MARJA ÄIKIÄ

Verbal memory in newly diagnosed partial epilepsy: A neuropsychological study.

To be presented with assent of the Faculty of Social Sciences of the University of Jyväskylä for public examination in Auditorium S 212, Seminarium building of the University of Jyväskylä, on Saturday 9th November 2002 at 12 noon.

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ABSTRACT

The purpose of this study was to investigate the verbal memory performance of adult patients with partial epilepsy. The study sample consisted of newly diagnosed and chronic patients with seizure disorder, who were treated in the Department of Neurology, Kuopio University Hospital. A group of healthy volunteers served as controls for neuropsychological evaluation. The aims of the present series of studies were to assess verbal memory in patients with newly diagnosed partial epilepsy, and to study the effects of the course of left temporal lobe epilepsy (LTLE) on verbal memory by comparing the memory performance of newly diagnosed patients with that of chronic patients with LTLE. Verbal memory was also evaluated as a prognostic factor for seizure control. In addition, the effects of antiepileptic drugs (AEDs) on verbal memory were assessed after one year of treatment.

The study showed that verbal memory may be affected already at the time of the diagnosis of epilepsy. Mild memory dysfunction (test performance one standard deviation below the mean performance of controls) was found in one third of the patients with newly diagnosed partial epilepsy. Clinically meaningful, moderate memory impairment (test scores two standard deviations below the control mean) was present in a minority of these patients. Memory dysfunction was shown mainly in retrieval of previously learned unrelated words after delay, and in the percentage of words retained. The verbal memory performance of patients with newly diagnosed LTLE was almost the same as that of patients with chronic LTLE. The groups differed in delayed recognition of words, patients with chronic LTLE having poorer performance. Clinically meaningful, moderate verbal memory impairment at the time of the diagnosis of partial epilepsy was one of the predictors of seizure outcome. The verbal memory of newly diagnosed patients did not decline during one year of treatment with different AEDs, and preliminary five-year follow-up of newly diagnosed LTLE patients also showed no deterioration of verbal memory.

These findings suggest that memory dysfunction becomes evident already in the early course of epilepsy, and memory performance remains relatively stable for the following years with partial epilepsy. In addition, moderate memory impairment at the time of diagnosis is one of the predictors of intractable epilepsy.

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ABBREVIATIONS

AED	antiepileptic drug
ANOVA	analysis of variance
ANCOVA	analysis of covariance
CBZ	carbamazepine
CI	confidence interval
CNS	central nervous system
CT	computed tomography
EEG	electroencephalogram
ES	effect size
FIQ	full scale intelligence quotient
FOV	field of view
LTLE	left temporal lobe epilepsy
LTP	long-term potentiation
MANOVA	multivariate analysis of variance
MANCOVA	multivariate analysis of covariance
MTLE	mesial temporal lobe epilepsy
MP-RAGE	magnetization-prepared rapid acquisition gradient echo
MRI	magnetic resonance imaging
OXC	oxcarbazepine
OR	odds ratio
PHT	phenytoin
SE	standard error
SD	standard deviation
SPSS	Statistical Package for Social Sciences
T1	longitudinal relaxation time
TE	time of echo
TLE	temporal lobe epilepsy
TR	time of repetition
VGB	vigabatrin
VIQ	verbal intelligence quotient

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications:

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

II   Äikiä M, Salmenperä T, Partanen K, Kälviäinen R. Verbal memory in newly diagnosed patients and patients with chronic left temporal lobe epilepsy. Epilepsy Behav 2001; 2: 20-27.

III   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.

IV   Äikiä M, Kälviäinen R, Sivenius J, Halonen T, Riekkinen PJ. Cognitive effects of oxcarbazepine and phenytoin monotherapy in newly diagnosed epilepsy: one-year follow-up. Epilepsy Res 1992; 11: 199-203.

V   Kälviäinen R, Äikiä M, Saukkonen AM, Mervaala E, Riekkinen PJ Sr. Vigabatrin vs carbamazepine monotherapy in patients with newly diagnosed epilepsy. A randomized, controlled study. Arch Neurol 1995; 52: 989-996.

In addition, the thesis includes previously unpublished data (analysis of the effect size and practice effect in antiepileptic drug studies).

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CONTENTS

1 INTRODUCTION

Learning is the process by which we acquire new information, and memory is the process by which we retain that knowledge over time. If a piece of information is to be recalled at a later date, three possibly related processes are necessary. The item must be registered, must be retained in memory and must be capable of being retrieved from memory. Memory is a complex and multifaceted aspect of human cognition, which forms the major vehicle for behavioral adaptation. It is one of the most essential higher brain functions since it provides continuity in time, personal history and awareness.

Epilepsy, a brain disorder that is characterized by recurrent seizures, refers to a collection of disorders that affect 1 – 2 % of the population world-wide. An epileptic seizure is a brief change in behavior caused by the disordered, synchronous and rhythmic firing of populations of neurons in the central nervous system (CNS). Seizures are thought to arise from discharging lesions in the cerebral cortex (Adams et al., 1997). The behavioral manifestations of a seizure are determined by the normal functions of the region of the cortex in which neurons fire abnormally and include stereotyped alterations in consciousness, behavior, emotion, motor function or sensation. By definition, epileptic seizures are always abnormal events which involve excessive electrical activity of neurons, resulting in disturbances of normal information processing in the brain (Dichter, 1997; Engel, 1989; McNamara, 1999). Seizure disorders or epilepsy syndromes have been classified into more than 40 distinct types based upon characteristic symptoms and signs, seizure types, cause, age of onset and electroencephalographic (EEG) patterns (Commission on Epidemiology and Prognosis of the International League Against Epilepsy, 1993).

Epilepsy should, however, not be seen only as a random succession of seizures but as a continuous process. Current understanding of human epileptic process derives largely from the sequence of events culminating in the appearance of spontaneous seizures in patients with partial epilepsy. The process includes three successive phases, the process begins after the initial insult, which could be, for instance, head trauma or hypoxia. The initial insult is followed by a latent period of varying length, and leads to recurrent seizures (Pitkänen and Halonen, 1998).

Disorders of learning and memory in people with epilepsy, particularly with chronic temporal lobe epilepsy (TLE), have long been recognized and documented (Delaney et al., 1980; Loiseau et al., 1983; Mungas et al., 1985; Hermann et al., 1987). Memory impairment has been associated with temporal lobe dysfunction (Squire, 1987), and the most prevalent form of human partial epilepsy is TLE which originates in the neural substrate for memory. In addition, the importance of memory problems to epilepsy patients themselves is emphasized by the finding that they seek help for memory problems more frequently than for any other cognitive impairment. Despite much concern for memory decline expressed in literature over the years, systematic studies evaluating memory in other epileptic patients than surgical candidates were rather few until 1980.

Most studies of memory in epilepsy are of patients with chronic and intractable epilepsy, and studies of memory performance in newly diagnosed epilepsy are rare. It is still unclear whether memory disorder is present at the time of the diagnosis of epilepsy or whether memory declines in the course of the disease. Our preliminary data of adults with either single or recurrent untreated cryptogenic seizures suggested that the patients have a subtle memory dysfunction at the time of the diagnosis (Kälviäinen et al., 1992).

The present study concentrates on verbal memory performance of adult patients with newly diagnosed partial epilepsy. The first aim of the study is to elucidate our preliminary results of memory dysfunction in newly diagnosed seizure disorder and to evaluate verbal memory performance of patients with newly diagnosed partial epilepsy before antiepileptic drug (AED) treatment is started.

Verbal memory deficits have been documented in chronic TLE but there are no studies comparing memory performance of newly diagnosed and chronic patients with TLE. In the current study verbal memory performance of patients with newly diagnosed and chronic left temporal lobe epilepsy (LTLE) was investigated, and we investigated whether memory performance is poorer in chronic than in newly diagnosed LTLE as a result of progression of memory dysfunction after longer periods of epilepsy with recurrent seizures and AED treatment.

The prognosis for most epilepsy patients is good, but about 30 % of the patients develop intractable epilepsy despite optimal treatment (Hauser and Hesdorffer, 2001). There is a need to find new prognostic factors of epilepsy in order to be able to identify already at the time of the diagnosis those patients whose seizures will prove to be intractable. In the present study verbal memory performance is evaluated as a predictor of seizure outcome.

The last part of the study investigates verbal memory performance during AED treatment The general opinion represented in the literature claims that all AEDs can compromise cognitive functioning, although the cognitive effects of specific AEDs are variable (Perrine and Kiolbasa, 1999; Kwan and Brodie, 2001). The aim of this study was to evaluate differential effects of AEDs on verbal memory performance.

2 REVIEW OF LITERATURE

2.1 Human memory

Over the past decades, there has been a gradual merger of two originally separated fields of science: neurobiology and cognitive psychology. One of the results of this collaboration has been awareness that memory constitutes an alliance of interacting systems serving different functions and operating in different ways (Kandel and Hawkins, 1992). Current research evidence from psychology and neuroscience has pointed toward a number of different forms of learning and memory involving different neural systems. The idea of multiple memory systems began to develop with the discovery that selective brain damage could result in severe impairment in one form of memory without affecting other learning capacities (Eichenbaum et al., 1999). Much of memory research was stimulated by observations concerning the amnesic patient H.M., who had a complete bilateral resection of the medial temporal lobes for relief of intractable TLE (Scoville and Milner, 1957).

2.1.1. Neuropsychology of memory

In psychological theories, memory has traditionally been divided into successive and interacting systems according to the time period involved in information processing. The modal model of memory (Atkinson and Shiffrin, 1968) assumed three types of memory stores: sensory register, short-term store and long-term store. In this model information enters the processing system through modality-specific sensory stores and then proceeds to a limited capacity short-term memory before entering a permanent and extensive long-term memory. In this model, serial position effects, which are shown as better recall of both the early items (primacy effect) and the last items (recency effect) of a list, have been held to be evidence supporting the distinction of short-term and long-term memory.

The concept of short-term memory was elaborated by Baddeley (1986, 1996) who proposed a memory system called working memory. The term working memory refers to a system that is responsible for the short-term maintenance and manipulation of information necessary for learning, comprehension and reasoning. The model of working memory consists of three components: the central executive, which is an attentional control system that operates in conjunction with two subsystems; the phonological loop and the visuo-spatial sketchpad. The working memory model combines the executive control system with specialized storage systems for maintaining and manipulating verbal and visual material.

Memory processing has three sequential stages: encoding, storage and retrieval. Encoding refers to the process of acquiring information or placing it into memory. Learning is the process of acquisition of new information, and it refers to effortful or attentive activity. Thus, memory is the byproduct of active perceptual and cognitive processing; the more deeply or meaningfully the information is processed the more well retained the information will be. This levels-of-processing view emphasizes the role of mental operations in memory, particularly in encoding, but also in retrieval. After encoding occur the processes involved in the storage of the information to be maintained in memory. Retrieval refers to the process of recovering previously encoded information, and remembering reflects the interaction between encoding and retrieval processes (Brown and Craik, 2000).

In addition to a distinction between short-term and long-term memory functions, a further distinction within the domain of long-term memory according to the way of expression of

the learned information has been used: declarative (explicit) and nondeclarative (implicit, procedural) memory (Squire and Zola-Morgan, 1988). Declarative memory refers to memories for facts and events that are recollected consciously, and it consists of two classes of memories, episodic and semantic. Episodic memories are associated with a specific time and setting, and they are experienced as coming from particular episodes in the past. Semantic memory involves general knowledge of facts and concepts not specified in time or space (Squire and Knowlton, 2000; Buckner, 2000; Eichenbaum et al., 1999). Most neuropsychological memory tests assess declarative, especially episodic memory.

Nondeclarative memory refers to non-conscious effects of previous experiences on performance in tasks without any requirement for conscious memory content. Nondeclarative memory is not a single entity but describes a collection of abilities: memory for skills and habits, simple forms of conditioning and priming. For instance, in skills and habits, procedural knowledge is acquired gradually through repetitive practice and is expressed primarily by improved performance (Squire and Knowlton, 2000; Eichenbaum et al., 1999).

2.1.2 Neurobiological basis of memory

The study of the neurobiology of memory has traditionally been based on the study of brain damaged patients and experimental animals. Functional neuroimaging techniques have provided a means of identifying specific brain regions and pathways that are differentially activated during memory tasks. The view of the structural organization of memory is changing, from localizing memories in specific areas to viewing memory as a distributed property of cortical systems. Memories are mediated and stored by overlapping and widely distributed networks of interconnected cortical neurons (Fuster, 1997).

Long-term memory systems and the associated brain structures that are important for each form of memory are presented in Figure 1. The categories of memory are, however, not exclusive and when something important is learned, several of these memory systems can become engaged.
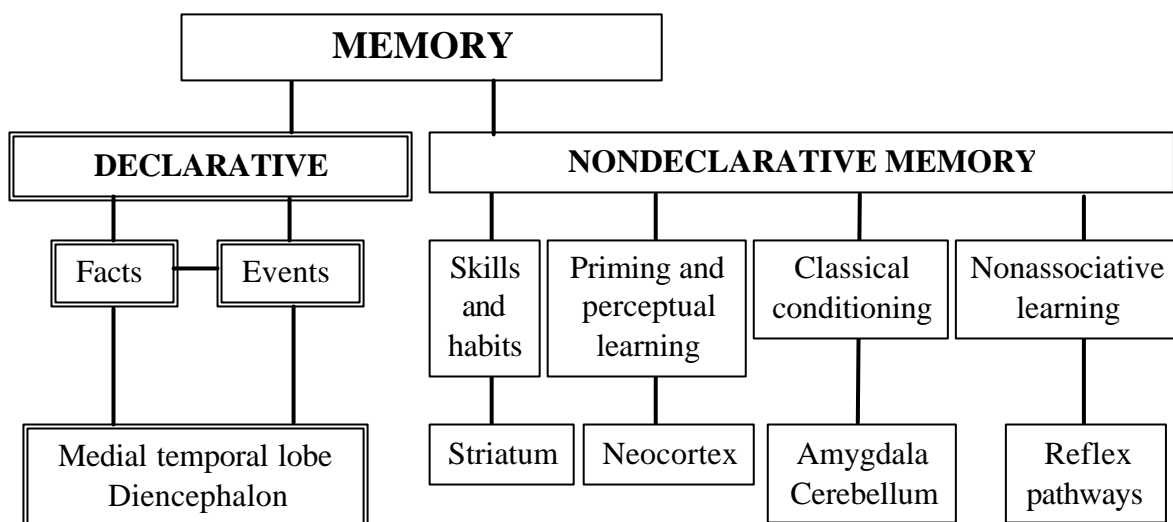

Figure 1. Schematic illustration of long-term memory systems and the associated brain structures (modified form Squire and Knowlton, 2000). Declarative memory is assessed with traditional memory tests.

Declarative and nondeclarative memory are described on the basis of their neuroanatomy and different properties and functions. Declarative memory is the product of a system that is dependent on medial temporal lobe and diencephalic structures, which operate with the neocortex. The important structures in the medial temporal lobe are the hippocampus, the entorhinal cortex, the parahippocampal cortex and the perirhinal cortex. These structures, presumably because of their widespread and reciprocal connections with cortical association areas, are essential for establishing long-term memory for facts and events. The medial temporal lobe memory system is crucial for the rapid acquisition of new information and for forming conjunctions between different stimuli. It has been suggested that the capacity for later retrieval is achieved because the hippocampal system has bound together the relevant cortical sites that together represent memory for a whole event. In partial epilepsy focal disorders often affect the medial temporal lobe structures that are important for declarative memory (Helmstaedter and Kurthen, 2001)

Nondeclarative memory refers to a collection of different learning abilities which do not depend on a single brain system. Nondeclarative memory is independent of declarative memory and is mediated by brain structures outside the medial temporal lobe (Squire and Knowlton, 2000; Eichenbaum, 2000).

Neuroimaging studies have demonstrated that both prefrontal cortices and medial temporal lobe structures, particularly in the parahippocampal cortex, activate during memory encoding process. Interaction between these regions seems to be crucial for the effective formation of memories. Laterality of the activation within these regions is modulated by the kinds of information; verbal materials almost always seem to activate left lateralized cortex and nonverbal materials seem to activate either left- or right-lateralized cortex, depending on the specific encoding task and encoding strategies. Retrieval shares much of the same anatomy as the encoding; the anterior prefrontal cortex specifically is active when episodic information is attempted to be retrieved, but activity in the hippocampus has rarely been reported (Buckner et al., 1999; Schacter and Wagner, 1999; Buckner 2000). However, a recent study showed that the hippocampus is selectively active during the retrieval of episodic memories. Activity in the hippocampus increased when retrieval was accompanied by recollection of the learning episode but not when memories were lacking the episodic content (Eldridge et al., 2000).

Memory is not fixed at the moment of learning but continues to consolidate with the passage of time. Memory consolidation at the cellular level is mediated by changes in the strength of synaptic connections among neurons, and the probable mechanism for this is long-term potentiation (LTP). It is a long-lasting increase in synaptic efficiency or strength that takes place when excitatory synapses are repetitively or extensively used. The hippocampus and anatomically related structures are involved for a period from several hours to weeks in consolidation processes that require new protein synthesis. Mesial temporal lobe structures may be a locus of temporary neural changes that influence the establishment of long-term memory, but the frequently proposed loci for long-term storage of information are the cerebral cortical areas and especially the association regions (Beggs et al., 1999; McGaugh, 2000; Markowitch, 2000).

2.2 Epilepsy

2.2.1 Definition and epidemiology

Epilepsy is not a specific disease or a single syndrome but rather a broad category of symptom complexes arising from disordered brain functions that themselves may be secondary to a variety of pathologic processes. Epilepsy refers to recurrent paroxysmal episodes of brain dysfunction manifested by stereotyped alterations in behavior. Epileptic seizures result from excessive, synchronous, abnormal firing patterns of neurons that are located predominantly in the cerebral cortex. Abnormal paroxysmal activity is usually intermittent and selflimited (Engel, 1989; Engel and Pedley, 1997). When unprovoked seizures occur recurrently, the condition is called epilepsy (Commission on Epidemiology and Prognosis of the International League Against Epilepsy, 1993).

The annual incidence rate of epilepsy varies between 24 and 50 per 100 000 person. Epilepsy is a disease with onset at the extremes of life; age-specific incidence is highest in the youngest age groups and in the elderly, but lowest during the adult years. Partial seizures are the predominant seizure type: slightly more than 50 % incidence cases have been classified as partial seizures (Hauser and Kurland, 1975; Keränen et al., 1989; Hauser, 1997).

2.2.2 Classification and prognosis

Epilepsies have been categorized and defined according to etiology or types of seizures they manifest and also by other associated clinical features. Idiopathic epilepsies are not associated with brain lesions, neurological abnormalities other than seizures, or mental impairment. They tend to be self-limited or respond readily to AEDs. Genetic factors are important, and manifestations are typically age related, starting in childhood or adolescence. In symptomatic epilepsies seizures are the consequence of an identifiable lesion or other specific etiology. When epilepsies are presumably symptomatic but currently of unknown specific etiology, they are termed cryptogenic (Commision on Epidemiology and Prognosis of the International League Against Epilepsy, 1993; Engel and Pedley, 1997). Depending on the seizures epilepsies are classified as partial when seizures originate in part of the brain, or generalized when seizures involve both sides of the brain in synchronous fashion from onset (Blume and Wolf, 1997).

The prognosis for most epilepsy patients is good in terms of seizure control: up to 70 of patients with epilepsy will have their seizures well controlled with appropriate AED treatment. However, despite optimal treatment 30 % of patients develop intractable epilepsy and continue to have recurrent seizures or other symptoms of epileptic syndrome restricting their ability to lead a full and safe life (Hauser and Hesdorffer, 2001). The long-term outcome of epilepsy is often predictable by observation of the early outcome of seizure control. The most consistently reported adverse prognostic factors for seizure outcome are the presence of complex partial or mixed seizure type and remote symptomatic etiology (Collaborative Group for the Study of Epilepsy, 1992; Cockerell et al., 1995; Mattson et al., 1996; Sillanpää, 2000).

2.2.3 Epileptic process

Most forms of epilepsy develop over a defined time period. That is, at some point in time, the brain functions normally, but either after a specific developmental sequence or in

response to some form of injury, a new state develops in which the neuronal circuits become hyperexcitable, leading to spontaneous recurrent seizures. This process is called epileptogenesis. Between the occurrence of injury and the emergence of epilepsy there is a latent period which may range from weeks to several years (Figure 2). A dynamic and evolving process takes place during this latent period and progressively alters neuronal excitability and establishes critical interconnections and perhaps requires critical structural changes before the first clinical seizure appears. The likelihood that epilepsy will develop after an epileptogenic insult depends on the area of the brain damaged, the type of damage, the age at which damage occurred and the genetic predisposition (Engel et al., 1997; McNamara, 1999).

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┌──────────┐     ┌──────────┐     ┌──────────────┐     ┌──────────┐
│Initiating│ ──▶ │ Latency  │ ──▶ │ Spontaneous  │ ──▶ │ Epilepsy │
│  event   │     │  period  │     │   seizures   │     │          │
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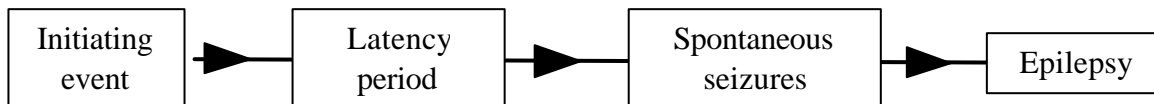
Figure 2. Development of epilepsy.

The development of epilepsy is a progressive phenomenon, and it is reasonable to assume that this process continues after initiation of seizures, at least in some cases, perhaps making seizures more severe or more difficult to treat, or leading to other aberrations in neuronal function that give rise to interictal behavioral disturbances (Engel et al., 1997). Current understanding of human epileptic process derives largely from studies of symptomatic TLE, which represents the most common form of human epilepsy and is modeled by scientists interested in the mechanisms of epileptogenesis (Engel, 1996).

2.3 Epilepsy and cognitive function

Cognitive functioning is a complex interaction of motivational, intellectual and mental abilities. It can be defined as the capacity of the brain to process information accurately and to program adaptive behavior. The origins of cognitive dysfunction in epilepsy are multifactorial (Figure 3). People with epilepsy as a group show impaired intellectual performance compared with healthy subjects matched for age and education (Perrine et al., 1991; Meador, 1996). However, considerable intersubject variability exists. Patients with well-controlled epilepsy usually have no significant cognitive problems, but a substantial minority of epilepsy patients have cognitive deficits, especially in attention, memory and motor speed (Perrine and Kiolbasa, 1999). Most of the studies of cognitive functioning in epilepsy are of patients with chronic epilepsy, but also newly diagnosed epilepsy patients have been shown to perform more poorly than control subjects in a number of cognitive tasks (Smith et al., 1986; Kälviäinen et al., 1992; Prevey et al., 1998; Pulliainen et al., 2000a).

Specific etiology	Genetic factors	Environmental factors

Neurological factors Laterality and anatomical locus	Cognitive disorders in epilepsy are multifactorial	Personality Psychosocial factors

Epileptic seizures	
Age at onset	Seizure type
Duration of epilepsy	Seizure frequency EEG discharges

Treatment
Antiepileptic drugs Epilepsy surgery
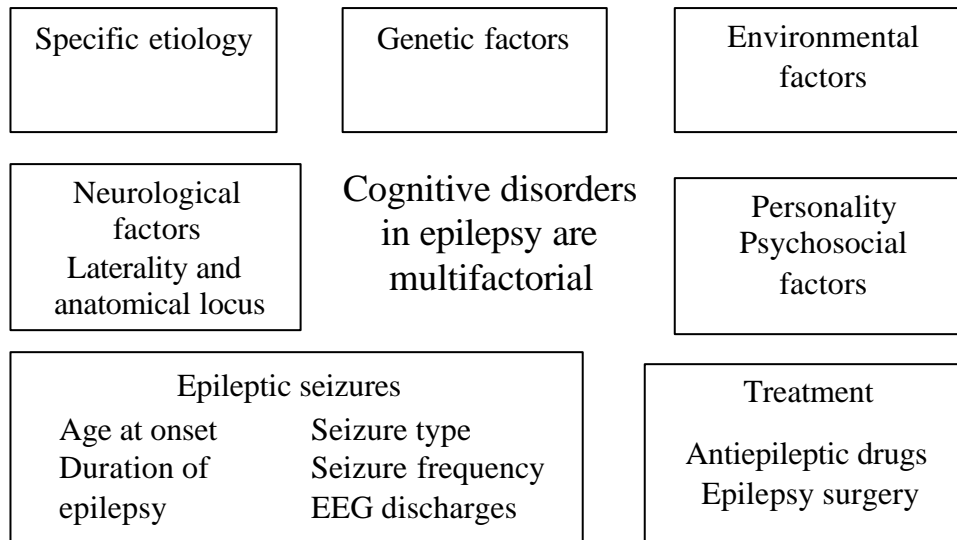
Figure 3. The origins of cognitive dysfunction in epilepsy.

2.3.1 Risk factors of cognitive impairment in epilepsy

Epilepsy, especially intractable epilepsy, is associated with risk factors for cognitive impairment. One of the most important risk factors that may detrimentally affect cognition in epilepsy is the age at onset of seizures, so that the earlier the age at the onset of epileptic symptoms, the more likely cognitive problems are to develop (Glosser et al., 1997). In a large study of neurocognitive and seizure variables as predictors of cognitive impairment in epilepsy, age at seizure onset was the best single indicator of intellectual ability and memory. However, the combined influence of the variables studied was relatively modest at predicting later cognitive status (Strauss et al., 1995). A long history of intractable TLE has been shown to be a risk of cognitive impairment. In a cross-sectional study patients with intractable TLE over 30 years had lower full-scale intelligence quotient (FIQ) than patients with epilepsy of shorter duration. The patient's educational level was a predictor for psychometric intelligence, suggesting that higher educational attainment is related to a higher reserve against cognitive impairment (Jokeit and Ebner, 1999).

Different etiologies of epilepsy have an important effect on the type and degree of cognitive deficits, and the cognitive impact of epilepsy closely correlates with the absence or presence of brain pathology, i.e. remote symptomatic epilepsy is associated with more cognitive impairment than idiopathic epilepsies. Seizure-related factors, such as seizure type, seizure frequency, duration and severity of seizures, as well as the lifetime number of seizures and structural cerebral damage due to repetitive or prolonged seizures or head injury, are associated with impairments in cognitive abilities (Perrine and Kiolbasa, 1999). Cognitive dysfunction has been shown to be greater in patients with generalized seizures than in patients with partial seizures (Giordani et al., 1985), and also in patients with early onset and long duration of epilepsy with repeated, especially generalized tonic-clonic seizures (Dodrill, 1992).

2.3.2 Follow-up studies of cognitive function in epilepsy

Long-term follow-up studies of epilepsy patients have shown cognitive functioning to be rather stable over long time periods, and only subtle losses are found in specific neuropsychological functions. In a study by Selva et al. (1994), patients with TLE were evaluated on two occasions on average two years apart: the second assessment was usually performed due to the patient's complaints of memory dysfunction. No changes were found from the first testing to the second on intelligence and memory measures beyond those that would be expected with normal adults. In a study by Dodrill and Wilensky (1992), patients with stable AED therapy and well-controlled epilepsy had no significant losses in cognitive abilities after five years' follow-up.

In a ten-year follow-up study of patients with intractable partial seizures, global measures of intelligence and neuropsychological functions did not deteriorate, but a few subtle losses were noted, particularly in tests that emphasize speed of response and visuo-spatial skills (Holmes et al., 1998). Correspondingly, in a Finnish ten-year follow-up study of a heterogeneous group of epilepsy patients, no systematic deterioration in cognitive functioning was found. The proportion of patients with improved test performance exceeded the proportion of those who showed impairments at follow-up assessment (Kalska, 1991).

2.3.3 Psychosocial and emotional factors and cognitive function

Epilepsy has long been a misunderstood and stigmatizing disorder. Perception of stigma as well as the psychological burden of chronic illness contributes to poor quality of life, locus of control, self-esteem, mood, and cognitive abilities (Hermann, 1991; Kwan and Brodie, 2001). Depressive disorders are widely recognized as representing a significant psychiatric complication of chronic epilepsy but the relation between depressive mood and cognition among patients with epilepsy has rarely been investigated.

A recent study of patients with chronic TLE showed that one third of the patients were depressed, and these patients had poorer performance in neuropsychological assessment of intelligence, language, visuo-perceptual ability, memory and executive function (Paradiso et al., 2001). On the other hand, in newly diagnosed patients with epilepsy, self-reported depressive or other negative mood states were not closely associated with cognitive functioning (Pulliainen et al., 2000b).

2.3.4 The effect of treatment of epilepsy on cognition

2.3.4.1 Antiepileptic drugs and cognition

Antiepileptic drugs are the major therapeutic intervention in epilepsy. However, it is estimated that 30 % of all patients with epilepsy have seizures that are not adequately controlled by AEDs, and at least 50 % of these patients are candidates for surgical therapy (Engel and Shewmon, 1993). Both these treatments may cause adverse cognitive effects.

AEDs can directly affect cognitive processing and interact with seizures. The general opinion represented in the literature claims that all AEDs can compromise cognitive functioning. The risk of cognitive side effects increases with polytherapy and higher AED blood levels. However, the individual variability is considerable: some patients do not tolerate low serum levels, where as others tolerate high levels without subjective or objective

effects. Pre-existing organic dysfunction may also increase the negative impact of AEDs. On the other hand, the use of AEDs should also exert a beneficial effect on cognition at least by controlling seizures (Devinsky, 1995; Perrine and Kiolbasa, 1999).

The major cognitive effects of AEDs have been seen in impairment of psychomotor and processing speed and of sustained attention: these effects may have an impact on learning and memory, and moreover AEDs may affect mood (Meador and Loring, 1991; Devinsky, 1995; Meador, 1996). The cognitive side effects of AEDs are generally mild: for instance, patients may fail to show practice effects experienced by normal control subjects (Smith, 1988; Prevey et al., 1996). Very sensitive tests are used to identify possible subtle changes in cognitive performance and thus statistically significant but clinically less meaningful findings may arise. However, in certain circumstances, e.g. in situations requiring intense vigilance and learning, effects of small magnitude may be significant for individual patients (Meador, 1996).

Recent research has demonstrated that cognitive effects of specific AEDs are variable. Striking differences among the commonly used AEDs, carbamazepine and valproate or even phenytoin, have not consistently been demonstrated, despite initial reports suggesting greater differential effects. Although data on newer AEDs, such as lamotrigine, gabapentin, vigabatrin and tiagabine are still limited, initial evidence suggests that these drugs have fewer adverse cognitive effects than the standard agents (Kälviäinen et al., 1996; Perrine and Kiolbasa, 1999; Kwan and Brodie, 2001). Among newer AEDs topiramate has a less favorable cognitive profile: it has been shown to cause psychomotor slowing, word finding difficulties and impaired immediate verbal memory at least with higher doses and if slow titration speed is not used. (Aldenkamp et al., 2000; Thompson et al., 2000).

2.3.4.2 Epilepsy surgery and cognitive function

Epilepsy surgery usually produces no general deterioration of cognitive functioning because primarily dysfunctional tissue is removed. It may even result in improved cognitive performance due to the elimination of the adverse effects of seizures and beneficial effects of reducing AED treatment. Cognitive functions may occasionally become impaired depending on the areas involved in the surgery. As most epilepsy surgery is directed at the temporal lobes, a selective decrease in memory functioning may occur. In particular, patients with left anterior temporal lobectomy who did not have evidence of atrophy in imaging studies and who had average or better presurgical verbal memory have been shown to be most at risk (Dodrill et al., 1993; Chelune and Najm, 2001).

2.4 Memory and epilepsy

Patients with epilepsy complain of memory problems more frequently than of other cognitive impairments. In partial epilepsy risk for memory impairment is increased because of the prominence of the temporal lobes in epileptogenesis and the importance of anterior and medial temporal lobe structures in memory processes (Jones-Gotman et al., 1993). The characteristics of memory impairment in epilepsy may reflect either temporary dysfunction (e.g. ictal or postictal), phasic disruption (following an epileptiform spike) or permanent structural damage (e.g. hippocampal sclerosis). In partial epilepsy, especially in TLE, the same pathology might be the cause of both the seizures and memory deficits (Halgren et al., 1991).

2.4.1 Seizures, epileptiform discharges and memory

Epileptic seizures disturb cognitive functioning and the brain is ictally dysfunctional, but post-ictal effects of seizures also usually impair alertness and cognitive performance over considerable periods. In a study of postictal memory deficits, the duration of impaired memory performance varied individually, the time of total cognitive recovery after seizure and after reorientation to the situation lasting up to one hour (Helmstaedter et al., 1994). Isolated brief seizures over a 48-hour period did not make the patients forget material they had recently learned (Bergin et al., 1995). In another study, patients with left-sided TLE showed impaired retention of newly learned verbal material relating to the occurrence of seizures during 24 hour retention interval (Jokeit et al., 2001). This suggests that seizures impair the consolidation of memory or accelerate forgetting.

Cognitive impairments in complex information processing tasks have been observed in patients with interictal, or subclinical, epileptiform discharges. By definition this kind of transient cognitive impairment has to be separated from the ictal and postictal effects of epileptic seizures. In memory tasks, the impairing effects of focal and generalized subclinical epileptiform activity have been shown to be greatest when the activity occurs during the presentation of the stimulus (Aarts et al., 1984). Correspondingly, in a small study of epilepsy patients with intracranial depth electrodes, the majority of the subjects showed deterioration in the accuracy of working memory performance during mesial temporal spiking (Krauss et al., 1997).

2.4.2 Temporal lobe epilepsy and memory

Epilepsy patients, especially with TLE, have been shown to have material-specific memory deficits related to the side of the epileptic focus, and after a unilateral surgical resection for seizure relief, to the side of temporal-lobe excision (Delaney et al., 1980; Loiseau et al., 1983; Mungas et al., 1985; Hermann et al., 1987; Rausch, 1991). Neuropathological studies have shown that presurgical memory impairment, primarily in verbal memory, is associated with neuron loss in the resected left hippocampus (Sass et al., 1990; Hermann et al., 1997). In addition, significant associations have been found between MRI volume measurements of the left hippocampus and verbal memory percent retention scores (Lencz et al., 1992). In recent studies the results have been somewhat contradictory. In a study of epilepsy patients who were candidates for temporal lobe surgery, verbal memory test scores did not correlate with hippocampal volumes, but regression analyses indicated that a significant part of the variation in test scores could be explained by MRI hippocampal measures in conjunction with age at testing and age at onset of epilepsy (Baxendale et al., 1998). Moreover, chronic left TLE patients have been shown to have impaired memory irrespective of the presence of structural damage, including hippocampal sclerosis (Giovagnoli and Avanzini, 1999).

The relationships between the left medial temporal lobe and verbal memory, and between the right medial temporal lobe and visual memory, have long been recognized. However, the relationship between right temporal lobe and visual memory has been much more variable than the relationship between left temporal lobe and verbal memory, and the lateralized memory deficits in TLE have been detected more consistently in verbal memory (Hermann et al., 1994; Moore and Baker, 1996). It has been suggested that robust associations between verbal memory deficits and pathology of the dominant temporal lobe, and the difficulties in documenting the association between visual memory deficits and the nondominant temporal lobe, reflect the inadequacies of the traditional memory tests, as many of the visual tests can

also be coded verbally. In addition, difference in the cognitive requirements of the tests may contribute to difficulties in lateralization of memory dysfunction (Jones-Gotman et al., 2000).

Most studies of memory in epilepsy have assessed the formation of new memories, and there has been little research into the effects of epilepsy on remote memory or memory for long time intervals. Two recent studies have provided evidence of a broader memory disturbance in TLE than has been previously shown. In a study of memory for past events (Bergin et al., 2000), patients with TLE performed less well on a test of knowledge of public events than other epilepsy patients and controls. Correspondingly, in a prospective study of verbal memory over an eight-week retention interval, patients with left TLE performed worse on the long-term memory test compared with right TLE patients and controls. It was suggested that accelerated forgetting of verbal material in left TLE may be caused by epileptic activation that compromises memory consolidation (Blake et al., 2000).

2.4.3 Subjective memory

Despite substantial evidence of memory impairment in epilepsy, studies examining the relationship between subjective and objective memory have often failed to detect an association between experienced memory problems and consistent memory deficits. Subjective memory problems reported in questionnaires have been found to correlate with performance in memory tasks as well as with higher levels of anxiety and depression (Thompson and Corcoran, 1992; Giovagnoli et al., 1997). In a study of quality of life in epilepsy, verbal memory test scores correlated with self-reported memory difficulties, and appeared to contribute to overall quality of life, although less than did mood and psychomotor speed (Perrine et al., 1995). However, in a recent study of memory change after temporal lobe epilepsy surgery, no relationship was found between subjective and objective memory decline. It was suggested that subjective memory decline may reflect depression or mood disorder rather than organically-based memory decline (Sawrie et al., 1999). Failure to find a clear association between subjective and objective memory impairment may be caused by poor ability of tests to identify everyday memory problems. In addition, memory complaints may be provoked by a variety of factors, including mood.

2.4.4 Antiepileptic drugs and memory

Although epilepsy patients treated with AEDs complain of memory difficulties and assume that AEDs impair memory performance, earlier AED studies rarely evaluated memory performance. In the 1980s a series of studies carried out at the National Hospitals in the United Kingdom (Thompson et al., 1981; Thompson and Trimble, 1983; Trimble and Thompson, 1984) evaluated immediate and delayed recall and delayed recognition of pictures and words. The results showed impairment in immediate recall associated with high serum levels of AEDs, which was thought to be secondary to decrements of concentration and mental slowing.

In studies reported during the 1990s, memory tasks, especially word list learning tasks, have been included in most of the neuropsychological test batteries for studying cognitive effects of AEDs. Dodrill and colleagues investigated psychological effects of many AEDs with the same neuropsychological test battery (Dodrill et al., 1995; 1997; 2000) and no negative effects on memory performance have been found. Meador and colleagues has used a randomized crossover study design with the same test battery in investigating cognitive

effects of AEDs, mainly in healthy adults. In volunteer studies, untoward effects on memory have been found (Meador et al., 1993), but patients with partial complex epilepsy showed no significant differential effects of AEDs on memory performance (Meador et al., 1990).

2.4.5 Follow-up studies of memory performance

Long-term follow-up studies of memory in epilepsy are rare. Immediate verbal and visual memory were evaluated in 5-year and 10-year follow-up studies of cognitive abilities, and no significant deterioration was found (Dodrill and Wilensky, 1992; Holmes et al., 1998). Mesial temporal lobe epilepsy (MTLE) is a specific TLE syndrome associated with hippocampal sclerosis (Engel, 1996). A recent cross-sectional study investigated interactions of memory performance and aging in intractable MTLE, and found that age regression measures of memory were much the same in patients and healthy individuals, aged 12 to 51 years. It was concluded that no accelerated deterioration of memory in MTLE can be found, even though the memory performance of the patients was inferior to that of the controls (Helmstaedter and Elger, 1999).

2.4.6 Newly diagnosed partial epilepsy and memory

Studies concerning memory performance of newly diagnosed and unmedicated patients with epilepsy are few, and those are mostly reports of the baseline evaluation in AED studies.

Our preliminary data from a study of adults with newly diagnosed seizure disorder suggested that the patients as a group have subtle memory and attention dysfunctions, although most of them had had single seizures and were not diagnosed with epilepsy or given AED treatment (Kälviäinen et al. 1992). In the Veterans Affairs Cooperative Study 264 adult patients with partial epilepsy showed mild to moderate impairment in verbal memory, decreased learning and ability to retain information over delay, as well as deficits in concentration and motor function (Prevey et al., 1996; Prevey et al., 1998). In a recent study, mildly impaired short interval retention of figural information and/or increased distractibility of figural memory was found in adult patients with newly diagnosed epilepsy (Pulliainen et al., 2000a).

Although associations between memory performance and hippocampal volumes have been found in intractable TLE, such findings are rare in newly diagnosed TLE. A preliminary report of newly diagnosed left TLE patients has demonstrated a positive significant correlation between left hippocampal volume and verbal memory (Kälviäinen et al., 1997).

Follow-up studies of newly diagnosed epilepsy patients with AED treatment, have shown no decline in cognitive functioning. However, the patients have failed to show practice effects that were experienced by normal control subjects (Smith, 1988; Prevey et al., 1996). Similarly, practice effect at six-month reassessment was clearly shown in test scores of healthy controls but was less evident and slightly different in two AED groups (Pulliainen and Jokelainen 1994). It has been suggested that the lack of practice effect may be the first indicator of adverse AED effects (Smith, 1988). It has also been suggested that any mild decline in cognitive function may be masked by a practice effect bias, i.e. the improvement in test scores that accompanies retesting (Meador, 1997).

3 AIMS OF THE STUDY

The purpose of the study was to evaluate verbal memory performance of patients with newly diagnosed partial epilepsy.

The specific aim of the present series of studies was to answer the following questions:

1. Is verbal memory affected in newly diagnosed partial epilepsy? (I)

2. Does the course of left temporal lobe epilepsy affect verbal memory performance? (II)

3. Does verbal memory performance at the time of the diagnosis of partial epilepsy have prognostic value for seizure outcome? (III)

4. Does the antiepileptic drug (AED) treatment affect verbal memory performance, and do the AEDs influence differently the practice effect in repeated assessments of verbal memory ? (IV, V)

4 SUBJECTS AND METHODS

4.1 Subjects with epilepsy

The study was conducted in the Neurological Department of Kuopio University Hospital between 1985 and 1998. The study was approved by the Ethics Committee of Kuopio University Hospital. All subjects gave informed consent before participating in the study.

The study included five different, but partly overlapping samples of subjects aged 15 to 64 at the time of the investigations. The samples were drawn from a population of newly diagnosed and chronic patients treated in the Department of Neurology in Kuopio University Hospital.

The newly diagnosed epilepsy patients included in the study were untreated adults and adolescents. Patients with alcohol related seizures, current alcohol or other drug abuse, progressive neurological disorders, mental retardation, severe psychiatric problems, or other severe medical disorders were excluded from the study. The pretreatment seizures were classified according to the revised International Classification of Epileptic Seizures (1981). Subjects underwent a full neurological examination, brain computed tomography (CT) and/or magnetic resonance imaging (MRI), a comprehensive neuropsychological evaluation and EEG before starting AED treatment. On the basis of all available information the putative etiology of the epilepsy was determined. Patients with unprovoked epileptic seizures were included in the study.

The patients with chronic TLE had had epilepsy for at least ten years and had had neuropsychological evaluation for clinical purposes or as a part of AED study. Patients with both remote symptomatic seizures and cryptogenic seizures (Hauser and Kurland 1975) were included in the study. Epilepsy was classified on the basis of seizure semiology, findings on the interictal scalp EEG or intensive video-EEG monitoring and/or standard qualitative MRI. The patients had partial seizures with or without secondary generalization. Most of the patients with chronic TLE had refractory seizure disorder despite adequate treatment with one to three AEDs.

4.2 Control subjects

The control group of 48 volunteers consisted of hospital staff with different jobs and their friends and relatives. They had no history of significant medical problems and were not taking any CNS-active medications. (Studies I, III). In Study II the number of controls was

Table 1. Demographic data and etiology of epilepsy in patient groups and in control groups in Studies I-III.

	Study I Patients	Controls	Study II Patients NLTLE	CLTLE	Controls	Study III Patients Group I	Group II	Controls
Number of patients	56	48	39	16	46	79	10	48
Male/Female	23/33	23/25	19/20	8/8	21/25	38/41	5/5	23/25
Age	34 ± 14	31 ± 12	35 ± 15	42 ± 10	31 ± 12	34 ± 15	29 ± 12	31 ± 12
Education (years)	11 ± 3	11 ± 2	10 ± 3	11 ± 3	12 ± 2	11 ± 3	11 ± 2	11 ± 2
FIQ	107 ± 13	111 ± 11				107 ± 13	106 ± 12	111 ± 11
VIQ			104 ± 14	101 ± 16	109 ± 11			
Etiology of epilepsy								
Cryptogenic	56 (100%)		24 (61 %)	12 (75 %)		60 (76 %)	5 (50 %)	
Remote symptomatic			15 (39 %)	4 (25 %)		19 (24 %)	5 (50 %)	

FIQ: Full Scale Intelligence Quotient
VIQ: Verbal Intelligence Quotient
NLTLE: newly diagnosed left temporal lobe epilepsy
CLTLE: chronic left temporal lobe epilepsy
Group I: patients with satisfactorily controlled epilepsy
Group II: patients with refractory seizures

46 because the two youngest controls were excluded in order to make the mean age similar to that in the study groups. In addition, 59 patients with a single seizure before the neuropsychological assessment and no relapse of seizures or AED treatment during the 12-month follow-up period served as a control group for neuropsychological evaluation in Study V.

4.3 Study groups and schedules

Study I: This study investigated verbal memory performance in newly diagnosed partial epilepsy. Fifty-six untreated adult patients (aged 15 to 63 years) with newly diagnosed partial epilepsy were studied. Only patients with no known etiological factor for epilepsy (i.e. cryptogenic seizures) on the basis of clinical and CT and/or MRI data were included. Neuropsychological performance was evaluated prior to AED treatment in newly diagnosed epilepsy patients and compared with that of 48 normal controls with no history of significant medical problems and not taking any CNS-active medications. The patients and controls matched closely with regard to demographic data, which are presented in Table 1.

Study II: This study compared verbal memory performance in newly diagnosed and chronic LTLE. Subjects were a sample of 39 untreated adult patients with newly diagnosed LTLE and 16 patients with chronic LTLE (aged 16 to 60 years). The patients were diagnosed on the basis of seizure description, findings on the scalp EEG or intensive EEG monitoring and/or standard qualitative MRI. Forty-six healthy volunteers served as a control group. Verbal memory performance and verbal intellectual ability were assessed in newly diagnosed patients before AED treatment was started and in chronic LTLE for clinical purposes or as a part of AED study. A subgroup of 20 newly diagnosed LTLE patients also had a five-year follow-up evaluation of cognitive performance. The demographic data of the patient groups and the controls are presented in Table 1.

Study III: This study evaluated verbal memory impairment as a predictor of seizure outcome in newly diagnosed partial epilepsy. Eighty-nine consecutive untreated adult patients, aged between 15 to 63 years, with newly diagnosed partial epilepsy entered the study. Both patients with remote symptomatic seizures and patients with cryptogenic seizures were included. Forty-eight healthy volunteers served as a control group for the neuropsychological evaluation. The demographic data are presented in Table 1. After a prospective follow-up period the patients were divided into two groups according to two-year seizure outcome: Group I (N = 79), patients who had satisfactorily controlled epilepsy (seizure free or only occasional seizures), and Group II (N = 10), patients who had refractory seizure disorder despite of adequate drug treatment. The seizure disorder was termed refractory if more than one generalized or more than four partial seizures occurred during one year. On the other hand, occasional seizures meant no more than one generalized or four partial seizures per year. The baseline neuropsychological, clinical and EEG data were analyzed as prognostic factors for two-year seizure outcome.

Studies IV, V: These two follow-up studies evaluated verbal memory performance during AED treatment in two different samples of newly diagnosed patients with epilepsy. Characteristics of the study groups are presented in Table 2.

Table 2. Demographic data and etiology of epilepsy in patient groups in Studies IV and V.

	Study IV Patients		Study V Patients		
	OXC	PHT	VGB	CBZ	Untreated
Number of patients	14	15	25	24	59
Male/Female	5/9	6/9	11/14	11/13	28/31
Age	34 ± 14	33 ± 12	38 ± 15	36 ± 16	35 ± 13
FIQ	98 ± 12	100 ± 14	107 ± 13	104 ± 13	106 ± 13
Etiology of epilepsy					
Cryptogenic	11 (79 %)	13 (87 %)	16 (64 %)	19 (79 %)	47 (80 %)
Remote symptomatic	3 (21 %)	2 (13 %)	9 (36 %)	5 (21 %)	12 (20 %)

FIQ: Full Scale Intelligence Quotient
OXC: oxcarbazepine, PHT: phenytoin, VGB: vigabatrin, CBZ: carbamazepine

In **Study IV,** 37 adult patients with newly diagnosed epilepsy and normal intellectual capacity initially entered the study. The patients were randomly allocated to treatment with either oxcarbazepine (OXC) or phenytoin (PHT). Because of treatment failures eight patients were withdrawn from the study, and 29 patients completed the one-year follow-up. Memory performance was evaluated at baseline and after 12 month treatment with either OXC or PHT.

In **Study V,** 100 newly diagnosed patients aged 15 to 64 years who had had at least two unprovoked epileptic seizures during the previous 2 years or one seizure and distinct EEG changes indicative of epilepsy were included in the study. Patients were randomized to treatment with either vigabatrin (VGB) or carbamazepine (CBZ). Patients who did not respond to the study drug, had intolerable side effects, or had problems with compliance were withdrawn from the study. Forty-nine successfully treated patients completed the one-year follow-up. Neuropsychological evaluations were performed at baseline and at 12 months. The control group, 59 patients with a single epileptic seizure and no seizure relapse or AED treatment during one year, had neuropsychological evaluations at baseline and at 12-month follow-up.

4.4 Neuropsychological assessment

The neuropsychological tests used in this study were part of a comprehensive test battery which was designed to be used in long-term evaluation and follow-up of cognitive abilities in epilepsy in the Department of Neurology, Kuopio University Hospital. The results of cognitive functions other than intellectual ability and verbal memory performance are not reported in this study.

General intellectual ability: On the basis of six subtests of the Wechsler Adult Intelligence Scale (Wechsler 1955), Information, Similarities, Digit Span, Digit Symbol, Picture Completion and Block Design, the score for general intellectual ability (Full Scale Intelligence Quotient, FIQ) was estimated. In Study II, Verbal Intellectual Ability (VIQ) was estimated on the basis of three subtests (Information, Similarities, Digit Span) of the

Wechsler Adult Intelligence Scale (Wechsler 1955) or Wechsler Adult Intelligence Scale-Revised (Wechsler 1981).

Verbal learning and memory: Verbal memory was assessed using the Logical Prose Subtest, Story A of the Wechsler Memory Scale (Wechsler 1945) as a measure for logical verbal memory. The immediate verbatim recall score was based on the number of story units immediately recalled. The delayed score was based on the units recalled from the story after a minimum of 60 minutes later. Delayed recall scores were divided by immediate recall scores to give the percentage of paragraph information retained after delay.

The List Learning Test was used to assess learning and recall of words. It is a modification of the Rey Auditory Verbal Learning Test (Lezak 1995). The test consisted of oral presentation of 15 semantically unrelated words, which subjects were requested to learn and recall in four consecutive trials. Scores for learning and immediate memory were the number of words recalled in each learning trial, and the total immediate recall score was the sum of correctly recalled words. Serial position effects were evaluated by both the primacy score, which was summarized across learning trials from the first four words of the list, and the recency score, which was summarized across learning trials from the last four words of the list. The score for delayed memory was the number of words recalled after a minimum of 60 minutes. A score for percent retention of words after delay was calculated by dividing the number of words correctly recalled after delay by the number of correct responses on the fourth learning trial. The score for delayed recognition was the number of correctly recognized words (15 targets and 15 distractors). False positive errors constituted a separate score.

The intellectual ability evaluation was identical in all studies. In Study IV which was the first of the follow-up studies of patients with epilepsy verbal memory assessment was performed with another List Learning test. A list of 10 words was read five times to the subject, and after each presentation, an immediate free recall was elicited. The delayed recall of words was elicited after 60 minutes filled with other tasks. The scores were the sum of the immediately recalled words and the number of correctly recalled words after delay.

4.5 Quantitative MRI methodology

The patients who had quantitative MRI examination, were scanned with a 1.5 T Magnetom (Siemens; Erlangen, Germany) using a standard head coil and a tilted coronal 3D gradient echo sequence (MP-RAGE: TR 10 ms, TE 4 ms, TI 250 ms, flip angle 12°, FOV 250 mm, matrix 256 × 192, 1 acquisition). This produced 128 T1-weighted partitions with a slice thickness of 2.0 mm that were oriented at right angles to the long axis of the hippocampus. All quantitative MRIs were analyzed by the same observer who was blind to the laterality of the seizure focus. The hippocampal volume included the volumes of the dentate gyrus, hippocampus proper, and the subicular complex. The boundaries of the region of interest were outlined by a trackball-driven cursor on computer images that included the whole rostrocaudal end of the hippocampus. The number of voxels within the region was calculated using an in-house program developed for a standard work console. The intraobserver variability was 6.7 % for the hippocampal volumes (Soininen et al., 1994; Kälviäinen et al., 1998). A ratio was used to correct hippocampal volumes for individual variance in head size according to Cendes et al. (1994) with a modification. This consisted of dividing the mean brain area (obtained from the coronal section cut at the level of the anterior commissure) of the controls by the corresponding brain area of the patient. In each patient, this ratio was then

multiplied by the measured volume of the hippocampus. Hippocampal volume reduction was classified as marked when the volume of the structure was at least 2 standard deviations (SD) below the mean volume in control material.

4.6 Statistical analysis

The data were analyzed by using the SPSS. Continuous variables are presented as means and standard deviations. Categorical data are presented as frequencies and were analyzed using the Chi-Square test or Fisher's exact test. Differences between two groups were assessed by Student's t test and in comparisons of three groups by an analysis of variance or covariance (ANOVA / ANCOVA), using age, FIQ and/or education as covariates. Pairwise comparisons were performed by one-way analysis of variance with Duncan's post hoc test. Nonparametric Kruskall-Wallis one-way ANOVA was used when significant inequality of variances existed, and pairwise comparisons were performed with Mann-Whitney tests, and Bonferroni correction was used when appropriate. Correlations were calculated using Pearson's correlation analysis (Studies I, II, IV). $P < 0.05$ was considered statistically significant.

The extent of memory dysfunction was estimated with cutoff scores which were determined so that mild memory dysfunction in a test was defined as scores falling one SD below the mean performance of the control group. For clinically meaningful, moderate memory impairment, the cutoff point was defined as scores falling two SDs below the control mean. The cutoff scores were subsequently used to identify the number of subjects scoring in the mildly or moderately deficient range on memory measures (Studies I and II).

Neuropsychological follow-up data were analyzed with a paired t test (Study II), with multivariate analysis of variance for repeated measures with the time as the within subjects factor and the group as the between subjects factor (MANOVA, Study IV) and in Study V IQ and age were used as covariates (MANCOVA).

In Study III, a backward stepwise logistic regression analysis was used to analyze predictive factors of two-year seizure outcome. The clinical variables included in the analyses were etiology of epilepsy, seizure type, pretreatment number of seizures, presence of spike focus and paroxysmal epileptiform EEG activity and age at the time of diagnosis. Neuropsychological variables were FIQ and verbal memory variables selected on the basis of analyses between the two epilepsy outcome groups and the controls. Odds ratios with 95% limits of confidence intervals (CI) were calculated from the logistic regression model. CI limits were calculated using the formula CI = exp (B $\forall$ 1.96 SE [B]) where B is the B coefficient in the logistic model.

In addition, in Studies IV and V the magnitude of change from baseline to one-year follow-up assessment was estimated by calculating the effect size, ES (Cohen, 1988) which is the difference between the baseline and the follow-up means divided by an averaged SD. It expresses the change as a standardized difference in mean scores. The effect size is used as an estimation for meaningful change which is of medium or moderate size when ES = 0.5.

5 RESULTS

5.1 Verbal memory performance in newly diagnosed partial epilepsy (I)

Patients with newly diagnosed partial epilepsy of cryptogenic etiology had worse performance in delayed recall of the word list ($p < 0.001$), although the learning and the total immediate recall of the words were comparable with the performance of the controls (Table 3). Also percent retention of the words was less in the patient group than in the control group ($p < 0.001$). The patients and the controls had comparable performance in delayed recognition of the word list, as well as in immediate and delayed recall of logical prose.

As shown in Table 4. the patients had mild memory dysfunction more frequently than the controls in delayed recall of the words ($p < 0.001$) and in percent retention of the words (28 / 50 % vs. 5 / 10 %; $p < 0.001$). Delayed recall of the words was also moderately impaired in a higher proportion of the patient group ($p < 0.05$). In addition, the patients showed moderate impairment in total immediate recall of the words ($p < 0.05$) as well as in delayed recognition of the words ($p < 0.05$).

Table 4. Number of patients with mild and moderate memory dysfunction in the list learning test.

	Study I Patients	Controls	Study II NLTLE	CLTLE	Controls
List learning					
Immediate recall					
Mild (< 1 SD)	19 (34 %)	8 (17 %)	17 (44 %)[c]	9 (56 %)[c]	8 (17 %)
Moderate (< 2 SD)	5 (9 %)[b]	0	0	0	0
Delayed recall					
Mild	29 (52 %)[a]	7 (15 %)	22 (56 %)[d]	11 (69 %)[d]	7 (15 %)
Moderate	13 (23 %)[c]	2 (4 %)	14 (36 %)[d]	5 (31 %)[c]	2 (4 %)
Delayed recognition					
Mild	14 (25 %)	9 (19 %)	14 (36 %)	12 (80 %)[d,e]	12 (26 %)
Moderate	8 (14 %)[b]	1 (2 %)	6 (16 %)	4 (27 %)[c]	1 (2 %)

NLTLE: Newly diagnosed left temporal lobe epilepsy, CLTLE: Chronic left temporal lobe epilepsy, SD: Standard deviation
Memory dysfunction more frequently than in the control group:
[a]Chi Square test, $p < 0.001$, [b]Fisher's Exact test, $p < 0.05$
[c]Chi Square test, $p < 0.05$, [d]Chi Square test, $p < 0.001$
Memory dysfunction more frequently than in NLTLE: [e] Chi Square test, $p < 0.05$

5.2 Verbal memory in newly diagnosed and chronic left temporal lobe epilepsy (II)

Newly diagnosed and chronic patients with LTLE and the controls had comparable performance in the Story Recall test. Differences between the groups were found in the List Learning test (Table 3). In the learning of the word list, performance improved across the four trials in all groups similarly ($p < 0.001$). However, the controls learned the words more effectively than both the LTLE groups ($p < 0.01$; Figure 4).
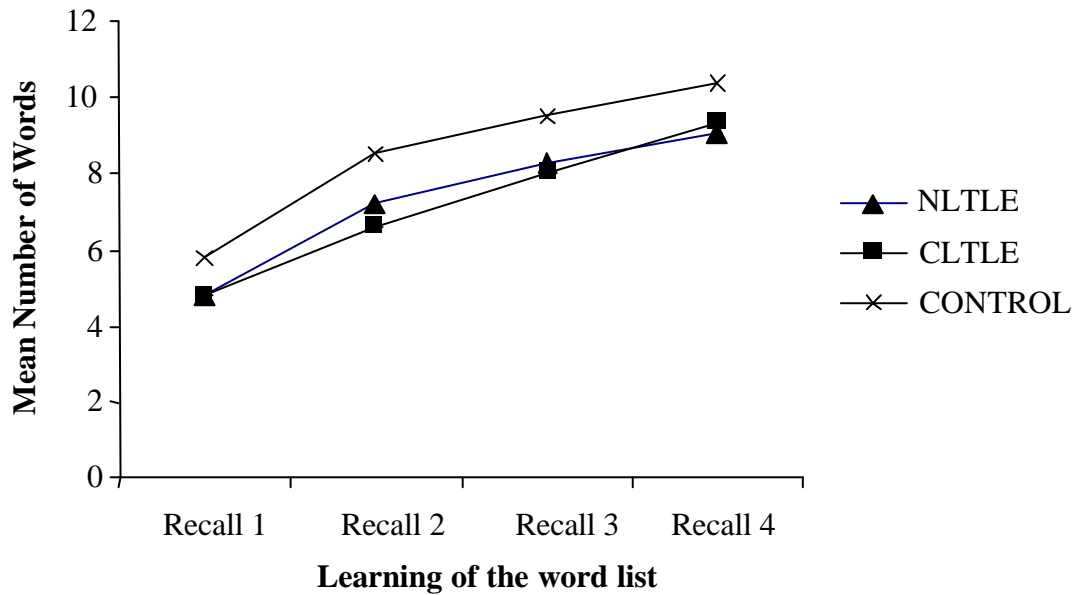

Figure 4. Mean number of words recalled in the List learning test.
NTLE: newly diagnosed left temporal lobe epilepsy; CLTLE: chronic left temporal lobe epilepsy.

In the List Learning Test, significant differences were found in the total immediate recall of the words ($p < 0.01$), and in delayed recognition of the words ($p < 0.001$), as well as in delayed recall of the words ($p < 0.001$) and in percentage retained of the words ($p < 0.001$). In the immediate recall of the word list, patients with newly diagnosed LTLE ($p < 0.01$) and those with chronic LTLE ($p < 0.05$) learned fewer words than the controls. Delayed recognition of the words was impaired in the chronic LTLE group compared with both normal controls ($p < 0.001$) and newly diagnosed LTLE patients ($p < 0.05$). Delayed recall and the retention of words were impaired in both LTLE patient groups compared with controls ($p < 0.001$ in both comparisons; Table 3).

Memory dysfunction was determined with the cutoff scores, and the only difference between newly diagnosed and chronic LTLE patients was shown in the higher proportion of patients with mild memory dysfunction in delayed recognition of the words in the chronic LTLE group ($p < 0.05$). Compared with the controls, the number of newly diagnosed LTLE patients with a mild memory dysfunction in immediate recall ($p < 0.05$) and in delayed recall ($p < 0.001$) of the word list was higher. In addition, their performance in the delayed recall of words was more often below the cutoff point for moderately impaired performance ($p < 0.001$). In the chronic LTLE group, there was a mild dysfunction in immediate recall more

frequently than in the control group (p < 0.05), as well as in delayed recall (p < 0.001) and in delayed recognition (p < 0.001) of the word list. Moderate impairment was observed in delayed recall (p < 0.05) and in delayed recognition (p < 0.05) of the list.

Moderately impaired delayed recall of the word list was associated with the presence of secondarily generalized seizures in newly diagnosed LTLE (p < 0.05), but memory impairment was not significantly associated with the etiology of epilepsy in LTLE groups. Early age (≤ 5 years) at onset of seizures was related to mild dysfunction in delayed recognition of words only when the two LTLE groups were combined.

Moreover, in a subgroup of patients with quantitative MRI data, hippocampal volumes did not correlate with verbal memory scores and there was no significant association between memory impairment and marked hippocampal volume reduction.

Five-year follow-up data of twenty newly diagnosed LTLE patients did not show any deterioration of verbal memory performance over time, whereas, in delayed recall of the word list the performance at five-year assessment was better than at baseline (p < 0.01).

5.3 Verbal memory impairment as a prognostic factor in partial epilepsy (III)

The patients in this study were divided into two groups according to two-year seizure outcome: patients with satisfactorily controlled epilepsy (n = 79), those and with refractory seizures (n = 10), and the baseline data at the time of the diagnosis of epilepsy were analyzed as prognostic factors of seizure outcome after two-year treatment. At the time of the diagnosis the patients with refractory seizures at two years had spike focus in EEG in a higher proportion (p < 0.01), especially left-side spike focus (p < 0.05). Verbal memory performance of the two outcome groups and the controls differed significantly in immediate recall of the words (p < 0.05), in delayed recall of the list (p < 0.001) and in delayed list recognition (p < 0.05): age and FIQ were covariates. Patients with refractory seizures learned fewer words than the controls and were poorer in delayed recognition than the two other groups, and the controls performed better in delayed recall of the words than the patient groups (p < 0.05 in all comparisons; Table 3).

To study predictors of two-year seizure outcome, logistic regression analysis was performed with five clinical and EEG variables as well as age and FIQ. Three verbal memory measures were selected on the basis of differences in test performance between the epilepsy patients and the controls, and the patients were classified according to presence of clinically meaningful moderate impairment in verbal memory performance (scores ≤ 2 SD from the control mean). Six risk factors were found to be significant predictors of refractory epilepsy: younger age at the time of diagnosis, moderately impaired performance in immediate recall and in delayed recognition of the word list, presence of spike focus in EEG, remote symptomatic etiology of epilepsy, and partial complex or mixed seizure type before the diagnosis (Table 5).

Table 5. Predictors of refractory seizure disorder in newly diagnosed patients with partial epilepsy.

Predictor	p value	OR	95 % CI
Younger age at diagnosis	0.02	0.89	0.82 - 0.98
Immediate list recall	0.04	12.1	1.06 - 136
Delayed list recognition	0.02	12.5	1.56 - 99.7
Spike focus	0.004	97.0	4.39 - 2140
Symptomatic etiology	0.04	10.0	1.16 - 86.3
Partial complex/mixed seizure type	0.02	16.0	1.52 – 168

OR: Odds ratio, CI: confidence intervals of odds ratios

The logistic regression model predicted the correct result in accordance with the observed two-year seizure outcome in 94 % of the cases. However, the model was better in predicting two-year outcome of satisfactorily controlled epilepsy (100 % correct) than refractory seizures (50 % correct). The contribution of verbal memory impairment to predicting two-year seizure outcome was estimated with a further logistic regression analysis which was performed with clinical variables, age, presence of spike focus in EEG, etiology of epilepsy and seizure type, whereas verbal memory impairment was left out of the analysis. With these predictors, 99 % of the patients with satisfactorily controlled epilepsy were correctly classified, but only 20 % of the patients with refractory seizures were correctly classified when the verbal memory variables were not included in the analysis.

As verbal memory impairment is frequently associated with LTLE, the contribution of left temporal spike focus to the seizure outcome was studied by performing an additional logistic regression analysis with original variables and left temporal spike focus. The significant independent predictors of refractory seizure disorder were both the presence of left temporal spike focus (OR 15.4 p = 0.02) and impairment in delayed list recognition (OR 7.8 p = 0.03). Most (99 %) of the patients with satisfactorily controlled epilepsy and 40 % of those with refractory seizures were correctly classified with this model.

5.4. Verbal memory in antiepileptic drug studies (IV, V)

In both AED studies, the groups that were compared did not differ in demographic and clinical characteristics (Table 2) or in pretreatment neuropsychological test scores (Tables 6 and 7). During the follow-up there was no significant decline in verbal memory performance in any of the groups studied. The mean test scores at baseline and at follow-up were about the same or slightly better in the study groups.

Table 6. The mean test scores in 10-word list learning task at baseline and after 12 month treatment.

Word list	Drug	Baseline	12-month	ES
Immediate recall	OXC	39.4 ± 5.7	39.2 ± 4.0	0.04
	PHT	35.7 ± 6.0	37.5 ± 5.0	0.3
Delayed recall	OXC	6.3 ± 2.8	5.9 ± 2.7	0.1
	PHT	4.7 ± 2.5	5.6 ± 2.7	0.3

Differences ns.
ES: effect size, OXC: oxcarbazepine, PHT: phenytoin

Study IV: There were no significant differences in immediate or delayed recall of the word list between the newly diagnosed patient groups after one-year treatment with OXC or PHT (Table 6). The mean memory test scores tended to be mostly the same at baseline and at one-year follow-up assessment. The extent of change from baseline to one-year follow-up assessment estimated with the effect size (ES) was less than 0.5 and thus not of moderate size.

Study V: The only significant difference in verbal memory scores between the three study groups was found in delayed recall of the word list (Table 7). Post hoc analysis showed that patients treated with VGB and the untreated patient group showed improvement in delayed recall of the words at one-year follow-up assessment, but the performance of the patients treated with CBZ did not change significantly. However, the change from baseline to one-year follow-up assessment estimated with the ES was of moderate size in delayed recall of the words in VGB group, and not in the untreated group.

Table 7. The mean verbal memory test scores at baseline and at 12-month follow-up.

Test	Drug	Baseline	12-month	ES
Story				
Immediate recall	VGB	11.7 ± 3.7	12.0 ± 3.3	0.08
	CBZ	9.7 ± 3.9	11.0 ± 5.1	0.3
	Untreated	11.4 ± 3.9	12.3 ± 3.3	0.3
Delayed recall	VGB	9.5 ± 3.7	10.1 ± 3.4	0.2
	CBZ	8.4 ± 4.3	8.8 ± 4.9	0.08
	Untreated	9.5 ± 3.9	11.1 ± 3.4	0.4
List learning test				
Immediate recall	VGB	29.1 ± 7.5	30.8 ± 8.1	0.2
	CBZ	30.3 ± 7.7	30.1 ± 8.8	0.02
	Untreated	30.4 ± 6.9	31.9 ± 7.0	0.2
Delayed recall	VGB	4.0 ± 2.8	6.0 ± 3.2[a]	0.6
	CBZ	4.5 ± 3.6	5.1 ± 3.4	0.2
	Untreated	4.6 ± 2.8	5.7 ± 2.9[a]	0.4
Delayed recognition	VGB	11.9 ± 2.3	12.7 ± 1.5	0.4
	CBZ	11.1 ± 3.3	11.9 ± 2.2	0.3
	Untreated	11.5 ± 2.5	12.1 ± 2.5	0.3

[a]Significant improvement: $p < 0.01$ MANCOVA
VGB: vigabatrin, CBZ: carbamazepine, ES: effect size

6 DISCUSSION

The present study evaluates verbal memory performance in newly diagnosed partial epilepsy of cryptogenic origin. Memory disorders in intractable epilepsy have long been reported, but studies of memory performance in newly diagnosed epilepsy are rare. Our results show that verbal memory can be adversely affected at the time of the diagnosis of epilepsy, as mild memory dysfunction was present in one third of the patients. In newly diagnosed and chronic LTLE, verbal memory disorders were found almost to the same extent. Delayed recognition was the memory process that was impaired in chronic LTLE but not in newly diagnosed LTLE. Clinically meaningful, moderate verbal memory impairment at the time of the diagnosis of partial epilepsy is one of the predictors of seizure outcome, and evaluation of memory can offer incremental prognostic information when other clinical risk factors of intractable epilepsy are present at the time of the diagnosis of epilepsy.

AED treatment is the major therapeutic intervention in epilepsy and it can compromise cognitive functioning. This study evaluated verbal memory performance after one-year treatment, and no significant decline in verbal memory performance was found. In general, the cognitive side effects of AEDs are subtle and not easily revealed in group studies, and new methods to find them are needed. Analysis of practice effects in repeated assessment might be useful in revealing differential effects of AEDs.

6.1 Methodological considerations

These studies are based on partly overlapping samples of newly diagnosed adult patients with partial epilepsy who were referred to Kuopio University Hospital for diagnostic evaluation. The Department of Neurology serves as a primary site of treatment for all patients with seizure disorder in the district and not only as a tertiary referral center for patients with intractable epilepsy. The patients were consecutive untreated patients and the samples can be considered representative of newly diagnosed partial epilepsy. In addition, patients with other medical conditions affecting cognitive performance were excluded from the study. Also, an unselected sample of patients with chronic LTLE treated in Kuopio University Hospital was included in the Study II. The controls were healthy volunteers among hospital staff and their friends and relatives. The patients in the study groups and the controls matched closely with respect to demographic variables.

Studies I – III were cross-sectional group comparison studies, and Studies IV and V were randomized, monotherapy clinical trials in newly diagnosed epilepsy patients with one-year follow-up: in Study V there was also a control group of untreated patients with single seizures. The studies included many variables and multiple comparisons were made. Thus, it is possible that some significant differences may have appeared by chance. At the 0.05 level of confidence one significant difference out of 20 comparisons can occur on the basis of chance alone. However, the results of these studies were consistent, and in addition Bonferroni correction was applied when appropriate.

6.1.1 Verbal memory assessment in epilepsy

The present study evaluated verbal memory performance in partial epilepsy, as memory deficits in epilepsy have been detected more consistently in verbal memory than in visual memory (Moore and Baker, 1996). It has also been suggested that associations between verbal memory and the left temporal lobe, and the difficulties in documenting the association

between visual memory and the right temporal lobe, reflect the inadequacies of the traditional memory tests, as many of the visual tests can be coded both verbally and visually. This may affect the more variable results of visual memory in epilepsy (Jones-Gotman et al., 2000).

The nature of the verbal memory task seemed to be a critical variable, as in this study memory impairments were found in the List Learning Test but not in the Story Recall task. This might reflect differences in the effortful processing needed in encoding and retrieval in these verbal memory tasks. It can be hypothesised that direct links can be created between elements of a story but not as easily between unrelated words in a serially presented list. The word list learning procedure has been shown to be a sensitive tool in clinical memory assessment, and it can provide several variables to characterize memory functioning (Lezak, 1995). Moreover, in studies of epilepsy surgery patients, the association of verbal memory deficits with the left temporal lobe has more consistently been shown by a list learning task than by a story recall task (Rausch and Babb, 1993; Jones-Gotman et al., 1997).

Clinical neuropsychological memory assessment is carried out with memory tasks, which have known validity and reliability (Lezak 1995). The memory tests assess declarative memory, which is the product of medial temporal lobe memory system. The integrity of hippocampal structures has been shown to be crucial for memory performance (Squire and Knowlton, 2000). Memory tests have high construct validity which is supported by the finding of the relationship between the degree of hippocampal pathology in epilepsy and impairment in neuropsychological measures of memory (Sass et al 1992; Sass et al 1995). In addition, memory tests need to have ecological validity, reflecting the daily memory problems of patients. Ecological validity has been sought by comparing questionnaires of subjective memory and objective test results, but correlations have been variable. In addition, attempts have been made to construct objective tests that tap the kind of memory used every day (Mayes 1986). In a study of LTLE patients and normal controls (Helmstaedter et al., 1998), the ecological validity of list learning tasks was evaluated by assessing 'Memory in reality', which was the incidental memory task of remembering a complex event in which the subject was actively involved. Ability to retrieve the event after long delay was found to correlate highly with verbal memory performance, suggesting that list learning tasks have a satisfying ecological validity.

6.2 Verbal memory in newly diagnosed partial epilepsy

Verbal memory performance was impaired in newly diagnosed partial epilepsy. In an unselected sample of newly diagnosed patients with partial epilepsy of cryptogenic etiology, about 50 % of the patients had mild verbal memory dysfunction in delayed recall, compared with 15 % of normal controls. Mild memory dysfunction was defined as scores falling one SD below the mean performance of the control group, and according to the normal probability curve about 15 % of scores will be under the cut off point. Considering this, 35 % of the newly diagnosed patients with partial epilepsy had mild memory dysfunction. Mild memory problems were shown in specific memory processes, mainly in retrieval of previously learned unrelated words after delay, although immediate recall and delayed recognition were normal. Also, in immediate and delayed recall of logical prose the performance of patients was comparable with that of controls'. Clinically meaningful moderate memory impairment was found to a smaller extent, in 10 - 20 % of the patients, and depending on the type of memory task. In the Veterans Affairs Epilepsy Cooperative study, adult patients with newly diagnosed partial epilepsy have also been shown to have

mild to moderate impairment in verbal memory, decreased learning, and ability to retain information over delay (Prevey et al., 1996; Prevey et al., 1998).

In learning of the word list, rehearsal improved the performance normally in newly diagnosed partial epilepsy and the number of learned words was comparable with that in the control group. Memory disorder can be caused by deficits in encoding during initial learning, in storage or in retrieval of the information. In this study, delayed retrieval of words, as well as the percentage of words retained from the list, was impaired in spite of normal or nearly normal learning ability. Retrieval difficulties have been suggested to underlie memory problems in epilepsy (Hermann et al., 1987). In this study retrieval after delay was impaired but delayed recognition of the words was not. Dysfunction in the storing process or abnormally rapid forgetting could explain the reduced ability to retain information. However, the patients and the controls had comparable performance in delayed recognition, which suggests that the storing process was adequate and the main deficit in delayed recall might be in retrieval. The retrieval difficulties were not seen in delayed story recall. It is possible that the complexity of the task is crucial for the success of retrieval: the connected discourse of a logical story is easier to retrieve than unrelated words.

6.3 Verbal memory in left temporal lobe epilepsy

Verbal memory dysfunction was found to almost the same extent in both newly diagnosed and chronic LTLE patients. The only difference between the two patient groups was found in delayed recognition of the word list, in which the patients with chronic LTLE had poorer performance. Thus, the differences in verbal memory performance were found mainly between normal controls and both LTLE patient groups, and verbal memory dysfunction in adults with newly diagnosed and with chronic LTLE differed only in recognition memory.

In both LTLE groups the total immediate and delayed recall of words as well as the percentage of words retained were worse than in the control group. Accordingly, the number of patients with mild memory dysfunction and moderate impairment in delayed recall was similar in both LTLE groups. In delayed recognition of the words chronic LTLE patients performed worst, and the number of patients with mild dysfunction in delayed recognition was also highest in chronic LTLE.

When the percentages of mild and moderate verbal memory impairments in the newly diagnosed LTLE patient group (Study II) and in the unselected and partly overlapping sample of newly diagnosed patients with partial epilepsy (Study I) are examined, it can be seen that the percentages are slightly higher in the LTLE group than in the partial epilepsy group. It can be suggested that verbal memory dysfunction is found particularly in patients with newly diagnosed LTLE.

There has been discussion about the progressive decline of memory function as a result of chronic and intractable epilepsy. In this study there were few differences in memory test performance between newly diagnosed patients and patients with chronic LTLE. Although there was a significant difference in the duration of epilepsy, the patients with chronic LTLE performed worse only in recognition of the words after delay. Patients with drug-resistant LTLE have previously been shown to have recognition memory impairment prior to epilepsy surgery (Seidenberg et al., 1993). It is possible that poorer recognition memory in chronic LTLE than in newly diagnosed LTLE reflects the progression of memory dysfunction over long periods of intractable epilepsy with recurrent seizures and AED treatment. However,

follow-up of a subgroup of newly diagnosed LTLE patients who were seizure free with monotherapy for five years did not show any deterioration in verbal memory performance. Other studies have also revealed the relatively stable nature of cognitive functioning in chronic refractory partial epilepsy by showing that neuropsychological performance generally does not deteriorate after long periods with epilepsy (Dodrill and Wilensky, 1992; Holmes et al., 1998). In addition, Helmstaedter and Kurthen (2001) supposed on the basis of their cross-sectional study of age regression of declarative memory in left mesial TLE patients and healthy controls that there is not an epilepsy related, independent and accelerated memory decline in patients with TLE. Instead, they suggested that memory impairment in TLE becomes evident in the early course of the disease, and then takes the course of physiological aging.

Most of the studies of memory and epilepsy are of patients with chronic and intractable TLE who also are candidates for epilepsy surgery. The previous research has established that verbal memory deficits are associated with chronic LTLE and especially with mesial LTLE. (Hermann et al., 1987; Moore and Baker, 1996; Giovagnoli and Avanzini, 1999). However, in the wider epileptic patient populations including newly diagnosed patients, TLE can be defined only as a collection of disorders in which the predominant epileptogenic abnormality is in the temporal lobe, and the electroclinical and imaging features available do not always permit distinction between mesial temporal disturbances and more neocortical abnormalities. Thus the etiology of memory impairment in newly diagnosed TLE is more ambiguous than in MTLE. In this study memory impairment was not associated with marked hippocampal volume reduction or the etiology of LTLE, but was associated with secondarily generalised seizures in newly diagnosed LTLE, and with early age at onset of seizures in LTLE.

6.4 Verbal memory impairment as a predictor of seizure outcome

The results of this study suggest that verbal memory impairment is one of the early interictal predictors of seizure outcome in newly diagnosed partial epilepsy. Impaired verbal memory performance had more importance in predicting refractory seizure disorder than satisfactorily controlled epilepsy. In the refractory epilepsy group, only 20 % of the patients could be correctly classified when the memory variables were not included in the model. When both clinical and memory variables were in the multivariate model, 50 % of these patients were correctly classified. On the other hand, satisfactorily controlled epilepsy could be correctly predicted with clinical variables alone in 99 % of the cases. Thus, evaluation of memory has more significance in predicting intractable epilepsy, especially when other clinical risk factors of intractable epilepsy are present at the time of the diagnosis of epilepsy.

The multivariate model of six risk factors consisted of presence of spike focus in EEG, partial complex or mixed seizure type, moderately impaired performance in immediate recall and in delayed recognition of the word list, remote symptomatic etiology of epilepsy and younger age at the time of diagnosis. The clinical variables included in this model have in previous studies been found to be predictors of refractory seizure disorder (Collaborative Group for the Study of Epilepsy, 1992; Camfield et al., 1993; Mattson et al., 1996; Schreiner and Pohlmann-Eden, 1997). Verbal memory impairment as a predictor for seizure outcome in partial epilepsy has not previously been used, but memory variables have been used in studies of predictors for epilepsy surgery outcome (Sawrie et al., 1998).

Our results of verbal memory impairment as a predictor of two-year seizure outcome can be regarded as preliminary because of the small number of patients, especially in the refractory

epilepsy group, which causes imprecision in the results, as seen in wide confidence intervals of odds ratios for the prognostic factors. The number of patients was also too small to allow us to perform a cross-validation of the model. However, memory performance data may offer an incremental increase in prediction of seizure outcome in epilepsy. MRI volumetric data might also add to the prediction of outcome in epilepsy.

6.5 Methodological aspects in antiepileptic drug studies

In this study the effects of AEDs on memory were investigated with randomized monotherapy clinical trials in newly diagnosed epilepsy patients with long-term follow-up. This study design represent the most accurate procedure for assessing the cognitive impact of AEDs. In this study design, the results are not confounded by the effect of concurrent or previous AED use, and it permits the collection of baseline data which are required for determining whether a particular treatment affects cognitive processing (Aldenkamp and Baker, 2001; Kälviäinen, 2001).

In previous studies there have been methodological limitations, such as failure to control confounding factors, selection biases, lack of uniform or validated test measures, and improper statistical analyses, which limit the value of prior findings on AEDs (Meador and Loring, 1991; Devinsky, 1995; Kälviäinen et al., 1996). In add-on studies of intractable epilepsy patients, interactions of the study drug with concomitant medications are common, and together with additive toxic effects, they can make it difficult to determine the true adverse effects of the study drug (Kälviäinen, 2001). Healthy adult volunteers have been used as subjects in AED studies to eliminate the confounding effects of epilepsy related factors (Meador et al., 2001). However, the data from healthy volunteers should be treated with caution because in general the power of these studies is limited by small sample sizes, and drug exposure periods are relatively brief. It is possible that chronic treatment results in different types of cognitive impairment that cannot be observed during short-term treatment. Also, the differing cerebral substrates in epilepsy patients and healthy volunteers suggest that cognitive responses to AEDs may be different in these populations (Aldenkamp and Baker, 2001).

6.5.1 Practice effect

The study design in most AED studies consists of evaluation of cognitive function at baseline, prior to the initiation of the study drug treatment, and at follow-up visits. Study designs with repeated neuropsychological assessments include potential practice-related measurement error, i.e. it has been shown that repeated testing results in improvement of test scores (Lezak, 1995). However, apart from practice effect possibly being a factor that invalidates or biases the results in a study with serial assessments, the analysis of change during drug treatment may also reveal differential effects of AEDs on cognitive performance.

In memory assessment there are two kinds of practice: test-specific practice refers to better test-taking strategies with repeated exposures of the same procedure, and item-specific practice appears when the subject is asked to memorize the same information repeatedly. Test-specific practice is unavoidable in serial assessment, but item-specific practice can be diminished by the use of alternate test forms (Benedict and Zgaljardic, 1998). Alternative versions of word list tasks have been reported to prevent practice effects (Crossen and Wiens, 1994; Parker et al., 1995). In addition, the length of the test-retest interval has an

impact on practice effect. When the interval between assessments is only weeks, practice effects in memory tasks are considerable (McCaffrey et al., 1992; McCaffrey et al., 1995), but they diminish when the test-retest interval is one year (Mitrushina and Satz, 1991).

In this study the interval between identical assessments was one year, which usually diminishes the practice effect (Mitrushina and Satz, 1991). However, test-specific practice can be seen as procedural memory that is resistant to decay over time, and can explain practice effect even after years (Rao, 1996; Spikman et al., 1999). This test-specific practice might be present also in this study despite the long assessment intervals.

The amount of practice effect in memory performance has been studied by Benedict and Zgaljardic (1998). They calculated the effect size (Cohen, 1988) and considered practice effect moderate when the effect size was 0.5. This criterion of 0.5 SD is an accepted statistical convention when there is no a priori standard for evaluating the magnitude of meaningful change, and this has also been used in studies of treatment effects on neuropsychological performance (Fischer et al., 2000).

6.6 Verbal memory in antiepileptic drug studies

In this study no decline of verbal memory performance was revealed after one-year treatment with AEDs. This is in accordance with the general view that most of the standard AEDs, administered in therapeutic doses, cause little or no cognitive impairment in group studies. However, all AEDs have the potential for adverse effects on cognition, especially in high dosages. The major cognitive side-effects of AEDs are on psychomotor processing speed and attention, and impairment in these functions may have a secondary effect on learning and memory. Clear differential effects of AEDs on cognitive processing have not been revealed in group studies but considerable individual variability may exist in experiencing cognitive side effects (Devinsky, 1995; Kälviänen et al., 1996; Meador, 1996). Thus the need for sensitive measures for detecting subtle drug effects is obvious.

Follow-up studies of newly diagnosed epilepsy patients with AED treatment have shown no decline in cognitive functioning. However, the patients have failed to show practice effects that were seen in cognitive performance of normal control subjects (Smith, 1988; Prevey et al., 1996), or the practice effect has been less evident or different in patients with AED treatment than in controls (Pulliainen and Jokelainen, 1994). It has been suggested that lack of practice effect may indicate cognitive side-effects of AEDs (Smith, 1988) and even mild cognitive decline may be masked by practice effect (Meador, 1997).

The performance in the word list task of patients treated with OXC or PHT did not differ in immediate or delayed recall during the follow-up. The magnitude of change in verbal memory performance was less than of moderate size.

In Study V, delayed recall of the word list improved in the VGB group and in untreated patients with a single seizure, but not in the CBZ group. The magnitude of change in delayed recall was moderate in the VGB group but the control group of untreated patients remained, however, below the criterion of meaningful change.

Our results show that differences in the magnitude of practice effects can be found in AED studies, and this can be used as an indicator of cognitive effects of AEDs. In addition, the estimation of the magnitude of the change can widen the analysis beyond the significant

statistical differences in group means. However, the further evaluation of practice effect would need a group of normal controls tested with the same intervals. In Study V, the untreated patients served as a control group, and moderate practice effect was shown only in delayed recall of words in the VGB group but not in controls or in patients treated with CBZ. Our results suggest that differences in the magnitude of practice effect can reveal subtle cognitive effects of AEDs. As practice effect cannot be totally excluded in repeated assessments, evaluation of differential effects of AEDs on practice would be worth studying, especially including a control group for the estimation of normal practice effect.

7 CONCLUSIONS

7.1   Mild verbal memory dysfunction is found in 35 % of patients with newly diagnosed partial epilepsy of cryptogenic etiology. Memory dysfunction is shown in delayed retrieval of previously learned words and in the percentage of words retained, despite normal immediate recall and delayed recognition of the words. Memory dysfunction in newly diagnosed partial epilepsy is mostly mild, and clinically meaningful, moderate memory impairment is found in a minority (10–20 %) of patients.

7.2   The longer duration of left temporal lobe epilepsy (LTLE) is not associated with a decline of verbal memory. Verbal memory dysfunction is found almost to the same extent in patients with newly diagnosed and chronic LTLE. The patient groups differed in delayed recognition of words, patients with chronic LTLE having poorer performance. These results suggest that verbal memory performance remains relatively stable for long time periods in LTLE. This is also supported by the prospective finding of no deterioration in verbal memory after five years of well-controlled LTLE.

7.3   Clinically meaningful moderate verbal memory impairment is one of the predictors of seizure outcome in newly diagnosed partial epilepsy. Verbal memory impairment has more importance in predicting refractory seizure disorder than satisfactorily controlled epilepsy. Thus, evaluation of memory can provide further predictive information when clinical risk factors of intractable epilepsy are present at the time of the diagnosis of epilepsy.

7.4   No decline of verbal memory performance was found after one-year of antiepileptic drug (AED) treatment. Slight differences in the magnitudes of practice effects during AED treatment were found, and evaluation of the change can reveal mild differential cognitive effects of AEDs.

In summary, the present study shows that verbal memory can be impaired already at the time of the diagnosis of partial epilepsy. Thus, memory dysfunction becomes evident in the early course of epilepsy, possibly during epileptogenesis. On the other hand, the longer duration of epilepsy is not necessarily associated with a decline of verbal memory. Finally, moderate verbal memory impairment at the time of the diagnosis is one of the predictors of intractable epilepsy.

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