LONGITUDINAL COGNITIVE CHANGES IN MEDICALLY AND SURGICALLY TREATED PATIENTS WITH DRUG RESISTANT PARTIAL EPILEPSY

Lena Andersson-Roswall

Epilepsy Research Group
Institute of Neuroscience and Physiology
The Sahlgrenska Academy, University of Gothenburg
Gothenburg, Sweden

UNIVERSITY OF GOTHENBURG

2010

To my son Erik
with
lots of love

In memory of my beloved father

with little you gave much
with joy you gave more
with love you gave everything

ABSTRACT

When this study was initiated, there were few published longitudinal studies on cognition in medically treated patients with refractory epilepsy, and none included reassessment data from healthy controls. At the time there were no long-term reports on surgically treated epilepsy patients. The rationale for this study was therefore to pursue a longitudinal study of cognitive changes in both medically and surgically treated epilepsy patients compared to controls. The aims were: in study I to explore the hypothesis that a cognitive decline across time would be disclosed; in study II to investigate whether verbal memory decline was influenced by verbal cognition or attention/processing speed; in study III to explore long-term cognitive changes after temporal lobe resection (TLR) for epilepsy and to investigate whether these relate to seizure outcome, and in study IV to describe individual changes in verbal memory after TLR and to explore specific risk factors for early and late decline.

Thirty-six medically treated patients with refractory partial epilepsy were tested twice, with a median test interval of 4.8 years (study I and II). Fifty-one patients with temporal lobe epilepsy (23 in the speech dominant temporal lobe, DTL; 28 in the non-dominant temporal lobe, NDTL) were tested preoperatively, 2 and 10 years after TLR (study III and IV). Thirty healthy controls were tested at baseline, and after 3 (25/30) and 10 (26/30) years (studies I-IV).

In medically treated patients a verbal memory decline in retention of word-pairs across time was found (study I). The decline could not be explained by performance in verbal cognition or in attention/processing speed (study II). Visuo-spatial memory and performance IQ (PIQ) (study I), and attention/processing speed (study II) were also found to be important correlates of epilepsy. In surgically treated patients, the main result was cognitive stability. In the DTL group there was a decline in verbal memory at the 10-year follow-up compared to the NDTL and the control group (study III). However, this decline was disclosed already at the 2-year follow-up after surgery, and no further decline occurred from 2 to 10 years. The verbal memory decline was not dependent on seizure outcome or antiepileptic drug treatment. At the individual level there was a profound variability in verbal memory outcome after TLR. Fewer patients in the whole TLR group showed decline at 10 (14%) compared to 2 years (28%) after surgery, while the proportion of patients with improvement was about the same at 2 (16%) and 10 (18%) years. Decline was more common in the DTL (2-year: 43.5%; 10-year: 26.1%) than in the NDTL group (2-year: 14.8%; 10-year: 3.7%), while improvement was more common in the NDTL (2-year: 18.5%; 10-year: 29.6%) than in the DTL group (2-year: 13.0%; 10-year: 4.3%). Intact verbal memory at baseline was identified as the strongest predictor of verbal memory decline 2 years after surgery, followed by dominant TLR, and older age at baseline, while only dominant TLR predicted verbal memory decline at 10 years (study IV). Less pronounced practice effects in PIQ were detected both in medically treated patients (study I) and after non-dominant TLR (study III). Continuing seizures was the most important correlate to inferior PIQ scores in surgically treated patients (study III).

In conclusion, our studies demonstrate that memory decline can be disclosed as early as within five years in medically treated epilepsy patients. The results also suggest a unique relationship with epilepsy for the verbal memory decline, since it could not be explained by any change in verbal cognition or attention/processing speed. After TLR the main result was cognitive stability from 2 to 10 years. The verbal memory decline in DTL patients found 2 years after epilepsy surgery was not progressive up to 10 years, and not dependent on seizure outcome. The individual variability in verbal memory outcome after TLR was considerable. A partial recovery seems to have occurred for some individuals, since fewer patients both in the DTL and NDTL group showed decline at the 10-year compared to the 2-year follow-up. Also, factors that are important predictors for verbal memory decline at earlier stages after surgery may be less important at later, since dominant TLR was the only remaining risk factor for verbal memory decline at the long-term follow-up. The results from these studies are relevant in the counselling process when epilepsy surgery is considered.

Correspondence: lenaar@privat.utfors.se

ORIGINAL PAPERS

The thesis is based on the following papers:

I.   Andersson-Roswall L, Engman E, Samuelsson H, Sjöberg-Larsson C, and Malmgren K. **Verbal memory decline and adverse effects on cognition in adult patients with pharmacoresistant partial epilepsy: a longitudinal controlled study of 36 patients.** Epilepsy & Behavior (2004) 5:677-686.

II.   Andersson-Roswall L, Engman E, Malmgren K, and Samuelsson H. **Verbal cognition and attention deficits do not explain the verbal memory decline associated with pharmacoresistant partial epilepsy.** Epilepsy & Behavior (2007) 11:413-420.

III.   Andersson-Roswall L, Engman E, Samuelsson H, and Malmgren K. **Cognitive outcome 10 years after temporal lobe epilepsy surgery: a prospective controlled study.** Neurology (2010) in press.

IV.   Andersson-Roswall L, Samuelsson H, Engman E, and Malmgren K. **Individual verbal memory outcome 10 years after temporal lobe epilepsy surgery: a prospective controlled study.** Manuscript.

CONTENTS

ABBREVIATIONS

AED   Antiepileptic drugs
ALF   Accelerated long-term forgetting
CD   Claeson-Dahl learning and retention test
CM   Cronholm-Molander memory test
DR   Delayed recall
DRec   Delayed recognition
DTL   Dominant temporal lobe
EEG   Electroencephalography
FLE   Frontal lobe epilepsy
FLR   Frontal lobe resection
FSIQ   Full scale IQ
GTCS   Generalized tonic-clonic seizure
HA   Hippocampal atrophy
HRB   Halstaed Reitan battery
ILAE   International League Against Epilepsy
IQ   Intelligence Quotient
IR   Immediate recall
IRec   Immediate recognition
LTM   Long term memory
MRI   Magnetic resonance imaging
NDTL   Non-dominant temporal lobe
PIQ   Performance IQ
RCI   Reliable change indices
RMI   Remote memory impairment
ROCF   Rey-Osterrieth complex figure test
RTM   Regression towards the mean
SE   Status epilepticus
STM   Short term memory
TEA   Transient epileptic amnesia
TGA   Transient global amnesia
TLE   Temporal lobe epilepsy
TLR   Temporal lobe resection
TMT   Trail making test
VIQ   Verbal IQ
WAIS-R   Wechsler adult intelligence scale-revised
WM   Working memory
WMS   Wechsler memory scale
WS   Weighted sum

1. INTRODUCTION AND BACKGROUND

1.1. Epilepsy

An epileptic seizure is a clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain. The clinical manifestations consist of sudden and transitory phenomena such as motor, sensory, autonomic or psychic events and may or may not include clouding of consciousness (ILAE, 1993). The clinical characteristics of a seizure depend on the cortical areas involved and the spread of the discharges. Epilepsy is a condition characterized by recurrent unprovoked epileptic seizures. Recently, however, a wider definition has been suggested stating that epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition (ILAE et al., 2005).

Epilepsy is one of the most common neurological disorders with prevalence figures ranging from 0.5 to 1 per cent in the general population (Forsgren, 1992; Hauser, 1997; Sander and Shorvon, 1996). In prospective studies of epilepsy in northern Sweden the prevalence of epilepsy was 0.55 %. Epilepsy has traditionally been classified according to seizure type (ILAE, 1981) or syndrome (ILAE, 1989). The International League Against Epilepsy (ILAE) is currently revising these classifications, but there is as yet no consensus on any new classification scheme. In the present classification, seizures are classified according to semiology (i.e. seizure symptoms and signs) and electroencephalographic (EEG) findings (ILAE, 1981). A seizure is classified as partial or focal if there is clinical and/or EEG evidence of a focal onset. The *partial seizures* are classified as simple if consciousness is not impaired, as complex if consciousness is impaired, and as secondary generalized if the partial seizure evolves to a generalized seizure. *Generalized seizures* are those in which the first clinical symptoms and the ictal EEG changes indicate initial involvement of both hemispheres. There are three main subtypes of generalized seizures: generalized convulsive seizures (with predominantly tonic, clonic, or tonic-clonic seizures), generalized non-convulsive seizures (absences) and myoclonic seizures. Finally the *unclassified seizures* include all seizures that cannot be classified because of inadequate or incomplete data (ILAE, 1981).

The present classification of epilepsies and epileptic syndromes divides the epilepsies into localisation-related (focal, partial), generalized, undetermined or associated with special syndromes. The localisation-related syndromes are further divided into idiopathic (primary), symptomatic (secondary) and cryptogenic depending on whether the aetiology is known or not (ILAE, 1989). The aetiology of partial epilepsies is heterogeneous and in prevalence studies the most commonly reported known causes of partial epilepsy are cerebrovascular disease, head trauma, brain tumour, birth trauma, infectious disease and congenital or genetic abnormalities (Forsgren, 1992; Forsgren et al., 1996; Hauser, 1993; Hauser, 1997; Sander and Shorvon, 1996)

1.2. Epilepsy related factors that may influence cognition

There is a wide range of multifaceted and overlapping epilepsy related factors of both medical and psychosocial nature that could influence cognition and behaviour in patients with epilepsy, e.g. underlying neuropathologies, neuronal discharges (ictal and interictal), antiepileptic drug treatment and epilepsy surgery, public attitudes and patients´ low assessment of self worth (Kwan and Brodie, 2001). The cognitive profiles in epilepsy patients have therefore been described to be "*as heterogeneous as the epileptic syndromes themselves*" (Elger et al., 2004).

1.2.1. Biological factors
Aetiology, epilepsy syndromes, and seizure types
In general, cognitive impairment is more likely to occur in patients with symptomatic than in those with idiopathic epilepsy syndromes (Dodrill, 1981; Klöve and Matthews, 1966; Klöve and Matthews, 1974; Meador, 2002; Tarter, 1972). In one study, data from over six hundred adult patients with different types of seizures was analyzed and it was found that generalized convulsive seizures were associated with more impaired general neuropsychological ability than other seizure types (Dodrill, 1992a), which is in line with other reports (Dikmen and Matthews, 1977; Dodrill, 2002; Dodrill, 1986; Dodrill and Troupin, 1976; Stefan and Pauli, 2002; Thompson and Duncan, 2005). In Dodrill´s study no association with deficits in general ability was found in patients with generalized non-convulsive seizures or partial seizures unless other factors were present (e.g. brain damage) (Dodrill, 1992a).

Localisation and laterality of seizure origin

Temporal lobe epilepsy (TLE) is the most frequent type of partial epilepsy and has often been associated with language difficulties, memory (verbal and visual) problems, and postictal psychotic symptoms (Helmstaedter and Elger, 2009; Huttenlocher and Hapke, 1990; Meador, 2002; Meador et al., 2001a; Motamedi and Meador, 2003; Perrine and Kiolbasa, 1999; Trebuchon-Da Fonseca et al., 2009; Umbricht et al., 1995). According to the classic model of material-specific memory (Jones-Gotman, 1992; Milner, 1973), left TLE may lead to verbal memory decline (Delaney et al., 1980; Helmstaedter and Elger, 2009; Hermann et al., 1987; Lee et al., 2002; Mungas et al., 1985; Saykin et al., 1989), while right TLE may lead to deficits in visual memory (Delaney et al., 1980; Giovagnoli et al., 1995; Kimura, 1963; Malec et al., 1991; Milner, 1975). However, the latter findings have been shown to be less consistent (Lee et al., 2002; Milner, 1967; Novelly et al., 1984), and the model of material-specific memory function has been questioned (Sailing, 2009), see section 1.5.3. Frontal lobe epilepsy (FLE) is the second most frequent type of partial epilepsy and may be associated with aspects of executive dysfunction (i.e. difficulties with attention and problem solving) or motor uncoordination (Helmstaedter et al., 1996b).

Age at seizure onset, seizure frequency and severity, and epilepsy duration

Age at epilepsy onset is the most consistently reported correlate of cognitive performance in patients with epilepsy. Early epilepsy onset has been shown to be associated with more severe impairment of general intellectual capacity, attention, and memory compared to late onset (Dodrill, 1981; Dodrill, 1992a; Hermann et al., 2002; Meador, 2002; Piazzini et al., 2006a; Seidenberg et al., 1986; Strauss et al., 1995). Children with early seizure onset (< 5 years) show lower intelligence quotient (IQ) irrespective of type of seizures, while those with late onset (> 5 years) show more behavioural problems than cognitive impairments (Meador et al., 2001a). It is difficult to evaluate the effects of seizure frequency independently from the effects of duration and severity of epilepsy (Motamedi and Meador, 2003). Higher seizure frequency and longer duration of TLE have been associated with more severe hippocampal atrophy (HA) and cognitive impairments (Dikmen and Matthews, 1977; Dodrill, 2002; Dodrill, 1986; Dodrill, 1992a; Jokeit and Ebner, 1999; Motamedi and Meador, 2003; O'Brien et al., 1999; Seidenberg et al., 1981a; Theodore et al., 1999). However, most studies only consider recent seizure history. A more adequate variable to investigate would be seizure severity and frequency

during lifetime (Dodrill, 1986; Dodrill, 1992a). In Dodrill´s study of a large cohort of epilepsy patients a history of more than 100 generalized tonic-clonic seizures (GTCS) or even one single episode of status epilepticus (SE) (seizure duration > 30 minutes) was associated with lower level of general neuropsychological ability (Dodrill, 1992a). In a recent study of 136 patients with severe intractable epilepsy who had undergone a cognitive assessment on two occasions at an interval of at least 10 years, the frequency of GTCS was the strongest predictor of cognitive decline (Thompson and Duncan, 2005). However, some studies report no correlations between the above mentioned variables (age at seizure onset, seizure frequency and severity, and epilepsy duration) and neuropsychological test performances (Engelberts et al., 2002; Kramer et al., 2006). Lack of associations, though, may partly be due to small sample size and also with difficulties to ascertain seizure frequency over time (Kerling et al., 2006).

1.2.2. Treatment related factors
Antiepileptic drugs
Antiepileptic drug (AED) treatment may affect cognition such as attention, vigilance, psychomotor speed and memory (Jokeit et al., 2005; Loring and Meador, 2001; Meador, 2002; Motamedi and Meador, 2004; Trimble, 1987), but also behavioural factors such as drive, mood and sociability (Mattson, 2004; Trimble, 1988). However, it is difficult to separate the effects from other important clinical factors (Baker and Taylor, 2009). Virtually all individuals with epilepsy are treated with AED and drug resistant patients often have polytherapy with higher AED dosages, which increases the risk for neurocognitive side effects (Loring and Meador, 2001; Mattson, 2004; Motamedi and Meador, 2003; Piazzini et al., 2006b). In a comparative review of newer versus older AEDs and effects on cognitive functions there was a tendency in favour of the new AEDs (Brunbech and Sabers, 2002). Patients themselves often attribute cognitive problems to side effects of AED treatment (Carpay et al., 2005), and often consider that they have side effects from drugs, even when seizures are in remission or when monotherapy is used (Carpay et al., 2005; Uijl et al., 2006). There is also increasing evidence suggesting that patients with epilepsy may be cognitively compromised before starting treatment and following few seizures (Kälviäinen et al., 1992; Prevey et al., 1998; Pulliainen et al., 2000; Taylor et al., 2010; Äikiä et al., 1995; Äikiä et al., 2001).

Newly diagnosed medically untreated epilepsy

Reports on newly diagnosed medically untreated patients with epilepsy were sparse until the early 90s (Kälviäinen et al., 1992; Prevey et al., 1998; Äikiä et al., 1995). In one study (Prevey et al., 1998), 201 patients with symptomatic partial epilepsy (complex partial or secondarily GTCS) were cognitively assessed prior to AED initiation and compared to neurologically healthy controls. Patients performed worse than controls in 17/18 variables in a screening battery covering motor speed, memory, concentration and mental flexibility. In one recent study (Taylor et al., 2010), 155 patients with newly diagnosed epilepsy (without known brain pathology) were assessed prior to AED treatment and compared with healthy controls. The patients performed significantly worse in 6/14 cognitive variables (mostly in the domains of memory and psychomotor speed) compared to controls. This implies that at least part of the cognitive disturbances in epilepsy may be due to the underlying etiology (Taylor et al., 2010).

Epilepsy surgery

Approximately one third of all epilepsy patients are refractory to medical therapy (Kwan and Brodie, 2000; Schuele and Lüders, 2008). For a selected subset of these patients, epilepsy surgery is an established and effective therapeutic option (Engel et al., 2003; Spencer et al., 2003; Spencer and Huh, 2008; Wiebe et al., 2001). The main objective of epilepsy surgery is seizure control. The chances of improvement in seizure control must be weighted against possible losses, e.g. the risk of surgical complications and decline in cognition. There are several variables that may influence the surgical outcome, e.g. the aetiology of the epilepsy, and the laterality and localization of the resection. Temporal lobe resection (TLR) is the most common resection type accounting for about two thirds of resections in adults (Helmstaedter, 2004a; Motamedi and Meador, 2003). TLR controls seizures in 60-85% of the patients and reduces seizures in another 15% (Spencer et al., 2003; Tonini et al., 2004; Wiebe et al., 2001). The most consistently reported post-operative cognitive change has been decline in verbal memory and learning after dominant TLR (Dodrill et al., 1993; Dulay et al., 2008; Helmstaedter and Elger, 1996a; Hermann et al., 1995a; Lee et al., 2002; Loring et al., 1991; Novelly et al., 1984; Rausch, 1996), while non-dominant TLR mainly has been associated with decline in visuo-spatial memory (Dodrill et al., 1993; Dulay et al., 2008; Milner, 1968b; Milner, 1975; Rausch, 1996). However, the negative changes seem to be more consistent after dominant TLR (Motamedi and Meador, 2003). Frontal lobe

resections (FLR) are the second most common resection type and may result in behavioural changes like deterioration in executive functions and reduced output on attention and fluency tasks (Helmstaedter, 2004a; Milner, 1964; Milner and Petrides, 1984). Epilepsy surgery and cognition is further described in section 1.5.

1.3. Cognitive domains of dysfunction in epilepsy

Neuropsychological studies have provided important information about cognitive functions in epilepsy for more than 70 years (Arieff and Yacorzynski, 1942; Baxendale, 2008a; Dodrill, 1986; Dodrill, 1992a; Hermann and Seidenberg, 2007; Klöve and Matthews, 1966; Meyer and Yates, 1955; Tarter, 1972). The cognitive alteration mainly considered in early studies was intellectual deterioration. Coinciding with the rapid development of neuropsychology since the 1950s, there has been an increasing awareness that a range of neuropsychological problems can be observed in patients with epilepsy (Thompson and Trimble, 1996). Deficits in both global mental functions, such as energy and drive, and specific and non-specific cognitive functions, such as memory, language, and attention may occur and can sometimes be more debilitating than the seizures themselves (Fischer et al., 2000; Rausch et al., 1997). Deficits in attention, concentration, memory, and word finding are the most commonly reported deficits associated with epilepsy (Perrine and Kiolbasa, 1999).

1.3.1. General cognitive level

Assessment of general cognitive level as measured by psychometric intelligence provides a valuable baseline status against which comparison of performance of other measures can be made. Several studies over the years have reported lower intellectual levels in patients with refractory epilepsy (Dikmen et al., 1975; Dodrill, 1986; Klöve and Matthews, 1966; Lennox and Lennox, 1960; Saykin et al., 1989; Selwa et al., 1994; Strauss et al., 1995; Thompson and Duncan, 2005). Lower IQ scores have particularly been associated with high frequencies of GTCSs or episodes of SE (Dikmen and Matthews, 1977; Dodrill and Wilensky, 1990; Dodrill, 1986; Dodrill, 1992a; Seidenberg et al., 1981a), earlier age of seizure onset (Dikmen et al., 1975; Dodrill, 1992a; O'Leary et al., 1981; Saykin et al., 1989; Seidenberg et al., 1986; Strauss et al., 1995; Tarter, 1972), and frequent subclinical epileptiform discharges (Brinciotti et al., 1989), especially for generalized discharges (Wilkus and Dodrill, 1976). However, there are also studies which do not report any intellectual impairment (Bornstein et al., 1988; Kälviäinen et al., 1992)

and patients with well-controlled epilepsy have been described rarely to suffer from significant impairment in global intellectual functioning as assessed by IQ-tests (Wechsler, 1981).

1.3.2. Memory

Memory impairment is a common finding in epilepsy populations (Delaney et al., 1980; Elger et al., 2004; Hermann et al., 1987; Loiseau et al., 1983; Mungas et al., 1985; Oyegbile et al., 2004; Prevey et al., 1998; Pulliainen et al., 2000). Deficits in new learning have often been reported, especially in patients with TLE, and impaired verbal episodic memory is the most consistent finding in left TLE (Helmstaedter and Kurthen, 2001). For further discussion about association between material specific memory and laterality of epilepsy onset, see section 1.2.1. and 1.5.3. There are several factors that may constitute a risk for memory impairment, e.g. TLE, frequent GTCS, earlier age of onset, longer duration of epilepsy, a concomitant structural lesion, and episodes of SE (Perrine et al., 1991).

The Memory System

The distinction of memory into *short-term memory* (STM) and *long-term memory* (LTM) is essential in current classification of memory. This temporal base for dividing memory was proposed by Hebb (Hebb, 1949), but the current understanding is that the two memory types should not be looked upon as unitary systems (Squire and Kandel, 2000). Short-term memory is described as a temporary memory system with limited storage capacity and short durability. In contrast, long-term memory is described as a memory system with large storage capacity and long-term durability. Long-term memory can be divided into *declarative* and *non-declarative* memory (Squire, 1992). Declarative memory refers to conscious recollection of personally experienced events or information (related to a temporal or spatial context), *episodic memory,* and learned facts (unrelated to a person's life), *semantic memory*. Non-declarative memory refers to situations where experience alters behaviour without conscious recollection of the memory content (e.g. skills and habits, perceptual priming and classical conditioning) (Squire, 1992). Episodic memory can be divided into three phases: encoding, storing and retrieval. The *encoding phase* comprises the initial registration of information and selection of further perceptual processing. The *storing phase* involves the fact that the information has to be stored in the brain for future retrieval. A process of

consolidation and integration of new information from short-term to long-term memory is an important component in the gradually increasing durability of memories. This gradual form of transformation makes the system always accessible for new information (Squire and Zola-Morgan, 1991). The *retrieval phase* implies a collection of processes that constitute a foundation for remembering earlier experienced events and can be described as the accessibility to information. Memory problems can be due to disturbances of one or more of these different phases of memory process. The functions of hippocampus (together with anatomical related structures) are considered essential in this process (Eichenbaum, 2004; Squire, 1992). However, different aspects of memory have been shown to have somewhat different anatomical correlates and performances in different memory tests can therefore dissociate in the very same patient (Baxendale, 2008a; Helmstaedter and Elger, 1998). Learning and acquisition of data has been associated with temporocortical functions, consolidation and retrieval with mesio-temporal structures (Baxendale, 2008a; Helmstaedter and Elger, 1998), while recognition may not be sensitive to pathology in the mesial temporal lobes (Baxendale, 1997; Baxendale, 2008a; Hermann et al., 1995a). In the study by Baxendale (1997), marked recognition deficits were found in patients with hippocampal sclerosis but only in those who also had additional cortical pathology. The role of the hippocampus and the temporal lobes in memory are further discussed in section 1.5.3. The psychometric testing of episodic memory includes verbal (e.g. learning and recall of word list, word-pairs and prose) as well as non-verbal (e.g. learning and recall of faces, locations, spatial conditions and geometric figures) assessments. Episodic memory is considered to be the most commonly affected type of memory in epilepsy, especially in patients with partial seizure disorders (Hermann et al., 1996b).

Three interrelated forms of memory impairment associated with epilepsy
Patients with epilepsy often complain about memory problems (Banos et al., 2004; Bolla et al., 1991; Corcoran and Thompson, 1993; Fischer et al., 2000; Hendriks et al., 2002; McCagh et al., 2009; Thompson and Corcoran, 1992), particularly if they have seizures originating from memory-related brain structures including the hippocampus, such as in TLE (Butler et al., 2008b). However, frequently the subjective apprehensions of memory do not correlate with performances on standard assessments (Banos et al., 2004; Elixhauser et al., 1999; Piazzini et al., 2001; Thompson and Corcoran, 1992; Vermeulen et al., 1993). The lack of agree-

ment of subjective and objective reports may have several explanations. Self-report of cognitive functioning may be influenced by mood or affective states such as anxiety, depression or dysphoria (Bolla et al., 1991; Elixhauser et al., 1999; Hermann and Wyler, 1989; Larrabee and Levin, 1986; Piazzini et al., 2001), but there might also be types of memory problems that standard neuropsychological assessments fail to detect. Three interrelated forms of memory impairment associated with epilepsy have been described: *transient epileptic amnesia* (TEA), *accelerated long-term forgetting* (ALF) and *remote memory impairment* (RMI) (Butler et al., 2008b; Butler et al., 2007; Butler and Zeman, 2008a).

Transient epileptic amnesia (TEA)

TEA is a form of TLE and is described to have a close relationship with memory (Butler et al., 2008b; Butler et al., 2007; Butler and Zeman, 2008a; Gallasi et al., 1988; Kapur, 1990; Zeman et al., 1998). The seizure manifestations are episodes of transient amnesia, while during the episodes other cognitive functions remain unaffected. This syndrome, usually commencing late in life, differs from transient global amnesia (TGA) in that the amnestic episodes are briefer and generally more frequent (Bell and Giovagnoli, 2007). In contrast to the apparently benign nature of TGA, interictally TEA is often associated with other forms of memory impairment, i.e. ALF and RMI.

Accelerated long-term forgetting (ALF)

ALF, is a form of accelerated forgetting that appears only over an extended period of time (Butler and Zeman, 2008a). The patients are able to learn new information and recall it after a relatively short delay, but then the memories fade over days to weeks (Bell and Giovagnoli, 2007; Butler and Zeman, 2008a). Consequently, acquired memories are forgotten in a pace that is abnormally fast. Such slowly developing memory problems can not be detected in standard memory assessments with retention intervals up to 30 minutes. Innovative memory assessment techniques have been developed and several studies have examined memory after long delays (Bell, 2006; Bell et al., 2005; Blake et al., 2000; Giovagnoli et al., 1995; Mameniskiene et al., 2006; Martin et al., 1991). In one controlled study of 70 patients with TLE (Mameniskiene et al., 2006), patients who had >4 seizures between the first and the second assessment (4 weeks later) performed significantly worse on long-term recall on all memory tests, despite results similar to those of controls on immediate and delayed recall. Presence of ALF could be one of the

explanations why patient complaints and performances on standard memory assessments sometimes fail to correspond.

Remote memory impairment (RMI)

RMI refers to a loss of memories of personal and public events, and can have a great impact on an individual's life (Bell and Giovagnoli, 2007; Butler and Zeman, 2008a). Relatively few studies have examined remote memory or retrograde amnesia (Barr et al., 1990; Bell and Giovagnoli, 2007; Bergin et al., 2000; Voltzen-logel et al., 2006). This is most likely a consequence of the evident difficulties in constructing tests that assess remote memory, which includes acquiring normative data and making tests culturally appropriate (Barr et al., 1990; Bell and Giovagnoli, 2007; Bergin et al., 2000; Kapur, 1990; Mayes et al., 1994). Presence of RMI could be another explanation for the lack of correspondence between subjective memory complaints and objective measures on standard memory tests.

1.3.3. Verbal cognition

Verbal cognition, as measured by Verbal IQ (VIQ) from the Wechsler Adult Intelligence Scale - Revised (WAIS-R) or its subtests is often impaired in patients with epilepsy (Bornstein et al., 1988; Giordani et al., 1985; Hermann et al., 1995b; Oyegbile et al., 2004).

The influence of verbal cognition on verbal memory

It has been suggested that deficits in language functions may explain some of the verbal memory impairments associated with left TLE (Brown, 1991; Hermann et al., 1988a; Mayeux et al., 1980). Since verbal cognition depends on language skills such as accessibility and comprehension of words (Lezak, 1995; Wechsler, 1981) it is reasonable to assume that the level of verbal cognition also may influence the verbal memory performance. Limited compensatory reserves (reflected by VIQ or its subtests) indicate an increased cognitive vulnerability, which may have impli-cations also for the verbal memory performance (Helmstaedter et al., 2003; Hermann et al., 2006; Jokeit and Ebner, 1999; Oyegbile et al., 2004).

1.3.4. Attention and processing speed

Deficits in attention and generalized slowing in the rate of cognitive/psychomotor processing have commonly been reported in patients with epilepsy (Aldenkamp et al., 1990; Boone et al., 1988; Oyegbile et al., 2004; Piazzini et al., 2006a; Piccirilli et al., 1994; Smith et al., 1986; Stella and Maciel, 2003; Stores, 1973).

The Attention and processing speed system

Attention is a complex process or set of processes (Mirsky et al., 1991), and different taxonomies have been presented (Mirsky and Duncan, 2001; Sohlberg and Mateer, 1989; Stuss et al., 1989; Van Zomeren and Brouwer, 1994). In Mirsky´s and Duncan´s taxonomy (Mirsky and Duncan, 2001) attention is divided into five distinct functions, of which two will be described here. The *encode element* refers to the capacity to hold information briefly in memory in order to enable performance on some mental operation of the information as measured by Digit span and Arithmetic from the WAIS-R. The term is considered equivalent to the working memory concept. The *focus/execute element* refers to the capacity to focus on a task in the presence of distracting stimuli, and to execute quickly the manual or verbal responses required by the task as measured by Digit Symbol from the WAIS-R and Trail Making Test (TMT) from the Halstead-Reitan Battery (HRB). In addition, the aspect of *divided attention* is included in several classifications of attention (Sohlberg and Mateer, 1989; Stuss et al., 1989; Van Zomeren and Brouwer, 1994) and refers to the ability to simultaneously divide attention between two or more sources of relevant information. Part B of the TMT is an example of a test that requires this ability. A capacity for *processing speed* is also crucial in several mental operations, and this important component is included in many of the attention tests such as TMT, Digit Symbol and Arithmetic. The speed of cognitive processing is considered especially vulnerable to brain damage (Spreen and Benton, 1965).

The influence of attention and processing speed on memory

It is a common view that memory and learning are partly influenced by attention capacity (Schmitter-Edgecombe, 1999). Studies have shown that as the amount of attention available during initial learning decreases, performance on tests of declarative memory also declines (Iidaka et al., 2000). In patients with epilepsy, a possible influence of attention on the level of performance in memory has been suggested (Kälviäinen et al., 1992). AED treatment may also induce impairments of attention, vigilance, and psychomotor speed (Meador, 2002), which can have secondary effects on memory (Meador, 2001b). However, in an early study based on correlation analysis Loiseau and co-workers concluded that decreased attention capacity probably is insufficient in explaining memory disability (Loiseau et al., 1984; Loiseau et al., 1988).

1.4. Cognition across time in patients with medically treated refractory epilepsy

1.4.1. Historical aspects

Since the first studies in the early 1940s (Arieff and Yacorzynski, 1942), there has been an ongoing discussion about the long-term effects on cognition in patients with refractory epilepsy. During the last decade a consensus has been reached, that cognitive impairment in patients with refractory epilepsy is mildly progressive (Dodrill, 2002; Dodrill, 2004; Seidenberg et al., 2007; Vingerhoets, 2006) and that memory function appears to be especially vulnerable (Dodrill, 2004; Seidenberg et al., 2007; Vingerhoets, 2006).

1.4.2. Methodological aspects

Observational designs have an important role in medical research, especially in detecting late adverse effects (Papanikolaou et al., 2006). However, they are also afflicted with significant methodological problems. When studying cognitive function across time in patients with epilepsy there are several important aspects that need to be taken into account. The heterogeneity between and within studied samples is considerable, different neuropsychological methods and statistical approaches are used, and study designs differ. These aspects are further discussed in section 1.6.

Study designs

Cross-sectional studies, where each patient is assessed only once, facilitate the inclusion of a large number of patients and generally produce more negative changes than longitudinal studies. Most series are cross-sectional and have been claimed to measure a "state" rather than a "change" (Vingerhoets, 2006). Another weakness of the cross-sectional design is that it cannot differentiate between the effects of seizures and the effects of co-existing factors e.g. aetiology (Dodrill, 2002; Vingerhoets, 2006). *Longitudinal studies,* where the patients are their own controls, are suitable for within group analyses of intra-individual changes and correlations with specific medical or demographic variables, but they too are subjected to confounders that could interfere with the interpretation (Vingerhoets, 2006). They may suffer from skewed samples due to increasing numbers lost to follow-up at each point of measurement (Baxendale, 2008a). There are also built in problems with serial testing e.g. the test-retest reliability of the neuropsychological test instruments and the degree of practice effects due to reassessment that also

have to be taken into account (Chelune et al., 1993; Hermann et al., 1996a; Martin et al., 1998; Nakhutina et al., 2009). In order to deal with these problems and to interpret changes over time in people with epilepsy, comparisons with a control group is needed. Inclusion of data from healthy controls, matched to the epilepsy samples (e.g. for age, length of education, sex and socio-cultural circumstances), makes it possible to evaluate if changes exceed the normal variation (Dodrill, 2002; Seidenberg et al., 2007). Few longitudinal studies of refractory epilepsy include reassessment data from a control group (Dodrill, 2002; Hermann et al., 2006; Piazzini et al., 2006a).

1.4.3. Changes in different cognitive domains

Cognitive decline across time in epilepsy seems to be most severe and dependable for verbal memory, attention, and psychomotor speed (Dodrill, 2002; Seidenberg et al., 2007).

General cognitive level

Longitudinal studies on refractory epilepsy have shown either mild (Arieff and Yacorzynski, 1942; Dodrill, 2002; Hermann et al., 2006; Seidenberg et al., 1981a) or no definite relationships between repeated number of seizures and deterioration in general cognitive level (Bjornaes et al., 2001; Dodrill and Wilensky, 1992b; Holmes et al., 1998; Kalska, 1991; Rausch et al., 2003; Selwa et al., 1994; Äikiä and Kälviäinen, 1999), except for the study of Thompson and Duncan which showed strong relationships in patients with very severe epilepsy (Thompson and Duncan, 2005).

Memory

In longitudinal studies of refractory epilepsy, *within-group analyses* have shown either deterioration (Holmes et al., 1998; Rausch et al., 2003; Thompson and Duncan, 2005), stability (Dodrill, 2002; Dodrill and Wilensky, 1992b; Griffith et al., 2007; Helmstaedter et al., 2000; Piazzini et al., 2006a; Selwa et al., 1994; Äikiä and Kälviäinen, 1999; Äikiä et al., 2001) or improvement (Kalska, 1991; Äikiä et al., 2001) across time. When patients have been compared to controls, *between-groups analyses* have shown additional deterioration in verbal and visual memory (Hermann et al., 2006). When investigating *changes in subsets of patients*, lack of practice effects (Dodrill, 2002; Griffith et al., 2007) and decline in proportions of patients (Helmstaedter et al., 2003; Hermann et al., 2006) have been found. Memory decline has been associated with seizure types and frequencies of GTCS

and SE (Dodrill, 2002; Helmstaedter et al., 2003; Thompson and Duncan, 2005), and with complex partial seizures (CPS) (Thompson and Duncan, 2005).

Verbal cognition

Capacity of verbal cognition, as measured by VIQ (WAIS-R) or its subtests, has in longitudinal studies often been described as stable across time (Bjornaes et al., 2001; Helmstaedter et al., 2003; Holmes et al., 1998; Selwa et al., 1994).

Attention and processing speed

Deterioration over time in various attention variables has been found in five longitudinal studies (Dodrill, 2002; Hermann et al., 2006; Holmes et al., 1998; Kalska, 1991; Thompson and Duncan, 2005), while some other studies have reported stability or improvement (Dodrill and Wilensky, 1992b; Helmstaedter et al., 2000; Holmes et al., 1998; Kalska, 1991).

1.5. Epilepsy surgery and cognitive outcome

1.5.1. Historical aspects

The first neuropsychological reports on epilepsy surgery date back to the late 30s and the early 40s (Hebb, 1939; Hebb and Penfield, 1940). At that time, three surgical centres (Montreal, London and Chicago) had begun to use neuropsychological assessments (before and after surgery) to explore cognitive morbidity (Hermann and Loring, 2008). Ever since, neuropsychology has been an important part of the epilepsy surgery evaluation.

1.5.2. Methodological aspects

There are several methodological aspects to consider, some of which have been described above (see section 1.4.2) and are discussed further in section 1.6, concerning heterogeneity, neuropsychological methods, statistical approaches, study designs, test-retest reliability, and practice effects. However, there are also surgery specific issues such such as type and extent of resection which may influence cognitive outcome (Baxendale, 2008a), see section 1.5.4. In addition, important information about the study populations e.g. eligibility criteria, numbers potentially eligible, subjects lost to follow-up and explanations of how missing data are handled are often lacking or unclear. This lack of information makes it difficult to know how representative the samples are of the populations and to compare different study samples. Patients who continue to have seizures after surgery might be more prone to continue to stay in contact with their neurological councellor.

Studies with such systematic bias may overrate cognitive and behavioural problems related to epilepsy surgery (Baxendale, 2008a).

1.5.3. Preoperative cognitive function

Comprehensive neuropsychological assessments both before and after surgery have been used to relate brain dysfunction to epileptic focus and to identify risks of cognitive loss after surgery, e.g. speech and memory problems. Neuropsychological predictions are based on cognitive functions rather than structures. The preoperative neuropsychological assessment aims at obtaining a pattern of impaired and preserved cognitive functions, and distinguishing between general cognitive level and specific cognitive functions such as memory, language, visuo-contruction, and executive function, and more non-specific measures of psycho-motor speed, fluency, and attention. Since most surgical candidates have seizures originating in the memory dependent temporal lobes, evaluations of verbal and non-verbal memory are vital. It is also important to evaluate functions of the frontal lobes such as executive functions, attention and processing speed.

The temporal lobes and memory

The critical role of the temporal lobes in memory function became evident when the first study of H.M. was published nearly 60 years ago (Scoville, 1954; Scoville and Milner, 1957). H.M. had been subjected to a bilateral TLR and afterwards suffered from a global and persistent amnesic syndrome. Most TLR are anterior-medial, i.e. resection of the temporal pole and the medial temporal lobe including hippocampus and structures in close proximity to hippocampus (parahippocampal gyrus, entorhinal cortex, perirhinal cortex), and may also include amygdala. The medial temporal lobe system is most important for memory function, and the system (especially the hippocampus) has a critical role in learning and establishing long-term declarative memories. The memory system is further described in section 1.3.2.

The material-specific model of memory

The material-specific model of memory originates from the pioneering work of Brenda Milner at the Montreal Neurological Institute (Milner, 1968a; Milner, 1970; Milner, 1975), and has been the most influential concept in the neuropsychology of TLE (Sailing, 2009), see also section 1.2.1. The model implies that verbal and non-verbal forms of memory are completely segregated and localized to the left or right

hippocampus, although the relationship between memory function and side of hippocampal pathology is more obvious in patients with left hippocampal atrophy (HA) than in patients with right HA on magnetic resonance images (MRI) (Adda et al., 2008; Baxendale, 1995; Baxendale et al., 1998a; Kilpatrick et al., 1997; Lencz et al., 1992; Rausch and Babb, 1993; Sailing et al., 1993; Trenerry et al., 1995). Thus, the importance of task specific demands in relation to material-specific memory has been stressed. For example, in a study by Sailing et al. (1993), patients with left hippocampal damage performed significantly worse compared to patients with right sided damage on paired associate learning, while the two groups were only mildy impaired in immediate and delayed recall of passages. Advances in the cognitive neuroscience of memory in combination with the growing understanding of the course of postoperative outcome have raised concerns about the simplicity of the material-specific model (Sailing, 2009).

Cerebral reorganisation

Findings from functional magnetic resonance imaging (fMRI) studies have demonstrated reorganisation of language functions in patients with TLE, i.e. greater involvement of the non-dominant hemisphere (Cousin et al., 2008; Powell et al., 2007). The probability of such cerebral reorganisation is higher the earlier in life the brain damage occurs (Cousin et al., 2008). Abnormal language representation has also been associated with impairment in non-language functions (Lansdell, 1969; Milner, 1973; Satz et al., 1994; Saykin et al., 1989; Strauss et al., 1990; Teuber, 1974), a phenonomen called "crowding". This signifies that language functions have been transferred to the right hemisphere following an early (≤ 5 years) damage to the left hemisphere. Accordingly, verbal functions have been fairly spared, but this had occurred on the expense of non-verbal functions (Strauss et al., 1995). Also, a preserved verbal memory function in patients with left hippocampal damage indicates that a reorganisation of function to the right medial temporal lobe has occurred (Richardson et al., 2003). The opposite has also been found, i.e. transfer of functions from the right to the left hemisphere which suggest an adaptive role for reorganization in supporting also preserved visual memory (Figueiredo et al., 2008). Functional plasticity for verbal memory has been shown to be greater in women with early-onset left TLE (Bjornaes et al., 2005; Helmstaedter et al., 2004b). Especially women with lesion- or epilepsy-driven atypical language dominance show verbal memory advantages over men. A gender

difference in encoding strategies has also been found in that women favour semantic clustering (Baxendale, 2008a).

1.5.4. Short-term cognitive outcome of temporal lobe surgery

Because of the intimate relationship between the temporal lobes and memory functions, most studies have focussed on memory outcome after TLR. Many studies have tried to associate different neuropsychological, medical or demographic variables with surgical cognitive outcome in order to be able to predict the cognitive consequences of surgery.

Preoperative capacities

A better baseline memory performance has been associated with greater losses in memory (Baxendale et al., 2006; Chelune, 1995; Helmstaedter, 2004a; Helmstaedter and Elger, 1996a; Ivnik et al., 1988; Jokeit et al., 1997; Stroup et al., 2003). Reserve capacities in such domains as attention, language and general cognitive level (IQ) also influence memory outcome, in that better reserve capacities are associated with less loss in memory function (Elger et al., 2004; Helmstaedter, 2004a; Helmstaedter et al., 2003). However, in another study higher level of education did not protect against decline (Marques et al., 2007), lending no support to the hypothesis of cerebral reserve.

Side of surgery and side of pathology

Verbal memory impairments are more common after dominant than non-dominant TLR, see section 1.2.2. Regarding language functions, stable results as well as decrements in visual confrontation naming has been reported after left TLR (Drane et al., 2008; Hermann et al., 1988a; Hermann, 1991a), and left TLR has been shown to involve a risk for naming deficits in adults with later age at epilepsy onset (≥ 5 years), i.e. patients with no early risk factors (Hermann et al., 1994; Stafiniak et al., 1990; Yucus and Tranel, 2007). Findings from the Bozeman epilepsy consortium also confirmed a decline in confrontation naming in a sample of 217 dominant TLR patients (Strauss et al., 1995). There are also associations between high-resolution MRI findings of pathology and verbal memory. A finding of unilateral pathology gives a better prognosis for verbal memory outcome compared to a contralateral or an additional pathology (Helmstaedter, 2004a).

Extent of resection

Whether the extent of resection may have an impact on cognitive outcome has also been discussed (Baxendale, 2008a). However, the results are not consistant and yet it is not clear which resection method gives the best result regarding seizure outcome and cognitive function. In a review of 53 studies (Schramm, 2008) somewhat better results were found with selective amygdalahippocampectomy (SAH) compared to a standard TLR but sometimes a SAH even produced worse cognitive outcome.

Medical and demographic variables

Later age of epilepsy onset and higher chronological age has been associated with poorer verbal memory outcome after left TLR. This could be explained in terms of less plasticity with age (Helmstaedter, 2004a). Memory outcome has also been found to be related to seizure outcome (Tellez-Zenteno et al., 2007), i.e. persisting seizures after surgery have been associated with greater loss in verbal memory and also less recovery (Helmstaedter, 2004a; Helmstaedter et al., 2003; Jokeit et al., 2001). Duration of epilepsy has only shown weak associations with postsurgical memory outcome (Hermann et al., 1995a; Saykin et al., 1989).

Prediction of memory outcome – two models

Prediction of postsurgical memory outcome is dominated by two theories. *The functional reserve* model implies that postoperative memory function is related to capacity of the contralateral temporal lobe to support memory after ipsilateral lobe resection (Bell et al., 2000; Chelune, 1995). This model suggests that a good memory performance after injection contralateral to the seizure focus during the intracarotid amobarbital procedure (IAP) could predict memory decline (Bell et al., 2000; Kneebone et al., 1995; Loring et al., 1990; Stroup et al., 2003). Conversely, *the functional adequacy* model implies that postoperative memory function is related to functional adequacy of the tissue in the ipsilateral temporal lobe. This model suggests that patients with high baseline memory performance are supposed to also have less damaged hippocampus in the ipsilateral temporal lobe, and there-fore are at a greater risk for memory decline (Chelune and Najm, 2000; Chelune, 1995; Helmstaedter and Elger, 1996a; Ivnik et al., 1988; Kneebone et al., 1995). The integrity of the hippocampus has also been assessed with recordings from hippocampal neurons (Cameron et al., 2001) and with hippocampal volumes confirmed by MRI (Baxendale et al., 1998a). Finally, functional imaging (fMRI)

studies have also been able to predict decline in verbal (Powell et al., 2008; Richardson et al., 2006; Richardson et al., 2004) as well as in visual memory (Janszky et al., 2005; Powell et al., 2008). However, it has also been questioned whether preoperative hippocampal activation asymmetry measured by IAP memory testing or with fMRI is predictive of verbal memory outcome (Binder et al., 2008; Binder et al., 2009). Hence, these techniques can not be used alone to assess the risk of postoperative memory impairment, instead they need to be combined with traditional neuropsychological assessments and findings from structural MRI studies and other presurgical investigations (Baxendale, 2002). Recently, there has been a shift in the role of the IAP in epilepsy surgery programmes (Baxendale, 2009). The IAP is still considered the "gold standard" for language lateralization, but not for predicting memory decline after surgery and the clinical indications for non-invasive alternatives should therefore carefully be considered for each patient (Baxendale, 2009; Baxendale et al., 2007).

1.5.5. Long-term cognitive outcome of temporal lobe surgery
The importance of long-term follow-up after surgery has been emphasized (ILAE et al., 2000), but yet most of the cognitive outcome literature concerns short-term follow-up periods of 1-2 years. Recently, the issue of late cognitive effects of TLR for epilepsy in adults has been addressed (Alpherts et al., 2004; Alpherts et al., 2006; Helmstaedter et al., 2003; Rausch et al., 2003), with patient samples ranging from 44 (Rausch et al., 2003) to 147 patients (Helmstaedter et al., 2003) and with mean test intervals varying between 4.8 (Helmstaedter et al., 2003) and 12.8 years (Rausch et al., 2003). Results from these studies are not consistent. Rausch as well as Helmstaedter reported progressive decline in learning and recall of verbal (Helmstaedter et al., 2003; Rausch et al., 2003) and non-verbal/visual (Rausch et al., 2003) memory following both DTL and NDTL resections. Alpherts (Alpherts et al., 2006), on the other hand, found an ongoing memory decline for consolidation and acquisition of verbal material for up to two years after DTL resection, which then levelled off and speculated that removal of the hippocampus could cause functional deficits elsewhere and that shrinkage of the hippocampal remnant is an ongoing degenerative process that probably affects both the surrounding tissue and the connections of the mesial structures. Postoperative hippocampal remnant shrinkage, confirmed with volumetric MRI, has been reported to influence postoperative memory change, although, this process appears to stabilize within the first 3 months (Baxendale et al., 2000). Helmstaedter reported that unsuccessful

epilepsy surgery could accelerate memory decline, while seizure freedom could stop or even reverse it (Helmstaedter et al., 2003). Neither Rausch nor Alpherts found any relationship between seizure freedom and less severe memory decline (Alpherts et al., 2006; Rausch et al., 2003).

1.6. Psychometrical issues

1.6.1. Test methods used

Internationally and nationally test batteries or single tests are used in neuropsychological epilepsy studies. The following tests are well-known and frequently used. <u>Batteries:</u> the Wechsler Adult Intelligence Scale (WAIS-R=the older version; WAIS-III=the latest version); the Wechsler Memory Scale (WMS-R=the older version; WMS-III=the latest version); the Halstaed-Reitan Battery (HRB); the Neuropsychological Battery for Epilepsy (NBE). <u>Single tests</u>: the Logical Prose (from WMS); the Paired associates (from WMS); the Visual Reproduction Test (from WMS); the Rey Auditory Verbal Learning Test; the California Verbal Learning Test; the Verbal Selective Reminding Test; the Rey-Osterrieth Complex Figure Test; the Recognition for Faces (Warrington); the Boston Naming Test; the FAS word fluency test; the Token Test. Other tests are also used and many countries have their own nationally developed tests (Jones-Gotman et al., 1993). Newer tests have been developed concerning non-verbal memory: the Aggie Figure Learning Test (Majdan et al., 1996); Aspects of Spatial Memory Test (Baxendale et al., 1998b). Finally, new assessment techniques for discovering ALF and RMI have also been developed (Bell and Giovagnoli, 2007). These are inspired partly by reports from patients' every-day memory problems (Bergin et al., 2000; Blake et al., 2000; Manning et al., 2005; Martin et al., 1991) and partly by theoretical constructions (Kapur et al., 1997; Mayes et al., 2003; Viskontas et al., 2000).

1.6.2. Assessment of change

At group level

Parametric or non-parametric group comparisons of change between two assessments (e.g. before and after surgery) test the hypothesis of no mean (or median) change at group level. They do not provide information about patterns of individual variability (Dikmen et al., 1999; Jacobson and Truax, 1991). Statistically significant changes in cognitive variables at group level do not provide information about the size, importance or clinical significance of the change.

At individual level

Neuropsychological assessments are often serially administered in order to follow a process (e.g. in medically treated epilepsy) or for analysing the outcome (after epilepsy surgery). Different fields of psychology, both in general (Jacobson and Truax, 1991) and in studies of the effects of epilepsy surgery (Chelune, 1998; Chelune et al., 1993; Hermann et al., 1996a; Hermann and Wyler, 1988b; McSweeny et al., 1993) have tried to establish conventions for defining clinically significant change, se below.

Change of clinical importance

A change can be of statistical significance without having any clinical relevance (Hermann and Wyler, 1988b). Various criteria for clinical relevance have been proposed such as a certain level of change in daily function or a certain level of deterioration in change scores (Kazdin, 1977; Kazdin and Wilson, 1978; Kendall and Norton-Ford, 1982; Mavissakalian, 1986; Nietzel and Trull, 1988; Wolf, 1978). A change score equal to or exceeding one standard deviation (SD) of the group mean or baseline mean is commonly used as a definition of clinically significant change (Hermann and Wyler, 1988b; Phillips and McGlone, 1995). Another suggestion is to consider >15% change as clinically relevant (Ivnik et al., 1988). Two methods for measuring change have been developed and applied, *Reliable Change Indices (RCI)* and *Standardized regression-based norms for change* (Baxendale and Thompson, 2005; Chelune et al., 1993; Hermann et al., 1996a; Martin et al., 1998; McSweeny et al., 1993; Nakhutina et al., 2009; Sawrie et al., 1996; Temkin et al., 1999). Changes of clinical significance are categorized by using cut-off scores based on the confidence intervals. Both methods have the advantage of including correction for practice effects, se 1.6.3. However, the methods are not without problems. Practice effects are not constant for all types of subjects (Dikmen et al., 1999), and variation in retest results - especially in memory variables - has been found to be more common than neuropsychological professionals usually expect (Bartfai, 2000; Dikmen et al., 1999). Finally, the methods assume that data are normally distributed with arithmetic properties of magnitude and distance. Thus, even with the use of such methods it is not certain that the definitions are more closely connected to subjective perception of change than usual measures of subtracting baseline scores from follow-up scores (Sawrie et al., 1999). We also do not know how much impairment and change it takes to make a difference for the patient (Helmstaedter, 2004a).

1.6.3. Effects of repeated testing

Practice effects

A methodological problem with repeated testing is the possibility of practice effects. The extent of practice effects may vary with the following variables: type of measure, the use of alternative tests, baseline performance and overall competency level of the subject, chronological age, follow-up interval and number of repeated assessments. Practice effects observed in the following conventional tests have been described as modest: Full Scale IQ (FSIQ): 2 points; Verbal IQ (VIQ): 1 point; Performance IQ (PIQ): 3 points (Hermann et al., 1996a). In normal controls, high increments in PIQ (11.0 and 7.0 points) have been found after test intervals of 2.5 and 5 years (Dodrill, 1983; Matarazzo et al., 1980). Low practice effects in memory tests have been reported; 1 to 2 points increase in reference groups (Chelune et al., 1993; Hermann et al., 1996a) and practically no increase in normal controls (Wilson et al., 2000). Substantial individual variation in practice effects has also been observed (Dikmen et al., 1999), i.e. different levels of impairment at baseline yield different performances at follow-up and subjects with severe impairment might not benefit from practice (Chelune et al., 1992; Dodrill and Troupin, 1975; Seidenberg et al., 1981b). The absence of test-retest effects in patient groups is often interpreted as a cognitive impairment (Vingerhoets, 2006).

Regression or egression towards the mean or median

Regression or egression towards the mean (or median) influences the nature and degree of change at an individual level (Hermann et al., 1991b; Nesselroade et al., 1980; Temkin et al., 1999) and has been reported in several studies of epilepsy samples (Chelune et al., 1991; Engman et al., 2006; Helmstaedter et al., 2000; Rausch et al., 2003). One way to deal with these methodological issues is to use a control group for comparison.

Reliability of test methods

Composite scores from a number of subtests such as WAIS-R IQs and HRB tend to have better reliability compared to each individual subtest. In an extensive study it was pointed out that reliability coefficients for most conventionally used tests such as the psychometric sum scores measures were ranging from 0.70 to 0.90, while memory subtests showed poorer reliability (≤ 0.60) (Dikmen et al., 1999).

1.6.4. Choice of statistical methods

Statistical methods differ between studies, which make comparisons difficult. Parametric statistics are often applied irrespective of sample size or assumptions of data distributions. The issue of non-normal data distributions could be attended to by choosing non-parametric methods or using log-transformations of raw scores. The issue of multisignificance or statistical power is seldom considered. Multivariate approaches have been successfully used to investigate associations between measures of structure and function preoperatively in order to predict postoperative decline (Baxendale et al., 2006; Baxendale et al., 1998a; Jokeit et al., 1997; Stroup et al., 2003).

2. AIMS OF THE STUDY

Drug resistant partial epilepsy is a detrimental disorder in many ways. Besides risks directly associated with uncontrolled seizures, there is a risk for cognitive decline across time. For some of these patients epilepsy surgery is a valuable treatment option which, however, also involves a risk for cognitive decline. Short-term (≤ 2 years) cognitive outcome of epilepsy surgery has been extensively reported, while reports on long-term outcome (≥ 10 years) are sparse. For the many patients with drug resistant epilepsy where surgery is not an option, continued antiepileptic drug treatment, often with polytherapy, is an additional risk for cognitive impairment. The literature on neuropsychological function across time in medically treated patients is also sparse. Since drug resistant epilepsy involves a risk for cognitive decline irrespective of the treatment options, it is important to further investigate the possible long-term cognitive effects.

The aims of the present thesis were:

- To investigate longitudinal cognitive changes in patients with drug resistant medically treated partial epilepsy compared to an adequate control group and to explore the hypothesis that a cognitive decline across time would be disclosed (study I).

- To investigate whether the relationship between drug resistant partial epilepsy and change in verbal memory across time is influenced by the level of performance in verbal cognition or in attention/processing speed (study II).

- To explore long-term cognitive changes after TLR for epilepsy at group level compared to longitudinal changes in healthy controls (study III).

- To investigate whether memory deterioration after dominant TLR is residual or progressive over time at group level and whether memory decline at long term relates to seizure outcome (study III).

- To describe early and late individual changes in verbal memory after TLR compared to individual changes in healthy controls and to explore risk factors for early and late verbal memory decline after TLR (study IV).

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3. SUBJECTS AND METHODS

3.1. Study groups

3.1.1. Medically treated patients

A consecutive series of patients with drug resistant partial epilepsy who had undergone presurgical investigations between 1987 and 1994 but not been operated went through a neuropsychological follow-up assessment (study I and II). Main inclusion criteria were: seizure frequency of at least one complex partial or secondarily generalized seizure per month at the time of follow-up and no progressive neurological disease. Thirty-one patients fulfilled the criteria and 27 accepted participation. Included in the study were also nine patients who had undergone two serial neuropsychological assessments before epilepsy surgery, in all 36 patients, see Figure 1. All patients had localization-related partial epilepsy. The reasons for not having surgery varied: some patients had widespread or bilateral seizure onset or seizure onset in eloquent cortex while others refused surgery. No significant differences were found between the non-operated and the eventually operated patients regarding medical, demographic, or neuropsychological variables. Median retest interval for patients was 4.8 years (Q1; Q3: 2.5; 7.3).

3.1.2. Surgically treated patients

A consecutive series of 62 patients who had undergone TLR for epilepsy between 1987 and 1998 were asked to participate in the study (study III and IV). Patients with major surgical complications or intercurrent severe disorders that could influence cognition were excluded. Five patients had died at long-term follow-up, four were excluded due to severe illness or complications, one lived abroad, and one declined participation. The remaining 51 accepted, see Figure 2. Twenty-three of these had seizures originating in the DTL and 28 in the NDTL. Speech hemisphere dominance, determined by the IAP (Malmgren et al., 1992), was left in 49 and right in two patients. A comprehensive preoperative investigation had been accomplished for all patients (Eriksson et al., 1999). The patients had also undergone neuropsychological assessment before surgery (baseline), at medium-term follow-up two years after surgery (median test interval 2.8 years) (Engman et al., 2001; Engman et al., 2004), and at long-term follow-up ten years after surgery (median test interval 10.9 years). Additionally, one of the NDTL patients (with left

speech dominance) was excluded from study IV due to missing verbal memory data at baseline.

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                    ┌─────────────────────────┐
                    │ 31 patients fulfilled   │
                    │ inclusion criteria      │
                    └─────────────────────────┘
┌─────────────────────────┐          │
│ 4 patients declined     │──────────┤
│ participation           │          │
└─────────────────────────┘          │
                    ┌─────────────────────────┐
                    │ 27/31 patients          │
                    │ accepted participation  │
                    └─────────────────────────┘
                                 │          ┌─────────────────────────┐
                                 │          │ 9 patients with         │
                                 ├──────────│ serial testing          │
                                 │          │ before surgery          │
                                 │          └─────────────────────────┘
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                    │ 36 patients serially    │
                    │ tested (Study I and II) │
                    └─────────────────────────┘
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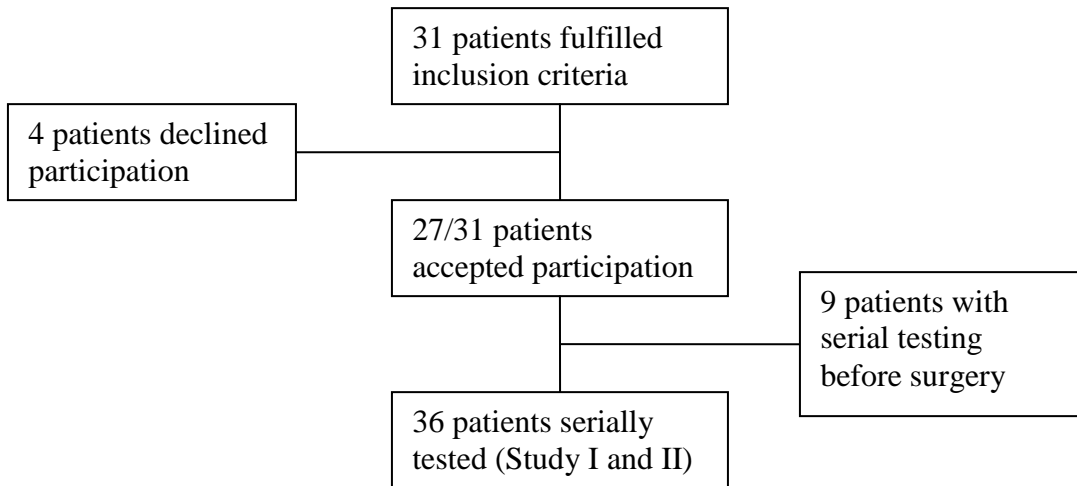
Figure 1. Medically treated patients in study I and II.

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                    ┌─────────────────────────┐
                    │ 62 patients fulfilled   │
                    │ inclusion criteria      │
                    └─────────────────────────┘
┌─────────────────────────┐          │
│ 5 patients had died     │          │
│ 1 lived abroad          │──────────┤
│ 1 declined participation│          │
└─────────────────────────┘          │
                    ┌─────────────────────────┐
                    │ 51 patients included    │
                    │ (Study III)             │
                    └─────────────────────────┘
                                 │          ┌─────────────────────────┐
                                 │          │ 1 patient excluded      │
                                 ├──────────│ due to missing          │
                                 │          │ data at baseline        │
                                 │          └─────────────────────────┘
                    ┌─────────────────────────┐
                    │ 50 patients analysed    │
                    │ (Study IV)              │
                    └─────────────────────────┘
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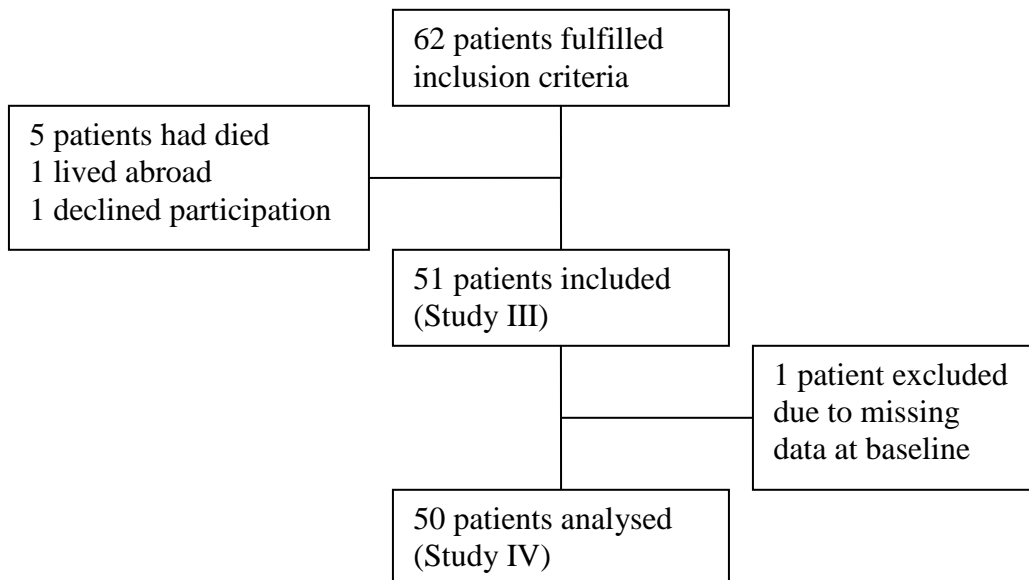
Figure 2. Surgically treated patients in study III and IV.

3.1.3. Controls

A control group consisting of 30 neurologically healthy individuals, matched at group level to the patients for gender, age, years of education and socio-cultural circumstances, was assessed at baseline. Twenty-five (25/30) participated in the medium-term (median test interval 3.1 years) and 26/30 in the long-term follow-up assessment (median test interval 9.9 years). In study I, data from the whole group (N=30) were used for baseline comparisons. In study II, data from the 25 who went through the medium-term follow-up were used for all comparisons. In study III and IV, data from the 23 controls who had all three assessments were used for all comparisons, see figure 3. There were no significant differences at baseline between the 23 controls who fulfilled all three assessments and the seven missing controls with respect to neuropsychological functions, chronological age or length of education.
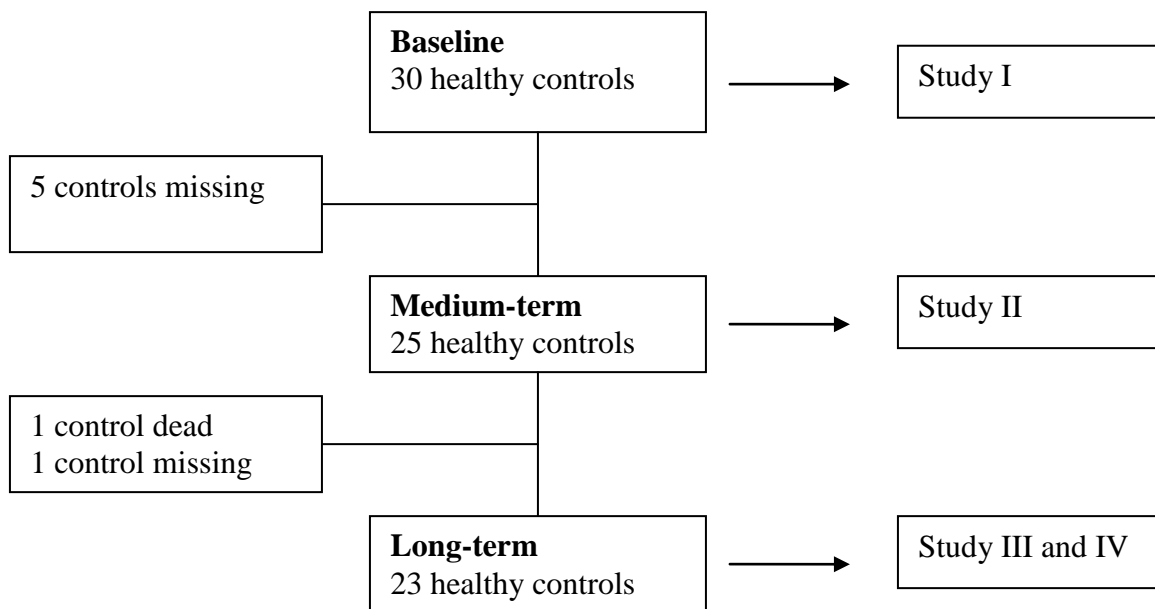
Figure 3. Healthy controls in studies I-IV.

3.2. Aspects of cognition and test instruments

The test instruments used in the present study at baseline, medium-term, and long-term follow-up are conventionally well-documented standard neuropsychological test batteries. The tests were used for both patients and controls. Aspects of cognition and test instruments included in the study are listed below.

3.2.1. General cognitive level
WAIS-R

WAIS-R was used for assessment of general cognitive level (Bartfai et al., 1992; Wechsler, 1981). The test battery includes three IQ measures: Full Scale IQ (FSIQ), Verbal IQ (VIQ) and Performance IQ (PIQ).

3.2.2. Verbal memory
Claeson-Dahl (CD) Learning and Retention Test

The CD Learning and Retention Test (Claeson et al., 1998; Claeson and Dahl, 1971) assesses learning and retention of a word list. The test consists of 10 (8 abstract and 2 concrete) words that are verbally presented and recalled after a 15-second delay. The words are repeated until the subject has either recalled the entire list correctly twice successively or has had 10 trials (Weighted Sum, WS). Retrieval of number of words as percentage of the maximum learned words is assessed after 30 minutes (Delayed Recall, DR). Alternate versions were used at follow-up.

Cronholm-Molander (CM) Memory Test

The verbal part of the CM Memory Test assesses immediate and delayed recall of paired associated words (Cronholm and Ottosson, 1963; Nordgren, 1978). The test consists of 30 word-pairs presented 10 by 10, simultaneously verbally and visually. After each presentation, the subject is given the first word and asked to recall the second from memory (Immediate Recall, IR). After a delay of three hours the subject is again given the first word and asked to recall the second from memory (DR). An alternate version was used at follow-up.

3.2.3. Visual memory
CM Memory Test

The visual part of the CM Memory Test assesses immediate and delayed recognition of familiar objects (Cronholm and Ottosson, 1963; Nordgren, 1978). The test consists of 30 line drawings of familiar objects, which are pointed to and named by the examiner. The subject is then asked to recognize the objects interfoiled with 30 distractors (Immediate Recognition, IRec). After a delay of three hours the subject is again asked to recognize the objects interfoiled with 30 distractors (Delayed Recognition, DRec). An alternate version was used at follow-up.

Rey-Osterrieth Complex Figure Memory Test (ROCF)

The complex figure assesses retention capacity for visuo-spatial material (Corwin and Bylsma, 1993; Lezak, 1983). The subject is asked to copy a complex figure. When this task is accomplished (and just before the stimulus is removed from sight) information is given that recall of the copied figure will be examined later (DR). An alternate version was used for two-thirds of the patients.

3.2.4. Verbal cognition

Information

Information is a subtest from the WAIS-R (Wechsler, 1981) and assesses academic achievement and retention. We used a version adapted to Swedish conditions (Bartfai et al., 1992).

Vocabulary

Vocabulary is a subtest from WAIS-R and assesses vocabulary level and has long been recognised as a strong correlate of general mental ability (Lezak, 1995). The score reflects both the extent of recall vocabulary and the effectiveness of speaking vocabulary (Wechsler, 1981). Vocabulary tests are among the most widely used of all mental ability tests, either alone or as part of test batteries (Lezak, 1995).

Similarities

Similarities is a subtest from WAIS-R and assesses capacity for verbal concept formation. The subject must explain what each of a pair of words has in common (Wechsler, 1981). It is considered to be a test of general mental ability (Lezak, 1995).

3.2.5. Attention and processing speed

Digit span

Digit span is a subtest from *WAIS-R* and assesses the subject's capacity for encoding and retaining in memory series of numbers and repeating them immediately. There are two parts, Digits forward and backward (Bartfai et al., 1992; Wechsler, 1981), which involve somewhat different mental activities (Kaplan, 1991). Both involve auditory attention and depend on a short-term retention capacity (Shum et al., 1990). The Digits forward has been described as a test of "passive span of apprehension" (Hayslip and Kennely, 1980) and measures the efficiency of attention (i.e. freedom from distractibility), while the Digits backward is more commonly thought of as working memory (Kaufmann et al., 1991). The

task also involves mental double tracking in that both the memory and the reversing operations must proceed simultaneously (Lezak, 1995).

Arithmetic

Arithmetic is a subtest from the WAIS-R and assesses the subject's capacity to encode arithmetic word problems, retain the problems in short-term memory, and to solve them without the aid of pencil and paper. The task is rather complex and will probably put demands on both working memory and attention. It also contains a processing speed component since the subject has to solve the problems within a time limit.

Digit symbol

Digit symbol is a subtest from the WAIS-R and requires the subject to transcribe the symbols paired with the numbers 1 through 9 as quickly as possible, within a given time limit (Bartfai et al., 1992; Wechsler, 1981). Skills of motor persistence, sustained attention, response speed, and visuo-motor coordination are needed (Schear and Sato, 1989). Accordingly, the test puts great demands on processing speed.

TMT

The TMT is a subtest from the HRB and consists of two parts. Part A of this timed task calls for connecting numbers in an ascending sequence, whereas part B requires alternation between numbers and letters in an ascending sequence (i.e. 1-A-2-B-3-C, etc.) (Bergman et al., 1988). The test assesses complex visual scanning (Shum et al., 1990), motor speed and agility (Schear and Sato, 1989). TMT B also includes demands of focus/executive attention (Mirsky and Duncan, 2001) and divided attention (Sohlberg and Mateer, 1989; Stuss et al., 1989; Van Zomeren and Brouwer, 1994).

3.3. Reliability coefficients based on test manuals and controls

The test-retest reliability coefficients of the tests are as follows (based on test manuals and controls, respectively): *general cognitive level*: FSIQ (0.95 and 0.97), VIQ (0.94 and 0.97) and PIQ (0.89 and 0.92) (Bartfai et al., 1992); *verbal memory*: CD wordlist - WS (0.85 and 0.69), and DR (0.41 and 0.73) (Claeson et al., 1998), CM word-pairs, IR (0.79 and 0.82), and DR (0.88 and 0.88) (Björkman, 1968; Cronholm and Ottosson, 1963); *visual memory*: CM familiar objects - IRec (0.52 and 0.64), and DRec (0.80 and 0.70) (Björkman, 1968; Cronholm and Ottosson, 1963), ROCF - DR (0.89 and 0.83) (Meyers and Meyers, 1995); *attention/ processing speed*: Digit span forward (0.89 and 0.79) and backward (0.89 and

0.85), Arithmetic (0.80 and 0.81), Digit symbol (0.86 and 0.92) (Bartfai et al., 1992), TMT, part A ($\leq$0.60 to $\geq$0.90 and 0.85) and part B ($\leq$0.60 to $\geq$0.90 and 0.93) (Spreen and Strauss, 1991); *verbal cognition*: Information (0.88 and 0.97), Vocabulary (0.93 and 0.98), and Similarities (0.82 and 0.86) (Bartfai et al., 1992).

3.4. Medical and demographic variables

For all patients (both medically and surgically treated), the following data were ascertained: age at epilepsy onset, epilepsy duration, seizure types and frequencies, and AED treatment. The information was collected at baseline and at the times of follow-up. Neuroimaging data and seizure monitoring results from the presurgical investigation were also ascertained for all patients and for the surgically treated patients also: laterality of resection, speech dominance, and presence of cortical dysgenesis (defined as any malformation of cortical development including microdysgenesis in the resected tissue). For all patients and controls, information on chronological age, length of education, and socioeconomic status was collected both at baseline and at the times of follow-up.

3.5. Statistical methods

Raw scores were analysed (except for the sum scores of FSIQ, VIQ and PIQ). Median and interquartile ranges (studies I-IV), mean and SD (study III and IV) were used to describe distribution. Missing data were not replaced by group or subgroup means (studies I-IV). Baseline scores were subtracted from follow-up scores to obtain change scores (studies I-III). Due to the small sample of the medically treated patients and skewed data distributions, non-parametric methods were used in study I and II. In the surgically treated group, data were approximately normally distributed and parametric methods were used (study III and IV).

Group changes
Between-group comparisons were made with the Mann-Whitney U-test and within-group comparisons with Wilcoxon signed rank test (studies I-III). In study III, a linear mixed model for a repeated measures design was used. Between-subjects treatment effect was group (DTL, NDTL and Controls), and within-subjects factor was time (2 and 10 years after surgery). Baseline scores were used as a covariate in the analyses in the mixed model. Group differences in the change in performance

between medium- and long-term follow-up were analysed by the time by group interactions. For the variables that showed significant group differences in the mixed model at the 10-year follow-up (study III), the size of the effect was described by the Cohen's d. Adjustments for multiple comparisons were made when appropriate with the Bonferroni-Holm sequentially rejective multiple test procedure (Holm, 1979) (study I). The Statview (study I and II) and the Statistical Package of Social Science (SPSS) programs (version 15) (study III and IV) have been used for statistical analyses.

Individual changes

Individual changes from baseline to follow-up were investigated for the patients by comparison with the individual changes of the controls (study I). Changes were categorized as follows: *decrement* (≤5th percentile of the distribution of the controls), *within the control interval* (between the 6th and 94th percentiles of the controls), *increment* (≥95th percentile of the controls). Individual changes at the 2- and 10-year follow-up were compared with the individual changes of the controls (study IV). RCI values were calculated from the test-retest data (baseline to 2-year and baseline to 10-year follow-up) of the controls. The method of Jacobson and Truax (1991) was used, i.e. a 90% confidence interval (CI) was established by multiplying SE_{diff} with ± 1.64. A factor for correction was added to the CI values based on the mean practice effect for the present variable, i.e. difference between the means at 2- and 10-year follow-up and baseline. Change scores exceeding the CI at either end of the distribution represent a statistically reliable change that would occur <5% of the time. The changes in memory were categorized based on how many of the four verbal memory variables that had changed negatively and positively according to the cut-off scores of RCI 90% CI. The following two levels of decline and improvement were used: '*Decline≥1*' (≥1 negative and no positive change), '*Decline≥2*' (≥2 negative and no positive changes), '*Improvement≥1*' (≥1 positive and no negative change) and '*Improvement≥2*' (≥2 positive and no negative changes).

Associations

Associations between neuropsychological variables and between neuropsychological and medical variables were evaluated with the Spearman rank correlation coefficient (study I and II). Forward stepwise logistic regression analysis was used in order to identify the most important correlates of epilepsy of the cognitive

variables in study I, and among the variables of verbal memory and attention in study II. In both studies (I and II), presence of epilepsy represented the dependent variable, and cognitive change scores the independent variables. The strength of the relationship between epilepsy and change (in those verbal memory variables showing significant differences between patients and controls) was given by odds ratios. The effect of confounding variables (estimated by odds ratios), was examined by forcing each of the verbal cognition and attention/processing speed variables, one by one, into the regression model (study II). For the variables that showed significant group differences in the mixed model at the 10-year follow-up (study III), a further analysis of the relationship between cognitive test scores and continuing seizures and AED treatment was conducted. Between group comparisons (patients with or without seizures and patients with or without AED at the 10-year follow-up) were analysed with Mann-Whitney U test. When significant group differences were disclosed for both seizures and AED, the strongest correlate to the test results was identified by a stepwise backward logistic regression analysis. Dependent variable was test results at the 10-year follow-up (dichotomised into scores below or on/above the median) and independent variables were seizures (yes/no) and AED treatment (yes/no). The probability for stepwise removal was 0.06.

Predictions
Predictors of verbal memory decline at 2 (baseline to 2 years) and 10 years after surgery (baseline to 10 years) were identified by using a forward stepwise logistic regression analysis (study IV). Dependent variable in these analyses was Decline≥1 or no decline 2 and 10 years after surgery. Independent variables were *laterality* (DTL vs NDTL), *verbal memory at baseline* (the number of memory tests [0-4] with an intact performance, i.e. a score above the 16th percentile of the controls), *verbal IQ at baseline*, *chronological age*, and *presence of cortical dysgenesis* (yes/no). The predictor variables were selected on the basis of findings in earlier studies and on availability of data. A stepwise selection procedure was used with the α to enter set at 0.05 and the α to remove set at 0.10 (study I, II and IV).

4. RESULTS

4.1. Study I
4.1.1. Medical and demographic data
The patients had a long duration of epilepsy (median 16.5 years at baseline) and frequent seizures (median 8.5 per month at baseline) (cf. Table 1 in paper I). No significant differences were noted between baseline and follow-up regarding seizure frequency or number of AED (z-values between -1.95 and -1.78). Fifty per cent of the patients (N=18) had GTCSs and partial seizures, and 50% had only partial seizures between baseline and follow-up. No significant differences were found between patients and controls with respect to test interval, chronological age, or length of education (z-values between -1.47 and -0.44) (cf. Table 1 in paper I).

4.1.2. Baseline test performance
General cognitive level
General cognitive level was lower in the patient group compared to the controls: FSIQ (z=-3.9, p=0.001), VIQ (z=-3.8, p=0.001), and PIQ (z=-3.7, p=0.002) (cf. Table 2 in paper I).
Memory
Patients performed lower compared to the controls in the verbal memory variables CD word-list – DR (z=-3.1, p=0.01) and CM word-pairs – IR (z=-2.7, p=0.03) (cf. Table 3 in paper I), and in the visual memory variable ROCF – DR (z=2.7, p=0.04) (cf. Table 4 in paper I).

Associations between baseline performance, medical and demographic variables
No significant relationships were found between the neuropsychological variables, and the medical and demographic variables: age at epilepsy onset; epilepsy duration; seizure frequency, chronological age; length of education (z-values between 0.06 and 0.48), and presence of GTCS (z-values between -0.04 and -1.12).

4.1.3. Change in test performance at follow-up
Within-group changes
There were no significant changes across time in general cognive level in the patient group (cf. Table 1), while the controls improved in both FSIQ (z=-3.6, p=0.003) and PIQ (z=-3.5, p=0.005) (cf. Table 1). The patients declined across time

in the verbal memory variable CM word-pairs – DR (z=-3.1, p=0.02) (cf. Table 1). No significant changes were disclosed for the remaining cognitive variables (z-values between -2.16 and -0.71).

Between groups changes
The patients' change scores across time in PIQ were lower compared to those of the controls (z=-3.7, p=0.002) (cf. Table 1). A stepwise logistic regression analysis was performed to further explore the relationship between epilepsy and cognitive change across time in all but one of the cognitive variables (FSIQ was excluded as it represents the sum of VIQ and PIQ). In the initial univariate comparison, a relationship (p<0.05) was disclosed between epilepsy and the change scores of all but one (CD word-list – DR) of the investigated cognitive variables. At the final step of the regression procedure, significant relationships were disclosed between epilepsy and decreasing change scores in PIQ, ROCF – DR, CM word-pairs – DR, and CD word-list – WS (cf. Table 5 in paper I). These variables were further analysed to investigate possible confounding effects, by forcing the scores from baseline performance and retest interval (one by one) into the regression model. After the adjustment for baseline performance, the relationship with epilepsy was still significant for all four variables (Wald χ^2-square values between 4.60 and 8.67; p-values between 0.025 and 0.003), and after adjustment for retest intervals for three of them (CD word-list – WS was excluded) (Wald χ^2-square values between 4.34 and 5.48, p-values between 0.037 and 0.019).

Individual changes
The patients' individual change scores were compared with the normative range of the controls only for variables that showed significant group differences at baseline or across time (cf. Table 6 in paper I). Approximately half (48%) of the patients had FSIQ change scores below the normative interval of the controls. Around two fifths (18%) to one third (32%) of the patients had change scores below the normative level of the controls in the variables ROCF – DR, CM word-pairs – DR, VIQ, and PIQ. In six of eight variables, no patients had increments above the normative interval. However, the variable CD word-list – DR constituted an exception with 31% of the patients showing increments at follow-up.

Table 1. Follow-up change scores in all cognitive variables for patients and controls

	N	Median (Q1; Q3)	Tied P value[b]
		Follow-up change scores	
General cognitive level			
Full Scale IQ			
Patients	31	0.0 (-2.5; 2.0)	NS
Controls	25	3.0 (1.0; 6.0)	0.003[c]
Verbal IQ			
Patients	31	0.0 (-3.0; 2.0)	NS
Controls	25	1.0 (0.0; 2.0)	NS
Performance IQ			
Patients	31	-1.0 (-4.5; 3.0)**	NS
Controls	25	6.0 (1.0; 10.0)	0.005[c]
Verbal memory			
CD word-list – weighted sum[e]			
Patients	30	4.5 (-30.3; 45.5)	NS
Controls	25	-26.0 (-55.0; -1.0	NS
CD word-list – delayed recall			
Patients	29	13.0 (0.0; 31.0)	NS
Controls	25	0.0 (-10.0; 10.0)	NS
CM word-pairs – immediate recall			
Patients	29	-2.0 (-6.0; 1.0)	NS
Controls	25	0.0 (-1.0; 3.0)	NS
CM word-pairs – delayed recall			
Patients	28	-2.5 (-5.3; -0.8)	0.02[d]
Controls	25	0.0 (-2.0; 4.0)	NS
Visual memory			
CM familiar objects – immediate recognition			
Patients	32	-1.0 (-3.0; 1.3)	NS
Controls	25	1.0 (-1.0; 4.0)	NS
CM familiar objects – delayed recognition			
Patients	29	-1.0 (-3.0; 2.0)	NS
Controls	25	1.0 (-1.0; 4.0)	NS
ROCF – delayed recall			
Patients	29	-0.5 (-4.1; 1.6)	NS
Controls	25	0.0 (-1.5; 2.0)	NS

[a]Interquartile range: 25th; 75th centile; [b] Wilcoxon signed rank test; [c] Significant increment ($p<0.01$) at follow-up compared with baseline; [d] Significant decrement ($p<0.05$) at follow-up compared to baseline; **$p<0.01$ median change score reflecting significantly more impairment at follow-up compared with the controls. All statistical analyses were corrected with Bonferroni-Holm sequentially rejective multiple test procedure. [e] An increase in change score = a decline in performance.

Associations between neuropsychological, medical and demographic variables
Baseline and follow-up change scores

A further analysis of the relationship between baseline and follow-up scores of the variables showing adverse effects for the patients (PIQ, ROCF – DR and CM word-pairs – DR) yielded significant correlations in PIQ (*rho*=-0.52, *p*= 0.02) and CM word-pairs – DR (*rho*=-0.68, *p*=0.004). Figure 4 illustrates a regression toward the median effect in the CM word-pairs - DR. There were marked decrements at follow-up in patients with high baseline scores. However, 71 % of the patients (10/14) who performed below the median at baseline had decrements or were unchanged at follow-up. A similar pattern was observed for PIQ.
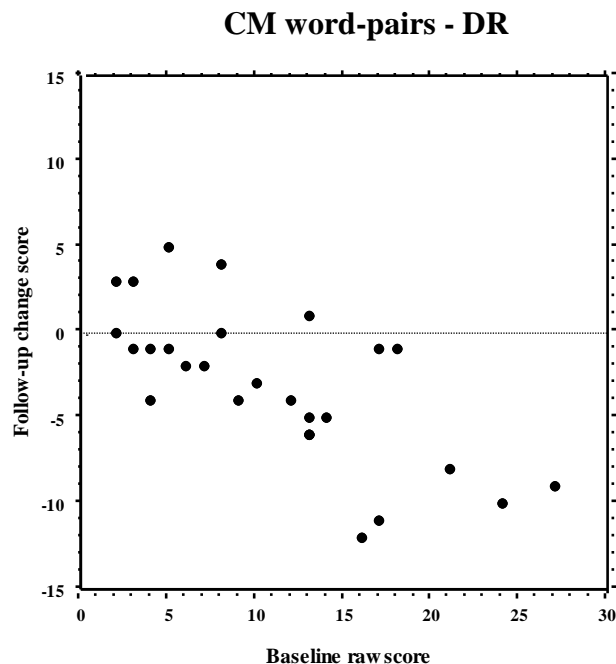
CM word-pairs - DR

Figure 4. This scatterplot illustrates a regression toward the median effect (*rho*=-0.68, *p*=0.004) in CM word-pairs DR in the patients, confounded by marked losses in scores at follow-up: patients with high baseline scores had substantial decrements and 10/14 patients, who performed below the median (11.0) at baseline, had decrements or were unchanged at follow-up. DR = delayed recall.

Follow-up change performance and medical and demographic variables

No significant associations were found in the patient group between the follow-up change scores and the medical and demographic variables, i.e. age at epilepsy onset, epilepsy duration, chronological age, length of education and seizure frequency at follow-up, change in seizure frequency, length of test interval (*rho-*

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values between 0.22 and -0.44) and presence of GTCS (z-values between -0.10 and -2.15).

Seizures involving left temporal lobe and decline in verbal memory

A post hoc subgroup analysis showed no significant differences in verbal memory change scores between patients with (N=17) and without (N=19) left temporal lobe involvement (z-values between -0.02 and -0.90), and hence seizure focus could not explain the verbal memory decline.

4.2. Study II

4.2.1. Baseline test performance

Verbal memory

Patients performed lower than the controls in three of four verbal memory variables (CD word-list – DR: z=-2.88, p=0.004; CM word-pairs – IR: z=-2.32, p=0.02; CM word-pairs – DR: z=-2.18, p=0.029) (cf. Table 3 in paper II).

Verbal cognition and attention/processing speed

Assessments of verbal cognition and attention/processing speed showed similar results, the patients performed lower than the controls in all three verbal cognition variables (Information: z=-2.68, p=0.007; Vocabulary: z=-2.98, p=0.003; Similarities: z=-3.52, $p<0.001$) and in five of the six attention/processing speed variables (Digit span – backward: z=-2.84, p=0.004; Arithmetic: z=-3.03, p=0.002; TMT A: z=-4.47, $p<0.001$; TMT B: z=-3.73, $p<0.001$; Digit Symbol: z=4.29, $p<0.001$).

4.2.2. Change in test performance at follow-up

Memory

Differences were observed between patients and controls for CD word-list - WS (z=-2.11, p=0.035) and CM word-pairs - DR (z=-2.65, p=0.008), i.e. the patients declined while the controls improved (for follow-up change scores cf Table 1). Figure 5 illustrates the different directions of change in performance for patients and controls.

Verbal Cognition and attention/processing speed

The verbal cognition variables remained stable across time for both patients and controls, while there were differences between the groups in three of the attention/processing speed variables (Digit span – forward: z=-2.14, p=0.032; Arithmetic: z=-2.06, p= 0.04; Digit symbol: z=-2.12, p=0.034), i.e. the patients deteriorated while the controls improved or did not change (cf. Table 2).
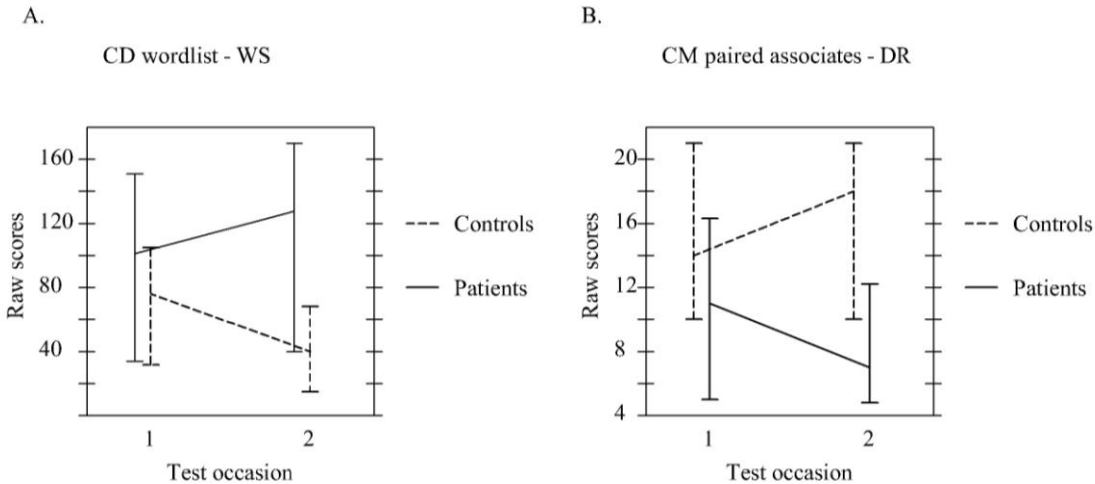
Figure 5. The figure illustrates different directions of performance for patients and controls in the verbal memory tests CD word-list – WS (weighted sum) (higher score = lower level of performance) and CM word-pairs (paired associates) – DR (delayed recall). Medians and interquartile ranges are marked for both patients and controls at the two test occasions.

Associations between neuropsychological variables, and between neuropsychological and medical variables

The relationship between epilepsy and changes in the two verbal memory variables with significant differences in change scores between patients and controls (CD word-list – WS and CM word-pairs - DR) was analysed using logistic regression. Presence of epilepsy was dependent variable and change scores and baseline scores were independent variables. The odds ratios for the verbal memory change were generally not influenced by the adjustments for the verbal cognition and attention/processing speed change variables, although the inclusion of the change scores of Arithmetic (Adjusted OR=1.17, CI=1-1.37, cf. Figure 2A in paper II; Adjusted OR=1.01, CI=1-1.02, cf. Figure 2B in paper II); and Digit Symbol (Adjusted OR=1.01, CI=1-1.02, cf. Figure 2B in paper II) showed slight influences. The change variable of CM word-pairs – DR was generally not influenced by the adjustments for the baseline scores of verbal cognition and attention/processing speed, although a slight influence was indicated for the inclusion of the baseline score of TMT A (Adjusted OR=1.19, CI=1-1.42, cf Figure 3A in paper II). For the CD wordlist – WS, the adjustments change was at most -0.003 for the odds ratio and -0.004 for the CI.

The relationship between verbal memory, attention/processing speed, and epilepsy was further analysed with stepwise logistic regression. Presence of epilepsy was the dependent variable and the change scores of verbal memory and attention/ processing speed (cf. Figure 2 and 3 in paper II) were included as independent variables. The CM word-pairs – DR was selected as the strongest correlate of epilepsy (β=-0.203; SE=0.077; χ^2 [Wald] =6.903; p=0.009) and the Digit symbol as the second strongest (β=-0.128; SE=0.059; χ^2 [Wald] =4.698; p=0.03).

Table 2. Follow-up change scores in verbal cognition and attention/processing speed in patients and controls

| | N | Follow-up change scores | |
		Median (Q1; Q3)	P-value
Verbal cognition			
Information			
Patients	28	0.0 (-1.0; 1.2)	NS
Controls	25	0.0 (-1.0; 1.0)	
Vocabulary			
Patients	27	-1.0 (-3.5; 4.0)	NS
Controls	25	1.0 (-1.0; 2.0)	
Similarities			
Patients	29	0.0 (-2.0; 1.0)	NS
Controls	25	0.0 (-1.0; 1.0)	
Attention/processing speed			
Digit span - forward			
Patients	28	-1.0 (-2.0; 0.0)*	0.032
Controls	25	0.0 (0.0; 1.0)	
Digit span - backward			
Patients	28	0.0 (-1.0; 2.0)	NS
Controls	25	1.0 (0.0; 1.1)	
Arithmetic			
Patients	28	-1.0 (-3.2; 1.0)	0.040
Controls	25	1.0 (-1.0; 2.0)	
Digit Symbol			
Patients	28	-2.5 (-6.2; 3.2)	0.034
Controls	25	0.0 (-1.0; 5.0)	
TMT A [b]			
Patients	31	-2.0 (-8.5; 17.0)	NS
Controls	25	-2.0 (-4.0; 2.0)	
TMT B [b]			
Patients	27	2.0 (-14.0; 18.0)	NS
Controls	25	-1.0 (-8.0; 5.0)	

[a]Interquartile range: 25th centile; 75th centile; [b] Mann-Whitney U test (tied P value). [c]An increase in change score=a decline in performance. TMT=Trail Making Test, part A and B from Halstaed Reitan Battery.

Associations were found between change scores in CM word-pairs – DR and Arithmetic in both patients (*rho*=0.493, *p*=0.014) and controls (*rho*=0.462, *p*=0.026). No significant associations were found between change scores in CD word-list – WS and verbal cognition or attention/processing speed in the patients or in the controls. There were no associations in the patient group between change scores in the verbal memory variables and the medical variables age at epilepsy onset, monthly seizure frequency (change) or number of AEDs (change) (*rho*-values between -0.147 and 0.316).

4.3. Study III

4.3.1. Medical data

All patients had a long duration of epilepsy and frequent seizures before surgery (cf. Table 1 in paper III). There were no significant differences between the patient subgroups regarding age at epilepsy onset (DTL: mean 17.0 years; NDTL: mean 13.5 years), epilepsy duration (DTL: mean 17.6; NDTL: mean 19.6 years), monthly seizure frequency (DTL: mean 20.4; NDTL: mean 14.4) or number of AED (DTL: mean 1.9; NDTL: mean 1.9) (*z*-values between -1.6 and -0.15). Two years after surgery, 61% (N=31) of the patients were seizure-free (without or with aura, ILAE class 1 and 2) (Wieser et al., 2001) (65% in the DTL and 57% in the NDTL group), and one of the seizure free NDTL patients was off AED. Ten years after surgery, 67% (N=34) were seizure free (74% in the DTL and 61% in the NDTL group), and 41% (N=14) of the seizure free patients were off AED (35% in the DTL and 47% in the NDTL group).

4.3.2. Demographic data, test interval, and general cognitive level

There were no significant differences between patients and controls in chronological age or length of education at any of the assessments (*z*-values between -1.3 and -0.65) (cf. Table 3). The patients' test interval was shorter than the controls' at medium-term (*z*=3.1, *p*=0.002) and longer at long-term follow-up (*z*=5.3, *p*<0.001). Test intervals between the DTL and NDTL group did not differ significantly, neither at medium-term (*z*=-1.9) or long-term follow-up (*z*=-1.7). General cognitive level was lower for patients than for controls at all assessments (cf. Table 3).

Table 3. Demographic data, test interval, and general cognitive level for patients and controls

	DTL (n=23)	NDTL (n=28)	Controls (n=23)
Age at baseline (years)	34.4 (9.8)	33.1 (10.4)	35.3 (9.4)
	33.0 (27.5; 43.0)	32.5 (25.8; 40.2)	36.0 (27.0; 41.5)
Length of education at baseline (years)	11.1 (1.8)	11.2 (1.9)	11.6 (2.0)
	11.0 (10.2; 12.0)	11.0 (9.8; 12.0)	11.5 (11.0; 12.0)
Test interval (years)			
Baseline to medium-term follow-up	2.5 (0.6)	2.9 (0.8)	3.1 (0.2)
	2.6 (2.2; 2.9)	2.8 (2.5; 3.3)	3.1 (3.0; 3.2)
Baseline to long-term follow-up	11.4 (1.4)	11.0 (1.6)	9.9 (0.2)
	11.1 (10.6; 11.8)	10.7 (10.2; 11.3)	9.9 (9.7; 10.0)
FSIQ			
Baseline	92.9 (9.5)	93.9 (10.8)	101.4 (10.5)
	94.5 (85.0; 99.0)	94.0 (87.8; 99.5)	101.0 (94.5; 106.0)
Medium-term follow-up	97.6 (13.7)	95.8 (10.7)	104.8 (12.1)
	97.0 (87.0; 104.0)	95.0 (90.8; 100.8)	103.0 (96.0; 109.0)
Long-term follow-up	98.6 (11.9)	99.0 (12.6	109.0 (11.2)
	97.0 (93.0; 102.0)	97.5 (92.0; 102.5)	109.0 (101.0; 114.5)

Mean (SD) / Median (Q1; Q3, range from 25th to 75th percentiles) is presented. DTL = Dominant Temporal Lobe resection group; NDTL = Non-Dominant Temporal Lobe resection group.

4.3.3. Cognitive outcome at group level 2 and 10 years after surgery
General cognitive level

A treatment effect was found for PIQ at the 10-year follow-up ($p=0.041$), with inferior scores in the NDTL group compared to the controls. The mean adjusted difference between the groups was 6.25, 95% CI=1.4; 11.1 (cf. Table 3 in paper III). The Cohen's *d* for effect size of the PIQ change scores from baseline to 10 years between the NDTL- and control group was 0.68. For VIQ, no significant treatment effect was found ($p=0.77$). Time effects 2 to 10 years were obtained for both IQ-variables (VIQ: $p=0.002$; PIQ: $p<0.001$), which indicates that a change in performance across time had occurred. Increases were found from baseline to the 10-year follow-up in VIQ for the NDTL ($p=0.038$) and the control group

($p<0.001$), and in PIQ for the DTL ($p<0.001$), NDTL ($p=0.002$) and the control group ($p<0.001$) (cf. Table 2 in paper III). However, the increase in PIQ across time was less favourable in the NDTL group relative to the controls (cf. Table 2 in paper III). There were no significant interaction effects found between time and treatment (VIQ: $p=0.39$; PIQ: $p=0.16$), indicating that the change in general was the same across the three groups.

Verbal memory
Treatment effects were obtained for all four variables (p-values between <0.0001 and 0.03) (cf. Table 3 in paper III). The 95% CI indicated significant effects between the DTL and NDTL group in all four variables and between the DTL and control group in three variables (cf. Table 3 in paper III). The Cohen's d for effect size of the verbal memory change scores from baseline to 10-year follow-up was in general medium to large. The largest effect size was observed between the DTL and NDTL group for CM word-pairs – IR (Cohen's $d = 0.86$) and for CM word-pairs – DR (Cohen's $d = 0.73$). A similar pattern was disclosed for all variables (cf. Figure 1 and Table 2 in paper III); the DTL group decreased in verbal memory from baseline to the 2-year follow-up and the results then remained stable on this low level and no further changes occurred from 2 to 10 years after surgery. This was most evident for the CM word-pairs – IR and DR (cf. Table 2 and Figure 1 C-F in paper III). There were no significant interaction effects found between time and treatment (cf. Table 3 in paper III: p-values between 0.09 and 0.98), indicating that the change from 2 to 10 years after surgery in general was the same across the three groups.

Visual memory
No significant treatment effects were found for the visual memory variables (p-values between 0.12 and 0.72 (cf. Table 3 in paper III). There was a time effect from 2 to 10 years for within subject differences in CM objects – IRec ($p=0.039$), the control group declined in scores from baseline to the 10-year follow-up (mean change -1.6, $p<0.05$). For the controls, both the CM object variables showed a non-significant increase in scores from baseline to 2 years followed by a decrease at the 10-year follow-up (cf. Figure 1 G-H in paper III). No changes across time were disclosed in the patient groups (cf. Table 2 in paper III).

Asscociations with epilepsy related factors
An additional analysis was made to explore the relationship between the test scores of the variables with group differences at the 10-year follow-up (PIQ and the four verbal memory variables), and seizure outcome and AED treatment. No significant differences were found for the variables of verbal memory between the seizure outcome groups (*p*-values between 0.33 and 0.78) or between the AED treatment groups (*p*-values between 0.42 and 0.51). For the PIQ variable, a lower mean (*p*=0.004) was obtained for the group with continuing seizures 97.4 (SD 14.1) compared to the group with no seizures 108.3 (SD 13.4) Also, a lower mean (*p*=0.015) was obtained for the AED treatment group 100.4 (SD 13.5) compared to the non-treatment group 112.4 (SD 14.8). Continuing seizures was selected as the most important correlate to inferior PIQ scores (*β*=-1.57, *SE*=0.608, *p*=0.010) in the stepwise backward logistic regression analysis, while AED treatment was excluded from the model.

4.4. Study IV

4.4.1. Medical and demographic data
Medical and demographic data for patients and controls are presented in Table 1 and 2 in paper IV. Patients and controls did not differ significantly at baseline in chronological age or length of education (*z*-values between -1.2 and -0.64). The controls' test interval was longer at medium-term (*z*=3.0, *p*=0.003) compared to the patients' and shorter at long-term follow-up (*z*=5.4, *p*<0.001). The DTL and NDTL group did not differ concerning age at epilepsy onset, epilepsy duration, seizure frequency, chronological age, length of education at baseline, and test interval (*z*-values between -1.9 and 0.18). Presence of cortical dysgenesis was less common in the DTL (30.4%) than in the NDTL group (55.5%).

4.4.2. Verbal memory outcome at individual level 2 years after surgery
Table 4 and Figure 1 in paper IV illustrate how many of the patients who had changed in verbal memory 2 years after surgery (baseline to 2 years) according to the criteria Decline≥1 or Improvement≥1 and Decline≥2 or Improvement≥2. In the total patient group, 40 % showed Decline≥1, while 30 % showed Improvement≥1. There were marked differences between the subgroups as more patients in the DTL than in the NDTL group showed Decline≥1 (DTL: 60.9 %; NDTL: 22.2%), while more patients in the NDTL than in the DTL group showed Improvement≥1 (NDTL: 40.7 %; DTL: 17.4 %). When the criterion ≥2 was used, 28% of the total group

showed Decline≥2, while 16 % showed Improvement≥2. Decline≥2 was much more common in the DTL than in the NDTL group (DTL: 43.5 %; NDTL: 14.8%). Improvement≥2 was observed in 18.5% of the NDTL group and in 13.0% of the DTL group.

Table 4. Individual changes 2 and 10 years after surgery

	RCI 90% CI			
	Decline≥1 N (%)	Improvement≥1 N (%)	Decline≥2 N (%)	Improvement≥2 N (%)
Baseline to 2 years				
TLR	20 (40.0)	15 (30.0)	14 (28.0)	8 (16.0)
DTL	14 (60.9)	4 (17.4)	10 (43.5)	3 (13.0)
NDTL	6 (22.2)	11 (40.7)	4 (14.8)	5 (18.5)
Baseline to 10 years				
TLR	16 (32.0)	15 (30.0)	7 (14.0)	9 (18.0)
DTL	13 (56.5)	3 (13.0)	6 (26.1)	1 (4.3)
NDTL	3 (11.1)	12 (44.4)	1 (3.7)	8 (29.6)

Proportions of patients with decline or improvement compared to the controls 2 and 10 years after temporal lobe resection (TLR) according to two criteria: Decline≥1 (≥1 negative and no positive change) or Improvement≥1 (≥1 positive and no negative change) and Decline≥2 (≥2 negative and no positive changes) or Improvement≥2 (≥2 positive and no negative changes). Change criteria were derived from the controls by using reliable change indices (RCI) 90% CI cut-off scores. TLR=Temporal Lobe Resection group; DTL=Dominant Temporal Lobe resection group; NDTL=Non-Dominant Temporal Lobe resection group.

Predictors of verbal memory decline 2 years after surgery

Five possible predictor variables of verbal memory decline were explored with a forward stepwise logistic regression analysis. The data for the variables are described in Table 3 in paper IV. The final step of the regression analysis selected the following variables as predictors of verbal memory Decline≥1: laterality,

chronological age at baseline, and verbal memory performance at baseline. The strongest predictor for verbal memory Decline≥1 was an intact verbal memory performance at baseline (β=1.529; SE=0.531; χ^2=[Wald]=8.294; p=0.004), followed by a dominant TLR (β=2.748; SE=1.056; χ^2=[Wald]=6.767; p=0.009), and older age at baseline (β=0.139; SE=0.058; χ^2=[Wald]=5.701; p=0.017).

4.4.3. Verbal memory outcome at individual level 10 years after surgery

Table 4 and Figure 2 in paper IV illustrate how many of the patients who had changed in verbal memory 10 years after surgery (baseline to 10 years) according to the criteria Decline≥1 or Improvement≥1 and Decline≥2 or Improvement≥2. In the total patient group, 32 % showed Decline≥1, while 30 % showed Improvement≥1. Similar to the 2-year follow-up, there were marked differences between the subgroups as a higher number of patients in the DTL than in the NDTL group showed Decline≥1 (DTL: 56.5 %; NDTL: 11.1%), while more patients in the NDTL than in the DTL group showed Improvement≥1 (NDTL: 44.4%; DTL: 13.0 %). When the criterion ≥2 was used, 14% of the total patient group had Decline≥2, while 18 % had Improvement≥2. Decline≥2 was more common in the DTL than in the NDTL group (DTL: 26.1%; NDTL: 3.7%), while Improvement≥2 was more common in the NDTL than in the DTL group (NDTL: 29.6%; DTL: 4.3%).

Predictors of verbal memory decline 10 years after surgery
A forward stepwise logistic regression analyses explored the five possible predictor variables of verbal memory decline. The data for the variables are described in Table 4 in paper IV. The final step of the regression analyses selected only the variable laterality as a predictor of verbal memory Decline≥1 10 years after surgery (β=2.565; SE=0.775; χ^2 [Wald]=10.952; p=0.001), i.e. dominant TLR predicted a verbal memory Decline≥1 10 years after surgery.

5. DISCUSSION

People with epilepsy have long been recognised to have a higher prevalence of neuropsychological dysfunction than the general population. The question whether this cognitive dysfunction is progressive or not has been a matter of debate. In medically treated patients, the current consensus is that long-term effects of epilepsy on cognition are mildly progressive (Dodrill, 2002; Dodrill, 2004; Seidenberg et al., 2007; Vingerhoets, 2006), and that the memory domain appears to be the most vulnerable cognitive function in adults with epilepsy (Dodrill, 2004; Seidenberg et al., 2007; Vingerhoets, 2006). When studying subjective impact of epilepsy, cognitive impairment was ranked highest among potential problems associated with epilepsy (Fischer et al., 2000), and memory complaints were the most common cognitive problems presented by patients with epilepsy (Banos et al., 2004; Bolla et al., 1991; Corcoran and Thompson, 1993; Fischer et al., 2000; Hendriks et al., 2002; McCagh et al., 2009; Thompson and Corcoran, 1992a; Vermeulen et al., 1993). Patients with a longer duration of epilepsy also complained more (Hendriks et al., 2002).

In surgically treated patients, there is a consensus about the risk for decline in verbal memory and learning after dominant TLR (Dodrill et al., 1993; Dulay et al., 2008; Helmstaedter and Elger, 1996a; Hermann et al., 1995a; Lee et al., 2002; Loring et al., 1991; Novelly et al., 1984; Rausch, 1996). Non-dominant TLR has been associated with visuo-spatial memory decline (Dodrill et al., 1993; Dulay et al., 2008; Milner, 1968b; Milner, 1975). However, most publications concern cognitive outcome 1-2 years after surgery, while little is known about the long-term cognitive effects of epilepsy surgery. Results from the few existing long-term reports diverge as both progression of decline (Helmstaedter et al., 2003; Rausch et al., 2003) and stability (Alpherts et al., 2004; Alpherts et al., 2006) in cognitive functions has been reported.

At the time when this study was initiated, there were few published longitudinal studies on cognition in medically treated patients, and none included reassessment data from healthy controls. Long-term reports on surgically treated patients are still sparse, and do not include long-term data of healthy controls. The rationale for this study was therefore to investigate long-term cognitive outcome using an adequate

study design, i.e. to compare longitudinal cognitive changes of both medically and surgically treated patients with those of healthy controls.

5.1. Methodological issues

5.1.1. Study design and statistical issues

Our study is prospective, longitudinal and controlled which is an advantage compared to studies with a cross-sectional design when making inferences about changes over time and for analyses of individual changes. Even with a proper study design, there are several problems that could bias the study. There is often inadequate or missing information about e.g. eligibility criteria, numbers potentially eligible and subjects lost to follow-up. This makes it difficult to compare the given prerequisites in different studies and therefore to compare results. It is important that the patient sample is representative of the population. Some studies are based on so-called 'convenience samples' drawn from patients who stay in contact with the clinic, i.e. the sample is biased to those with more severe epilepsy (Baxendale, 2008a). In our study, the patient samples can be considered representative of the populations of patients who are investigated for epilepsy surgery in Sweden. First we have a regional referring system (Malmgren et al., 2008) and secondly there were small losses to follow-up (especially in the surgically treated group), minimizing the risk of any systematic bias. The losses to follow-up were also limited in the control group. In study III and IV we used data from the 23 controls who underwent all three assessments. However, there were no baseline differences (demographic and neuropsychological data) between them and the remaining seven controls.

The medically treated patient sample was small and their data distribution skewed, why non-parametric statistics was used (study I and II). However, parametric statistical methods are widely used also with small sample sizes (range 17-47) and with no attention to the issue of non-normal data distributions (Griffith et al., 2007; Helmstaedter et al., 2000; Holmes et al., 1998; Selwa et al., 1994). The use of non-parametric vs parametric statistics could be one explanation for differing study results.

5.1.2. Test methods and definitions of change

There might also be other explanations for differing results, e.g. different cut-off scores for decline. In the study by Helmstaedter et al. (2003), changes were

determined by means of praxis-corrected RCI (90% CI) (Hermann et al., 1996a) derived from test intervals of approximately 9 months. We used the same method with the same CI, but with the difference that the RCI cut-off scores were calculated for the adequate test intervals of 2-3 and 10 years in our controls. Secondly, verbal memory tests differ in sensitivity. In study I and III we used seven different variables to assess memory (four verbal and three visual) and in study II and IV we used four variables to assess verbal memory, i.e. we have covered several aspects of memory (e.g. learning, immediate and delayed recall and immediate and delayed recognition). In study IV we made a sum score of the four verbal memory variables when we defined change in order to get an overall verbal memory variable that would reflect verbal memory better. We also used two different definitions: Decline$\geq$1 or Improvement$\geq$1 and Decline$\geq$2 or Improvement$\geq$2. When using the criterion Decline$\geq$1 or Improvement$\geq$1 the proportions of individuals who changed increased dramatically. Baxendale and Thompson (2005) have addressed this issue by comparing different measures of postoperative change on a list-learning task (RCI at an 80% CI; RCI at a 90% CI; $\pm$1 SD) in order to define meaningful postoperative change in epilepsy surgery patients. However, even if there were a "gold standard" for definition of change, it is not certain that such a definition would be more closely connected to subjective perception of change (Sawrie et al., 1999), since we do not know how much impairment and change it takes to make a difference for the patient (Helmstaedter, 2004a) - but at least it would be easier to compare different study results. The only way of knowing if a change (e.g. after surgery) is of clinical relevance is to ask the patients themselves: Do you experience new or worsened impairment? Besides patients' experiences, clinical change could also be based on judgements by clinicians (who know the patients well), family members, friends or external references such as teachers and colleagues.

5.1.3. Practice effects, normal ageing, and regression towards the mean (or median)

The inclusion of a control group undergoing the same testing procedure as the patients is the only valid way to assess the magnitude and relevance of the presence or absence of test-retest effects (Vingerhoets, 2006) across time. It is important that the length of test intervals is fairly equal for patients and controls so that potential practice effects could be compared, but also in order to assess effects of normal ageing. This is of particular interest when memory functions are investigated at

long test intervals, since these functions are especially vulnerable in normal ageing. In our study, analyses of change scores across time between patients and controls disclosed patterns that were concealed in the within group evaluation. The practice effect seen in the controls had no equivalence at group level in the medically treated patients (study I), and was less pronounced for the NDTL resection group in PIQ compared to the controls (study III). A practice effect might have been expected since such effects, although less pronounced than in controls, have been reported in patients with drug resistant epilepsy as reflected in the mean difference from baseline to retest (Bjornaes et al., 2001; Dodrill and Troupin, 1975; Dodrill and Wilensky, 1992b; Hermann et al., 1996a; Holmes et al., 1998; Kalska, 1991; Selwa et al., 1994). Hence, the lack of increment in score due to a missing practice effect in the patient group could indicate an impaired capacity for some type of incidental or procedural learning across time.

5.1.4. Test-retest reliability
Test-retest reliability coefficients (based on test manuals) concerning general cognitive level as measured by WAIS-R are known to be very high (0.89-0.95), and we found the test-retest reliability coefficients based on our own controls (study I and II) to be equally high (0.92-0.97). The reliability coefficients based on the controls concerning verbal cognition (0.86-0.98) and attention processing/speed (0.79-0.93) did also show high values. In contrast to these psychometric variables, repeated memory testing is usually more problematic and lower reliability coefficients on a second testing have been reported (Dikmen et al., 1999; Wilson et al., 2000). However, the memory reliability coefficients based on the controls in our study were below 0.70 in only two of the memory variables (0.64 and 0.69), while they exceeded 0.70 in the remaining five variables of which three were high (0.83-0.88). Hence, the test-retest reliability ought not to be considered an important methodological problem in our study.

5.2. Medically treated patients
5.2.1. Cognitive level at baseline
Lower baseline performance in patients was to be expected since previous studies have reported impairments in *general intellectual capacity* (Bjornaes et al., 2001; Dodrill, 1986; Klöve and Matthews, 1966; Selwa et al., 1994; Thompson and Duncan, 2005), *verbal cognition* (Bornstein et al., 1988; Giordani et al., 1985; Hermann et al., 1995b; Oyegbile et al., 2004), *memory* (Elger et al., 2004; Hermann

et al., 1987; Mungas et al., 1985; Oyegbile et al., 2004; Prevey et al., 1998; Pulliainen et al., 2000), and *attention/processing speed* (Oyegbile et al., 2004) (Piazzini et al., 2006a; Piccirilli et al., 1994; Stella and Maciel, 2003; Stores, 1973).

5.2.2. Cognitive change at follow-up

The non-significant within-in group changes across time in general cognitive level for patients are in accordance with several non-controlled studies reporting no associations between number of seizures and deterioration in general cognitive level (Bjornaes et al., 2001; Dodrill and Wilensky, 1992b; Holmes et al., 1998; Kalska, 1991; Rausch et al., 2003; Selwa et al., 1994; Äikiä and Kälviäinen, 1999). However, when patients were compared to controls, important additional findings were revealed, as earlier discussed. The expected increase in general cognitive level occurred for the controls but not for the patients and the forward stepwise logistic regression analysis showed a clear relationship between epilepsy and a negative change in the PIQ variable, a relationship that also remained after controlling for the possible confounding variables: baseline performance and retest interval. Strong relation-ships between number of seizures and decline in general cognitive level have been reported in longitudinal studies, but only in groups of patients with very severe epilepsy (Thompson and Duncan, 2005).

The decline in verbal memory (CM word-pairs – DR) seen in the within-group analysis is in accordance with findings of progressive memory decline in large series of patients with refractory TLE (Helmstaedter et al., 2003; Hermann et al., 2006; Thompson and Duncan, 2005). The lack of practice effects in verbal memory in the control group has also been seen in other groups of normal controls (Wilson et al., 2000), and may be due to the fact that alternative versions were used at retest (Benedict and Zgaljardic, 1998; Vingerhoets, 2006). However, the current study design and the statistical method applied made it possible to disclose further details concerning memory change in the patients. A relationship between decreasing performance and epilepsy was not restricted to the verbal memory variable already mentioned (CM word-pairs - DR), but occurred also in verbal learning and visuospatial memory (CD word-list – WS and ROCF – DR). Two later longitudinal controlled studies have also shown memory decline across time in periods of 2 to 4 years (Griffith et al., 2007; Hermann et al., 2006).

The important correlation between epilepsy and negative change in the attention/ processing speed variable Digit symbol is similar to findings in other studies (Hermann et al., 2006; Holmes et al., 1998; Pai and Tsai, 2005; Piazzini et al., 2006a; Rodin, 1968; Thompson and Duncan, 2005). In the study by Hermann et al. (2006), processing speed was identified as one of four cognitive variables most vulnerable to change across time (the others were memory, aspects of executive functions, and naming). However, no change across time or even improvement has also been described in other non-controlled studies (Kalska, 1991; Seidenberg et al., 1981a).

Associations between verbal memory, verbal cognition, and attention/ processing speed

The lack of association between change in verbal cognition and memory decline in patients with epilepsy speaks against the suggestion that deficits in language skills (e.g. auditory comprehension or accessibility of words), here reflected by verbal cognition (Lezak, 1995; Wechsler, 1981), explains some of the verbal memory impairments associated with left temporal lobe seizures (Brown, 1991; Hermann et al., 1988a; Mayeux et al., 1980), and does not lend support to the notion that reduced mental reserves increases cognitive vulnerability (Helmstaedter et al., 2003; Hermann et al., 2006; Jokeit and Ebner, 1999; Oyegbile et al., 2004). The lack of an association between change in attention, memory decline, and epilepsy confirms earlier studies based on correlation analyses (Loiseau et al., 1984; Loiseau et al., 1988), in which the conclusion was that decreased attention capacity probably is insufficient in explaining memory disability. However, a possible influence of attention on the level of performance in memory in patients with epilepsy has been suggested for newly diagnosed patients with epilepsy (Kälviäinen et al., 1992).

Associations between cognition, medical and demographic variables

The lack of associations between medical and demographic variables and neuropsychological performance at baseline and change at follow-up could be due to our limited sample size and to heterogeneity within the sample. However, it is notable that the Bozeman Epilepsy Consortium (Strauss et al., 1995) with as many as 1185 patients found that the magnitude of the effects from a combination of medical variables on neuropsychological performance was modest. The only

association considered obvious was between early age at epilepsy onset and poorer cognitive performance, which also is the most common finding in other studies (Dodrill, 1981; Dodrill, 1992a; Hermann et al., 2002; Meador, 2002; Piazzini et al., 2006a; Seidenberg et al., 1986). However, studies have also reported associations between cognitive performance and the following medical and demographic variables: history of GTCS, partial seizures and status epilepticus, duration of epilepsy, older chronological age, seizure frequency, and quantitative MRI abnormalities (Hermann et al., 2006; Piazzini et al., 2006a; Thompson and Duncan, 2005).

5.2.3. Psychosocial implications

Our findings of lower performance at baseline in general cognitive level, memory and attention/processing speed and of decline across time in the latter two cognitive domains ought to have important psychosocial implications, since deficits in these functions may significantly disrupt employment, school, family life, and other aspects of daily living (Perrine and Kiolbasa, 1999). The learning process in school could have been interrupted by seizures, by the postictal reorientation phase or by absence from school due to frequent and severe seizures. At the time of the baseline testing, the median duration of epilepsy was 16.5 years which means that most of the patients have had severe epilepsy almost half of their lives. The baseline testing was the first neuropsychological assessment for most of the patients, i.e. the majority of the patients have had an affected cognition without being properly evaluated. When making decisions about important psychosocial issues it is helpful to have information available based on objective data of cognitive status in relation to those demands in life that a person meets in studies, at work or in daily living. It will improve the clinicians' counselling and care and enlighten the patients' self-knowledge about cognitive liabilities and advantages which could facilitate adjustment.

5.3. Surgically treated patients

5.3.1. Cognitive outcome at group level

The main finding between 2 and 10 years after TLR was cognitive stability compared to healthy controls. The verbal memory decline found at the 2-year follow-up in the DTL group - expected on the basis of earlier findings (Dodrill et al., 1993; Dulay et al., 2008; Helmstaedter and Elger, 1996a; Hermann et al., 1995a; Lee et al., 2002; Loring et al., 1991; Novelly et al., 1984; Rausch, 1996) -

was not progressive up to the 10-year follow-up, lending no support to the notion of an ongoing progressive delince in verbal memory after TLR (Helmstaedter et al., 2003; Rausch et al., 2003). In another study where assessments were performed at 6 months, 2 and 6 years after TLR, an ongoing decline of verbal memory was found up to 2 years after surgery but with no further decline up to 6 years (Alpherts et al., 2006). These authors speculated that removal of the hippocampus could have caused deficits in other parts of the brain and that the hippocampal remnant had continued to degenerate and hence could had affect both the surrounding tissue and the connections of the mesial structures (Alpherts et al., 2006). Postoperative shrinkage of the hippocampal remnant has been confirmed with volumetric MRI (Baxendale et al., 2000), although this shrinkage process appears to stabilize within the first three months. Finally, it is noteworthy that the NDTL group showed a trend towards positive verbal memory changes 2 years after surgery, which may be related to results of release of function (Grunwald et al., 1998; Helmstaedter et al., 2003; Hermann and Wyler, 1988b).

The long-term positive course in general cognitive level for both patients and controls (study III) was expected, since such effects of practice have been reported earlier both in patients with epilepsy (Alpherts et al., 2004; Chelune et al., 1993; Keogan et al., 1992; Sawrie et al., 1996) and in normal controls (Dodrill, 1983; Matarazzo et al., 1980). The lower occurrence of practice effects seen in the NDTL group at the 10-year follow-up was explained by the fact that seizure freedom was less common in the NDTL compared to the DTL group, since the stepwise backward regression analysis identified seizure outcome as the most important correlate to inferior PIQ scores.

Associations with seizure outcome and AED treatment
The lack of associations between verbal memory decline, and seizure outcome and AED treatment is in line with findings from two other long-term studies (Alpherts et al., 2006; Rausch et al., 2003). This could be due to the limited sample sizes (44-85 patients), since associations between memory decline and seizure outcome have been found in another long-term study of 147 patients (Helmstaedter et al., 2003). In this study, however, the test interval ranges were 2-10 years. In a recent review article, it was concluded that long-term memory is associated with seizure outcome (Tellez-Zenteno et al., 2007), but most of the studies in adults meeting the inclusion criteria were based on few patients and had wide test interval ranges: 2-11 years

(Paglioli et al., 2004); 1-14 years (Kirkpatrick et al., 1993); and 3-15 years (Keogan et al., 1992). Studies grouping all postoperative patients together regardless of the length of time elapsed since surgery do not control for the critical variable length of time (Baxendale, 2008a), and could be claimed to rather be cross-sectional than longitudinal in their design.

5.3.2. Verbal memory outcome at individual level

When using the criterion for change Decline≥2 and Improvement≥2, our findings that 28% of the patients had lost and 16% had gained at the 2-year follow-up are in accordance with previous outcome studies 1-2 years after surgery reporting decline in approximately one third (Baxendale, 2008a; Baxendale and Thompson, 2005; Baxendale et al., 2006; Dulay et al., 2006; Martin et al., 2002) and improvement in 10-25% of the patients (Baxendale, 2008a; Baxendale and Thompson, 2005; Baxendale et al., 2008b; Martin et al., 1998). In our sample there was no indication of progression of verbal memory decline at group level from 2 to 10 years after surgery. The main result at individual level was also no further decline and there were even indications of a partial recovery in verbal memory between 2 and 10 years after surgery as fewer patients demonstrated Decline≥2 at the 10 year-follow-up (14%) compared to the 2-year follow-up (28%). Finally, the proportion of patients who had Improvement≥2 was nearly the same at 2 (16%) and 10 years (18%) after surgery, which also indicates non-progression of memory decline.

There was an expected unequal distribution between the DTL and NDTL groups regarding both decline and improvement 2 and 10 years after surgery, i.e. more patients in the DTL declined compared to the NDTL group, while more patients in the NDTL improved compared to the DTL group. The fact that fewer patients showed Decline≥2 at the 10-year compared to the 2-year follow-up indicates that a partial recovery must have occurred for several individuals in both groups. However, this was not true for improvements as more NDTL but fewer DTL patients had Improvement≥2 at the 10-year compared to the 2-year follow-up.

Predictors of early and late verbal memory decline

Intact baseline memory performance was the strongest predictor for verbal memory Decline≥1 at 2 years after surgery, followed by dominant TLR, and older age at baseline. These variables have previously been identified as predictors of verbal memory decline 1-2 years after surgery (Baxendale et al., 2006; Chelune, 1995;

Chelune et al., 1991; Helmstaedter and Elger, 1996a; Hermann et al., 1995a; Kneebone et al., 1995; Stroup et al., 2003), and concerning intact memory performance at baseline also at long-term in one study (Rausch et al., 2003). However, in our study only a dominant TRL predicted verbal memory Decline≥1 at the 10-year follow-up.

5.3.3. Implications for presurgical counselling

The results from our studies have important implications for presurgical counselling. Even if patients who are offered a DTL resection for drug resistant partial epilepsy are at risk for further verbal memory decline early after surgery, this decline is not progressive at long-term. The implication for a candidate for an NDTL resection is the probability of verbal memory improvement as an effect of release of function. For both groups of surgical candidates, there is also a possibility of partial recovery in verbal memory at long-term. However, it has been emphasized that it is important to be aware of the fact that these predictions are based on statistics and not on patients' subjective experience (Baxendale and Thompson, 2005), since no significant relationships have been reported between subjective ratings of postoperative memory function and objective indices of change. It has also been reported that seizure control rather than memory outcome influences patients' ratings of quality of life (Langfitt et al., 2007). The discrepancy between subjective memory complaints and objective measures of change after surgery should be discussed with the patient in the preoperative counselling process (Baxendale and Thompson, 2005; Sawrie et al., 1999).

6. CONCLUSIONS

The follow-up assessment of the medically treated epilepsy patients revealed progressive decline in verbal and visual memory and in attention/processing speed as well as adverse effects on general cognition already after 4.8 years. Also, the results did not support the notion that inferior performance in verbal cognition and attention/processing speed can explain the verbal memory decline across time in patients with epilepsy. These findings underline the importance of earlier neuro-psychological interventions as well as follow-up assessments at regular intervals during the course of the disease.

In surgically treated epilepsy patients the main finding at group level was cognitive stability from 2 to 10 years after TLR. The verbal memory decline seen at the 2-year follow-up in the DTL group was not progressive from 2 to 10 years after surgery, and not dependent on seizure outcome or AED treatment. As for the medically treated patients, the performance aspect of general intellect, PIQ, indicated less practice effects at the 10-year follow-up in the NDTL group. This was probably due to the worse seizure outcome in that group, since continuing seizures was the most important correlate to inferior PIQ scores.

The application of two-level criteria for defining individual postsurgical change provided additional important outcome features in aspects of verbal memory, as varying outcome patterns in proportions of patients were discernible. Apart from a considerable individual variability, with more negative changes in the DTL and more positive changes in the NDTL group, a partial recovery seems to have occurred for several individuals as fewer patients in both the DTL and NDTL group showed decline in verbal memory at the 10-year compared to the 2-year follow-up. Important predictors for verbal memory decline at earlier stages after surgery may be less important at later since DTL resection was the only remaining risk factor for verbal memory decline at long-term follow-up.

The results are highly relevant in the comprehensive care and counselling of epilepsy patients since cognitive functions and especially memory functions are essential in the prime basis of day-to-day living. The difference seen in cognitive trajectories between medically and surgically treated patients with drug resistant epilepsy and between DTL and NDTL resections can be helpful in the presurgical

counselling process. The risk for early postoperative verbal memory decline after a DTL resection is well-known and patients are informed about this. It is also noteworthy that there is a possibility of improvement in verbal memory after a resection in the NDTL, as a result of a release of function. However, information on outcome after 1-2 years is not enough when the irrevocable treatment option of epilepsy surgery is discussed. The possibility of a long-term partial recovery of verbal memory for some patients (in the DTL as well as in the NDTL group) is exciting but needs to be further studied in larger patient cohorts.

7. ACKNOWLEDGEMENTS

This thesis could not have been accomplished without the help and support of several colleagues, friends and my family. I would especially like to express my sincere gratitude to:

All patients and controls for willingly participating in the studies and making them possible.

My supervisor Kristina Malmgren for her excellent scientific guidance into the field of epilepsy research; for her insistent efforts to teach me critical thinking; for always finding the extra time needed for supervision, with me being at a distance and for caring about me and my family's well-being.

My co-supervisor Hans Samuelsson for providing me with indispensable neuro-psychological and statistical expertise; for his careful supervision of manuscripts; for his generosity with time and for many fruitful discussions filled with humour and warmth.

My co-supervisor and mentor Elisabeth Engman for her indispensable clinical expertise which has helped me join research and clinic; for her help to navigate through the bureaucracy of the university and for her friendly, caring and encouraging peptalks when most needed.

Co-author Charlotte Sjöberg-Larsson for kindly providing necessary parts of medical and demographic data in study I.

Statistician Nils-Gunnar Pehrsson for his excellent statistical guidance.

Aldina Paldovic for her elegant illustrations in study III.

Gerd Ekstedt for her fine contact with the epilepsy patients, which was a necessary condition for the patients' willingness to participate in the study.

Lisbeth Lindberg for generously provided excellent secretarial assistance.

Marianne Bilting, Inger Hagström and Eva Norlin-Bagge for neuropsychological data assessments and development of the data base.

My work-place at Geriatrik och Rehab, Ystad for generous understanding and contribution during the years and for showing flexibility with how I have organized my working time.

My friend Lotta for always listening, making me laugh, and for putting most of the things in the world in the right perspective.

My mother Ingalill for always lovingly being there for me and my family; for always listening, encouraging and supporting me through ups and downs.

My husband Dennis for his continuous love and support during the years and for all the time he has spent solving the computer related problems that I have created.

My son Erik for just being the most wonderful thing that happened to me; for always reminding me of what is important in life; and for sharing so many wize thoughts with me: "Children think more with there bodies and less with their brains – that's why we have so much more fun, mummy". Tivoli in Copenhagen – here we finally come, Erik!

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