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Epilepsy in young adulthood: medical, psychosocial and functional aspects

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To my daughter
Emilia Lilly Charlotta

Abstract

The aim of this thesis was to describe the medical, cognitive and psychosocial consequences of epilepsy in young adulthood. Four studies were carried out with this patient group. The first two papers were based on a follow-up study regarding young adults with epilepsy that investigated medical and psychosocial aspects and compared the present results with those five years earlier. We then conducted focus group interviews with young adults with epilepsy and subjective cognitive decline to assess the deeper meaning of living with epilepsy accompanied by cognitive difficulties. In the fourth study we studied cognitive dysfunction further, choosing the language function in young adults with epilepsy. We firstly examined whether language impairments were associated to functional brain alterations and secondly related the language performance to demographics, clinical data, Quality of life (QoL) and self-esteem.

The five-year follow up of young adults with uncomplicated epilepsy revealed no improvement regarding seizure frequency or side effects from anti-epileptic drugs (AEDs) over time, even though many new-generation generation AEDs had been established during this period. During the study period 21% had recovered from epilepsy. Seizure frequency among those who still had epilepsy had not improved, and 42% had experienced seizures during the past year. New-generation AEDs had been introduced, especially to women. There is still a need for new and more effective treatments for therapy-resistant epilepsy. It is essential to find alternative approaches to develop better treatment options for this group in the future. However, QoL was normal compared to the general population, indicating that new options regarding treatment can have made an impact. Lower QoL was correlated to high seizure frequency and to cognitive side effects. Self-esteem and Sence of Coherence were impaired compared to the situation at adolescence. Self-esteem was correlated to seizure frequency and to side-effects of antiepileptic drugs. Sence of Coherence was not correlated to epilepsy-related factors in the same way as QoL, but mirrored the phenomenon of epilepsy.

The qualitative study showed that the consequences of epilepsy are not only restricted to the effects of seizures, but also concerns many other aspects of life. The interviews revealed four themes of interest; “Affecting the whole person“, “Influencing daily life”, ”Affecting relations” and ”Meeting ignorance in society”. Another important factor was language function; when one loses some language ability, this gives a feeling of losing one’s capability.

The fourth study examined language by neuropsychological methods and correlated this function to brain activation measured by fMRI. Language functions measured in verbal fluency and abstract language comprehension were impaired in participants with both generalized epilepsy and epilepsy of focal onset. Age at onset of epilepsy and education are the most important factors correlating to language function. An additional factor that impacts abstract language comprehension is the frequency of convulsive seizures, while use of topiramate/zonisamide affects verbal fluency negatively. QoL was not correlated to language impairments, but for patients with focal onset seizures there was a correlation between self-esteem and abstract language comprehension. The fMRI investigation revealed altered activity during language tasks in participants with epilepsy compared to controls. In epilepsy with focal seizures originating in the left hemisphere, we found increased bilateral activation of supporting areas, in the anterior mid-cingulate cortex and the anterior ventral insulae, indicating a compensational functional reorganization. In generalized epilepsy, the functional language network showed an imbalance, as this group expressed an inadequate suppression of activation in the anterior temporal lobe during semantic processing. Subtle language impairment can, even if it does not occur in everyday dialogue, be of importance and have consequences for the person affected. The negative consequences of language decline must be addressed in people with epilepsy of different etiology.

Young adults with epilepsy are still substantially affected by the condition. The consequences are not only restricted to the seizures, but concern many aspects of life and there is great need for new treatment options for this group in the future.

Key words

Epilepsy, young adult, Quality of Life, self-esteem, daily life, antiepileptic drugs, cognition, language, fMRI, Sence of Coherence

List of original publications

This thesis is based on the following articles, which will be referred to in the text by their Roman numerals:

I. Helena Gauffin, Lena Räty, Birgitta Söderfeldt. Medical outcome in epilepsy patients of young adulthood: A5-year follow-up study. Seizure 2009:18:293-297

II. Helena Gauffin, Anne-Marie Landtblom, Lena Räty. Self-esteem and sense of coherence in young people with uncomplicated epilepsy: A 5-year follow-up. Epilepsy & Behavior 2010; 17:520-524

III. Helena Gauffin, Gullvi Flensner, Anne-Marie Landtblom. Living with epilepsy accompanied with cognitive difficulties: Young adults' experiences. Epilepsy & Behavior 2011; 22(4)293-7

IV. Helena Gauffin, Helene Van Ettinger Veenstra, Anne-Marie Landtblom, Daniel Ulrici, Anita Mc Allister, Thomas Karlsson, Maria Engström: Cognitive problems in young adults with epilepsy: Language deficits correlate to brain activation and self-esteem. Submitted to Brain.

The original articles (I, II and III) have been printed with permission from the publishers.

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Abbreviations

AE	Adverse event
AED	Anti-epileptic drug
AISM	As I see me
aMCC	Anterior mid cingulate cortex
ANOVA	Analysis of variance
BA	Brodmann area
BeSS	Assessment of subtle language deficits
CC	Correlation Coefficient
BOLD	Blood oxygenation level dependent
CBZ	Carbamazepine
CNS	Central nervous system
CT	Computerized tomography
EEG	Electroencephalogram
FAS	Controlled oral word association test with cue letter, F,A and S
fMRI	Functional magnetic resonance imaging
GE	Generalized epilepsy
GABA	Gamma amino butyric acid
HRQoL	Health-Related Quality of Life
IFG	Inferior frontal gyrus
ILAE	International league against epilepsy
LEV	Levetiracetam
LHE	Focal onset seizure originating left hemisphere
LTG	Lamotrigine
MRI	Magnetic resonance imaging
mTLE	Mesial temporal lobe epilepsy
NNT	Number needed to treat
OXC	Oxcarbazepine
PGB	Pregabalin
PHT	Phenytoin
PWE	People with epilepsy
QLI	Quality of Life Index
QoL	Quality of Life
RHE	Focal onset seizure originating right hemisphere
ROI	Region Of Interest
SEN	fMRI paradigm for language comprehension
SOC	Sence of Coherence
Std	Standard deviation
T	Tesla
TLE	Temporal lobe epilepsy
TPM	Topiramate
TR	Repetition time for fMRI images
vAIC	Anterior ventral insula
VPA	Sodium valproate
WHO	World Health Organization
WORD	fMRI paradigm for verbal fluency
ZNS	Zonisamide

1 Background

1.1 Introduction

Epilepsy is a chronic disease that largely influences the patient's life. It is the most common neurological disorder requiring long-term health care contact (Forsgren 1992; Sander and Shorvon 1996). Worldwide approximately 50 million people have epilepsy (Banerjee 2009). One of 21men and one of 28 women will develop epilepsy during their lifetime (Hesdorffer et al. 2011). Epilepsy is not a single disease, but rather an expression of many different brain disorders, and as a consequence investigations and treatment must be individualized. Genetic factors are often likely to play a role, either because the underlying cause of epilepsy is primarily genetic or because genes modulate susceptibility to an epileptogenic insult (Pandolfo 2011).

Most people with epilepsy (PWE) experience seizures for a limited time during their life, followed by remission (Goodridge and Shorvon 1983). The possibility of remission 20 years after diagnosis is approximately 70% (Annegers et al. 1979). The probability for remission is highest in patients with generalized-onset seizures diagnosed before ten years of age. Patients with focal seizures and adult-onset seizures run a greater risk of developing therapy-resistant epilepsy (Annegers et al. 1979), but even among patients with childhood-onset epilepsy it has been shown that one-third will have a poor long-term outcome (Sillanpää and Schmidt 2006). Patients with therapy-resistant epilepsy often suffer neuropsychological difficulties regarding their memory and language (Moore and Baker 2002), while higher executive functions appear to be unaffected. All these factors impact patient's daily life and, by the extension, their quality of life (QoL).

1.2 Psychosocial effects of epilepsy

Psychosocial functioning deals with the effectiveness of the individual in the social environment (Ricker 2008). It describes how well a person functions in the very complex reality of the world with it's many interpersonal relations. The concept of epilepsy signifies not only

a medical diagnosis, but also a social label. Epilepsy is much more than recurrent seizures and PWE may also experience psychiatric problems, difficulties in cognition and sometimes maladaptive social function (Jacoby and Austin 2007). The social stigma of epilepsy remains strong in many parts of the world, and can be predictor of future psychosocial problems. Negative attitudes towards PWE still exist; in a study from Austria 10% of the respondents in the general public expressed negative attitudes regarding PWE (Spatt et al. 2005). A person's perception of stigma can result from previous negative experiences or the anticipation of future ones. More than half of the epilepsy patients in a study reported feeling stigmatized (Taylor et al. 2011a). More than one of three children and teenagers with epilepsy expect their condition to hinder their lives in the future and are especially concerned about employment opportunities, travelling, exploring and education (Baker et al. 2008; Jacoby and Baker 2008). The unpredictable nature of epilepsy often causes stress even if the disease is fairly well controlled. If frequent seizures occur this may force PWE to be absent from ongoing education, which will result in poorer academic achievements (Katzenstein et al. 2007).

In several studies PWE more often report poor health, unemployment and the inability to work. PWE more often live in households with the lowest annual income, and have a history of co-occurring disorders (Kobau et al. 2008; O'Donoghue et al. 1999; Stavem et al. 2000; Strine et al. 2005; Wiebe et al. 1999). PWE are also more likely to be obese, physically inactive, current smokers and have a higher risk of experiencing major events that affect their lives significantly. PWE also have a higher mortality rate (Cockerell et al. 1994; Cockerell 1996; Cockerell et al. 1997; Lindsten et al. 2000) and even a higher risk of suicide (Christensen et al. 2007). People who have experienced even a single seizure have been shown to be discriminated against on the labour market (Holland et al. 2009). A low socioeconomic status has been shown to be a risk factor for developing epilepsy (Heaney et al. 2002; Hesdorffer et al. 2005) and also to cause more hospital admissions for epilepsy (Li et al. 2008). Normal activity limitation in areas in school, work or socialization with family and friends as well as poor social and emotional support are all significant predicators of poor mental health in PWE (Lu and Elliott 2012).

1.2.1 Quality of life

The World Health Organization (WHO) defines QoL as an individual's "perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns" (WHO 1998). WHO describes six domains of QoL; physical health, psychological health, level of independence, social relationships, environment and spirituality/religion/personal beliefs. Each person has different determinants of QoL (Katz 1987) and these determinates are also depending on if the individual is at good health or suffers from a disease (Bowling 1995). The determinants of QoL are also decided by which disease the person is affected by (Bowling 1996). However, the term QoL is often used in different disciplines and it's definitions vary depending on which field it is implicated in. Many different instruments have been developed for measuring QoL, and have been used to different extents. Among the epilepsy-specific instruments, the Quality of Life Epilepsy Inventories (QUALIE-89, QUALIE-31 and QUALIE-10) are most often used, and among the generic ones, the Short Form health survey (SF-36). The advantage with epilepsy-specific instruments is that they cover the domains that are important for epilepsy patients. Condition-specific instruments are believed to be more sensitive to changes within

and differences between individuals with a specific medical condition and may therefore be more suitable when comparing treatment options. Using generic instruments makes it possible to compare the results with other conditions, and these instruments also emphasize mental health rather than physical functions (Smith et al. 1999).

There is a lack of consensus regarding the definition of HRQoL. It is often referred to as the impact of disease and treatment on QoL. It may be described as the patient's perception of disease impact on well-being, and is used as a subjective measure in population studies. The determinants of HRQoL are not only biomedical factors, but also socio-demographic and psychosocial ones. Psychological factors like self-esteem, Sence of Coherence (SOC) and perceived control have been found to relate to HRQoL. In a review of different HRQoL measures, both depression and anxiety were correlated to impaired HRQoL (Taylor et al. 2011b). Psychological factors contribute to 30-35% of the variance in HRQoL, while around 20% is explained by seizure-related factors. In a large study from the Cleveland clinic, depression, driving restrictions and unemployment are pointed out as the most important determinants of QoL (Jehi et al. 2011). QoL can also be an important instrument for assessing the efficacy of medical interventions or to use in discussions about allocating resources to health care providers. A new instrument, developed for the economic evaluation of epilepsy treatments, is the NEWQOL-6D (Mulhern et al. 2012). QoL can also be used in evaluating patients` own experiences in relation to the cost of the treatment.

There is a complex relationship between cognitive functioning, psychological well-being and QoL. For PWE the most evident determinant is having active epilepsy with ongoing seizures, a connection has also been demonstrated by several authors (Baker et al. 1997; Jacoby et al. 1996; Leidy et al. 1999; Senol et al. 2007). More surprising is that PWE who have been seizure-free for a long time still exhibit impaired QoL (Strine et al. 2005); childhood epilepsy still has an impact on the QoL of the adult (Sillanpää et al. 2004). Even compared to those who had another chronic disease, PWE had a worse outcome regarding QoL (Wiebe et al. 1999). The relationship between QoL and different demographic and epilepsy-specific factors has been studied with different results about which predictive factors are the greatest determinants of QoL. There is however evidence that there is an association between seizure severity and QoL even when controlling for depression (Harden et al. 2007). In a recent review of 93 HRQoL studies, increases in seizure frequency, seizure severity, level of depression, level of anxiety and presence of comorbidity were all correlated to a decrement in QoL (Taylor et al. 2011b). Another large study on therapy-resistant epilepsy stated that adverse events (AEs) of medication and depressive symptoms were more important predicting factors for HRQoL than were the seizures themselves (Luoni et al. 2011). Other authors also support the notion that affective symptoms are more important in predicting QoL than is seizure frequency (Boylan et al. 2004; Loring et al. 2004; Park et al. ; Senol et al. 2007; Tracy et al. 2007; Zeber et al. 2007). The relationship between seizure reduction and QoL have been examined after epilepsy surgery, and it has been shown that QoL improves in all groups just after surgery and declines if a person experiences persistent seizures (Spencer et al. 2007). People who are seizure-free can improve to normalization in this group (Mikati et al. 2006; Wilson et al. 2001). There are different views on whether seizure reduction is sufficient for achieving an increase in QoL (Leidy et al. 1999) or if seizure freedom is required for this (Birbeck et al. 2002). Side effects from AEDs also contribute to impaired QoL (Perucca et al. 2009b). People with therapy-resistant epilepsy reported a mean of 6.6 side effects and diminishing these side effects was associated with improvements in QoL

(Perucca et al. 2009a). Another factor contributing to QoL is educational level. More years of formal education improve QoL in PWE (Pulsipher et al. 2006). However, most authors agree that optimizing QoL requires more than controlling the seizures; multiple biological and social processes must be considered. Interictal negative symptoms like affective flattening, apathy and loss of social drive have been reported in temporal lobe epilepsy (TLE) and are associated with increased psychosocial morbidity and impaired QoL as well (Getz et al. 2002; Getz et al. 2003).

1.2.2 Self-esteem and Sense of Coherence

Self-esteem is the most important part of the ego and has also been found to be the most important factor contributing to psychosocial well-being (Torres and Fernandez 1995). There are previous studies that suggest that children with epilepsy may be at risk of developing poor self-esteem (Matthews et al. 1982; Westbrook et al. 1992). Low self-esteem could be predicted by high seizure frequency and the belief that epilepsy was stigmatizing. Young people who live with epilepsy have a significantly higher incidence of depression related to interpersonal problems, social anxiety, and more obsessive symptoms than do adolescents without epilepsy (Baker et al. 2005). However, there are other studies that do not support the notion that epilepsy correlates to low self-esteem (Lee et al. 2008; Reeve and Lincoln 2002). Another factor closely related to psychosocial well-being is the Sence of Coherence (SOC) (Antonovsky 1987). This concept was defined by Antonovsky as the ability to perceive a stressor as comprehensible, manageable and meaningful. In this salutogenic model he searched for the reason for health rather than the cause of disease. Studies have shown that people with strong SOC handle stress better and are healthier than people with weak SOC (Adams et al. 2000; Skirka 2000). According to Antonovsky, SOC is stable by the end of early adulthood and thereafter fluctuates slightly depending on life patterns (Antonovsky 1993).

1.3 Definitions of seizures and epilepsy

According to the definitions by the International League Against Epilepsy (ILAE) 2005, an epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Fisher et al. 2005). Unprovoked seizures are those for which no responsible condition is found as an explanation. Acute symptomatic seizures are those that occur in temporal association with for example: brain insult, metabolic derangements, intoxication, drug withdrawal or CNS-infection. Epilepsy is in 2005 defined as 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. If there is an enduring predisposition to generate seizures, the diagnosis of epilepsy still requires the occurrence of at least one epileptic seizure.

1.4 Classification of seizures and epilepsy

The classification of a disease mirrors current knowledge and it is therefore crucial to reform it when science makes progress. The classifications of epilepsy and seizures have been changed several times over the years. In Study I and II classification was performed according to ILAE's classification of seizures 1981 (ILAE 1981) and syndromes 1989 (ILAE 1989). Since a new classification was proposed in 2010 this was used in papers III and IV (Berg et al. 2010).

1.4.1 *Classification of seizures*

The seizure classification is based on semiology and EEG findings. In the classification in 1981, partial seizures indicate the initial activation of neurons limited to parts of one cerebral hemisphere (1981). Partial seizures were then classified on the basis of whether consciousness was impaired (complex partial seizures) or not (simple partial seizures). Partial seizures were then grouped into partial seizures with motor signs, autonomic symptoms, somatosensory symptoms or psychiatric symptoms. It may evolve into secondary generalized seizures. In the same classification a seizure was generalized if findings indicated the initial involvement of both hemispheres. Generalized seizures were subdivided into the following categories: absence, myoclonic, clonic, tonic, tonic-clonic and atonic.

According to the recently proposed classification, a focal seizure starts within a network limited to one hemisphere and is either discretely localized or more widely distributed (Berg et al. 2010). Focal seizures can occur with or without impaired conscience, and can progress into bilateral convulsive seizures. A specification of seizure symptoms should follow thereafter. Generalized seizures are defined as those occurring in and rapidly engaging bilaterally distributed networks, and are subdivided in the same way as before. If there are no data to determine whether a seizure is focal or generalized, it will be classified as unknown.

1.4.2 *Classification of epilepsy*

The classification of epilepsy is based on semiology, aetiology and if fulfilled, a constellation of clinical characteristics constituting an epileptic syndrome. In the former classification of epilepsies from 1989, the following classes were given: Localization-related epilepsies and syndromes, generalized epilepsies and syndromes, epilepsies and syndromes undetermined whether focal or generalized and special syndromes. The epilepsies were also defined by aetiology as symptomatic epilepsy with known aetiology, idiopathic, with age-related onset, or cryptogenic epilepsy. A syndrome was defined as a complex of signs and symptoms that define a unique epilepsy condition, but it was not obligatory to always have the same aetiology and prognosis. In the new classification from 2010 the terms symptomatic, idiopathic and cryptogenic have been replaced by structural-metabolic, genetic and unknown. Epilepsy should first be classified according to aetiology, followed by a description of the semiology of the seizure. The term electroclinical syndrome is now restricted to a group of clinical entities that are identified by electroclinical characteristics. If this term is not completely fulfilled the classification will be other epilepsies. However, this new classification has also been criticized and authors have expressed the need for a more modern approach to the classification of epileptic seizures and epilepsies (Luders et al. 2012).

1.5 *Diagnosis of seizures and epilepsy*

The diagnosis of epilepsy is based on the clinical history and physical examination. It is crucial to get as accurate a description of the seizure's semiology as possible. Ictal symptoms, particularly at onset, are determined by the localization of seizure foci. Information about the circumstances, timing, triggering factors and position must all be obtained. It is also important to consider differential diagnoses like syncope, arrhythmia and non-epileptic seizures, since misdiagnosis of epilepsy is common (Chadwick and Smith 2002). Interictal EEG can offer

information, but a normal EEG cannot exclude the diagnosis of epilepsy. However, the EEG findings can offer information about the classification of epilepsy. Ictal EEG findings often add more information to the diagnosis. The investigation also includes a MRI which gives a detailed picture of the brain structures and may show lesions explaining the epilepsy diagnosis.

1.5.1 Generalized epilepsies

Generalized epilepsies are a diversified group in which diagnoses are considered to have a genetic inheritance (Poduri and Lowenstein 2011). There are epilepsies in which a single gene has been found as explanation and these genes often code for ion channels like in genetic epilepsy with febrile seizures plus. Inheritance by single genes has also been found as the explanation in for example juvenile myoclonic epilepsy and juvenile absence epilepsy. Epilepsies with complex inheritance are more common than single-gene inheritance. There is probably often an interaction between susceptibility genes and environmental factors that is the cause of epilepsy. A new model, the system epilepsies concept, has recently been proposed (Avanzini et al. 2012). This postulates that system epilepsies depend on a specific susceptibility of a given neural system to epileptogenic factors. In absence epilepsy for instance the thalamocortical system has a genetically determined susceptibility, but a trigger zone within this system is also needed to provoke seizures.

1.5.2 Temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is the most frequent type of focal onset epilepsy. TLE is also not a homogenous group but can be caused by different underlying neuropathologies (McMillan et al. 1987). For example it can be caused by mesial temporal sclerosis, cortical dysgenesis or low-grade tumours. Hippocampal sclerosis is the most common histological abnormality in mesial temporal lobe epilepsy (mTLE) (Margerison and Corsellis 1966). It is most common with cell loss in the regions CA 1 and hilus (Blumcke et al. 2002). TLE is often followed by an impairment of language and memory and is associated with postictal psychotic symptoms (Helmstaedter et al. 2003; Helmstaedter and Elger 2009; Lee et al. 2002; Motamedi and Meador 2003; Perrine and Kiolbasa 1999; Trebuchon-Da Fonseca et al. 2009). mTLE patients with confirmed hippocampal sclerosis have been shown to have cognitive impairment affecting not only memory but also intelligence quotient, executive functions, language and sensorimotor abilities (B. P. Hermann et al. 1997; Marques et al. 2007; Oyegbile et al. 2004b). Patients with left temporal lobe seizures often have deficits in verbal memory (Alessio et al. 2004; Helmstaedter and Kurthen 2001; Hermann et al. 1992). They often have anomia which can sometimes be noticed in spontaneous discourse and is often discovered in neuropsychological naming tests. The volume of the left hippocampus is a predictor of performance in general memory, verbal memory and verbal fluency in mTLE (Alessio et al. 2006). Patients with right temporal lobe seizures can have impaired non-verbal and visual memory (Giovagnoli et al. 1995; Gleissner et al. 1998; Lee et al. 2002).

The cause of TLE is often unknown but it is often seen some years after an injury or disease such as febrile seizures, head trauma, meningitis or encephalitis (Lewis 2005; Mathern et al. 1995; Mathern et al. 1996). An early start of recurrent seizures can be associated with a more sinister development regarding cognitive functions (Dikmen et al. 1975; Glosser et al. 1997), and mTLE often debuts in childhood or adolescence. Left-sided TLE can induce a reorganiza-

tion of speech lateralization (Janszky et al. 2006). Young people with TLE reach their learning peak at an earlier age (16-17 years) than controls (23-24 years) (Helmstaedter and Elger 2009). The cognitive decline in TLE may be stopped or even reversed if the seizures are fully controlled (Helmstaedter et al. 2003).

Neurogenesis is a process of generation of new neurons, through the division of neural stem cells and the neuronal differentiation of newly born cells (Kuruba et al. 2009). Certain regions of the brain maintain neurogenesis during a person's entire life. Hippocampal neurogenesis is important for functions such as learning, memory and mood (Kuruba et al. 2009). Seizures alter the amount and pattern of neurogenesis and are associated with neuro-degeneration, abnormal reorganization of the circuitry, and loss of functional inhibition in the hippocampal and extrahippocampal regions (Hattiangady and Shetty 2008). In mTLE the new cells that generate in the hippocampus do not differentiate in the normal way but instead turn into glia (Hattiangady and Shetty 2010). mTLE patients have dentate granule cell loss at the end stage of the disease (Siebzehnrubl and Blumcke 2008). This pattern of atrophy may be explained by cell loss secondary to a disruption of entorhinal-hippocampal connections and can be visualized by neuroimaging (Bernasconi et al. 2003).

Other parts of the brain are also affected by atrophy in mTLE (Keller and Roberts 2008). Patients with mTLE have also been shown to have more widespread cortical thinning and abnormalities in gyral complexity (Lin et al. 2007; McDonald et al. 2008b; Oyegbile et al. 2004a; Pulsipher et al. 2007). This is described as occurring bilaterally even if the aetiology of the TLE is found to be localized in one temporal lobe. The most salient finding was bilateral cortical thinning in the precentral gyrus, adjacent paracentral region and pars opercularis of the inferior frontal gyrus. A decrease in white matter volume is also present in TLE (Seidenberg et al. 2005). Patients with mTLE exhibit white matter fibre disconnections that involve predominately limbic structures (Bonilha et al. 2010). It is proposed that the deafferentation from hippocampal fibre loss could be responsible for the gray matter atrophy. A connection between cognitive performance and the integrity of several white matter tracts has also been demonstrated (McDonald et al. 2008a).

1.6 The limbic system

The limbic system includes the hippocampus and the hippocampal gyrus, uncus, amygdala, gyrus cinguli, part of the insula, the isthmus, Broca's olfactory area and the orbital surface of the frontal pole (Patten 1996). This is an older part of the brain than the cerebrum, and plays a primary role in the elaboration and expression of emotional feelings (Trimble 1992). The widespread connections to the cerebral cortex by the limbic system explain the prominent role of the medial temporal lobe in seizure propagation. Seizures originating in the temporal lobe often also invade the insula, giving emotional symptoms such as fear and anxiety (Isnard et al. 2000). The insula has different functions such as engendering self-awareness associated with positive feelings and consciousness (Craig 2009; Landtblom et al. 2011), but activation of the insula also correlates with subjective feelings from the body; actually with all emotional feelings (Craig 2011). The insula is known as a great mimicker and the semiology of seizures starting in the insula may resemble TLE or seizures starting in the frontal or parietal region (Nguyen et al. 2009). The insulae are important for cognitive demand, in the sense that they show increased activity when a task demands more effort (Karlsson 2010). The anterior

lobule of the insula is believed to be involved in speech planning (Price 2000). The superior precentral gyrus of the left insula is involved in articulating more complex words, prior to end-stage execution of speech production (Baldo et al. 2011). Ipsilateral projection of the hippocampus to the insula has been observed in epilepsy patients (Catenoix et al. 2011).

1.7 Comorbidity

PWE have a high rate of co-occurrence with other diseases that contribute to the burden of epilepsy (Kessler et al. 2011; Tellez-Zenteno et al. 2005). The reason for this can be a common factor that explains both the epilepsy and the other medical conditions. Other morbidities can lead to epilepsy or conversely, epilepsy or it's treatment can explain comorbidities. The prevalence of psychiatric comorbidity among PWE is especially high. Anxiety is estimated to affect between 10 and 25% of PWE (Gaitatzis et al. 2004), while between 10 and 60% suffer from depression (Beghi et al. 2002; Gilliam and Kanner 2002; O'Donoghue et al. 1999; Tellez-Zenteno et al. 2007). The connection between epilepsy and depression is not fully understood, but several possible factors have been proposed. These include a recurrence of a premorbid depression, increased risk for severe epilepsy due to a history of depression, shared risk factors for depression and epilepsy, or AED-induced depression (Hesdorffer and Lee 2009). A discontinuation of AEDs can result in an improvement in symptoms of depression and irritability (Hessen et al. 2007), but if the AEDs have positive psychotropic effects the withdrawal can lead to depression. It is recommended to screen for depression in PWE. Today depression in PWE is not mainly regarded as a consequence because of the obstacles in life that epilepsy cause, but rather as an effect of a common neurobiological pathogenic pathway (Kanner et al. 2012). Altered regional brain activity and disruption in the mood regulation network have been demonstrated in treatment-naive patients with TLE and has been proposed as one common pathogenic explanation for TLE and depression (Chen et al. 2012). It is essential to diagnose and treat even milder symptoms of depression (Kerr et al. 2011), as depression has a high influence on the seizure severity (Cramer et al. 2003).

1.8 Therapy-resistant epilepsy

Epilepsy is still resistant to treatment in up to a third of patients (Kwan et al. 2010). Drug-resistant epilepsy is defined as a failure of adequate trials of two tolerated, appropriately chosen and used anti-epileptic drug schedules, either in monotherapy or in combination (Kwan et al. 2010; Kwan and Brodie 2010). In this patient group, the likelihood of remission over a longer time is low (Choi et al. 2011). Pseudo-resistance must be avoided and can be explained by, for example, inadequate doses of AED, an inappropriate choice of drug, incorrect diagnosis or low compliance. The mechanisms of drug resistance are believed to be multifactorial. Predictors of drug-resistant epilepsy include a known structural cause and a high number of seizures, during a short period at an early phase of the disease (Kwan and Brodie 2000; Sillanpää and Cross 2009). The cause of drug-resistance is not known, but there are two major hypotheses (Kwan et al. 2011). The transporter hypothesis says that there is an over-expression of multidrug efflux transporters at the epileptic focus, reducing the cerebral concentration of the drug. In resected brain tissue from these patients, up-regulation of efflux transporters has been demonstrated (Sisodiya et al. 2002). The target hypothesis states that alteration in the cellular targets of the antiepileptic drugs causes impaired sensitivity to treatment (Remy and Beck 2006). Genetic factors influence the response to AEDs and can be one of the explanations

for drug-resistant epilepsy. Many human epilepsies involve a mutation in either a voltage- or receptor -gated ion channel. Polymorphisms of the SCN2A gene have been postulated as one reason for drug resistance (Kwan et al. 2008). The weakness of this theory, however is that patient often has resistance to drugs with different modes of action. The available AEDs, only prevent seizures; they do not do not change the pathogenic process of epilepsy.

1.9 Cognition

1.9.1 Memory

There are five memory systems: working memory, episodic memory, semantic memory, the perceptual representation system and the procedural memory (Schacter 2000). The last four of these involve long-term memory. The human memory is divided into two systems, explicit and implicit memory. The explicit memory is the part we are aware of, for example our experiences (Tulving 1972). This includes the semantic and episodic memory. The implicit memory consists of procedural memory and the perceptual representation system. Impaired memory is among the most common complaints of PWE. Multiple factors contribute to memory impairment (Motamedi and Meador 2004). The use of AEDs can impair memory. The mechanism of AEDs is to decrease neuronal excitability and thus suppress epileptiform discharges; other neuronal networks that maintain normal neuro-cognitive functions may also be affected. A balance of seizure control and the side effects of AEDs must be sought for every patient. Memory can also be affected by underlying neuropathology or mood. High numbers of generalized tonic-clonic seizures have been associated with a drop in intelligence scores and altered prefrontal brain activation on fMRI (Vlooswijk et al. 2008). In patients with TLE, findings indicate that episodic rather than semantic memory is impaired, particularly in TLE with mesial temporal sclerosis (Helmstaedter 2002). In another study, patients with TLE have been shown to have both episodic and semantic memory impairments (Messas et al. 2008).

1.9.2 Language

The classical language model describes the language system as composed primarily of two cortical regions in the left hemisphere, the areas of Broca and Wernicke. These are usually defined as the posterior part of the left inferior frontal gyrus and the posterior superior temporal gyrus. Current language models depict a more dynamic network system in which multiple regions are interconnected and each function is represented by a network of several brain areas (Rombouts 2007). Language is not a single procedure but instead involves several specialized systems for speech, text and object recognition. Language features can be subdivided into phonology (the sound of words), orthography (the spelling of words), semantics (knowledge of the world) and syntax (knowledge of grammatical relationship between words). There is evidence of two projections streams, whereby one pathway supports speech comprehension and the other supports sensory-motor integration (Hickok 2009). The auditory cortex is hierarchically organized in the superior temporal sulci. High level systems in the superior temporal gyrus and areas surrounding the superior temporal lobe ventrally and posteriorly are important for linking auditory information with the semantic system. This is bilateral in the early stages of the process, but becomes more lateralized when semantic processing is involved. The articulatory network is localized in the frontal lobe, involving the posterior inferior frontal gyrus and more dorsal premotor cortex (Hickok and Poeppel 2007).

The main reason for mapping the language system in epilepsy is to prevent postoperative deficits that can result from epilepsy surgery. fMRI studies of language are typically performed using different tasks in different laboratories and are therefore not always comparable (Binder et al. 1997; Price 2000). In fMRI investigations on language, word fluency is primarily associated with activation in Broca's area in the language-dominant hemisphere. In addition, activation is also frequently observed in a larger network involving the prefrontal regions surrounding Broca's area, the anterior cingulate cortex, and at temporal and parietal sites (Fu et al. 2002; Heim et al. 2009; Medford and Critchley 2010). Semantic sentence processing activates mainly Wernicke's area in the language-dominant hemisphere, with additional clusters in the inferior frontal and parietal lobes.

1.9.3 Cognition in people with epilepsy

Cognitive problems are common in epilepsy and various epilepsy syndromes differ in terms of cognitive outcome. Many children and adolescents with epilepsy face educational difficulties (Besag 2006). The causes of cognitive impairments in PWE are thought to be multifactorial and to involve effects of underlying aetiology, effects of recurrent seizures, side effects of AEDs and psychosocial effects (Aldenkamp and Bodde 2005; Kwan and Brodie 2001; Meador 2002; Motamedi and Meador 2003). Cognitive profiles in epilepsy are as heterogeneous as the epileptic syndromes (Elger et al. 2004). Localization–related epilepsy disorders are accompanied by focal deficits that mirror the function of this specific area. Cognitive impairments in epilepsy have been investigated in relation to seizure frequency, aetiology, seizure classification, duration of epilepsy and EEG pathology (Aldenkamp et al. 2004; Aldenkamp et al. 2005; Aldenkamp and Bodde 2005; Dodrill 1992). It is important to distinguish state-dependent cognitive impairment as epileptic activity or side effects, from permanent cognitive decline (Trimble 2011). The state dependent problems are reversible and treatable. It has been demonstrated that the deficit in cognitive function is present at the time of epilepsy onset (Aikia et al. 2001) and is not only an effect of recurrent seizures and side effects from AEDs. Recent researchers have emphasized how cognitive abnormalities are linked to structural, functional, metabolic and other neurobiological markers of cerebral integrity independent of their association with clinical epilepsy characteristics (Schachter 2009). Among a group with newly diagnosed epilepsy, a five-year follow-up showed that cognitive measures were stable for the majority but among 38% a decline was noted in memory and psychomotor speed (Taylor and Baker 2010). TLE is associated with progressive memory decline, but PWE who have seizure control from monotherapy usually have no cognitive problems. Hippocampal sclerosis is associated with greater impairment in intelligence, memory, language and visuospatial functions than in other pathologies related to epilepsy (Hermann et al. 1997).

People affected by epilepsy can also have impaired memory and concentration problems due to side effects from AEDs (Perucca et al. 2009b). The reduced neuronal excitability is thought to contribute to this decreased cognition. Deficits in attention, concentration, memory and word finding are the most common. It is very common that PWE attribute their memory difficulties to side effects from AEDs and not to the underlying pathology or psychosocial difficulties which are also important (Baker et al. 2009). There is a discrepancy between subjective memory and memory performance on neuropsychological tests. It is the generalized tonic-clonic seizures, not the focal seizures that over time damage brain function. This is most pronounced if the patient suffers from serial seizures in a status epilepticus (Bjornaes

et al. 2001; Dodrill and Wilensky 1990). Generalized absence seizures are less damaging on cognition than tonic-clonic seizures are (Dodrill 1992). Complex problem solving and cognitive flexibility is often impaired in severe epilepsy with generalized seizures (Dikmen and Matthews 1977). Seizure-frequency (Dikmen and Matthews 1977; Seidenberg et al. 1981) duration and severity of epilepsy disease are all risk factors for impaired cognitive function.

Generalized tonic-clonic seizures may cause a progressive neuronal dysfunction or loss (Tasch et al. 1999). It has been shown that cognitive prognosis is especially poor for the subset of patient with TLE who are characterized by chronic symptoms of epilepsy, older age, lower intellectual ability and more baseline abnormalities in quantitative magnetic resonance volumetric (Hermann et al. 2006). Interictal discharges i.e. epileptiform EEG discharges not accompanied by a clinical event can be associated with impaired cognitive functions (Aarts et al. 1984) but this is limited to generalized discharges (Aldenkamp et al. 2005). A great impact of seizures on cognition also occurs through postictal effects (Giovagnoli and Avanzini 1999).

1.9.4 Correlation between cognitive problems and psychological impairments.

Some PWE experience memory and learning, attention and concentration problems and slower information processing and psychomotor speed, language deficits and executive functions compared to controls in neuropsychological tests (Hermann et al. 2007; Oyegbile et al. 2004b). There is a discrepancy between subjective memory and memory performance in the cognitive test. People in general may claim to have poor memory, but this cannot be confirmed in cognitive test, while others have poor results in the cognitive tests but no subjective memory problems. According to Elixhauser self-experienced memory problems are strongly correlated to mood (Elixhauser et al. 1999). The lack of correlation can be explained by depression or anxiety, which increase the patients reporting of memory problems (Thompson and Corcoran 1992). Seizure frequency, on the other hand, influences mood and therefore consequently affects memory awareness (Piazzini et al. 2001). The tendency to overstate memory problems was not connected to classification of epilepsy or duration of disease.

It has also been proposed that neuropsychological tests are not sufficient for measuring the real problem of the epilepsy patient (Helmstaedter et al. 1998). There is relatively little research on the impact impaired cognitive function may have on psychological functioning and QoL. In one study patients with well controlled partial epilepsy had impaired cognition and HRQoL but there was no relationship with epilepsy-related factors (Engelberts et al. 2002). In another study no relationship between QoL and cognitive performance could be found (Loring et al. 2004). Patients with TLE show a correlation between self-reported memory and QoL (Giovagnoli and Avanzini 2000).

1.10 Treatment of epilepsy

The most common treatment for epilepsy is pharmacological treatment and most patients are prescribed antiepileptic drugs (AEDs). Great care has to be taken in the decision to prescribe an AED, since the treatment is often life long. The choice of drug needs to be individualized and based on a careful risk-benefit ratio (Perucca and Tomson 2011), taking into account factors including but not limited to seizure type, age, sex, childbearing potential, comorbidities and concomitant medication. The goal is to find a treatment that offers seizure freedom

without adverse effects. With the introduction of new AED there are now around 20 different medications available on the Swedish market. The International League Against Epilepsy (ILAE) has presented an analysis of AED efficacy and effectiveness as initial monotherapy (Glauser et al. 2006). Carbamazepine (CBZ), levetiracetam (LEV) and phenytoin (PHT) have the highest level of evidence A in focal epilepsy. Trials regarding generalized epilepsy have lower evidence (C), but valproat (VPA), lamotrigine (LTG) or topiramate (TPM) are recommended as first choice.

1.10.1 Old and new generation antiepileptic drugs

AEDs are often classified as either "older" (drugs that were in widespread use before the 1990s) or "newer" (introduced in the 1990s or later). To be approved as add-on therapy all AEDs have to show superior efficacy to placebo in double blind randomized trials. In Europe the primary efficacy measure responder rate is defined as >50% reduction in seizure frequency. Due to the differences in methodology it is often hard to compare different studies. A meta analysis has been performed and when the analysis was based on NNT (number needed to treat) TPM and LEV were the most efficacious, but the differences were small (Costa et al. 2011). When the number of AEDs increased, the probability of finding a safe and effective medication for each individual increased as well. There are no significant differences in efficacy, but the new AEDs often have better tolerability which includes neuropsychological factors and psychiatric side effects. The newer drugs are generally associated with more favourable neuropsychological profiles (Loring et al. 2007).

1.10.2 Mechanism of antiepileptic drugs

In the CNS the voltage dependent sodium and calcium channels depolarize the cell membrane toward action potential threshold. There are also voltage dependent potassium channels that function to dampen excitation in the nervous system. The main inhibitory synaptic transmitter is GABA (Gamma butyric acid). It will bind to GABA A and GABA B receptors. Glutamate is the principal excitatory transmitter. The inotropic glutamate receptors are the NMDA, AMPA and kainate receptors.

The most common targets for AEDs are sodium channels, calcium channels and the GABA-ergic system. Other potential targets include hyperpolarization-activated cyclic nucleotide gated channels, potassium channels, the glutamergic system, synaptic vesicle protein SV2A and some amines (Shorvon 2009). The main mechanism of action of AEDs is to decrease neuronal excitability, which is thought to contribute to decreased neuropsychological function. All AEDs do not have the same relationship between electrophysiological slowing and decreased neuropsychological ability (Salinsky et al. 2007).

1.10.3 Old generation antiepileptic drugs: Brief summary

Carbamazepine

Carbamazepine (CBZ) is structurally related to the tricyclic antidepressants and was first used for the treatment of pain. It's main mechanism is a prevention on the repetitive firing of sodium-dependent action potentials in depolarized neurons via voltage-dependent blockage

of sodium channels. CBZ has high level evidence of efficacy in focal seizures, but is usually ineffective in epilepsy with absences or myoclonies. It has been shown to be cost-effective for new onset focal seizures (Brodie and Kwan 2012), and has been associated with a number of adverse events (AE) such as dizziness, drowsiness, hyponatremia, diplopia and rash, but most of these are dose-related.

Clonazepam
Clonazepam is a GABA receptor agonist (Shorvon 2009). Even though it is effective in all types of epilepsy, it is used for absences. The disadvantage of this formula is sedation and development of tolerance.

Ethosuximide
Ethosuximide is mainly used as therapy for generalized absence seizures and some generalized epilepsies of childhood (Shorvon 2009). Its presumed mechanism of action is reduction of low-threshold T-type calcium currents in thalamic neurones.

Phenobarbital
Phenobarbital is the oldest AED still in use, but mainly in developing countries. Behavioural effects are common, with a high rate of discontinuation due to hyperactivity. Sedation is also common. Its mechanism of action is interaction with the GABA receptor.

Phenytoin
Phenytoin (PHT) is highly effective for many seizure types (Merrit and Putnam 1938) and is used as adjunctive treatment or monotherapy in focal and generalized seizures, except for myoclonic and absence seizures. Its mechanism is an inactivation of voltage-dependent sodium channels. PHT is the most used AED in the world, but in Sweden it is rarely used today for long-term treatment because of complicated pharmacokinetics with narrow therapeutic range and adverse effects. It is often used as emergency treatment in status epilepticus.

Primidone
Primidone is metabolized to Phenobarbital but may also have some effect by itself. Like PHT it also causes CNS depression.

Sodiumvalproate
Sodiumvalproate (VPA) probably affects neurons through a combination of different mechanisms. It both inhibits both voltage-sensitive sodium channels and activates calcium-dependent potassium conductance, and also increases GABA. VPA has a broad spectrum of mechanisms including both generalized and focal seizures and can be titrated rapidly (Brodie and Kwan 2012). In the SANAD study on generalized epilepsy VPA was considered more effective than LTG and better tolerated than TPM (Marson et al. 2007b). It is less suitable for fertile women however, because of its teratogenic effects and other side effects like the polycystic ovary syndrome. VPA has been associated with acute and chronic encephalopaties that are reversible (Zaret and Cohen 1986).

1.10.4 New-generation AEDs in Study I: Brief summary

Gabapentin

Gabapentin (GPA) is approved as adjunctive therapy or monotherapy for focal seizures. It was developed as similar to GABA but does not seem to be a GABA-agonist. GPA probably blocks high voltage-activated calcium channels, but this is not clear. It has a good adverse profile, with relatively few cognitive adverse effects. It has a rather low efficiency for seizure control, however, but can be advantageous for the elderly (Rowan et al. 2005) or when adverse effects are of concern.

Lamotrigine

Lamotrigine (LTG) is approved for monotherapy or adjunctive therapy in both focal seizures and generalized epilepsy. It is generally well tolerated, but there is a risk of serious adverse skin reaction. LTG acts by blocking the fast-inactivated state of sodium channel and reducing glutamate. LTG is associated with fewer CNS adverse effects than CBZ (Hamilton et al. 1993), and is also associated with better neuropsychological outcome compared to CBZ in more than half of the neuropsychological measures such as cognitive speed, memory, mood factors, sedation, perception, cognitive performance and quality of life in healthy volunteers (Meador et al. 2001). In a study comparing LTG to VPA, LTG has shown improved cognitive activation on simple reaction-time measurement, a more positive subjective report about the impact of drug treatment relative to VPA and positive mood changes (Aldenkamp et al. 2002). There are also studies demonstrating beneficial effects of LTG on QoL compared to CBZ (Brodie et al. 1995; Gillham et al. 1996). Positive psychotropic properties have been reported for LTG (Meador and Baker 1997). One disadvantage of the substance is the slow up-titration that is necessary.

Levetiracetam

The mechanism of action of levetiracetam (LEV) is believed to be modulation of the protein functions of the synaptic vesicle protein SV2A, thereby reducing excitatory neurotransmitter release during trains of high-frequency activity. It has high efficiency for seizures, can be rapidly titrated and has no interactions. LEV has a favourable side effect profile. Two studies have demonstrated that LEV is as efficient as CBZ (Brodie et al. 2007) but has fewer cognitive side effects (Meador et al. 2007; Mecarelli et al. 2004). LEV can cause irritability in some individuals and in the study comparing new AEDs LEV reported the highest rate of psychiatric side effects (Mula et al. 2003; Weintraub et al. 2007) as well as a possible link to suicidal intention (Mula and Sander 2007). It is approved for monotherapy (Ben-Menachem and Falter 2000) and adjunctive treatment in both focal seizures and generalized epilepsy.

Oxcarbazepine

Oxcarbazepine (OXC) is a derivate of CBZ and also mainly blocks fast inactivated state of sodium channels, but has different metabolites than CBZ. It is approved for monotherapy and adjunctive therapy for focal seizures, but is also useful for generalized seizures not associated with absence or myoclonic seizures. Compared to CBZ it is less likely to cause rash but more often gives hyponatremia. There are few studies on cognition, but in one small study OXC was similar to PHE regarding neuropsychological effects (Salinsky et al. 2004).

Pregabalin
Pregabalin (PGB) is similar to GPA and is indicated for adjunctive therapy on focal seizures. PGB binds to the calcium channel subunit reducing calcium influx. PGB is not frequently prescribed for epilepsy today and has a narrow spectrum. However the formula is widely uses for the treatment of generalized anxiety disorder and painful neuralgia. PGB demonstrates no neuropsychological impairment compared to placebo (Hindmarch et al. 2005).

Topiramate
Topiramate (TPM) has multiple mechanisms of action including sodium and calcium channel blockade, GABA potentiating and glutamate receptor antagonism. TPM is a sulfamate substituted monosaccharide and is highly efficient in treating seizures. Of the new AEDs TPM is believed to cause the greatest neuropsychological problems and has greater neuropsychological side effects than VPA (Meador et al. 2003). TPM worsens the cognitive speed and verbal fluency as well as short-term memory. These findings suggest that TPM impairs frontal functions (Gomer et al. 2007). TPM is associated with anorexia, weight loss, word-finding difficulties and neuropsychiatric complications. In one study, withdrawal of TPM caused improvement in frontal lobe-associated measures like verbal fluency and working memory (Kockelmann et al. 2003). Decreased language function has been associated with TPM in other studies as well (de Araujo Filho et al. 2006; Gross-Tsur and Shalev 2004; Martin et al. 1999; Meador 2008). TPM is a broad-spectrum AED and is approved for monotherapy in both focal seizures and generalized epilepsy.

Vigabatrin
Vigabatrin enhances the effect of the inhibitory neurotransmitter GABA. It was licensed for adjunctive treatment in focal seizures, but in 1997 it was revealed that this substance caused irreversible visual field–defects (Eke et al. 1997). Today, it is used mainly for infantile spasm, and rarely in therapy resistant epilepsy in adults. If vigabatrin is used today, visual fields must be regularly examined using perimetry.

1.10.5 Anti-epileptic drugs marketed after Study I: Brief summary

Eslicarbazepine
Eslicarbazepine is the single S-enatiomer in the dibenzazepine derivates in CBZ and OXC, and is also a blocker of the voltage gated sodium channel. Eslicarbazepine has recently been approved as adjunctive therapy for focal onset seizures in Sweden (Elger et al. 2007).

Lacosamide
Lacosamide is approved as adjunctive therapy for focal onset seizures. It enhances a slow-inactivated state of the sodium channel without affecting fast inactivation and may also interact with the Collapsin response mediator protein-2. The most important AE in the studies was dizziness, but there was no increase in psychiatric AEs (Ben-Menachem et al. 2007).

Retigabine
The mechanism of action of retigabine involves direct activation of the voltage-gated potassium (KCNQ, Kv 7) channels that conduct the M-current (Gunthorpe et al. 2012). Retigabine is approved for adjunctive treatment in focal onset epilepsy (Plosker and Scott 2006).

Rufinamide
Rufinamide is approved for adjunctive therapy for seizures in Lennox-Gastaut syndrome (Perucca et al. 2008). The mechanism is not fully known but involves prolongation of the inactive state of the sodium channel.

Zonisamide
Zonisamide (ZNS) is approved as adjunctive treatment and recently as monotherapy for focal seizures. It has multiple mechanisms as well, including blockade of sodium channel, blockade of T-type calcium channel, potentiating of GABAergic transmission and inhibition of carbonic anhydrase. The most common side effects in one study were somnolence and dizziness (Brodie 2006). The molecule is sulpha-containing and ZNS has also been associated with impaired cognitive functions especially language functions like word recall and verbal fluency (Park et al. 2008).

1.11 Side effects of antiepileptic drugs

Side effects from AEDs are divided into type A (pharmacology related) or class B (idiosyncratic adverse effects). Type A reactions are predictable and often occur at the beginning of a treatment. Type B adverse effects are unpredictable and not possible to foresee (Zaccara et al. 2007). Apart from barbiturates and TPM there is no clear evidence that one AED affects cognitive functions more than others (Kerr et al. 2011). Studies of the cognitive side effects of AEDs have demonstrated effects in the areas of psychomotor speed, visual-spatial performance, concentration and memory (Martin et al. 1999; Vermeulen and Aldenkamp 1995). Language can also be affected. TPM and high doses of ZNS can cause language-specific toxicity in vulnerable individuals (Ojemann et al. 2001). Naming is often the function that is first affected. Recently it has been shown that one single dose of TPM impacts language negatively in healthy volunteers (Marino et al. 2012). It is very common that PWE attribute their memory difficulties to side effects from AEDs and not to the underlying pathology or psychosocial difficulties, which are also important (Baker et al. 2009). For some patients, the cognitive side effects can be more debilitating than the seizures and contribute to a loss in QoL (Gilliam 2002). For patients that have infrequent seizures, it is very important with seizure control. Patients with poor seizure control are more sensitive to medication side effects, maybe beacuse they are dissatisfied with the situation. (Cramer et al. 2007). The average rate of AED-related intolerable cognitive side effects was 12,8% in a recent study (Arif et al. 2009). Most intolerable cognitive side effects were attributed to TPM, but ZNS, PHT and OXC were also associated with cognitive side effects. Psychiatric side effects are common in patients taking AEDs. Irritability is the most common complaint, followed by depression and behavioural changes (Weintraub et al. 2007). There are differences between the newer AEDs regarding psychiatric side effects profiles (Weintraub et al. 2007). Patients taking LEV experience more psychiatric side effects than the average, while fewer psychiatric side effects are associated with LTG and GAB. A past psychiatric condition is the most important predictor of AED-related psychiatric side effects. Patients with a previous history of psychosis or affective disorder tend to develop the same psychiatric disorder with a new AED (Trimble et al. 2000).

1.12 Neuroimaging in epilepsy

Magnetic Resonance Imaging, (MRI) plays an important role in the detection and anatomical localization of epileptogenic lesions, and most epilepsy patients are examined using MRI (Bastos 2002). MRI alone can not determine the epileptogenecity of an abnormality: it must be evaluated in concordance with EEG findings and semiology. MRI has been important in detecting hippocampal sclerosis with a high degree of accuracy, but can also detect developmental cortical malformations, vascular malformations, gliosis or tumours that can explain epilepsy with focal seizures. The principal MRI features of hippocampal sclerosis are hippocampal atrophy, signal alternations and loss of internal architecture.

1.12.1 fMRI

The applications of functional brain mapping (fMRI) include mapping of language function, memory function, sensory motor function and sometimes interictal EEG abnormalities. (Ulmer 2010). One clinical application for fMRI is investigations prior to epilepsy-surgery (Binder 2002). fMRI is applied to map eloquent areas and evaluate language dominance prior to surgery. The most widely used functional imaging technique is the blood-oxygenation level-dependent signal (BOLD-fMRI) (Ogawa et al. 1993). The BOLD contrast is dependent on changes in blood flow, and is an indirect measure of neural activity. It is now thought that neurotransmitters, particularly glutamate, generate activity-induced blood flow and much of this control is mediated by the astrocytes (Attwell et al. 2010). To sustain neuronal function, the brain has developed a mechanism to increase the flow of blood to regions in which neurons are active; this is called functional hyperaemia. Therefore, areas of the brain that are engaged in a certain task experience a local increase in the cerebral blood flow. The magnitude of the blood flow increase exceeds the increase of the local oxygen consumption, which leads to a localized increase in the ratio of oxyhemoglobin to deoxyhemoglobin. Oxyhemoglobin is diamagnetic whereas deoxyhemoglobin is paramagnetic, and this difference in magnetic properties is detectable by MRI.

fMRI requires measurement that detects chances over time. Images are collected with a repetition time (TR), resulting in several hundreds of images. An fMRI examination is usually divided into periods in which images are acquired during a specific task, followed by a control period of rest called block design. This paradigm is commonly referred to as blocked design, the activity is sustained for a period of 15-30 seconds and is interspaced by control activity. An alternative is the event-related design with short-duration stimuli followed by rest for a longer period.

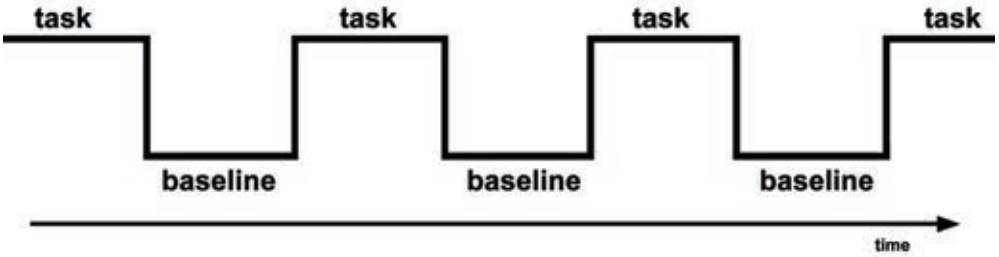

Figure 1 *Block design paradigm*

The choice of fMRI paradigm is important since it must activate the function you intend to map. It is also crucial that the subject understands the task and performs them correctly. Therefore, there must be realistic training of the task before the scanning to ensure that the subject understands the task requirements. It is also important to design a suitable control task, since significant cognitive processes are present at rest.

To evaluate the functional mapping of the brain, regions of interest (ROIs) for the analysis are selected. The material must be corrected for involuntary head movements. A cross–relation analysis is then performed to identify the voxels whose signals change at the activation phase. The collected voxel time-series are compared to the model of the expected BOLD signal of an activated voxel. The voxels whose time-series resemble the activation phase closely enough are labelled as active. Before the statistical analysis, the data must be pre-processed. First they must be corrected for movement. Small movements during the investigation are inevitable, so the images must be corrected so that any voxel contain the same brain tissue in all the images. Before the analysis, the images are also smoothed with a Gaussian filter to improve the signal to noise ratio. All images are affected by random noise, which is reduced by this method. The statistical analysis is most commonly performed using the General Linear Model. The time course of the hemodynamic response function for each voxel is compared to the paradigm time course, and the statistical significance is calculated using a t-test or a linear regression coefficient. This gives an image of the statistical value for each voxel. For every fMRI process, a statistical threshold criterion must be selected. The statistical analysis of the data will result in a statistic value for each voxel. A threshold value is then set, for example $p<0.001$, to discriminate between active and non-active voxels. This determines which voxels are considered to be significantly activated, and the activation map of every analysis will be dependent of these threshold criteria. The activation map is then overlaid on matching slices from anatomical images. The fMRI investigation contains a large amount of data from perhaps 100000 voxels. The family-wise error rate is the standard measure of type I errors in multiple testing. To avoid the problem of false positives when carrying out multiple comparisons a family-wise error correction is performed.

2 The aims of the study

The general aim of this PhD project is to describe medical and psychosocial consequences of epilepsy in young adulthood, also adressing concurrent cognitive dysfunction.

The specific aims of the PhD projects are:

1 To study medical aspects, such as seizure-frequency and side effects of pharmacotherapy, in epilepsy in young adulthood in a five-year follow up.

2 To study psychosocial aspects such as Quality of Life, Sense of Coherence and self-esteem in young adults with epilepsy, in a five-year follow-up.

3 To describe the consequences of living with epilepsy and cognitive decline in daily life in young adulthood.

4 To investigate cognitive function (exemplified by language) in young adults with epilepsy and assess possible correlations between brain activity when performing language tasks, neuropsychological data and epilepsy-related factors.

3 Subjects

3.1 Medical outcome in epilepsy patients of young adulthood: A 5-year follow-up study (Study I) and Self-esteem and Sense of coherence in young people with uncomplicated epilepsy – A 5-year follow-up (Study II).

Study I and II were based on the same subjects. In 1999, all adolescents aged 13-22 years registered with uncomplicated epilepsy at four Swedish hospitals, Linköping, Karlstad, Örebro, and Jönköping were invited to participate in the studies (I-II) and 151 (82%) accepted. Of the participants 67 were males and 84 females. The diagnosis of epilepsy was defined as the occurrence of at least two unprovoked epileptic seizures. To be included the patient should be using AEDs or have had at least one seizure during the preceding year. Uncomplicated epilepsy was defined as epilepsy without associated neurological impairment, mental retardation cerebral palsy or other concomitant disease that could influence psychosocial variables. The excluded patients (n=65) suffered from mental retardation, asthma, diabetes mellitus, psychiatric conditions, physical handicaps and obesity. Patients with epilepsy classified as benign childhood epilepsy with centro-temporal spikes were excluded as well. At the five-year follow-up, the participants were young adults aged 18-27 years. All data were acquired from 97 participants. Some participants could not be located, some did not answer the questionnaire, and for some the data were incomplete.

3.2 Living with epilepsy accompanied by cognitive difficulties: Young adults' experiences (Study III).

The subjects in Study III were young adults with epilepsy (18-35 years). They were recruited from the open clinic, Department of Neurology, University Hospital of Linköping and from the open clinic of neurology, General Hospital of Motala. The inclusion criteria were being

treated for epilepsy with AEDs and having subjective cognitive impairment. The participants had to be fluent in Swedish and to have completed at least elementary school (9 years). Patients with mental retardation were excluded. Seven men and seven women took part in this study.

3.3 Cognitive problems in young adults with epilepsy: Language deficits correlate to brain activation and self-esteem (Study IV).

Some of the participants (n=7) in Study III also took part in Study IV. Study IV had no requirement for subjective cognitive decline, but many of the participants in Study III were interested in contributing to further studies in this field. The participants were recruited from the open clinic, Department of Neurology, University Hospital of Linkoping and from the open clinic of neurology, General Hospital of Motala. Patients with generalized epilepsy (GE), patients with epilepsy with foci in the right hemisphere (RHE) and patients with epilepsy with foci in the left hemisphere (LHE) were recruited with the aim of recruiting ten patients in each of these three groups. Participants had to be fluent in Swedish and to have completed at least elementary school (9 years). Exclusion criteria were the use of vagal nerve stimulator or other electrical devices that could interfere with the MRI investigation, other concomitant medical, neurological or psychiatric illness and the use of psychoactive drugs (apart from epilepsy treatment) that could interfere with performance. Patients with additional psychogenic non-epileptic seizures were excluded as well. Some participants were later excluded due to lacking imaging data or technical problems. The final study group consisted of 11 participants with generalized epilepsy, nine with epilepsy with foci in left hemisphere, (all in the temporal lobe) and nine with epilepsy with foci in the right hemisphere (five in the temporal lobe, one occipito-temporal, two fronto-temporal and one centro-parietal). Seven patients had undergone brain surgery: four temporal lobe resection left, one temporal lobe resection right and two extra temporal lobe resection. All participants are described in Study IV (table 1). The controls were recruited by advertisement and were matched to the participants for age, sex, education and handedness. Twenty-eight controls were recruited, but one exhibited right-hemispheric language dominance and was excluded leading to 27 controls.

4 Methods

Studies I and II were based on questionnaires sampling medical data, and the response to different instruments.

4.1 Medical outcome in epilepsy patients of young adulthood – A 5-year follow-up study (Study I). The following instruments were used

4.1.1 Medical data

Medical information was extracted from medical records by one of the authors. To obtain as accurate a classification as possible, the medical records were evaluated including semiology, EEG registrations and imaging results and compared to the written description of the seizure.

4.1.2 Seizure outcome measures

To classify how well the seizures were controlled we used a three-graded scale (Eriksson 1997). (1) Good control: no seizures during the past year, (2) Partial control: one or more seizures during the past year, but not more than one per month and (3) Poor control: more than one seizure per month.

A modified version of the national hospital seizure severity scale (O'Donoghue et al. 1996) translated to Swedish was also used. Three questions were added concerning seizure frequency, AED and side-effects of AED. The participants were asked to describe their seizures.

4.1.3 *Quality of Life Index*

To measure QoL we used the generic version of the Quality of Life Index (QLI) (Ferrans and Powers 1985, 1992) developed by Ferrans and Power, but translated into Swedish. The QLI consists of two parts each compromising 34 items. It measures a person's satisfaction with various aspects of life and how important these factors are to him or her. Items are distributed on four dimensions: health and functioning, psychological/spiritual domain, social and economic domain and family. The six-point response scale ranges from 1 (very unsatisfied/very unimportant) to 6 (very satisfied/ very important). Total scores range from 0 to 30 and higher scores indicate better QoL. The mean score for the Swedish population is 21.0 (Gullberg et al. 2010).

Are you satisfied with:	Very satisfied	Modestly satisfied	Slightly satisfied	Slightly unsatisfied	Modestly unsatisfied	Very unsatisfied
Your education?	6	5	4	3	2	1
Your health?	6	5	4	3	2	1

How important is:	Very important	Modestly important	Slightly important	Slightly unimportant	Modestly unimportant	Very unimportant
Your education?	6	5	4	3	2	1
Your health?	6	5	4	3	2	1

Table 1 *Examples of questions in Quality of life index (QLI)*

4.2 *Self-esteem and Sense of Coherence in young people with uncomplicated epilepsy: A 5-year follow-up (Study II)*

In Study II medical data were obtained from Study I and the following instruments were used:

4.2.1 *Sense of Coherence*

The original version of the Sense of Coherence (SOC) questionnaire comprises 29 items distributed across three categories: Comprehensibility (understanding a stimulus as predictable and explicable); Manageability (there are resources available to meet the demands); and Meaningfulness (demands or challenges worthy of emotional investment). In this study, the shorter 13-item version was used; SOC-13 contains 13 items that are rated on a seven-point scale. Total scores range from 13 to 91 points and the mean for healthy controls in adolescence and young adulthood is 63.73 (Räty et al. 2003).

	Happens often						Never happens
Do you have the feeling that you're being treated unfairly?	1	2	3	4	5	6	7
Has it happened in the past that you were surprised by the behaviour of people whom you thought you knew well?	1	2	3	4	5	6	7

Table 2 *Examples of questions in SOC-13 scale*

4.2.2 Self-esteem questionnaire

In the first study in 1999 an instrument developed for adolescents," I think I am", was used to measure self-esteem (Ouvinen-Birgerstam 1999). This instrument was developed by deriving items from well established instruments such as the Piers-Harris Self-Concept Scale and Rosenberg's Self-Esteem Scale. The concordant instrument for adults, "As I see me" (AISM) replaced" I think I am" in this study. These two instruments were developed to be comparable. The questionnaire comprises 78 items intended to measure physical, psychological and social self-esteem on five subscales: Physical index, Skills, Psychological well-being, Relationships with family and Relationship with others. The four-point response scale ranges from -2 to +2 with the alternatives "Exactly like me"," Fairly like me"," Not exactly like me" and "Not at all like me". Total scores range from -156 to 156. Positive scores reflect positive self-esteem and higher scores reflect higher self-esteem. The mean for healthy controls in adolescence and young adulthood is 68.8 (Räty et al. 2003).

	Exactly like me	Fairly like me	Not exactly like me	Not at all like me
I'm proud of my knowledge	2	1	-1	-2
I have made many bad and unwise decisions	-2	-1	1	2
I take care of my body and my appearance	2	1	-1	-2

Table 3 *Examples of questions "As I see me"*

4.2.3 Seizure outcome measures

To describe how well the patients' seizures were controlled, we used a four-degree scale. In the study in 1999 a three-degree scale in accordance with Eriksson (Eriksson 1997) was used. To be more explicit, a fourth group (seizures occurring more than once a week) was added.; (1) Good control: no seizures during the past year; (2) Partial control: one or more seizures during the past year, but not more an one per month; (3) Poor control: more than one seizure per month; (4) Very poor control: more than one seizure per week.

4.3 *Living with epilepsy accompanied by cognitive difficulties: Young adults' experiences (Study III)*

Study III is a qualitative study of the experience of living with epilepsy and subjective cognitive decline. This method was chosen to obtain a deeper meaning of the phenomenon. Data collection was performed during focus group interviews, conducted in a semistructured manner according to an interview guide. The interviews took place in four focus groups, two with women and two with men. The participants were encouraged to narrate their experience of cognitive difficulties while living with epilepsy, but were also free to discuss other subjects important to them.

The tape-recorded interviews were transcribed, and then analysed, in accordance with Graneheim and Lundman's content analysis guidelines (Graneheim and Lundman 2004). The transcripts were first read several times, and then meaning units were identified. The meaning units were condensed without changing their inherent meaning and in the next step these statements were examined and interpreted to establish their deeper meaning. Following this, meaning units with similar content were grouped together into subthemes and finally into themes. Each of these themes reflects the meaning as perceived by the participants of the study.

Text from interview	Condensation	Interpretation	Subtheme	Theme
My phone reminds me when it's time to take my medication otherwise I'd forget to take it anyway and sometimes I can think that I've switched off the alarm after taking the medication and still 2 hours later I'm thinking about it. Did I take my medicine? Yes, you did. You switched off the alarm. But I'm still worried, for like, something that weird.	The strategy is to take the medication when he hears the alarm. Afterwards he can't remember if he really took the medication and is worried about it.	Can't remember if he has taken the medication as prescribed even though he uses a strategy. This causes anxiety.	Strategies can help to overcome memory difficulties but are sometimes difficult to follow.	Epilepsy influencing daily life.
I have always had a great passion for dancing and I still do. But when the epilepsy took over and I had seizures at dance class and my class mates complained that I was difficult, I felt like I couldn't go on so I dropped out.	Dancing was very important in her life, but when she had seizures during dancing lessons she heard the other students complaining about it and therefore stopped dancing.	She had seizures during dancing lessons and her classmates thought this was a problem. She therefore stopped with an activity that meant a lot to her.	Difficulties with personal development and fulfilling dreams in life.	Affects the whole person and results in a struggle to maintain dignity.

Table 4 *Analytical procedure Study III*

4.4 *Cognitive problems in young adults with epilepsy: Language deficits correlate to brain activation and self-esteem (Study IV)*

Study IV is a part of a more comprehensive study on cognition in epilepsy. Apart from language abilities, we also studied different aspects of the human memory representing different parts of the neuronal network. We will in our further studies continue to analyze the semantic and episodic memory, including source monitoring, which will be presented separately.

4.4.1 Neuropsychological investigation in Study IV

We tested fluency and higher language abilities with the help of a subset of tests (FAS and BeSS) from the Test of Language Competence translated into Swedish (Testbatteri för subtila språkstörningar) (Laakso 2000). This battery consisted of the verbal fluency Controlled Oral Word Association Test (COWAT), with the phonemic cue letters F, A and S (here called the FAS test) (Lezak 1983). The participant is asked to generate as many different words (excluding proper names) as possible within one minute. The language assessment also consisted of seven subtasks of the BeSS (Bedömning av Subtila Språkstörningar, 'Assessment of Subtle Language Deficits') battery. The Bess was developed to provide an in-depth assessment of patients with milder but significant language compromise. The BeSS investigates the following abilities:

Repetition of long sentences: The sentences designed to be included in this subtest consist of 9-16 words each. To get the highest score the subject has to repeat the sentence exactly as given.

Recreating sentences: The subject is presented with three keywords and is asked to form a sentence including them. Maximum score is given for a syntactically, semantically and pragmatically correct sentence.

Making inferences: This subtest consists of short passages which the subject may hear or read. Questions are asked that require inferential reasoning.

Comprehension of complex grammatical constructions: This subtest contains ten sentences with complex grammatical construction that are presented verbally twice. The subject is to explain the meaning of the sentence.

Comprehension of ambiguous sentences: Ten sentences with at least two meanings are presented in this subtest. Six sentences contain lexical ambiguities and four syntactical ambiguities. The subject must give two explanations for each sentence.

Comprehension of metaphors: The subject is asked to explain the meaning of ten metaphorical expressions.

Definition of words: Ten words are presented and the subject must give a precise definition.

Each subtest of 10 questions could result in a maximum of 30 points and a total of 210 points for the entire test.

4.4.2 fMRI investigation in Study IV

The functional images were obtained using a gradient echo-based echo planar imaging sequence, sensitive to the blood oxygen level dependent (BOLD) response. The stimuli were presented to the participants using high-resolution video goggles. For experimental design and task presentation the Superlab Pro 4 was used.

4.4.2.1 Language paradigm in Study IV

The fMRI examination consisted of two block design language paradigms: sentence reading (SEN) and word fluency (WORD). The SEN paradigm consisted of blocks in which the participants read sentences with either logical (easy condition) or illogical (hard condition) sentences. These blocks were alternated with control blocks showing signs or arrows. To check whether the participants had read the sentence they were asked to described whether an event took place indoors or outdoors. Reaction time to answer was recorded. In the WORD paradigm the participants were instructed to silently generate a word cued by a visually presented letter. The letter used occur frequently (easy condition) or infrequently (hard condition) in the Swedish dictionary. The number of correct answers was counted. The letters were presented in six blocks for each condition, each containing seven letters. This was alternated with control blocks showing a number or a star.

4.4.2.2 Image analysis in Study IV

Analysis of the fMRI data were performed using SPM8. The statistical differences between task compared to baseline and between the difficult task compared to the easier task were estimated for the two paradigms. These data were entered in an analysis of variance test (ANOVA) with four cells; controls, GE, LHE and RHE. The result of the ANOVA were corrected for small volumes according to our predefined regions of interest (ROIs). The ROIs were the anterior mid-cingulate cortex (aMCC); three regions in the inferior frontal gyrus (IFG) namely pars opercularis (Brodmann area, or BA, 44), pars triangularis (BA45) and pars orbitalis (BA47); two regions in the insulae namely the anterior ventral insula (vAIC) and the anterior dorsal insula; and lastly Wernicke's area, defined as the superior and middle temporal gyri combined (BA21 and BA22). This resulted in seven ROIs in each hemisphere. Results of the post-hoc t-test corrected for small volumes that were significant at peak-level threshold $p<0.05$, with family wise error rate (FEW) correction are reported.

4.4.3 Psychosocial investigations in Study IV

4.4.3.1 Quality of Life Index (QLI)

The instrument was the same as that used in Study I (see 4.1.3)

4.4.3.2 Self-esteem questionnaire

The instrument was the same as that in Study II (see 4.2.2)

4.5 Data analysis and Statistics

For statistical evaluations, SPSS (Statistical Program for the Social Sciences 12.0, 15.0 and 18.0), was used in Study I, II and IV. Significance was assumed for p-values <0.05.

In Study I and II frequencies were calculated and cross-tabulations were carried out. When non-parametric methods were applied the Mann-Whitney U-test and the Kruskal Wallis test were used. The Wilcoxon signed-ranks test was used for comparison between dependent groups over time. For correlations on an ordinal level Spearman's rho was used for assessing correlation between data. Parametric methods were used when the item response scale had sufficient variation to be regarded as interval data and the group studies were large with approximately normal distribution.

Study III used a qualitative method and content analysis and no statistical analysis was performed.

In paper IV both parametric and non parametric methods were applied. For the fMRI analysis in Study IV, the contrast files were entered into ANOVA with a cell for controls and one for each subtype of epilepsy. The results that were significant at peak-level threshold were investigated using post hoc tests for differences between groups. Significant results of the post hoc t-test corrected for small volumes at peak-level threshold $p<0.05$ with a family-wise error rate correction are reported. For parametric values, independent samples t-test and one-way ANOVA were performed and then a linear multiple regression analysis was carried out including the variables measured in the study. When non-parametrical statistics were applied, the Mann-Whitney U-test was used for comparisons between groups and for correlations on an ordinal and nominal level according to Spearman's rho.

5 Results

5.1 Medical outcome in epilepsy patients of young adulthood – A 5-year follow-up study (Study I)

The five-year follow up study on young adults (aged 18-27 years) with uncomplicated epilepsy showed that 21.6% considered themselves to have recovered from epilepsy. Most of these participants had also been seizure-free five years earlier. The remaining participants suffering from epilepsy used the following AEDs.
Old-generation AEDs: CBZ, PHE, VPA
New-generation AEDs: LTG, OXC, Vigabatrin, GAB, LEV, TPM

In the group that still had epilepsy, 25% used di- or polytherapy and 75% were being treated through monotherapy. In this group there was no significant change in seizure frequency compared with the investigation five years earlier. Of these participants 42,1% reported having experienced seizures during the past year despite the fact that everyone except one person used AEDs. We have not investigated how many AEDs each participant had been prescribed over the years, but most of them must probably be therapy-resistant. A smaller group (15.8%) reported having seizures at least every month. Three people had been treated with surgery of epilepsy focus and three had had a Vagal Nerve Stimulator implanted. The use of new-generation AEDs increased between the years of the study (1999-2004) ($p<0.05$). More female participants had received treatment with new-generation AEDs than men had ($p<0.05$). The most common new drug was LTG which was used by more than half the women (women 54%, men 33%). More men than women were prescribed monotherapy with a traditional AED ($p<0.05$) and more men also reported having been seizure-free during the past year ($p<0.05$). Of the group using AEDs, 82% experienced side effects, tiredness was the most common side effect reported.

The reported mean QLI index score was 21.87 (Std=3.87). Participants who had recovered from epilepsy had better QoL ($p<0.05$), while the group with the highest seizure frequency (at least every month) had lower QoL ($p<0.05$). Participants with di- or polytherapy scored lower than participants with monotherapy ($p<0.05$). There was no association between QoL and the presence of side effects in general, but the group reporting cognitive side effects as irritability, memory and concentration deficits, scored lower than those who did not ($p<0.05$).

5.2 Self-esteem and Sense of Coherence in young people with uncomplicated epilepsy: A 5-year follow-up (Study II)

During the five-year study period (1999-2004) both SOC and self-esteem decreased for the whole group ($p<0.05$). Participants who had recovered from epilepsy had significantly better self-esteem than those who had not recovered ($p<0.001$). Participants with the highest seizure frequency, had the lowest self-esteem ($p<0.05$) The group with increasing self-esteem during this five-year period had better seizure control than the other participants ($p<0.05$). Self-esteem was also lower in the group that had experienced side effects from AEDs ($p<0.05$). Participants who were seizure-free scored higher on SOC than did those who still had seizures ($p<0.05$). There was no correlation between SOC and seizure frequency. Participants with poly-therapy had significantly lower scores for SOC than did those on mono therapy ($p<0.001$).

5.3 Living with epilepsy accompanied by cognitive difficulties: Young adults' experiences (Study III)

The analysis of the interviews revealed the following key issues of living with epilepsy and subjective cognitive decline as reflected in the following themes 1) Affecting the whole person, 2) Influencing daily life, 3) Affecting relationships, 4) Meeting ignorance in society.

The themes illustrated different hardships faced by the participants. A person affected by epilepsy struggles with many different problems: seizures are just one of them. Cognitive problems had an important impact on the lives of the participants. They truly fought to maintain their independence and dignity despite the disease but this involved great effort.

Affecting the whole person
The participants experienced that the epilepsy had changed so may aspects in their life that their whole person had been affected. Without epilepsy they would have developed into someone else, another person. Academic underachievement was pointed out as an important factor in the failure to reach their goals in life. Fatigue was also one reason why they had to lower their ambitions.

Influencing daily life
Cognitive problems, large or small, had an impact on the lives of all participants. Negative consequences on employment and social relationships were highlighted as important. The problems were consistent and the consequences increased with time. Memory was influenced by seizures and was worse the days that seizures occurred. Different strategies, such as daily routines, notes or frequent use of the cell phone, were used to compensate for cognitive problems.

Affecting relationships
Epilepsy affected relationships with both family and friends. The participants expressed that it was difficult to establish friendships because of the epilepsy. Close relationships were also affected by the cognitive problems and misunderstandings often occurred. They sometimes felt guilty from the feeling of being a burden to the family. Living with guilt is an additional burden on the person with epilepsy.

Meeting ignorance in the society
Many participants felt alone in facing their problems, and expressed gratitude at meeting people with similar experiences as they could not always share these feelings with their relatives. They expressed the need for more education about epilepsy to the general public, as well as employers and schools since they often encountered ignorance.

5.4 Cognitive problems in young adults with epilepsy: Language deficits correlate to brain activation and self-esteem (Study IV)

5.4.1 Neurocognitive results

Performance on the BeSS and FAS was significantly lower for PWE than for controls (BeSS: $t(49) = 2.013$ $p < 0.05$; FAS: $t(49) = 4.564$, $p < 0.001$). There was no difference between different classifications of epilepsy. The BeSS score revealed a bisection in the PWE group.

A multiple regression analysis showed that education and age at onset predicted BeSS performance, but did not fully explain the bivariate distribution. We then divided the PWE into two groups split at the mean BeSS score, with 13 PWE in the high-scoring group and 15 in the low-scoring group, and compared the groups for the predictor variables with the non-parametric Mann-Whitney U-test. PWE in the low-scoring group had a higher number of convulsive seizures ($U = 36, 5$, $z = -3$, $p < 0.05$). Results regarding FAS showed that PWE using TPM or ZNS scored lower on FAS than did participants not using these AEDs ($U = 18.5$; $z = -3$, $p < 0.05$) (Mann-Whitney).

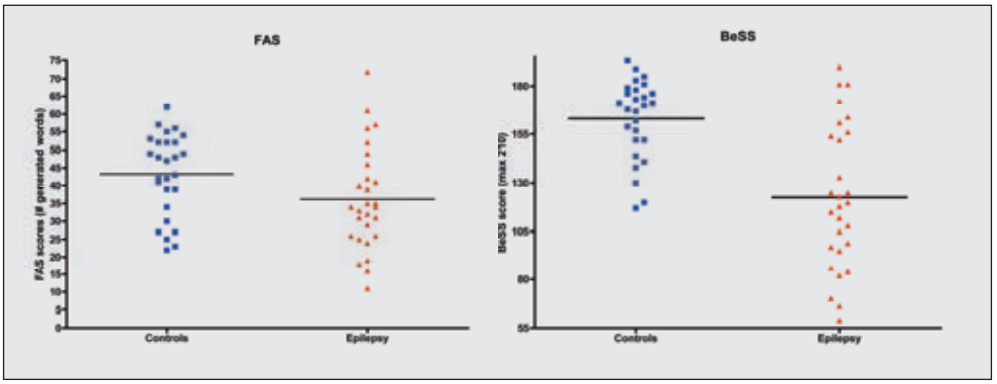

Figure 2 *Left: Graph of FAS scores (number of generated words) for healthy control group and the group with people with epilepsy. The horizontal line depicts the mean for each group.*

Figure 3 *Right: Graph of BeSS scores (out of a maximum of 210 points) for the healthy control group and the group of people with epilepsy.*
The horizontal lines depict the mean for each group.

	Focal seizure right hemisphere n = 9	Focal seizure left hemisphere n = 9	Generalized epilepsy n = 11	Healthy controls n = 27
BeSS	128.2 (59-181) std 47.5	117.6 (84-190) std 32.2	122.6 (66-181) std 35.6	163.1 (117-193) std 20.4
FAS	41.2 (18-72) std 18.9	33.6 (16-56) std 12.2	34.7 (11-57) std 12.7	43.3 (22-62) std 11.5
Reaction time SEN baseline (ms)	817 (594-1146) std 183.9	742 (624-999) std 115.1	869 (735-1400) std 190.5	694 (550-825) std 81.5
QoL	18.5 (12.8-21.8) std 2.9	17.1 (7.5-23.6) std 5.2	22.7 (20.7-26.2) std 2.0	21.9 (10.6-26.8) std 3.5
AISM	46.6 (-12-106) std 40.0	26.1 (-53-112) std 51.1	88.3 (58-118) std 20.2	101.6 (52-133) std 20.7
Topiramate /zonisamide (n)	3	3	1	0

Table 5 *Language performance, reaction time regarding language comprehension, psychosocial data and use of topiramat/zonisamide in participants with different classification of epilepsy and healthy controls. BeSS: Assessment of subtle language deficits, FAS: Controlled oral Word Association Test. AISM: As I see me. Std: Standard deviation.*

5.4.2 Neuroimage results in Study IV

Brain activity for both participants with epilepsy and controls, showed activation for SEN paradigm in the left hemisphere in the Inferior frontal gyrus (IFG), the superior and middle temporal gyri, the fusiform gyri and the anterior cingulate cortex, continuing to the supplementary motor area. In the right hemisphere additional activation was observed in IFG.

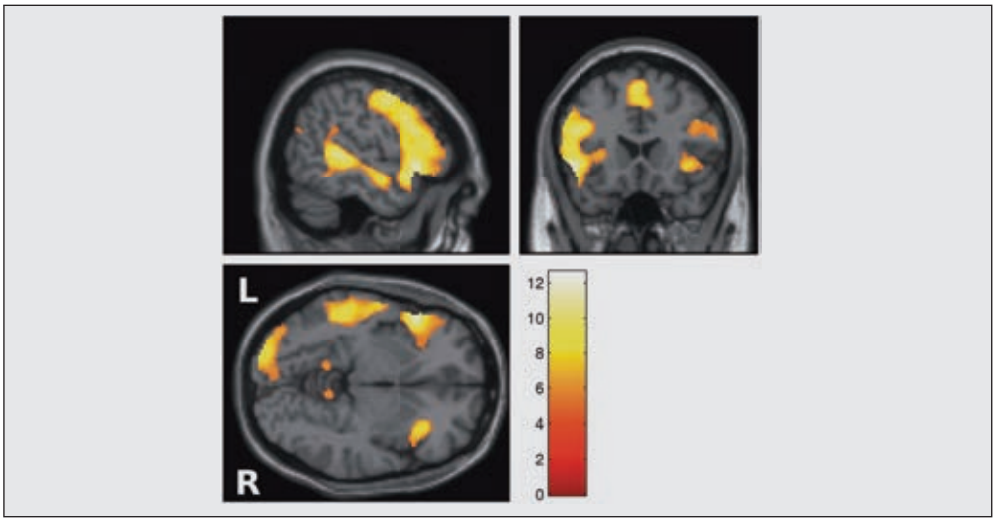

Figure 4 *Activation for language comprehension paradigm (SEN) for participants with epilepsy and healthy controls.*

Activation for WORD paradigm for participants with epilepsy and controls together, showed left-hemispheric activation in the IFG and adjacent frontal regions, medially in the middle frontal gyrus, the putamen and the thalamus. Bilateral activation was also observed in the

anterior cingulate cortex (acc) continuing to the supplementary motor area, the anterior insula, the lateral fusiform gyrus and the superior cerebellum. The healthy controls showed additional activation in the superior intraparietal sulcus.

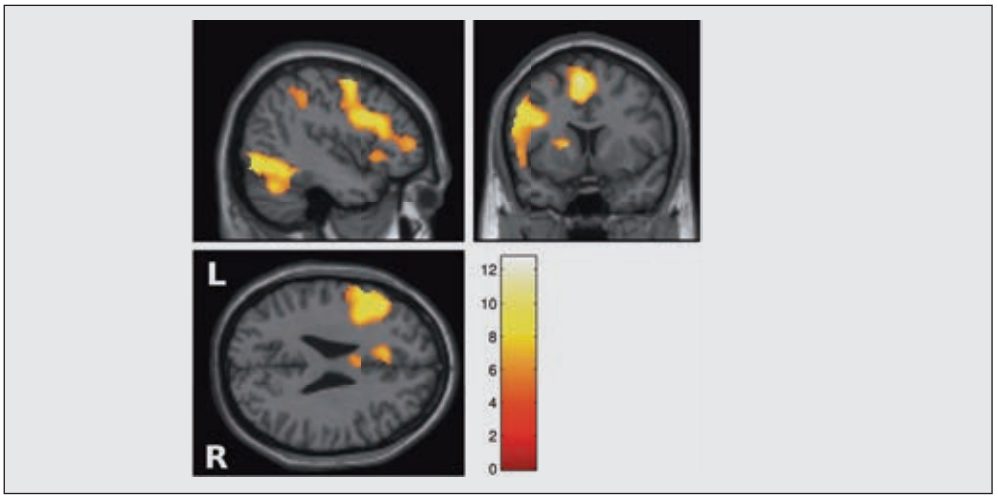

Figure 6 *Activation for verbal fluency paradigm (WORD) for participants with epilepsy and healthy controls.*

Brain activation for ANOVA differences for the different tasks and the difficulty contrasts are described in table 6.

fMRI Paradigm Contrasts	Groups	Location	BA	MNI coordinates x	y	z	Cluster Size (voxels)
SEN Task > Baseline	RHE > GE	left STG/MTG post	21	-54	-42	8	141
	GE > controls	left STG ant	22	-52	-8	0	106
	GE > LHE	left STG ant	22	-50	-8	0	110
WORD task > Baseline	PWE > controls	right IFG pars orb	47	36	16	-24	23
		left STG	22	-46	-16	8	219
		left aMCC	32	0	32	30	130
		right aMCC	32	4	34	34	269
	LHE + RHE > controls	right IFG pars orb	47	36	16	-24	21
		left STG	22	-46	-18	6	180
	LHE > controls	left aMCC	32	0	32	30	90
		right aMCC	32	2	34	30	116
	LHE > GE	left aMCC	32	-2	32	28	60
		right aMCC	32	4	38	28	16
WORD Difficulty Hard > Easy	PWE > controls	left aMCC	32	0	20	20	29
	LHE > controls	left vAIC	-	-36	14	-10	30
		left aMCC	32	0	22	18	19
	LHE > RHE	left vAIC	-	-34	16	-10	29

Table 6 *Results for post-hoc t-tests on the 4-group ANOVA (healthy controls, people with generalized epilepsy – GE, people with seizures focalized in the left hemisphere – LHE or in the right hemisphere – RHE), for the contrast of interest on the fMRI paradigms WORD and SEN. The presented t-test results survived a threshold of p = 0.05, Family-wise Error (FWE) rate corrected after being selected from the ANOVA at threshold p = 0.01 uncorrected. Task = task > baseline contrast, Difficulty = hard > easy contrast, PWE = people with epilepsy, STG = superior temporal gyrus, MTG = middle temporal gyrus, post = posterior, ant = anterior, IFG pars orb = inferior frontal gyrus – pars orbitalis, aMCC = anterior mid-cingulate cortex, vAIC = ventral anterior insular cortex, BA = Brodmann area, MNI coordinates = millimeter coordinates of activated brain regions reported in the Montreal Neurological Institute system, Cluster size = number of activated voxels.*

For the language comprehension task (SEN) a cluster in the left anterior superior temporal gyrus showed increased activation for PWE in the generalized epilepsy group compared to both groups with focal onset seizure and the control group (See figure 7 and 8). This is an area that shows significant deactivation in the both epilepsy with focal onset seizures and in healthy controls, thus denoting a lack of deactivation in the GE group.

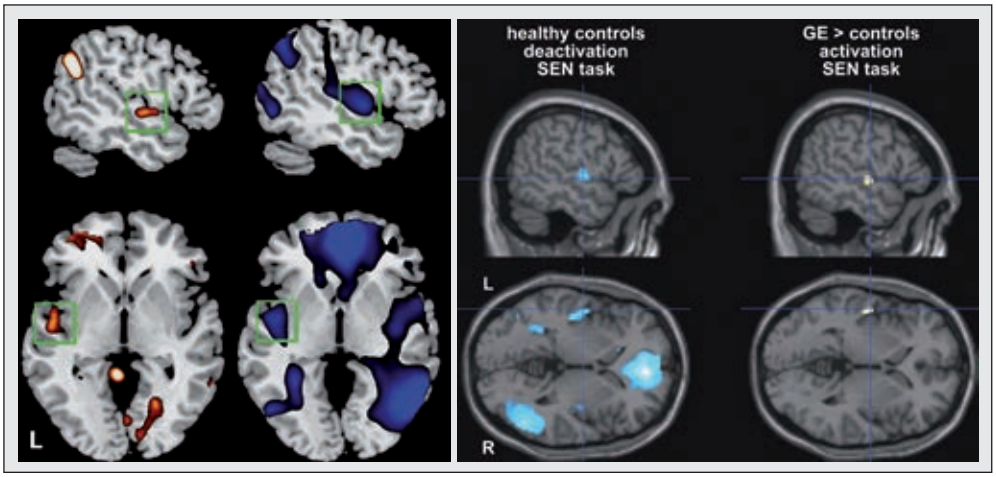

Figure 7 *Left: Language comprehension task for participants with generalized epilepsy (left in red). The left anterior superior temporal gyrus showed additional activation for participants with generalized epilepsy compared to both participants with focal onset seizures left hemisphere and healthy controls that showed deactivation (right in blue).*

Figure 8 *Right: fMRI deactivation of the healthy control group during the SEN task contrast (task > baseline). fMRI activation of the GE group contrasted to the healthy control group during the SEN task contrast. The images are thresholded at p = 0.001 uncorrected. The region under the cross-line fell in the Wernicke ROI and was significant after small volume correction at a threshold of p = 0.05 FWE corrected (for both images/comparisons).*

There were no differences found between epilepsy participants and healthy controls for the contrast between hard and easy condition regarding language comprehension.

During the verbal fluency task (SEN) increased activation was found in the right IFG, left superior temporal gyrus and bilateral aMCC when the epilepsy group was compared to healthy controls.

Participants with focal onset seizure left hemisphere exhibited compared to controls and to the group with generalized epilepsy increased activation in bilateral aMCC. See figure 9.

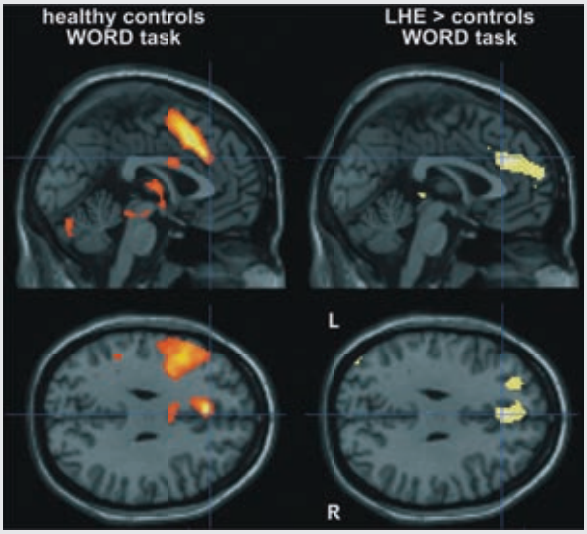

Figure 9 *Left: fMRI activation of the healthy control group during the WORD task contrast (task > baseline). Right: fMRI activation of the LHE group contrasted to the healthy control group during the WORD task contrast. The images are thresholded at p = 0.001 uncorrected. The peak activation under the cross-line fell in the mACC ROI and was significant after small volume correction (for the ROI) at a threshold of p = 0.05 FWE corrected (for both images/comparisons).*

For the verbal fluency difficulty contrast the participants with focal seizure onset left hemisphere had increased activation in left vAIC compared to controls and participants with focal onset seizures right hemisphere. See figure 10.

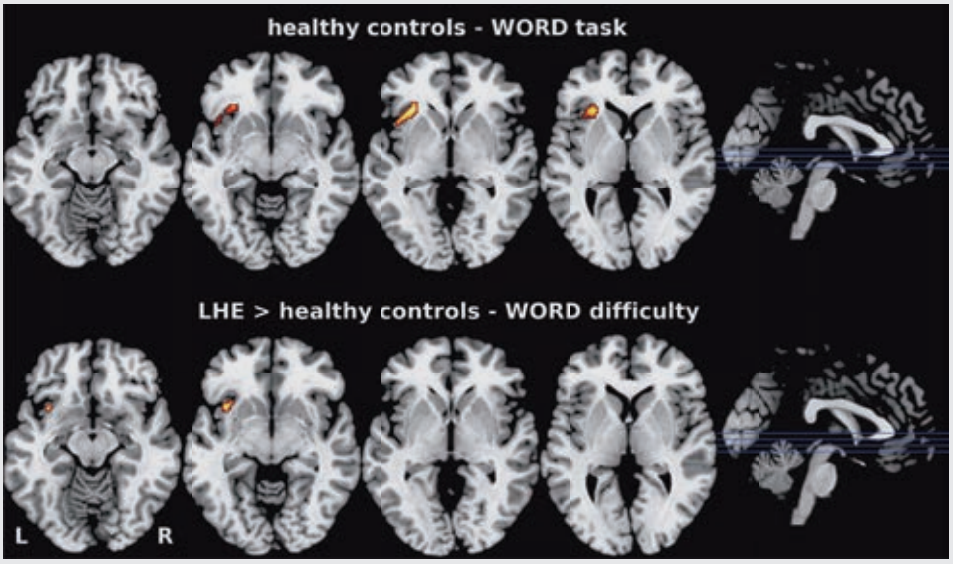

Figure 10 *Top: fMRI activation of the healthy control group during the WORD task contrast (task > baseline). Bottom: fMRI activation of LHE contrasted to healthy control group during the WORD difficulty contrast (hard > easy). The images show significant activation after applying the ventral and dorsal anterior insula ROIs with small volume correction, p < 0.05, FWE-corrected.*

5.4.3 Results on Quality of Life and Self-esteem

The epilepsy group had impaired QoL (U = 148, z = -2, p<0.05) as well as self-esteem (U = 100, z = -4 , p <0.001) compared to healthy controls. This result was explained by significantly impaired scores in participants with focal seizures, QoL (U = 63, z = -3, p<0.05) and self-esteem (U = 32, z = -5, p<0.001) compared to controls. This group also had impaired results compared to the generalized epilepsy patients for both parameters, QoL (U = 10.0, z = -3, p<0.05) and self-esteem (U = 20.5, z = -3, p<0.05). However, participants with GE had normal QoL and self-esteem compared to controls.

There was a correlation between abstract language comprehension (BeSS) and low self-esteem (p<0.05) for participants with focal onset seizures. There was no correlation between result on language investigation and QoL.

		Self-esteem			**Quality of Life**	
	healthy controls	**focal onset seizures**	**generalized epilepsy**	**healthy controls**	**focal onset seizures**	**generalized epilepsy**
Result on BeSS	p = 0.83 CC = -0.47	p = 0.004 CC = 0.65	p = 0.89 CC = 0.50	p = 0.63 CC=-1.14	p = 0.35 CC = 0.24	p = 0.91 CC = 0.48
Result on FAS	p = 0.15 CC = 0.30	p = 0.75 CC = 0.84	p = 0.80 CC = -0.10	p = 0.63 CC = -0.11	P = 0.30 CC = -0.26	p = 0.86 CC = 0.72

Table 7 *Correlation (Spearman's rho) between result on language tests (BeSS or FAS) and psychosocial variables. CC=Correlation coefficient.*

6 Discussion

6.1 Medical outcome in epilepsy patients of young adulthood – A 5-year follow-up study (Study I)

Study I was performed between 1999 and 2004. During this period new-generation AEDs, for example LTG was introduced and this was especially true for female patients. In 2007 the results of the SANAD study, whose primary outcome was time to treatment failure, were published. They showed that VPA was more efficacious than LTG for generalized seizures (Marson et al. 2007b) but that LTG was superior to CBZ for focal seizures (Marson et al. 2007a). The group studied in Study I had a high representation of generalized epilepsy, which could be one explanation for why we found no improvement in efficacy of treatment in this study. Stephen and colleagues have recently investigated different combinations of AEDs, including new-generation AEDs, and conclude that these have not had a substantial impact on the overall outcome for patients with epilepsy (Stephen et al. 2012). Nor do newer AEDs improve the outcome in status epilepticus (Jaques and Rossetti 2012). Giliolo and co-workers, on the on the other hand, state that a small percentage of patients with therapy-resistant epilepsy reached seizure freedom after trying several AEDs (including new AEDs), suggesting that it is possible to achieve seizure control (Giliolo et al 2012). Since there is still no real solution to therapy-resistant seizures there is a need for new innovative strategies for developing new drugs and methods.

The impact of epilepsy varies over a lifetime and people of higher age seem to be better able to cope with the consequences of epilepsy and to have a less compromised QoL (Pugh et al. 2005). Therefore it is reasonable to assume that QoL will increase or stabilize as one gets older. This was also true for the participants in Study I who had normal QoL compared to healthy controls. Seizure-frequency and cognitive side effects were both associated with lower QoL. However, compared to other medical conditions epilepsy seems to have a high impact on QoL. Occasional focal seizures have the same negative impact as myocardial infarction or

congestive heart failure and even only auras compromise the lives of PWE as much as diabetes mellitus (Vickrey et al. 1994). Patients who fail the initial AED trial after diagnosis are at an increased risk of experiencing impaired health outcome for many years, than are patients who respond to the first AED tried (Perucca et al. 2011).

The AEDs presently available do not have the capacity to prevent all seizures and also not to change the pathogenic process of epilepsy. New potential mechanisms must therefore be sought. To discover therapies that have the ability to prevent, delay or modify epilepsy, further research into the pathophysiological basis of the disease is necessary (Bialer and White 2010). Promoting a better understanding of the molecular and genetic basis of the different seizure types and syndromes will probably be necessary to find better treatment options. There is no evidence that the new generation AEDs have improved efficacy for the whole epilepsy population.

6.2 *Self-esteem and sense of coherence in young people with uncomplicated epilepsy: A 5-year follow-up (Study II)*

SOC is rather stable in adulthood according, to Antonovsky, but in this study, a decline among young PWE was seen in adolescence or early adulthood. SOC is not clearly associated with epilepsy-related factors, even though participants who were seizure-free had a higher SOC than those who were not. We interpret the results concerning SOC as a mirror of the phenomenon of epilepsy, and this result adds to the burden of epilepsy as it leads to a lower ability to cope with difficult situations in life. We regard self-esteem as a measure that is more easily affected by circumstances in life than SOC is. Self-esteem is correlated to present epilepsy-related variables like seizure frequency and side effects of AEDs. Compromised self-esteem may have an impact on the ability to cope with different hardship in life and the possibility to discover future opportunities. Therefore it is more than one factor that PWE have to overcome to reach their goals in life. Each and every obstructing factor can have a small but substantial impact on the possibility to live a fulfilling life and self-esteem seems to be one of these factors.

6.3 *Living with epilepsy accompanied by cognitive difficulties: Young adults' experiences (Study III)*

The consequences of epilepsy are not only restricted to the consequences of seizures but concern many other aspects in life as well. The participants in the focus group interviews (epilepsy with subjective cognitive decline) expressed that epilepsy causes changes in so many aspects of life that it affects the whole person. The daily lives of young adults with epilepsy can be affected by seizures, but they can also be affected by subjective cognitive decline. If one experiences cognitive decline it is ever-present, while seizures are intermittent. The problem is consistent and the experience of those affected is that the consequences increase over time. Strategies like taking notes, using cell phones and establishing strict routines are important methods for trying to overcome this problem. The experience was also that epilepsy affected relationships with family and friends. Close friendship was more difficult because of epilepsy and cognitive decline. Feelings of dependency on relatives were common, as were feelings of guilt. Losing some one's language function gives a feeling of losing one's capability.

Meeting other people with similar problems was very important for the participants in the focus group interviews. Comprehensive intervention programmes that address psychosocial aspects, medical information and support for both the affected individual an to his or her family would be beneficiary to young adults with epilepsy. It provides information, increases coping levels and motivate those affected to learn more about the diagnosis. Many participants expressed that the most important thing was meeting other PWE. A multidisciplinary team is present today at neurological clinics, but more resources would benefit the young adults who need the help of this team. There is a need for neuro-rehabilitation to treat cognitive handicaps: for example, memory training and the demonstration of strategies would help in daily life of these young adults. They would also benefit from additional help in finding reachable goals in life. Guidance in possible education and career options, but also discussions about what is not suitable, could hinder future disappointments. To study the impact of epilepsy from the patient's perspective and to determine the content validity of HRQoL, PWE have been asked to list factors of importance of living with epilepsy. The most mentioned concerns were driving, independence and employment (Gilliam et al. 1997). These factors were also mentioned by especially men in the focus groups interviews. Being able to do what they were restricted from doing was very important for achieving freedom and independence. The interviews also showed that loosing language functions were debilitating. It was described as it was like loosing capability, or to lose a part of one's self.

6.4 Cognitive problems in young adults with epilepsy: Language deficits correlate to brain activation and self-esteem (Study IV)

Language was negatively affected in patients with both GE and in epilepsy with focal origin and it is important to address language function in all patients with epilepsy. Subtle language deficits are not always noticed in a conversation, but a neuropsychological investigation is required to disclose the decline in language function. These subtle deficits are however often noticed by the patient and can impact on the daily life negatively. In this study PWE with focal onset seizures had lower language comprehension and lower self-esteem than controls. We could however not find that QoL was correlated to language deficits. It could be that self-esteem is a more sensitive measure than QoL and that self-esteem should be continuously measured to detect early changes, to be able to foresee and hopefully prevent future psychosocial consequences.

The fMRI analysis revealed a different pattern for the LHE group which we interpret as functional reorganization. A striking finding was that this group exhibited increased activation in bilateral aMCC. This area is normally activated in many cognitive tasks, and is increasingly activated when a task is more demanding and requires more effort. In this group several patients had undergone a temporal lobe resection which could contribute to these findings. The LHE group also exhibited increased activation in ventral anterior insula at more strenuous verbal fluency tasks. This finding is more difficult to understand since ventral insula is most often attributed to emotional responses. Could it be that a more strenuous and difficult task also give rise to mixed emotions that are exhibited in the fMRI? Another explanation could be functional reorganization, the neural response to cognitive demand, which could be attributed to the dorsal AIC, might be extended to the adjacent vAIC in focal onset seizures left hemisphere. The dorsal region of insula is linking information between different functional

systems and have previously shown increased activation at more difficult tasks. In GE the functional language network showed an imbalance since this group expressed an inadequate suppression of activation in the anterior temporal lobe during semantic processing. McGill studied the default mode network, which is a task-negative network, and found reduced functional connectivity in GE, which relates to our finding of reduced deactivation in GE (McGill et al 2012). White and grey matter abnormalities have been demonstrated in GE (Bernhardt et al. 2009; Ciumas and Savic 2006; Doelken et al. 2010). One possible explanation for these findings is that these structural changes are secondary to repeated seizures. Liu et al. recently showed white matter changes in juvenile myoclonic epilepsy but not in generalized epilepsy, generalized tonic-clonic seizures only, and potential grey matter abnormalities in both juvenile myoclonic epilepsy and generalized epilepsy, generalized tonic-clonic seizures only, but saw no correlation to number of experienced seizures and stated that these two entities can be associated with distinctly different anatomic substrates (Liu et al. 2011). Impaired white matter connectivity has also been demonstrated as an explanation for cognitive decline in patients with focal epilepsy (Vaessen et al. 2011). Ipsilateral projection of the hippocampus to the insula has been shown in epilepsy patients (Catenoix et al. 2011), and the projection to the insula might be altered in participants with right TLE. Recently altered functional connectivity have been demonstrated in mTLE and these findings may explain cognitive impairment in mTLE (Pittau et al. 2012).

Even though only a small number of participants used TPM or ZNS, a correlation was found between use of these sulfa-containing AEDs and impaired verbal fluency. Most of these patients had therapy resistant epilepsy which can be a confounding factor. The effect of TPM on fMRI activation pattern have been evaluated by Jansen et al who found declined prefrontal cortex activation in patients with TPM therapy (Jansen 2006). Szaflarski showed a dose dependent effect on fMRI activation by TPM (Szlaflarski and Allendorfer 2012).

6.5 Limitations to the study

In none of the studies in this thesis are the participants representative of the whole epilepsy population in this age group. The participants in Study I and II were selected because they were classified as uncomplicated. Among the patients excluded were many with different comorbidities who probably have an even more difficult situation regarding both epilepsy-related factors and their psychosocial situation. The participants in Study III all had subjective cognitive decline and many, but not all, had therapy-resistant epilepsy. They represent a group with a heavier burden of disease.

The participants in Study IV were a more heterogeneous group comprising both people with therapy- resistant epilepsy and with subjective cognitive impairments, but also people who were seizure-free and had no subjective problems. However they were recruited from a specialized centre at the university hospital and are not likely representative of the whole population either.

The number of participants was relatively small in these studies. In the qualitative study (III) the identified themes reflect the view of a relatively small number of people. However, the number of participants in other qualitative studies is comparable to the number in this study. In Study I and II, non parametric statistical methods were mainly applied. These were chosen

since many variables were considered ordinal. It could have been possible to use parametric methods for some variables like seizure frequency, SOC and self-esteem, but we chose not to do so because the seizure frequency was a retrospective estimation: we chose instead to group this information and use an ordinal scale. However a parametric method as a multiple regression analysis could have yielded more information.

There are several methodological difficulties in the fMRI investigation that can affect the result. Language was not performed during the fMRI investigation since this would give rise to movements. To silently generate words is close to language performance, but not necessarily exactly the same. The paradigm is the key to the result and must be carefully chosen. It is really important that the participant understands the task, otherwise the fMRI will reveal other functional activity than the investigator intend to measure. The choice of the best analysis threshold of language fMRI signals is also a difficult matter, since the results strongly depend on which threshold is chosen.

7 Conclusions

We have studied the medical and psychosocial consequences of epilepsy among young adults with a focus on cognitive dysfunction, including language.

We did not find an improvement regarding seizure frequency or side effects from AEDs over time in young adults with epilepsy in the five-year follow up study, even though many new-generation AEDs had been established during this period. Female patients were prescribed new-generation AEDs, preferably lamotrigine, more frequently than men. There is still a demand for new treatment options for epilepsy.

We observed that QoL for young adults with uncomplicated epilepsy was normal, but higher seizure frequency and cognitive side effects were associated with lower QoL.

Self-esteem and Sense of Coherence (SOC) decreased over time in young adults with epilepsy during the five-year study period. SOC was higher for seizure free participants but showed no correlation to seizure frequency or side effects of AEDs in those who still had seizures. Self-esteem was correlated to seizure frequency and side-effects.

The focus group interviews with young adults with epilepsy and subjective cognitive decline revealed some problematic domains with four themes regarding their condition: 'Affecting the whole person'', ''Influencing daily life'', ''Affecting relationships'' and "Meeting ignorance in the society''. The participants expressed that epilepsy affected their whole personality, without epilepsy they would have been some one else. The participants desiderated educational programmes for young adults with epilepsy, as well as information campaigns for the general public regarding epilepsy. Cognitive problems as language impairments affected daily life and required the use of planned strategies.

We found that language function is impaired in both generalized epilepsy and epilepsy with focal onset. The most important factors affecting language functions are age at onset of epilepsy and education. Another factor that impacts abstract language comprehension is frequency of convulsive seizures, while verbal fluency is affected by use of topiramate/ zonisamide. Subtle language impairment can be difficult to discover, but must be addressed in young people with epilepsy.

We confirmed altered brain activation in both focal onset seizures and generalized epilepsy during language tasks. In epilepsy with focal seizures originating in the left hemisphere we found increased bilateral activation of supporting areas, that is in the anterior mid-cingulate cortex and the anterior ventral insulae, indicating a compensational functional reorganization. In generalized epilepsy the functional language network showed an imbalance, as this group expressed an inadequate suppression of activation in the anterior temporal lobe during semantic processing.

8 Future perspectives

The working group on recommendations for preclinical epilepsy drug discovery writes in 2012 that there is an urgent demand for 1) new symptomatic antiseizure treatment for drug-resistant seizures with improved efficacy and tolerability profiles, 2) disease-modifying treatments that prevent or ameliorate the process of epileptogenesis and 3) treatment for the common comorbidities (Galanopoulou et al. 2012). Löscher claims that all new AEDs have been discovered using the same animal models and have not shown higher efficiency in therapy-resistant epilepsy than earlier AEDs (Loscher and Schmidt 2011). It is necessary to develop drugs that target the underlying disease. Epileptogenesis is a process that changes neuronal excitability before a seizure occurs. Animal studies indicate that this process can be modified and that it may be possible to find treatment in the future (Pitkanen and Lukasiuk 2011). Another new strategy is the methylation hypothesis which suggests that seizures themselves can induce epigenetic chromatin modifications (Kobow and Blumcke 2011). Epigenetic refers to information that is inheritable besides the DNA sequences themselves. Hopefully, this can identify molecular targets for pharmacologic treatment. Other future possible therapies are stem cell therapy and gene therapy (Naegele et al. 2010). Inflammation has also been revealed as one possible factor in the mechanism behind epileptogenesis. Inflammatory cytokines such as interleukin-1beta, tumor necrosis factor and interleukin-6, can contribute to an acute excitability of neurons and play a role in the development of the epilepsy (Friedman and Dingledine 2011). A disease-modifying drug that regulates inflammation to reduce the frequency or intensity of seizures could be an option in the future (Vezzani et al. 2012).

The present research also points to the need for cognitive and psychosocial interventions for young adults with epilepsy. The cognitive difficulties, including impaired language function, arise already in childhood and the person affected has to fight these obstacles for their whole life. Low onset age of epilepsy negatively impacts language function so possibly are young children with epilepsy the ones that would benefit the most from intervention. Adolescents have more language impairments and linguistic deficits compared to younger children (Ca-

plan et al. 2009) indicating the usefulness of early intervention. One could assume that when adulthood is reached the cognitive problems are already manifest, but linguistic training and strategies can possibly still improve language ability. Better diagnostic tools to identify the exact nature of cognitive decline are required. If it would be possible to detect subtle changes in an early stage intervention could be performed, one could speculate that fMRI could be used for this purpose in the future.

To regularly administer support in school for children with epilepsy could improve the situation, but also on the other hand increase the feeling of stigma. At adulthood when the situation in life often requires more efforts from each and everyone, young adults with epilepsy would benefit from more support than they receive at present, and possibly have a more positive attitude to interventions when they have reached a higher age. The participants of young adulthood in these studies recommend more information about epilepsy to the general public, but are also themselves interested in taking part in interventions in the future. Future interventions should be evaluated to find the best treatment options for young adults with epilepsy.

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