures in TLE. In contrast, hippocampal damage was apparent in chronic TLE patients with years of frequent seizures. Chronic cryptogenic drug-resistant TLE patients had smaller mean hippocampal volumes and T2 relaxation times in the body of the hippocampus ipsilateral to the seizure focus than controls. In all TLE patients, ipsilateral hippocampal volume correlated negatively and T2 relaxation time positively with the lifetime seizure number. The mean amygdaloid volumes in chronic TLE patients did not differ from those in controls. However, about 20% of chronic patients had ≥ 20% volume reduction and T2 time prolongation in the amygdala. There were no differences in the hippocampal and amygdaloid volumes and T2 relaxation times between patients with different durations of ETE/UC and controls. The mean volumes of the entorhinal cortex ipsilateral to the epileptic focus in cryptogenic TLE patients did not differ from those in controls. However, the entorhinal cortex was damaged in a subpopulation of TLE patients with associated hippocampal damage. Status epilepticus did not lead to the development of marked volume reduction of the hippocampus, amygdala, or the entorhinal and perirhinal cortices in adult patients treated promptly in hospital with a predetermined protocol.

The findings of the present series of studies support the hypothesis that damage in the medial temporal lobe structures may be both the cause and consequence of TLE. The data provide evidence that in some patients hippocampal damage may progress as a function of repeated seizures, and argue for efficient drug therapy or early surgery to reach complete seizure control. Future research should address strategies for disease-modifying therapies and ultimately remission of the epileptic process.

National Library of Medicine Classification: WL385

Medical Subject Headings: amygdala; entorhinal cortex; epilepsy; hippocampus; magnetic resonance imaging; status epilepticus; temporal lobe

ACKNOWLEDGEMENTS

This study was carried out at the Departments of Neurology and Radiology at the University of Kuopio and the Kuopio University Hospital and at the A.I.Virtanen Institute during years 1995-2000.

I am grateful to the principal supervisor of this study, professor Asla Pitkänen for her guidance and teaching of neuroscience and research.

I owe my gratitude to the second supervisor, docent Reetta Kälviäinen for sharing with me her expert knowledge in clinical neurology and research.

I express my gratitude to professor Hilkka Soininen, Head of the Department of Neurology, University of Kuopio for supervising and providing the excellent facilities to carry out this work.

I am thankful to all the supervisors for their support to me during these years.

I thank the collaborators of the study docent Kaarina Partanen, Pauli Vainio, PhL and docent Esa Mervaala for their valuable contributions.

I am indebted to professor Ricardo Insausti, School of Medicine, University of Castilla-La Mancha and docent Jouko Isojärvi, Department of Neurology, University of Oulu for their expert reviewing of the manuscript.

My thanks go to Pirjo Halonen, MSc for statistical advice, to Mrs Liisi Saarela for help in editing the manuscript and to Vivian Paganuzzi, MA for revising the language.

I am thankful to my colleagues for the friedship and support they have provided. I would like to thank the staff of the Departments of Neurology and Radiology for the help and co-operation during the study. I thank also the members of the ”EpiClub” at the A.I.Virtanen Instute for our work together.

I express my gratitude to all the patients who have participated in this study.

My warmest thanks belong to my friends and to my family for their ample encouragement, support, patience and kindness to me during this work.

This work was financially supported by the Finnish Epilepsy Society, the Finnish Medical Society Duodecim, the Instrumentarium Foundation, the Kuopio University Hospital, the Kuopio Doctoral Program of Medical Sciences, the Neurology Foundation, the North-Savo Regional Fund of the Finnish Cultural Foundation and the Vaajasalo Foundation.

Kuopio, May 2001

Tuuli Salmenperä

ABBREVIATIONS

AMY	amygdala
CA1	Cornu Ammonis 1 (field)
CA2	Cornu Ammonis 2 (field)
CA3	Cornu Ammonis 3 (field)
CBF	cerebral blood flow
CNS	central nervous system
CMRglc	cerebral metabolic rate of glucose
CI	confidence interval
Cr	creatine
ΔAMY	volume of the right amygdala − volume of the left amygdala
ΔT2	right transverse relaxation time − left transverse relaxation time
EC	entorhinal cortex
EEG	electroencephalogram
e.g.	exempli gratia
ETE/UC	extratemporal/unclassified partial epilepsy
ETL	echo time length
FOV	field of view
HC	hippocampus
i.e.	id est
IL	Illinois
ILAE	International League Against Epilepsy
L	left
MP-RAGE	magnetization-prepared rapid acquisition gradient-echo
MRI	magnetic resonance imaging
MRSI	magnetic resonance spectroscopic imaging
NAA	N-acetyl-aspartate
OR	odds ratios
PC	personal computer
PET	positron emission tomography
PRh	perirhinal cortex
R	right
rAMY	volume of the right amygdala divided by the volume of the left amygdala
rT2	right transverse relaxation time divided by left transverse relaxation time

s-NSE	serum neuron-specific enolase
SD	standard deviation
SPSS	Statistical Package for Social Sciences
TE	time of echo
TLE	temporal lobe epilepsy
TR	time of repetition
T1	longitudinal relaxation time
T2	transverse relaxation time
V	version
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications:

I. Kälviäinen R, Salmenperä T, Partanen K, Vainio P, Riekkinen P Sr, Pitkänen A. Recurrent seizures may cause hippocampal damage in temporal lobe epilepsy. Neurology 1998; 50: 1377-1382.

II. Kälviäinen R, Salmenperä T, Partanen K, Vainio P, Riekkinen P Sr, Pitkänen A. MRI volumetry and T2 relaxometry of the amygdala in newly diagnosed and chronic temporal lobe epilepsy. Epilepsy Res 1997; 28: 39-50.

III. Salmenperä T, Kälviäinen R, Partanen K, Pitkänen A. Hippocampal and amygdaloid damage in partial epilepsy. A cross-sectional MRI study of 241 patients. Epilepsy Res 2001; 46: 69-82.

IV. Salmenperä T, Kälviäinen R, Partanen K, Pitkänen A. Quantitative MRI volumetry of the entorhinal cortex in temporal lobe epilepsy. Seizure 2000; 9: 208-215.

V. Salmenperä T, Kälviäinen R, Partanen K, Mervaala E, Pitkänen A. MRI volumetry of the hippocampus, amygdala, entorhinal cortex, and perirhinal cortex after status epilepticus. Epilepsy Res 2000; 40: 155-170.

In addition, the thesis includes previously unpublished data (T2 relaxometry of the hippocampus and the amygdala in partial epilepsy).

CONTENTS

1. INTRODUCTION

Epilepsy is a common chronic brain disorder characterized by recurrent seizures due to excessive discharge of cerebral neurons. More than 10% of the population will experience a seizure at some time and around 1% of the population has epilepsy (Hauser and Hesdorffer, 1990). Up to 30% of all epilepsy patients develop intractable epilepsy (Sander and Sillanpää, 1999). Despite optimal treatment these patients continue to have seizures or other symptoms of epileptic syndrome restricting their ability to lead a full life (Hauser and Hesdorffer, 2001). The majority of intractable epilepsy patients referred for surgical consideration have complex partial seizures (Wieser et al., 1993; Williamson et al., 1993a). Most commonly, the origin of recurrent complex partial seizures is in the temporal lobe. Patients with temporal lobe epilepsy (TLE) have typical clinical and electroencephalographic characteristics. Furthermore, a distinctive pattern of structural damage is frequently found in the medial temporal lobe structures of TLE patients.

Neuropathological studies indicate that 70% of intractable TLE patients have hippocampal damage characterized by neuronal loss and gliosis in the dentate hilus and in Ammon's horn (Bruton, 1988). The structural damage often extends beyond the confines of the hippocampus to the amygdala and the adjacent cortex (Margerison and Corsellis, 1966; Bruton, 1988). The etiology and the pathogenesis of this frequently encountered medial temporal lobe damage is not known. Several studies have reported a correlation between severe childhood illness (infection, febrile convulsions, status epilepticus) and hippocampal atrophy in TLE (Cavanagh and Meyer, 1956; Falconer et al., 1964; Margerison and Corsellis 1966; Bruton, 1988). However, not all TLE patients with hippocampal damage have a history of initial insult. Some experimental and human data suggest that recurrent seizures may cause progressive damage to the hippocampus (Sloviter, 1983; Cavazos et al., 1994; Mathern et al., 1995).

Magnetic resonance imaging (MRI) offers a sensitive noninvasive technique to investigate the medial temporal lobe structures of TLE patients during the course of the disease. Quantitative MRI volumetric analysis of the hippocampus proved to be nearly 100% sensitive and specific for hippocampal sclerosis in a series of surgically treated TLE patients (Cascino et al., 1991; Cascino et al., 1992). Furthermore, quantifying transverse relaxation time (T2) -weighted signal intensity allows MRI diagnosis of hippocampal damage in cases with mild bilateral structural abnormalities.

In line with previous histopathological results, current neuroimaging data provide evidence that TLE begins with an early hippocampal injury. However, the initial damage may be followed by a gradual and progressive course of further neuronal damage (Nohria et al., 1994; Tien and Felsberg, 1995; VanLandingham et al., 1998). O'Brien et al. (1999) recently provided the first prospective MRI evidence that progressive atrophy of the hippocampus may develop even in the absence of initial insult due to uncontrolled temporal lobe seizures. The case study adds a link to the theory uniting data from experimental and clinical studies indicating that neuronal damage in the hippocampus is both the cause and effect of seizures.

This series of studies investigated with MRI the medial temporal lobe damage during the course of partial epilepsy, particularly whether recurrent or prolonged seizures contribute to the damage. The predictive factors of medial temporal lobe damage were analysed with the aim of contributing to a better understanding of the epileptic process and the care of epilepsy patients with frequent seizures.

2. REVIEW OF THE LITERATURE

2.1. EPILEPSY

2.1.1. Definition

Epileptic seizures can be defined as manifestations of abnormal excessive neuronal activity in the gray matter of the cerebral cortex. The clinical features of seizures are determined by the normal functions of the region of cortex in which neurons fire abnormally and include stereotyped alterations in consciousness, behavior, emotion, motor function or sensation. Seizures can be caused by a variety of pathologic conditions, including acquired brain injuries and genetic abnormalities. Many physiologic disturbances of brain functions can also provoke seizures (Dichter, 1997; Engel and Pedley, 1999; McNamara, 1999). When unprovoked seizures occur recurrently, characterizing a diverse collection of brain disorders, the condition is called *epilepsy* (Commission on Epidemiology and Prognosis of the International League Agaist Epilepsy (ILAE), 1993).

2.1.2. Epidemiology

The prevalence rate for epilepsy is 4-8 cases per 1 000 population (Hauser and Kurland, 1975; Goodridge and Shorvon, 1983) and the annual incidence rate including patients with recurrent unprovoked seizures typically varies between 30 and 50 per 100 000 population per year (Hauser and Kurland, 1975; Joensen, 1986). In Finland, Keränen (1988) reported an incidence rate of 24/100 000 and a prevalence of 6.3/1 000 in adult patients with epilepsy. His study population was collected from the Kuopio University Hospital district, situated in East-Central Finland and covering the same area as the present series of studies. The estimates of lifetime prevalence, which is the measure of people in a population who have ever had epilepsy, vary from 2 to 6% of the population (WHO, 1957; Hauser and Kurland, 1975; Goodridge and Shorvon, 1983; Zielinski, 1988; Hauser et al., 1993). These statistics suggest that 1 in 20 persons will have suffered epilepsy at some point in their lives and, conservatively, 1 in 200 will currently have epilepsy (Shorvon, 1996).

2.1.3. Classification

The classification of epileptic seizures by the Commission on Classification and Terminology of the ILAE (1981) is based on clinical events (seizure type) and characteristics of electroencephalogram (EEG). According to the classification, epileptic seizures are divided into *partial* and *generalized* seizures. Partial seizures are those in which, in general, the first clinical and EEG changes indicate initial activation of a system of neurons limited to part of one cerebral hemisphere. Partial seizures are classified as *simple* when consciousness is retained and *complex* when consciousness is impaired. Simple partial seizures can progress to become complex and they are further classified according to symptoms: motor, sensory, autonomic and psychic. Both simple and complex partial seizures can further evolve into *secondarily generalized* seizures with characteristic tonic and clonic motor manifestations. Generalized seizures are those in which the first clinical changes indicate initial involvement of both hemispheres. The initial ictal EEG patters are bilateral and presumably reflect neuronal discharge, which is widespread in both hemispheres. Generalized seizures are further divided into tonic-clonic, tonic, clonic, absence, myoclonic and atonic seizures.

A myriad different conditions may express themselves by occurrence of recurrent seizures. This heterogeneity of epilepsy is recognized in the ILAE (1989) classification of epilepsies and epileptic syndromes which reflect the etiology and prognosis. The classification specifies more than 40 distinct types of epileptic syndromes characterized by signs and symptoms, seizure types, cause, age at onset and EEG patterns occurring together. Once the diagnosis of epilepsy is established, a syndromic

diagnosis should be attempted. According to the classification, the disorder of the brain may be apparently localized and known as "localization related" (partial) or generalized. Both localization related and generalized epilepsies and syndromes are divided according to the etiology into idiopathic and symptomatic varieties. *Idiopathic* epilepsies are not associated with brain lesions, neurologic abnormalities other than seizures, or cognitive impairment. The onset of manifestations are typically age-related. Conversely, in *remote symptomatic* epilepsy, seizures are the consequence of a focal brain abnormality or other specific etiology. When epilepsies are probably remote symptomatic, but currently of unknown etiology, they are termed *cryptogenic*.

2.1.4. Etiology

Certain postnatal insults such as brain trauma, central nervous system (CNS) infections, cerebrovascular disease, and brain tumors greatly increase the incidence of epilepsy (Annegers, 1996). In a classical study in Rochester, Minnesota, 1935-1984, the presumed predisposing cause of epilepsy was vascular in 11% of all the incident cases of epilepsy, followed by congenital (8%), traumatic (5.5%), neoplastic (4.1%), degenerative (3.5%) and infective (2.5%) causes (Hauser et al., 1993). More recently, a prospective cohort population-based study in the United Kingdom reported that the etiology of epilepsy was vascular disease in 15%, cerebral tumor in 6%, alcohol-related in 6% and post-traumatic in 3% of the patients (Sander et al., 1990). The etiology of epilepsy varies considerably in different age groups and may be multifactorial. Notably, epidemiological studies have reported that in about 65% of cases the etiology of seizures was idiopathic/cryptogenic (Sander et al., 1990; Hauser et al., 1993).

It is evident that the more extensive the investigation, the more likely etiological factors are to be identified. Brain magnetic resonance imaging (MRI) identifies a high rate of positive causes in hospital-based surveys (Li et al., 1995). However, no population-based epidemiological study with modern neuroimaging has yet been reported. Therefore, it is likely that the true incidence of symptomatic epilepsies is higher than reported in previous studies, and that MRI will have an important impact on the diagnosis of previously undetectable structural abnormalities such as cortical dysplasias underlying epilepsy.

The majority of epilepsies, both cryptogenic and symptomatic, lack an overt genetic determinant. However, genetics may contribute to susceptibility to epilepsy arising after a brain insult. The inherited pattern is prominent in many of the epilepsy syndromes. A single genetic locus controls more than 300 disorders in which epileptic seizures are an important feature. However, they account for less than 1% of all epilepsies. Genetic determinants also contribute strongly to risk of idiopathic epilepsies, although most of them have complex inheritance in which the phenotypic variation within and between families is generally much greater than that observed in epilepsies with simple inheritance.

2.1.5. Epileptic process

Epileptogenesis refers to the development of an epileptic disorder (Figure 1). It is well known from experimental studies with animal models (Cavalheiro et al., 1991; Mello et al., 1993) as well as from studies with patients (Annegers et al., 1980; Weiss et al., 1986) that there is a latent period between induction of a localized cerebral insult such as head trauma or status epilepticus and the appearance of a chronic epileptic condition. During the latent period, neuronal loss and abnormal synaptic reorganization occurs (Mello et al., 1993; Leite et al., 1996). This reorganization of the neuronal integration leads to abnormally increased excitability and synchronization, and eventually to the occurrence of spontaneous seizures (Cavalheiro et al., 1991; Isokawa and Mello, 1991). Once developed, epilepsy should not be viewed as a random succession of seizures but as a dynamic process which results in both ictal phenomena and interictal functional and structural abnormalities in the brain

(Rodin, 1972; Shorvon and Reynolds, 1986; Engel et al., 1991). Patients who develop chronic intractable epilepsy demonstrate progression in both the number of seizures and in seizure-related neurological symptoms such as cognitive and behavioral disorders (Elwes et al., 1984; Engel et al., 1991; French et al., 1993; Williamson et al., 1993b, Cockerell et al., 1997). A challenge arising from the existing data is to fill the gaps of the hypothesis of progression of epileptic damage. In the future, neuroprotective therapy could be developed either for the time period after a brain insult that is known to be associated with structural damage and the development of epilepsy later in life, or after epilepsy diagnosis as a part of a rational antiepileptic polytherapy if the patient is not seizure-free (Pitkänen et al., 1999).

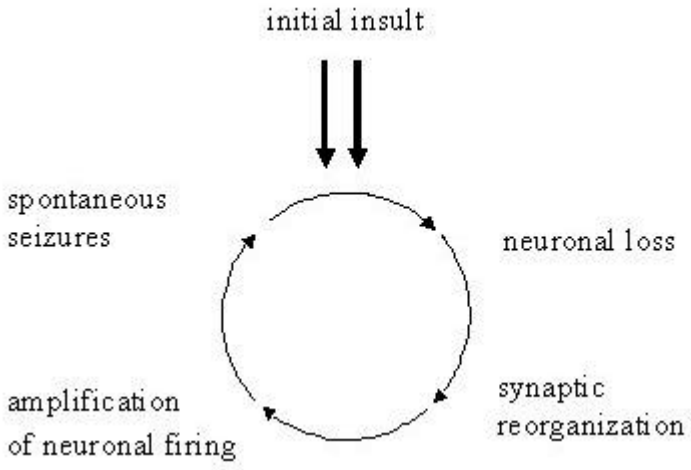

Figure 1. Model of development of epilepsy – epileptogenesis. After initial cerebral insult, the damaged brain reorganizes during the latent period in a manner that ultimately predisposes to the development of spontaneous seizures.

2.1.6. Prognosis

Overall, the prognosis for most epilepsy patients with antiepileptic treatment today is good in terms of seizure control. Evidence from population-based studies show that 70-80% of patients will ultimately become seizure-free (Annegers, 1979; Goodridge and Shorvon, 1983; Cockerell et al., 1995; 1997). The long-term outcome of epilepsy is often predictable by observation of the early outcome of seizure control (Goodridge and Shorvon, 1983; Sillanpää, 2000). In 50-70% of the patients, seizures will be controlled with an initial antiepileptic drug, regardless of the specific drug used (Elwes et al., 1984; Smith et al., 1987; Collaborative Group for the Study of Epilepsy, 1992). Switching to a second antiepileptic drug affords control in about one-third of initially uncontrolled patients (Smith et al., 1987). There are no clear differences in efficacy between first line monotherapy drugs such as carbamazepine, phenytoin, valproate, lamotrigine and oxcarbazepine (Mattson et al., 1985; 1992; Brodie et al., 1995; Bill et al., 1997), nor have the newer antiepileptic drugs (gabapentin, levetiracetam, tiagabine, topiramate, vigabatrin and zonisamide) shown significant difference in efficacy or tolerability in a meta-analysis of trials in drug-resistant partial epilepsy (Chadwick et al., 1996; Marson and Chadwick, 2001).

Up to 30% of all epilepsy patients will develop intractable epilepsy (Sander and Sillanpää, 1999). The epilepsy is considered intractable when a patient has epileptic seizures or other symptoms of epileptic syndrome despite optimal treatment and these symptoms restrict the patient's ability to lead a full and safe life (Hauser and Hesdorffer, 2001). In a prospective study of newly-referred epilepsy patients, the risk factors that predicted the development of intractable epilepsy were a large number of seizures before treatment, combined seizure types, early age at onset, and prolonged disease duration (Beghi

and Tognoni, 1988). Moreover, the factors associated with intractable epilepsy include syndromes of secondarily generalized epilepsies (e.g., Lennox-Gastaut syndrome, West syndrome), certain seizure types such as atonic and tonic seizures, and certain etiologies such as sequlae of cerebral infections or trauma. Epilepsy patients with associated neurologic deficits and detectable structural brain damage have lower remission rates (Shorvon, 1990; 1996; Sander, 1993). Drug-resistant seizures and associated neurological disabilities are further related to poor social outcome and higher mortality rate (Hauser et al., 1980; Cockerell et al., 1997; Sillanpää, 2000). Overall, patients with epilepsy have a mortality rate two to three times higher than expected (Annegers, 1999). The greatest increase in mortality occurs in the early years of diagnosis, in the symptomatic group and in patients with high frequency of tonic-clonic seizures (Hauser et al., 1980; Cockerell et al., 1997; Walczak et al., 2001).

2.1.7. Status epilepticus

Status epilepticus is defined as a condition characterized by an epileptic seizure that is so frequently repeated or so prolonged as to create a fixed and lasting condition (Gastaut, 1970). Previously, the term has been applied to continuous seizures lasting at least 30 minutes (Working Group on Status Epilepticus, 1993). However, clinicians have long recognized the need to terminate the convulsive status as soon as possible to prevent the development of structural damage and functional incapacity in patients with prolonged seizure disorder. Therefore, Lowenstein and Alldredge (1998) advocated the use of an operational definition of status epilepticus: either continuous seizures lasting at least 5 minutes, or two or more discrete seizures between which there is incomplete recovery of consciousness.

Any type of seizure can develop into status epilepticus, although the form most often seen in adults is tonic-clonic status epilepticus (Leppik, 1990). In a prospective, population-based study the incidence of status epilepticus was 41/100 000, and the mortality rate 22% (DeLorenzo et al., 1996). The majority of status epilepticus patients had no history of epilepsy. Furthermore, infants less than one year of age had the highest incidence of status epilepticus, but the elderly population represented the largest number of status epilepticus cases (DeLorenzo et al., 1995). Frequent causes of status epilepticus include noncompliance with antiepileptic medication, cerebral vascular disease, drug (including ethanol) abuse and withdrawl, CNS infection, metabolic disorder, tumor, and trauma (Lothman, 1990; Towne et al., 1994). In some cases, the cause is multifactorial; in others, no cause is identified (Lothman, 1990).

The morbidity and mortality from status epilepticus are related to three factors: damage to the CNS caused by acute insult precipitating the status epilepticus, systemic stress from repeated generalized tonic-clonic convulsions, and injury from repetitive electrical discharges within the CNS (Leppik, 1990). Systemic effects of repeated generalized seizures can influence cardiovascular, respiratory, and renal failure (Leppik, 1990). In addition, a number of biochemical changes not related to systemic effects of tonic-clonic activity occur in the CNS. Sixty minutes of repeated neuronal discharge results in severe neuronal death (Meldrum and Brierley, 1973). Neuropathological and imaging studies have shown damage in the hippocampus and in the amygdala, piriform cortex, thalamus, cerebellum and cerebral cortex after convulsive and nonconvulsive status epilepticus episodes in patients (Norman, 1964; Corsellis and Bruton, 1983; DeGiorgio et al., 1992; Wasterlain et al., 1993; Nohria et al., 1994; Tien and Felsberg, 1995; Wieshman et al., 1997). In vivo, the measurement of neuron-specific enolase provides further evidence of acute cerebral damage following status epilepticus. The enzyme was elevated in the serum of both generalized convulsive and nonconvulsive status epilepticus patients within 24 to 48 hours after the onset of status (DeGiorgio et al., 1995; Rabinowicz et al., 1995).

Time is of the essence in the treatment of status epilepticus. Every emergency unit should have a predetermined protocol that includes a time frame (Leppik, 1990). The therapy for status epilepticus currently consists of agents which stop seizures (benzodiazepines, phenytoin, barbiturates) (Bleck, 1991). In a study trial comparing treatments for generalized convulsive status epilepticus, diazepam plus

phenytoin, lorazepam or phenobarbital were equally effective therapies (Treiman et al., 1998). If status epilepticus is refractory, barbiturates (tiopental, pentobarbital) are used to induce anesthesia (Osorio and Reed, 1989).

The three broad types of sequlae of status epilepticus include epileptic brain damage, neurological/cognitive deficits, and epilepsy with spontaneous recurrent seizures (Krumholz et al., 1995). Due to the significant morbidity and mortality associated with the insult despite current medical treatment, status epilepticus remains one of the most serious disorders affecting the CNS.

2.2. STRUCTURES AND CONNECTIONS OF THE MEDIAL TEMPORAL LOBE

The limbic system forms a border (limbus) around the upper brain stem, diencephalon and corpus callosum. The main components of the limbic system are (1) the hippocampal formation, (2) the limbic association cortices including parahippocampal gyrus, and (3) the amygdaloid complex (Braak et al., 1996). Both the amygdala and hippocampus are located in the medial part of the temporal lobe, adjacent to the parahippocampal gyrus. This gyrus is a “continuation” of the cingulate gyrus onto the inferior surface of the brain. The cortex of the parahippocampal gyrus includes the subiculum and entorhinal cortex, both of which are functionally related to the hippocampus.

The hippocampal formation is a prominent, bulging eminence in the floor of the temporal horn of the lateral ventricle. During development, the hippocampal formation undergoes an enfolding into the temporal lobe. This results in the interdigitation of two c-shaped structures, the hippocampus and the dentate gyrus. There is further subdivision of the hippocampus into three regions, which are referred to as CA (Cornu Ammonis) fields. The CA3 field borders the hilus of the dentate gyrus; a short CA2 field follows; and a more extensive CA1 merges with the subiculum (Amaral and Insausti, 1990).

The major source of cortical inputs to the hippocampal circuit is formed by the entorhinal cortex (Witter and Amaral, 1991) (Figure 2). The term entorhinal cortex was coined by Brodmann (1909) as a synonym for his area 28 and it covers the rostral parahippocampal gyrus (Insausti et al., 1995). The human entorhinal cortex is made up of six layers, of which layer IV does not appear throughout all subfields of the entorhinal cortex (Insausti et al., 1995). In the most classical hippocampal pathway, cells in layers II and III of the entorhinal cortex give rise to the perforant path that distributes to all subfields of the hippocampal formation, including the dentate gyrus (Witter and Amaral, 1991). From the dentate gyrus, granule cells project to the CA3 field of the hippocampus. The CA3 pyramidal cells, in turn, send a major projection to the CA1 field (although some fibres from the CA3 field leave the hippocampus at this point, via the fornix). Much of the input from the CA1 field is then sent on to the subiculum. From the subiculum, information can be conveyed to the deep layers of the entorhinal cortex (Amaral et al., 1984; Witter, 1993).

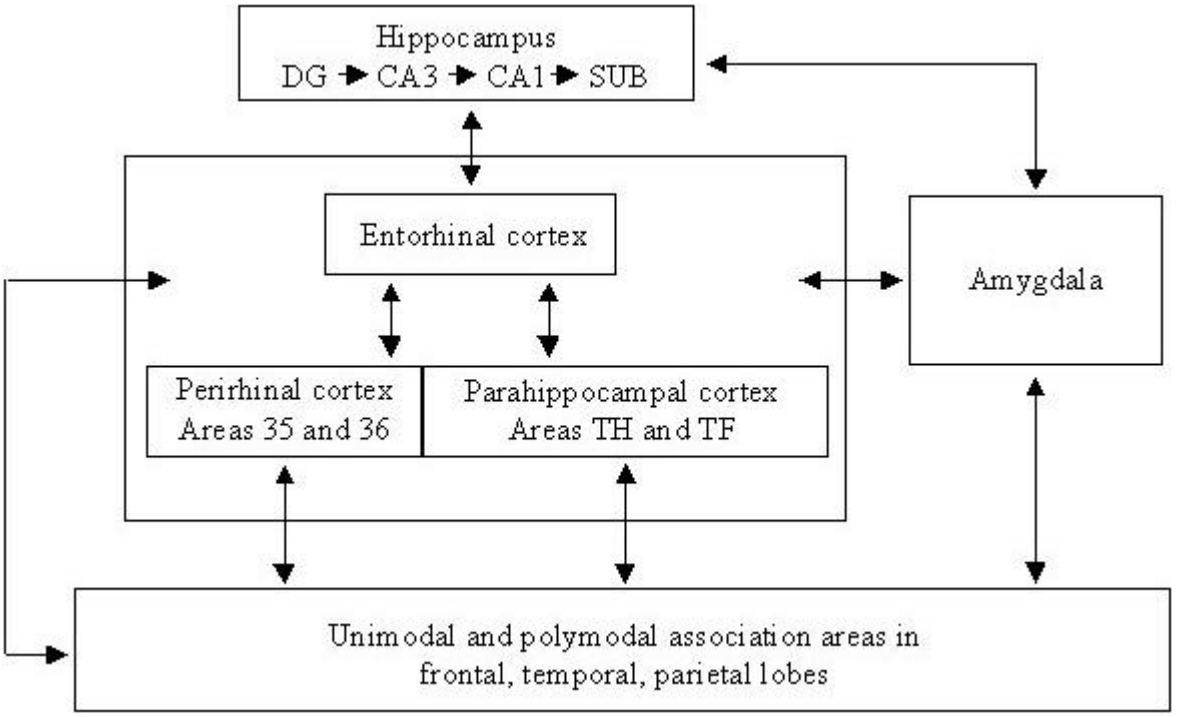

Figure 2. A schematic view of the cortical connections and the inter-connectivity of the medial temporal lobe structures. The entorhinal cortex is the major source of projections to the hippocampus. Two-thirds of the cortical input to the entorhinal cortex originates in the adjacent perirhinal and parahippocampal cortices which in turn receive projections from unimodal and polymodal areas in the frontal, temporal and parietal lobes. The entorhinal cortex also receives direct projections from these cortical areas. All the projections are reciprocal. Abbreviations: CA, Cornu Ammonis; DG, dentate gyrus; SUB, subiculum. (Adapted from Suzuki, 1996a).

The entorhinal cortex receives prominent cortical innervation (Amaral and Insausti, 1990). Two-thirds of this cortical input originates in the perirhinal and parahippocampal cortices (Insausti et al., 1987). The perirhinal cortex (areas 35 and 36 by Brodmann (1909)) is bounded medially by the entorhinal cortex and laterally by temporal association areas. It also extends anteriorly to include the medial portion of the temporal pole (Suzuki, 1996a). The parahippocampal cortex is caudally adjacent to both the entorhinal cortex and the perirhinal cortex, and is made up of a smaller, medially situated area TH and a larger, laterally situated area TF (Suzuki and Amaral, 1994a). Direct input to the entorhinal cortex orginates in several cortical regions in the frontal and temporal lobes, and in the insular and cingulate cortices, as well as in the adjacent perirhinal and parahippocampal cortices (Insausti et al., 1987). All these projections are reciprocal.

There are extensive reciprocal connections with the hippocampus, the entorhinal cortex and the amygdala (Amaral, 1987). The amygdaloid complex is composed of more than ten nuclei and their subdivisions which have different cytoarchitectonic, chemoarchitectonic, and connectional characteristics (Amaral et al., 1992; Pitkänen et al., 1997). The lateral nucleus of the amygdala gives rise to a prominent projection to layer III of the entorhinal cortex (Amaral and Insausti, 1990). There are also additional projections from the amygdaloid complex to the hippocampus and to the subiculum (Aggleton, 1986; Amaral, 1986; Amaral and Insausti, 1990). Conversely, the subiculum and the entorhinal cortex originate return projections to the amygdala (Aggleton, 1986; Amaral, 1986). In general, the amygdaloid complex projects to a greater number of cortical regions than those from which it receives projections (Amaral, 1987). Essentially, all major divisions of the temporal cortex receive a projection from the amygdala. The perirhinal cortex, particularly, has prominent interconnections with the amygdala nuclei (Suzuki, 1996b). Moreover, there is evidence of reciprocal connectivity with the

amygdala and portions of the frontal and insular cortices. The general conclusion about the functional connectivity is that the amygdaloid complex is directly and reciprocally linked to a wide variety of cortical regions and can influence and be influenced by sensory information processed to various degrees. In contrast, cortical information is funneled into and out of the hippocampal formation through polysensory border regions and appears to be highly processed before reaching the hippocampus (Amaral, 1987; Insausti et al., 1987; Suzuki and Amaral, 1994a,b).

2.3. THE CONCEPT OF TEMPORAL LOBE EPILEPSY (TLE)

2.3.1. Definition and epidemiology

Temporal lobe epilepsy is a localization related epilepsy with typical clinical and EEG characteristics (ILAE, 1989). Complex partial seizures originating from the temporal lobe are the single most common type of seizure encountered in the adult population (Hauser and Kurland, 1975; Williamson et al., 1987; Engel, 1989). Patients with temporal lobe complex partial seizures constitute the majority of patients referred for surgical consideration (Wieser et al., 1993; Williamson et al., 1993b).

In most TLE patients, seizures begin in the mesial temporal structures (Wieser et al., 1993), specifically in the hippocampus (Spencer et al., 1990). Regional onsets including hippocampus, amygdala, and temporal neocortex may account for more than 50% of temporal lobe seizures (Zentner et al., 1999). The entorhinal cortex, in particular, serves as a gate of seizure propagation both in experimental in vitro seizure models (Walther et al., 1986; Bragdon et al., 1992) and in depth-electrode studies of TLE patients (Rutecki et al., 1989; Wilson et al., 1990; Spencer and Spencer, 1994).

Temporal lobe epilepsy with seizure onset from the mesial temporal lobe structures and with distinctive hippocampal pathology is recognized as a syndrome of mesial temporal epilepsy (Williamson and Engel, 1999). If seizures begin outside mesial temporal lobe structures in the temporal neocortex, epilepsy is referred to as lateral or neocortical TLE (Williamson and Engel, 1999). Seizures may also begin outside the temporal lobe. In large surgical series, seizures originating from the frontal lobe were the second most commonly reported localization related epileptic disorder (Williamson et al., 1987; Williamson et al., 1993a; Wieser and Hajek, 1995). When the location of seizure focus is outside the temporal lobe, epilepsy is termed extratemporal partial epilepsy. If the seizure focus is unknown, partial epilepsy is unclassified.

2.3.2. Seizure semiology and electroencephalographic findings

Temporal lobe seizures are characterized by simple partial seizures, complex partial seizures and secondarily generalized seizures, or a combination of these (ILAE, 1989). Most temporal lobe seizures begin with a simple partial seizure such as abdominal visceral sensations or experiential (e.g., fear or *deja vu*) phenomena (Gloor, 1982; French et al., 1993; Bancaud et al., 1994). Following the initial symptoms, prominent ictal features include an arrest of activity, oral-alimentary automatisms, motor phenomena, and commonly, amnesia (Fakhoury et al., 1994; Saygi et al., 1994; Kuzniecky and Jackson, 1995). Secondary generalization may occur (Fakhoury et al., 1994).

Distinctive interictal and ictal EEG patterns may be observed in TLE. The interictal scalp EEG may show unilateral or bilateral, synchronous or asynchronous temporal spikes, sharp waves, and/or slow waves (Gambardella et al., 1995). Interictal scalp EEG is normal in the majority of partial epilepsy patients at the time of the epilepsy diagnosis (Walczak and Jayakar, 1999). Conversely, the large majority (94%) of intractable TLE patients without circumscribed, potentially epileptogenic lesion had paroxysmal abnormalities localized in the anterior temporal region in the preoperative scalp EEG (Williamson et al., 1993b). Bilateral independent paroxysmal activity occurred in 42% of the patients

and was preponderant over the side of seizure origin in half (Williamson et al., 1993b). If series of scalp EEGs do not reveal the onset and evolution of the seizure discharges in partial epilepsy patients, intracranial recordings may provide additional information (Quesney , 1986).

2.3.3. Etiology

Temporal lobe epilepsy may develop after a variety of insults such as head trauma, birth injury or CNS infection (French et al., 1993; Mathern et al., 1995; Lancman and Morris, 1996). When seizures result from a specific cerebral pathologic substrate in the temporal lobe, such as a traumatic scar, TLE is classified as remote symptomatic. A common factor predisposing some patients to TLE is the occurrence of complex febrile convulsions. Falconer et al. suggested already in 1964 that prolonged febrile seizures lead to the development of TLE. Several studies since then have recognized the association between complex febrile convulsions and TLE (Abou-Khalil et al., 1993; French et al., 1993; Maher and McLachlan, 1995).

Cryptogenic TLE refers to an epileptic disorder where no etiology of the condition can be determined. A finding frequently encountered in patients with intractable TLE, both cryptogenic and symptomatic, is a distinctive pathological change in the hippocampus, i.e. hippocampal sclerosis. However, it is not known whether the damage found in the hippocampus is the cause or the consequence of TLE.

2.3.4. Histopathologic findings in TLE

2.3.4.1. The hippocampus

Unilateral atrophy of Ammon's horn was reported in 1867 by Meynert and in 1880 by Sommer in autopsies of epilepsy patients (Babb and Brown, 1987). Since then, a myriad of neuropathological studies have shown that hippocampal damage is by far the most common structural lesion in intractable TLE patients: it is observed in 50 to 75% of surgical and autopsy specimens (Earle et al., 1953; Cavanagh and Meyer, 1956; Falconer et al., 1964; Margerison and Corsellis, 1966; Mouritzen Dam, 1980; Bruton, 1988). The primary morphological change in the hippocampus consists of neuronal loss. Following neuronal degeneration, glial proliferation and hypertrophy occur, and, as the areas of neuronal loss become occupied by astrocytes and their processes, the hippocampus generally shrinks in size and appears "sclerotic". The classic histological pattern of hippocampal sclerosis in TLE patients is characterized by loss of pyramidal cells in the prosubiculum and CA1 field of the hippocampus (Mathern et al., 1997). The findings also include neuronal loss in the hilus of the dentate gyrus and the adjacent CA3 field of the hippocampus (Mouritzen Dam, 1982; Babb et al., 1984; Houser, 1992). Another pathologic marker of hippocampal damage in TLE are the reorganized axons. In many cases, mossy fibers from the dentate granule cells which normally innervate the hilar mossy cells and CA3 pyramidal cells become reorganized and project into the inner third of the molecular layer of the dentate gyrus (Sutula et al., 1989; Babb et al., 1991; Houser, 1992).

The available pathologic data suggest that the hippocampal damage is asymmetrically bilateral in many patients with chronic TLE (Margerison and Corsellis, 1966; Mouritzen Dam, 1982). Bilateral symmetric damage in the hippocampus is less frequent, probably occurring in <10% of TLE cases (Babb and Brown, 1987). Hippocampal sclerosis may coexist with an extrahippocampal lesion, for example with a tumor, i.e. there is a dual pathology (Babb and Brown, 1987; Levesque et al., 1991). Interestingly, Levesque et al. (1991) reported that the distribution and severity of hippocampal neuronal damage was associated with the pathological type of extrahippocampal lesion. While the hamartoma and glioma group had the least cell loss in the hippocampus, the heterotopia group had the most severe damage.

2.3.4.2. The amygdala and the entorhinal cortex

Neuronal loss and gliosis extend frequently beyond the confines of the hippocampus to the amygdala and the adjacent cortex in intractable TLE patients (Gastaut et al., 1959; Falconer et al., 1964; Margerison and Corsellis, 1966; Bruton, 1988). In fact, the collective term "mesial temporal sclerosis" has been introduced to describe the damage in the hippocampus, amygdala, and entorhinal cortex (Falconer et al., 1964). Neuropathological studies suggest that neuronal loss in the amygdala most commonly occurs with lesions in the hippocampus (Margerison and Corsellis, 1966; Bruton 1988). In surgically treated TLE patients with hippocampal damage, 76% also had damage in the amygdala and 27% in the adjacent medial temporal cortex (Bruton, 1988). This contrasts with the much lower percentage of TLE patients (10%) who had isolated amygdaloid damage (Miller et al., 1994). Overall, amygdaloid damage has been found in 30 to 50% of patients with intractable TLE (Margerison and Corsellis, 1966; Bruton, 1988). Recently, Zentner et al. (1999) reported that up to 85% of patients with surgically treated intractable TLE had a severely altered amygdaloid body.

In early neuropathological reports, the parahippocampal gyrus, which contains the entorhinal cortex, is often mentioned as one of the affected areas in TLE (Earle et al., 1953; Cavanagh and Meyer, 1956; Gastaut et al., 1959; Falconer et al., 1964). However, data on morphological changes in the functionally distinct area of the entorhinal cortex in TLE are scarce. Two recent histological studies indicate that specifically the entorhinal cortical layers II and III have remarkable neuronal loss in patients operated on for drug-refractory seizures (Du et al., 1993; Mikkonen et al., 1998). Furthermore, as a marker of synaptic reorganization, the polysialylated neural cell adhesion molecule was increased in layer II of the entorhinal cortex (Mikkonen et al., 1998).

2.3.5. Causes of medial temporal lobe damage

2.3.5.1. Initial insult

2.3.5.1.1. Epilepsy patients

The etiology and pathogenesis of structural damage in the medial temporal lobe of epilepsy patients has been the subject of controversy and debate for years in epilepsy reasearch. Sommer concluded already in 1880 that Ammon's horn sclerosis was the cause of epilepsy. Later, Earle et al. (1953) suggested that an early brain injury such as birth trauma was the pathogenic etiology of hippocampal sclerosis. They hypothesized further that the acquired brain lesion gradually ripened into an epileptogenic focus (Earle et al., 1953). Clinically, TLE often starts as an isolated, prolonged convulsion in early life followed by a period of remission, after which seizures reemerge and may become intractable (Wieser et al., 1993). Several previous histopathological studies have reported a significant correlation between serious childhood illness (infection, febrile convulsions, head injury, status epilepticus) and hippocampal sclerosis in patients with TLE (Cavanagh and Meyer, 1956; Falconer et al., 1964; Margerison and Corsellis, 1966; Falconer and Taylor, 1968; Sagar and Oxbury, 1987; Bruton, 1988). Patients with a history of complex febrile seizures (longer than 15 minutes, multiple or focal) are more likely to develop recurrent nonfebrile seizures than those with uncomplicated febrile seizures or none at all (Nelson and Ellenberg, 1976). Marks et al. (1992) showed that mesial temporal sclerosis was significantly associated with CNS infection before but not after the age of 4 years. Moreover, Cavanagh and Meyer (1956) indicated that typical hippocampal sclerosis was found in adult temporal lobectomies more frequently when the habitual seizures started at 4 years of age or earlier.

Other studies have provided evidence that the pathogenesis of sclerosis is not age-dependent and that it is not essential for a patient to experience a childhood seizure (DeGiorgio et al., 1992; Mathern et al., 1995). For example, Mathern et al. (1995) found that patients with an initial precipitating injury such as

prolonged seizures, status epilepticus, head trauma or encephalitis before the onset of chronic TLE had severe neuron loss in the pattern of hippocampal sclerosis. However, the age at which the initial injury occurred did not influence the amount of hippocampal damage seen at surgery (Mathern et al., 1995).

2.3.5.1.2. Experimental animal models

The damage typically preceeds the appearance of seizures in several animal models of human partial epilepsies. Status epilepticus induced by systemic injection of pilocarpine causes structural brain damage in rats. Cell loss is observed in the hilus and CA3 region of the hippocampus as well as in the amygdala, entorhinal cortex, thalamus and cerebral cortex (Turski et al., 1983). Moreover, prominent mossy fiber sprouting occurs (Mello et al., 1993). A similar widespread pattern of neuronal changes in the hippocampus and amygdala as in the pilocarpine model is observed after status epilepticus induced by kainate and corticotrophin releasing hormone (Schwob et al., 1980; O'Shaughnessy and Gerber, 1986; Baram and Ribak, 1995; Tuunanen et al., 1996). It was originally suggested by Olney et al. (1974) that kainic acid and other analogues of glutamate (termed) excitotoxins are toxic because they activate glutamate receptors on neuronal surfaces, resulting in prolonged depolarization, neuronal swelling and death. In these experimental designs, recurrent spontaneous seizures occur after a silent period, which is reminiscent of human TLE (Mathern et al., 1992; Mello et al., 1993). Recently, Koh et al. (1999) found that the first kainate-induced seizure during the second week of life in rats predisposes to more extensive neuronal injury in the hippocampus after kainate-induced seizures in adulthood. The evidence provided links early seizures with the later development of epilepsy and selective hippocampal neuronal loss (Koh et al., 1999).

2.3.5.2. Recurrent seizures

2.3.5.2.1. Epilepsy patients

Since the time of Gowers, in 1881, clinical, pathological and experimental studies of epilepsy have enquired whether seizures beget more seizures, i.e. whether epilepsy is a progressive disease. Although structural damage in the hippocampus precedes the appearance of TLE in many patients with uncontrolled complex partial seizures, not all the cases with hippocampal sclerosis have a history of initial insult such as complex febrile convulsions or nonfebrile status epilepticus. Some data have suggested that hippocampal sclerosis may be acquired in human epilepsy as a consequence of repeated seizures.

Mouritzen Dam (1980) was the first to show quantitatively examined neuron loss from seizures in epilepsy patients. She found in an autopsy study that generalized seizures occurring more frequently than twice per month and epilepsy with over 30 years of duration was related to loss of pyramidal neurons in the hippocampus (Mouritzen Dam, 1980). More recently, Mathern et al. (1995) reported that surgically-treated TLE patients with longer duration of disease showed a progressive decrease in the number of hippocampal CA1 neurons. The progression was slow, but after approximately 22 years, all patients showed at least a 60% neuronal loss (Mathern et al., 1995). As further evidence of ongoing seizure activity resulting in neuronal injury, Beach et al. (1995) found that specimens of temporal lobectomy showed signs of reactive microglia in intractable TLE patients. Since microglial activation is an acute or subacute response to injury, the finding contradicts the hypothesis of structural damage in the medial temporal lobe as an inactive scar.

2.3.5.2.2. Experimental animal model of kindling

Experimental animal models provide a useful approach to assessing the degree to which repeated brief seizures produce neuronal damage. Kindling is an animal model of TLE, where increasingly stronger

seizures are induced by stimulating the undamaged brain (Goddard et al., 1969). Neuronal loss occurs in the hilus of the dentate gyrus and CA1 after three generalized tonic-clonic seizures, and with increasing seizure number damage eventually evolve into a pattern that resembles hippocampal sclerosis (Sloviter, 1983; Cavazos et al., 1994). Repeated seizures induce progressive cellular alterations not only in the hippocampus, but also in the amygdala, and the entorhinal cortex (Cavazos and Sutula, 1990; Cavazos et al., 1994; Tuunanen et al., 1997; Nissinen, 2000). Futhermore, other studies have demonstrated that the neuronal loss is accompanied by aberrant mossy fiber axonal growth of dentate granule cells in the hippocampus (Sloviter, 1994).

2.3.6. Functional consequences of medial temporal lobe damage

The hippocampus and the adjacent anatomically-related cortex, including the entorhinal, perirhinal, and parahippocampal cortices, form the neural system for declarative memory (memory for facts and events) (Squire and Zola-Morgan, 1991). A bilateral lesion limited to field CA1 of the hippocampus leads to permanent loss of ability to consolidate short-term memory to long-term memory in adults (Zola-Morgan et al., 1986). Although most sensory input to the hippocampus formation enters via the entorhinal cortex (Insausti et al., 1987), complete bilateral lesions of the entorhinal cortex produced only mild and transient memory deficits in monkeys (Leonard et al., 1995). In contrast, selective lesions of the perirhinal cortex in monkeys resulted in significant memory impairment of visual recognition memory (Meunier et al., 1993). In humans, damage involving the parahippocampal gyrus produces a syndrome of topographic disorientation (Habib and Sirigu, 1987). The perirhinal cortex may also participate with the amygdala in the emotional memory system. Indeed, the perirhinal cortex may be an important interface of interaction for both the declarative and emotional memory system (Suzuki, 1996a).

The amygdala is linked by numerous cortical and subcortical routes to brain regions involved in behaviors ranging from sexual behavior, aggression and defense to the highest level of cognitive function (Amaral, 1987). Studies in animal models show that the amygdala is crucial for the normal regulation of emotions (Meunier et al., 1999). In monkeys, partial or complete damage to the amygdala caused marked alterations in emotional behavior (Zola-Morgan et al., 1991). Specifically, the monkeys were less fearful than normal and unusually willing to touch and otherwise interact with novel stimuli. Furthermore, the experimental evidence supported the distinction between the functions of the hippocampal formation and the amygdala. In monkeys with amygdaloid damage, memory evaluated by delayed nonmatching to sample task was intact unless there was also damage to the hippocampal formation or the adjacent cortex. However, the amygdala is critically involved in learning and storage of information about the emotional significance of events (LeDoux, 1993). Selective damage in the emotional memory system, such as inability to identify emotional facial expressions, has been observed in some epilepsy patients after amygdalectomy (Young et al., 1995).

Patients with epilepsy complain of memory problems more frequently than other cognitive impairment. Studies evaluating memory performance have shown that mild verbal memory dysfunction as shown in delayed recall of word lists is present already at the time of diagnosis in partial epilepsy patients (Äikiä et al., 1995). Moreover, the presence of verbal memory impairment is a significant predictor of seizure outcome (Äikiä et al., 1999). In chronic intractable TLE, patients with left focus have memory deficits especially on verbal memory tests, and patients with right focus have such deficits on visual memory tests (Milner et al., 1975; Mungas et al., 1985). In addition to material-specific memory effects, Hermann et al. (1997) reported that the syndrome of mesial temporal lobe epilepsy was associated with considerable generalized cognitive impairment in intelligence, academic achievement, language, and visuospatial functions, reflecting possibly not only the primary neuropathological substrate per se but also the generalized neurobiological consequences of intractable seizures.

2.3.7. Course of TLE

Temporal lobe epilepsy patients have an increased incidence in family history of epilepsy, suggesting a genetic predisposition (Currie et al., 1971). Consequently, familial disturbances could be a necessary precursor that permits noxious insults to give rise to epileptogenesis in TLE (Engel et al., 1999). After a presumed initial insult such as complex febrile convulsions, status epilepticus, CNS infection or trauma, a retrospective evaluation of intractable TLE patients reported a mean seizure-free interval of 7.5 years before the development of unprovoked recurrent seizures (French et al., 1993) (Figure 3). Habitual seizures usually begin during the first 10-15 years of life in TLE (French et al., 1993; Wieser et al, 1993; Engel, 1996), although in a large survey of patients the range of age of onset varied between 1 year and 77 years (Currie et al., 1971). A very young age of onset (less than 2 years) is a predictor of unfavorable outcome (Hauser, 1991). Other factors suggestive to poor prognosis of TLE include intelligence quotient under 90, more than five secondarily generalized seizures, daily partial seizures, and left-sided focus (Lindsay et al., 1979).

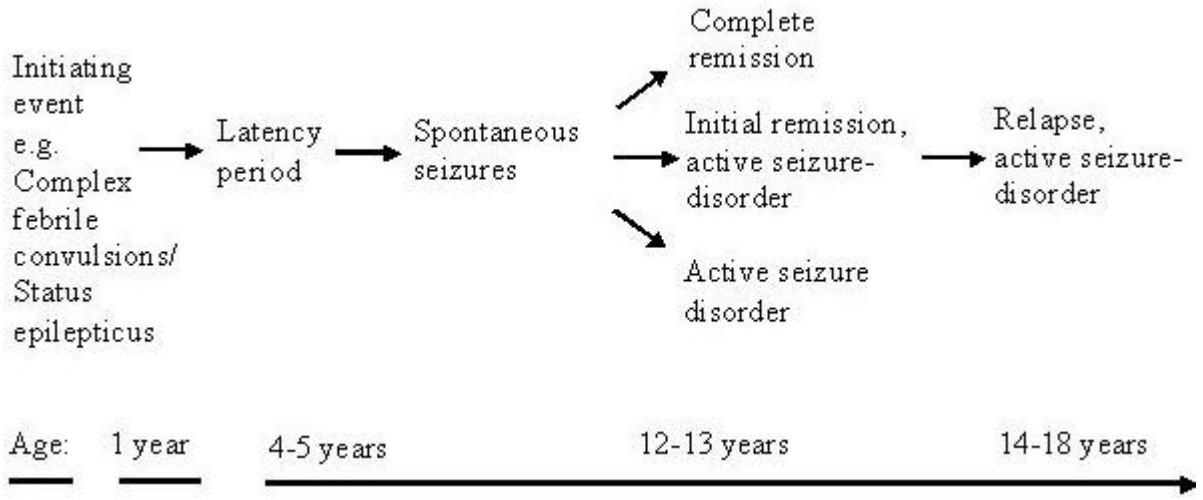

Figure 3. Course of TLE. The initiating event during early childhood is followed by a seizure-free interval before unprovoked recurrent seizures begin, usually during the first 10 – 15 years of life. Some patients who develop uncontrolled TLE reach intial remission after antiepileptic medication has been started. However, seizures recur later and then become intractable.

The drug of choice for the first line monotherapy in TLE is carbamazepine, oxcarbazepine, valproate, or lamotrigine (Mattson et al., 1985; Mattson et al., 1992; Brodie et al., 1995; Bill et al., 1997). There are no significant differences in the efficacy of these drugs in treating secondarily generalized seizures. However, carbamazepine provided better control of complex partial seizures than valproate in a comparison of the two drugs (Mattson et al., 1992). Some patients reach complete remission after the antiepileptic treatment has been started (Figure 3). Other patients who develop intractable TLE have a seizure-free interval initially. However, seizures may recur during adolescence or later, and often then become intractable (Engel, 1996). There are also intractable patients who have an evolutionary pattern of TLE, with seizures becoming progressively more elaborate over time (French et al., 1993).

Of all TLE patients treated with antiepileptic medication, 60 to 70% are not satisfactory controlled (Currie et al., 1971; Lindsay et al., 1979). If temporal lobe seizures persist, the disorder may lead to neuronal damage followed by impaired neuropsychological performance and behavioral disturbances (Girvin, 1992). Therefore, when the clinical situation of TLE points to a progression of the disorder despite the appropriate antiepileptic medication, the patient should be evaluated for surgical treatment. Previous studies have shown that patients with mesial temporal lobe epilepsy syndrome have an

excellent response to surgical treatment, reaching seizure-freedom in 70-80% of cases (Babb and Brown, 1987; Duncan and Sagar, 1987; Abou-Khalil et al., 1993).

2.4. MAGNETIC RESONANCE IMAGING (MRI) STUDIES

2.4.1. Qualitative MRI of the hippocampus

Magnetic resonance imaging is a sensitive noninvasive technique for detecting pathology in medial temporal lobe structures of epilepsy patients (Kuzniecky et al., 1987). In a qualitative MRI study, temporal lobe abnormalities were observed in 180 (81%) of 222 consecutively-referred TLE patients (Lehericy et al., 1997) The most common structural change was hippocampal atrophy (55%), followed by developmental abnormality (7.2%), tumors (6.8%), scars (5%) and cavernous angiomas (4.5%).

Longitudinal (T1) and transverse relaxation (T2) are processes by which the system of spins reaches thermal equilibrium in the external magnetic field (Felmlee, 1996). T1 and T2 represent properties of tissue (Felmlee, 1996). An increased T2-weighted signal and the signal's confinement to a unilaterally small hippocampus were the initially identified MRI features of hippocampal damage (Jackson et al., 1990; Berkovic et al., 1991). Imaging was performed in coronal and axial planes, specially orientated along and perpendicular to the long axis of the hippocampus. Further findings included decreased T1-signal intensity and disruption of the internal structure of the hippocampus (Jackson et al., 1993a). Atrophy can be found in about 80 to 85% of patients with pathologically identified hippocampal sclerosis, using optimized images and visual inspection (Kuzniecky and Jackson, 1995). Bronen et al. (1997) achieved sensitivies of 87-98% and specificities of 45-100% when comparing qualitative MRI findings with the histology of the hippocampus. In most patients, signal and volume changes associated with hippocampal sclerosis affect the entire hippocampus. However, Bronen et al. (1995) reported that 44% of the patients with pathologically proven hippocampal sclerosis had abnormal qualitative MRI findings regionally. The most frequently affected region found with qualitative MRI segmentation in TLE patients was the body of the hippocampus (Bronen et al., 1995; Kuzniecky et al., 1996).

2.4.2. MRI volumetry of the hippocampus

Volumetric analysis can quantify hippocampal atrophy in TLE patients (Jack et al., 1988; 1990; Watson et al., 1992; Cook, 1994). This quantitative measurement improves the diagnostic yield of MRI evaluation, as it may reveal subtle disease-related changes not apparent by routine clinical inspection and not associated with a visible lesion (Lencz et al., 1992). Although neuropathological examination rather than MRI is the reference standard for the diagnosis of hippocampal sclerosis, measurements of unilateral hippocampal atrophy have proven to be the most accurate method of detecting hippocampal sclerosis (Kuzniecky and Jackson, 1995).

Absolute volumetric abnormality is difficult to define because of the large variation in the volumes of medial temporal lobe structures of controls. A small female control subject may have smaller absolute volumes than a large male patient with a sclerotic hippocampus. Therefore, measures such as the cerebral volume or the cranial area may be used as correlates to enable normalized absolute volumes to be calculated (Free et al., 1995). The correction procedures reduce the variance in absolute volumes in controls, and provide a method for defining abnormally small volumes. Furthermore, the method overcomes the problem of detecting the bilateral volume loss (Free et al., 1995). No significant age-group difference in the hippocampal volumes has been found in normative groups of healthy volunteers aged from 16 to 65 (Bigler et al., 1997). Thus, in healthy persons, hippocampal volume remains stable from late adolescence through the mid-seventh decade of life (Bigler et al., 1997).

Volumetric MRI studies have reported that 45-88% of the patients with intractable TLE have hippocampal damage (Cascino et al., 1991; Adam et al., 1994; Baulac et al., 1994; Van Paesschen et al., 1997a). In studies of patients who had had temporal lobe surgery for intractable seizures, such quantitative MRI demonstration of hippocampal atrophy was nearly 100% sensitive and specific for mesial temporal sclerosis (Cascino et al., 1991; Cascino et al., 1992). The measured hippocampal volume reduction correlates with the severity of neuropathological evidence of cell loss (Cascino et al., 1991; Lee et al., 1995a). In a study by Lencz et al. (1992), hippocampal volumetric ratio (ipsilateral/contralateral to the seizure focus) correlated significantly with the neuronal density in all hippocampal subfields except CA2. Many MRI studies have also found a positive correlation between the reduced hippocampal volumes and EEG lateralization of the epileptogenic region in TLE (Jack et al., 1992; Lencz, 1992; Cendes et al., 1993a; Spencer et al., 1993; Adam et al., 1994; Baulac et al., 1994). Cendes et al. (1993a) showed that hippocampal volumes alone agreed with the extracranial and/or intracranial EEG lateralization of the epileptogenic region in 87% of cases, and that combined hippocampal and amygdaloid volumes agreed with EEG lateralization in 93% of cases. The specificity of MRI-detected hippocampal damage is high in clear-cut, pure, temporal lobe cases, but relative in mixed partial epilepsy. Spencer et al. (1993) reported that among chronic epilepsy patients who required intracranial EEG localization of seizure onset because of a lack of concordance of noninvasive studies, there was a rare but definite subgroup of patients with unilateral hippocampal volume reduction who had EEG localization elsewhere than atrophy.

The predictive value of MRI-determined hippocampal atrophy and outcome following temporal lobectomy has been established in several studies (Jack et al., 1992; Kuzniecky et al., 1993; Garcia et al., 1994). Arruda et al. (1996) reported that patients with unilateral medial temporal atrophy in volumetric MRI had excellent postoperative result (class I or II outcome according to Engel's modified classification) in 94% of cases. Moreover, according to Jack et al. (1992), 97% of intractable TLE patients had a favorable postoperative outcome if hippocampal MRI volumetric data were concordant with the clinical and EEG localization. However, if the hippocampal measurements were nonlateralizing, the percentage of patients with a favorable outcome dropped to 42% (Jack et al., 1992).

Preoperative memory function of intractable TLE patients is associated with the severity of hippocampal atrophy in volumetric MRI (Lencz, 1992; Trenerry, 1993a). Studies correlating postoperative memory outcome with hippocampal volumetric measurements indicate that the group at least risk for a postoperative verbal memory deficit after a dominant left temporal lobectomy comprises those with marked unilateral left hippocampal atrophy (Trenerry, 1993a; 1995). Conversely, the patients at greatest risk for a decline of verbal memory are those with bilateral symmetric severe atrophy of both left and right hippocampi (Trenerry, 1996).

2.4.3. T2 relaxation time of the hippocampus

Visually assessed hippocampal T2-weighted signal hyperintensity has been reported in 65% of TLE patients with hippocampal sclerosis (Kuzniecky et al., 1987). Other studies conducted during the same period demonstrated a range of variability from 8 to 90% (Brooks et al., 1990; Bronen et al., 1991; Dowd et al., 1992), which may partly be attributed to the subjective nature of visual assessment of subtle signal abnormalities in images of varying quality (Jackson et al., 1993b). In an analogous way to the quantification of hippocampal atrophy by volumetric analysis, T2-weighted signal intensity may be quantified reproducibly by measurement of hippocampal T2 relaxation time. The main advantage of this technique is that since the range of normal hippocampal T2 relaxation times is small, the measured values are absolute and immediately comparable against controls (Jackson et al., 1993b). Furthermore, the T2 values allow detection of mild, bilateral abnormalities, and can be measured within a few seconds (Van Paesschen et al., 1997a).

Hippocampal T2 time reflects the pathology of the tissue. As water content is often higher in tissue with a pathological change than in the surrounding normal tissue, the change results in longer T2 relaxation time. Van Paesschen et al. (1997b) found a positive correlation between hippocampal T2 time and the ratio of glial to neuronal density in the hippocampus of TLE patients. Moreover, hippocampal T2 time prolongation correlated with the severity of hippocampal volume loss in TLE (Van Paesschen et al., 1995; Pitkänen et al., 1996a). Jackson et al. (1993b) studied patients suffering from intractable partial epilepsy and found abnormal ipsilateral hippocampal T2 values in 70 % of them. Marked elevations (>10 ms) were observed in 65% of TLE patients, correlating strongly with the presence of pathologic evidence of hippocampal sclerosis (Jackson et al., 1993b). Volumetric measurement showed no abnormality in a subgroup of 5 to 10% of intractable TLE patients with hippocampal sclerosis (Jackson et al., 1994). In these difficult cases, hippocampal T2 signal quantification allows the MRI diagnosis of unilateral hippocampal sclerosis (Jackson et al., 1994).

2.4.4. Bilateral hippocampal damage

In line with the previous pathologic data, an increasing number of imaging studies indicate the bilateral involvement of hippocampal damage in TLE patients (Jackson et al., 1993b; Jack et al., 1995; Barr et al., 1997; Quigg et al., 1997a; Van Paesschen et al., 1997a). King et al. (1995) assessed the frequency of bilateral hippocampal damage using absolute hippocampal volumes in 53 medically refractory TLE patients: 5 (9%) patients had hippocampal atrophy bilaterally, and four of them were undetected by volumetric ratios. This finding agrees with the results of Fish and Spencer (1995), who observed significant bilateral atrophy in 10% of intractable TLE patients with hippocampal volume decrease. In a series of drug-resistant TLE patients with a history of febrile seizures, the mean volume reduction was 30% in the hippocampus ipsilateral to the seizure focus, and 15% in the hippocampus contralaterally (Barr et al., 1997). This pattern of bilateral reductions was seen in two-thirds of patients altogether. Moreover, bilateral hippocampal volume loss is common in patients with a history of encephalitis or meningitis (Free et al., 1996).

2.4.5. Hippocampal damage in extratemporal epilepsy

Several previous MRI studies have reported normal hippocampal volumes in patients with extratemporal epilepsy (Cook et al., 1992; Watson et al., 1997). However, experience with large numbers of patients has shown that some extratemporal epilepsy patients may demonstrate MRI features of hippocampal damage (Cascino et al., 1993; Adam et al., 1994; Baulac et al., 1994; Fish and Spencer, 1995). Adam et al. (1994) reported that 29% of patients with intractable complex partial seizures of extratemporal origin had hippocampal atrophy although the degree of atrophy was milder than in TLE patients.

The data agree with those of imaging studies reporting dual pathology in 10 to 15% of cases with lesional epilepsy (Cascino et al., 1993; Raymond et al., 1994; Cendes et al., 1995a). In a recent multicenter study involving 167 patients with extratemporal or extrahippocampal temporal lesions, Cendes et al. (1995a) found only 25 patients (15%) with dual pathology. However, developmental abnormalities exhibited a higher incidence of coexisting hippocampal sclerosis, in the range of 25 to 30% (Cendes et al., 1995a). Watson et al. (1996) reported that 25% of their patients with pathologically proved hippocampal sclerosis exhibited dual pathology, and 80% of those patients had neuronal migration disorders. The simultaneous presence of hippocampal damage and developmental changes could create potential multiple epileptogenic zones in these patients.

2.4.6. MRI of the amygdala and the entorhinal cortex

The volume and T2 relaxation time measurements can be used as tools to study not only the hippocampus but also other structures involved in the epileptic process, such as the amygdaloid complex (Watson et al., 1992; Van Paesschen et al., 1996). Watson et al. (1992) showed that measurement of the amygdaloid volume is reliable when special attention is paid to the differentiation of the amygdala from adjacent structures. Previous MRI studies of the amygdala report a volume decrease of approximately 20 to 30% in patients with drug-refractory TLE (Cendes et al., 1993a,b,c). In some patients, the damage in the amygdala is isolated, although the majority of cases had lesion in both the amygdala and the hippocampus (Cendes et al., 1993b,d; Van Paesschen et al., 1996). Using qualitative MRI segmentation analysis, Kuzniecky et al. (1996) studied the patterns of atrophy in the amygdala and hippocampus of 47 patients with histologically confirmed hippocampal sclerosis. They found amygdaloid atrophy in 23% of cases with hippocampal damage (Kuzniecky et al., 1996). Furthermore, in a quantitative MRI study by Van Paesschen et al. (1996), an abnormal amygdaloid T2 signal was present ipsilaterally in 52% of patients with unilateral hippocampal sclerosis. The volumetric measurements of both the amygdala and hippocampus lateralize the epileptogenic area concordantly with the EEG to an accuracy of over 90% in TLE patients (Cendes et al., 1993a,c). A series of TLE patients also demonstrated that amygdaloid damage was associated with the clinical symptom of ictal fear (Cendes et al., 1994). Moreover, the study showed a good correlation with the volume of the amygdala and the postoperative pathology (Cendes et al., 1994).

Parahippocampal gyral abnormalities have received little attention in the imaging study of epileptic process. Saukkonen et al. (1994) reported that in patients with intractable left TLE the rostral portion of the ipsilateral parahippocampal gyrus (the area that is mostly composed of the entorhinal cortex) was 12% smaller than in controls. A recent quantitative MRI study evaluated more specifically the volume of the entorhinal cortex in TLE patients (Bernasconi et al., 1999). In agreement with previous volumetric studies of the hippocampus and amygdala (Cendes et al., 1993a), the volume of the entorhinal cortex ipsilateral to the epileptic focus was significantly reduced suggesting an involvement of the structure in seizure generation and propogation.

2.4.7. Damage outside medial temporal lobe structures

Magnetic resonance imaging studies of epilepsy patients have demonstrated volume deficits not only in the medial temporal lobe structures but also in the unilateral temporal lobe or hemisphere (Jack et al., 1990; Lencz et al., 1992, Breier et al., 1996). Briellmann et al. (1998) found that TLE patients had smaller hemicranial volume ipsilateral to the seizure focus, irrespective of the presence or absence of hippocampal sclerosis. Other reports have suggested a bilateral temporal lobe or cortical volume reduction in patients with TLE (Lee et al., 1995b; Marsh et al., 1997). The fornix and mamillary body, representing part of the limbic system, were smaller ipsilateral to an abnormal hippocampus (Baldwin et al., 1994; Kim et al., 1995; Ng et al., 1997). Furthermore, the diverse range of structural abnormalities observed in MRI outside the temporal lobe include the ipsilateral thalamus, and caudate, gyrus gingulate, bilateral frontoparietal gray matter, cerebellum, and, in some cases, ventricular enlargement (Marsh et al., 1997; Specht et al., 1997; DeCarli et al., 1998).

2.4.8. MRI findings in generalized epilepsy

Visual inspection of routine MRI is normal in patients with generalized epilepsy. Correspondingly, Watson and Williamson (1995) did not find any reductions of hippocampal or amygdaloid volumes in a quantitative MRI study involving patients with long-standing generalized epilepsy. However, pathological studies have shown microdysgenesis in grey and white matter of the brain in a large percentage of autopsies of cases of generalized epilepsy (Meencke and Janz, 1984; Meencke, 1985).

Woermann et al. reported in 1998 that patients with generalized epilepsy had significantly larger cortical grey matter volumes than control subjects. Furthermore, significant abnormalities of the regional distribution of cerebral grey and subcortical matter were found in eight out of 20 patients with juvenile myoclonic epilepsy, one out of 10 patients with juvenile absence epilepsy, and two out of five patients with tonic-clonic seizures on awakening, but in none of the 30 control subjects (Woermann et al., 1998). Since widespread volumetric MRI changes in cortical and subcortical matter were found also in patients with apparently focal cerebral dysgenesis (Sisodiya et al., 1995), and in TLE patients with hippocampal sclerosis correlating with unfavorable outcome after anterior temporal lobe resections (Sisodiya et al., 1997), the changes may be related to epileptogenicity both in partial and generalized epilepsies.

2.4.9. MRI studies of the causes of medial temporal lobe damage

2.4.9.1. Initial insult

The notion that the pathologic template which becomes hippocampal sclerosis probably starts with an initial precipitating insult before the onset of chronic epilepsy is supported by findings reported in the neuroimaging literature. Several MRI studies have shown a significant relationship between hippocampal and amygdaloid damage and a history of febrile convulsions in early childhood (Cendes et al., 1993b; Kuks et al., 1993; Trenerry et al., 1993b; Harvey et al., 1995). In series of drug-resistant epilepsy patients with a history of febrile seizures, hippocampal atrophy was diffuse and located ipsilateral to seizure focus (Kuks et al., 1993; Free et al., 1996; Barr et al., 1997; VanPaesschen et al. 1997a; Theodore et al., 1999). As diffuse hippocampal volume loss is more strongly associated with febrile convulsions than focal volume loss, recent imaging studies have hypothesized that pre-existing hippocampal focal abnormality may facilitate febrile convulsions and contribute to the development of subsequent widespread sclerotic changes in the hippocampus (Kuks et al., 1993; Fernandez et al., 1998). VanLandingham et al. (1998) demonstrated for the first time the development of structural damage in the hippocampus after complex febrile convulsions in a prospective follow-up MRI study. They showed that prolonged, focal febrile convulsions in four infants resulted in acute hippocampal injury and swelling, and this evolved into hippocampal atrophy in two of them (VanLandingham et al., 1998).

It is likely that many other etiological factors in addition to febrile convulsions play a part in the development of hippocampal sclerosis. Bigler et al. (1997) showed with quantitative MRI that head trauma produced hippocampal atrophy. Furthermore, 75% of TLE patients with a history of meningitis or encephalitis had bilateral hippocampal volume reductions (Free et al., 1996). Progressive hippocampal damage has also been reported after status epilepticus associated with encephalitis both with and without persistent seizures, even when acute increases in T2 signal resolve (Nohria et al., 1994; Tien and Felsberg, 1995; Wieshmann et al., 1997). In a case study by Wiehsmann et al. (1997), the progression of hippocampal atrophy continued up to 58 months after onset of status epilepticus due to herpes encephalitis.

As in previous correlative histopathological studies, quantitative imaging studies investigating the effect of age at seizure onset on hippocampal damage show contradictory results. Trenerry et al. (1993b) observed that the younger the left temporal lobectomy patients patients were when spontaneous seizures began, the smaller were the left hippocampal volumes. Hippocampal damage was also related to early onset of habitual epilepsy in a large study of 100 intractable TLE patients (Van Paesschen et al., 1997a). However, even in children with new-onset TLE there was a strong association between hippocampal damage and a history of significant illness/event prior to the onset of seizure disorder (Harvey et al., 1997). Recently, in an MRI study of patients with uncontrolled TLE the effect of age at

seizure onset was not a significant factor in predicting the severity of hippocampal atrophy (Theodore et al., 1999).

2.4.9.2. Recurrent seizures

Several previous imaging studies have failed to find a correlation between MRI-determined hippocampal atrophy and either the estimated severity or the duration of the seizure disorder (Cendes et al., 1993d; Kuks et al., 1993; Trenerry et al., 1993b; Grunewald et al., 1994; Kuzniecky et al., 1996; Van Paesschen et al., 1996; Barr et al., 1997). In a retrospective MRI report of 50 patients with intractable TLE, neither hippocampal nor amygdaloid volumes correlated with duration of epilepsy, seizure frequency, or the occurrence of generalized seizures (Cendes et al., 1993a). The study concluded that habitual seizures do not lead to progressive hippocampal damage.

In contrast to other imaging studies, Spencer et al. (1993) reported that hippocampal atrophy in quantitative MRI was significantly correlated with longer duration of epilepsy. More recent imaging studies have produced evidence that epilepsy duration has a significant effect on the severity of hippocampal damage in intractable TLE patients (Jokeit et al., 1999; Tasch et al., 1999; Theodore et al., 1999). As long duration of drug-resistant TLE is related to a considerable number of focal or secondarily generalized seizures, both hippocampal and hemispheric volume reductions were associated with high seizure frequency in MRI series of TLE patients (Barr et al., 1997; Marsh et al., 1997). VanPaesschen (1997a,c) reported that the extent of hippocampal damage correlated with the number of secondarily generalized seizures in both newly diagnosed and chronic TLE patients.

In addition to correlational approaches, one can compare patient groups with different duration and severity of epilepsy, or follow cohorts of patients longitudinally to examine the progression of disease. Quantitative MRI studies have shown that while hippocampal damage is found in 73% of intractable TLE patients (Van Paesschen et al., 1997b), only 10% of newly diagnosed patients with partial seizures have volume reduction and T2 time prolongation in the hippocampus (Van Paesschen et al., 1997c). Saukkonen et al. (1994) compared hippocampal volumes in newly diagnosed and chronic patients with TLE, and found that those patients with a long history of recurrent seizures had more severe hippocampal damage. The first follow-up MRI study demonstrated that subtle changes in hippocampi may occur during one year in association with frequent and daily seizures in adults with newly diagnosed partial epilepsy (Van Paesschen et al., 1998).

Magnetic resonance spectroscopic imaging (MRSI) is a more sensitive indicator of neuronal dysfunction in vivo than MRI volumetry, since one can detect acute chemical changes with it (Ebisu et al., 1996; Cendes et al., 1997). Several MRSI studies of TLE patients have observed reduced signals from the cerebral metabolite N-acetyl-aspartate (NAA) in temporal lobes, reflecting focal neuronal dysfunction or loss (Cendes et al., 1995b; 1997). In patients with partial epilepsy, the decreasing NAA correlated with high seizure frequency, but not with the duration of epilepsy (Garcia et al., 1997). Recently, Tasch et al. (1999) found an inverse relationship also between the duration of epilepsy and the ratio of NAA and creatine (Cr) in the temporal lobes of TLE patients ipsilateral and contralateral to the EEG focus. Moreover, echoing the previous autopsy results of Mouritzen Dam (1980), which showed increased hippocampal cell loss in patients with generalized tonic-clonic seizures, bilateral lower NAA / Cr ratios were associated with generalized seizures (Tasch et al., 1999).

The hypothesis of progressive functional impairment in temporal lobe epileptogenic zones is further supported by positron emission tomography (PET) studies. Theodore et al. (1988) found an inverse correlation between length of seizure history and the mean ipsilateral local cerebral metabolic rate of glucose (CMRglc) in patients with TLE. Subsequent PET studies have shown an uncoupling between cerebral blood flow (CBF) and CMRglc in temporal lobe epileptic foci, with greater relative impairment

of CMRglc (Gaillard et al., 1995; Breier et al., 1997). The widening of the CBF- CMRglc mismatch was not related to a history of febrile seizures, frequency of complex partial seizures, history of secondary generalization or age at seizure onset: the duration of epilepsy was the factor producing significant effects on the interictal metabolism and blood flow (Breier et al., 1997). The difference between the two measures increased with duration, even though both appeared to decline (Breier et al., 1997). Hypometabolism was also associated with longer duration of epilepsy in a prospective study of children with partial-onset seizures (Gaillard et al., 1996).

The cumulative data from neuropathological and imaging studies suggest that TLE begins with an early hippocampal injury occurring asymmetrically, and is followed by a gradual and progressive course of further neuronal damage (Pitkänen et al., 1996b) (Figure 4). The imaging data so far indicate that in some patients the hippocampus is damaged acutely, with enlargement and increased T2 signal, reflecting edema in the acute stages and progression toward MRI features of hippocampal sclerosis such as atrophy with an increased hippocampal T2 signal in the ensuing months, and with onset of TLE months or years later (Nohria et al., 1994; Cendes et al., 1995c; Tien and Felsberg, 1995; VanLandingham et al., 1998). After the diagnosis of epilepsy, the epileptic process continues, leading to intractable seizures, functional disability and progressive structural damage. Recently, O'Brien et al. (1999) provided the first prospective MRI evidence that progressive atrophy of the hippocampus may develop in the absence of initial insult such as status epilepticus, due to uncontrolled temporal lobe seizures. This case report adds a link to the theory uniting data from experimental and clinical studies indicating that hippocampal damage is both the cause and effect of seizures.

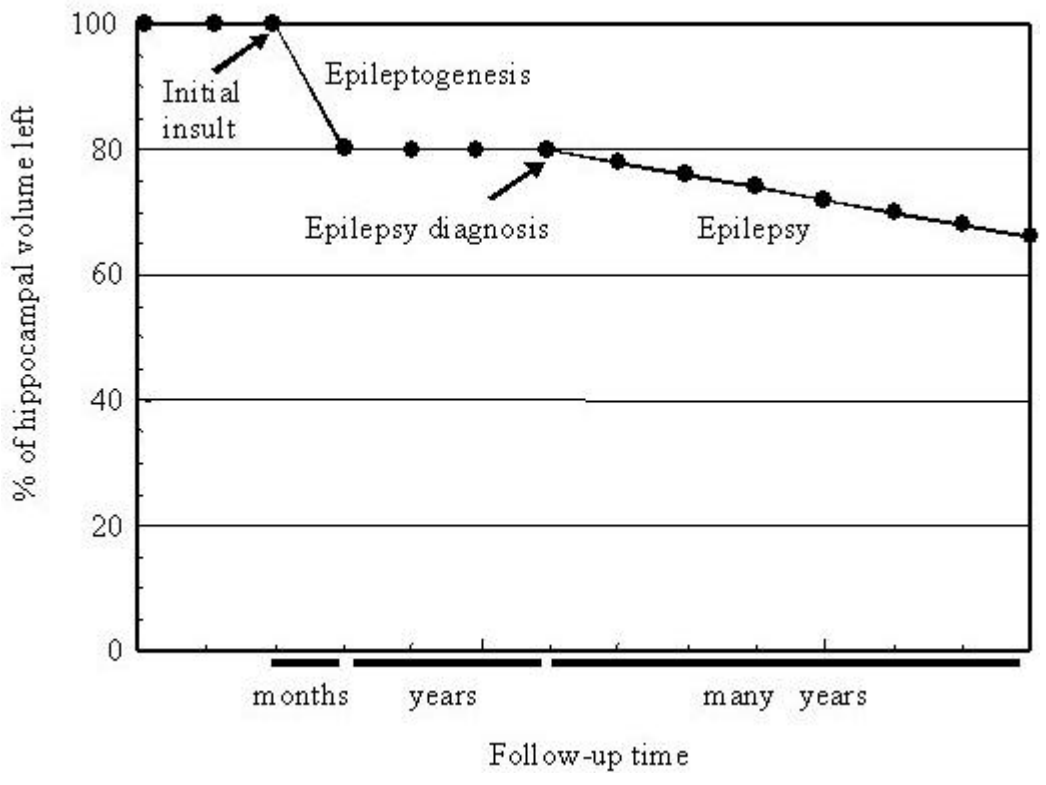

Figure 4. Hypothesis of the progression of hippocampal damage in TLE. Various initial insults may cause structural damage over a period of weeks or months. These changes favor the development of spontaneous seizures after a delay period which may last for several years. Once epilepsy is diagnosed, recurrent seizures may cause further damage to the hippocampus.

3. AIMS OF THE STUDY

Patients with chronic intractable TLE frequently have damage in the structures of the medial temporal lobe. The purpose of the present series of studies (I-V) was to investigate with MRI the appearance of medial temporal lobe damage during the course of partial epilepsy, and, particularly, to determine whether recurrent or prolonged seizures contribute to the damage. The determination of the factors predictive of damage in the medial temporal lobe will contribute to a better understanding of epileptic process and the care of patients having frequent seizures.

The specific aim of the present series of studies (I-V) was to answer the following questions:

1. Do recurrent seizures cause hippocampal damage in cryptogenic TLE? (I)

2. Is there damage in the amygdala in newly diagnosed and chronic patients with TLE? (II)

3. Which factors are associated with the occurrence and severity of hippocampal or amygdaloid damage in patients with partial epilepsy? (III)

   a) What are the predictive risk factors associated with hippocampal or amygdaloid damage in TLE?

   b) Is the damage in the hippocampus or in the amygdala present already at the time of the first spontaneous seizures?

   c) Are recurrent seizures associated with hippocampal or amygdaloid damage? Is the appearance of hippocampal or amygdaloid damage dependent on the etiology of TLE?

   e) Is the appearance of hippocampal or amygdaloid damage dependent on the location of the epileptic focus?

4. Do patients with cryptogenic chronic TLE have damage in the entorhinal cortex? (IV)

5. Is there damage in the hippocampus, amygdala, entorhinal, or perirhinal cortex in patients with status epilepticus when assessed soon after the insult or in long-term follow-up? (V)

4. MATERIALS AND METHODS

4.1. CONTROLS

The control group in the series of studies (I–V) comprised 29 healthy students or staff members (14 males, 15 females) with a mean age of 33±11 (range 21–64) years who had volunteered for the study. All controls were interviewed in order to exclude those with neurological diseases.

4.2. PATIENTS

Altogether 259 (132 males, 127 females; age 33±12 years, range 15–68 years) partial epilepsy patients of the Department of Neurology in Kuopio University Hospital were included in studies I–IV (Table 1). The patients were investigated with quantitative MRI during 1993–1996. The Department of Neurology serves as a primary site of treatment for all patients with newly diagnosed seizure disorder in a district of 250 000 inhabitants. Therefore, the majority of all patients had visited a neurologist at the epilepsy unit regularly since the time of their epilepsy diagnosis. At the time of the MRI, the patients were also examined by a neurologist.

The patients were divided into two groups according to the localization of the seizure focus: patients with TLE, and patients with extratemporal/unclassified partial epilepsy (ETE/UC). There were 167 patients with clinical symptoms, interictal temporal EEG discharges, or a temporal lobe lesion determined by MRI consistent with the diagnosis of TLE. Furthermore, TLE patients were divided into subgroups based on their seizure lateralization. The group of patients with ETE/UC consisted of 92 patients whose seizure foci were either outside the temporal lobe or could not be localized. Ictal EEG recordings were available for analysis from 54 patients included in the study. In studies I, II and IV, only TLE patients were included.

Patients with both cryptogenic and symptomatic etiology of seizures were included. In all remote symptomatic patients, the underlying causes for seizures were head trauma (n=22), disorder of neuronal migration and organization (n=21), other developmental disorder (n=14), CNS infection (n=18), perinatal insult (n=20), brain tumor (initial symptom or postoperatively) (n=9), and others (n=8).

Table 1. Patients in studies I-IV

Study	Epileptic disorder	Etiology	No of patients	Patient groups		Median seizure number (range)
I	TLE	Cryptogenic	64	Newly diagnosed (18)		3 (1-482)
				Chronic (46)		
				Well-controlled (14)		10 (4-401)
				Drug-resistant (32)		1128 (38-6912)
II	TLE	Cryptogenic/ Symptomatic	84	Newly diagnosed (29)		
				Cryptogenic (18)		3 (1-482)
				Symptomatic (11)		8 (2-723)
				Chronic (54)		
				Cryptogenic (31)		1128 (38-6912)
				Symptomatic (23)		1830 (121-9600)
III	Partial epilepsy	Cryptogenic/ Symptomatic	259	TLE (167) Cryptogenic Symptomatic	ETE/UC (92) Cryptogenic Symptomatic	250 (2-16625)
				= 1 year	= 1 year	
				2-10 years	2-10 years	
				11-20 years	11-20 years	
				= 21 years	= 21 years	
				= 2 sz/year	= 2 sz/year	
				>2 sz/year	>2 sz/year	
IV	TLE	Cryptogenic	36	HC damage		978 (3-6909)
				Without damage (20)		
				With damage (16)		
V	Status epilepticus	Cryptogenic/ Symptomatic	9	Partial secondarily generalized (8)		
				Complex partial (1)		

The number of patients in different patient groups is in parenthesis. Abbreviations: ETE/UC, extratemporal/unclassified partial epilepsy; HC, hippocampal; No, number: TLE, temporal lobe epilepsy; sz, seizures.

Patients with a medical history of complex febrile convulsions (n=10) were also classified as symptomatic. However, if only hippocampal atrophy and/or change in the T2-signal intensity was observed in MRI the epilepsy was classified as cryptogenic because it is unclear whether hippocampal damage is the cause or the consequence of TLE and this was the main question asked in the present series of studies. Also, if there were no other potential etiologic factors in the medical history or the MRI study of the patients, they were classified as cryptogenic. There were only cryptogenic TLE patients in studies I and IV.

In order to calculate the number of partial and secondarily generalized seizures each patient had experienced, and to verify the cryptogenic etiology of seizures, an extensive search for the lifetime hospital records of the patients was performed. In Finland, the maintenance of hospital services for patients with epilepsy is the responsibility of the community, and the Finnish health care system makes it possible, with the permission of the patient, to obtain copies of hospital records from all community hospitals. The majority of the patients had visited a neurologist at the epilepsy unit of the Department of Neurology at least once a year, depending on seizure frequency, since the time of their diagnosis. Patients with frequent seizures were typically seen once a month or once every three months. During each visit, the patient's seizure calendar had been reviewed and the number of seizures recorded.

Both TLE and ETE/UC patients included in study III were further divided into patient groups based on the duration of epilepsy (≤1 year, 2-10 years, 11-20 years, and ≥21 years) (Table 1). Mean seizure frequency determined whether the patient was assigned to a subgroup with rare seizures (≤2 seizures per year) or frequent seizures (>2 seizures per year). The TLE patients in studies I-II were divided into two categories based on the duration of the seizure disorder: newly diagnosed and chronic. All newly diagnosed patients were imaged at the time of the diagnosis before any antiepileptic medication was started. Chronic TLE patients had had symptoms of epilepsy for at least two years. Chronic patients were further divided into two groups based on the level of seizure control: well-controlled and chronic drug-resistant. The duration of epilepsy and the lifetime number of seizures differed significantly between chronic TLE patients and newly diagnosed patients with TLE.

Study V comprised nine patients with status epilepticus requiring intravenous antiepileptic medication and treated at the emergency unit of Kuopio University Hospital between 1 January 1996 and 31 December 1997 (Table 2). Seven of the nine patients had partial epilepsy prior to the insult. Status epilepticus was defined as more than 30 min of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures (Working Group on Status Epilepticus, 1993). The time of the onset of status epilepticus was obtained from an eye-witness. Status epilepticus was considered to be over when the patient regained consciousness, or continuous epileptiform activity in EEG stopped. The patients were investigated with MRI within 3 weeks after the onset of status epilepticus, and at 6 and 12 months after the insult. The study was approved by the Ethical Committee of Kuopio University Hospital. Informed consent was obtained from each patient after awakening and/or from responsible relatives after the nature of the procedures was fully explained. Once the diagnosis of status epilepticus was made, the patients were treated according to the predetermined protocol of the Department of Neurology of Kuopio University Hospital for the management of all status epilepticus patients (Kälviäinen et al., 1993). The treatment was initiated with diazepam, followed by phenytoin. If status epilepticus persisted, the patient was treated with general barbiturate anesthesia using thiopental. With each MRI study, a complete medical history was taken and a physical examination was performed. Electroencephalogram and serum neuron-specific enolase (s-NSE) were obtained from all patients initially.

Table 2. Clinical data of epilepsy in patients with status epilepticus

No of patient	Sex	Age (yrs)	Etiology	Duration (yrs)	Seizure type	AED
1	M	18	-	-	-	-
2	F	33	right temporo-parietal polymicrogyria	17	CP, CPGTC	TGB 45 mg
3	F	61	cryptogenic	59	CP, CPGTC	CBZ 1400 mg VGB 3000 mg
4	F	30	-	-	-	-
5	F	19	left MCA infarction perinatally	19	CP, CPGTC	TGB 30 mg
6	F	49	cryptogenic	2	CPGTC	VPA*
7	M	37	developmental (fragile-X)	22	CPGTC	CBZ 1600 mg
8	M	74	head trauma	27	CPGTC	CBZ 800 mg VPA 1000 mg
9	M	43	two right and one left MCA aneurysms operated, right MCA infarctation	5	SP, SPCGTC	VPA 2500 mg

Abbreviations: AED, antiepileptic drug; CBZ, carbamazepine; CP, complex partial; CPGTC, complex partial evolving to generalized tonic-clonic; F, female; M, male; MCA, middle cerebral artery; No, number; SP, simple partial; SPCGTC simple partial evolving to complex partial evolving to generalized tonic-clonic; TGB, tiagabine; VGB, vigabatrin; VPA, valproate. * did not use

4.3. MR IMAGING

The patients and controls were scanned with a 1.5-Tesla imager (Siemens Magnetom) using a standard head coil and a tilted coronal 3-D magnetization-prepared rapid acquisition gradient-echo (MP-RAGE) sequence with parameters: time of repetition (TR) 10 ms, time of echo (TE) 4 ms, inversion time 250 ms, flip angle 12º, field of view (FOV) 250 mm, matrix 256 × 192. This resulted in 128 contiguous T1-weighted images with a slice thickness of 1.5 - 2 mm which were oriented at right angles to the long axis of the hippocampus.

T2- and proton density weighted axial 5-mm-thick images of the whole brain were obtained in study V, with the following imaging parameters: 2525/16/98 ms (TR/TE/TE), echo time length (ETL) 5 ms, FOV 250 mm, matrix 260 × 512, interslice gap 1.5 mm, two acquisitions. Coronal T2-weighted 4-mm slices were taken at right angles to the long axis of the hippocampus using TR 5400 ms, TE 99 ms, ETL 11

ms, FOV 230 mm, matrix 512 × 512 and 0.4 mm interslice gap. MR images were reviewed qualitatively by visual inspection alone in study V to determine which scans appeared to have abnormal volumes or T2-weighted signal intensity changes in the mesial temporal structures or any other abnormalities.

4.3.1. MRI volumetry

4.3.1.1. The hippocampus and the amygdala

The hippocampal and amygdaloid volumes were measured by the same observer (Kaarina Partanen, MD, PhD) in studies I-V according to the method described by Soininen et al. (1994). The hippocampal volume included the volumes of the dentate gyrus, hippocampus proper, and the subicular complex. The amygdaloid volume consisted of the volumes of the deep nuclei of the amygdala (lateral, basal, accessory basal, and paralaminar nuclei), the superficial nuclei of the amygdala (anterior cortical nucleus, medial nucleus, nucleus of the lateral olfactory tract, periamygdaloid cortex, posterior cortical nucleus), and the remaining nuclei of the amygdala (anterior amygdaloid area, central nucleus, amygdalohippocampal area, and intercalated nuclei) (for details see Soininen et al., 1994; Sorvari et al., 1995). The boundaries of the hippocampus and amygdala were outlined by a trackball-driven cursor on coronal MR images oriented perpendicular to the long axis of the hippocampus and covering the whole rostrocaudal end of the region of interest (Figure 5). The number of voxels within the region was calculated using an in-house program developed for a standard work console. The intraobserver variability expressed as mean of the coefficient of variation of each control was 6.8% for the hippocampal volumes and 8.9% for the amygdaloid volumes.

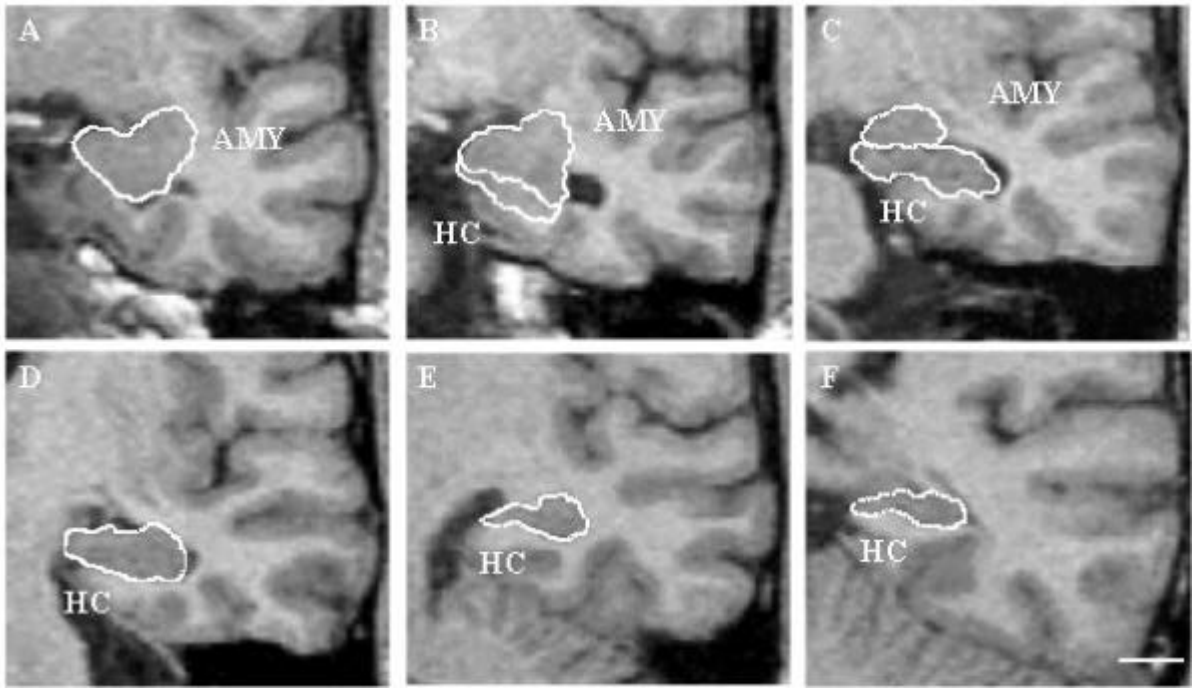

Figure 5. Manually traced boundaries of the amygdala and the hippocampus on coronal MR images from six rostrocaudal levels of the medial temporal lobe. Panel A is the most rostral and panel F is the most caudal. Abbreviations: AMY, amygdala; HC, hippocampus. Scale bar 10 mm.

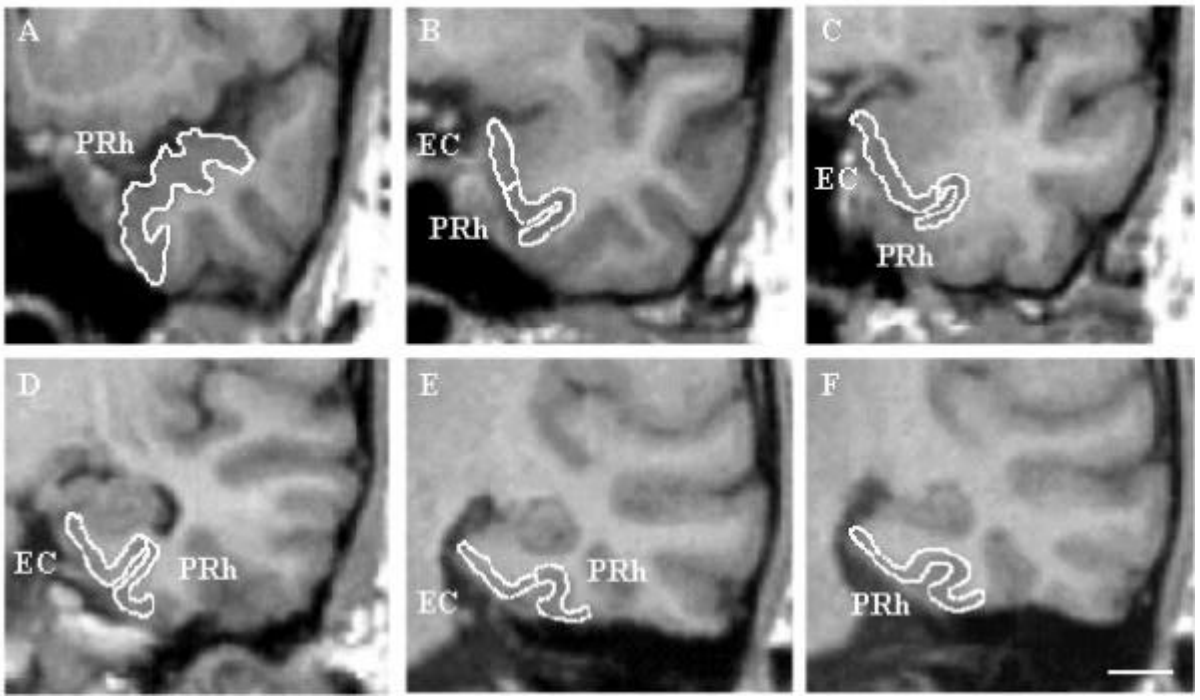

Figure 6. Manually traced boundaries of the perirhinal cortex and the entorhinal cortex on coronal MR images from six rostrocaudal levels of the medial temporal lobe. Panel A is the most rostral and panel F is the most caudal. Abbreviations: EC, entorhinal cortex; PRh, perirhinal cortex. Scale bar 10 mm.

4.3.1.2. The entorhinal and the perirhinal cortices

One investigator (Tuuli Salmenperä, MD) measured the volumes of all entorhinal and perirhinal cortices in studies IV-V using a recently described histology-based method (Insausti et al., 1998). The entorhinal cortex (Brodmann's area 28) lies adjacent to the amygdala and hippocampus, and forms the major portion of the anterior parahippocampal gyrus (Brodmann, 1909; Amaral and Insausti, 1990). Laterally, the entorhinal cortex borders the perirhinal cortex, which encompasses the area around the collateral sulcus (areas 35 and 36 of Brodmann (1909)). In order to adapt the histological boundaries to determine the borders of the entorhinal and perirhinal cortices on MR images, partitions throughout the entire rostrocaudal extent of the entorhinal and perirhinal cortices were reconstructed into 2-mm-thick contiguous slices oriented perpendicular to the line drawn between the anterior and posterior commissures at the midsagittal level. For volumetry, the images were magnified and interpolated fourfold, which resulted in an effective pixel size of 0.25 mm. The outlines of the entorhinal and perirhinal cortices were then manually traced using a trackball-driven cursor on successive MR images as described by Insausti et al. (1998) (Figure 6). The volumes were calculated with software developed in-house for a standard work console. The intraobserver variability was 4.9% for entorhinal volumes and 4.0% for perirhinal volumes.

Figure 7 shows the repeatability of the volumetric measurements of the entorhinal and perirhinal cortices according to Bland and Altman (1986). The mean differences between two measurements of the entorhinal and perirhinal cortices were near zero and the limits of agreement below the volume considered as marked volume reduction (i.e., ≥2 standard deviations (SD) from the mean of the controls; 424 mm^3 for the entorhinal cortex, 654 mm^3 for the perirhinal cortex).

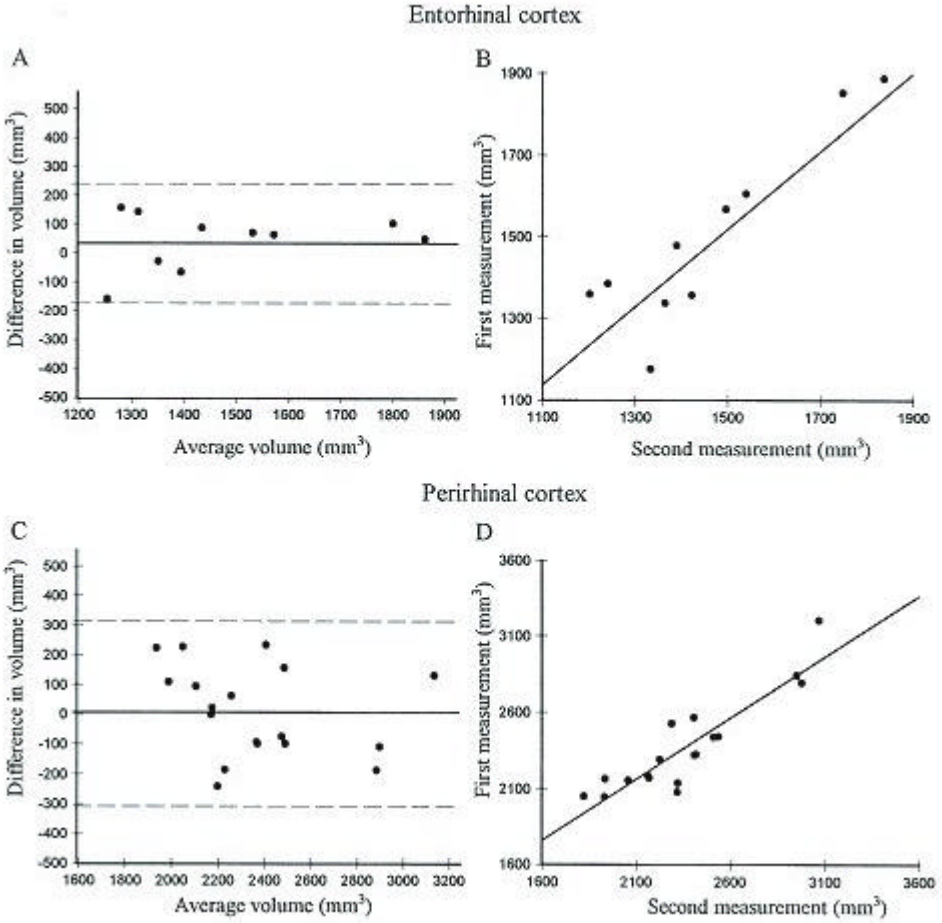

Figure 7. (A) A scatterplot showing the intraobserver variability for repeated measurements in the entorhinal cortex of ten control subjects. The limits of agreement (dashed lines) between the first and second measurements are expressed as the mean difference in volume [volume in the first measurement - volume in the second measurement (mm^3) ± 2 SD]. (B) Correlation between the first and second measurement of the volume of the entorhinal cortex ($r = 0.9038$, $p < 0.001$). (C) A scatterplot showing the intraobserver variability for repeated measurements in the perirhinal cortex of 18 control subjects. The limits of agreement (dashed lines) between the first and second measurements are expressed as the mean difference in volume [volume in the first measurement - volume in the second measurement (mm^3) ± 2 SD]. (D) Correlation between the first and the second measurement of the volume of the perirhinal cortex ($r = 0.9035$, $p < 0.001$).

4.3.2. T2 relaxometry of the hippocampus and the amygdala

The method used for T2 relaxometry in studies I-III was similar to that described by Jackson et al. (1993b). T2 maps were calculated in each of three oblique coronal 8-mm slices from 16 images obtained at echo times of 22 to 262 ms using an interleaved acquisition Carr-Purcell-Meiboom-Gill sequence. The tilting angle was oriented perpendicular to the longitudinal axis of the hippocampus. The interslice gap was 4.0 mm. The T2 maps were generated by a computer program that fitted a single exponential to the signal intensity data from corresponding pixels from all 16 echoes. The T2 relaxation time was then calculated for each pixel and an image was constructed in which pixel intensity corresponded to the calculated T2 relaxation time. The T2 images generated were magnified by a factor of from 2.3 to 2.5. Mean hippocampal T2 was measured within anatomic boundaries of the hippocampus by placing the largest possible circular region of interest with 30 to 50 pixels (40-60 mm^3) within the anterior, middle, and posterior sections corresponding to the three sections of the hippocampus designated as hippocampal head, hippocampal body, and hippocampal tail, respectively.

Anatomically, the head of the hippocampus exhibits three or four digitations and turns medially to form the posterior segment of the uncus. The body of the hippocampus curves around the upper midbrain and is concave medially. Posteriorly, the hippocampal body tapers into the tail, which turns medially just anterior to and below the splenium of the corpus callosum. The amygdala is distinguished from the hippocampal head by the temporal horn (Duvernoy, 1988; Watson et al., 1992). Mean amygdaloid T2 was measured within the anatomical boundaries of the amygdala in the most rostral section. Boundaries where partial volume effects might occur were avoided. In order to study the stability of T2, five repeated measurements were made in a normal volunteer within a 12-month period. The mean coefficient of variation was 2.6% in different locations of the hippocampus and 6.6% in different locations of the amygdala.

4.4. ELECTROENCEPHALOGRAM

Twenty-one channel EEGs were recorded using the International 10-20 electrode placements in studies I-V. The interictally recorded EEGs included hyperventilation and photic stimulation. The interpretation of EEG was done according to the accepted guidelines (Moshe and Pedley, 1999). Ictal EEG included electrographic seizure activity associated with clinical seizure symptomatology.

All EEG recordings of the status epilepticus patients in study V were analyzed blindly to the MRI data by the same investigator (Esa Mervaala, MD, PhD). Early and late postictal EEGs refer to recordings obtained while a patient was on acute status epilepticus medication, but did not exhibit clinical seizures. Interictal EEGs refer to recordings obtained soon after clinical recovery from the acute status epilepticus.

4.5. STATISTICAL ANALYSIS

A ratio was used to correct the volumes of the hippocampi, amygdala, entorhinal and perirhinal cortices for interindividual differences in head size according to Cendes et al. (1994) with a modification. Instead of brain volume, the area of brain which correlates with the brain volume ($r=0.67$, $p<0.001$, $n=20$) was used. The mean brain area (obtained at the level of the anterior commissure) of the controls was divided by the corresponding brain area of the patient, and then this ratio was multiplied by the measured volume of the hippocampus, amygdala, entorhinal or perirhinal cortex. The correction for brain area assumes a linear relation between the volumes of the hippocampus or the amygdala and brain area at the level of the anterior commissure (linear regression analysis, $n=25$; $F=19.8$, $p<0.001$ for the left hippocampus; $F=11.6$, $p<0.01$ for the right hippocampus; $F=12.7$, $p<0.01$ for the left amygdala; $F=15.4$, $p<0.001$ for the right amygdala). In study IV the hippocampal volume correlated with the brain area of controls ($n=21$; $r=0.606$, $p=0.004$ for the left hippocampus; $r=0.586$, $p=0.005$ for the right hippocampus). However, no correlation was found between the volumes of the left or right entorhinal cortices and the brain area ($n=21$; $r=-0.048$, $p=0.837$ for the left entorhinal cortex; $r=0.173$, $p=0.453$ for the right entorhinal cortex).

The data were analyzed with SPSS/PC+ V 4.1 and SPSS Win V 7.5 and V 8.0 software (Chicago, IL). The mean hippocampal and amygdaloid volumes and T2 relaxation times were compared between the unilateral TLE patient groups and controls using the ANOVA test with Duncan's post hoc analysis in studies I and II. Hemispheric differences for the amygdaloid volumes (ΔAMY) were calculated as the volume of the structure in the right minus the volume in the left hemisphere (study II). The hemispheric ratio (rAMY) was calculated as the volume of the structure in the right/volume in the left hemisphere. The amygdaloid ΔT2 and rT2 were calculated accordingly. Student's paired *t*-test was used to analyze hemispheric differences of the amygdaloid volumes and T2 times within a group.

In study III, the volumes and T2 relaxation times (data of T2 times not published) of the hippocampus and amygdala were compared between the patient groups and controls. The analyses were conducted separately in unilateral TLE and ETE/UC patients. Nonparametric analyses with the Bonferroni correction were used to compare the means over the study groups and to determine the differences between the groups. The number of all TLE and ETE/UC patients with marked volume reduction (i.e., volume of the structure was ≥2 SD below the mean volume in controls) or T2 time prolongation (i.e., T2 time was ≥2 SD longer than the mean T2 in controls) were compared using the χ^2-test and Fisher's exact test. Logistic regression analysis was used to analyze predictive factors of the hippocampal and the amygdaloid volume reduction of ≥2 SD or T2 time prolongation of ≥2 SD in TLE patients. The clinical variables included in the analyses were age at onset of seizures, lifetime seizure number, complex febrile convulsions, intracranial infection, and status epilepticus in the medical history (Margerison and Corsellis, 1966; Cendes et al., 1993a,b; Mathern et al., 1995; Free et al., 1996; Van Paesschen et al., 1997a; Wieshmann et al., 1997; Van Landingham et al., 1998). Additionally, gender was included as a demographic variable. From the EEG data, the presence of epileptiform EEG was used. For the purpose of the analyses, the lifetime seizure number was divided into quartiles: otherwise, the factors were dichotomous. Odds ratios (OR) with 95% limits of confidence intervals (95% CI) were calculated from the logistic regression model.

The volumes of the entorhinal cortex, hippocampus and amygdala were compared between the patient groups and controls in cryptogenic chronic unilateral TLE (study IV). Degree of asymmetry between the volumes of the left (L) and right (R) entorhinal cortex, hippocampus and amygdala were examined by calculating asymmetry ratios according to Bernasconi et al. (1999) as follows: asymmetry $\% = 100 \times (R-L)/((R+L)/2)$. The Kruskal-Wallis test was used to compare the mean volumes and the asymmetry ratios over the study groups. Differences between the groups were determined using the Mann-Whitney U-test with the Bonferroni correction.

In studies I-IV, the correlations were calculated using the two-tailed Pearson's correlation test. To reduce the effect of outlying values on correlation analysis, a logarithmic transformation of the hippocampal and amygdaloid volumes was performed before the calculation of correlation.

In study V, Wilcoxon's analysis with two related samples was used to compare the volumes of the hippocampi, amygdala, and entorhinal and perirhinal cortices measured 3 weeks and 6 months, 3 weeks and 12 months, 6 months and 12 monts after the status epilepticus in each patient. The mean volumes between controls and patients at different follow-up visits (3 weeks, 6 months, and 12 months after the status epilepticus) were compared using the Mann-Whitney test with the Bonferroni correction.

The level of statistical significance was set at $p<0.05$ in studies I-V.

5. RESULTS

5.1. HIPPOCAMPAL VOLUMETRY AND T2 RELAXOMETRY IN CRYPTOGENIC TEMPORAL LOBE EPILEPSY (STUDY I)

5.1.1. Damage at the time of diagnosis

The mean hippocampal volume in patients with newly diagnosed TLE did not differ from that in controls. Correspondingly, there was no difference in the mean T2 relaxation time of the body of the hippocampus between newly diagnosed TLE patients and controls.

5.1.2. Damage after years of TLE

5.1.2.1. Well-controlled chronic TLE

The mean hippocampal volume in patients with chronic well-controlled epilepsy did not differ from that in controls. However, the analyses of hippocampal T2 relaxation times showed that the entire group of chronic well-controlled patients had prolonged T2 relaxation times in the body of the left and right hippocampus compared with those in the control group ($p<0.05$).

5.1.2.2. Chronic drug-resistant TLE

In all chronic drug-resistant TLE patients, the volumes of the left and right hippocampi did not differ from those in controls. However, in the group of patients with left TLE the left hippocampus was 18% smaller than in the control group. Correspondingly, in chronic drug-resistant patients with seizure focus on the right, the right hippocampal volume was 14% smaller than in controls ($p<0.05$).

The analyses showed that the group of chronic cryptogenic drug-resistant patients had longer T2 relaxation times in the body of the left and right hippocampus than controls ($p<0.01$). In line with volumetric results, chronic drug-resistant TLE patients with seizure focus on the left had longer T2 relaxation times in the body of the left hippocampus than did the control group ($p<0.001$) or the newly diagnosed patients ($p<0.01$). Furthermore, chronic drug-resistant patients with seizure focus on the right had longer T2 relaxation times in the body of the right hippocampus than controls ($p<0.001$). The T2 relaxation times measured from the tail or the head of the hippocampus did not show any significant differences between the groups.

5.1.3. Correlation of damage with seizure number or duration of TLE

In all patients with a left seizure focus, the left hippocampal volume correlated inversely with the estimated total number of partial ($r=-0.391$, $p<0.01$) and generalized ($r=-0.312$, $p<0.05$) seizures the patient had experienced. The prolongation of the left T2 relaxation time in the hippocampus correlated with the total number of both partial ($r=0.670$, $p<0.001$) and generalized ($r=0.481$, $p<0.001$) seizures and with the duration of TLE ($r=0.580$, $p<0.001$). In all patients with seizure focus on the right, no correlation was found between the right hippocampal volume and the total seizure number or the duration of TLE. The right T2 relaxation time did correlate with the number of partial seizures the patient had experienced.

5.2. AMYGDALOID VOLUMETRY AND T2 RELAXOMETRY IN TEMPORAL LOBE EPILEPSY (STUDY II)

5.2.1. Damage at the time of diagnosis.

The mean amygdaloid volumes in newly diagnosed TLE patients did not differ from those in controls. No hemispheric differences in the amygdaloid volumes were observed between the study groups. Only one symptomatic case (4%, 1/27) of newly diagnosed patients had an amygdaloid volume reduction of at least 20%. Correspondingly, the mean T2 relaxation times in newly diagnosed TLE patients did not differ from those in controls. Also, no hemispheric differences in T2 times were observed between study groups. The T2 relaxation time of the left amygdala was ≥111 ms (i.e., ≥2 SD over the mean T2 time of the left amygdala in controls) in one of the newly diagnosed TLE patients. The T2 times of the right amygdala were ≥109 ms (i.e., ≥2 SD over the mean T2 time of the right amygdala in controls) prolonged in three patients. Altogether, 15% (4/26; one cryptogenic, three symptomatic) of the newly diagnosed patients had prolonged T2 times.

5.2.2. Damage after years of TLE

The mean amygdaloid volumes in chronic TLE patients did not differ from those in controls. No hemispheric differences in the amygdaloid volumes were observed between the study groups. However, in 19% (8/45; 4 cryptogenic, 4 symptomatic) of the chronic patients the amygdaloid volume was reduced by at least 20%. The T2 relaxation times in chronic TLE patients did not differ from those in controls. Also, no hemispheric differences in T2 times were observed between the study groups. The T2 relaxation times of the left amygdala were ≥111 ms (i.e., ≥2 SD over the mean T2 time of the left amygdala in controls) in six of the chronic TLE patients patients. The T2 times of the right amygdala were ≥109 ms (i.e., ≥2 SD over the mean T2 time of the right amygdala in controls) prolonged in five patients. Altogether, 21% (9/43; 8 cryptogenic, 1 symptomatic) of the chronic patients had prolonged T2 times. Two patients had bilaterally prolonged T2 relaxation times.

5.2.3. Correlation of damage with seizure number and duration of TLE

In all TLE patients with seizure focus on the left, the volume of the left amygdala correlated negatively with the lifetime seizure number ($r=-0.371$, $p<0.01$) and the duration of epilepsy ($r=-0.327$, $p<0.01$). When the different seizure types were analyzed separately, the amygdaloid volume was negatively correlated with the number of partial seizures ($r=-0.426$, $p<0.01$). In all TLE patients with focus on the right side, the volume of the right amygdala was negatively correlated with the lifetime seizure number ($r=-0.348$, $p<0.05$), but not with the duration of epilepsy. When different seizure types were analyzed separately, the amygdaloid volume was negatively correlated with the number of generalized seizures ($r=-0.418$, $p<0.05$). In right TLE patients, the volume of the left amygdala correlated with the duration of seizure disorder ($r=-0.536$, $p<0.01$). There was no correlation between the T2 relaxation time and the lifetime seizure number or the duration of TLE.

5.3. HIPPOCAMPAL AND AMYGDALOID VOLUMETRY AND T2 RELAXOMETRY IN PARTIAL EPILEPSY (STUDY III)

5.3.1. Risk factors for hippocampal and amygdaloid damage in TLE

Logistic regression analysis was used to identify predictors of volume reduction and T2 time prolongation of ≥2 SD in the hippocampus and the amygdala. Six clinical variables, one demographic variable, and one variable from the EEG data were included in the analyses. Risk factors found to be

significant predictors of hippocampal volume reduction of ≥2 SD were high lifetime seizure number, medical history of complex febrile convulsions, and age ≤5 years at the time of the first spontaneous seizure (Table 3). Patients grouped in the quartile with the highest number of seizures experienced during lifetime were more likely to have a hippocampal volume reduction of ≥2 SD than those grouped in the quartile with the lowest number of seizures. There was a 16-fold increased risk of hippocampal damage in patients with a lifetime seizure number of ≥1461 compared with the patients with ≤13 seizures ($p<0.05$). Furthermore, patients with a medical history of complex febrile convulsions were 16 times more likely to have hippocampal damage than those without ($p<0.01$). When age of seizure onset was ≤5 years, the risk of volume reduction in the hippocampus increased 5.3-fold ($p<0.05$). On the other hand, gender, epileptiform activity in the EEG, intracranial infection or status epilepticus in the medical history did not predict hippocampal atrophy. The risk factor that predicted hippocampal T2 time prolongation was seizure onset at age ≤5 years (Table 3). Patients who had suffered from intracranial infection or had had complex febrile seizures in early childhood were more likely to have an amygdaloid volume reduction of ≥2SD than those who did not have these etiologic factors in their medical history (Table 4). Unlike in the hippocampus, the risk factor for the amygdaloid T2 time prolongation was the onset of seizures at age >5 years (Table 4).

Table 3. Predictors of ≥2 SD hippocampal volume reduction and T2 time prolongation in TLE patients

Predictor	p value	OR	95% CI
HC volume reduction			
Age at onset (£ 5 years)	**0.0028**	**5.3**	**1.8 - 16**
Complex febrile convulsions	**0.0036**	**16**	**2.5 - 105**
Seizure number (³ 1461)	**0.014**[a]	**16**	**2.3 - 117**
EEG (epileptiform)	0.86	0.91	0.33 - 2.5
Gender (female)	0.27	1.7	0.65 - 4.5
Intracranial infection	0.11	4.8	0.69 - 34
Status epilepticus	0.76	1.2	0.34 - 4.3
HC T2 time prolongation			
Age at onset (£ 5 years)	**0.0004**	**6.2**	**2.3 - 16**
Status epilepticus	0.071	2.9	0.91 - 9.0
Complex febrile convulsions	0.56	1.6	0.35 - 7.1
EEG (epileptiform)	0.96	1.0	0.41 - 2.6
Gender (female)	0.22	1.7	0.71 - 4.3
Intracranial infection	0.31	2.1	0.49 - 9.3
Seizure number (≥ 1461)	0.086[a]	6.8	1.2 - 37

Odds ratios with 95% limits of confidence intervals were calculated from logistic regression model. For the purpose of the analysis the lifetime seizure number was divided into quartiles ([a] test over all quartiles), otherwise the factors were dichotomous. Abbreviations: HC, hippocampal; OR, odds ratio; CI, confidence interval of OR; TLE, temporal lobe epilepsy.

Table 4. Predictors of ≥2 SD amygdaloid volume reduction and T2 time prolongation in TLE patients.

Predictor	p value	OR	95% CI
AMY volume reduction			
Complex febrile convulsions	**0.025**	**12**	**1.4 - 100**
Intracranial infection	**0.014**	**14**	**1.7 - 115**
Age at onset (≤ 5 years)	0.60	1.6	0.28 - 8.8
EEG (epileptiform)	0.37	2.3	0.38 - 13
Gender (female)	0.06	6.1	0.91 - 42
Seizure number (≥ 1461)	0.66[a]	0.56	0.051 - 6.2
Status epilepticus	0.81	1.3	0.18 - 8.8
AMY T2 time prolongation			
Age at onset (£ 5 years)	**0.043**	**0.069**	**0.0052 - 0.92**
Complex febrile convulsions	0.26	5.6	0.28 - 113
EEG (epileptiform)	0.47	1.5	0.49 - 4.7
Gender (female)	0.74	0.82	0.26 - 2.6
Intracranial infection	0.98	1.0	0.087 - 12
Seizure number (≥ 1461)	0.14[a]	9.3	1.4 - 61
Status epilepticus	0.72	0[b]	-

Odds ratios with 95% limits of confidence intervals were calculated from logistic regression model. For the purpose of the analysis the lifetime seizure number was divided into quartiles ([a] test over all quartiles), otherwise the factors were dichotomous. Abbreviations: AMY, amygdaloid; OR, odds ratio; CI, confidence interval of OR; TLE, temporal lobe epilepsy.

5.3.2. Damage relative to the duration of TLE

5.3.2.1. Damage at the time of first spontaneous seizures

The mean hippocampal (Table 5) or amygdaloid (Table 6) volumes in patients with duration of ≤1 year of TLE with seizure focus on the left or right did not differ from those in controls. Only one (5%) patient had a volume reduction of ≥2 SD in the left hippocampus (Figure 8A) and one patient (5%) in the right amygdala (Figure 9A).

The mean T2 relaxation times of the hippocampus (Table 7) or the amygdala (Table 8) did not differ between patients with ≤1 year of TLE and controls (data not published). In line with the volumetric data one (5%) patient had a T2 time prolongation of ≥2 SD in the left hippocampus (Figure 8B) and two patients (11%) in the right amygdala (9B). There were no patients with volume reduction or T2 time prolongation both in the hippocampus and in the amygdala.

Table 5. Volumes (mm^3) of the left and right hippocampus (HC) in patients with temporal lobe epilepsy

	Left HC	Damage %	Right HC	Damage %
Controls (25)	3348 ± 424		3589 ± 436	
Patients with focus on the left (90)				
£ **1 year** (13)	3163 ± 656	6	3679 ± 333	0
with rare seizures (7)	3062 ± 875	9	3813 ± 266	0
with frequent seizures (6)	3282 ± 285	2	3522 ± 357	2
2-10 years (19)	3114 ± 607	7	3654 ± 321	0
with rare seizures (5)	3285 ± 345	2	3736 ± 304	0
with frequent seizures (14)	3054 ± 677	9	3625 ± 333	0
11-20 years (27)	3226 ± 666	4	3527 ± 577	2
with rare seizures (9)	3287 ± 366	2	3531 ± 402	2
with frequent seizures (18)	3195 ± 782	5	3525 ± 658	2
³ **21 years** (31)	2853 ± 717	14	3460 ± 524	4
with rare seizures (2)	3131 ± 49	6	3635 ± 191	0
with frequent seizures (29)	2834 ± 738	15	3448 ± 539	4
Patients with focus on the right (55)				
£ **1 year** (5)	3692 ± 590	0	4051 ± 602	0
with rare seizures (1)	4315	0	4459	0
with frequent seizures (4)	3536 ± 549	0	3949 ± 644	0
2-10 years (16)	3249 ± 526	3	3463 ± 656	4
with rare seizures (3)	3355 ± 120	0	3589 ± 344	0
with frequent seizures (13)	3224 ± 583	4	3434 ± 716	4
11-20 years (12)	3257 ± 533	3	3085 ± 856	14
with rare seizures (1)	3809	0	2259	37
with frequent seizures (11)	3206 ± 528	4	3160 ± 856	12
³ **21 years** (22)	3124 ± 541	7	2555 ± 977**^¤	29
with rare seizures (4)	3461 ± 555	0	3469 ± 1033	3
with frequent seizures (18)	3049 ± 524	9	2351 ± 866***^¤	34

HC volumes are shown as mean ± standard deviation of the mean. Damage % shows the percentage of volume reduction below the mean in controls. Number of patients, from which the volumetry data was available, is in parenthesis. In the table we show the normalized hippocampal volumes. Statistical significances were calculated with Kruskal-Wallis and Mann-Whitney analyses: **p<0.01, ***p<0.001 compared to controls, ^p<0.05 compared to patients with ≤1 year of epilepsy, ¤p<0.05 compared to patients with 2-10 years of epilepsy.

Table 6. Volumes (mm^3) of the left and right amygdala (AMY) in patients with temporal lobe epilepsy

	Left AMY	Damage %	Right AMY	Damage %
Controls (25)	2476 ± 401		2299 ± 250	
Patients with focus on the left (89)				
£ **1 year** (13)	2646 ± 191	0	2457 ± 336	0
with rare seizures (7)	2716 ± 210	0	2379 ± 376	0
with frequent seizures (6)	2565 ± 143	0	2548 ± 285	0
2-10 years (19)	2485 ± 555	0	2315 ± 360	0
with rare seizures (5)	2541 ± 267	0	2395 ± 161	0
with frequent seizures (14)	2466 ± 634	0	2287 ± 410	0
11-20 years (26)	2449 ± 358	1	2275 ± 251 (27)	1
with rare seizures (9)	2409 ± 171	3	2285 ± 254	1
with frequent seizures (17)	2470 ± 429	0	2270 ± 257 (17)	1
³ **21 years** (31)	2281 ± 303	8	2252 ± 296	2
with rare seizures (2)	2017 ± 96	19	2077 ± 229	10
with frequent seizures (29)	2299 ± 305	7	2264 ± 299	2
Patients with focus on the right (51)				
£ **1 year** (5)	2581 ± 324	0	2480 ± 212	0
with rare seizures (1)	2872	0	2511	0
with frequent seizures (4)	2509 ± 323	8	2472 ± 244	1
2-10 years (15)	332 ± 270	6	2341 ± 299	0
with rare seizures (3)	2238 ± 151	10	2219 ± 380	3
with frequent seizures (12)	2355 ± 292	5	2372 ± 287	0
11-20 years (11)	2406 ± 301	0	2384 ± 489	0
with rare seizures (1)	2864	0	1778	23
with frequent seizures (10)	2361 ± 274	0	2445 ± 469	0
³ **21 years** (20)	2329 ± 276	6	2155 ± 521	6
with rare seizures (4)	2161 ± 222	13	2060 ± 131	10
with frequent seizures (16)	2372 ± 277	4	2179 ± 581	5

AMY volumes are shown as mean ± standard deviation of the mean. Damage % shows the percentage of volume reduction below the mean in controls. Number of patients, from which the volumetry data was available, is in parenthesis. In the table we show the normalized amygdaloid volumes.

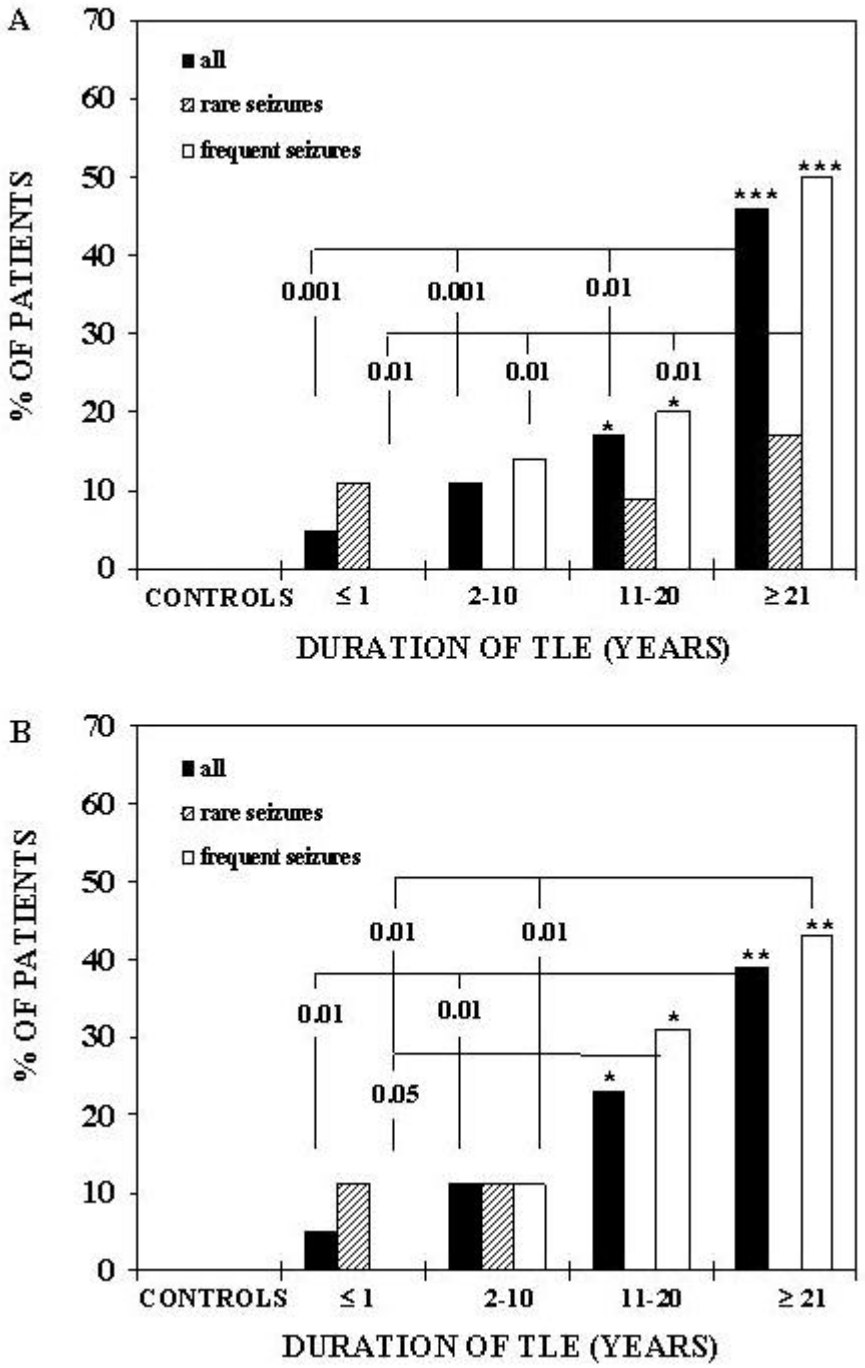

Figure 8. (A) The percentage of patients with a decrease in hippocampal volume of ≥2 SD of the control mean in patient groups with different durations of TLE. (B) The percentage of patients with a prolongation in the hippocampal T2 relaxation time of ≥2 SD of the control mean in patient groups with different durations of TLE. The percentages of patients with a hippocampal volume reduction or T2 time prolongation of ≥2 SD that differ from each other in the χ2-test or Fisher's exact test are connected with lines indicating the level of statistical significance (0.05, $p<0.05$; 0.01, $p<0.01$; 0.001, $p<0.001$). The percentages of patients with a hippocampal volume reduction or T2 time prolongation of ≥2 SD that differ from controls in the χ2-test or Fisher's exact test are marked with asterisks (*, $p<0.05$; **, $p<0.01$; ***, $p<0.001$). Some preliminary data of Figure 8A have been published previously (Salmenperä et al., 1998). Abbreviations: TLE, temporal lobe epilepsy.

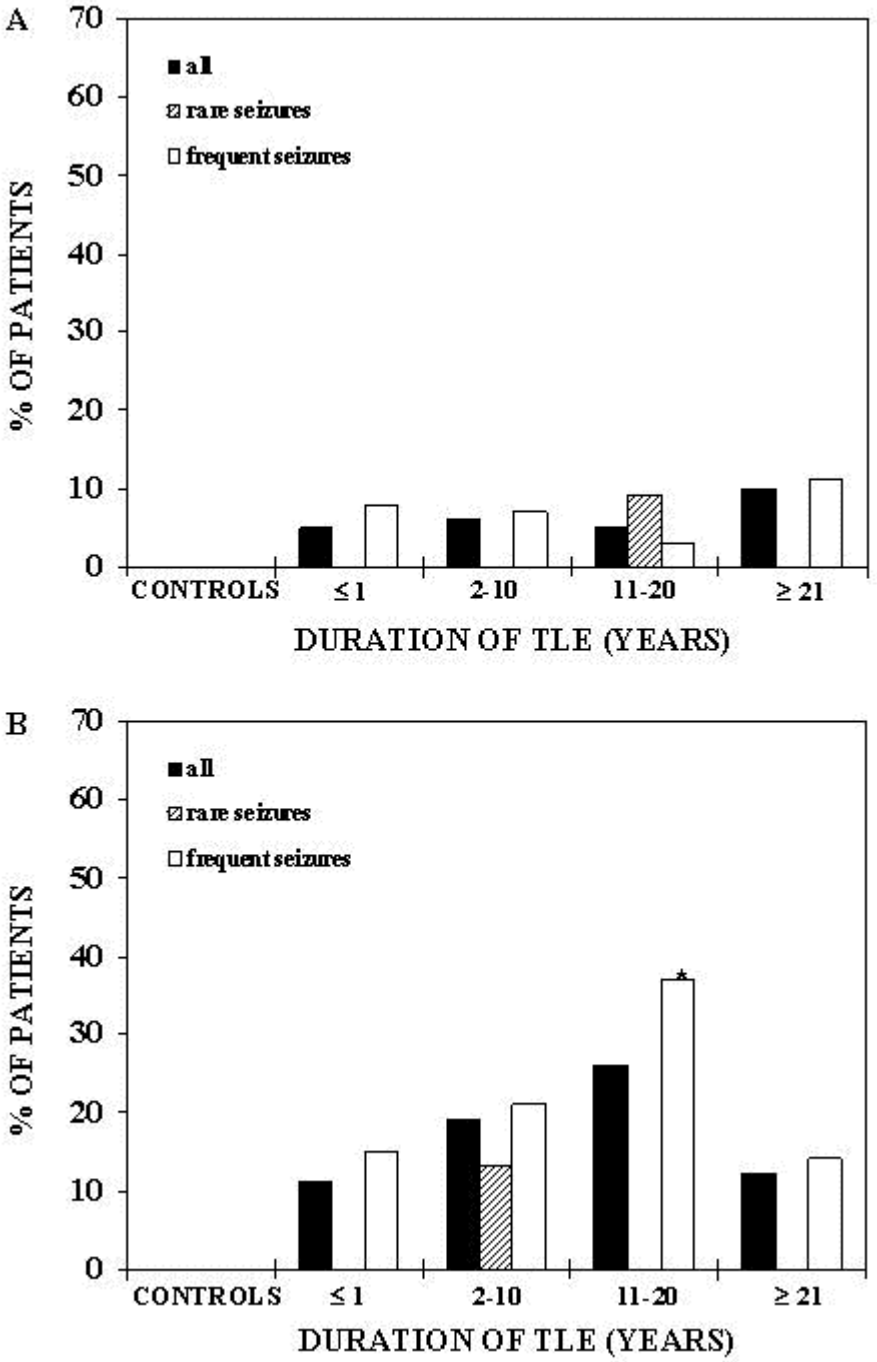

Figure 9. (A) The percentage of patients with a decrease in the amygdaloid volume of ≥2 SD of the control mean in patient groups with different durations of TLE. (B) The percentage of patients with a prolongation in the amygdaloid T2 relaxation time of ≥2 SD of the control mean in patient groups with different durations of TLE. The percentage of patients with an amygdaloid T2 time prolongation of at least 2 SD that differs from controls in Fisher's exact test is marked with asterisks (*, $p<0.05$). Abbreviation: TLE, temporal lobe epilepsy.

Table 7. T2 relaxation times (ms) of the left and right hippocampus (HC) in patients with temporal lobe epilepsy

	Left HC	T2 time prolongation	Right HC	T2 time prolongation
Controls (16)	92.9± 8.0		93.3 ± 7.5	
Patients with focus on the left (97)				
£ **1 year** (15)	95.3 ± 8.1	2	96.3 ± 5.7	3
with rare seizures (7)	98.6 ± 7.9	6	95.3 ± 6.7	2
with frequent seizures (8)	92.5 ± 7.7	0	97.3 ± 4.9	4
2-10 years (22)	99.6 ± 8.1	7	96.8 ± 6.0	4
with rare seizures (6)	99.3 ± 5.3	6	99.6 ± 6.0	6
with frequent seizures (16)	99.7 ± 9.1	7	95.8 ± 5.8	3
11-20 years (26)	100.4 ± 9.4	8	98.6 ± 6.5	5
with rare seizures (9)	96.6 ± 7.8	4	96.6 ± 6.4	3
with frequent seizures (17)	102.5 ± 9.7*	10	99.7 ± 6.5	6
³ **21 years** (34)	104.2 ± 13.4*	11	99.3 ± 9.0	6
with rare seizures (2)	98.5 ± 2.1	6	100.5 ± 4.6	7
with frequent seizures (32)	104.6 ± 13.7*	12	99.2 ± 9.2	6
Patients with focus on the right (52)				
£ **1 year** (5)	99.0 ± 4.8	6	98.8 ± 4.5	6
with rare seizures (1)	98.0	5	102.0	9
with frequent seizures (4)	98.7 ± 5.1	6	101.3 ± 6.7	8
2-10 years (13)	97.9 ± 5.4	5	100.7 ± 6.4*	7
with rare seizures (3)	95.3 ± 7.0	2	98.3 ± 5.5	5
with frequent seizures (10)	98.7 ± 5.1	6	101.3 ± 6.7	8
11-20 years (12)	96.9 ± 7.2	4	103.2 ± 10.4	10
with rare seizures (1)	93.3	0	100.0	7
with frequent seizures (11)	97.2± 7.5	4	103.5 ± 10.8	10
³ **21 years** (22)	99.2 ± 8.9	6	109.3 ± 13.3*	16
with rare seizures (4)	95.5 ± 4.1	3	95.3 ± 5.2	2
with frequent seizures (18)	100.1 ± 9.5	7	112.4 ± 12.6***	19

HC T2 times are shown as mean ± standard deviation of the mean. T2 time prolongation shows the prolongation of T2 time (ms) above the mean in controls. Number of patients, from which the T2 relaxometry data was available, is in parenthesis. Statistical significances were calculated with Kruskal-Wallis and Mann-Whitney analyses: *$p<0.05$, ***$p<0.001$ compared to controls.

Table 8. T2 relaxation times (ms) of the left and right amygdala (AMY) in patients with temporal lobe epilepsy

	Left AMY	T2 time prolongation	Right AMY	T2 time prolongation
Controls (15)	97.2 ± 6.9		98.1 ± 5.3	
Patients with focus on the left (72)				
£ **1 year** (13)	97.4 ± 7.8	0	97.1 ± 8.3	0
with rare seizures (5)	101.4 ± 4.0	4	96.8 ± 4.6	0
with frequent seizures (8)	94.9 ± 8.7	0	97.3 ± 10.3	0
2-10 years (15)	99.6 ± 8.1 (16)	2	96.8 ± 6.0	0
with rare seizures (4)	97.3 ± 9.7 (5)	0	98.4 ± 5.8	0
with frequent seizures (11)	103.1 ± 13.5	6	98.6 ± 7.8	1
11-20 years (19)	101.0 ± 9.6 (22)	4	97.0 ± 7.1	0
with rare seizures (6)	95.5 ± 7.6 (7)	0	96.0 ± 6.8	0
with frequent seizures (13)	103.5 ± 9.5 (15)	6	97.5 ± 7.4	0
³ **21 years** (25)	98.8 ± 8.1 (27)	2	98.3 ± 10.5	0
with rare seizures (1)	99.0	2	104.0	6
with frequent seizures (24)	98.8 ± 8.3 (26)	2	98.1 ± 10.7	0
Patients with focus on the right (35)				
£ **1 year** (3)	90.7 ± 7.0	0	93.7 ± 5.9	0
with rare seizures (0)	-	-	-	-
with frequent seizures (3)	90.7 ± 7.0	0	93.7 ± 5.9	0
2-10 years (11)	103.0 ± 5	6	102.4 ± 4.6	4
with rare seizures (2)	106.5 ± 7.8	9	104.5 ± 2.1	6
with frequent seizures (9)	102.2 ± 6.4	5	101.9 ± 4.9	4
11-20 years (6)	99.5 ± 8.5	2	102.2 ± 8.8	4
with rare seizures (0)	-	-	-	-
with frequent seizures (6)	99.5 ± 8.5	2	102.2 ± 8.8	4
³ **21 years** (15)	97.7 ± 8.3	1	100.5 ± 7.0	2
with rare seizures (3)	95.3 ± 6.4	0	96.7 ± 8.1	0
with frequent seizures (12)	98.3 ± 8.9	1	101.5 ± 6.7	3

AMY T2 times are shown as mean ± standard deviation of the mean. T2 time prolongation shows the prolongation of T2 time (ms) above the mean in controls. Number of patients, from which the T2 relaxometry data was available, is in parenthesis. Statistical significances were calculated with Kruskal-Wallis and Mann-Whitney analyses.

5.3.2.2. Damage in patients with years of TLE

There was a significant difference in the mean volumes of the right hippocampus when analysis was performed on controls and patients with different durations of right TLE ($p<0.001$) (Table 5). The right hippocampus was 29% smaller in patients with ≥21 years of right TLE than in controls ($p<0.01$). The difference in the mean right hippocampal volume was also significant when patients with ≥21 years of epilepsy were compared with patient groups with ≤1 year or 2 to 10 years of epilepsy ($p<0.05$). No significant difference was observed in the mean hippocampal volumes when controls and patients with different durations of left TLE were compared with each other. However, there was a trend towards left hippocampal volume reduction in patients with longer duration of TLE. The left hippocampus was 14% smaller in patients with ≥21 years of left TLE compared with controls. The number of all TLE patients with a hippocampal volume reduction of ≥2 SD was significantly higher in patients with 11 to 20 years (17% (7/41), $p<0.05$) and with ≥21 years (46% (25/54), $p<0.001$) of TLE compared with controls (Figure 8A). Furthermore, the number of patients with reduced hippocampal volume was significantly higher in patients with ≥21 years of TLE (46% (25/54)) than in patients with ≤1 year (5% (1/21), $p<0.001$), 2 to 10 years (11% (4/37), $p<0.001$), or 11 to 20 years (17% (7/41), $p<0.01$) of epilepsy.

The mean hippocampal T2 relaxation times in all TLE patients with seizure focus on the left or right are summarized in Table 7 (data not published). There was a significant difference in the mean T2 relaxation times of the left hippocampus between patients with different durations of left TLE and controls ($p<0.01$). Patients with ≥21 years of left TLE had longer mean T2 times than did controls ($p< 0.05$). Correspondingly, there was a significant difference in mean T2 relaxation times of the right hippocampus between patient groups with different durations of right TLE and controls ($p<0.01$). T2 times were the most prolonged in patients with ≥21 years of seizures compared with controls (16 ms; $p <0.05$). Compared with controls, the number of all TLE patients with hippocampal T2 prolongation was higher in patient groups with 11 to 20 years (23% (9/40), $p<0.05$) and ≥21 years (39% (22/57), $p<0.01$) of TLE (Figure 8B). Moreover, the number of patients with a hippocampal T2 relaxation time prolongation of ≥2 SD was significantly higher in patients with ≥21 years of epilepsy (39% (22/57)) than in patient groups with ≤1 year or 2 to 10 years of epilepsy (5% (1/22) and 11% (4/37) respectively; $p<0.01$).

There were no significant differences in mean amygdaloid volumes (Table 6) or T2 relaxation times (Table 8) (data not published) when controls and patients with a different duration of left or right TLE were compared. Moreover, no differences were observed in the number of all TLE patients with an amygdaloid volume reduction (Figure 9A) or prolongation of T2 relaxation time (Figure 9B) (data not published) of ≥2 SD between patient groups with different durations of TLE and controls.

We found volume reduction in both the hippocampus and in the amygdala in 5% of all TLE patients. Correspondingly, 5% of all the patients had hippocampal and amygdaloid T2 time prolongation. Of all the TLE patients with reduced hippocampal volume, 19% also had a reduced amygdala volume. Moreover, 16% of all the patients with a hippocampal T2 time prolongation had a prolonged T2 time in the amygdala. When all the TLE patients with amygdaloid damage were analyzed separately, 70% of the patients with reduced amygdaloid volume also had hippocampal atrophy. Only 32% of the patients with amygdaloid T2 time prolongation, however, had a prolonged T2 time in the hippocampus.

5.3.3. Damage relative to the seizure number in TLE

5.3.3.1. Damage in patients with rare and frequent seizures

There was a significant difference when the mean hippocampal volumes in right TLE patient subgroups with frequent seizures were compared with each other or with controls ($p<0.001$) (Table 5). In patients with ≥21 years of frequent seizures, the volume of the right hippocampus was 34% smaller than in controls ($p<0.001$), 40% smaller than in patients with ≤1 year, and 32% smaller than in patients with 2 to 10 years of frequent seizures ($p<0.05$). The number of all TLE patients with a hippocampal volume reduction of ≥2 SD was higher in patients with 11 to 20 years (20% (6/30), $p<0.05$) and with ≥21 years (50% (24/48), $p<0.001$) of frequent seizures than in controls (Figure 8A). Moreover, the number of patients with decreased hippocampal volume was higher in patients with ≥21 years of frequent seizures (50% (24/48)) than in patient groups with ≤1 year (0% (0/12), $p<0.01$), with 2 to 10 years (14% (4/29), $p<0.01$), or with 11 to 20 years (20% (6/30), $p<0.01$) of frequent seizures.

We found significant differences in mean T2 relaxation times of the left hippocampus when subgroups of left TLE patients with frequent seizures were compared with each other or with controls ($p<0.01$) (Table 7). Patient groups with 11 to 20 or ≥21 years of frequent seizures had longer mean T2 relaxation times than did controls (10 ms and 12 ms, respectively; $p<0.05$). Correspondingly, the data indicated significant differences when subgroups of right TLE patients with frequent seizures were compared with each other or with controls ($p<0.001$). In patients with ≥21 years of frequent seizures, the mean right hippocampal T2 time was 19 ms longer than in controls ($p<0.001$). The number of all patients with a hippocampal T2 time prolongation of ≥2 SD was higher in patients with 11 to 20 years (31% (9/29), $p<0.05$) and ≥21 years (43% (22/51), $p<0.01$) of frequent seizures than in controls (Figure 8B). Moreover, in patients with ≥21 years of frequent seizures (43% (22/51)), the number of patients with T2 prolongation was higher than in patients with ≤1 year (0% (0/13)) or 2 to 10 years (11% (3/28)) of frequent seizures ($p<0.01$). The group with 11 to 20 years (31% (9/29)) of frequent seizures had a higher number of patients with T2 prolongation than patients with ≤1 year (0% (0/13)) of frequent seizures ($p<0.05$).

The mean amygdaloid volumes did not differ significantly between the study groups (Table 6). There were no significant differences in the number of patients with an amygdaloid volume reduction of ≥2 SD when the patient groups with frequent or rare seizures were compared with each other or with controls (Figure 9A). Correspondingly, the analysis did not reveal any differences in the mean amygdaloid T2 relaxation times over the various study groups (Table 8). Comparison between patient groups and control subjects revealed that the number of patients with a T2 time prolongation of ≥2 SD was higher in patients with 11 to 20 years (33% (7/21), $p<0.05$) of frequent seizures than in controls (Figure 9B). Otherwise, no differences were observed between the study groups.

5.3.3.2. Correlation of damage with seizure number

In all TLE patients with seizure focus on the left, the left hippocampal volume correlated inversely with the total number of partial ($r=-0.221$, $p<0.05$) and generalized ($r=-0.239$, $p<0.05$) seizures the patients experienced during their lifetime (Table 9). Correspondingly, the left hippocampal T2 relaxation time correlated with the total number of both partial ($r=0.444$, $p<0.001$) and generalized ($r=0.339$, $p<0.01$) seizures (Table 9). No correlation was found between right hippocampal volume and seizure number. The right hippocampal T2 relaxation time, however, correlated with the number of partial seizures ($r=0.297$, $p<0.01$).

In all TLE patients with seizure focus on the right, the right hippocampal volume correlated inversely with the total number of both partial ($r=-0.366$, $p<0.01$) and generalized ($r=-0.344$, $p<0.05$) seizures (Table 9). Correspondingly, the prolongation of right hippocampal T2 relaxation time correlated with the number of partial ($r=0.442$, $p<0.01$) but not with the number of generalized seizures (Table 9). No correlation was observed between the left hippocampal volume or T2 relaxation time and the number of partial or generalized seizures.

Table 9. Correlation between the hippocampal volumes or T2 relaxation times and the lifetime seizure number in patients with temporal lobe epilepsy

	HC VOLUME		**HC T2 TIME**	
	left	**right**	**left**	**right**
Focus on the left				
partial seizures	r = -0.221 n = 90 p = 0.036	ns	r = 0.444 n = 97 p = 0.000	r = 0.297 n = 97 p = 0.003
generalized seizures	r = -0.239 n = 90 p = 0.023	ns	r = 0.339 n = 97 p = 0.001	ns
Focus on the right				
partial seizures	ns	r = -0.366 n = 55 p = 0.006	ns	r = 0.442 n = 52 p = 0.001
generalized seizures	ns	r = -0.344 n = 55 p = 0.010	ns	ns

Correlations between the hippocampal volumes or T2 relaxation times and the lifetime number of partial and generalized seizures are shown separately in patients with seizure focus on the left or right temporal lobe. Correlations were calculated using two-tailed Pearson's correlation test. Abbreviations: HC, hippocampus; n, number of patients; ns, not significant; r, Pearson's correlation coefficient.

In all TLE patients with seizure focus on the left, the volumes of the left or right amygdala did not correlate with the number of seizures the patient experienced (Table 10). Correspondingly, there was no significant correlation between prolongation of left amygdala T2 times and the number of seizures (Table 10). The T2 relaxation time of the right amygdala, however, correlated with the number of partial seizures ($r=0.246$, $p<0.05$).

In all TLE patients with right seizure focus, the right amygdala volume correlated inversely with the number of generalized seizures ($r=-0.332$, $p<0.05$) (Table 10). There was no correlation between left amygdaloid volume and seizure number. Correspondingly, there was no correlation between the T2 relaxation time of the left or right amygdala and number of seizures the patient experienced (Table 10).

Table 10. Correlation between the amygdaloid volumes or T2 relaxation times and the lifetime seizure number in patients with temporal lobe epilepsy

	AMY VOLUME		AMY T2 TIME	
	left	**right**	**left**	**right**
Focus on the left				
partial seizures	ns	ns	ns	r = 0.246 n = 72 p = 0.038
generalized seizures	ns	ns	ns	ns
Focus on the right				
partial seizures	ns	ns	ns	ns
generalized seizures	ns	r = -0.332 n = 51 p = 0.017	ns	ns

Correlations between the amygdaloid volumes or T2 relaxation times and the lifetime number of partial and generalized seizures are shown separately in patients with seizure focus on the left or right temporal lobe. Correlations were calculated using two-tailed Pearson's correlation test. Abbreviations: AMY, amygdaloid; n, number of patients; ns, not significant; r, Pearson's correlation coefficient.

5.3.4. Damage relative to the etiology of TLE

No significant differences were observed in the number of patients with a hippocampal volume reduction of ≥2 SD between patients with cryptogenic and symptomatic TLE (Table 11). In both cryptogenic and symptomatic patient groups, however, the longer the duration of TLE, the higher the number of patients with hippocampal volume reduction. There were significantly more cases with hippocampal damage in patients with ≥21 years of cryptogenic TLE than in patients with ≤1 year ($p< 0.01$), with 2 to 10 years ($p<0.05$) and with 11 to 20 years ($p<0.05$) of TLE. Correspondingly, the group of patients with ≥21 years of symptomatic TLE had a significantly higher number of cases with hippocampal damage than the groups of patients with 2 to 10 years or 11 to 20 years of symptomatic TLE ($p<0.05$).

As with hippocampal volumetry, there was no difference in the number of patients with a hippocampal T2 time prolongation of ≥2 SD when compared between cryptogenic and symptomatic etiology of TLE (Table 11). In cryptogenic patients, the number of patients with a hippocampal T2 time prolongation of ≥2 SD was higher in patients with ≥21 years of TLE than in patients with ≤1 year or 2 to 10 years of TLE ($p<0.05$). No significant differences were observed between symptomatic TLE patients divided according to duration of TLE.

Table 11. Percentages of patients with ≥2 SD hippocampal volume reduction and T2 time prolongation in cryptogenic and symptomatic TLE

	Cryptogenic TLE	Symptomatic TLE	Difference
HC volume reduction			
All patients	20 % (17/86)	30 % (20/67)	ns (p = 0.18)
≤ 1 year	0 % (0/12)	11 % (1/9)	ns (p = 0.43)
2-10 years	8 % (2/24)	15 % (2/13)	ns (p = 0.60)
11-20 years	14 % (3/22)	21 % (4/19)	ns (p = 0.68)
≥ 21 years	43 % (12/28)**^¤	50 % (13/26)^¤	ns (p = 0.79)
HC T2 time prolongation			
All patients	17 % (15/86)	30 % (21/70)	ns (p = 0.09)
≤ 1 year	0 % (0/12)	10 % (1/10)	ns (p = 0.46)
2-10 years	8 % (2/25)	17 % (2/12)	ns (p = 0.58)
11-20 years	14 % (3/21)	32 % (6/19)	ns (p = 0.27)
≥ 21 years	36 % (10/28)*^	41 % (12/29)	ns (p = 0.79)

The numbers of patients with ≥2 SD hippocampal volume reduction and T2 time prolongation were compared with χ^2-test and Fisher's exact test between cryptogenic and symptomatic TLE patient groups. The second comparison was made separately in cryptogenic and symptomatic TLE patients between patient subgroups divided according to the duration of TLE. Abbreviations: HC, hippocampal; ns, not significant; TLE, temporal lobe epilepsy. *p<0.05 compared to patients with ≤1 year of TLE, **p<0.01 compared to patients with ≤1 year of TLE, ^p<0.05 compared to patients with 2-10 years of TLE, ¤p<0.05 compared to patients with 11-20 years of TLE.

The number of patients with an amygdaloid volume reduction or T2 time prolongation of ≥2 SD did not differ when compared between all cryptogenic and all symptomatic TLE patients (Table 12). Moreover, when divided according to the duration of epilepsy, the two different etiologic patient groups did not differ from each other. When cryptogenic TLE patients with different durations of TLE were analyzed separately, the number of patients with amygdaloid damage of ≥2 SD did not differ from each other. Correspondingly, no differences were observed between study groups with symptomatic TLE.

Table 12. Percentages of patients with ≥2 SD amygdaloid volume reduction and T2 time prolongation in cryptogenic and symptomatic TLE

	Cryptogenic TLE	Symptomatic TLE	Difference
AMY volume reduction			
All patients	5 % (4/86)	10 % (6/63)	ns (p = 0.32)
≤ 1 year	8 % (1/12)	0 % (0/9)	ns (p = 1.00)
2-10 years	4 % (1/24)	8 % (1/12)	ns (p = 0.43)
11-20 years	5 % (1/22)	6 % (1/18)	ns (p = 1.00)
≥ 21 years	4 % (1/28)	17 % (4/24)	ns (p = 0.17)
AMY T2 time prolongation			
All patients	15 % (11/73)	17 % (8/47)	ns (p = 0.80)
≤ 1 year	0 % (0/10)	22 % (2/9)	ns (p = 0.21)
2-10 years	20 % (4/20)	13 % (1/8)	ns (p = 1.00)
11-20 years	22 % (4/18)	25 % (3/12)	ns (p = 1.00)
≥ 21 years	12 % (3/25)	11 % (2/18)	ns (p = 1.00)

The numbers of patients with ≥2 SD amygdaloid volume reduction and amygdaloid T2 time prolongation were compared with χ^2-test and Fisher's exact test between cryptogenic and symptomatic TLE patient groups. The second comparison was made separately in cryptogenic and symptomatic TLE patients between patient subgroups divided according to the duration of TLE. Abbreviations: AMY, amygdaloid; ns, not significant; TLE, temporal lobe epilepsy.

5.3.5. Damage relative to the location of seizure focus

5.3.5.1. Damage in patients with extratemporal or unclassified partial epilepsy (ETE/UC)

There were no significant differences in the volumes (Table 13) or T2 relaxation times (Table 14) of the left or right hippocampus when patients with different durations of ETE/UC were compared with each other or with controls. Furthermore, no difference was observed between patient groups with rare or frequent seizures and controls. The number of patients with a hippocampal volume decrease of ≥2 SD was higher in patients with ≤10 years of epilepsy (16% (7/43), the patient groups of ≤1 year and 2 to 10 years of epilepsy were combined) than in controls ($p<0.05$) (Figure 10A). The difference was significant, however, only in patients with frequent seizures. Altogether, 17% (4/23) of the patients with ≤10 years of frequent seizures had a volume reduction in the hippocampus ($p<0.05$ compared with controls). The number of ETE/UC patients with a hippocampal T2 time prolongation of ≥2 SD in different patient groups did not differ from each other or from controls (Figure 10B).

Table 13. Volumes (mm^3) of the left and right hippocampus (HC) in patients with extratemporal or unclassified partial epilepsy

	Left HC	Damage %	Right HC	Damage %
Controls (25)	3348 ± 424		3589 ± 436	
All patients (87)				
£ **1 year** (19)	3064 ± 599	8	3452 ± 545	4
with rare seizures (9)	3311 ± 609	1	3665 ± 491	0
with frequent seizures (10)	2842 ± 522	15	3261 ± 543	9
2-10 years (24)	3186 ± 414	5	3357 ± 747	6
with rare seizures (11)	3165 ± 420	5	3328 ± 611	7
with frequent seizures (13)	3204 ± 426	4	3381 ± 870	6
11-20 years (15)	3216 ± 490	4	3505 ± 526	2
with rare seizures (1)	2630	21	3007	16
with frequent seizures (14)	3257 ± 480	3	3541 ± 527	1
³ **21 years** (29)	3192 ± 627 (30)	5	3458 ± 639	4
with rare seizures (2)	3343 ± 251	0	3586 ± 470	0
with frequent seizures (27)	3182 ± 646 (28)	5	3448 ± 655	4

HC volumes are shown as mean ± standard deviation of the mean. Damage % shows the percentage of volume reduction below the mean in controls. Number of patients, from which the volumetry data was available, is in parenthesis. In the table we show the normalized hippocampal volumes.

Table 14. T2 relaxation times (ms) of the left and right hippocampus (HC) in patients with extratemporal or unclassified epilepsy

	Left HC	T2 time prolongation	Right HC	T2 time prolongation
Controls (16)	92.9 ± 8.0		93.3 ± 7.5	
All patients (87)				
£ **1 year** (20)	96.4 ± 9.2	4	96.6 ± 7.4	3
with rare seizures (10)	94.3 ± 6.7	1	95.2 ± 7.5	2
with frequent seizures (10)	98.6 ± 11.2	6	97.9 ± 7.5	5
2-10 years (21)	96.0 ± 6.3	3	95.8 ± 5.4	3
with rare seizures (10)	95.0 ± 7.2	2	94.4 ± 6.0	1
with frequent seizures (11)	96.9 ± 5.5	4	97.1 ± 4.7	4
11-20 years (15)	99.8 ± 6.4	7	100.0 ± 9.7	7
with rare seizures (1)	105	12	99	6
with frequent seizures (14)	99.4 ± 6.5	7	100.1 ± 10.0	7
³ **21 years** (31)	95.5 ± 5.8	3	103.4 ± 32.3	10
with rare seizures (3)	96.0 ± 4.0	3	97.3 ± 5.1	4
with frequent seizures (28)	95.5 ± 6.0	3	104.0 ± 34.0	11

HC T2 relaxation times are shown as mean ± standard deviation of the mean. T2 time prolongation shows the prolongation of T2 time (ms) above the mean in controls. Number of patients, from which the T2 relaxometry data was available, is in parenthesis.

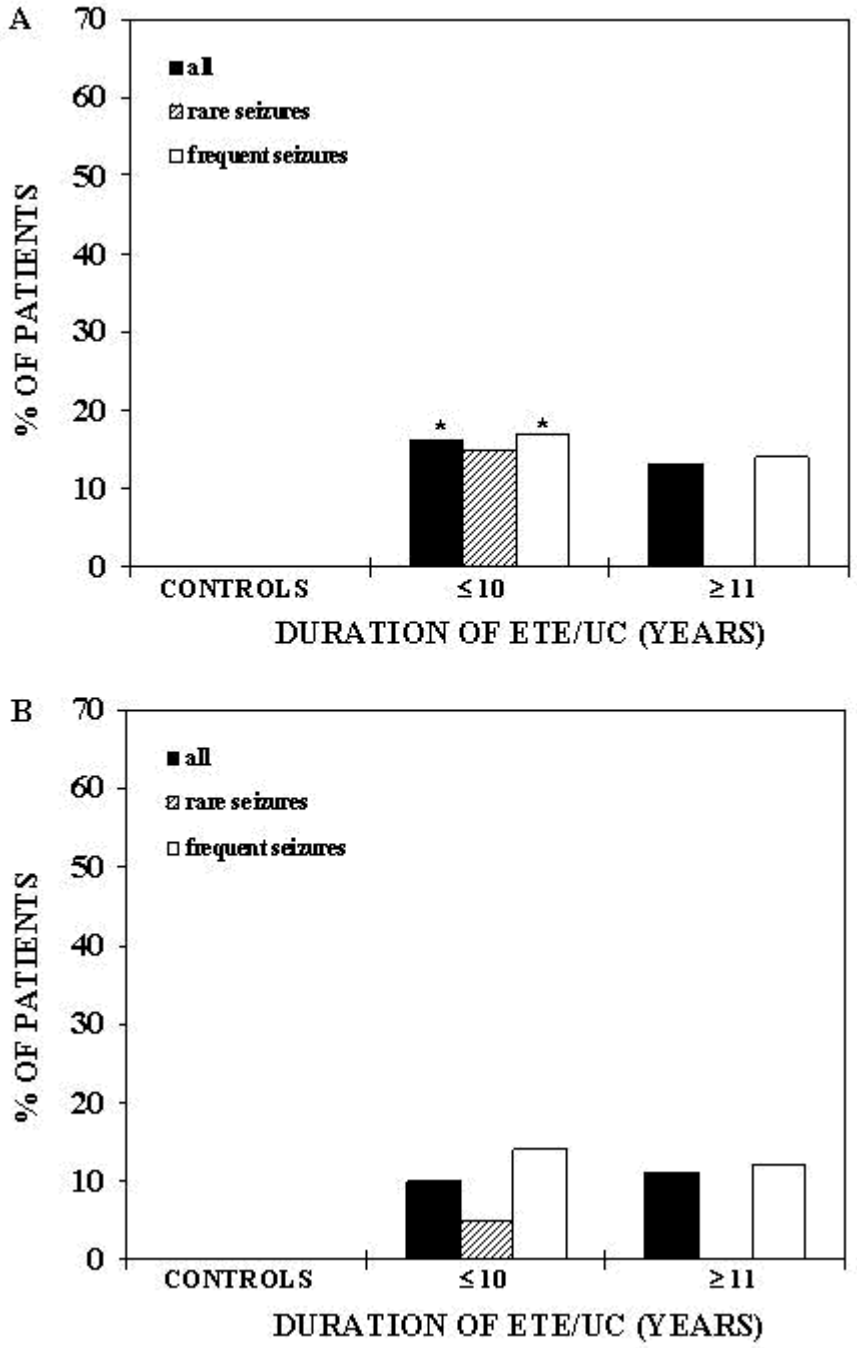

Figure 10. (A) The percentage of patients with a decrease in the hippocampal volume of ≥2 SD of the control mean in patient groups with different durations of ETE/UC. (B) The percentage of patients with a prolongation in the hippocampal T2 relaxation time of ≥2 SD of the control mean in patient groups with different durations of ETE/UC. The percentages of patients with a hippocampal volume reduction of ≥2 SD that differ from controls in Fisher's exact test are marked with asterisks (*, $p<0.05$). Abbreviation: ETE/UC, extratemporal/unclassified partial epilepsy.

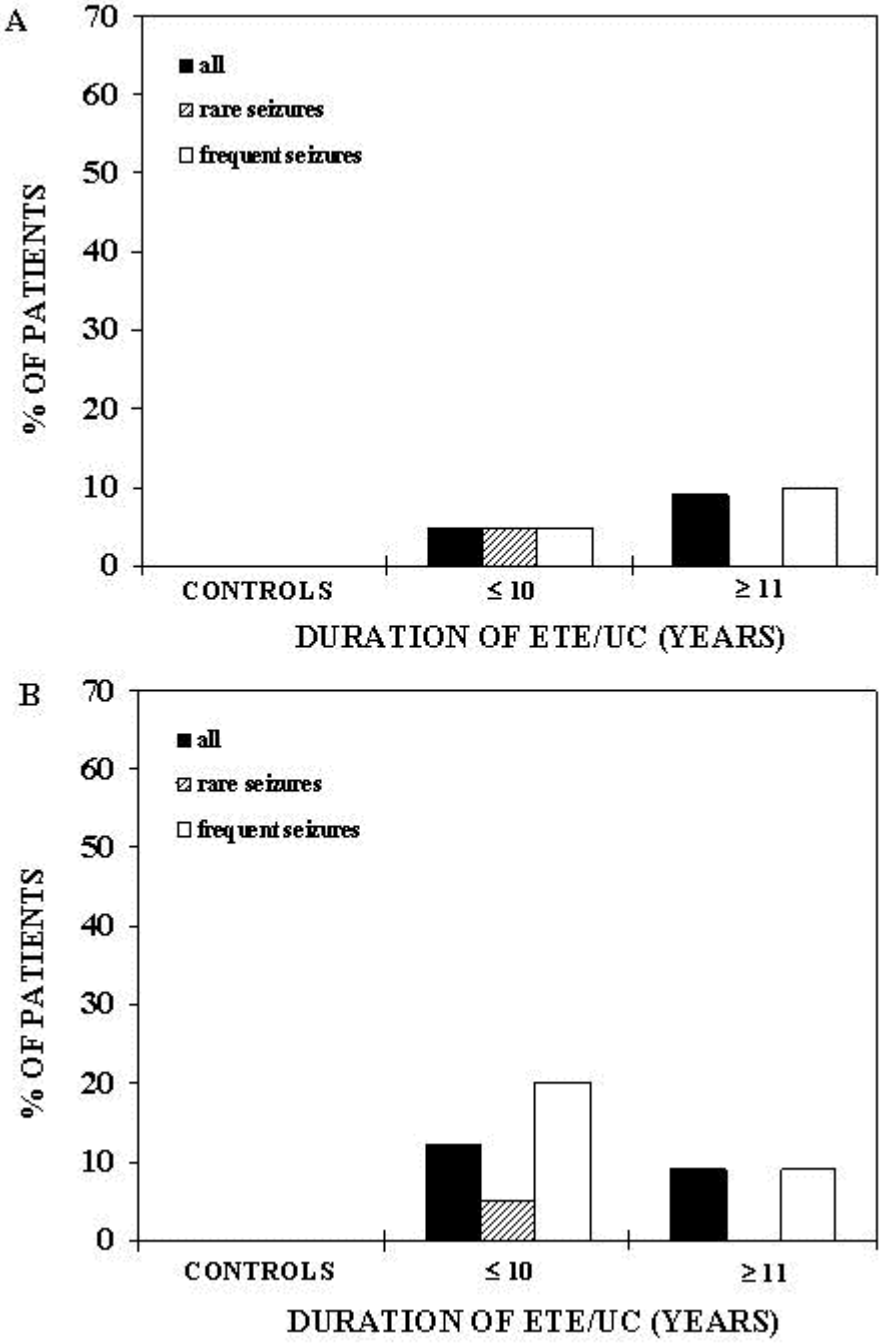

Figure 11. (A) The percentage of patients with a decrease in the amygdaloid volume of ≥2 SD of the control mean in patient groups with different durations of ETE/UC. (B) The percentage of patients with a prolongation in the amygdaloid T2 relaxation time of ≥2 SD of the control mean in patient groups with different durations of ETE/UC. Abbreviation: ETE/UC, extratemporal/unclassified partial epilepsy.

No significant differences were observed in the mean volumes (Table 15) or the T2 relaxation times (Table 16) of the left or right amygdala between different patient groups and controls. The number of cases with reduced amygdaloid volume (Figure 11A) or T2 prolongation (Figure 11B) in patient groups with ≤10 years or ≥11 years of ETE/UC epilepsy did not differ from each other or from controls. Also, no differences were observed when the different subgroups with rare or frequent seizures were compared with each other or controls.

Table 15. Volumes (mm^3) of the left and right amygdala (AMY) in patients with extratemporal or unclassified epilepsy

	Left AMY	**Damage %**	**Right AMY**	**Damage %**
Controls (25)	2476 ± 401		2299 ± 250	
All patients (86)				
£ **1 year** (19)	2361 ± 300	5	2318 ± 265	0
with rare seizures (9)	2366 ± 365	4	2313 ± 331	0
with frequent seizures (10)	2356 ± 249	5	2323 ± 207	0
2-10 years (23)	2356 ± 352	5	2233 ± 341	3
with rare seizures (11)	2308 ± 352	7	2292 ± 199	0
with frequent seizures (12)	2399 ± 362	3	2178 ± 435	5
11-20 years (15)	2384 ± 311	4	2228 ± 307	3
with rare seizures (1)	1966	21	1882	21
with frequent seizures (14)	2414 ± 300	3	2253 ± 302	2
³ **21 years** (29)	2378 ± 367 (30)	4	2374 ± 403	0
with rare seizures (2)	2326 ± 165	6	2405 ± 143	0
with frequent seizures (27)	2381 ± 379 (28)	4	2372 ± 418	0

AMY volumes are shown as mean ± standard deviation of the mean. Damage % shows the percentage of volume reduction below the mean in controls. Number of patients, from which the volumetry data was available, is in parenthesis. In the table we show the normalized hippocampal volumes.

Table 16. T2 relaxation times (ms) of the left and right amygdala (AMY) in patients with extratemporal or unclassified epilepsy

	Left AMY	T2 time prolongation	Right AMY	T2 time prolongation
Controls (15)	97.2 ± 6.9		98.1 ± 5.3	
All patients (68)				
£ **1 year** (17)	100.0 ± 6.9	3	98.2 ± 6.7	0
with rare seizures (9)	97.8 ± 5.3	1	97.1 ± 6.3	0
with frequent seizures (8)	102.5 ± 7.9	5	99.5 ± 7.3	1
2-10 years (17)	98.0 ± 8.0	1	95.1 ± 5.9	0
with rare seizures (10)	95.5 ± 8.2	0	93.1 ± 5.0	0
with frequent seizures (7)	101.4 ± 6.9	4	98.1 ± 6.0	0
11-20 years (13)	103.3 ± 13.4	6	98.8 ± 9.8	1
with rare seizures (1)	109.0	12	105.0	7
with frequent seizures (12)	102.8 ± 13.9	6	99.9 ± 9.4	2
³ **21 years** (21)	95.8 ± 6.4 (22)	0	96.9 ± 5.4	0
with rare seizures (2)	102.0 ± 8.5	5	95.5 ± 6.4	0
with frequent seizures (19)	95.2 ± 6.1 (20)	0	97.0 ± 5.4	0

AMY T2 relaxation times are shown as mean ± standard deviation of the mean. T2 time prolongation shows the prolongation of T2 time (ms) above the mean in controls. Number of patients, from which the T2 relaxometry data was available, is in parenthesis.

5.4. VOLUMETRY OF THE ENTORHINAL CORTEX IN CHRONIC CRYPTOGENIC TEMPORAL LOBE EPILEPSY (STUDY IV)

5.4.1. Volume of the entorhinal cortex

There were no significant differences in the volumes of the left or right entorhinal cortex when patients with left focus, right focus and controls were compared. Also, the asymmetry index did not differ between the study groups.

Two of 36 patients had ≥2 SD volume reduction of the entorhinal cortex (i.e., at least a 31% volume reduction on the left side or 41% on the right side). In 11 out of 36 patients, entorhinal volume was reduced by at least 25% (5 ipsilateral, 3 contralateral, 3 bilateral volume reduction).

Further analysis showed significant differences in the entorhinal volume when the occurrence of hippocampal damage (≥2 SD volume reduction compared to controls) was taken into account. The entorhinal volume correlated with the hippocampal volume ipsilaterally ($n=36$, $r=0.454$, $p<0.01$) and contralaterally ($n=36$, $r=0.340$, $p<0.05$) in TLE patients. Overall, 8 of 16 patients with hippocampal damage had a 25% volume decrease in the ipsilateral entorhinal cortex. In right TLE patients with ipsilateral hippocampal damage, the mean volume of the ipsilateral entorhinal cortex was reduced by

19% compared with controls ($p<0.05$). Also, the left TLE patients with left hippocampal damage had a 16% volume reduction of the ipsilateral entorhinal cortex compared with controls but the difference did not reach significance ($p=0.0936$). Otherwise, 8 of 11 patients with over 25% entorhinal damage had hippocampal damage ipsilaterally. Hippocampal damage was unilateral in 4 patients and bilateral in 4 patients.

In all patients, the entorhinal and amygdaloid volumes correlated ipsilaterally ($n=36$, $r=0.346$, $p<0.05$) but not contralaterally. Only 2 of 11 patients with 25% entorhinal damage had ipsilateral amygdaloid damage (≥2 SD volume reduction). Three of 4 patients with amygdaloid damage had over 25% volume reduction in the ipsilateral entorhinal cortex.

5.4.2. Correlation of the volume with duration of TLE and seizure number

The ipsilateral entorhinal volume correlated inversely with the duration of TLE ($n=36$, $r=-0.335$, $p< 0.05$) in all patients. We did not, however, find any difference in the mean entorhinal volume between the patient groups with TLE onset ≤5 or >5 years of age. No correlation was found between the total seizure number (partial, secondarily generalized or all seizures) and the entorhinal volume ipsilaterally or contralaterally.

5.5. VOLUMETRY OF THE HIPPOCAMPUS, AMYGDALA, ENTORHINAL AND PERIRHINAL CORTEX AFTER STATUS EPILEPTICUS (STUDY V)

5.5.1. Clinical findings of status epilepticus episodes

The clinical data of status epilepticus episodes experienced by patients are summarized in Table 17. Status epilepticus was secondarily generalized tonic-clonic in eight patients, one of whom (Patient 6) had a total of four prolonged seizure episodes during the study period. Before the initial MRI, Patient 6 had two episodes of status epilepticus within 1 week, and two more within the next 6 months.

The mean duration of all 11 secondarily generalized tonic-clonic status epilepticus episodes in 8 patients was 1 h 44 min (range 45 min-4 h 30 min). One patient (Patient 2) had complex partial status epilepticus that lasted a total of 21 h. In her case, the EEG recording confirmed the diagnosis. The summary of EEG findings in all status epilepticus patients is presented in Table 18. Postictal or interictal EEGs revealed no evidence of electrographic seizure activity. In all, however, the EEGs were interpreted as abnormal, which most likely relates to the earlier etiologies for insult.

The etiology of prolonged seizure episode was a chronic process in eight patients, including preexisting epilepsy and operated brain tumor (Table 17). Moreover, acute alcohol abuse contributed to status epilepticus in two patients (Patients 6 and 9). In Patient 1, the cause of status epilepticus was acute encephalitis (Varicella zoster).

Status epilepticus was controlled with intravenous diazepam and a loading dose of phenytoin in five patients (Table 17). The seizures were abolished with acute administration of intravenous diazepam in Patient 7, and Patient 8 received only an intravenous phenytoin bolus (repeated once). Full anesthesia with thiopental was required in Patients 1 and 4 for management of the refractory status. Patient 1 reached burst suppression during EEG monitoring in 1 h and 15 min, and Patient 4 in 1 h and 20 min after the onset of status epilepticus. In Patient 1, the anesthesia was tapered off without recurrence after 12 h and in Patient 4 after 8 h of maintaining the burst suppression activity.

Table 17. Clinical data of status epilepticus

No of patient	Type of status epilepticus	Etiology	Duration	AED treatment
1	generalized tonic-clonic	encephalitis (varicella zoster)	1 h 15 min	DZP 60 mg iv DPH 1500 mg iv thiopental anesthesia
2	complex partial	drug-resistant epilepsy	21 h	DZP 40 mg iv DPH 1250 mg iv
3	generalized tonic-clonic	drug-resistant epilepsy	1 h 30 min	DZP 20 mg iv DPH 1375 mg iv
4	generalized tonic-clonic	left temporo-parietal astrocytoma gr II operated	1 h 20 min	DZP 12.5 mg iv DPH 1000 mg iv thiopental anesthesia
5	generalized tonic-clonic	drug-resistant epilepsy	45 min	DZP 22.5 mg iv DPH 1000 mg iv
6	I. generalized tonic-clonic (July 4, 1997)	alcohol abuse, non-compliance in AED medication	1 h 15 min	DZP 30 mg iv DPH 1000 mg iv
	II. generalized tonic-clonic (July 7, 1997)		4 h 30 min	DZP 40 mg iv DPH 1000 mg iv
	III. generalized tonic-clonic (July 24, 1997)		1 h 30 min	DZP 10 mg iv DPH 1150 mg iv
	IV. generalized tonic-clonic (December 20, 1997)		2 h	DZP 15 mg iv DPH 1250 mg iv
7	generalized tonic-clonic	noncompliance in AED medication	1 h	DZP 10 mg iv
8	generalized tonic-clonic	AED medication reduced	2 h	DPH 500 mg iv
9	generalized tonic-clonic	drug-resistant epilepsy, alcohol abuse	2 h	DZP 20 mg iv DPH 1250 mg

Abbreviations: AED, antiepileptic drug; DPH, phenytoin; DZP, diazepam; No, number.

In the clinical follow-up period, three patients (Patients 3, 5, and 9) continued to have recurrent seizures after status epilepticus. The other patients (Patients 2, 6, 7, and 8) were well-controlled with antiepileptic treatment. Patients 1 and 4 did not develop epilepsy during the 1-year follow-up period after the status epilepticus. There was no deteriorating in the clinical neurological status and the sociofunctional capacity including ability to work in any of the study patients during the 1-year follow-up suggesting the development of structural damage.

5.5.2. Serum neuron-specific enolase

Table 18 summarizes the s-NSE samples drawn 24 h (Patients 1, 2, 3, 4, 5 and 6) to 72 h (Patients 8 and 9) after status epilepticus. The mean s-NSE level was 6.1 ng/ml (range 2.4 - 22.5 ng/ml) for the nine status epilepticus episodes occurring in eight patients. Only one patient included in the study demonstrated an elevated s-NSE level. Patient 6 had an s-NSE level of 22.5 ng/ml 24 h after the second episode of status epilepticus. The duration of her status epilepticus was the longest (4 h 30 min) of all the prolonged secondarily generalized tonic-clonic status epilepticus episodes observed in the study. Moreover, Patient 6 had her first status epilepticus only 7 days earlier.

Table 18. Summary of EEG, MRI and s-NSE findings in status epilepticus patients

No of patient	Clinical stage during EEG recording	EEG findings	MRI	s-NSE ≤12 ng/ml
1	General anesthesia	Burst-suppression. No focal or slow-wave abnormalities.	Normal	3.7
2	Ictal	Generalized continuous epileptiform and slow-wave discharges, with at times shifting right-sided predominance. Mild disturbance of background activity.	Right temporo-parietal polymicrogyria	2.4
3	Interictal/ late postictal	Left temporal intermittent slow-wave abnormalities.	Left HC volume↓, T2 signal ↑, cerebellar atrophy	8.1
4	Early postictal	Intermittent bilateral fronto-temporal slow-wave paroxysms. Severe disturbance of background activity.	Left parietal resection cavity, left HC volume ↓, T2 signal ↑	4.8
5	Early postictal	Left fronto-central intermittent slow-wave abnormalities. Mild disturbance of background.	Left MCA infarction, left hemisphere atrophy, left HC volume ↓, T2 signal ↑	5.8
6	Early postictal (2^{nd} episode)	Generalized slow-wave paroxysms. Moderate disturbance of backgrond activity.	Brain atrophy, lacunar infarction, periventricular white matter signal intensities frontally and around trigonum	22.5 (2^{nd} episode)
7	Interictal	Right fronto-temporal epileptiform abnormalities. Mild disturbance of background activity.	Brain atrophy	
8	Interictal	Right centro-temporo-parietal intermittent epileptiform and slow-wave abnormalities. Moderate disturbance of background activity.	Brain atrophy, vascular changes in white matter, right HC volume ↓	5.5
9	Interictal	Widespread intermittent slow-wave abnormality over right hemisphere, intermittent focal slow-wave abnormality over left temporal region. Moderate disturbance of background activity.	Right MCA infarction, bilateral aneurysm clips in MCA bifurcations	4.3

Abbreviations: EEG, electroencephalography; HC, hippocampus; MCA, middle cerebral artery; MRI, magnetic resonance imaging; S-NSE, serum neuron-specific enolase.

5.5.3. MRI findings

5.5.3.1. Visual inspection of MR images

The qualitative MRI findings of status epilepticus patients in the series of studies after the insult are shown in Table 18. Visual inspection revealed no obvious changes in the medial temporal lobe structures during the 1-year follow-up period. Five of the nine study patients (Patients 2, 3, 4, 5, and 9) were also examined with qualitative MRI 2 to 24 months prior to the status epilepticus. A visual comparison indicated no difference between the MRI findings before and after status epilepticus in these patients. The study included four patients (Patients 3, 4, 5, and 8) with pre-existing unilateral hippocampal atrophy. Additionally, the T2 signal intensity was constantly increased in three of them.

5.5.3.2. Volumetry of the hippocampus

The mean left hippocampal volume was significantly smaller in patients with status epilepticus than in controls as studied 3 weeks, 6 months, and 12 months after the status epilepticus ($p<0.05$). There was no difference in the mean right hippocampal volumes between controls and patients with status epilepticus. The left hippocampal volume had ≥2 SD reduction of the control mean in four of the nine (44%) patients in the study. Correspondingly, a volume reduction of ≥2 SD of the right hippocampus was observed in two of the nine (22%) patients. One patient (Patient 9) had bilateral hippocampal atrophy.

There was no difference in hippocampal volumes were measured 3 weeks or 12 months after status epilepticus. Correspondingly, there were no differences between the volumes of the hippocampi studied 3 weeks and 6 months, or 6 months and 12 months after the insult. There were no patients with progressive ≥2 SD hippocampal volume reduction during the long-term follow-up.

5.5.3.3. Volumetry of the amygdala

The mean amygdaloid volumes did not differ between controls and patients studied 3 weeks, 6 months, and 12 months after the insult. At least a 2-SD reduction in the volume of the left amygdala was observed in two (25%) of the eight patients. One of these two patients had amygdaloid damage bilaterally (1/8, 13%; Patient 3).

There were no statistically significant differences between the amygdaloid volumes studied at 3 weeks and 12 months after the status epilepticus. Correspondingly, there was no difference in the amygdaloid volumes measured at 3 weeks and 6 months or at 6 months and 12 months after status epilepticus. There were no patients with progressive volume reduction of ≥2 SD in the left or right amygdala over the 12 months follow-up period.

5.5.3.4. Volumetry of the entorhinal and perirhinal cortices

There was no difference in the mean volumes of the entorhinal and perirhinal cortices between controls and patients studied at different time points. There were no patients with a volume reduction of ≥2 SD in the entorhinal cortex. One patient had a volume reduction of ≥2 SD in the left perirhinal cortex (1/8, 13%; Patient 8).

The volumes of the entorhinal and perirhinal cortices measured at 3 weeks and 12 months, 3 weeks and 6 months, or 6 months and 12 months after the status epilepticus did not differ from each other. Furthermore, none of the patients had a progressive volume reduction of ≥2 SD during the 12-month follow-up period.

6. DISCUSSION

Few data are available on the temporal appearance and progression of structural damage observed in TLE patients. In the present series of studies, the hippocampal and amygdaloid damage were assessed with quantitative MRI first in newly diagnosed and chronic TLE patients (I, II) and then, to widen the scope of the study, in partial epilepsy patients during the course of seizure disorder (III). Furthermore, as the surrounding cortical areas including the entorhinal and perirhinal cortices are functionally interconnected with the hippocampus and the amygdala, the volume of the entorhinal cortex was measured in chronic TLE patients (IV). Previous studies have shown that progressive neuronal damage may develop after prolonged seizure episodes. To investigate in a longitudinal study the appearance of structural damage in patients with status epilepticus, the volumes of the hippocampus, amygdala, entorhinal and perirhinal cortices were measured repeatedly during one year follow-up after the insult (V).

6.1. METHODOLOGICAL CONSIDERATIONS

6.1.1. Study methods and material

Studies I-IV in the present series represent a large sample of patients with varying severity of epilepsy, as found in routine clinical practice, rather than only surgical candidates with intractable epilepsy. We were able to include patients with milder forms of epilepsy, as the Department of Neurology in Kuopio University Hospital serves as a primary site of treatment for all patients with seizure disorder in the district and not solely as a tertiary referral center. Importantly, the findings in the series of studies might not have been found had it not been for the large study population with variable and long duration of TLE. This may partly explain why previous MRI reports based on a smaller number of patients clustered at the more severe end of the continuum have not shown any correlations suggesting progressive hippocampal volume reduction (Cendes et al., 1993a,d; Trenerry et al., 1993b; Kuzniecky et al., 1996; Van Paesschen et al., 1997a).

The contradiction between earlier study results and the present data might also be related to methodological difficulties in human studies to reliably quantify the duration of seizure history and the number of seizures the patient has experienced. Whereas retrospective calculation of seizures is always subject to error, the patients included in the present series of studies (I-IV) had been under the care of a neurologist at Kuopio University Hospital for most of their epilepsy history, and the calculation of total seizure number was based on hospital records of the patients collected over the years. All study patients were directed to keep meticulous seizure calendars, if necessary with the help of a responsible relative, and visited the neurologist regularly depending on the seizure frequency (at least once a year), which improved the accuracy of the seizure count. Overall, even considering that some variation existed in the seizure count using retrospective methods, the total lifetime seizure number is more likely to be underestimated than the opposite.

According to careful calculation from the hospital records and the collected seizure calendars, the median total seizure number in 259 study patients (III) was 250 (range 2 to 16625). In patients with frequent seizures, the median total seizure number was 663 (mean seizure number ± standard deviation 1489±2357). Conversely, patients with rare seizures had a median total seizure number of 4 (mean seizure number ± standard deviation 7±9). The determination of the cut off number of seizures the patients had experienced (rare seizures = ≤2 seizures per year, frequent seizures = >2 seizures per year) was based on clinical treatment principles of epilepsy in the Department of Neurology at Kuopio University Hospital. According to the therapy scheme used, an epilepsy patient is generally regarded as well-controlled if he experiences up to two seizures per year. However, the epilepsy is regarded as drug-resistant, and more effective treatment is required, if there are more than two seizures per year.

Such a low cut off number may have led to different sizes of the various subgroups, with the frequent seizure group being more heterogeneous in terms of seizure frequency. On the other hand, the classification served the aim of the series of studies, which was to further improve the management of epilepsy patients in clinical practice: i.e. to answer the question, do patients with good seizure control during the years of epilepsy have less structural damage than those with recurrent seizures?

The design used in studies I-IV was cross-sectional. Therefore, the data are suspect for several kinds of bias: for example, accumulation of refractory cases with damage caused by an initial injury into a patient group with long duration of epilepsy (Semah et al., 1998), and a drop-out of seizure-free patients from the follow-up. Contrary to the prospective follow-up method used in study V, these studies did not include serial MRI scans to track the development of hippocampal atrophy in individual patients across time. The results showed significant group differences, but predicting any individual patient's clinical and pathological features would be problematic. Thus, our studies could only infer a causal relationship between seizures and hippocampal damage, suggesting progressivity. Future prospective studies, some of which are already ongoing (Kälviäinen et al., 1997; Van Paesschen et al., 1998), will be able to provide an answer to the question of whether the structural damage represents the consequence and end state of years of poorly controlled epilepsy. However, while waiting for the results of follow-up studies, a cross-sectional study design still provides another informative approach (Sutula and Hermann, 1999).

6.1.2. Quantitative MRI

The principle role of MRI is in the definition of structural abnormalities that underlie seizure disorders (see review, Duncan, 1997). While marked damage in the structures of the medial temporal lobe is reliably identified with quantitative MRI (Jack et al., 1990; Bronen et al., 1991; Watson et al., 1992; Cendes et al., 1993a; Insausti et al., 1998), subtle forms of cell loss may remain below the detection threshold of current MRI volumetric measurement techniques. In the present series of studies (I-V), the boundaries of the hippocampus, amygdala, and entorhinal and perirhinal cortices were outlined on successive coronal MR images. The volumes for each cortical area were then calculated using an in-house program. However, neuronal loss can be restricted focally along the rostrocaudal axis of the hippocampus (Jackson et al., 1994; Kucniecky et al., 1996) or in a specific nucleus of the amygdala (Pitkänen et al., 1998), or in a specific cortical layer (Du et al., 1995; Mikkonen et al., 1998). Therefore, we cannot exclude the possibility that the imaging technique used in the studies was not sensitive enough to detect a subfield-specific damage in the structures of interest.

Another relevant factor is that the 2-SD limit from the mean of the controls, used in the studies (I-V) as the limit of abnormality, may exclude patients with mild pathologic changes in the medial temporal lobe structures (Quigg et al., 1997b). Hippocampal sclerosis defined by marked atrophy and T2 time prolongation in MRI is likely to represent the end of the continuum of various degrees of structural damage, not an absolute cut-off point to distinguish abnormal from normal hippocampus.

In the prospective follow-up study after status epilepticus (V), the first MRI was taken up to three weeks after the insult. Therefore, some signs of acute damage could have resolved and escaped observation before the initial scan. We did detect an elevated s-NSE level in Patient 6 with the longest status epilepticus (4 h 30 min), providing indirect *in vivo* evidence for at least a transient seizure-induced neuronal injury. The last follow-up MRI of the patients with status epilepticus was performed 12 months after the insult. Previous reports indicate that the duration of the follow-up was adequate to demonstrate the development of progressive damage (Nohria et al., 1994; Tien and Felsberg, 1995; Meierkord et al., 1997; Wieshmann et al., 1997).

6.1.3. Normalization of volumes

Larger people tend to have larger heads, brains, and hippocampi (Jack, 1996). Hippocampal volumes of men are larger on average than those of women. However, this is accounted for by the difference in head size. Therefore, in comparing absolute volumes among different groups, the measured volume values should be scaled by the measure of head size (Jack, 1996). The commonly used normalization variables in the literature are intracranial or intracerebral volumes (Jack et al., 1990; Cendes et al., 1993d; Free et al., 1995; Van Paesschen et al., 1997a). We found that in normal persons the brain volume correlated with the brain area measured at the level of the anterior commissure. Moreover, since there was a linear relationship between the volume of the hippocampus or the amygdala and the brain area (I-III), the volumes of the hippocampus and the amygdala were normalized using brain area as a variable to correct the inter-individual variance in head size.

Although the hippocampal volume correlated with the brain area of controls in study IV, the volume of the entorhinal cortex did not. Why this is the case remains to be studied. However, it seems unlikely that some medial temporal lobe structures require normalization, while others do not. Therefore, normalization was performed for the raw volumes of the hippocampus, amygdala, and entorhinal and perirhinal cortices in the series of studies (I-V).

6.2. INITIAL INSULT PREDICTING MEDIAL TEMPORAL LOBE DAMAGE

6.2.1. Status epilepticus

The major finding of the quantitative MRI study (V) after status epilepticus was that a prolonged seizure episode did not lead to progressive volume reduction in the medial temporal lobe structures of adult patients treated in hospital with a predetermined protocol. However, both histologic and imaging studies have previously observed damage in the hippocampus, amygdala and surrounding cortical areas in status epilepticus patients (Falconer et al., 1964; Corsellis and Bruton, 1983; Nohria et al., 1994; Wieshmann et al., 1997). In animal models, the severity and duration of seizure activity correlate with the extent and severity of damage (Schwob et al., 1980; Nevander et al., 1985; O'Shaughnessy et al., 1986; Tuunanen et al., 1996). Furthermore, recent imaging studies have described progressive hippocampal atrophy in patients with generalized status epilepticus lasting for two weeks (Wieshmann et al., 1997) or after several relapsing status epilepticus episodes (Nohria et al., 1994). In the present study (V), the mean duration of secondarily generalized tonic-clonic status epilepticus was 1 h and 44 min (range 45 min-4 h 30 min) and the EEGs obtained soon after the successful clinical recovery from status revealed no persistent seizure activity. Thus, it is likely that the prompt treatment of status prevented or reduced cellular events which might result in damage in the medial temporal lobe. Moreover, in eight of the nine study patients the cause of status epilepticus was a chronic process, including preexisting epilepsy and sequelae to brain tumor operation. Generally, these patients respond well to antiepileptic therapy and recover from the acute episode of status epilepticus (Lowenstein and Alldredge, 1998).

6.2.2. Complex febrile convulsions

There was a 16-fold increased risk of hippocampal and a 12-fold increased risk of amygdaloid volume reduction in all TLE patients with a history of complex febrile convulsions compared with those who did not have complex febrile convulsions in their medical history (III). Several previous MRI studies have reported a correlation between childhood febrile seizures and hippocampal damage (Kuks et al., 1993; Harvey et al., 1995; Barr et al., 1997; Bronen et al., 1997; Theodore et al., 1999). Cendes et al. (1993b) demonstrated that in addition to the atrophy in the hippocampus, prolonged febrile convulsions also correlate with a decreased amygdala volume. Perhaps the most convincing evidence linking complex

febrile seizures and hippocampal atrophy comes from a follow-up study of VanLandingham et al. (1998), who reported acute hippocampal injury evolving to hippocampal atrophy after complex febrile convulsions. Together, the data provided support for the hypothesis that a history of complex febrile convulsions constitute a significant etiologic factor in TLE.

6.2.3. Intracranial infection

Besides complex febrile convulsions, intracranial infection was an initial insult that predicted amygdaloid volume reduction in TLE patients (III). The patients who had suffered from intracranial infection had a 14-fold risk of amygdaloid atrophy compared with those who had not had intracranial infection. Previously, herpes simplex encephalitis has been reported to cause widespread damage to various brain areas, including both the amygdala and the hippocampus (Kapur et al., 1994). In contrast to the unilateral hippocampal volume loss found in TLE patients with a history of febrile convulsions, the damage may be bilateral in patients with a history of encephalitis or meningitis (Free et al., 1996).

6.2.4. Age at the onset of initial insult

The data obtained in study III demonstrated that all TLE patients who were 5 years old or younger at the onset of first spontaneous seizure were more likely to have hippocampal volume reduction and T2 time prolongation (unpublished data) than those who were older than 5 years at the onset of seizures. Moreover, the re-evaluation of the raw data in study I, taking into account the age at onset of seizure disorder, showed that the early onset of TLE was one of the determinants for the development of hippocampal damage in chronic TLE (Kälviäinen et al., 1999). Our findings are in line with those in previous data recognizing hippocampal sclerosis and young age of seizure onset as common features of the syndrome of mesial temporal lobe epilepsy (Engel, 1996). Duncan and Sagar (1987) showed that surgically treated TLE patients with Ammon's horn sclerosis had their first convulsion at the mean age of 2.2 years and first partial seizure at the mean age of 5.5 years. More recently, correlative analyses in MRI studies have demonstrated a significant association between hippocampal damage and the early onset of seizures (Trenerry et al., 1993b; Lehericy et al., 1997; Van Paesschen et al., 1997a). In a qualitative MRI study, patients with a normal hippocampus had an older age of seizure onset than patients with hippocampal damage (Lehericy et al., 1997). Confirming the visually assessed results, Van Paesschen et al. (1997a) reported that intractable TLE patients with hippocampal atrophy were significantly younger at the onset of epilepsy than patients with normal hippocampal MRI measures. Based on the previous data, it has been suggested that childhood-onset and adult-onset TLE may be different entities, each with a different course of disease. Since both groups were included in the present studies, one can debate the question of whether those patients with more severe hippocampal sclerosis had refractory epilepsy initially (Semah et al., 1998). Due to the limited number of patients with seizure onset $\leq$5 years of age (n=25) in the present studies (I-V), we could not examine hippocampal volumes of patient groups with childhood onset and adult onset TLE separately. Logistic regression analysis did show in a subgroup of patients with seizure onset >5 years of age that complex febrile convulsions and high lifetime seizure number remained as predictive factors for hippocampal volume reduction.

A corresponding association with structural damage and early onset of epilepsy was not observed in the amygdala (III). In fact, amygdaloid T2 time prolongation was associated with older age of seizure onset (unpublished data). Interestingly, a previous histological study by Miller et al. (1994) reported that patients with isolated amygdaloid sclerosis did not have a clinical history of seizures in early childhood, suggesting a different pathogenesis of damage.

6.3. DAMAGE IN THE ENTORHINAL CORTEX OF CRYPTOGENIC TEMPORAL LOBE EPILEPSY PATIENTS

Our data (IV) indicate that the entorhinal cortex is damaged in a subgroup of patients with cryptogenic TLE. In most cases, entorhinal volume reduction was associated with hippocampal damage. Altogether 73% of patients with over 25% entorhinal damage had hippocampal atrophy. Further, in 50% of cases, hippocampal damage was associated with entorhinal damage. Therefore, in a substantial percentage of cases with TLE , the damage occurs in more than one structure of the medial temporal lobe.

An other factor associated with entorhinal damage was the duration of epilepsy. However, unlike hippocampal damage (III), entorhinal damage was no more severe in patients with the onset of epilepsy <5 years of age than in patients with later onset of epilepsy. There was not such a clear association between the lifetime seizure number and entorhinal damage as previously found with hippocampal damage. This suggests that the hippocampus may be a more sensitive structure for seizure-induced damage than the entorhinal cortex.

In the present study, the appearance of entorhinal damage had a limited value as a lateralizing measure. There was no difference in the mean entorhinal volumes ipsilateral to the seizure focus, unlike Bernasconi et al. (1999) reported earlier. The discrepancy may partly relate to the difference between the two study groups. Although the largest reduction in the volume of the entorhinal cortex was 42%, overall the TLE and brain damage were less severe than they were in the study by Bernasconi et al. (1999). The assumption of difference in the severity of TLE between two study groups is supported by the finding that the asymmetry indexes for the hippocampus, amygdala and the entorhinal cortex were less abnormal. Together with data from previous histological and imaging studies (Du et al., 1993, Mikkonen et al., 1998; Bernasconi et al., 1999), these data emphasize the fact that damage outside the hippocampus has to be taken into account when tracing the structural substrates for TLE.

6.4. HIPPOCAMPAL AND AMYGDALOID DAMAGE IN EXTRATEMPORAL AND UNCLASSIFIED PARTIAL EPILEPSY

Some ETE/UC patients in the present study (III) had hippocampal or amygdaloid damage. The data obtained, however, did not indicate any association between the duration of epilepsy and the occurrence of damage. Previous imaging studies have also recognized hippocampal damage in patients with extratemporal partial epilepsy (Cascino et al., 1993; Adam et al., 1994; Baulac et al., 1994; Fish and Spencer, 1995). For example, Adam et al. (1994) found hippocampal atrophy in 29% of patients with extratemporal epilepsy and in 6% of patients with unclassified partial epilepsy. When interpreting the present results one must keep in mind that the study group of patients with unclassified partial epilepsy may have included patients with undetected temporal lobe seizure focus. The possibility cannot be excluded that some of those unclassified partial epilepsy patients with a significant volume reduction actually had a focus of temporal origin.

6.5. DAMAGE IN CRYPTOGENIC AND SYMPTOMATIC TEMPORAL LOBE EPILEPSY PATIENTS

None of the cryptogenic epilepsy patients with MRI-detected hippocampal damage had an initial insult in their medical history (I, III). We found chronic cryptogenic drug-resistant TLE patients who had significant hippocampal volume reduction and T2 time prolongation on the focal side (I). These patients did not have any potential etiologic factors underlying the seizures, including complex febrile convulsions. In study II, amygdaloid damage was observed in approximately one-fifth of patients with both symptomatic and cryptogenic etiology. Moreover, most of the patients with damage in the

amygdala had chronic TLE. Earlier, Mathern et al. (1995) suggested that although most of the hippocampal damage occurs with the acquired injury, there can be additional neuronal loss associated with long seizure histories. The present results indicate that the appearance of hippocampal and amygdaloid damage did not depend on the cryptogenic or symptomatic etiology of TLE (III). In both cryptogenic and symptomatic patient groups, however, the number of patients with hippocampal damage increased over time (III).

6.6. RECURRENT SEIZURES

The question of whether intractable epilepsy with recurrent seizures can cause or aggravate structural damage in the temporal lobe is a long-standing issue with important implications for the management of epilepsy in particular. To answer the question, we investigated with MRI volumetry and T2 relaxometry TLE patients at the onset of their seizure disorder, and compared the presence and magnitude of structural abnormalities in these patients and in patients with chronic epilepsy (I, II, III).

6.6.1. Hippocampal and amygdaloid damage at the onset of epilepsy

Our data indicate that structural damage in TLE at the time of the first spontaneous seizures is mild (III). Only 5% of patients with ≤1 year of TLE had a unilateral hippocampal or amygdaloid volume reduction of ≥2 SD. Furthermore, there was no detectable reduction in the mean hippocampal or amygdaloid volumes. Correspondingly, no damage was observed in the mean hippocampal volumes when newly diagnosed cryptogenic TLE patients were compared with controls (I). Moreover, in newly diagnosed TLE patients, the mean volume of the amygdala did not differ from that in controls (II). Van Paesschen et al. (1997c) found hippocampal sclerosis in 10% of newly diagnosed partial epilepsy patients referred to neurology clinics. Their findings are comparable with the present data, considering that the Department of Neurology in Kuopio University Hospital serves as a primary site of treatment for all patients with newly-diagnosed seizure disorder in the district.

6.6.2. Hippocampal damage in chronic TLE patients

No detectable hippocampal volume reduction or T2 time prolongation was found in cryptogenic chronic well-controlled TLE patients, compared with controls (I). However, chronic drug-resistant patients had approximately a 16% reduction in the hippocampal volume and a significant prolongation of T2 time ipsilaterally.

Correspondingly, when controls and patients with different durations of TLE were compared, the mean right hippocampal volume was significantly reduced in patients with ≥21 years of right TLE (III). Furthermore, there was a significant prolongation of the mean T2 relaxation time in the hippocampus on the focal side in patients with ≥21 years of TLE (unpublished data). We could not statistically show differences in the mean volume of the left hippocampus in left TLE patients over years. However, there was a clear trend towards a smaller left hippocampus in patients with ≥21 years of left TLE.

The findings are consistent with the time course of the increased neuron losses described in the histopathological studies of both Mouritzen Dam's (1980) and Mathern et al. (1995). Mouritzen Dam (1980) reported that patients with seizure histories longer that 30 years and/or increased frequency of generalized seizures showed greater neuron losses in all regions of the hippocampus. Mathern et al. (1995) indicated that after 22 years of epilepsy, all patients with drug-refractory TLE had at least a 60% loss of CA1 pyramidal cells. Accordingly, in the present series of patients (III), the longer the duration of TLE with frequent seizures, the higher the number of patients with hippocampal damage. The data also agree with those of a recent MRI study showing that ipsilateral hippocampal atrophy was

related to the duration of TLE in patients with uncontrolled complex partial seizures (Theodore et al., 1999).

When patients with ≥21 years of TLE were divided into subgroups according to seizure frequency, the hippocampal volume reduction and T2 time prolongation (data not published) were apparent only in the patient subgroups with frequent seizures (III). The mean T2 relaxation time was also significantly prolonged in the patient group with 11 to 20 years of frequent seizures (data not published). Compared with both visual interpretation and volumetric analysis, the definition of a normal hippocampal T2 relaxation is very precise (Jackson et al., 1993b). Therefore, the finding possibly indicates greater sensitivity of the T2 quantification to underlying hippocampal pathology (Jackson et al., 1993b; Grunewald et al., 1994; Jackson et al., 1994).

Correlation analyses showed that the more seizures the cryptogenic TLE patient had experienced, the more severe the volume reduction and the longer T2 time in the hippocampus (I). Similarly, in all TLE patients, both cryptogenic and symptomatic, hippocampal volume on the focal side correlated inversely with the total number of partial and generalized seizures (III). In line with these results, Tasch et al. (1999) reported that TLE patients with frequent generalized seizures had reduced N-acetyl aspartate (a putative MRI spectroscopic measure of neuronal number) levels bilaterally in temporal lobes and smaller hippocampal volumes ipsilaterally than patients with none or rare seizures. Convincing evidence is also provided by recent longitudinal MRI studies which have reported hippocampal changes occurring during follow-up of both newly diagnosed and intractable partial epilepsy patients (Van Paesschen et al., 1998; O'Brien et al., 1999). These histologic and neuroimaging studies together with our current data suggest that hippocampal damage may be progressive in some patients with epilepsy.

6.6.3. Amygdaloid damage in chronic TLE patients

The mean amygdaloid volume or T2 time did not significantly differ from control values in patients with chronic TLE (II), nor did the damage in the amygdala differ between patient groups with different durations of partial epilepsy or frequency of seizures (III). In all TLE patients, the volume of the right amygdala correlated with the number of generalized seizures (III). However, there was no correlation between left amygdaloid volume or T2 time on the left or right amygdala (data not published) and the seizure number (III). Approximately 20% of the chronic TLE patients had at least 20% volume reduction or T2 time prolongation in the amygdala (II). Further, amygdaloid volume reduction was observed in 10% of patients with ≥21 years of TLE, which is in accord with previous MRI studies (Cendes et al., 1993a,c). These results raise the question of whether the mechanism underlying the development of neuronal damage in the amygdala of TLE patients differs from that in the hippocampus (Hudson et al., 1993; Miller et al., 1994). According to the neuropathologic literature, the pathology of epileptogenic lesions of the amygdala may consist of a wider variety of lesions than in the hippocampus (Falconer and Cavanaugh, 1959; Bruton, 1988). While sclerosis is the predominant feature of damaged hippocampus, small tumors, cortical dysplasia and vascular anomalies may occur in the amygdala (Falconer and Cavanaugh, 1959; Bruton, 1988).

6.7. FUTURE STUDIES

The findings of the present series of studies support the idea that damage in the medial temporal lobe structures may be both the cause and consequence of TLE. The data provide evidence that in some patients hippocampal disease may progress as a function of repeated seizures. Future longitudinal studies are likely to be more thorough in fully exploring the effects of age of onset, repeated seizures, and duration of seizures. Already there are ongoing prospective MRI studies on newly diagnosed patients with epilepsy, which will hopefully gain further insights on the development of damage in TLE (Kälviäinen et al., 1997; Van Paesschen et al., 1998). However, our findings suggest that it may be

decades before prospective long-term brain imaging studies reveal the causes of a decline in brain structures of patients with intractable TLE. Meanwhile, the accumulating evidence of the deleterious effects of persistent seizures argue for efficient drug therapy or early surgery to reach complete seizure control. In future research should address strategies for disease-modifying therapies and ultimately the remission of epileptic process.

7. CONCLUSIONS

7.1. Chronic cryptogenic drug-resistant TLE patients have smaller mean hippocampal volumes and T2 relaxation times in the body of the hippocampus ipsilateral to the seizure focus than controls. The total number of partial and generalized seizures that left TLE patients have experienced during their lifetime correlate negatively with the left hippocampal volume and positively with the left hippocampal T2 relaxation time. In patients with cryptogenic epilepsy, recurrent seizures may cause damage to the hippocampus throughout the lifetime of the patient.

7.2. The mean amygdaloid volumes in chronic and newly diagnosed TLE patients do not differ from the mean amygdaloid volumes in controls. However, about 20% of chronic patients have ≥20% volume reduction and T2 time prolongation in the amygdala. At the time of diagnosis, the amygdaloid volume is reduced in 4% and T2 time is prolonged in 15% of patients. The ipsilateral amygdaloid volume correlates negatively with the total lifetime seizure number in all TLE patients.

7.3. a) High lifetime seizure number, complex febrile convulsions in the medical history and early age at the onset of spontaneous seizures contribute to hippocampal damage in patients with TLE. The risk factors that predict amygdaloid volume reduction are intracranial infection and complex febrile seizures. Unlike in the hippocampus, the onset of epilepsy over 5 years of age is a risk factor for T2 time prolongation in the amygdala.

b) Damage in the hippocampus or in the amygdala is rare at the time of first spontaneous seizures in TLE.

c) Hippocampal damage is apparent in chronic TLE patients with years of frequent seizures, but not in patients with rare seizures. Ipsilateral hippocampal volume correlates negatively and T2 relaxation time positively with the lifetime seizure number. The severity of amygdaloid damage does not differ between TLE patients with different duration of epilepsy or seizure frequency.

d) The appearance of hippocampal or amygdaloid damage does not differ when TLE patient groups with cryptogenic and symptomatic etiology are compared with each other.

e) The appearance of hippocampal or amygdaloid damage in patients with ETE/UC differs from that in patients with TLE. Unlike between TLE patients and controls, there are no differences in the hippocampal and amygdaloid volumes and T2 relaxation times between patients with different durations of ETE/UC and controls.

7.4. The mean volumes of the entorhinal cortex ipsilateral to the epileptic focus in cryptogenic TLE patients do not differ from those in controls. However, the entorhinal cortex is damaged in a subpopulation of patients with TLE. In most cases, entorhinal volume reduction is associated with hippocampal damage. Additionally, the volume of the entorhinal cortex correlates with the duration of TLE.

7.5. Status epilepticus does not invariably lead to the development of marked volume reduction of the hippocampus, amygdala, or the entorhinal and perirhinal cortices in adult patients treated promptly in hospital with a predetermined protocol.

REFERENCES

Abou-Khalil B, Andermann E, Andermann F, Olivier A, Quesney LF. Temporal lobe epilepsy after prolonged febrile convulsions: excellent outcome after surgical treatment. Epilepsia 1993; 34: 878-883.

Adam C, Baulac M, Saint-Hilaire J-M, Landau J, Granat O, Laplane D. Value of magnetic resonance imaging-based measurements of hippocampal formations in patients with partial epilepsy. Arch Neurol 1994; 51: 130-138.

Aggleton JP. A description of the amygdalo-hippocampal interconnections in the macaque monkey. Exp Brain Res 1986; 64: 515-526.

Amaral DG. Amygdalohippocampal and amygdalocortical projections in the primate brain. In: Excitatory Amino Acids and Epilepsy. Eds. Schwarcz R, Ben-Ari Y. Plenum, New York, 1986; 3-17.

Amaral DG. Memory: anatomical organization of candidate brain regions. In: Handbook of Physiology – The Nervous System V. Ed. Mountcastle VB. The Williams & Wilkins Company, Baltimore, 1987; 211-294.

Amaral DG, Insausti R. Hippocampal formation. In: The Human Nervous System. Ed. Paxinos G. Academic Press, San Diego, 1990; 711-755.

Amaral DG, Insausti R, Cowan WM. The commissural connections of the monkey hippocampal formation. J Comp Neurol 1984; 224; 307-336.

Amaral DG, Price JL, Pitkänen A, Carmichael ST. Anatomical organization of the primate amygdaloid complex. In: The Amygdala. Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction. Ed. Aggleton JP. Wiley-Liss, New York, 1992; 1-66.

Annegers JF. The epidemiology of epilepsy. In: The Treatment of Epilepsy: Principles and Practice. 2nd ed. Ed. Wyllie E. Williams & Wilkins, Baltimore, 1996; 165-172.

Annegers JF. Mortality. In: Epilepsy. The Comprehensive CD-ROM. Eds. Engel J Jr, Pedley T. Lippincott Williams and Wilkins, Baltimore MD, 1999.

Annegers JF, Grabow JD, Groover RV, Laws ER Jr, Elveback LR, Kurland LT. Seizures after head trauma: a population study. Neurology 1980; 30: 683-689.

Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. Epilepsia 1979; 20: 729-737.

Arruda F, Cendes F, Andermann F, Dubeau F, Villemure JG, Jones-Gotman M, Poulin N, Arnold DL, Olivier A. Mesial atrophy and outcome after amygdalohippocampectomy or temporal lobe removal. Ann Neurol 1996; 40: 446-450.

Babb TL, Brown WJ. Pathological findings in epilepsy. In: Surgical Treatment of the Epilepsies. Ed. Engel J Jr. Raven Press, New York, 1987; 511-540.

Babb TL, Kupfer WR, Pretorius JK, Crandall PH, Levesque MF. Synaptic reorganization by mossy fibers in human epileptic fascia dentata. Neuroscience 1991; 42: 351-364.

Babb TL, Lieb JP, Brown WJ, Pretorius J, Crandall PH. Distribution of pyramidal cell density and hyperexcitability in the epileptic human hippocampal formation. Epilepsia 1984; 25: 721-728.

Baldwin GN, Tsuruda JS, Maravilla KR, Hamill GS, Hayes CE. The fornix in patients with seizures caused by unilateral hippocampal sclerosis: Detection of unilateral volume loss on MR images. AJR 1994; 162: 1185-1189.

Bancaud J, Brunet-Bourgin F, Chauvel P, Halgren E. Anatomical origin of deja vu and vivid ”memories” in human temporal lobe epilepsy. Brain 1994; 117: 71-90.

Baram TZ, Ribak CE. Peptide-induced infant status epilepticus causes neuronal death and synaptic reorganization. NeuroReport 1995; 6: 277-280.

Barr WB, Ashtari M, Schaul N. Bilateral reductions in hippocampal volume in adults with epilepsy and a history of febrile seizures. J Neurol Neurosurg Psychiatry 1997; 63: 461-467.

Baulac M, Saint-Hilaire JM, Adam C, Martinez M, Fontaine S, Laplane D. Correlations between magnetic resonance imaging-based hippocampal sclerosis and depth electrode investigation in epilepsy of the mesiotemporal lobe. Epilepsia 1994; 35: 1045-1053.

Beach TG, Woodhurst WB, MacDonald DB, Jones MW. Reactive microglia in hippocampal sclerosis associated with human temporal lobe epilepsy. Neurosci Lett 1995; 191: 27-30.

Beghi E, Tognoni G. Prognosis of epilepsy in newly referred patients: A multicenter prospective study. Collaborative Group for the Study of Epilepsy. Epilepsia 1988; 29; 236-243.

Berkovic SF, Andermann F, Olivier A, Ethier R, Melanson D, Robitaille Y, Kuzniecky R, Peters T, Feindel W. Hippocampal sclerosis in temporal lobe epilepsy demonstrated by magnetic resonance imaging. Ann Neurol 1991; 29: 175-182.

Bernasconi N, Bernasconi A, Andermann F, Dubeau F, Feindel W, Reutens DC. Entorhinal cortex in temporal lobe epilepsy. A quantitative MRI study. Neurology 1999; 52: 1870-1876.

Bigler ED, Blatter DD, Anderson CV, Johnson SC, Gale SD, Hopkins RO, Burnett B. Hippocampal volume in normal aging and traumatic head injury. AJNR 1997; 18: 11-23.

Bill PA, Vigonius U, Pohlmann H, Guerreiro CAM, Kochen S, Saffer D, Moore A. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. Epilepsy Res 1997; 27: 195-204.

Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1: 307-310.

Bleck TP. Convulsive disorders: status epilepticus. Clin Neuropharmacol 1991; 14: 191-198.

Braak H, Braak E, Yilmazer D, Bohl J. Functional anatomy of human hippocampal formation and related structures. J Child Neurol 1996; 11: 265-275.

Bragdon AC, Kojima H, Wilson WA. Suppression of interictal bursting in hippocampus unleashes seizures in entorhinal cortex: a proepileptic effect of lowering $[K+]o$ and raising $[Ca\ 2+]o$. Brain Res 1992; 590: 128-135.

Breier JI, Leonard CM, Bauer RM, Roper S, Lucas TH, Gilmore RL. Quantified volumes of temporal lobe structures in patients with epilepsy. J Neuroimaging 1996; 6: 108-114.

Breier JI, Mullani NA, Thomas AB, Wheless JW, Plenger PM, Gould KL, Papanicolaou A, Willmore LJ. Effects of duration of epilepsy on the uncoupling of metabolism and blood flow in complex partial seizures. Neurology 1997; 48: 1047-1053.

Briellman RS, Jackson GD, Kalnins R, Berkovic SF. Hemicranial volume deficits in patients with temporal lobe epilepsy with and without hippocampal sclerosis. Epilepsia 1998; 39: 1174-1181.

Brodie MJ, Richens A, Yuen AWC. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. Lancet 1995; 345: 476-479.

Brodmann K. Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellet auf Grund des Zellenbaues. Barth, Leipzig, 1909.

Bronen RA, Cheung G, Charles JT, Kim JH, Spencer DD, Spencer SS, Sze G, McCarthy G. Imaging findings in hippocampal sclerosis: correlation with pathology. AJNR 1991; 12: 933-940.

Bronen RA, Fulbright RK, Kim JH, Spencer SS, Spencer DD, Al-Rodhan NRF. Regional distribution of MR findings in hippocampal sclerosis. AJNR 1995; 16: 1193-1200.

Bronen RA, Fulbright RK, King D, Kim JH, Spencer SS, Spencer DD, Lange RC. Qualitative MR imaging of refractory temporal lobe epilepsy requiring surgery: correlation with pathology and seizure outcome after surgery. AJR 1997; 169: 875-882.

Brooks BS, King DW, El Gammal T, Meador K, Yaghmai F, Gay JN, Smith JR, Flanigin HF. MR imaging in patients with intractable complex partial epileptic seizures. AJR 1990; 154: 577-583.

Bruton CJ. The neuropathology of temporal lobe epilepsy. Institute of Psychiatry, Maudsley monographs, number thirty-one. Oxford University Press, New York, 1988.

Cascino GD, Jack CR Jr, Parisi JE, Marsh WR, Kelly PJ, Sharbrough FW, Hirschorn KA, Trenerry MR. MRI in the presurgical evaluation of patients with frontal lobe epilepsy and children with temporal lobe epilepsy: pathologic correlation and prognostic importance. Epilepsy Res 1992; 11: 51-59.

Cascino GD, Jack CR Jr, Parisi JE, Sharbrough FW, Hirschorn KA, Meyer FB, Marsh WR, O'Brien PC. Magnetic resonance imaging-based volume studies in temporal lobe epilepsy: pathological correlations. Ann Neurol 1991; 30: 31-36.

Cascino GD, Jack CR Jr, Sharbrough FW, Kelly PJ, Marsh WR. MRI assessments of hippocampal pathology in extratemporal lesional epilepsy. Neurology 1993; 43: 2380-2382.

Cavalheiro AE, Leite JP, Bortolotto ZA, Turski WA, Ikonomidou C, Turski L. Long-term effects of pilocarpine in rats: structural damage of the brain triggers kindling and spontaneous recurrent seizures. Epilepsia 1991; 32: 778-782.

Cavanagh JB, Meyer A. Aetiological aspects of Ammon's horn sclerosis associated with temporal lobe epilepsy. BMJ 1956; 2: 1403-1407.

Cavazos JE, Das I, Sutula TP. Neuronal loss induced in limbic pathways by kindling: evidence for induction of hippocampal sclerosis by repeated brief seizures. J Neurosci 1994; 14: 3106-3121.

Cavazos JE, Sutula TP. Progressive neuronal loss induced by kindling: a possible mechanism for mossy fiber synaptic reorganization and hippocampal sclerosis. Brain Res 1990; 527: 1-6.

Cendes F, Andermann F, Carpenter S, Zatorre RJ, Cashman NR. Temporal lobe epilepsy caused by domoic acid intoxication: evidence for glutamate receptor-mediated excitotoxicity in humans. Ann Neurol 1995c; 37: 123-126.

Cendes F, Andermann F, Dubeau F, Arnold DL. Proton magnetic resonance spectroscopic images and MRI volumetric studies for lateralization of temporal lobe epilepsy. Magn Reson Imaging 1995b; 13: 1187-1191.

Cendes F, Andermann F, Dubeau F, Gloor P, Evans A, Jones-Gotman M, Olivier A, Andermann E, Robitaille Y, Lopes-Cendes I, Peters T, Melanson D. Early childhood prolonged febrile convulsions, atrophy and sclerosis of mesial structures, and temporal lobe epilepsy: an MRI volumetric study. Neurology 1993b; 43: 1083-1087.

Cendes F, Andermann F, Gloor P, Evans A, Jones-Gotman M, Watson C, Melanson D, Olivier A, Peters T, Lopes-Cendes I, Leroux G. MRI volumetric measurements of amygdala and hippocampus in temporal lobe epilepsy. Neurology 1993a; 43: 719-725.

Cendes F, Andermann F, Gloor P, Gambardella A, Lopes-Cendes I, Watson C, Evans A, Carpenter S, Olivier A. Relationship between atrophy of the amygdala and ictal fear in temporal lobe epilepsy. Brain 1994; 117: 739-746.

Cendes F, Andermann F, Gloor P, Lopes-Cendes I, Andermann E, Melanson D, Jones-Gotman M, Robitaille Y, Evans A, Peters T. Atrophy of mesial structures in patients with temporal lobe epilepsy: cause or consequence of repeated seizures. Ann Neurol 1993d; 34: 795-801.

Cendes F, Caramanos Z, Andermann F, Dubeau F, Arnold DL. Proton magnetic resonance spectroscopic imaging and magnetic resonance imaging volumetry in the lateralization of temporal lobe epilepsy: a series of 100 patients. Ann Neurol 1997; 42: 737-746.

Cendes F, Cook MJ, Watson C, Andermann F, Fish DR, Shorvon SD, Bergin P, Free S, Dubeau F, Arnold DL. Frequency and characteristics of dual pathology in patients with lesional epilepsy. Neurology 1995a; 45: 2058-64.

Cendes F, Leproux F, Melanson D, Ethier R, Evans A, Peters T, Andermann F. MRI of amygdala and hippocampus in temporal lobe epilepsy. J Comput Assisted Tomogr 1993c; 17: 206-210.

Chadwick DW, Marson T, Kadir Z. Clinical administration of new antiepileptic drugs: an overview of safety and efficacy. Epilepsia 1996; 37: S17-S22.

Cockerell OC, Johnson AL, Sander JWAS, Hart YM, Shorvon SD. Remission of epilepsy: results from the National General Practice Study of Epilepsy. Lancet 1995; 346: 140-144.

Cockerell OC, Johnson AL, Sander JWAS, Shorvon SD. Prognosis of epilepsy: a review and further analysis of the first nine years of the British National General Practice Study of Epilepsy, a prospective population-based study. Epilepsia 1997; 38: 31-46.

Collaborative Group for the Study of Epilepsy. Prognosis of epilepsy in newly referred patients: a multicenter prospective study of the effects of monotherapy on the long-term course of epilepsy. Epilepsia 1992; 33: 45-51.

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981; 22: 489-501.

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989; 30: 389-399.

Commission on Epidemiology and Prognosis of the International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia 1993; 34: 592-596.

Cook MF. Mesial temporal sclerosis and volumetric investigations. Acta Neurol Scand 1994; Suppl.152: 109-114.

Cook MJ, Fish DR, Shorvon SD, Straughan K, Stevens JM. Hippocampal volumetric and morphometric studies in frontal and temporal lobe epilepsy. Brain 1992; 115: 1001-1015.

Corsellis JAN, Bruton CJ. Neuropathology of status epilepticus in humans. In: Status Epilepticus. Advances in Neurology. Eds. Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ. Raven Press, New York, 1983; 34: 129-139.

Currie S, Heathfield G, Henson RA, Scott DF. Clinical course and prognosis of temporal lobe epilepsy. A survey of 666 patients. Brain 1971; 94; 173-190.

DeCarli C, Hatta J, Fazilat S, Fazilat S, Gaillard WD, Theodore WH. Extratemporal atrophy in patients with complex partial seizures of left temporal origin. Ann Neurol 1998; 43: 41-45.

DeGiorgio CM, Correale JD, Gott PS, Ginsburg DL, Bracht KA, Smith T, Boutros R, Loskota WJ, Rabinowicz AL. Serum neuron-specific enolase in human status epilepticus. Neurology 1995; 45: 1134-1137.

DeGiorgio CM, Tomiyasu U, Gott PS, Treiman DM. Hippocampal pyramidal cell loss in human status epilepticus. Epilepsia 1992; 33: 23-27.

DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, Garnett L, Fortner CA, Ko D. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 1996; 46: 1029-1035.

DeLorenzo RJ, Pellock JM, Towne AR, Boggs JG. Epidemiology of status epilepticus. J Clin Neurophysiol 1995; 12: 316-325.

Dichter MA. Basic mechanisms of epilepsy: targets for therapeutic intervention. Epilepsia 1997; 38(Suppl. 9): S2-S6.

Dowd CF, Dillon WP, Barbaro NM, Laxer KD. Intractable complex partial seizure: correlation of magnetic resonance imaging with pathology and electroencephalography. Epilepsy Res 1992; (Suppl. 5): S101-S110.

Du F, Eid T, Lothman EW, Köhler C, Schwarcz R. Preferential neuronal loss in layer III of the medial entorhinal cortex in rat models of temporal lobe epilepsy, J Neurosci 1995; 10: 6301-6313.

Du F, Whetsell WO Jr, Abou-Khalil B, Blumenkopf B, Lothman EW, Schwarcz R. Preferential neuronal loss in layer III of the entorhinal cortex in patients with temporal lobe epilepsy. Epilepsy Res 1993; 16: 223-233.

Duncan JS. Imaging and epilepsy. Invited Review. Brain 1997; 120: 339-377.

Duncan JS, Sagar HJ. Seizure characteristics, pathology and outcome after temporal lobectomy. Neurology 1987; 37: 405-409.

Duvernoy HM. The Human Hippocampus: An Atlas of Applied Anatomy. Ed. Bergman JF. Munchen, 1988

Earle KM, Baldwin M, Penfield W. Incisural sclerosis and temporal lobe seizures produced by hippocampal herniation at birth. Arch Neurol Psychiatr 1953; 69: 27-42.

Ebisu T, Rooney WD, Graham SH, Mancuso A, Weiner MW, Maudsley AA. MR spectroscopic imaging and diffusion-weighted MRI for early detection of kainate-induced status epilepticus in the rat. MRM 1996; 36: 821-828.

Elwes RDC, Johnson AL, Shorvon SD, Reynolds EH. The prognosis for seizure control in newly diagnosed epilepsy. N Engl J Med 1984; 311: 944-947.

Engel J Jr. Diagnostic evaluation. In : Seizures and Epilepsy. Ed. Engel J Jr. F.A. Davis Company, Philadelphia, 1989; 303-309.

Engel J Jr. Introduction to temporal lobe epilepsy. Epilepsy Res 1996; 26; 141-150.

Engel J Jr, Bandler R, Griffith NC, Caldecott-Hazard S. Neurobiological evidence for epilepsy-induced interictal disturbances. In: Advances in Neurology. Eds. Smith D, Treiman D, Trimble M. Raven Press, New York, 1991; 97-111.

Engel J Jr, Pedley TA. Introduction: what is epilepsy? In: Epilepsy. The Comprehensive CD-ROM. Eds. Engel J Jr, Pedley T. Lippincott Williams and Wilkins, Baltimore MD, 1999.

Engel J Jr, Williamson PD, Wieser H-G. Mesial temporal lobe epilepsy. In: Epilepsy. The Comprehensive CD-ROM. Eds. Engel J Jr, Pedley T. Lippincott Williams and Wilkins, Baltimore MD, 1999.

Fakhoury T, Abou-Khalil B, Peguero E. Differentiating clinical features of right and left temporal lobe seizures. Epilepsia 1994; 35: 1038-1044.

Falconer MA, Cavanagh JB. Clinico-pathological considerations of temporal lobe epilepsy due to small focal lesions. Brain 1959; 82: 483-503.

Falconer MA, Serafetinides EA, Corsellis JAN. Etiology and pathogenesis of temporal lobe epilepsy. Arch Neurol 1964; 10: 233-248.

Falconer MA, Taylor DC. Surgical treatment of drug-resistant epilepsy due to mesial temporal sclerosis. Arch Neurol 1968; 19: 353-361.

Felmlee JP. Magnetic resonance imaging principles. In: Neuroimaging in Epilepsy. Principles and Practice. Eds. Cascino GD, Jack CR Jr. Butterworth-Heinemann, Newton, MA, 1996; 1-22.

Fernandez G, Effenberger O, Vinz B, Steinlein O, Elger CE, Döhring W, Heinze HJ. Hippocampal malformation as a cause of familial febrile convulsions and subsequent hippocampal sclerosis. Neurology 1998; 50: 909-917.

Fish DR, Spencer SS. Clinical correlations: MRI and EEG. Magn Reson Imaging 1995; 13: 1113-1117.

Free SL, Bergin PS, Fish DR, Cook MJ, Shorvon SD, Stevens JM. Methods for normalization of hippocampal volumes measured with MR. AJNR 1995; 16: 637-643.

Free SL, Li LM, Fish DR, Shorvon SD, Stevens JM. Bilateral hippocampal volume loss in patients with a history of encephalitis or meningitis. Epilepsia 1996; 37: 400-405.

French JA, Williamson PD, Thadani VM, Darcey TM, Mattson RH, Spencer SS, Spencer DD. Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. Ann Neurol 1993; 34: 774-780.

Gaillard WD, Fazilat S, White S, Malow B, Sato S, Reeves P, Herscovitch P, Theodore WH. Interictal metabolism and blood flow are uncoupled in temporal lobe cortex of patients with complex partial epilepsy. Neurology 1995; 45: 1841-1847.

Gaillard WD, Weistein S, Conry J, Fazilat S, Kolodgie M, Reeves P, Kelley K, Theodore WH. Regional FDG-PET hypometabolism is related to duration of partial epilepsy. Epilepsia 1996; 37(Suppl. 5): S199.

Gambardella A, Gotman J, Cendes F, Andermann F. Focal intermittent delta activity in patients with mesiotemporal atrophy: a reliable marker of the epileptogenic focus. Epilepsia 1995; 36: 122-129.

Garcia PA, Laxer KD, Barbaro NM, Dillon WP. Prognostic value of qualitative magnetic resonance imaging hippocampal abnormalities in patients undergoing temporal lobectomy for medically refractory seizures. Epilepsia 1994; 35: 520-524.

Garcia PA, Laxer KD, van der Grond J, Hugg JW, Matson GB, Weiner MW. Correlation of seizure frequency with N-acetyl-aspartate levels determined by 1H magnetic resonance spectroscopic imaging. Magn Reson Imaging 1997; 15: 475-478.

Gastaut H. Executive Committee of the International League against Epilepsy. Clinical and EEG classification of epileptic seizures. Epilepsia 1970; 11: 102-113.

Gastaut H, Toga M, Roger J, Gibson WC. Correlation of clinical, electroencephalographic and anatomical findings in nine autopsied cases of ”temporal lobe epilepsy”. Epilepsia 1959; 1: 56-85.

Girvin JP. Is epilepsy a progressive disorder? J Epilepsy 1992; 5: 94-104.

Gloor P, Olivier A, Quesney LF, Andermann F, Horowitz S. The role of the limbic system in experiental phenomena of temporal lobe epilepsy. Ann Neurol 1982; 12: 129-144.

Goddard GV, McIntyre DC, Leech CK. A permanent change in brain function resulting from daily electrical stimulation. Exp Neurol 1969; 25: 295-330.

Goodridge DMG, Shorvon SD. Epileptic seizures in a population of 6000. I: Demography, diagnosis and classification, and role of the hospital services. II. Treatment and prognosis. Br Med J 1983; 287: 641-647.

Gowers WR. Epilepsy and Other Chronic Convulsive Diseases; Their Causes, Symptoms and Treatment. Dover, New York, 1964.

Grunewald RA, Jackson GD, Connelly A, Duncan JS. MR detection of hippocampal disease in epilepsy: factors influencing T2 relaxation time. AJNR 1994; 15: 1149-1156.

Habib M, Sirigu A. Pure topographical disorientation: a definition and anatomical basis. Cortex 1987; 23: 73-85.

Harvey AS, Berkovic SF, Wrennall JA, Hopkins IJ. Temporal lobe epilepsy in childhood: clinical, EEG, and neuroimaging findings and syndrome classification in a cohort with new-onset seizures. Neurology 1997; 49: 960-968.

Harvey AS, Grattan-Smith JD, Desmond PM, Chow CW, Berkovic SF. Febrile seizures and hippocampal sclerosis: frequent and related findings in intractable temporal lobe epilepsy of childhood. Pediatr Neurol 1995; 12: 201-206.

Hauser WA. The natural history of temporal lobe epilepsy. In: Epilepsy Surgery. Ed. Luders H. Raven Press, New York, 1991; 133-141.

Hauser WA, Annegers JF, Elveback LR. Mortality in patients with epilepsy. Epilepsia 1980; 21: 399-412.

Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia 1993; 34: 453-468.

Hauser WA, Hesdorffer DC. Epilepsy: Frequency, Causes and Consequences. Demos, New York, 1990.

Hauser WA, Hesdorffer DC. Epidemiology of intractable epilepsy. In: Epilepsy Surgery. Eds. Luders HO, Comair YG. Lippincott Williams and Wilkins, Philadelphia, 2001; 55-61.

Hauser WA, Kurland LT. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. Epilepsia 1975; 16: 1-66.

Hermann BP, Seidenberg M, Schoenfeld J, Davies K. Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. Arch Neurol 1997; 54: 369-376.

Houser CR. Morphological changes in the dentate gyrus in human temporal lobe epilepsy. In: The Dentate Gyrus and Its Role in Seizures. Eds. Ribak CE, Gall CM, Mody I. Elsevier Science Publishers, 1992: 223-234.

Hudson LP, Munoz DG, Miller L, McLachlan RS, Girvin JP, Blume WT. Amygdaloid sclerosis in temporal lobe epilepsy. Ann Neurol 1993; 33: 622-631.

Insausti R, Amaral DG, Cowan WM. The entorhinal cortex of the monkey: II. Cortical afferents. J Comp Neurol 1987; 264: 356-395.

Insausti R, Juottonen K, Soininen H, Insausti AM, Partanen K, Vainio P, Laakso MP, Pitkänen A. MRI-based volumetric analyses of the human entorhinal, perirhinal and temporopolar cortices. AJNR 1998; 19: 659-671.

Insausti R, Tunon T, Sobreviela T, Insausti AM, Gonzalo LM. The human entorhinal cortex: a cytoarchitectonic analysis. J Comp Neurol 1995; 355: 171-198.

Isokawa M, Mello LEAM. NMDA receptor-mediated excitability in dendritically deformed dentate granule cells in pilocarpine-treated rats. Neurosci Lett 1991; 129: 69-73.

Jack CR Jr. Mesial temporal sclerosis: magnetic resonance-based hippocampal volume measurements. In: Neuroimaging in Epilepsy. Principles and Practice. Eds. Cascino GD, Jack CR Jr. Butterworth-Heinemann, Newton, MA, 1996; 111-118.

Jack CR Jr, Gehring DG, Sharbrough FW, Felmlee JP, Forbes G, Hench VS, Zinsmeister AR. Temporal lobe volume measurements from MR images: accuracy and left-right asymmetry in normal persons. J Comput Assist Tomogr 1988; 12: 21-29.

Jack CR Jr, Sharbrough FW, Cascino GD, Hirschorn KA, O´Brien PC, Marsh WR. Magnetic resonance image-based hippocampal volumetry: correlation with outcome after temporal lobectomy. Ann Neurol 1992; 31: 138-146.

Jack CR Jr, Sharbrough FW, Twomey CK, Cascino GD, Hirschorn KA, Marsh WR, Zinsmeister AR, Scheithauer B. Temporal lobe seizures: lateralization with MR volume measurements of the hippocampal formation. Radiology 1990; 175: 423-429.

Jack CR Jr, Trenerry MR, Cascino GD, Sharbrough FW, So EL, O'Brien PC. Bilaterally symmetric hippocampi and surgical outcome. Neurology 1995; 45: 1353-1358.

Jackson GD, Berkovic SF, Duncan JS, Connelly A. Optimizing the diagnosis of hippocampal sclerosis using MR imaging. AJNR 1993a; 14: 753-62.

Jackson GD, Berkovic SF, Tress BM, Kalnins RM, Fabinyi GCA, Bladin PF. Hippocampal sclerosis can be reliably detected by magnetic resonance imaging. Neurology 1990; 40: 1869-1875.

Jackson GD, Connelly A, Duncan JS, Grunewald RA, Gadian DG. Detection of hippocampal pathology in intractable partial epilepsy: increased sensitivity with quantitative magnetic resonance T2 relaxometry. Neurology 1993b; 43: 1793-1799.

Jackson GD, Kuzniecky RI, Cascino GD. Hippocampal sclerosis without detectable hippocampal atrophy. Neurology 1994; 44: 42-46.

Joensen P. Prevalence, incidence, and classification of epilepsy in the Faroes. Acta Neurol Scand 1986; 74: 150-155.

Jokeit H, Ebner A, Arnold S, Schuller M, Antke C, Huang Y, Steinmetz H, Seitz RJ, Witte OW. Bilateral reductions of hippocampal volume, glucose metabolism, and WADA hemispheric memory performance are related to the duration of mesial temporal lobe epilepsy. J Neurol 1999; 246: 926-933.

Kapur N, Barker S, Burrows EH, Ellison D, Brice J, Illis LS, Scholey K, Colbourn C, Wilson B, Loates M. Herpes simplex encephalitis: long term magnetic resonance imaging and neuropsychological profile. J Neurol Neurosurg Psychiatr 1994; 57: 1334-1342.

Keränen T. Epilepsy in adults. An epidemiological study in eastern Finland. Series of Reports. Department of Neurology, University of Kuopio, 1988.

Kim JH, Tien RD, Felsberg GJ, Osumi AK, Lee N. Clinical significance of asymmetry of the fornix and mamillary body on MR in hippocampal sclerosis. AJNR 1995; 16: 509-515.

King D, Spencer SS, McCarthy G, Luby M, Spencer DD. Bilateral hippocampal atrophy in medial temporal lobe epilepsy. Epilepsia 1995; 36: 905-910.

Koh S, Storey TW, Santos TC, Mian AY, Cole AJ. Early-life seizures in rats increase susceptibility to seizure-induced brain injury in adulthood. Neurology 1999; 53: 915-921.

Krumholz A, Sung GY, Fisher RS, Barry E, Bergey GK, Grattan LM. Complex partial status epilepticus accompanied by serious morbidity and mortality. Neurology 1995; 45: 1499-1504.

Kuks JB, Cook MJ, Fish DR, Stevens JM, Shorvon SD. Hippocampal sclerosis in epilepsy and childhood febrile seizures. Lancet 1993; 342: 1391-1394.

Kuzniecky RI, Burgard S, Bilir E, Morawetz R, Gilliam F, Faught E, Black L, Palmer C. Qualitative MRI segmentation in mesial temporal sclerosis: clinical correlations. Epilepsia 1996; 37: 433-439.

Kuzniecky R, Burgard S, Faught E, Morawetz R, Bartolucci A. Predictive value of magnetic resonance imaging in temporal lobe epilepsy surgery. Arch Neurol 1993; 50: 65-69.

Kuzniecky R, de la Sayette V, Ethier R, Melanson D, Andermann F, Berkovic S, Robitaille Y, Olivier A, Peters T, Feindel W. Magnetic resonance imaging in temporal lobe epilepsy: pathological correlations. Ann Neurol 1987; 22: 341-347.

Kuzniecky RI, Jackson GD. Temporal lobe epilepsy. In: Magnetic Resonance in Epilepsy. Eds. Kuzniecky RI, Jackson GD. Raven Press, New York, 1995; 107-182.

Kälviäinen R, Mervaala E, Riekkinen PJ. Current treatment of status epilepticus. Suomen Lääkärilehti (in Finnish) 1993; 48: 2184-2189.

Kälviäinen R, Salmenperä T, Partanen K, Vainio P, Riekkinen P Sr, Pitkänen A. Hippocampal damage and the onset of epilepsy. Neurology 1999; 52: 1717. (Correspondence).

Kälviäinen R, Äikiä M, Partanen K, Salmenperä T, Vainio P, Pitkänen A. Hippocampal damage correlates with poor memory performance but not with early prognosis of newly diagnosed patients with epilepsy. Epilepsia 1997; 38(Suppl. 8); S144-S145.

Lancman ME, Morris HH 3rd. Epilepsy after central nervous system infection: clinical characteristics and outcome after epilepsy surgery. Epilepsy Res 1996; 25: 285-290.

LeDoux JE. Emotional memory system in the brain. Behav Brain Res 1993; 58: 69-79.

Lee JW, Reutens DC, Dubeau F, Evans A, Andermann F. Morphometry in temporal lobe epilepsy. Magn Reson Imaging 1995b; 13: 1073-80.

Lee N, Tien RD, Lewis DV, Friedman AH, Felsberg GJ, Crain B, Hulette C, Osumi AK, Smith JS, VanLadingham KE, Radtke RA. Fast spin-echo, magnetic resonance imaging-measured hippocampal volume: correlation with neuronal density in anterior temporal lobectomy patients. Epilepsia 1995a; 36: 899-904.

Lehericy S, Semah F, Hasboun D, Dormont D, Clemenceau S, Granat O, Marsault C, Baulac M. Temporal lobe epilepsy with varying severity: MRI study of 222 patients. Neuroradiology 1997; 39: 788-796.

Leite JP, Babb TL, Pretorius JK, Kulhman PA, Yeoman KM, Mathern GW. Neuronal loss, mossy fiber sprouting, and interictal spikes after intrahippocampal kainate in developing rats. Epilepsy Res 1996; 26: 219-231.

Lencz T, McCarthy G, Bronen RA, Scott TM, Inserni JA, Sass KJ, Novelly RA, Kim JH, Spencer DD. Quantitative magnetic resonance imaging in temporal lobe epilepsy: relationship to neuropathology and neuropsychological function. Ann Neurol 1992; 31: 627-637.

Leonard BW, Amaral DG, Squire LR, Zola-Morgan S. Transient memory impairment in monkeys with bilateral lesions of the entorhinal cortex. J Neurosci 1995; 15: 5637-5659.

Leppik IE. Status epilepticus: the next decade. Neurology 1990; 40(Suppl. 2): S4-S9.

Levesque MF, Nakasato N, Vinters HV, Babb TL. Surgical treatment of limbic epilepsy associated with extrahippocampal lesions: the problem of dual pathology. J Neurosurg 1991; 75: 364-370.

Li LM, Fish DR, Sisodiya SM, Shorvon SD, Alsanjari N, Stevens JM. High resolution magnetic resonance imaging in adults with partial or secondary generalized epilepsy attending a tertiary referral unit. J Neurol Neurosurg Psychiatry 1995; 59: 384-387.

Lindsay J, Ounsted C, Richards P. Long-term outcome in children with temporal lobe seizures. I: Social outcome and childhood factors. Dev Med Child Neurol 1979; 21: 285-298.

Lothman E. The biochemical basis and pathophysiology of status epilepticus. Neurology 1990; 40(Suppl. 2): S13-S23.

Lowenstein DH, Alldredge BK. Status epilepticus. N Engl J Med 1998; 338: 970-976.

Maher J, McLachlan RS. Febrile convulsions. Is seizure duration the most important predictor of temporal lobe epilepsy? Brain 1995; 118: 1521-1528.

Margerison JH, Corsellis JAN. Epilepsy and the temporal lobes. A clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes. Brain 1966; 89: 499-530.

Marks DA, Kim J, Spencer DD, Spencer SS. Characteristics of intractable seizures following meningitis and encephalitis. Neurology 1992; 42: 1513-1518.

Marsh L, Morrell MJ, Shear PK, Sullivan EV, Freeman H, Marie A, Lim KO, Pfefferbaum A. Cortical and hippocampal volume deficits in temporal lobe epilepsy. Epilepsia 1997; 38: 576-587.

Marson AG, Chadwick DW. New drug treatments for epilepsy. J Neurol Neurosurg Psychiatry 2001; 70: 143-147.

Mathern GW, Babb TL, Armstrong DL. Hippocampal sclerosis. In: Epilepsy: A Comprehensive Textbook. Eds. Engel J Jr, Pedley TA. Lippincott-Raven Publishers, Philadelphia, 1997; 133-155.

Mathern GW, Babb TL, Vickrey BG, Melendez M, Pretorius JK. The clinical-pathogenic mechanisms of hippocampal neuron loss and surgical outcomes in temporal lobe epilepsy. Brain 1995; 118: 105-118.

Mathern GW, Kupfer WR, Pretorius JK, Babb TL, Levesque MF. Onset and patterns of hippocampal sprouting in the rat kainate seizure model: evidence for progressive cell loss and neo-innervation in regio inferior and superior. Dendron 1992; 1: 69-84.

Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. N Engl J Med 1992; 327: 765-771.

Mattson RH, Cramer JA, Collins JF, Smith DB, Delgado-Escueta AV, Browne TR, Williamson PD, Treiman DM, McNamara JO, McCutchen CB, Homan RW, Crill WE, Lubozynski MF, Rosenthal NP, Mayersdorf A. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. N Engl J Med 1985; 313: 145-151.

McNamara JO. Emerging insights into the genesis of epilepsy. Nature 1999; 399(Suppl.): A15-22.

Meencke HJ. Neuron density in the molecular layer of the frontal cortex in primary generalized epilepsy. Epilepsia 1985; 26: 450-454.

Meencke HJ, Janz D. Neuropathological findings in primary generalized epilepsy: a study of eight cases. Epilepsia 1984; 25: 8-21.

Meierkord H, Wieshmann U, Niehaus L, Lehmann R. Structural consequences of status epilepticus demonstrated with serial magnetic resonance imaging. Acta Neurol Scand 1997; 96: 127-132.

Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates: ischemic cell change and its relation to ictal physiological events. Arch Neurol 1973; 28: 10-17.

Mello LEAM, Cavalheiro EA, Tan AM, Kupfer WR, Pretorius JK, Babb TL, Finch DM. Circuit mechanisms of seizures in the pilocarpine model of chronic epilepsy: cell loss and mossy fiber sprouting. Epilepsia 1993; 34: 985-995.

Meunier M, Bachevalier J, Mishkin M, Murray EA. Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkey. J Neurosci 1993; 13: 5418-5432.

Meunier M, Bachevalier J, Murray EA, Malkova L, Mishkin M. Effects of aspiration versus neurotoxic lesions of the amygdala on emotional responses in monkeys. Eur J Neurosci 1999; 11: 4403-4418.

Mikkonen M, Soininen H, Kälviäinen R, Tapiola T, Ylinen A, Vapalahti M, Paljärvi L, Pitkänen A. Remodeling of neuronal circuitries in human temporal lobe epilepsy: increased expression of highly polysialylated neural cell adhesion molecule in the hippocampus and the entorhinal cortex. Ann Neurol 1998; 44: 923-934.

Miller LA, McLachlan RS, Bouwer MS, Hudson LP, Munoz DG. Amygdalar sclerosis: preoperative indicators and outcome after temporal lobectomy. J Neurol Neurosurg Psychiatry 1994; 57: 1099-1105.

Milner B. Psychological aspects of focal epilepsy and its surgical management. In: Advances in Neurology. Eds. Purpura DP, Penry JK, Walter RD. Raven Press, New York, 1975; 8: 299-321.

Moshe SL, Pedley TA. Diagnostic evaluation. EEG In: Epilepsy. The Comprehensive CD-ROM. Eds. Engel J Jr, Pedley T. Lippincott Williams and Wilkins, Baltimore MD, 1999.

Mouritzen Dam A. Epilepsy and neuron loss in the hippocampus. Epilepsia 1980; 21: 617-629.

Mouritzen Dam A. Hippocampal neuron loss in epilepsy and after experimental seizures. Acta Neurol Scand 1982; 66: 601-642.

Mungas D, Ehlens C, Walton N, McCuthen CB. Verbal learning differences in epileptic patients with left and right temporal lobe foci. Epilepsia 1985; 26: 340-345.

Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. N Engl J Med 1976; 4: 1029-1033.

Nevander G, Ingvar M, Auer R, Siesjö BK. Status epilepticus in well-oxygenated rats causes neuronal necrosis. Ann Neurol 1985; 18: 281-290.

Ng SES, Lau TN, Hui FKH, Chua GE, Lee WL, Chee MWL, Chee TSG, Boey HK. MRI of the fornix and mamillary body in temporal lobe epilepsy. Neuroradiology 1997; 39: 551-555.

Nissinen J, Halonen T, Koivisto E, Pitkänen A. A new model of chronic temporal lobe epilepsy induced by electrical stimulation of the amygdala in rat. Epilepsy Res 2000; 38: 177-205.

Nohria V, Lee N, Tien RD, Heinz ER, Smith JS, DeLong GR, Skeen MB, Resnick TJ, Crain B, Lewis DV. Magnetic resonance imaging evidence of hippocampal sclerosis in progression: A case report. Epilepsia 1994; 35: 1332-1336.

Norman RM. The neuropathology of status epilepticus. Med Sci Law 1964; 4: 46-51.

O'Brien TJ, So EL, Meyer FB, Parisi JE, Jack CR. Progressive hippocampal atrophy in chronic intractable temporal lobe epilepsy. Ann Neurol 1999; 45: 526-529.

Olney JW, Rhee V, Ho OL. Kainic acid: a powerful neurotoxic analogue of glutamate. Brain Res 1974; 77: 507-512.

O'Shaughnessy D, Gerber GJ. Damage induced by systemic kainic acid in rats is dependent upon seizure activity – a behavioral and morphological study. Neurotoxicology 1986; 7: 187-202.

Osorio I, Reed RC. Treatment of refractory generalized tonic-clonic status epilepticus with pentobarbital anesthesia after high-dose phenytoin. Epilepsia 1989; 30: 464-471.

Pitkänen A. Treatment with antiepileptic drugs: Possible neuroprotective effects. Neurology 1996b; 47(Suppl. 1): S12-S16.

Pitkänen A, Laakso M, Kälviäinen R, Partanen K, Vainio P, Lehtovirta M, Riekkinen P Sr, Soininen H. Severity of hippocampal atrophy correlates with the prolongation of MRI T2 relaxation time in temporal lobe epilepsy but not in Alzheimer's disease. Neurology 1996a; 46: 1724-1730.

Pitkänen A, Salmenperä T, Äikiä M, Partanen K, Kälviäinen R. Seizure-induced damage to the medial temporal lobe in temporal lobe epilepsy. In: Epilepsy and Mental Retardation. Eds. Sillanpää M, Gram L, Johannessen SI, Tomson T. Wrightson Biomedical Publishing LTD, 1999; 147-163.

Pitkänen A, Savander V, LeDoux JE. Organization of intra-amygdaloid circuitries in the rat: an emerging framework for understanding functions of the amygdala. Trends Neurosci 1997; 20: 517-523.

Pitkänen A, Tuunanen J, Kälviäinen R, Partanen K, Salmenperä T. Amygdala damage in experimental and human temporal lobe epilepsy. Epilepsy Res 1998; 32: 233-253.

Quesney LF. Clinical and EEG features of complex partial seizures of temporal lobe origin. Epilepsia 1986; 27(Suppl. 2): S27-S45.

Quigg M, Bertram EH, Jackson T. Longitudinal distribution of hippocampal atrophy in mesial temporal lobe epilepsy. Epilepsy Res 1997b; 27: 101-110.

Quigg M, Bertram EH, Jackson T, Laws E. Volumetric magnetic resonance imaging evidence of bilateral hippocampal atrophy in mesial temporal lobe epilepsy. Epilepsia 1997a; 38: 588-594.

Rabinowicz AL, Correale JD, Bracht KA, Smith TD, DeGiorgio CM. Neuron-specific enolase is increased after nonconvulsive status epilepticus. Epilepsia 1995; 36: 475-479.

Raymond AA, Fish DR, Stevens JM, Cook MJ, Sisodiya SM, Shorvon SD. Association of hippocampal sclerosis with cortical dysgenesis in patients with epilepsy. Neurology 1994; 44: 1841-1845.

Rodin EA. Medical and social prognosis in epilepsy. Epilepsia 1972; 13: 121-131.

Rutecki PA, Grossman RG, Armstrong D, Irish-Loewen S. Electrophysiological connections between the hippocampus and entorhinal cortex in patients with complex partial seizures. J Neurosurg 1989; 70: 667-675.

Sagar HJ, Oxbury JM. Hippocampal neuron loss in temporal lobe epilepsy: correlation with early childhood convulsions. Ann Neurol 1987; 22: 334-340.

Salmenperä T, Kälviäinen R, Partanen K, Pitkänen A. Hippocampal damage caused by seizures in temporal lobe epilepsy. Lancet 1998; 35: 35(Letter).

Sander JWAS. Some aspects of prognosis in the epilepsies: a review. Epilepsia 1993; 34: 1007-1016.

Sander JWAS, Hart YM, Johnson AL, Shorvon SD. National general practice study of epilepsy: newly diagnosed epileptic seizures in a general population. Lancet 1990; 336: 1267-1271.

Sander JWAS, Sillanpää M. Natural History and Prognosis. In: Epilepsy. The Comprehensive CD-ROM. Eds. Engel J Jr, Pedley T. Lippincott Williams and Wilkins, Baltimore MD, 1999.

Saukkonen A, Kälviäinen R, Partanen K, Vainio P, Riekkinen P, Pitkänen A. Do seizures cause neuronal damage? A MRI study in newly diagnosed and chronic epilepsy. NeuroReport 1994; 6: 219-223.

Saygi S, Spencer SS, Scheyer R, Katz A, Mattson R, Spencer DD. Differentiation of temporal lobe ictal behavior associated with hippocampal sclerosis and tumors of temporal lobe. Epilepsia 1994; 35: 737-742.

Schwob JE, Fuller T, Price JL, Olney JW. Widespread patterns of neuronal damage following systemic or intracerebral injections of kainic acid: a histological study. Neuroscience 1980; 5: 991-1014.

Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, Cavalcanti D, Baulac M. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology 1998; 51: 1256-1262.

Shorvon SD. Epidemiology, classification, natural history, and genetics of epilepsy. Lancet 1990; 336: 93-96.

Shorvon SD. The epidemiology and treatment of chronic and refractory epilepsy. Epilepsia 1996; 37(Suppl. 2): S1-S3.

Shorvon SD, Reynolds EH. The nature of epilepsy: evidence from studies of epidemiology, temporal patterns of seizures, prognosis and treatment. In: What Is Epilepsy? Eds. Trimble MR, Reynolds EH. Churchill Livingstone, Edinburgh, 1986; 36-45.

Sillanpää M. Long-term outcome of epilepsy. Epileptic Disord 2000; 2: 79-88.

Sisodiya SM, Free SL, Stevens JM, Fish DR, Shorvon SD. Widespread cerebral structural changes in patients with cortical dysgenesis and epilepsy. Brain 1995; 118: 1039-50.

Sisodiya SM, Moran N, Free SL, Kitchen ND, Stevens JM, Harkness WF, Fish DR, Shorvon SD. Correlation of widespread preoperative magnetic resonance imaging changes with unsuccessful surgery for hippocampal sclerosis. Ann Neurol 1997; 41: 490-496.

Sloviter RS. ”Epileptic” brain damage in rats induced by sustained electrical stimulation of the perforant path. I. Acute electrophysiological and light microscopic studies. Brain Res Bull 1983; 10: 675-697.

Sloviter RS. The functional organization of the hippocampal dentate gyrus and its relevance to the pathogenesis of temporal lobe epilepsy. Ann Neurol 1994; 35: 640-654. O

Smith DB, Mattson RH, Cramer JA, Collins JF, Novelly RA, Craft B. Results of a nationwide Veterans Administration Epilepsy Cooperative Study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin and primidone. Epilepsia 1987; 28(Suppl. 3): S50-S58.

Soininen HS, Partanen K, Pitkänen A, Vainio P, Hänninen T, Hallikainen M, Koivisto K, Riekkinen PJ Sr. Volumetric MRI analysis of the amygdala and the hippocampus in subjects with age-associated memory impairment. Neurology 1994; 44: 1660-1668.

Sorvari H, Soininen H, Paljärvi L, Karkola K, Pitkänen A. Distribution of parvalbumin-immunoreactive cells and fibers in the human amygdaloid complex. J Comp Neurol 1995; 360: 185-212.

Specht U, May T, Schulz R, Rohde M, Ebner A, Schmidt RC, Schutz M, Wolf P. Cerebellar atrophy and prognosis after temporal lobe resection. J Neurol Neurosurg Psychiatry 1997; 62: 501-506.

Spencer SS, McCarthy G, Spencer DD. Diagnosis of medial temporal lobe seizure onset: relative specificity and sensitivity of quantitative MRI. Neurology 1993; 43: 2117-2124.

Spencer SS, Spencer DD. Entorhinal-hippocampal interactions in medial temporal lobe epilepsy. Epilepsia 1994; 35: 721-727.

Spencer SS, Spencer DD, Williamson PD, Mattson R. Combined depth and subdural electrode investigation in uncontrolled epilepsy. Neurology 1990; 40: 74-79.

Squire LR, Zola-Morgan S. The medial temporal lobe memory system. Science 1991; 253: 1380-1386.

Sutula T, Cascino G, Cavazos J, Parada I, Ramirez L. Mossy fiber synaptic reorganization in the epileptic human temporal lobe. Ann Neurol 1989; 26: 321-330.

Sutula TP, Hermann B. Progression in mesial temporal lobe epilepsy. Ann Neurol 1999; 45: 553-556.

Suzuki WA. Neuroanatomy of the monkey entorhinal, perirhinal and parahippocampal cortices: organization of cortical inputs and interconnections with amygdala and striatum. Semin Neurosci 1996b; 8: 3-12.

Suzuki WA. The anatomy, physiology and functions of the perirhinal cortex. Curr Opin Neurobiol 1996a; 6: 179-186.

Suzuki WA, Amaral DG. Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. J Comp Neurol 1994a; 350: 497-533.

Suzuki WA, Amaral DG. Topographic organization of the reciprocal connections between the monkey entorhinal cortex and the perirhinal and parahippocampal cortices. J Neurosci 1994b; 14: 1856-1877.

Tasch E, Cendes F, Li LM, Dubeau F, Andermann F, Arnold DL. Neuroimaging evidence of progressive neuronal loss and dysfunction in temporal lobe epilepsy. Ann Neurol 1999; 45: 568-576.

Theodore WH, Bhatia S, Hatta J, Fazilat S, DeCarli C, Bookheimer SY, Gaillard WD. Hippocampal atrophy, epilepsy duration, and febrile seizures in patients with partial seizures. Neurology 1999; 52: 132-136.

Theodore WH, Fishbein D, Dubinsky R. Patterns of cerebral glucose metabolism in patients with partial seizures. Neurology 1988; 38: 1201-1206.

Tien RD, Felsberg GJ. The hippocampus in status epilepticus: demonstration of signal intensity and morphologic changes with sequential fast spin-echo MR imaging. Radiology 1995; 194: 249-256.

Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. Epilepsia 1994; 35: 27-34.

Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, Handforth A, Faught E, Calabrese VP, Uthman BM, Ramsay RE, Mamdani MB. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998; 339: 792-798.

Trenerry MR, Jack CR Jr, Cascino GD, Sharbrough FW, Ivnik RJ. Gender differences in post-temporal lobectomy verbal memory and relationships between MRI hippocampal volumes and preoperative verbal memory. Epilepsy Res 1995; 20: 69-76.

Trenerry MR, Jack CR Jr, Cascino GD, Sharbrough FW, So EL. Bilateral magnetic resonance imaging-determined hippocampal atrophy and verbal memory before and after temporal lobectomy. Epilepsia 1996; 37: 526-533.

Trenerry MR, Jack CR Jr, Ivnik RJ, Sharbrough FW, Cascino GD, Hirschorn KA, Marsh WR, Kelly PJ, Meyer FB. MRI hippocampal volumes and memory function before and after temporal lobectomy. Neurology 1993a; 43: 1800-1805.

Trenerry MR, Jack CR Jr, Sharbrough FW, Cascino GD, Hirschorn KA, Marsh WR, Kelly PJ, Meyer FB. Quantitative MRI hippocampal volumes: association with onset and duration of epilepsy, and febrile convulsions in temporal lobectomy patients. Epilepsy Res 1993b; 15: 247-252.

Turski WA, Cavalheiro EA, Schwarz M, Czuczwar SJ, Kleirok Z, Turski L. Limbic seizures produced by pilocarpine in rats: behavioural, electroencephalographic and neuropathological study. Behav Brain Res 1983; 9: 315-335.

Tuunanen J, Halonen T, Pitkänen A. Status epilepticus causes selective regional damage and loss of GABAergic neurons in the rat amygdaloid complex. Eur J Neurosci 1996; 8: 2711-2725.

Tuunanen J, Halonen T, Pitkänen A. Decrease in somatostatin-immunoreactive neurons in the rat amygdaloid complex in a kindling model of temporal lobe epilepsy. Epilepsy Res 1997; 26: 315-327.

VanLandingham KE, Heinz ER, Cavazos JE, Lewis DV. Magnetic resonance imaging evidence of hippocampal injury after prolonged focal febrile convulsions. Ann Neurol 1998; 43: 413-426.

Van Paesschen W, Connelly A, Johnson CL, Duncan JS. The amygdala and intractable temporal lobe epilepsy: a quantitative magnetic resonance imaging study. Neurology 1996; 47: 1021-1031.

Van Paesschen W, Connelly A, King MD, Jackson GD, Duncan JS. The spectrum of hippocampal sclerosis: a quantitative magnetic resonance imaging study. Ann Neurol 1997a; 41: 41-51.

Van Paesschen W, Duncan JS, Stevens JM, Connelly A. Etiology and early prognosis of newly diagnosed partial seizures in adults: a quantitative hippocampal MRI study. Neurology 1997c; 49: 753-757.

Van Paesschen W, Duncan JS, Stevens JM, Connelly A. Longitudinal quantitative hippocampal magnetic resonance imaging study of adults with newly diagnosed partial seizures: one-year follow-up results. Epilepsia 1998; 39: 633-639.

Van Paesschen W, Revesz T, Duncan JS, King MD, Connelly A. Quantitative neuropathology and quantitative magnetic resonance imaging of the hippocampus in temporal lobe epilepsy. Ann Neurol 1997b; 42: 756-766.

Van Paesschen W, Sisodiya S, Connelly A, Duncan JS, Free SL, Raymond AA; Grunewald RA, Revesz T, Shorvon SD, Fish DR, Stevens JM, Johnson CL, Scaravilli F, Harkness WFJ, Jackson GD. Quantitative hippocampal MRI and intractable temporal lobe epilepsy. Neurology 1995; 45: 2233-2240.

Walczak TS, Jayakar P. Interictal EEG. In: Epilepsy. The Comprehensive CD-ROM. Eds. Engel J Jr, Pedley T. Lippincott Williams and Wilkins, Baltimore MD, 1999.

Walczak TS, Leppik IE, D'Amelio M, Rarick J, So E, Ahman P, Ru K, Cascino GD, Annegers JF, Hauser WA. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology 2001; 27: 56: 519-525.

Walther H, Lambert JDC, Jones RSG, Heinemann U, Hamon B. Epileptiform activity in combined slices of the hippocampus, subiculum and entorhinal cortex during perfusion with low magnesium medium. Neurosci Lett 1986; 69: 156-161.

Wasterlain CG, Fujikawa DG, Penix L, Sankar R. Pathophysiological mechanisms of brain damage from status epilepticus. Epilepsia 1993; 34(Suppl. 1): S37-S53.

Watson C, Andermann F, Gloor P, Jones-Gotman M, Peters T, Evans A, Olivier A, Melanson D, Leroux G. Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. Neurology 1992; 42: 1743-1750.

Watson C, Cendes F, Fuerst D, Dubeau F, Williamson B, Evans A, Andermann F. Specificity of volumetric magnetic resonance imaging in detecting hippocampal sclerosis. Arch Neurol 1997; 54: 67-73.

Watson C, Nielsen SL, Cobb C, Burgerman R, Williamson B. Pathological grading system for hippocampal sclerosis: correlation with magnetic resonance imaging-based volume measurements of the hippocampus. J Epilepsy 1996; 9: 56-64.

Watson C, Williamson B. Volumetric magnetic resonance imaging in patients with primary generalized epilepsy. J Epilepsy 1995; 8: 104-109.

Weiss GH, Salazar AM, Vance SC, Grafman JH, Jabbari B. Predicting posttraumatic epilepsy in penetrating head injury. Arch Neurol 1986; 43: 771-773.

Wieser HG, Engel J Jr, Williamson PD, Babb TL, Gloor P. Surgically remediable temporal lobe syndromes. In: Surgical Treatment of the Epilepsies. Ed. Engel J Jr. Raven Press, New York, 1993; 49-63.

Wieser HG, Hajek M. Frontal lobe epilepsy: compartmentalization, presurgical evaluation, and operative results. In: Epilepsy and the Functional Anatomy of the Frontal Lobe. Eds. Jasper HH, Riggio S, Golman-Rakic PS. Raven Press, New York, 1995; 297-319.

Wieshmann UC, Woermann FG, Lemieux L, Free SL, Bartlett PA, Smith SJM, Duncan JS, Stevens JM, Shorvon SD. Development of hippocampal atrophy: a serial magnetic resonance imaging study in a patient who developed epilepsy after generalized status epilepticus. Epilepsia 1997; 38: 1238-1241.

Williamson PD, Engel J Jr. Complex partial seizures. In: Epilepsy. The Comprehensive CD-ROM. Eds. Engel J Jr, Pedley T. Lippincott Williams and Wilkins, Baltimore MD, 1999.

Williamson PD, French JA, Thadani VM, Kim JH, Novelly RA, Spencer SS, Spencer DD, Mattson RH. Characteristics of medial temporal lobe epilepsy: II. Interictal and ictal scalp electroencephalography, neuropsychological testing, neuroimaging, surgical results, and pathology. Ann Neurol 1993b; 34: 781-787.

Williamson PD, Van Ness PC, Wieser HG, Quesney LF. Surgically remediable extratemporal syndromes. In: Surgical Treatment of the Epilepsies. Ed. Engel J Jr. Raven Press, New York, 1993a; 65-76.

Williamson PD, Wieser HG, Delgado-Escueta AV. Clinical characteristics of partial seizures. In: Surgical Treatment of the Epilepsies. Ed. Engel J Jr. Raven Press, New York, 1987; 101-120.

Wilson CL, Isokawa M, Babb TL, Crandall PH. Functional connections in the human temporal lobe. I. Analysis of limbic system pathways using neuronal responses evoked by electrical stimulation. Exp Brain Res 1990; 82: 279-292.

Witter MP. Organization of the entorhinal-hippocampal system: a review of current anatomical data. Hippocampus 1993; 3(Suppl.): 33-44.

Witter MP, Amaral DG. Entorhinal cortex of the monkey: V. Projections to the dentate gyrus, hippocampus, and subicular complex. J Comp Neurol 1991; 307: 437-459.

Woermann FG, Sisodiya SM, Free SL, Duncan JS. Quantitative MRI in patients with idiopathic generalized epilepsy. Evidence of widespread cerebral structural changes. Brain 1998; 121: 1661-1667.

Working Group on Status Epilepticus. Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. JAMA 1993; 270: 854-859.

World Health Organization. Juvenile Epilepsy. Report of a study group. WHO Tech Rep Ser 1957; 130: 1-44.

Young AW, Aggleton JP, Hellawell DJ, Johnson M, Broks P, Hanley JR. Face processing impairments after amygdalotomy. Brain 1995; 118: 15-24.

Zentner J, Wolf HK, Helmstaedter C, Grunwald T, Aliashkevich AF, Wiestler OD, Elger CE, Schramm J. Clinical relevance of amygdala sclerosis in temporal lobe epilepsy. J Neurosurg 1999; 91: 59-67.

Zielinski JJ. Epidemiology. In: A Textbook of Epilepsy. Eds. Laidlaw J, Richens A, Oxley J. Churchill Livingstone, Edinburgh, 1988; 21-48.

Zola-Morgan S, Squire LR, Alvarez-Royo P, Clower RP. Independence of memory functions and emotional behavior: separate contributions of the hippocampal formation and the amygdala. Hippocampus 1991; 1: 207-220.

Zola-Morgan S, Squire LR, Amaral DG. Human amnesia and the medial temporal lobe region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J Neurosci 1986; 6: 2950-2967.

Äikiä M, Kälviäinen R, Riekkinen PJ. Verbal learning and memory in newly diagnosed partial epilepsy. Epilepsy Res 1995; 22: 157-164.

Äikiä M, Kälviäinen R, Mervaala E, Riekkinen PJ Sr. Predictors of seizure outcome in newly diagnosed partial epilepsy: memory performance as a prognostic factor. Epilepsy Res 1999; 37: 159-167.