DISSERTATIONES
NEUROSCIENTIAE
UNIVERSITATIS
TARTUENSIS
20

MAARIKA LIIK

Cognitive functioning, perceived cognition, subjective complaints and symptoms of depression in patients with epilepsy: Neuropsychological assessment and SPET brain imaging study

DISSERTATIONES NEUROSCIENTIAE UNIVERSITATIS TARTUENSIS
20

DISSERTATIONES NEUROSCIENTIAE UNIVERSITATIS TARTUENSIS
20

MAARIKA LIIK

Cognitive functioning, perceived cognition, subjective complaints and symptoms of depression in patients with epilepsy: Neuropsychological assessment and SPET brain imaging study

UNIVERSITY OF TARTU
PRESS
1632

Department of Neurology and Neurosurgery, University of Tartu, Tartu, Estonia

Dissertation was accepted for the commencement of the degree of Doctor of Philosophy (Neurosciences) on June 4th, 2014 by the Council of the Commencement of Doctoral Degree in Neuroscience

Supervisor: Associate Professor Sulev Haldre MD, PhD, Department of Neurology and Neurosurgery, University of Tartu, Estonia

Reviewers: Professor Veiko Vasar, MD, PhD, Department of Psychiatry, University of Tartu, Estonia

Associate Professor Janika Kõrv, MD, PhD, Department of Neurology and Neurosurgery, University of Tartu, Estonia

Opponent: Professor Reetta Kälviäinen, MD, PhD, Department of Neurology, University of Eastern Finland, Kupio, Finland

Commencement: August 27th, 2014

Publication of this dissertation is granted by the University of Tartu.

The research was supported by the European Union through the European Social Fund.

ISSN 1736-2792
ISBN 978-9949-32-611-2 (print)
ISBN 978-9949-32-612-9 (pdf)

University of Tartu Press
www.tyk.ee

Dedicated to

Ruth Soekõrv

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

I Liik M, Vahter L, Gross-Paju K, Haldre S. Cognitive profile and depressive symptoms in patients with epilepsy. Medicina (Kaunas) 2013; 49: 254–261.

II Liik M, Vahter L, Gross-Paju K, Haldre S. Subjective complaints compared to the results of neuropsychological assessment in patients with epilepsy: the influence of comorbid depression. Epilepsy Research 2009; 84: 194–200.

III Liik M, Paris M, Vahter L, Gross-Paju K, Haldre S. ^{123}I-ADAM SPET imaging of serotonin transporter in patients with epilepsy and comorbid depression. BMC Neurol 2013; 13: 204.

Applicant's contribution to the preparation of the original publications:

Paper I and II: study design, data collection, assessment of patients, data analysis, and writing the manuscript

Paper III: study design, finding the subjects, participation in the data analysis, and writing the manuscript

ABBREVIATIONS

^{123}I-ADAM	2-((2-((dimethylamino)methyl)phenyl)thio)-5-(123)iodophenylamine
5-HT	5-hydroxytryptamine or serotonin
5-HT$_{1A}$	Serotonin receptor subtype 1A
AEDs	Antiepileptic drugs
ANOVA	Analysis of variance
BDI	Beck depression inventory
BSRT	Buschke selective reminding test
CT	Computerized tomography
EEG	Electroencephalography
EST-Q	Emotional State Questionnaire
fMRI	Functional magnetic resonance imaging
FLE	Frontal lobe epilepsy
GABA	γ-aminobutyric acid
GCAE	Global Campaign Against Epilepsy
GEPR	Genetically epilepsy prone rat
GTCS	Generalized tonic-clonic seizures
HPA	Hypothalamic-pituitary-adrenal axis
HRQoL	Health-related quality of life
IBE	International Bureau for Epilepsy
IDD	Interictal dysphoric disorder
IGE	Idiopathic generalized epilepsy
ILAE	International League Against Epilepsy
JME	Juvenile myoclonic epilepsy
LEV	Levetiracertam
LTG	Lamotrigin
LTM	Long-term monitoring
MRI	Magnetic resonance imaging
NA	Noradrenaline
NMDA	N-methyl-D-aspartate
OXC	Oxcarbazepine
PB	Phenobarbital
PDS	Paroxysmal depolarizing shift
PET	Positron emission tomography
PHT	Phenytoin
PWE	People with epilepsy

ROIs	Regions of interest
SDMT	Symbol digit modalities test
SERT	Serotonin transporter
SPET	Single photon emission tomography
SSRIs	Selective serotonin reuptake inhibitors
TLE	Temporal lobe epilepsy
TPM	Topiramate
VPA	Valproate
WHO	Wold Health Organization

1. INTRODUCTION

Epilepsy is a chronic neurological disorder affecting up to 50 million people in the world (WHO, 2012), 6 million people in Europe (Pugliatti *et al.*, 2007; ILAE/IBE/WHO Global Campaign Against Epilepsy, 2010) and probably about 6300 people in Estonia (Haldre *et al.*, 2009). It is not a single disease but a group of disorders described by the recurrence of seizures. Additionally, epilepsy can have several consequences to person's health and life, as also reflected in the International League Against Epilepsy (ILAE) renewed definition for epilepsy (Fisher *et al.*, 2005). Among these neuropsychological, psychological, and psychiatric aspects can have the most prominent effect on person's quality of life.

Epilepsy has high socioeconomic burden at individual, family, health services, and societal level. Estimated total cost of epilepsy in Europe was €15.5 billion in 2004 (Pugliatti *et al.*, 2007). In a more recent Danish study the direct net annual health care and indirect costs were €14,575 for patients with epilepsy (Jennum *et al.*, 2011). Among other brain disorders this is a costly disorder with high direct and indirect costs (Olesen *et al.*, 2012).

Although epilepsy is a disease with effective treatment options, it remains a problem for many patients with epilepsy. In 2010 the Global Campaign Against Epilepsy (GCAE) published a report indicating that around 40% of patients with epilepsy in Europe are missing out on treatment, there is not enough epilepsy specialists, and not all the patients with need have the access to neuropsychological or rehabilitation services (ILAE/IBE/WHO Global Campaign Against Epilepsy, 2010). The stigma attached to epilepsy is partly the cause for this and at the same time is fortified by this – leading to the risk of behavioural problems, underachievement at school, underemployment, depression, and suicide.

It has been emphasized that epilepsy must become a higher priority in Europe in order to decrease treatment gap, and to improve access to neuropsychological and rehabilitation services. There is a need for better legislation in order to remove discrimination and for better healthcare arrangement in order to improve effectiveness of treatment and access to it. In order to do so, we need to have more profound research on epilepsy – addressing basic mechanisms of epileptogenesis, epidemiology of epilepsy, economic aspects, and especially behavioural issues of epilepsy.

Epidemiology of epilepsy in Estonia has been previously studied both in adults (Õun *et al.*, 2003a; Õun *et al.*, 2003b) and children (Beilmann *et al.*, 1999a; Beilmann *et al.*, 1999b); also quality of life of people with epilepsy has been extensively investigated (Rätsepp *et al.*, 2000; Herodes *et al.*, 2001).

The main aim of this thesis was to shed light on cognitive functioning and depression in patients with epilepsy. To reveal the prevalence and pattern of cognitive problems in patients with epilepsy, to compare it with perceived cognitive functioning, to estimate the effect of symptoms of depression on cognition, and to look for possible associations between depression in epilepsy and serotonergic system functioning.

We aimed to further investigate the idea that epilepsy is more than seizures.

2. LITERATURE REVIEW

2.1. Definition of epilepsy

According to the International League Against Epilepsy (ILAE) and International Bureau for Epilepsy (IBE) definitions, epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition (Fisher *et al.*, 2005). More recent operational definition adds that epilepsy can be defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome (Fisher *et al.*, 2014). 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).

Epilepsy is not a singular disease entity but a variety of disorders reflecting underlying brain dysfunction that may result from many different causes. The nature of the clinical manifestations of epileptic seizures depends on the part of the brain involved in the epileptic neuronal discharge, and the physiology and spread of the discharge (Badawy *et al.*, 2009). Previously both, epileptic seizures and epilepsy syndromes were divided into focal or generalized groups and the etiology of epilepsy was classified as idiopathic, symptomatic, and cryptogenic (Commission on Classification and Terminology of the ILAE, 1981; Commission on Classification and Terminology of the ILAE, 1989). Revised terminology for organization of seizures and epilepsies preserved the dichotomous manner of dividing seizures into generalized and focal seizures (Berg *et al.*, 2010) – generalized seizures occur in and rapidly engage bilaterally distributed networks and focal seizures occur and engage networks limited to one hemisphere. But the etiology of epilepsy is classified as genetic, structural/metabolic, or unknown causes (Berg *et al.*, 2010).

2.2. Pathophysiologic basis of epilepsy

According to our current knowledge, epileptic seizures are a result of excessive discharge in a population of hyperexcitable neurons (Avanzini and Franceschetti, 2003). The cerebral cortex and hippocampus are particularly prone to the generation of this synchronized excessive neuronal activity (McCormick and Contreras, 2001). Due to its complexity and heterogeneous causes the pathogenetic mechanisms of epilepsy are poorly understood and a singular fundamental pathophysiologic mechanism shared by all epilepsies is difficult to underline (Kobow *et al.*, 2012).

On cellular level it was proven that neurons in the epileptogenic focus possess a specific property which was named paroxysmal depolarization shift (PDS) and involves unusually high amplitude and prolonged duration bursts of membrane depolarization (Matsumoto and Ajmone Marsan, 1964). The spread and maintenance of epileptic activity is achieved via circuitry reorganization that can occur at the synaptic or network level (Pitkänen and Lukasiuk, 2011). In general, as a result excitatory transmission is facilitated or inhibitory transmission is reduced (Bagdy *et al.*, 2007). This process of epileptogenesis alters neuronal excitability, establishes critical interconnections, and requires structural changes for spontaneous recurrent seizures to occur (Pitkänen and Lukasiuk, 2011). On the neuronal level this network is essential for the existence and maintenance of the epileptic disorder (Spencer, 2002).

The changes described in animal and human epileptic tissue include neurodegeneration, neurogenesis, gliosis, axonal damage or sprouting, dendritic plasticity, blood-brain barrier damage, inflammatory changes, reorganization of the molecular architecture of neuronal cells, and epigenetic changes in gene expression (Pitkänen *et al.*, 2007; Kobow *et al.*, 2012).

Recently, the involvement of serotonin (5-HT) system in the pathogenesis of epilepsies has become more evident (Bagdy *et al.*, 2007). The pathogenic role of 5-HT has been identified in various animal models of epilepsy (Kondziella *et al.*, 2007). In genetically epilepsy-prone rat (GEPR) – GEPR-3 and GEPR-9 – the predisposition to seizures has been associated with inborn defects in pre- and postsynaptic transmission of 5-HT and noradrenaline (NA) (Dailey *et al.*, 1992). The role of 5-HT has been studied in other animal models of epilepsy. It has been concluded that agents that elevate extracellular 5-HT levels inhibit both focal and generalized seizures and at the same time, depletion of brain 5-HT lowers the seizure threshold in audiogenic, chemical, and electrical seizure models (Bagdy *et al.*, 2007).

The data regarding the dysfunction of serotonergic system in epilepsy from the animal studies is supported by the results of imaging studies in humans. In patients with TLE a decrease in 5-HT_{1A} receptor binding in the epileptogenic areas has been found (Toszek *et al.*, 2003; Merlet *et al.*, 2004; Savic *et al.*, 2004; Giovacchini *et al.*, 2005). It is important that reductions are not associated with hippocampal atrophy and are more pronounced in seizure onset areas than regions of secondary spread (Savic *et al.*, 2004; Giovacchini *et al.*, 2005).

2.3. Epidemiology of epilepsy

Epilepsy is one of the most frequent chronic central nervous system disorders and has considerable medical, social and economic burden. According to the epidemiologic studies of epilepsy in the world, the age-adjusted incidence ranges from 16 to 51 per 100,000 and age-adjusted prevalence estimates from 2.7–17.6 per 1000. Studies done in Estonia showed that the incidence rate for

adult epilepsy was 35 per 100,000 person/years and prevalence rate was 5.3 per 1000, which is comparable to prevalence and incidence rates in other similar regions (Õun *et al.*, 2003a and 2003b). Therefore, it is estimated that there is about 6300 people suffering from epilepsy in Estonia and 560 new cases are added yearly.

Mortality rate for patients with epilepsy is 2–3 times higher compared to general population and standardized mortality rate for patients with epilepsy is 1.6–9.3 according to different population-based studies (Rafnsson *et al.*, 2001; Gaitazis and Sander, 2004).

2.4. Quality of life in epilepsy

Numerous studies in patients with epilepsy have indicated impaired quality of life due to the disorder or its comorbidities (Baker *et al.*, 1997; Jacoby *et al.*, 2011; Jehi *et al.*, 2011).

The influence of epilepsy on a person's life can be complex and multifactorial (Kerr *et al.*, 2012) involving physical, psychological, cognitive, social, and occupational factors (Jacoby *et al.*, 2013). Large population based studies of prevalence of social, psychological, and quality of life complications in epilepsy have indicated that people with epilepsy (PWE) consistently reported higher rates of unemployment, lower income, lower education, being single, depression, and anxiety compared with people without epilepsy (Strine *et al.*, 2005; Kobau *et al.*, 2006).

Similarly to studies from various regions over the world, research on Estonian population revealed reduced quality of life and high stigmatization in PWE (Rätsepp *et al.*, 2000; Herodes *et al.*, 2001). Fifty-two percent of respondents felt themselves stigmatized by epilepsy, and 24.7% of them highly. Study respondents scored lower in all domains of the RAND-36 than did persons from the control group.

Epilepsy can affect patient's quality of life through many different factors (Figure 1) Seizure frequency and severity, seizure worry, AED side-effects, psychiatric comorbidity, especially depression have all been found to be important predictors of quality of life in PWE (Loring *et al.*, 2004; Hessen *et al.*, 2009; Auriel *et al.*, 2009; Jehi et al, 2011). In a longitudinal study of adults with new-onset epilepsy an interesting phenomenon was described as patients whose seizures appeared poorly controlled during the study reported decreased quality of life measures already at the baseline (Jacoby *et al.*, 2011). These results indicate that there might be a pathogenetic relationship between epilepsy and quality of life.

Among other factors cognitive functioning may be an important aspect in quality of life in epilepsy but this has been poorly studied. In a study by Perrine and colleagues mood, psychomotor speed, verbal memory, and language correlated significantly with the Quality of Life in Epilepsy—89 inventory and

the mood factor showed the highest correlations and was the strongest predictor of quality of life in regression analyses (Perrine *et al.*, 1995). Therefore, it was concluded that the level of cognitive functioning is a critical aspect to quality of life in patients with epilepsy (Perrine *et al.*, 1995).

A systematic review analysing 93 health-related quality of life (HRQoL) studies in epilepsy underlined 5 factors which appeared to be strongly associated with reduced HRQoL across multiple studies: seizure frequency and severity, level of depression and anxiety, and presence of comorbidity (Taylor *et al.*, 2011).

Therefore, it appears repeatedly that depression is one of the most important predictors of poor HRQoL (Cramer *et al.*, 2003; Loring *et al.*, 2004; Kwan *et al.*, 2008) and in some studies it has been the only predictive factor (Boylan *et al.*, 2004).

In patients with pharmacoresistant epilepsy and TLE depression appears to be the most powerful predictor for each domain of HRQoL. Psychiatric comorbidity explains more variance in HRQoL than clinical seizure or demographic variables.

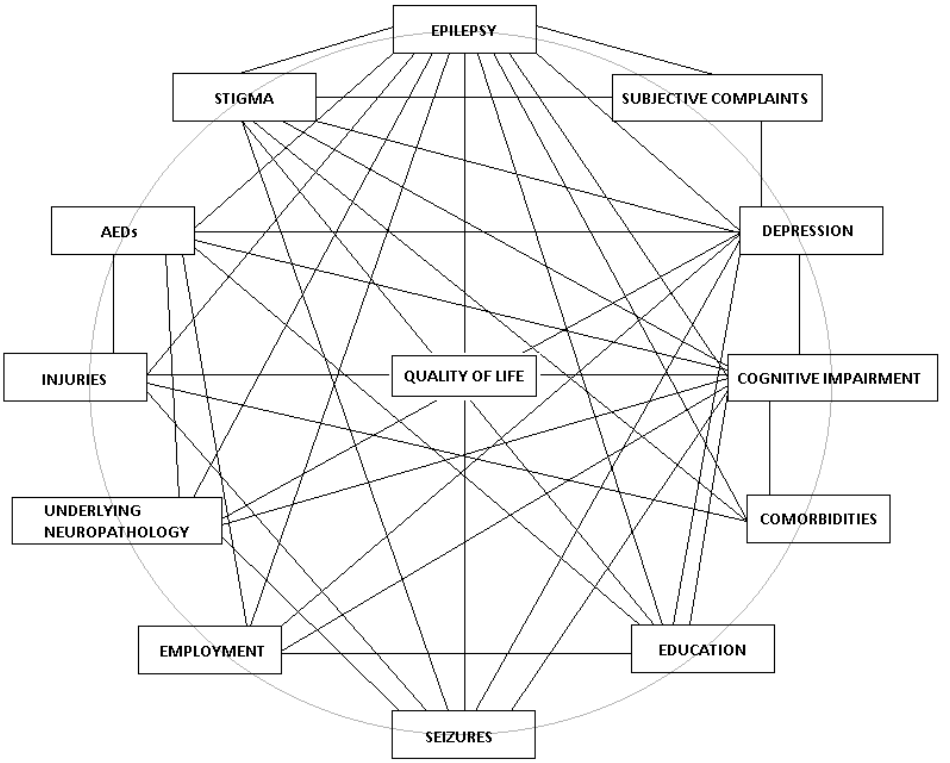

Figure 1. Interrelationships of different factors in epilepsy influencing each other and quality of life in general.

2.5. Epilepsy and cognitive functions

Cognitive function is defined as the capacity of the brain to process information and to program adaptive behaviour. It involves the ability to solve problems, communicate, memorize information, or focus attention (Aldenkamp *et al.*, 2004). People with epilepsy have increased risk for cognitive disturbances (Meador, 2002). Previous studies have found that cognitive changes are common in people with all forms of epilepsy (Barr, 2007) and that compared to their peers PWE may have reduced performance in different cognitive domains, including slowing on speeded tasks, complex information processing disturbances, memory impairment, and attentional and concentration difficulties (Aldenkamp *et al.*, 2004). This is a well-recognized but poorly understood concept (Badawy *et al.*, 2012). Heterogeneity of epilepsy syndromes is reflected in complexity of cognitive profiles in epilepsy and in factors contributing to the dysfunction. The etiology of the disease and underlying neuropathology, recurrent epileptic seizures, side-effects of antiepileptic drugs (AED), and psychosocial factors all play significant roles in the cognitive functioning of PWE (Kwan and Brodie, 2001; Elger *et al.*, 2004; Aldenkamp and Bodde, 2005).

It would be reasonable to assume that epileptic activity arising from the cortical regions that are responsible for certain physiological functions would disturb these functions, including cognitive function. Indeed, in several studies examining the effect of subtle nonconvulsive seizures and frequent interictal epileptiform EEG activity in children, transient changes in global cognitive function, speed of central information processing, and memory function are described (Aldenkamp and Arends, 2004a; Nicolai *et al.*, 2012). It has also been hypothesized that epileptiform activity and subtle seizures can have cumulative detrimental sequences for cognition (Aldenkamp and Arends, 2004b). The negative effect of history of status epilepticus or greater lifetime number of generalized tonic-clonic seizures on cognitive functioning was described several decades ago (Dodrill, 1986). Memory impairment in TLE has been associated with continuing and high frequency of seizures (Hendriks *et al.*, 2004).

Studies of patients with newly diagnosed epilepsy prior to treatment have been used in order to estimate the effect of seizures on cognition (Dodrill, 2004). In this paper Dodrill reviewed 22 studies examining the effect of seizures on mental abilities in patients with newly diagnosed epilepsy. The results were somewhat contradictory but in 12 out of 22 studies a relationship between seizures and a decline in mental abilities were found (Dodrill, 2004).

The other aspect that these studies have revealed is that cognitive deficits are already present at the onset of epilepsy. Patients with previously untreated newly diagnosed focal and generalized epilepsy perform worse than healthy volunteers on measures of several cognitive domains: attention, concentration, motor function, mental flexibility, psychomotor speed, and especially memory

and learning (Kälviäinen *et al.*, 1992; Prevey *et al.*, 1998; Pulliainen *et al.*, 2000; Äikiä *et al.*, 2001; Taylor *et al.*, 2010). Prevey *et al.* found that patients with secondarily generalized seizures have the greatest impairment (Prevey *et al.*, 1998). Furthermore, it has been hypothesized that at least in children cognitive and behavioural changes may even precede the first seizure (Austin *et al.*, 2001; Berg *et al.*, 2005). This points to the possibility that cognitive disturbances are not a mere result of seizures but are related to the epileptogenic process itself. This idea is supported by the finding that cognitive performance at the beginning of epilepsy may serve as a predictive factor for seizure outcome (Äikiä *et al.*, 1999).

Seizures seem to play a critical role in the development of neuropsychological and behavioural problems, as described above, but other epilepsy-related factors have also been associated with cognitive disturbances. In children with TLE earlier onset of epilepsy is associated with poorer intellectual outcome (Cormack *et al.*, 2007). Younger age at seizure onset has been associated with less favourable cognitive outcome in adults with TLE (Äikiä *et al.*, 2001; Lespinet *et al.*, 2002) and with differential impairment profiles depending upon differences of age at epilepsy onset in FLE (Upton and Thompson, 1997).

Temporal course and long-term outcome of cognitive function in epilepsy has been an issue for a debate. Due to methodological problems the separation of the effect of younger onset from longer duration of illness is difficult to achieve – these factors may be collinear and may be affected by several confounding factors, e.g. accumulating number of experienced seizures, the influence of ageing on cognitive functions etc. (Lin *et al.*, 2012). In many cross-sectional studies longer duration of epilepsy has been associated with worsening mental status (Jokeit and Ebner, 1999; Oyegbile *et al.*, 2004). In a large cross-sectional study of verbal memory and learning 1156 patients with chronic TLE were compared to 1000 healthy control subjects (Helmstaedter and Elger, 2009). The authors found that the learning peak was seen earlier in patients with epilepsy than for controls. They hypothesize that "initial hit" may disturb the build-up of adequate learning and memory performance in the adolescence. Decline in performance with ageing in patients and controls runs in parallel but due to the initial distance between the groups, patients reach very poor performance levels much earlier than controls (Helmstaedter and Elger, 2009).

In fewer longitudinal studies a decline in cognitive functions has been described. Currently the longitudinal studies cover the time period up to 10 years and indicate that global measures of intelligence remain quite stable over these years (Holmes *et al.*, 1998). Nevertheless, there is progressive decline in some neuropsychological measures, namely memory (Helmstaedtler *et al.*, 2003), psychomotor speed (Taylor and Baker, 2010), and higher executive functioning (Baker *et al.*, 2011).

When PWE are compared to a control group in longitudinal studies of neuropsychological function a lack of practice effects has been repeatedly noted

(Hermann *et al.*, 2006; Baker *et al.*, 2011). Control participants show a broad test-retest improvement over time, while PWE exhibit a minimal or lacking practice effect (Hermann *et al.*, 2008; Lin *et al.*, 2012).

It seems that not all patients with TLE are affected equally, but there may be a subgroup of patients (approximately 30%) with more pronounced cognitive dysfunction (Kälviäinen *et al.*, 1992). This subset of patients has wider and more severe distribution of neuropsychological dysfunction involving executive functions and memory; and this subset has different cognitive trajectory over a 4-year interval (Hermann *et al.*, 2006; Hermann *et al.*, 2007).

It can be concluded that although epilepsy may not be directly related to dementia per se (Helmstaedtler and Elger, 1999 and 2009), persons with epilepsy seem to enter their elder years at a distinct cognitive disadvantage what could be characterized as age-accelerated cognitive pathological damage (Lin *et al.*, 2012).

Temporal lobe epilepsy is the most prevalent and frequently treatment resistant epilepsy syndrome in adults and therefore, research on cognitive functioning in patients with epilepsy has concentrated on the TLE. Since the hippocampus and the neighbouring rhinal cortex are major components of the frontotemporal system, which is involved in the formation of episodic declarative memory, a large proportion of research has evolved around memory function in TLE (Elger *et al.*, 2004). This led to the concept of a complex of neuropsychological symptoms related to the syndrome of mesial TLE, with material specific memory disturbances playing a leading role (Helmstaedter, 2002). Patients with TLE have been described to have more memory impairments than patients with extratemporal or generalized epilepsy (Bergin *et al.*, 2000). Left-sided TLE is associated with deficits in verbal memory functions (Giovagnoli and Avanzini, 1999), but the corresponding assumption that right-sided TLE would be linked to deficits in non-verbal memory has not been so uniformly proven (Helmstaedter *et al.*, 1991; Hermann *et al.*, 1997). The frequent absence of non-verbal memory impairment in patients with right-sided TLE may be explained by covert verbalization strategies in tests of non-verbal memory, or by more widespread organization of non-verbal memory (Elger *et al.*, 2004). Later studies have indicated that neuropsychological changes in TLE are not limited to hippocampal functions but extend to a much wider cognitive profile (Bell *et al.*, 2011). Besides dysfunction in material specific memory, impairment in intellectual functions, language, psychomotor speed, and higher executive function have been described (Oyegbile *et al.*, 2004). The existence of concept of material specificity in TLE has been questioned (Saling, 2009).

Frontal lobe epilepsy as the second most frequent focal type of epilepsy has gained less attention and as frontal lobes are functionally heterogeneous, a consistent uniform cognitive profile of FLE has been difficult to establish (Elger *et al.*, 2004). FLE is associated with a more diffuse pattern of cognitive disturbances – deficits in motor coordination and planning, reduced attention

span, and difficulties in response inhibition in complex cognitive tasks in patients with FLE have been reported (Patrikelis *et al.*, 2009). The possibility of using neuropsychological testing to differentiate between patients with frontal and temporal lobe epilepsy has been considered (McDonald *et al.*, 2005). When patients with FLE are compared to patients with TLE, impaired motor coordination and response inhibition have been identified (Helmstaedter *et al.*, 1996). Exner and colleagues found that frontal and temporal epilepsy subjects differed on only one subtest of memory, where patients with FLE demonstrated a significantly reduced verbal short term memory span compared to patients with TLE (Exner *et al.*, 2002). A summary of this study stated that as both epilepsy groups showed wide array of impairment in most measures (intelligence, memory, executive functions, and emotional conceptualization), there were no distinguishable neuropsychological profiles for these groups (Exner *et al.*, 2002). These global and overlapping impairments have been explained by the reciprocal connections between prefrontal, temporal, and limbic areas (Patrikelis *et al.*, 2009). Also, studies comparing patients with left-sided vs right-sided FLE have had contradictory results. Some studies have indicated that executive functions are more disturbed in patients with left-sided FLE (McDonald *et al.*, 2005), other studies associate greater dysfunction with right-sided FLE (Upton and Thompson, 1996).

There are even fewer studies addressing cognitive functioning in adults with idiopathic generalized epilepsies (Hommet *et al.*, 2006). In patients with juvenile myoclonic epilepsy (JME) a specific cognitive profile has been described which indicates the role of frontal lobe dysfunction and has been named the dysexecutive syndrome (Schmitz *et al.*, 2013). Disturbances of prefrontal functions, such as concept formation, abstract reasoning, mental flexibility, cognitive speed, planning, and organization have been described (Piazzini *et al.*, 2008). In some studies the impairment has been showed to extend to functions outside the limits of frontal lobes – e.g. verbal and visual memory (Sonmez *et al.*, 2004; Pascalicchio *et al.*, 2007).

Cognitive disturbances are related to morphological changes on imaging studies. Hippocampal cell loss was associated with memory impairment in patient with TLE a long time ago (Sass *et al.*, 1992). Hippocampal volumes on the MRI were correlated with pre- and postoperative memory performance in patients with TLE undergoing surgical treatment (Trenerry *et al.*, 1993). This was later confirmed on fMRI studies which indicated that greater activation in the damaged hippocampus was correlated with better memory performance preoperatively and greater memory decline postoperatively (Powell *et al.*, 2007; Bonelli *et al.*, 2010). It has become evident that as cognitive changes in patients with TLE are not limited to hippocampal functions but may extend to a much wider and diffuse neuropsychological profile, the imaging studies have also revealed extensive metabolic and volumetric changes in case of TLE outside the borders of the temporal lobe (Bell *et al.*, 2011). Atrophy has been found in enthorhinal cortex and amygdala (Salmenperä *et al.*, 2001), fornix (Kuzniecky

et al., 1999), parahippocampal gyrus (Bernasconi *et al.*, 2003), basal ganglia (Dreifuss *et al.*, 2001), thalamus (Natsume *et al.*, 2003; Szabo *et al.*, 2006), and cerebellum (Sandok *et al.*, 2000). Diffuse neuroanatomical changes in TLE are in correlation with diffuse neuropsychological impairments (Dabbs *et al.*, 2009). It has been hypothesized that cognitive impairment in TLE is a result of network disruption rather than specific damage to a specific brain structure (Bell *et al.*, 2011).

Similar correlations between morphological changes and cognitive dysfunction have been found in patients with JME (Wandschneider *et al.*, 2012). In one study subjects with JME had significantly lower thalamic volumes and more frontal cerebrospinal fluid than control subjects, and these changes were in correlation with related executive functioning (Pulsipher *et al.*, 2009). In another study using structural and diffusion tensor MRI, fractional anisotropy in the supplementary motor area predicted performance in word naming and expression tasks and grey matter volumes of the posterior cingulate cortex correlated with scores on the mental flexibility task (Muircheartaigh *et al.*, 2011).

Controversies around the cognitive effects of AEDs have set the stage for long-lasting discussion. On one hand, as described above, recurrent seizures and even epileptiform EEG discharges have been shown to have negative effect on cognition. It would therefore suggest that AED therapy would improve cognition in PWE – an idea that has been proven in several studies (Holmes and Lenck-Santini, 2006). On the other hand there are numerous reports of cognitive side-effects of AEDs' and high number of patients associating their cognitive complaints with AED side-effects (Baker *et al.*, 1997; Kerr, 2012).

There are general treatment-related factors that are associated with increased risk for developing drug-induced cognitive and psychiatric complications in PWE. These include rapid titration of the drug, polypharmacy, a history of psychiatric disorder, and limbic system functional or structural abnormalities (Mula and Monaco, 2009; Lin *et al.*, 2012). Different AEDs carry different risks for cognitive impairment but generally, older AEDs have worse effect on cognition than newer AEDs (Drane and Meador, 2002). Impaired attention, vigilance, and psychomotor speed have been the main cognitive effects associated with AEDs (Park and Kwon, 2008). Concerning individual drugs, topiramate has been considered as the most problematic drug, with cognitive impairments being reported to be greater for topiramate than for lamotrigine, valproate, tiagabine, and oxcarbazepine (Meador *et al.*, 2003; Fritz *et al.*, 2005; Blum *et al.*, 2006; Kim *et al.*, 2006).

Memory functions in patients with treatment resistant TLE have been extensively studied in the last decades. This is not the case for other types of epilepsies.

2.6. Epilepsy, perceived cognition and subjective complaints

Simultaneously to findings of cognitive impairment on neuropsychological assessment, PWE themselves report different complaints regarding their cognitive functioning, including decreased levels of attention, slowness of thinking, and poor memory (Engelberts *et al.*, 2002; Moore and Baker, 2002). Even in a study of patients with well-controlled epilepsy 67% of the subjects reported moderate to severe subjective complaints and cognitive complaints were the most frequent among these (Uijl *et al.*, 2006). In the epilepsy and cognitive function survey conducted by the IBE (IBE, 2004) the most frequently reported problems by PWE were difficulties learning something new, slowness of thought, sleepiness/tiredness, and lethargy/sluggishness. Importantly, 56% of patients associated their cognitive impairment with their epilepsy medication (IBE, 2004). This association has been found in other studies as well (Carpay *et al.*, 2005).

Studies have shown that perceived memory status of epilepsy patients is significantly lower than that of controls and that the prevalence of subjective memory problems in the case of epilepsy can be as high as 50% (Hendriks *et al.*, 2002). The majority of studies of subjective complaints in epilepsy patients has concentrated on memory problems. It has been shown that there are very few epilepsy-related factors influencing the amount of subjective complaints. Different studies have shown somewhat contradictory results about the association of seizure type and frequency, type of epilepsy and antiepileptic treatment, and localization or lateralization of the epileptic disturbances with memory complaints. The identified factors associated with increased levels of complaints could be polytherapy – when complaints are assessed in the frame of AED side-effects (Uijl *et al.*, 2005), later onset of seizures (Thompson and Corcoran, 1992; Corcoran and Thompson, 1993) and older age of patients (Hendriks *et al.*, 2002). The last mentioned study demonstrated that patients of older age and higher intelligence level and with longer duration of epilepsy complained more about memory problems. Other factors showing clear association with subjective memory complaints are neuroticism, anxiety and depression (Thompson and Corcoran, 1992; Corcoran and Thompson, 1993; Hendriks *et al.*, 2002).

Paradoxically, there are only moderate correlations between self-reported memory complaints and results of neuropsychological memory tests (Vermeulen *et al.* 1993; Piazzini *et al.*, 2001; Fargo *et al.*, 2004; Hall *et al.*, 2009; Marino *et al.*, 2009). It has been found that 61% of patients with epilepsy estimate their cognitive abilities inaccurately, and among these patients with incomplete awareness of their abilities, under- and over-estimators are divided about evenly (Giovagnoli, 2013). There are different causes that are suggested to explain the discrepancy between subjective and objective memory status. Once again, epilepsy-related factors seem to have minor impact on the

association between subjective and objective measures of memory (Sawrie *et al.*, 1999; Piazzini *et al.*, 2001).

In few studies that have reported the relationship between subjective and objective memory in control subjects, measures were significantly correlated in control subjects (Piazzini *et al.*, 2001), and controls were more accurate at rating their memory than people with right hemisphere epileptogenic lesions (Andelman, et al, 2004).

Helmstaeder and Elger have suggested that attribution of memory refers to a subjective view of memory which is wider than its neuropsychological definition. In their work they have demonstrated that memory is preferentially concluded from verbal behaviours (including vocabulary, word fluency) (Helmstaeder and Elger, 2000).

Rayner and colleagues reported that memory complaints were predicted by objective memory function and depression in patients with mesial temporal lobe refractory epilepsy and by history of depression and not objective dysfunction in patients with non-mesial temporal lobe refractory epilepsy (Rayner *et al.*, 2010).

One of the reasons for this discrepancy could be concurrent depression (Piazzini *et al.*, 2001; Fargo *et al.*, 2004; Marino *et al.*, 2009). In a study assessing the influence of cognitive, psychosocial, and emotional factors on self-reported cognitive functioning in patients with temporal lobe epilepsy, it was demonstrated that psychosocial and emotional factors appeared to be significant predictors of subjective cognitive functioning (Banos *et al.*, 2004). It has been shown that patients with TLE who report to be more depressed underestimate their memory function, although their actual memory performances with neuropsychological testing does not differ from those patients who do not indicate that they are depressed (Deutsch *et al.*, 1996). Elixhauser *et al.* have also shown that objective memory performance in patients with epilepsy was weakly correlated with perceived cognitive functioning but perceived functioning was strongly correlated with mood (Elixhauser *et al.*, 1999).

So far, investigation in this field has concentrated mainly on memory problems and mostly on cases of intractable temporal lobe epilepsy. Since subjective cognitive complaints can affect the patient's quality of life and be one of the most important signs for the clinician, a wider analysis of subjective cognitive problems and objective test results in the case of various forms of epilepsy could be helpful in clinical situations.

2.7. Epilepsy and depression

Great amount of burden related to epilepsy is associated with psychiatric comorbidities (Hesdorffer and Krisnamoorthy, 2011). Psychiatric disorders, including depression, anxiety, attention-deficit hyperactivity disorder and psychoses are common in patients with epilepsy (Gaitatzis *et al.*, 2004).

Depression is the most common psychiatric disorder among PWE and occurs at a higher rate among people with epilepsy compared to the general population (Kanner, 2003). The prevalence rates are the lowest in large population based epidemiological studies and the highest in cross-sectional studies of tertiary care samples of patients with epilepsy (Hoppe and Elger, 2011). In smaller cross-sectional studies the life-time prevalence of major depression has been shown to vary between 8–48% (Hermann *et al.*, 2000). In a population-based study in the frame of the Canadian Community Health Survey involving 36,984 subjects Tellez-Zenteno and colleagues found that lifetime prevalence of major depressive disorder in patients with epilepsy was 17.4% versus 10.7% in the general population (Tellez-Zenteno *et al.*, 2007). In the same study it was shown that patients with epilepsy have a 24.4% lifetime prevalence for any type of mood disorder versus 13.2% among the general population and that the lifetime prevalence of suicidal ideation is twice as high in patients with epilepsy (25%) compared with that of the general population (13.3%) (Tellez-Zenteno *et al.*, 2007). Similar findings have been reported in population based studies in UK (Rai *et al.*, 2012) and US (Kessler *et al.*, 2012). In the study by Rai and colleagues associations between psychiatric disorders and epilepsy were consistently stronger than associations with psychiatric problems in people with asthma or diabetes (Rai *et al.*, 2012). In a recent meta-analysis all included studies indicated uniformly increased active depression prevalence rates and life-time depression prevalence rates for PWE compared to general population (Fiest *et al.*, 2013).

Epilepsy is associated with increased risk of suicide (Meador, 2009; Bell and Sander, 2009). Suicidal ideation, attempted, and completed suicide rates have been reported to be significantly more prevalent in PWE compared to general population (Jones *et al.*, 2003; Pompili *et al.*, 2005). Higher risk of suicide is reported in patients with epilepsy and concurrent psychiatric disorders (Nilsson *et al.*, 2002). In a large Danish population based study PWE were found to be at three times higher risk of committing suicide than controls and the risk ratio remained significantly higher after excluding individuals with a history of psychiatric disease and adjusting for socioeconomic factors (Christensen *et al.*, 2007).

The controversial issue of depression phenotype in PWE revolves around the concept of interictal dysphoric disorder (IDD) (Mula, 2011). This implies to the atypical phenomenology of depression in PWE. It has been observed that in a subset of patients with epilepsy the concurring psychopathology has some unique manifestations that are poorly reflected by conventional criteria

(Krishnamoorthy *et al.*, 2007). Blumer *et al*. emphasized the key symptoms of mood disorders seen in PWE as periodicity of mood changes and the presence of outbursts of irritability and aggressive behaviour (Blumer *et al.*, 2004). Later studies have confirmed that the concept of IDD represents a homogenous construct that can be diagnosed in a proportion of PWE but it is not typical only of epilepsy, occurring also in other central nervous system disorders such as migraine (Mula *et al.*, 2008). It has been hypothesized that a number of these atypical and pleomorphic features attributed to IDD are related to peri-ictal symptoms and are therefore specific only to patients with epilepsy (Kanner *et al.*, 2012).

For a long time the etiology of depression in epilepsy has been thought to be associated with psychosocial factors. It is clear that chronic stress associated with epilepsy can bring about feelings of unpredictability and uncertainty, low self-esteem, feelings of shame, stigma, and various social problems which may affect the development of depression in PWE. Attributional style and learned helplessness have been associated with greater rates of depression in PWE (Hermann *et al.*, 2000)

Associations between several epilepsy related factors and depression have been searched but the findings have been quite inconsistent and contradictory (Hoppe and Elger, 2011). Frequency of seizures has been the factor that has shown greater consistency across multiple studies, although not always (O'Donoghue *et al.*, 1999; Attarian *et al.*, 2003; Grabowska-Grzyb *et al.*, 2006). Age at onset, duration of epilepsy, and focus lateralization have not been consistently associated with depression in epilepsy (Adams *et al.*, 2008; Filho *et al.*, 2008; Babu *et al.*, 2009; Fuller-Thomson and Brennenstuhl, 2009). In several studies, higher depression rate was found in patients with temporal lobe seizure foci and was compatibly explained by limbic system dysfunction in these patients (Altshuler *et al.*, 1999). Conversely, in other studies the excess of psychiatric symptoms in patients with TLE vs. extra-TLE has not been found (Swinkels *et al.*, 2006).

More recently, it has become apparent that depression in epilepsy may be directly related to dysfunction of brain regions involved in mood regulation. Hippocampal atrophy has been found to be associated with the presence of depression (Shamim *et al.*, 2008; Salgado *et al.*, 2010; Briellmann *et al.*, 2011) and decrease of amygdala volumes may be related to dysphoric symptoms in patients with TLE (Elst *et al.*, 2009).

Partly, the evidence to support the idea that depression in epilepsy may be more than a reactive process and that these disorders may share the common neurobiological basis, came from studies indicating that depression may precede epilepsy. In their renowned paper Forsgren and Nyström reported that depression was seven times more common among patients with new onset epilepsy, preceding the diagnosis of epilepsy, than among age- and sex-matched controls (Forsgren and Nyström, 1990). Similar results were later replicated by Hesdorffer and colleagues who found that depression was associated with a

fourfold increased risk for developing a first unprovoked seizure in older adults (Hesdorffer *et al.*, 2000). The presence of a psychiatric disorder, such as depression, has been shown to reduce seizure threshold, and depression and attempted suicide themselves are risk factors for epilepsy (Hesdorffer *et al.*, 2006; Alper *et al.*, 2007). It was shown that psychiatric pathology could be a risk factor for the development of unprovoked seizures and epilepsy in children (McAfee *et al.*, 2007). These findings have led to the concept of a bidirectional relation between epilepsy and depression (Kanner, 2005). Thus, epilepsy may lead to depression and vice versa. More recently, Hesdorffer *et al.* demonstrated that psychiatric disorders (psychosis, depression, and anxiety) and suicidality were associated with increased risk for developing epilepsy, and following a diagnosis of epilepsy, the risk for developing the psychiatric disorders was increased (Hesdorffer *et al.*, 2012), confirming the possibility of bidirectional relationship between epilepsy and depression.

Neuropsychological studies have reported that depression itself can affect a wide range of cognitive abilities, especially executive functions (Murrough et al, 2011) Patients with depression are more likely to have impaired cognitive speed, episodic memory and learning, verbal fluency, naming ability, planning, attention, and problem solving impairment compared to subjects without depression (Austin *et al.*, 2001; Stordal *et al.*, 2004; Mondal *et al.*, 2005).

The relationship between depression and cognitive functioning in PWE has been poorly studied. Paradiso *et al.* (Paradiso *et al.*, 2001) demonstrated that patients with TLE concurrent with depression performed significantly poorer on measures of intelligence, language, visuo-perceptual ability, memory and executive function than patients with TLE without depression. In addition, these authors found that effects of depression on cognition may be greater in patients with left TLE. Conversely, Tracy *et al.* (Tracy *et al.*, 2007) found no relationship between cognition and depression in patients with TLE. In patients with newly diagnosed epilepsy depression and negative mood states were not associated with cognitive measures in a study by Pulliainen *et al.* (Pulliainen *et al.*, 2000) and more recently by Taylor *et al.* (Taylor *et al.*, 2010). Helmstaedter and colleagues (Helmstaedter *et al.*, 2004) found that depression and memory deficits were correlated only in patients with left lateral temporal focal epilepsy. A study of patients with FLE undergoing surgical treatment showed that patients with depressed mood before surgery had greater difficulty on a mental flexibility task compared to patients without depression and only pre-surgical depression status explained a significant amount of variance in executive functioning performance after surgery in regression analysis (Dulay *et al.*, 2012). Although the results of studies assessing the influence of depression on cognitive function in PWE have been contradictory, it has been hypothesized that as depression is known to cause several disturbances in cognitive functioning, patients with epilepsy could be at a heightened risk of a double burden.

Although, psychiatric comorbidities in epilepsy have gained increasing attention in recent years, it has been concluded that depression in PWE is common, can be severe, is still underdiagnosed and under-/untreated (Barry *et al.*, 2008). As noted above, this issue is important, as the presence of depression is likely to be the most important factor influencing quality of life in patients with epilepsy (Cramer *et al.*, 2003a; Boylan *et al.*, 2004; Kwan *et al.*, 2008), and can negatively impact both medical and surgical treatment outcomes (Hitiris *et al.*, 2007: Kanner *et al.*, 2009; Metternich *et al.*, 2009). It can influence the subjective complaint rate, can increase perceived seizure severity (Cramer *et al.*, 2003b), and is associated with higher rates of AED side-effect reporting (Carpay *et al.*, 2005). Depression, and especially untreated depression, is associated with work absenteeism, increased health care system utilization, and increased medical costs in PWE (Cramer *et al.*, 2004; Lacey *et al.*, 2009).

Few reports on influence of depression on cognitive dysfunction in PWE have given contradictory results and have been rarely investigated.

2.8. Role of the serotonergic system

There is a growing body of evidence that epilepsy, depression and possibly other neuropsychiatric disorders may share common pathogenetic mechanisms (Kondziella *et al.*, 2007). Besides the hyperactivity of hypothalamic-pituitary-adrenal (HPA) axis, disturbances of glutamate and γ-aminobutyric acid (GABA) metabolism, the dysfunction of the brain serotonin (5-hydroxytryptamine or 5-HT) system has been suspected to be the common denominator for these shared pathogenic mechanisms (Kanner, 2011).

Alterations in serotonergic signalling are associated with the pathogenesis of depression in otherwise healthy patients with major depressive disorder – findings that are clinically supported by the effect of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression. Several neuro-imaging studies using different positron emission tomography (PET) or single photon emission tomography (SPET) tracers for various components of serotonergic system in the brain have supported the involvement of 5-HT in major depressive disorder. These alterations include increased serotonin transporter (SERT) binding in the thalamus and limbic regions (Meyer, 2007), or decreased brainstem and midbrain SERT binding (Malison *et al.*, 1998; Lehto *et al.*, 2006; Parsey *et al.*, 2006), as well as reduced 5-HT_{1A} receptor binding potential in various limbic and neocortical regions and the raphe nuclei (Drevets *et al.*, 1999).

Mounting research implicates the serotonin system in relation to depression and epilepsy. Depression-like behaviour has been observed in various animal models of epilepsy (Kanner *et al.*, 2012). Strains of GEPR have been reported to express affective disturbances manifested by decreased saccharin consumption in the saccharin consumption test and increased immobility time

in the forced swim test (Jobe, 2003). Similar findings have been described for models of acquired epilepsy, for example the lithium and pilocarpine-induced status epilepticus model (Mazarati *et al.*, 2008). In their work, the depression-like behaviour was associated with a decrease of 5-HT concentrations and turnover in the hippocampus. In line with these findings, several experimental models have proved that SSRIs may have anticonvulsant properties in animal studies (Igelstrom, 2012). Using the post-status epilepticus model, which is considered to be one of the best models of chronic epilepsy, Hernandez *et al.* found that five days fluoxetine treatment inhibited spontaneous recurrent seizures after pilocarpine-induced status epilepticus (Hernandez *et al.*, 2002). In another study four days of citalopram treatment reduced seizure frequency and cumulative seizure duration in the post-kainic acid-induced status epilepticus model (Vermoesen *et al.*, 2012).

Similarly, in humans, there are studies where the anticonvulsant effects of SSRIs have been confirmed, such as Favale *et al.* (Favale *et al.*, 2003). In this study, citalopram was administered to non-depressed patients with poorly controlled epilepsy who then experienced a marked drop in seizure frequency (Favale *et al.*, 2003).

While SSRIs show anticonvulsant properties, several AEDs are efficacious in the management of affective disorders. Valproate, carbamazepine and lamotrigine are proven to be effective mood stabilizers.

Previous neuroimaging studies have used PET tracers for 5-HT_{1A} receptors to investigate the role of the serotonergic system in epilepsy and depression. These studies have concentrated on patients with both TLE and depression and have shown reduced 5-HT_{1A} receptor binding potential in the ipsilateral temporal lobe as well as in thalamic regions, hippocampus, anterior insula, anterior cingulate, and the raphe nuclei in the depressed patients (Savic *et al.*, 2004; Hasler *et al.*, 2007; Theodore *et al.*, 2007; Lothe *et al.*, 2008). An inverse correlation between increased severity of symptoms of depression and 5-HT_{1A} receptor binding has been described in some of these studies (Hasler *et al.*, 2007; Theodore *et al.*, 2007).

A recent PET study investigated SERT binding properties in addition to 5-HT_{1A} receptor binding in TLE (Martinez *et al.*, 2013). Besides 5-HT_{1A} receptor binding reductions in the hippocampus and other limbic areas on the epileptogenic side, the authors reported that diagnosis of depression was associated with SERT binding asymmetry in the insular cortex (Martinez *et al.*, 2013).

Thus, in TLE patients with depression, there appear to be alterations in the serotonergic system not only in the brain regions affected by epilepsy, but also more generally in ipsilateral and contralateral areas associated with regulation of emotion, changes that are similar to those described in patients with major depressive disorder alone.

2-((2-((dimethylamino)methyl)phenyl)thio)-5-(123)iodophenylamine (^{123}I-ADAM) is a novel SPET tracer that has shown a high binding affinity for SERT

as well as high selectivity for 5-HT transporter over those for norepinephrine and dopamine, and which has been proven to have excellent brain uptake in rats (Oya *et al.*, 2000). Subsequently, other studies demonstrated the feasibility of its use in human subjects (Lin *et al.*, 2006; Frokjaer *et al.*, 2008; Chou *et al.*, 2009; van de Giessen and Booij, 2010). Newberg *et al.* (Newberg *et al.*, 2005) used SPET to demonstrate alterations in SERT binding in patients with major depression; in this study, SERT binding was decreased in the midbrain region of patients with major depressive disorder and the degree of decrease correlated significantly with the severity of depressive symptoms (Newberg *et al.*, 2005). These findings were generally corroborated by a later study by the same group using a larger sample size (Newberg *et al.*, 2012).

So far, there is only one study of SERT binding in patients with TLE and questions regarding functions of SERT and symptoms of depression in patients with epilepsy remain unclear.

3. AIMS OF THE STUDIES

1. To describe the cognitive profile of patients with epilepsy. To investigate if cognitive performance of patients with epilepsy is different from that of control subjects' and whether the cognitive profile of patients with focal epilepsy is different from cognitive profile of patients with generalized epilepsy (Paper I).

2. To describe the effect of epilepsy related factors on cognitive performance (Paper I).

3. To investigate whether depression affects neuropsychological functioning of patients with various forms of epilepsy compared to control subjects (Paper I).

4. To compare subjective complaints of epilepsy patients with objective results of neuropsychological assessment (Paper II).

5. To describe factors influencing the relationship between subjective and objective cognitive performance and to investigate the possible influence of depression on self-reported complaint rate (Paper II).

6. To investigate SERT binding in the midbrain of patients with epilepsy with symptoms of depression, and to determine differences in SERT binding compared to patients with epilepsy without symptoms of depression (Paper III).

4. SUBJECTS AND METHODS

This study was approved by the Research Ethics Committee of the University of Tartu. For all studies the participants gave their signed informed consent in order to be included in the study.

4.1. Subjects

4.1.1. Subjects for the studies on objective and perceived cognitive functioning and depression

Patients with epilepsy from the Department of Neurology out-patient clinic of Tartu University Hospital were included in the study. The diagnosis of epilepsy was confirmed by clinical data, EEG study, and in majority of cases MRI study. The diagnosis was confirmed by an experienced neurologist who was member of the study team.

Patients considered for inclusion had to meet the following criteria: (1) Age between 18 and 65 years; (2) no other neurological diseases; and (3) native Estonian speaking person. Since the study was carried out during the time when the dichotomous classification of epilepsy syndromes by the ILAE (ILAE 1981; 1989) was valid, patients were divided into groups of focal and generalized epilepsy (based on medical history, clinical data, and investigations). Patients with questionable diagnosis of epilepsy were not included in the study, as well as patients who were intellectually and cognitively incapable of filling the questionnaires and Beck Depression Inventory (BDI). All efforts were made to include all consecutive patients to the study.

The control group for the neuropsychological assessment consisted of 53 healthy volunteers who were recruited during the test validation process and studies regarding cognitive assessment in patients with multiple sclerosis in West-Tallinn Central Hospital by Liina Vahter (Vahter, 2009). The control group did not statistically differ from the patient group by sex, age, or years of formal education. Control subjects had no history of seizures or other neurological disorders.

4.1.2. Subjects for the ^{123}I-ADAM SPET study of SERT binding

For the ^{123}I-ADAM SPET study of SERT binding patients with epilepsy were included from the out-patient clinic at the Department of Neurology of Tartu University Hospital and West-Tallinn Central Hospital, Estonia. Patients were otherwise healthy, with no history of other neurological disorders except epilepsy, and did not use antidepressant medications prior to this study.

In this study, all patients with symptoms of depression were consulted regarding their affective symptoms, and treatment with antidepressant medications was offered following the ^{123}I-ADAM SPET study.

4.2. Methods

4.2.1. Neuropsychological screening

Objective neuropsychological status was screened with a battery of tests mainly based on the Brief Repeatable Battery of Neuropsychological Tests (Boringa *et al.*, 2001).

Verbal memory was assessed by the Buschke Selective Reminding Test (BSRT), which is a test to measure verbal learning and memory during a six trial list learning task (Buschke and Altman Fuld, 1974). Short-term and long-term components as well as consistency of retrieval from long-term memory was evaluated.

Visual memory was assessed by the 10/36 Spatial Recall Test. 10/36 Spatial recall test is an adapted version of the 7/24 test with a wider checkerboard (6 × 6) and 10 checkers. It allows the assessment of visuospatial learning and delayed recall. The exact methodology of the test has been described elsewhere (Boringa *et al.*, 2001).

Symbol Digit Modalities Test (SDMT) was used to examine sustained attention and concentration by complex visual scanning and tracking. A series of nine meaningless geometric symbols labelled 1–9 were presented to the subject. The subject was then asked to substitute the symbols in a row by the corresponding number during a 90 seconds period. The score is the number of correct substitutions.

Word List Generation test evaluates the spontaneous production names of a given category within a limited amount of time. The subjects were asked to give as many names of "animals" as possible during 90 seconds. For the verbal fluency test the subjects were asked to give as many words beginning with a designated letter as possible within a 90 seconds period as well.

Trail Making A and B Tests allow the assessment of visual search, scanning, speed of processing, mental flexibility, and executive functions (Lezak, 2004).

4.2.2. Subjective complaints questionnaire

Subjective complaints of the patients were assessed using a simple subjective complaints questionnaire (Toomela *et al.*, 2004) which was modified for this particular study adding epilepsy specific items (Appendices A and B). Items for the questionnaire were selected with the purpose to describe the general and cognitive subjective complaint rate. The questionnaire consisted of thirteen items where patients had to assess the presence and the degree of different complaints on a four-point scale, where higher scores were indicative of a

higher degree of subjective complaints (from 1 (*never*) to 4 (*constantly*)). The questionnaire included questions about possible problems with forgetting, retrieving information from the memory, attention, speech, mood, dizziness, coordination, vision, fatigue, headache, and pain.

Scores for the items were analysed separately and total score of the questionnaire was calculated.

4.2.3. Assessment of symptoms of depression

In all parts of the study patients were screened for self-reported symptoms of depression using the Beck Depression Inventory (BDI) (Beck *et al.*, 1961). A cut-off score of > 11 points was used to define presence of depressive symptoms.

Additionally, in the ^{123}I-ADAM SPET study the Emotional State Questionnaire (EST-Q) was used (Aluoja *et al.*, 1999). EST-Q is a self-report questionnaire for depression and anxiety that uses the rating of 33 items on a five-point frequency scale. This questionnaire has five subscales: depression, anxiety, agoraphobia–panic, fatigue, and insomnia. As recommended, a cut-off score of > 11 points was used to define the presence of symptoms of depression on the EST-Q depression subscale (Ööpik *et al.*, 2006).

In the SPET imaging of SERT study questionnaires were administered directly before the start of the ^{123}I-ADAM SPET imaging session.

4.2.4. SPET imaging of SERT

The serotonin transporter (SERT) binding potential was examined by performing brain SPET study with 2-((2-((dimethylamino)methyl)phenyl)thio)-5-(123)iodophenylamine (^{123}I-ADAM). The subjects received a dose of 185 MBq ^{123}I-ADAM (MAP Medical Finland) intravenously. To block the thyroid gland, potassium perchlorate (KClO4; 800 mg) was given orally at least 20 min prior to the injection of ^{123}I-ADAM. Brain SPET studies were acquired 4 hours after the injection of ^{123}I-ADAM.

SPET studies were performed using a SPET/CT INFINIA Hawkeye 4 (GE Healthcare) dual head gamma camera with low energy high-resolution collimators (Lehr collimators). The energy window was centered on 159 keV (+/–10%). SPET scans were acquired in a step and shoot mode with total angular range of 360 degrees thereby arc per detector being 180 degrees. View angle 3 degrees, 120 views, 30 sec per projection. Acquisition time was 30 min. Matrix size was 128 x 128, with a zoom of 1.0.

Data were reconstructed using the Xeleris Functional Imaging Workstation software (GE Healthcare). Transverse slices were reconstructed parallel to the canthomental plane. SPET data were reconstructed using a Butterworth filter (critical frequency 0.4, power 6), followed by the Chang attenuation correction (threshold 5, coefficient 0.11). SPET and MRI data were automatically

coregistered using MPI Tool software (ATV Inc., Kerpen, Germany). To measure the individual SERT occupancy, irregular regions of interest (ROIs) were manually drawn over the midbrain and over the cerebellum as the reference area. The ^{123}I-ADAM binding was assessed using MRI-guided ROIs in the midbrain and cerebellum. ROIs were placed on transaxial MRI slices over the midbrain and cerebellum and then transferred onto corresponding SPET slices. In addition, radio-uptake and the specific uptake ratios (SURs) of midbrain were assessed. As a measure of brain SERT availability, the ratio of specific-to-nonspecific ^{123}I-ADAM binding for the midbrain compared to the cerebellum were calculated in mean counts/pixel using the following equation: SUR = specific binding/nonspecific binding = target- cerebellum/cerebellum.

4.2.5. Statistical analysis

Data were analysed by STATISTICA 7.0, STATISTICA 8.0, and SAS 9.1 software. Neuropsychological test performance comparisons between patient groups of focal and generalized epilepsy and control group were performed with one-way analysis of variance (ANOVA) followed by Duncan's post-hoc test of pair-wise comparisons. Significance was set to $p \leq 0.05$. Correlation analyses were used to study the relationship between neuropsychological test scores, demographic as well as epilepsy related factors, and BDI score in all study groups. A multiple regression analysis was carried out to evaluate the effects of demographics, epilepsy related factors, and depression on neuropsychological test measures. Neuropsychological test measures were set as dependent variables and various demographic and epilepsy related factors and BDI score as independent variables.

To compare the results of the subjective complaints questionnaire with the objective test measures, Spearman ranked correlation was used. Linear regression analysis was performed with the subjective complaints questionnaire as a dependent variable and BDI as independent variable. The comparison of depressed vs. non-depressed patient groups was conducted by Mann-Whitney U test. Basic characteristics between depressed and non-depressed patient groups were compared using unpaired Student's t-test. Significance was set at a p-value of 0.05.

For the analysis of SPET imaging study Student's *t*-tests were used to compare variables between the two groups of patients (with symptoms of depression *vs*. without symptoms of depression). A correlation analysis was used to assess the relationship between depression scale scores, demographic, and clinical characteristics, and SERT binding potential.

5. RESULTS

5.1. Demographic and clinical features of the subjects in the neuropsychological assessment and subjective complaints studies

Sixty two patients with epilepsy, treated in the out-patient clinic of Department of Neurology of Tartu University Hospital, which is a tertiary medical centre, were included in the study.

There were 87 patients with epilepsy screened for the study, 19 refused to participate and 6 did not meet inclusion criteria. Of the 62 remaining patients, there were more females (n = 37) than males (n = 25) as indicated in Table 1 which summarizes all demographic and clinical characteristics of the patients and demographic characteristics of control subjects. The mean age of the patients was 34.6 years and mean duration of epilepsy was 19.2 years with a mean age of seizure onset of 15.4 years. All patients had completed the first nine years of regular primary and secondary education and the mean number of formal years of education was 13.4.

Thirty-six of the patients with epilepsy were diagnosed with focal epilepsy and 26 were diagnosed with generalized epilepsy. There were no significant demographic differences between the two groups. The focal epilepsy group had a later onset of epilepsy and a higher number of patients having generalized tonic-clonic seizures on a weekly basis.

Thirty-one patients were on monotherapy, 26 were taking two or more AEDs, and 5 were not taking any medication. Valproate and carbamazepine were the most prevalent medications (both were present in the treatment regimen of 25 patients), followed by lamotrigine (n=12), oxcarbazepine (n=11), topiramate (n=4), phenytoin (n=3), phenobarbital (n=2), primidone (n=1), and levetiracetam (n=1). All participants had an MRI or CT scan of the brain performed. In 15 patients focal pathologies, including hippocampal sclerosis (n = 7) were demonstrated. Atrophy was detected in two patients, nonspecific white matter lesions in 3, arachnoid cysta in 2, and old frontal contusional lesions in 1 patient.

Table 1. Demographic characteristics of the healthy control and epilepsy patient groups along with clinical characteristics of epilepsy patients

Characteristics	Controls (n=53)	Focal epilepsy (n=36)	Gene-ralized epilepsy (n=26)	All Patients with epilepsy (n=62)	P-value
Age[a]	38.2 ± 13.3	36.3 ± 12.3	32.2 ± 8.7	34.6 ± 11	0.13
Gender					0.64
Male	17	15	10	25	
Female	36	21	16	37	
Education (years)[a]	14.8 ± 3.1	12.9 ± 3.6	14.2 ± 4.4	13.4 ± 4	0.06
Duration of epilepsy (years)[a]		18.7 ± 12	19.7 ± 8.1	19.2 ± 10.5	0.14
Age at seizure onset (years)[a]		17.5 ± 15.1	12.7 ± 4.7	15.4 ± 12.1	0.67
Seizure frequency for GTCS					0.0007*
Weekly		10	3	13	
Monthly		12	3	15	
A year		5	19	24	
Medications					0.30
Monotherapy		15 (42%)	16 (61%)	31	
Polytherapy		18 (50%)	8 (31%)	26	
No medication		3 (8%)	2 (8%)	5	

[a] Mean ± standard deviation. * Statistically significant difference; GTCS – generalized tonic-clonic seizures

5.2. Neuropsychological assessment in patients with epilepsy compared to control subjects

The epilepsy patient groups performed significantly worse than the control group on all verbal memory test subscales (Table 2). The control group also scored significantly higher on verbal fluency and Word List Generation tests. While there was a tendency for patients with epilepsy to perform poorer than controls in other tests of attention, concentration, and mental flexibility, as well as non-verbal memory none of these measures were statistically different between groups.

Patients with focal epilepsy scored significantly worse than patients with generalized epilepsy on the BSRT consistent long-term retrieval subscales and on the Word List Generation test. There were no other statistically significant differences between the two epilepsy patient groups, although there was a general tendency of patients with focal epilepsy to have lower scores on all tests of neuropsychological functioning.

Table 2. Comparison of neuropsychological test scores in healthy controls and epilepsy patient groups

	Controls	Focal epilepsy	Generalized epilepsy	F	P
Executive functioning					
SDMT	53.4 ± 11.7	48.6 ± 13.8	50.5 ± 16.2	1.4	NS
Word List Generation	27.1 ± 7.0	22.1 ± 6.4	26.5 ± 8.2	5.7	<0.01
Verbal Fluency	25.7 ± 7.1	14.0 ± 7.0	19.5 ± 7.3	9.2	<0.001
Trail Making A	28.0 ± 8.4	48.1 ± 25.0	44.5 ± 33.2	1.4	NS
Trail Making B	52.7 ± 20.2	116.4 ± 74.7	107.9 ± 98.1	1.5	NS
Verbal memory					
BSRT long-term storage					
Trial 1	6.9 ± 2.3	4.6 ± 2.1	5.3 ± 2.8	10.8	<0.001
Trial 2	8.8 ± 2.4	6.7 ± 2.7	6.6 ± 3.3	9.2	<0.001
Trial 3	10.0 ± 2.1	7.9 ± 2.7	7.8 ± 3.5	9.0	<0.001
Trial 4	10.6 ± 1.9	8.9 ± 2.5	8.8 ± 3.9	6.3	<0.001
Trial 5	11.0 ± 1.7	9.3 ± 2.5	9.5 ± 3.8	5.8	<0.001
Trial 6	11.0 ± 1.7	9.4 ± 2.5	9.5 ± 3.8	5.6	<0.001
Total	58.4 ± 11.3	46.8 ± 14.0	47.5 ± 20.6	8.5	<0.001
BSRT consistent long-term retrieval					
Trial 1	5.8 ± 2.8	2.6 ± 1.9	4.0 ± 2.7	17.2	<0.001
Trial 2	7.4 ± 3.0	3.7 ± 2.7	5.0 ± 3.1	18.1	<0.001
Trial 3	8.5 ± 2.9	4.4 ± 3.0	6.2 ± 3.4	20.3	<0.001
Trial 4	9.4 ± 2.9	5.6 ± 3.1	7.6 ± 4.0	15.0	<0.001
Trial 5	10.1 ± 2.5	6.5 ± 3.3	8.5 ± 4.1	13.7	<0.001
Trial 6	10.1 ± 2.5	6.5 ± 3.3	8.5 ± 4.1	13.7	<0.001
Total	51.3 ± 15.7	29.3 ± 16.4	39.8 ± 20.5	18.0	<0.001
BSRT late recall	10.5 ± 2.0	8.0 ± 2.8	9.0 ± 3.4	10.1	<0.001
Visuospatial memory					
10/36 Spatial Recall					
Trial 1	6.2 ± 2.1	5.7 ± 1.9	6.6 ± 2.9	1.3	NS
Trial 2	7.3 ± 1.9	7.5 ± 2.0	7.8 ± 2.7	0.5	NS
Trial 3	7.9 ± 1.9	8.0 ± 2.0	7.7 ± 3.1	0.1	NS
Total score	21.2 ± 5.4	21.3 ± 4.8	22.2 ± 8.3	0.2	NS
10/36 late recall	7.7 ± 2.2	7.1 ± 2.6	7.6 ± 3.0	0.5	NS
BDI score	9.7 ± 8.0	14.1 ± 12.7	11.6 ± 10.5	1.8	NS

SDMT – Symbol Digit Modalities Test; BSRT – Buschke Selective Reminding Test; BDI – Beck Depression Inventory. All test results are expressed as mean ± standard deviation.

5.3. Prevalence of symptoms of depression in study groups

The mean BDI score for control subjects was 9.7 (± 8.0) compared to 11.6 (± 10.5) for patients with generalized epilepsy, and 14.1 (± 12.7) for patients with focal epilepsy. The difference among groups was not statistically significant. There were 17 (32%) patients with a BDI score above 11 points in the control group, 14 (38.9%) patients above 11 in the focal epilepsy and 10 (38.5%) patients scoring above 11 in the generalized epilepsy group.

5.4. The effect of demographic and clinical variables, and depression on cognitive test scores

Correlation analysis revealed statistically significant correlations between two subscales of BSRT and Trail Making Test B with years of education in the focal epilepsy group (Table 3) while education correlated significantly with most cognitive test measures among patients with generalized epilepsy (Table 4). In the focal epilepsy group frequency of seizures correlated negatively with Verbal Fluency Test, but in the generalized epilepsy group in addition to the Verbal Fluency with tests of visual memory and Trail Making Tests A and B. Interestingly, epilepsy related factors such as age at seizure onset and duration of epilepsy did not have any significant correlations with neuropsychological test measures in the generalized epilepsy group and in the focal epilepsy group duration of epilepsy had only one negative correlation with Verbal Fluency.

The BDI score was significantly correlated with a number of cognitive test scores, including verbal memory subtests, SDMT, Word List Generation and Trail Making Test A and B in the generalized epilepsy group and BSRT delayed recall, SDMT, and Trail Making Test A in the focal epilepsy group. The number of AEDs taken by patients correlated significantly with some tests of executive functioning (Word List Generation and Verbal Fluency, and Trail Making Test A) and verbal memory (BSRT delayed recall) in the focal epilepsy patients group. In the generalized epilepsy group number of AEDs correlated significantly only with Word List Generation test.

Unlike patient groups, BDI score did not have any significant correlations with neuropsychological test measures in the control group (Table 5). In this group age and years of education had statistically significant correlations with majority of test measures.

The results of ANOVA confirmed that in BSRT the presence of symptoms of depression did not influence the results of consecutive verbal memory learning trials in control group (Figure 2), while the gap was wider for the patients with generalized epilepsy with and without symptoms of depression.

Multiple regression analysis revealed that age and years of education were the prominent significant predictive variables for many neuropsychological test measures in the control group (Table 6). BDI score was a significant factor together with age and years of education for the SDMT.

In the focal epilepsy group BDI score was a single predictive variable for the BSRT delayed recall subscale and SDMT, and it was also significant in combination with number of AEDs for the Trail Making Test A. Any other epilepsy related factors except number of AEDs, were not significant in the focal epilepsy group.

In the generalized epilepsy group the only important epilepsy related factor among significant predictors of test performances was seizure frequency (for the 10/36 Spatial Recall total score and Trail Making Test B). BDI score was predictive for the Verbal Fluency and verbal memory subscales (together with years of education). Duration of epilepsy and age at seizure onset were not significant factors in any of the models.

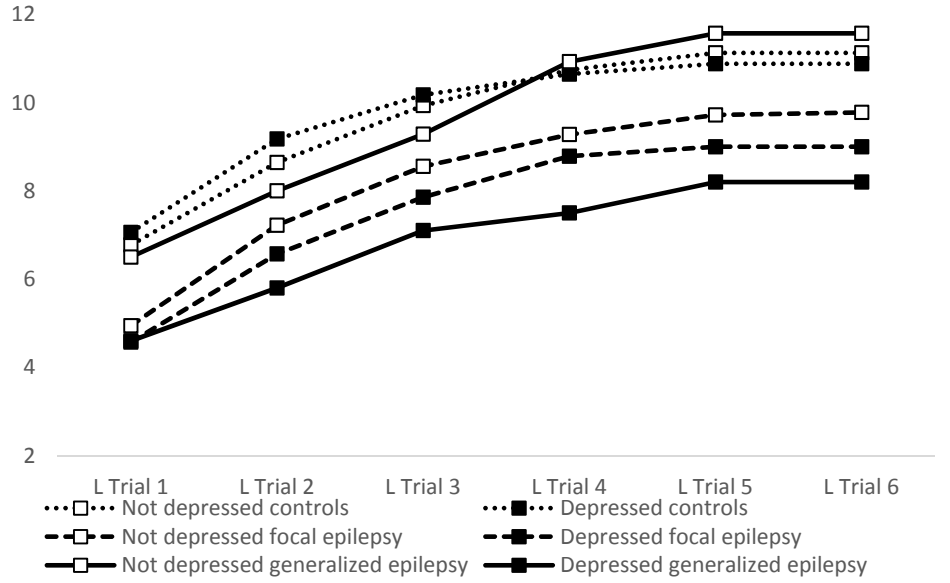

Figure 2. Comparison of patient groups and healthy controls (with and without symptoms of depression) on six verbal memory learning trials (Buschke Selective Reminding Test Long-term Recall). L Trial – learning trial

Table 3. Correlations between demographic factors, epilepsy related factors, depressive symptoms and neuropsychological test scores in focal epilepsy group patients

	BSRT long-term storage	BSRT consistent long-term retrieval	BSRT delayed recall	10/36 total score	10/36 delayed recall	SDMT	Word list generation	Verbal fluency	Trail making A	Trail making B
Age	–0.08	–0.20	–0.08	–0.26	–0.19	–0.10	0.01	–0.14	0.002	0.10
Years of education	0.54*	0.47*	0.35	0.30	0.31	0.24	0.21	0.26	–0.34	–0.37*
Frequency of seizures	–0.17	–0.14	–0.30	0.18	0.05	–0.15	–0.18	–0.41*	0.29	0.05
Seizure onset	0.12	–0.25	0.07	–0.23	0.02	0.03	0.23	0.23	–0.13	0.06
Duration of epilepsy	–0.25	–0.25	–0.18	0.02	–0.23	–0.15	–0.28	–0.46*	0.17	0.03
BDI score	–0.27	–0.29	–0.42*	0.07	0.04	–0.57*	–0.33	–0.25	0.50*	0.27
Number of AEDs	–0.25	–0.19	–0.37*	–0.01	–0.08	–0.31	–0.50*	–0.53*	0.43*	0.35

BSRT – Buschke Selective Reminding Test; SDMT – Symbol Digit Modalities test; BDI – Beck Depression Inventory; AEDs – antiepileptic drugs. * = $P < 0.05$.

Table 4. Correlations between demographic factors, epilepsy related factors, depressive symptoms and neuropsychological test scores in generalized epilepsy syndrome group patients

	BSRT long-term storage	BSRT consistent long-term retrieval	BSRT delayed recall	10/36 total score	10/36 delayed recall	SDMT	Word list generation	Verbal fluency	Trail making A	Trail making B
Age	–0.23	–0.36	–0.23	–0.21	–0.25	–0.45*	–0.30	–0.08	0.27	0.20
Years of education	0.54*	0.57*	0.57*	0.40	0.43*	0.45*	0.30	0.49*	–0.51*	–0.49*
Frequency of seizures	–0.37	–0.36	–0.26	–0.49*	0.47*	–0.39	–0.41	–0.42*	0.62*	0.64*
Seizure onset	–0.31	–0.35	–0.27	–0.18	–0.10	–0.34	–0.26	–0.11	–0.01	0.02
Duration of epilepsy	–0.07	–0.19	–0.11	–0.17	–0.23	–0.28	–0.17	–0.03	0.29	0.19
BDI score	–0.62*	–0.64*	–0.59*	–0.35	–0.33	–0.55*	–0.65*	–0.10	0.49*	0.51*
Number of AEDs	–0.10	–0.22	–0.05	–0.35	–0.36	–0.40	–0.51*	–0.36	0.24	0.16

BSRT – Buschke Selective Reminding Test; SDMT – Symbol Digit Modalities test; BDI – Beck Depression Inventory; AEDs – antiepileptic drugs. * = $P < 0.05$.

Table 5. Correlations between demographic factors, depressive symptoms and neuropsychological test scores in control group subjects

	BSRT long-term storage	BSRT consistent long-term retrieval	BSRT delayed recall	10/36 total score	10/36 delayed recall	SDMT	Word list generation	Verbal fluency	Trail making A	Trail making B
Age	–0.59*	–0.60*	–0.61*	–0.25	–0.31*	–0.53*	–0.17	–0.80*	0.72*	0.97*
Years of education	0.43*	0.43*	0.45*	0.42*	0.36*	0.52*	0.44*	0.23	0.49	0.21
BDI score	0.17	0.15	–0.02	–0.18	–0.03	–0.15	–0.002	0.08	–0.60	–0.38

BSRT – Buschke Selective Reminding Test; SDMT – Symbol Digit Modalities test; BDI – Beck Depression Inventory; AEDs – antiepileptic drugs. * = $P < 0.05$.

Table 6. Results of multiple regression analysis in different groups indicating statistically significant predictive variables for individual neuropsychological test measures. Only models with statistically significant predictive variables are presented.

		β	R	R^2	Adjusted R^2	F
Control group						
BSRT long term storage			0.61	0.37	0.35	14.9*
	Age	–0.47				
	Years of education	0.27				
BSRT consistent long-term retrieval			0.64	0.42	0.39	17.7*
	Age	–0.53				
	Years of education	0.25				
BSRT delayed recall			0.65	0.43	0.4	18.5*
	Age	–0.47				
	Years of education	0.33				
10/36 spatial recall total score			0.37	0.14	0.12	8.03*
	Years of education	0.37				
10/36 delayed recall			0.3	0.09	0.07	4.87*
	Age	–0.3				
SDMT			0.68	0.47	0.43	12.6*
	Age	–0.50				
	Years of education	0.31				
	BDI score	–0.21				
Verbal fluency			0.5	0.23	0.23	16.7*
	Years of education	0.5				
Focal epilepsy group						
BSRT long term storage			0.52	0.27	0.25	11.7*
	Years of education	0.52				
BSRT consistent long-term retrieval			0.41	0.17	0.14	6.4*
	Years of education	0.41				
BSRT delayed recall			0.38	0.14	0.11	4.74*
	BDI score	–0.37				
10/36 delayed recall			0.36	0.13	0.10	4.81*
	Years of education	0.36				

		β	R	R^2	Adjusted R^2	F
SDMT			0.58	0.34	0.31	15.1*
	BDI score	–0.58				
Word list generation			0.49	0.24	0.22	10.6*
	Number of AEDs	–0.49				
Verbal fluency			0.50	0.25	0.21	11.2*
	Number of AEDs	–0.5				
Trail making A			0.65	0.42	0.38	10.0*
	BDI score	0.46				
	Number of AEDs	0.38				
Trail making B			0.48	0.23	0.18	4.43*
	Years of education	–0.29				
	Number of AEDs	0.37				
Generalized epilepsy group						
BSRT long term storage			0.72	0.51	0.47	11.0*
	Years of education	0.37				
	BDI score	–0.49				
BSRT consistent long-term retrieval			0.75	0.56	0.52	13.5*
	Years of education	0.4				
	BDI score	–0.51				
BSRT delayed recall			0.71	0.5	0.45	10.2*
	Years of education	0.42				
	BDI score	–0.44				
10/36 spatial recall total score			0.55	0.3	0.27	10.4*
	Frequency of seizures	–0.55				
Word list generation			0.63	0.4	0.38	16.2*
	Years of education	0.635				
Verbal fluency			0.66	0.44	0.41	17.1*
	BDI score	–0.66				
Trail making A			0.55	0.3	0.27	9.9*
	Years of education	–0.55				
Trail making B			0.61	0.37	0.34	13.6*
	Frequency of seizures	0.61				

BSRT – Buschke Selective Reminding Test; SDMT – Symbol Digit Modalities Test; BDI – Beck Depression Inventory; AEDs – antiepileptic drugs. * – $P<0.05$

5.5. Congruity between perceived cognition and objective neuropsychological assessment

The correlation analysis revealed some weak or non-existent correlations between self-reported complaints and objective test measures of cognitive functioning (Table 7 and 8). However, despite the fact that majority of the results show no statistical significance, generally the correlations between objective neuropsychological tests and subjective complaint items have a trend for negative directionality, except the results of Trail Making A and B test in which higher score is indicative of greater impairment. This could mean that subjects with better neuropsychological functioning tend to have greater subjective complaint rate and vice versa.

The results of the tests assessing verbal and visuospatial memory have no correlations with the complaint of problems with retrieving information from the memory, although there are some negative correlations between subjective forgetting and verbal memory (Table 8). Forgetting has also some correlations with the results of the Symbol Digits Modalities Test and both self-reported memory problems are strongly related to BDI score.

Subjective estimation of problems with attention is not related to any of the results of different tests assessing executive functioning but has a strong positive correlation with BDI (Table 8). More general subjective complaints of fatigue, headache, and pain, problems with vision or speech have no correlation with different neuropsychological tests on a statistically significant level. Interestingly self-reported disturbances of coordination or dizziness show some negative correlations with measures of verbal memory, sustained attention, concentration and executive functions.

As the majority of self-reported complaints have a strong correlation with the results of BDI, so does the subjective questionnaire total score.

Linear regression analysis with subjective complaints questionnaire total score as a dependent variable and BDI as an independent variable resulted in $r^2=0.362$, $P<0.05$, indicating that 36% of subjective complaints can be explained by the BDI score. Adding demographic or neuropsychological variables to the regression model did not reveal any statistically significant factors influencing the subjective complaint rate.

The results of the t-test were calculated by dividing patients into two groups on the basis of presence or lack of depressive symptoms, defined as a score over or under 11 points in the BDI (Table 9). Altogether there were 24 (38.7%) patients with a BDI score over 11 points. The two groups of patients did not have statistically significant differences in age, years of formal education, or duration of epilepsy.

Patients with higher scores on BDI were presenting statistically significantly more complaints concerning subjective cognitive functioning on all subscales of the subjective complaints questionnaire, except speech and pain (Figure 3).

Table 7. Correlation between self-reported complaints of memory and mood and the results of specific neuropsychological measures of memory, executive functioning and BDI.

	Buschke Selective RemindingTest			10/36 Spatial Recall Test		Symbol Digits Modalities Test	Word List Generation	Verbal Fluency	Trail Making Test		BDI
	Long – term storage	Consistent long-term retrieval	Delayed recall	Total score	Late retrieval				Part A	Part B	
Problems with retrieving information from the memory	–0.169	–0.258	–0.218	–0.234	–0.211	–0.251	–0.244	–0.05	0.127	0.210	0.553*
Forgetting	–0.206	–0.246	–0.284*	–0.181	–0.109	–0.279*	–0.114	–0.064	0.113	0.091	0.313*
Mood	–.219	–0.400*	–0.346*	–0.081	–0.171	–0.397*	–0.326*	–0.298*	0.179	0.341*	0.648*

BDI – Beck Depression Inventory

Table 8. Correlation between self-reported complaints of attention, coordination, speech, vision and subjective complaints questionnaire total score and the results of specific neuropsychological measures of memory, executive functioning and BDI.

	Buschke Selective Reminding Test			10/36 Spatial Recall Test		Symbol Digits Modalities Test	Word List Generation	Verbal Fluency	Trail Making Test		BDI
	Long-term storage	Consistent long-term retrieval	Delayed recall	Total score	Late retrieval				Part A	Part B	
Problems with attention	–0.158	–0.163	–0.217	0.242	0.255	–0.115	–0.088	0.059	–0.075	–0.082	0.433*
Coordination	–0.183	–0.303*	–0.322*	–0.239	–0.169	–0.314*	–0.290*	–0.246	0.343*	0.340*	0.351*
Dizziness	–0.281*	–0.355*	–0.360*	–0.047	–0.028	–0.370	–0.304*	–0.190	0.215	0.311*	0.371*
Problems with speech	0.038	0.037	–0.020	0.068	0.025	–0.022	–0.036	0.112	0.029	–0.051	0.299*
Fatigue	–0.152	–0.237	0.231	0.107	0.058	–0.220	–0.181	0.006	–0.015	0.068	0.443*
Headache	–0.196	–0.266*	–0.243	0.005	–0.015	–0.283	–0.229	–0.028	0.180	0.220	0.449*
Pain	–0.031	–0.114	–0.010	0.079	0.093	–0.024	0.126	0.083	0.001	0.057	–0.008
Problems with vision	–0.106	0.005	–0.134	0.131	0.086	–0.160	–0.249	–0.256	0.189	0.257	0.264
Subjective complaints total score	–0.211	–0.348*	–0.357*	–0.064	–0.052	–0.377*	–0.350*	–0.201	0.238	0.316*	0.628*

Table 9. Characteristics of groups with respect to BDI score.

	BDI < 11 (N=32)	BDI > 11 (N=24)	P value
Age	33.8 (±11.5)	35.3 (±10.8)	P>0.05
Gender			
Male	16 (28.6%)	5 (8.9%)	
Female	16 (28.6%)	19 (33.9%)	
Years of education	14.5 (±3.7)	12.9 (±4)	P>0.05
Duration of epilepsy	17.4 (±10)	19.8 (±10.1)	P>0.05
Age at seizure onset	16.4 (±12)	15.5 (±12.8)	P>0.05
AEDs			
No medications	2	3	
Monotherapy	21	8	
Polytherapy	9	13	
Subjective complaints total score	23.3	31	P<0.05

The comparison of patients presenting depressive symptoms with patients not presenting any indication of depression for objective neuropsychological test measures of memory revealed statistically significant differences on the delayed recall of BSRT, with the group of patients showing indications of depression scoring lower. Regarding the measures of executive functioning, there were significant differences in the Symbol Digit Modalities Test, the Word List Generation and Trail Making Test Part A and B (Figures 4 and 5), indicating the negative effect of depressive symptoms on objective executive test measures.

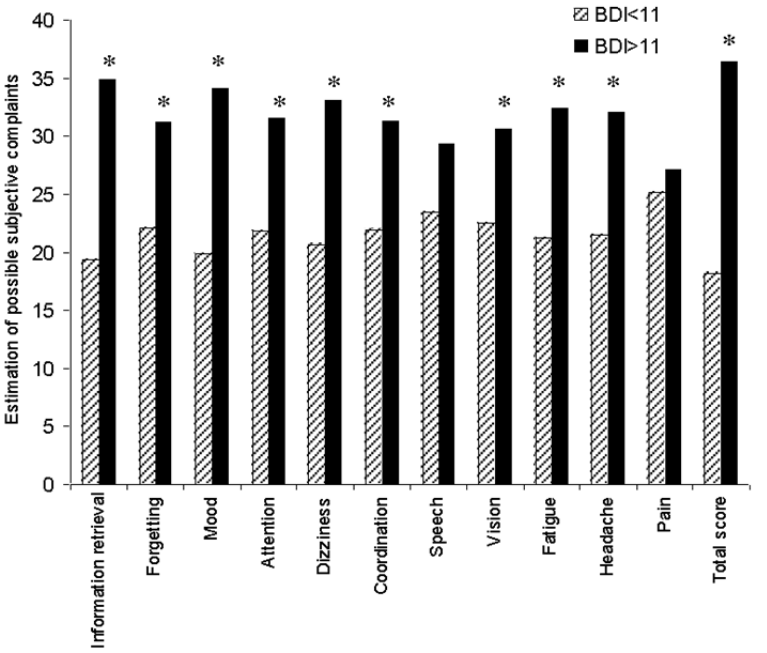

Figure 3. The distribution of subjective cognitive complaints in groups of patients with or without the presence of depressive symptoms, with a BDI (Beck Depression Inventory) score over 11 points as a marker for the presence of depressive symptoms. Statistically significant difference of p-value < 0.05 is marked with asterisks.

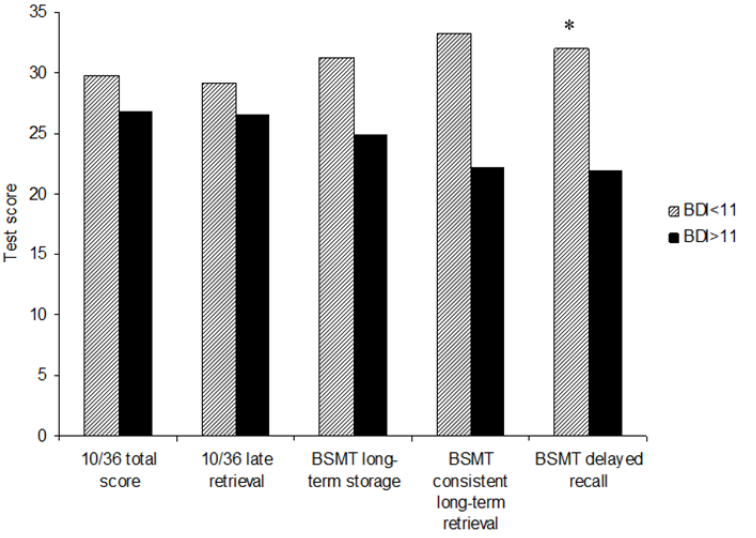

Figure 4. The distribution of objective neuropsychological test measures of memory in groups of patients with or without the presence of depressive symptoms. Group means presented. BDI – Beck Depression Inventory; 10/36 – 10/36 Spatial Recall Test; BSMT – Buschke Selective Memory Test.

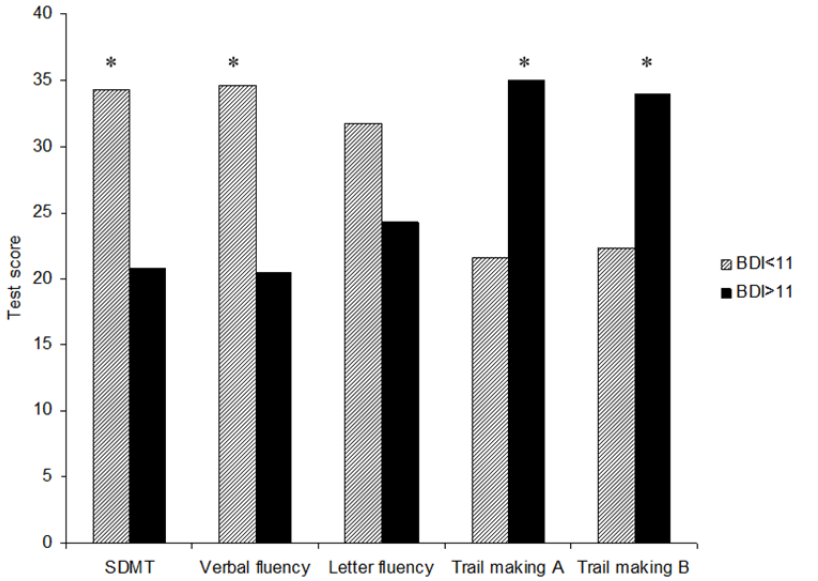

Figure 5. The distribution of objective neuropsychological test measures of executive functioning in groups of patients with or without the presence of depressive symptoms. Group means presented. BDI – Beck Depression Inventory; SDMT – Symbol Digit Modalities Test.

5.7. Clinical characteristics of subjects for the ^{123}I-ADAM SPET imaging

A summary of patient characteristics of the ^{123}I-ADAM SPET imaging study, including their demographic and clinical characteristics is included in Table 9. (7 men and 5 women; ages ranging from 21 to 55 years; mean age 36.3 ± 8.9 years). Seven patients had focal epilepsy; six of these had had long-term EEG monitoring performed in order to define focus localization. Of these seven patients, six patients had TLE (two with right sided and four with left sided TLE) and one patient had probable frontal lobe epilepsy (FLE; lateralization to the right side). Five patients had generalized epilepsy syndrome. MRI scans for the generalized epilepsy patients were all normal. On the MRI, three patients with focal epilepsy presented with mesial temporal sclerosis, one with hippocampal atrophy, and one with cysts in temporomesial structures. Epilepsy could be considered treatment resistant in the majority of the patients, eight of whom were on polytherapy with antiepileptic drugs (AEDs). The patients with focal epilepsy, as a group, were comparable to the patients with generalized epilepsy regarding age, age at epilepsy onset, epilepsy duration, use of AEDs, as well as their mean BDI and EST-Q questionnaire scores.

5.6. Prevalence of symptoms of depression in ^{123}I-ADAM SPET imaging study group

Seven patients had BDI and EST-Q depression subscale scores greater than 11 points, which was interpreted as the presence of symptoms of depression. The mean BDI and EST-Q depression subscale scores for the whole patient group were 11.5±6 and 14±4.3, respectively. The maximal BDI score was 20; in all patients with symptoms of depression, the BDI score was in the range of mild to moderate severity.

In the current study, patients with symptoms of depression, as a group, did not significantly differ from patients without symptoms of depression in either demographic or clinical variables (Table 11). A comparison of these patient groups indicated that patients with symptoms of depression showed a trend towards a longer duration of epilepsy, which did not reach statistical significance.

5.7. ^{123}I-ADAM binding to SERT

Using SPET, we observed that ^{123}I-ADAM binding to SERT did not differ significantly between the patients with epilepsy who had symptoms of depression *vs*. those without. In addition, SERT binding potential of ^{123}I-ADAM did not show any statistically significant correlation with either the BDI or the EST-Q depression subscale scores. SERT binding potential was also not correlated with any demographic or clinical characteristics, including age, duration of epilepsy, or age at disease onset. We also observed that the SERT binding potential did not differ between patients with focal *vs*. generalized epilepsy.

Table 10. Demographic and clinical characteristics, presence of symptoms of depression and ^{123}I-ADAM binding potential to SERT of individual patients.

Age (years)	Sex	Age at onset (years)	Duration of epilepsy (years)	Frequency of seizures	Syndrome	Localization	Interictal EEG	LTM	MRI	AEDs (daily dose, mg)	Symptoms of depression	^{123}I-ADAM binding to SERT
32	M	17	15	2–5/mo	Generalized	N/A	Generalized spike-wave activity	Not performed	Normal	LEV (2000) VPA (1800) LTG (75)	No	1.3
24	F	5	19	1/mo	Generalized	N/A	Generalized spike-wave activity	Not performed	Normal	VPA (1500) OXC (1200)	No	1.39
36	M	21	15	1/year	Generalized	N/A	Negative	Not performed	Normal	VPA (600)	No	0.87
21	F	15	6	3/week	Generalized	N/A	Generalized spike-wave activity	Generalized tonic.clonic seizures	Normal	LTG (400) OXC (600)	Yes	1.36
55	M	23	32	1/mo	Generalized	N/A	Generalized spike-wave activity	Not performed	Normal	VPA (2000) LTG (150)	Yes	1.16
39	M	27	12	2/year	Focal	Left temporal	Left temporal interictal discharges	Left temporal ictal activity	Small cysts in left temporomesial structures	LTG (250)	No	1.42
40	F	24	16	4–5/mo	Focal	Left temporomesial	Left temporal interictal discharges	Left temporal ictal activity	Colloidal cyst in left frontotemporal regions	PB (50) LTG (200)	No	1.1

Table 10. Continuation

Age (years)	Sex	Age at onset (years)	Duration of epilepsy (years)	Frequency of seizures	Syndrome	Localization	Interictal EEG	LTM	MRI	AEDs (daily dose, mg)	Symptoms of depression	^{123}I-ADAM binding to SERT
38	M	22	16	1/mo	Focal	Left temporal	Negative	Not performed	Hippocampal atrophy on the left side	OXC (1800) VPA (900)	Yes	0.98
42	M	4	38	4–6/mo	Focal	Right temporomesial	Right temporal interictal discharges	Right temporal ictal activity	Mesial temporal sclerosis on the right side	PHT (375)	Yes	1.28
42	F	14	28	2/mo	Focal	Right frontal	Negative	Right frontal ictal activity	2 small hyperintensive lesions in the right parietal lobe	OXC (1800)	Yes	1.46
34	F	7	27	4–5/week	Focal	Left temporo-mesial	Left temporal interictal discharges	Left temporal ictal activity	Mesial temporal sclerosis on the left side	VPA (1000) TPM (100)	Yes	1.32
32	M	2	30	3/week	Focal	Right temporo-mesial	Right temporal interictal discharges	Right temporal ictal activity	Mesial temporal sclerosis on the right side	OXC (1800) TPM (400)	Yes	1.26

EEG – electroencephalography; LTM – long-term monitoring; MRI – magnetic resonance imaging; AEDs – antiepileptic drugs; LEV – levetiracetam; VPA – valproate; LTG – lamotrigin; OXC – oxcarbazepine; PB – phenobarbital; PHT – phenytoin; TPM – topiramate; ^{123}I-ADAM – 2-((2-((dimethylamino)methyl)phenyl)thio)-5-(123)iodophenylamine; SERT – serotonin transporter

Table 11. Comparison of clinical characteristics, depression questionnaire results and SERT binding affinity on ^{123}I-ADAM between groups of patients with symptoms of depression (BDI and EST-Q score > 11 points) and without symptoms of depression

	Symptoms of depression (n=7)	No symptoms of depression (n=5)	*P*-value
Age	37.7 (± 10.5)	34.2 (±6.5)	NS
Age at onset	12.4 (±8.4)	18.8 (±8.6)	NS
Duration of epilepsy	25.3 (±10.8)	15.4 (±2.5)	NS
BDI	15.3 (±3.8)	6.0 (±1.4)	0.004
EST-Q	15.8 (±2.6)	7.0 (±1.0)	0.04
^{123}I-ADAM binding to SERT	1.26 (±0.2)	1.216 (±0.2)	NS

NS – not significant; BDI – Beck Depression Inventory; EST-Q – Emotional State Questionnaire; ^{123}I-ADAM – 2-((2-((dimethylamino)methyl)phenyl)thio)-5-(123)iodophenylamine; SERT – serotonin transporter

6. DISCUSSION

6.1. Neuropsychological assessment and symptoms of depression

This part of the study aimed to describe cognitive functioning and depression in a group of patients with focal and generalized epilepsy syndromes in comparison with healthy control subjects, to detect if depression is correlated with the neuropsychological functioning, and to evaluate possible significant sociodemographic and disease-related predictors of performance on neuropsychological measures.

In agreement with previous descriptions in the literature (Kwan and Brodie, 2001; Barr, 2007; Badawy *et al.*, 2012), the overall neuropsychological performance of patients with epilepsy was somewhat worse than in healthy volunteers, especially in the subscales of verbal memory and verbal fluency domains.

Among the two groups of epilepsy patients, those with focal onset epilepsy tended to perform worse on all tests of cognitive functioning compared to those with generalized epilepsy. However, the difference between the groups only reached statistical significance in verbal memory long-term retrieval subscales and word list generation.

While our results indicate that the performance on subtests of verbal memory and word list generation was poorer in the generalized epilepsy group than in the control group, we expected to see a wider area of affected domains in this patient population. Memory disturbances have been previously described in patients with generalized epilepsy but impairment of executive functioning is emphasized in the majority of prior studies (Hommet *et al.*, 2006; Dickson *et al.*, 2006; Piazzini *et al.*, 2008; Schmitz *et al.*, 2013). Research on juvenile myoclonic epilepsy has found certain thalamo-frontal circuits as the possible cause of these disturbances (Pulsipher *et al.*, 2009). Controversially, several studies have shown that patients with different localizations of focal epilepsy or generalized epilepsy cannot be reliably differentiated based on their neuropsychological performance (Exner *et al.*, 2002). This may be the case in our study group as well. The present finding may also be explained by the heterogeneity of the generalized epilepsy group, since it included patients with juvenile myoclonic epilepsy as well as patients with absence epilepsy. This heterogeneity may account for the similar cognitive profile between patients with generalized epilepsy and patients with focal epilepsy in our study.

Depression was more prevalent among both groups of patients with epilepsy (38.9% in the focal epilepsy group and 38.5% in the generalized epilepsy group) compared to previous studies on depression in the general population. According to the general population study in Estonia the prevalence of depressive symptoms is 11.1%, with a female preponderance (Aluoja *et al.*, 2004) and the point prevalence of major depressive episode in the Estonian

population was 5.6% (Kleinberg *et al.*, 2010). Interestingly, the prevalence of depression in our control group was higher (32%) than in the general population and almost as high as in our patient groups. This finding may be explained by a relatively small study sample and relatively large proportion of female subjects in the control group. Since BDI is a subjective self-rating scale and we did not perform thorough psychiatric assessment to all patients and control subjects in order to confirm the diagnosis of depression on clinical grounds, there is a chance that not all subjects with symptoms of depression are clinically depressed and vice versa. This could change the prevalence rate of depression among our study sample and influence our results on both directions, but in this case it would affect both patient and control groups and we could still estimate the difference between groups.

Depression scale scores showed negative associations with performance on number of neuropsychological tests and it appeared to be an important predictive factor for several neuropsychological test measures in both patient groups, but not in the control group. The influence of depressive symptoms to neuropsychological status in patients with epilepsy has been previously reported (Paradiso *et al.*, 2001; Dulay *et al.*, 2012). However, in other studies (Pulliainen *et al.*, 2000; Tracy *et al.*, 2007; Taylor *et al.*, 2010) the authors did not find that depression influenced cognitive functioning in patients with epilepsy. Tracy *et al.* surmised in their paper, however, that the overall level of depression found in their study may have been too mild to exert an effect on cognition. In a study of male patients with idiopathic epilepsy, BDI score was not significantly correlated with performance on any cognitive scales (Shehata *et al.*, 2009) and these results were particularly surprising since the mean BDI scores in their patient groups were extremely high.

In studies of depression, deficits in episodic memory, working memory, and more widely in various executive functions are commonly described (Murrough *et al.*, 2011). In our study, verbal memory scores, verbal fluency and various test of executive functioning were associated with BDI score.

Depression in patients with epilepsy could be the result of interplay between several factors including stigma, illness-related, and psychosocial factors but recent investigations addressing the comorbidity of epilepsy and depression have led to the concept of their common pathogenesis (Kanner *et al.*, 2009). This idea is supported by the fact that epilepsy is associated with increased risk for depression, but depression could also be a risk factor for acquiring epilepsy (Kanner *et al.*, 2009). If this is true and both disorders are separately associated with increased risk for cognitive dysfunction, it could mean that patients with epilepsy bear double risk for neuropsychological disturbances. Our results, therefore, stress the importance of recognizing and treating depression in patients with epilepsy. Remission of symptoms of depression could have positive effects on cognitive functioning, and patients with epilepsy could gain in several factors influencing their quality of life.

Education was an important factor in determining neuropsychological test measures in patient groups (especially in the generalized epilepsy group) and in the control group. The correlation between education and neuropsychological measures has been previously noted (Lespinet *et al.*, 2002). This again indicates that good education may give better reserves for people with epilepsy in coping with possible cognitive dysfunction. Education has been shown to prevent long-term effects of cognition in TLE (Jokeit and Ebner, 1999). Also, in a study with patients with JME, the group of patients with > 11 years of education did not undergo the same cognitive decline with increasing number of years with epilepsy as patients with < 11 educational years (Pascalicchio *et al.*, 2007).

There was surprisingly few strong associations between epilepsy related factors and cognitive test measures. Frequency of seizures showed few correlations with tests of executive functioning in generalized epilepsy group and number of AEDs had a correlation with executive functioning in the focal epilepsy group, but age at seizure onset and duration of epilepsy did not have almost any associations with cognitive functioning. The latter are also considered to be important epilepsy-related factors in the development of cognitive dysfunction (Jokeit and Ebner, 1999; Kwan and Brodie, 2001; Hendriks *et al.*, 2004).

Our study has several limitations, including small sample size, female preponderance, and heterogeneity of the patient groups, as mentioned before. Also, high number of correlations increases the risk of alpha/type I error. Although, multiple regression analysis indicated compatible tendencies with correlation analysis in the current study.

6.2. Congruity between subjective and objective cognitive functioning

The second part of the study aimed to compare the subjective and objective neuropsychological functioning in different cognitive domains of patients with epilepsy and to estimate the influence of depressive symptoms on these measures, especially on subjective complaint rate.

The results confirmed that in general, with some exceptions, subjective cognitive complaints are not strongly associated with the results of objective cognitive functioning measures in epilepsy patients. Although there was a trend for negative correlations, possibly referring to the tendency of patients with better neuropsychological functioning presenting more self-reported problems and vice versa.

Memory is one of the most widely investigated areas of subjective complaints in the epilepsy population, since self-reported memory problems are one of the most frequent subjective complaints in patients with epilepsy, and since objective memory decline in certain cases of epilepsy is also well documented. It is known from previous studies that patients with epilepsy tend

to present more complaints about their memory than control subjects (Hendriks *et al.*, 2002) and that there are very weak associations between subjective and objective memory performance in these patients (Piazzini *et al.*, 2001; Marino *et al.*, 2009). As expected, the results of the study showed that the estimation of self-perceived memory was not associated with objective test measures of memory, although there were some correlations between the complaint of forgetting and verbal memory test scores. Similarly, problems with attention did not have any consistent association with the results of test of executive functioning.

The discrepancy described does not have a very clear explanation, although depression has been one of the main factors thought to influence self-perceived memory in patients with epilepsy (Corcoran and Thompson, 1993; Piazzini *et al.*, 2001; Fargo *et al.*, 2004). Correlation analysis indicated that the majority of subjective complaints had a strong correlation with the BDI score, and regression analysis revealed that the score in BDI could explain up to 36% of subjective complaints in our study. It is a statistically significant amount, but there is still 64% not explained by that factor. As presented, the distribution of subjective complaints in two groups of patients – with or without depressive symptoms – differed on a statistically significant level. More general subjective complaints had similar associations with the symptoms of depression as more specific cognitive complaints. The distribution of neuropsychological test results also had some significant differences in the two groups of patients. Depression does not only influence the general subjective complaint rate but may also have some deteriorating influences on objective neuropsychological functioning. These results stress even more the need to look for and to treat any depressive symptoms in patients with epilepsy.

The majority of patients with epilepsy taking AEDs associate their subjective cognitive complaints with side-effects of the drugs (Carpay *et al.*, 2005). Doctors in their everyday practice and numerous clinical research trials rely often on patient self-reported cognitive performance when assessing the side-effects of AEDs (May, 2013). In a study of medical records of 1694 adult patients with epilepsy taking AEDs the cognitive side-effects of the drugs were assessed and no other predictor of cognitive side-effect rate except AEDs was found (Arif *et al.*, 2009). Paradoxically, in this study, no data regarding the objective neuropsychological functioning was obtained. These authors also concluded that comorbid psychiatric conditions were not significant predictors of cognitive side-effects but did not use any of the measures for state of mood at the moment of cognitive complaint assessment (Arif *et al.*, 2009). Therefore, subjective cognitive complaints are very often taken at the face value and are associated with side-effects of AEDs without any objective basis. In a study by Marino *et al.* it was shown that subjective perception of AED cognitive effects was mainly predicted by mood (Marino *et al.*, 2009). The results of our study emphasize that subjective complaints should not be trusted as the indication of cognitive impairment but may be the sign of concurrent mood disorder.

Comparable results have been found in studies of subjective and objective functioning and depression in other chronic disorders as multiple sclerosis (Maor *et al.*, 2001) or after moderate to severe head injury (Lannoo *et al.*, 1998). Additionally, it has been shown that alleviation of depression results in improvement of subjective memory status (Antikainen *et al.*, 2001).

There are a few limitations to this study, including rather small sample. The fact that the department of neurology is a university hospital may mean that patients referred to this out-patient clinic may have more serious epilepsy than would be the case for patients in a population-based study and may result in selection bias. The correlation between subjective memory complaints and objective measures could depend a great deal on study sample selection. There is a study on a very well defined intractable TLE group after epilepsy surgery that indicates a strong correlation between objective and subjective memory performance (Gleißner *et al.*, 1998), probably because these patients are well informed about the possible memory loss and their actual memory performance.

6.3. SERT binding in patients with epilepsy and depression

In the last part of the study, we sought to study SERT binding properties in the midbrain region in patients with epilepsy, and to determine whether SERT binding differed between depressed vs. non-depressed patients with epilepsy. Our results did not indicate any difference in SERT binding potential between these patient groups.

There could be several reasons for these negative results. Previous work with PET and SPET tracers for SERT in depressed patients has shown some conflicting results. The majority of reports show increased SERT binding in the thalamus and limbic regions of depressed patients compared to controls (Cannon *et al.*, 2007), but others have shown decreased SERT binding potential in the amygdala and midbrain of depressed patients (Malison *et al.*, 1998; Lehto *et al.*, 2006; Parsey *et al.*, 2006). Studies using ^{123}I-ADAM SPET to measure SERT binding in major depressive disorder have also indicated decreased SERT binding in the midbrain, medial temporal lobe, and basal ganglia of depressed patients compared to controls (Newberg *et al.*, 2005; Newberg *et al.*, 2012). At the same time, however, reports showing no differences in midbrain SERT availability for ^{123}I-ADAM in patients with depression compared to healthy controls have also been published (Herold *et al.*, 2006; Catafau *et al.*, 2006). It has been hypothesized that in case of major depressive disorder the SERT binding potential is elevated, but in major depressive disorder with comorbid psychiatric illnesses, regional SERT binding could be decreased (Meyer, 2007). Taking this into account, and considering the fact that almost no SERT binding studies have been done in patients with epilepsy, it could be difficult to predict the directionality of alterations in SERT binding in patients with epilepsy and

comorbid depression. Addressing this hypothesis more fully would likely require a study with a larger sample size.

Another contributing factor to these negative results may be the genetic variability that has been shown for SERT expression in the human brain. For example, individuals with polymorphisms in the promoter (5-HTTLPR) of the *SLC6A4* gene, which encodes the SERT protein, exhibit differences in SERT binding properties in neuroimaging studies (Ruhe at al., 2009; van Dyck *et al.*, 2004; Joensuu *et al.*, 2010). Genetic studies have shown that there may even be an association between the presence of the combined 5-HTTLPR and 5-HTTVNTR genotype, which results in less efficient transcription of SERT, and the presence of TLE (Schenkel *et al.*, 2011). Genetic variability of SERT expression may influence the development of affective disorders, it would likely affect SERT imaging studies, and could even be related to epileptogenesis. Unfortunately, in the current study we did not genotype our patients for polymorphisms in *SLC6A4*.

There are several limitations to the current study. Perhaps the most important, and the one likely to be largely responsible for our negative results is the relatively small study sample size. The statistical power of the comparison of SERT binding in groups of patients with and without depression was 0.755. We calculated that increasing the power to 0.8 under the same conditions would need 40 subjects, which considering the nature and cost of SPET imaging, would be unachievable.

Since in all patients with symptoms of depression, the BDI score was in the range of mild to moderate severity, it could also be considered as a weakness contributing to the negative results of our study.

The heterogeneity of our study group, regarding the clinical characteristics of epilepsy, could have also led to the observed lack of differences in SERT binding properties. The characteristics of depression, depression-related treatment outcomes, and serotonergic system involvement based on 5-HT_{1A} receptor imaging studies, are all well-documented in cases of TLE. Little is known about the same aspects in case of focal extra-temporal epilepsies and even less about generalized epilepsy syndromes. Although some findings have indicated that depression could be specifically related to TLE and mesial temporal sclerosis (Quiske *et al.*, 2000), this has not been confirmed by other reports (Swinkels *et al.*, 2006). It has been shown that the prevalence of depression is similar between patients with TLE and FLE. There are no reports of focal *vs*. generalized epilepsy in terms of the prevalence of depression. One work assessed symptoms of anxiety and found that patients with FLE have much higher anxiety scores than patients with generalized epilepsy (Tang *et al.*, 2012). In our study, groups of patients with focal *vs.* generalized epilepsy were comparable in terms of presence of depressive symptoms.

These previous findings seem to indicate that the bidirectional relationship between epilepsy and depression is not specific to TLE. It has been shown that preoperative depressive symptoms predict postoperative seizure outcome in

both TLE and FLE (Metternich *et al.*, 2009). Therefore, common pathogenic mechanisms may be involved in the etiology of depression comorbid with different epilepsy syndromes, and we would expect that this should be demonstrable in patients having different clinical characteristics of epilepsy, such as those included in the current study. Our findings support the notion that depression and the involvement of the serotonergic system in various epilepsy syndromes requires a deeper exploration with further studies.

6.4. Practical implications and future perspectives

Although, cognitive functioning in PWE has been extensively studied in the last decades, several questions still remain unanswered. There is a need for larger long-term studies of cognition in PWE in order to elucidate the long-term effects of epilepsy and associated factors on cognition. Some studies have indicated that cognitive disturbances, depression, and reduced quality of life may be present in the very beginning of epilepsy or may even precede the first seizure. Does this apply to the subjective cognitive complaints? Could these measures be used to predict the treatment outcome and find the patients with potentially refractory epilepsy much earlier?

The results of our study and other similar studies highlight the importance of education as one of the factors which may prevent the appearance of cognitive deficits, at least to some extent. Simultaneously, PWE are frequently limited in terms of academic achievement. Whether cognitive disturbance itself or psychosocial problems and stigma, result in educational underachievement which is frequently described by PWE. A vicious circle may be formed when neuropsychological problems disturb academic achievement and poor education fails to prevent further cognitive decline in later years of life. Therefore, helping to "climb as high" as possible in academic terms, increasing the possibilities for education, and making a maximal effort to control the disorder during the school-years, would probably decrease the cognitive comorbidities of epilepsy.

For every-day practice, the importance of depression screening and management is stressed by the finding that prevalence of symptoms of depression in PWE is high. As it appeared in our studies, depression had an effect on neuropsychological functioning. It may indicate that this feared double burden of cognitive disturbances due to epilepsy and concurrent depression is a reality indeed. Further, larger sample, studies should investigate the effect of depression on cognitive functions in PWE and it would be interesting to see if treatment of depression could have a positive effect on cognition in patients with epilepsy.

A great number of PWE, many neurologists, and numerous drug research trials have associated subjective cognitive complaints uniformly with side-effects of AEDs. Our study as well as other studies have found that subjective cognitive complaints should not be taken at face value for cognitive dysfunction and should be validated by objective measures of cognition. Few studies have

assessed the influence of symptoms of depression on AED side-effects and have found a significant association between these (Marino *et al.*, 2009). These issues extend beyond theoretical interest and have important clinical implications since diagnostics, treatment, research and regulatory decisions rely on them.

Depression can reveal itself by several indirect symptoms. In a patient with epilepsy who expresses multiple subjective complaints – including complaints of AED side-effects and cognitive problems – symptoms of concurrent depression should be searched.

Regarding the serotonergic system involvement, there is a need for further studies addressing the role of 5-HT receptor in epilepsies arising in other brain areas outside the temporal lobe. Could 5-HT or SERT imaging be used as a biomarker for treatment options in patients with epilepsy and depression? And last but not least, could SSRIs have true antiepileptic properties and could they be used as antiepileptic drugs in patients with epilepsy (Hamid and Kanner, 2013)?

7. CONCLUSIONS

1. The present study indicated that patients with epilepsy, especially focal epilepsy, have cognitive disturbances which are most apparent in the verbal memory and verbal fluency domains compared to the healthy control subjects. Age and education were the main sociodemographic factors influencing neuropsychological test measures in both patients with epilepsy and control test subjects.

2. Epilepsy related factors such as duration of illness, age at onset, or frequency of seizures showed surprisingly few associations with cognitive test measures.

3. Study groups of both focal and generalized epilepsy had a high proportion of subjects with symptoms of depression, and depression showed compounding negative effects on cognitive functioning only in patients with epilepsy, it is therefore emphasized that depression needs to be adequately diagnosed and treated in this patient population.

4. The results of this study show the lack of overlap between the measures of subjective complaints and objective neuropsychological functioning in patients with epilepsy. The need to investigate different subjective complaints, not only memory problems is stressed.

5. Self-reported functioning appears to be affected by the presence of depressive symptoms.

6. The results of our SERT SPET imaging study failed to demonstrate alterations of SERT binding potential in patients with epilepsy with symptoms of depression compared to patients with epilepsy without symptoms of depression. Further studies are needed to clarify the role of SERT and, more generally, the serotonergic system in the common pathogenesis of epilepsy and depression.

8. REFERENCES

Adams SJ, O'Brien TJ, Lloyd J, Kilpatrick CJ, Salzberg MR, Velakoulis D. Neuropsychiatric morbidity in focal epilepsy. Br J Psychiatry 2008; 192: 464–469.

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

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

Aldenkamp A, Arends J. The relative influence of epileptic EEG discharges, short nonconvulsive seizures, and type of epilepsy on cognitive function. Epilepsia 2004a; 45: 54–63.

Aldenkamp A, Arends J. Effects of epileptiform EEG discharges on cognitive function: is the concept of „transient cognitive impariment“ still valid? Epilepsy Behav 2004b; 5: 25–34.

Aldenkamp AP, Baker GA, Meador KJ. The neuropsychology of epilepsy: what are factors involved? Epilepsy & Behav 2004; 5: S1–S2.

Aldenkamp AP, Bodde N. Behaviour, cognition and eplepsy. Acta Neurol Scand 2005; 112: 19–25.

Alper K, Schwartz KA, Kolts RL, Khan A: Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. Biol Psychiatry 2007, 62: 345–354.

Aluoja A, Leinsalu M, Shlik J, Vasar V, Luuk K. Symptoms of depression in the Estonian population: prevalence, sociodemographic correlates and social adjustment. Journal of Affective Disorders 2004; 78: 27–35.

Aluoja A, Shlik J, Vasar V, Luuk K, Leinsalu M. Development and psychometric properties of the Emotional State Questionnaire, a self-report questionnaire for depression and anxiety. Nord J Psychiatry 1999, 53: 443–449.

Andelman F, Zuckerman-Feldhay E, Hoffien D, Fried I, Neufeld MY. Lateralization of deficit in self-awareness of memory in patients with intractable epilepsy. Epilepsia 2004; 45: 826–833.

Antikainen, R., Hänninen, T., Honkalampi, K., Hintikka, J., Koivumaa-Honkanen, H., Tanskanen, A., Viinamäki, H., 2001. Mood improvement reduces memory complaints in depressed patients. Eur Arch Psychiatry Clin Neurosci 251, 6–11.

Arif H, Buchsbaum R, Weintraub D, Pierro J, Resor SR Jr, Hirsch LJ. Patient-reported cognitive side effects of antiepileptic drugs: predictors and comparison of all commonly used antiepileptic drugs. Epilepsy Behav 2009; 14: 202–209.

Attarian H, Vahle V, Carter J, Hykes E, Gilliam F. Relationship between depression and intractability of seizures. Epilepsy Behav 2003; 4: 298–301.

Auriel E, Landov H, Blatt I, Theitler J, Gandelman-Marton R, Chistik V, Margolin N, Gross B, Parmet Y, Andelman F, Neufeld MY. Quality of life in seizure-free patients with epilepsy on monotherapy. Epilepsy Behav 2009; 14: 130–133.

Austin JK, Harezlak J, Dunn DW, Huster GA, Rose DF, Ambrosius WT. Behavior problems in children before first recognized seizures. Pediatrics 2001; 107: 115–122.

Avanzini G, Franceschetti S. Cellular biology of epileptogenesis. Lancet Neurology 2003; 2: 33–42.

Babu CS, Satishchandra P, Sinha S, Subbakrishna DK. Co-morbidities in people living with epilepsy: hospital based case-control study from a resource-poor setting. Epilepsy Res 2009; 86: 146–152.
Badawy RAB, Harvey AS, Macdonell RAL. Cortical hyperexcitability and epileptogenesis: Understanding the mechanisms of epilepsy – Part 2. J Clin Neuroscience 2009; 16: 485–500.
Badawy RAB, Johnson KA, Cook MJ, Harvey AS. A mechanistic appraisal of cognitive dysfunction in epilepsy. Neuroscience Biobehav Rev 2012; 36: 1885–1896.
Bagdy G, Kecskemeti V, Riba P, Jakus R. Serotonin and epilepsy. J Neurochemistry 2007; 100: 857–873.
Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. Epilepsia. 1997; 38: 353–362.
Baker GA, Taylor J, Aldenkamp AP; SANAD group. Newly diagnosed epilepsy: cognitive outcome after 12 months. Epilepsia 2011; 52: 1084–1091.
Baker, G.A., 2002. The psychosocial burden of epilepsy. Epilepsia 43(Suppl. 6), 26–30.
Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy-a review. Epilepsy Res 2009; 85: 31–45.
Banos, J.H., LaGory, J., Sawrie, S., Faught, E., Knowlton, R., Prasad, A., Kuzniecky, R., Martin, R.C., 2004. Self-report of cognitive abilities in temporal lobe epilepsy: cognitive, psychosocial, and emotional factors. Epilepsy & Behavior 5, 575–579.
Barr WB. Epilepsy and neuropsychology: Past, present, and Future. Neuropsychol Rev 2007; 17: 381–383.
Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archives of General Psychiatry 1961, 4, 561–571.
Beilmann A, Napa A, Hämarik M, Sööt A, Talvik I, Talvik T. Incidence of childhood epilepsy in Estonia. Brain Dev 1999a; 21: 166–174.
Beilmann A, Napa A, Sööt A, Talvik I, Talvik T. Prevalence of childhood epilepsy in Estonia. Epilepsia 1999b; 40: 1011–1019.
Bell B, Lin JJ, Seidenberg M, Hermann B. The neurobiology of cognitive disorders in temporal lobe epilepsy. Nat Rev Neurol 2011; 7: 154–164.
Bell GS, Sander JW. Suicide and epilepsy. Curr Opin Neurol 2009; 22: 174–178.
Berg AT, Berkovic SF, Brodie MJ, Bucchalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshe S, Nordli D, Plouin P, Scheffer IE. Revised terminilogy and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2010; 51: 676–685.
Berg AT, Smith SN, Frobish D, Levy SR, Testa FM, Beckerman B, Shinnar S. Special education needs of children with newly diagnosed epilepsy. Dev Med Child Neurol 2005; 47: 749–753.
Bergin PS, Thompson PJ, Baxendale SA, Fish DR, Shorvon SD. Remote memory in epilepsy. Epilepsia. 2000; 41: 231–239.
Bernasconi N, Bernasconi A, Caramanos Z, Antel SB, Andermann F, Arnold DL. Mesial temporal damage in temporal lobe epilepsy: a volumetric MRI study of the hippocampus, amygdala and parahippocampal region. Brain 2003; 126: 462–469.
Blum D, Meador K, Biton V, Fakhoury T, Shneker B, Chung S, Mills K, Hammer A, Isojärvi J. Cognitive effects of lamotrigine compared with topiramate in patients with epilepsy. Neurology 2006; 67: 400–406.

Blumer D, Montouris G, Davies K. The interictal dysphoric disorder: recognition, pathogenesis, and treatment of the major psychiatric disorder of epilepsy. Epilepsy Behav 2004; 5: 826–840.

Bonelli SB, Powell RH, Yogarajah M, Samson RS, Symms MR, Thompson PJ, Koepp MJ, Duncan JS. Imaging memory in temporal lobe epilepsy: predicting the effects of temporal lobe resection. Brain 2010; 133: 1186–1199.

Boringa, J.B., Lazeron, R.H.C., Reuling, I.E.W., Ader, H.J., Pfennings, L.E.M.A., Lindeboom, J., de Sonneville, L.M.J., Kalkers, N.F., Polman, C.H., 2001. The Brief Repeatable Battery of Neuropsychological Tests: normative values allow application in multiple sclerosis clinical practice. Multiple Sclerosis 7, 263–267.

Boylan LS, Flint LA, Labovitz DL, Jackson SC, Starner K, Devinsky O. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. Neurology 2004; 62: 258–261.

Briellmann RS, Hopwood MJ, Jackson GD. Major depression in temporal lobe epilepsy with hippocampal sclerosis: clinical and imaging correlates. J Neurol Neurosurg Psychiatry 2007; 78: 1226–1230.

Buschke H, Altman Fuld P. Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology 1974; 24: 1019–1025.

Cannon DM, Ichise M, Rollis D, Klaver JM, Gandhi SK, Charney DS, Manji HK, Drevets WC. Elevated serotonin transporter binding in major depressive disorder assessed using positron emission tomography and [11C]DASB; comparison with bipolar disorder. Biol Psychiatry 2007, 62: 870–877.

Catafau AM, Perez V, Plaza P, Pascual JC, Bullich S, Suarez M, Penengo MM, Corripio I, Puigdemont D, Danus M, Perich J, Alvarez E. Serotonin transporter occupancy induced by paroxetine in patients with major depression disorder: a 123I-ADAM SPECT study. Psychopharmacology (Berl) 2006, 189: 145–153.

Chou YH, Yang BH, Chung MY, Chen SP, Su TP, Chen CC, Wang SJ. Imaging the serotonin transporter using (123)I-ADAM in the human brain. Psychiatry Res 2009, 172: 38–43.

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

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

Corcoran, R., Thompson, P., 1993. Epilepsy and poor memory: who complains and what do they mean? Br J Clin Psychol 32, 199–208.

Cormack F, Cross JH, Isaacs E, Harkness W, Wright I, Vargha-Khadem F, Baldeweg T. The development of intellectual abilities in pediatric temporal lobe epilepsy. Epilepsia 2007; 48: 201–204.

Cramer JA, Blum D, Reed M, Fanning K; Epilepsy Impact Project Group. The influence of comorbid depression on quality of life for people with epilepsy. Epilepsy Behav 2003a; 4: 515–521.

Cramer JA, Blum D, Reed M, Fanning K; Epilepsy Impact Project Group. The influence of comorbid depression on seizure severity. Epilepsia 2003b; 44: 1578–1584.

Cramer JA, Blum D, Fanning K, Reed M; Epilepsy Impact Project Group. The impact of comorbid depression on health resource utilization in a community sample of people with epilepsy. Epilepsy Behav 2004; 5: 337–342.

Dabbs K, Jones J, Seidenberg M, Hermann B. Neuroanatomical correlates of cognitive phenotypes in temporal lobe epilepsy. Epilepsy Behav 2009; 15: 445–451.
Dailey JW, Mishra PK, Ko KH, Penny JE, Jobe PC. Serotonergic abnormalities in the central nervous system of seizure-naive genetically epilepsy-prone rats. Life Sci 1992; 50: 319–26.
Deutsch, G.K., Saykin, A.J., Sperling, M.R., 1996. Metamemory in temporal lobe epilepsy. Assessment 3, 255–263.
Dickson JM, Wilkinson ID, Howell SJL, Griffiths PD, Grünewald RA. Idiopathic generalised epilepsy: a pilot study of memory and neuronal dysfunction in the temporal lobes, assessed by magnetic resonance spectroscopy. J Neurol Neurosurg Psychiatry 2006; 77: 834–840.
Dodrill CB. Correlates of generalized tonic-clonic seizures with intellectual, neuropsychological, emotional, and social function in patients with epilepsy. Epilepsia 1986; 27: 399–411.
Dodrill CB. Neuropsyhological effects of seizures. Epilepsy Behav 2004; 5: S21–S24.
Drane DL, Meador KJ. Cognitive and behavioral effects of antiepileptic drugs. Epilepsy Behav 2002; 3: 49–53.
Dreifuss S, Vingerhoets FJ, Lazeyras F, Andino SG, Spinelli L, Delavelle J, Seeck M. Volumetric measurements of subcortical nuclei in patients with temporal lobe epilepsy. Neurology 2001; 57: 1636–1641.
Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, Huang Y, Gautier C, Mathis C: PET imaging of serotonin 1A receptor binding in depression. Biol Psychiatry 1999; 46: 1375–1387.
Elger CE, Helmstaedtler C, Kurthen M. Chronic epilepsy and cognition. Lancet Neurol 2004; 3: 663–672.
Elixhauser A, Leidy NK, Meador K, Means E, Willian MK. The relationship between memory performance, perceived cognitive function, and mood in patients with epilepsy. Epilepsy Research 1999; 37: 13–24.
Elst LT, Groffmann M, Ebert D, Schulze-Bonhage A. Amygdala volume loss in patients with dysphoric disorder of epilepsy. Epilepsy Behav 2009; 16: 105–112.
Engelberts NHJ, Klein M, van der Ploeg HM, Heimans JJ, Ader HJ, van Boxtel MPJ, Jolles J, Kasteleijn-Nolst Trenite DGA. Cognition and health-related quality of life in a well-defined subgroup of patients with partial epilepsy. J Neurol 2002; 249: 294–299.
Exner C, Boucsein K, Lange C, Winter H, Weniger G, Steinhoff BJ, *et al.* Neuropsychological performance in frontal lobe epilepsy. Seizure 2002; 11: 20–32.
Fargo JD, Schefft BK, Szaflarski JP, Dulay MF, Testa SM, Privitera MD, Yeh HS. Accuracy of self-reported neuropsychological functioning in individuals with epileptic or psychogenic nonepileptic seizures. Epilepsy & Behavior 2004; 5: 143–150.
Favale E, Audenino D, Cocito L, Albano C: The anticonvulsant effect of citalopram as an indirect evidence of serotonergic impairment in human epileptogenesis. Seizure 2003, 12: 316–318.
Filho GM, Rosa VP, Lin K, Caboclo LO, Sakamoto AC, Yacubian EM. Psychiatric comorbidity in epilepsy: a study comparing patients with mesial temporal sclerosis and juvenile myoclonic epilepsy. Epilepsy Behav 2008; 13: 196–201.
Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J Jr. Epileptic seizures and epilepsy: definitions proposed by the International League

Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005; 46: 470–472.
Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J Jr, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshé SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. ILAE Official Report: A practical clinical definition of epilepsy. Epilepsia. 2014; 55: 475–482.
Forsgren L, Nyström L. An incident case-referent study of epileptic seizures in adults. Epilepsy Res 1990; 6: 66–81.
Fritz N, Glogau S, Hoffmann J, Rademacher M, Elger CE, Helmstaedter C. Efficacy and cognitive side effects of tiagabine and topiramate in patients with epilepsy. Epilepsy Behav 2005; 6: 373–381.
Frokjaer VG, Pinborg LH, Madsen J, de Nijs R, Svarer C, Wagner A, Knudsen GM. Evaluation of the Serotonin Transporter Ligand 123I-ADAM for SPECT Studies on Humans. J Nucl Med 2008; 49: 247–254.
Fuller-Thomson E, Brennenstuhl S. The association between depression and epilepsy in a nationally representative sample. Epilepsia 2009; 50: 1051–1058.
Gaitatzis A, Sander JW. The mortality of epilepsy revisited. Epileptic Disord 2004; 6: 3–13.
Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. Acta Neurol Scand 2004; 110: 207–20.
Gilliam FG, Santos J, Vahle V, Carter J, Brown K, Hecimovic H. Depression in epilepsy: ignoring clinical expression of neuronal network dysfunction? Epilepsia 2004; 45: 28–33.
Giovacchini G, Toczek MT, Bonwetsch R, Bagic A, Lang L, Fraser C, Reeves-Tyer P, Herscovitch P, Eckelman WC, Carson RE, Theodore WH. 5-HT1A receptors are reduced in temporal lobe epilepsy after partial-volume correction. J Nucl Med 2005; 46: 1128–1135.
Giovagnoli AR, Avanzini G. Learning and memory impairment in patients with temporal lobe epilepsy: relation to the presence, type, and location of brain lesion. Epilepsia 1999; 40: 904–911.
Giovagnoli AR. Awareness, overestimation, and underestimation of cognitive functions in epilepsy. Epilepsy Behav 2013; 26: 75–80.
Gleißner U, Helmstaedter C, Quiske A, Elger CE. The performance-complaint relationship in patients with epilepsy: a matter of daily demands? Epilepsy Research 1998; 32: 401–409.
Grabowska-Grzyb A, Jedrzejczak J, Nagańska E, Fiszer U. Risk factors for depression in patients with epilepsy. Epilepsy Behav 2006; 8: 411–417.
Haldre S, Karro H, Nurmiste A, Reinhard V, Sander V, Talvik T, Tomberg T, Treial M, Õun A. Estonian epilepsy treatment guidelines 2009. Eesti Arst 2009; 88: 533−544.
Hall KE, Isaac CL, Harris P. Memory complaints in epilepsy: An accurate reflection of memory impairment or an indicator of poor adjustment? A review of the literature. Clinical Psychology Review 2009; 29: 354–367.
Hamid H, Kanner AM. Should antidepressant drugs of the selective serotonin reuptake inhibitor family be tested as antiepileptic drugs? Epilepsy Behav 2013; 26: 261–265.
Hasler G, Bonwetsch R, Giovacchini G, Toczek MT, Bagic A, Luckenbaugh DA, Drevets WC, Theodore WH: 5-HT1A receptor binding in temporal lobe epilepsy patients with and without major depression. Biol Psychiatry 2007; 62: 1258–1264.
Helmstaedter C, Elger CE. Chronic temporal lobe epilepsy: a neurodevelopmental or progressively dementing disease? Brain 2009; 132: 2822–2830.

Helmstaedter C, Elger CE. The phantom of progressive dementia in epilepsy. Lancet 1999; 354: 2133–2134.
Helmstaedter C, Kemper B, Elger CE. Neuropsychological aspects of frontal lobe epilepsy. Neuropsychologia 1996; 34: 399–406.
Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger C. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. Ann Neurol 2003; 54: 425–432.
Helmstaedter C, Pohl C, Hufnagel A, Elger CE. Visual learning deficits in nonresected patients with right temporal lobe epilepsy. Cortex 1991; 27: 547–555.
Helmstaedter C, Sonntag-Dillender M, Hoppe C, Elger CE. Depressed mood and memory impairment in temporal lobe epilepsy as a function of focus lateralization and localization. Epilepsy Behav 2004; 5: 696–701.
Helmstaedter C, Elger CE. Behavioral markers for self- and other-attribution of memory: a study in patients with temporal lobe epilepsy and healthy volunteers. Epilepsy Research 2000; 41: 235–243.
Hendriks MPH, Aldenkamp AP, Alpherts WCJ, Ellis J, Vermeulen J, van der Vlugt H. Relationships between epilepsy-related factors and memory impairment. Acta Neurol Scand 2004; 110: 291–300.
Hendriks MPH, Aldenkamp AP, van der Vlugt H, Alpherts WCJ, Vermeulen J. Memory complaints in medically refractory epilepsy: relationship to epilepsy-related factors. Epilepsy & Behavior 2002; 3: 165–172.
Henry TR, Juhász C. Serotonergic PET in temporal lobe epilepsy: biomarking or etiologic mapping? Neurology 2013; 80: 1450–1451.
Hermann B, Seidenberg M, Jones J. The neurobehavioural comorbidities of epilepsy: can a natural history be developed? Lancet Neurol 2008; 7: 151–160.
Hermann B, Seidenberg M, Lee EJ, Chan F, Rutecki P. Cognitive phenotypes in temporal lobe epilepsy. J Int Neuropsychol Soc 2007; 13: 12–20.
Hermann BP, Seidenberg M, Bell B. Psychiatric comorbidity in chronic epilepsy: identification, consequences, and treatment of major depression. Epilepsia 2000; 41: 31–41.
Hermann BP, Seidenberg M, Dow C, Jones J, Rutecki P, Bhattacharya A, Bell B. Cognitive prognosis in chronic temporal lobe epilepsy. Ann Neurol 2006; 60: 80–87.
Hermann BP, Seidenberg M, Schoenfeld J, Davies K. Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. Arch Neurol 1997; 54: 369–76.
Hernandez EJ, Williams PA, Dudek FE. Effects of fluoxetine and TFMPP on spontaneous seizures in rats with pilocarpine-induced epilepsy. Epilepsia 2002; 43: 1337–1345.
Herodes M, Oun A, Haldre S, Kaasik AE. Epilepsy in Estonia: a quality-of-life study. Epilepsia 2001; 42: 1061–73.
Herold N, Uebelhack K, Franke L, Amthauer H, Luedemann L, Bruhn H, Felix R, Uebelhack R, Plotkin M. Imaging of serotonin transporters and its blockade by citalopram in patients with major depression using a novel SPECT ligand [123I]-ADAM. J Neural Transm 2006; 113: 659–670.
Hesdorffer DC, Hauser WA, Olafsson E, Ludvigsson P, Kjartansson O: Depression and suicide attempt as risk factors for incident unprovoked seizures. Ann Neurol 2006, 59: 35–41.

Hesdorffer DC, Krisnamoorthy ES. Neuropsychiatric disorders in epilepsy: epidemiology and classification. In: Trimble M, Schmitz B (eds). The neuropsychiatry of epilepsy. 2nd ed. Cambridge University Press: Cambridge, 2011, 3–13.
Hessen E, Lossius MI, Gjerstad L. Health concerns predicts poor quality of life in well-controlled epilepsy. Seizure. 2009; 18: 487–491.
Hitiris N, Mohanraj R, Norrie J, Sills GJ, Brodie MJ: Predictors of pharmacoresistant epilepsy. Epilepsy Res 2007, 75: 192–196.
Holmes GL, Lenck-Santini PP. Role of interictal epileptiform abnormalities in cognitive impairment. Epilepsy Behav 2006; 8: 504–515.
Holmes MD, Dodrill CB, Wilkus RJ, Ojemann LM, Ojemann GA. Is partial epilepsy progressive? Ten-year follow-up of EEG and neuropsychological changes in adults with partial seizures. Epilepsia 1998; 39: 1189–1193.
Hommet C, Sauerwein HC, De Toffol B, Lassonde M. Idiopathic epileptic syndromes and cognition. Neurosci Biobehav Rev 2006; 30: 85–96.
Igelström KM. Preclinical antiepileptic actions of selective serotonin reuptake inhibitors – implications for clinical trial design. Epilepsia 2012; 53: 596–605.
ILAE/IBE/WHO Global Campaign Against Epilepsy. Epilepsy in the WHO European region: Fostering Epilepsy Care in Europe. 2010. http://www.ibe-epilepsy.org/epilepsy-in-the-who-fostering-epilepsy-care-in-europe/downloads/European%20report.pdf
International Bureau for Epilepsy. IBE Epilepsy and Cognitive Function Survey. 2004. http://www.ibe-epilepsy.org/downloads/IBE%20Epilepsy%20and%20CognitiveFunctionResults.pdf
Jacoby A, Baker GA, Crossley J, Schachter S. Tools for assessing quality of life in epilepsy patients. Expert Rev Neurother 2013; 13: 1355–1369.
Jacoby A, Lane S, Marson A, Baker GA; MESS Study Group. Relationship of clinical and quality of life trajectories following the onset of seizures: findings from the UK MESS Study. Epilepsia 2011; 52: 965–974.
Jacoby, A., Baker, G.A., Steen, N., Potts, P., Chadwick, D.W., 1996. The clinical course of epilepsy and its psychological correlates: findings from a UK community study. Epilepsia 37, 148–161.
Jehi L, Tesar G, Obuchowski N, Novak E, Najm I. Quality of life in 1931 adult patients with epilepsy: seizures do not tell the whole story. Epilepsy Behav 2011; 22: 723–727.
Jennum P, Gyllenborg J, Kjellberg J. The social and economic consequences of epilepsy: a controlled national study. Epilepsia 2011; 52: 949–956.
Jobe PC. Common pathogenic mechanisms between depression and epilepsy: an experimental perspective. Epilepsy Behav 2003; 4: 14–24.
Joensuu M, Lehto SM, Tolmunen T, Saarinen PI, Valkonen-Korhonen M, Vanninen R, Ahola P, Tiihonen J, Kuikka J, Pesonen U, Lehtonen J: Serotonin-transporter-linked promoter region polymorphism and serotonin transporter binding in drug-naïve patients with major depression. Psychiatry Clin Neurosci 2010; 64: 387–393.
Jokeit H, Ebner A. Long term effects of refractory temporal lobe epilepsy on cognitive abilities: a cross sectional study. J Neurol Neurosurg Psychiatry 1999; 67: 44–50.
Kälviäinen R, Aikiä M, Helkala EL, Mervaala E, Riekkinen PJ. Memory and attention in newly diagnosed epileptic seizure disorder. Seizure 1992;1: 255–262.
Kanner A. Depression in epilepsy: a frequently neglected multifaceted disorder. Epilepsy Behav 2003; 4: 11–19.

Kanner AM, Byrne R, Chicharro A, Wuu J, Frey M: A lifetime psychiatric history predicts a worse seizure outcome following temporal lobectomy. Neurology 2009, 72: 793–799.

Kanner AM, Schachter SC, Barry JJ, Hersdorffer DC, Mula M, Trimble M, Hermann B, Ettinger AE, Dunn D, Caplan R, Ryvlin P, Gilliam F: Depression and epilepsy: Epidemiologic and neurobiologic perspectives that may explain their high comorbid occurrence. Epilepsy Behav 2012a, 24: 156–168.

Kanner AM, Schachter SC, Barry JJ, Hersdorffer DC, Mula M, Trimble M, Hermann B, Ettinger AE, Dunn D, Caplan R, Ryvlin P, Gilliam F. Depression and epilepsy, pain and psychogenic non-epileptic seizures: clinical and therapeutic perspectives. Epilepsy Behav 2012b; 24: 169–181.

Kanner AM. Depression and epilepsy: a bidirectional relation? Epilepsia 2011; 52: 21–27.

Kanner AM. Psychiatric issues in epilepsy: The complex relation of mood, anxiety disorders, and epilepsy. Epilepsy Behav 2009; 15: 83–87.

Kanner AM: Depression in epilepsy: a neurobiologic perspective. Epilepsy Curr 2005, 5: 21–27.

Kerr MP. The impact of epilepsy on patients' lives. Acta Neurol Scand 2012; 194: 1–9.

Kim SY, Lee HW, Jung DK, Suh CK, Park SP. Cognitive Effects of Low-dose Topiramate Compared with Oxcarbazepine in Epilepsy Patients. J Clin Neurol 2006; 2: 126–133.

Kleinberg A, Aluoja A, Vasar V. Point prevalence of major depression in Estonia. Results from the 2006 Estonian Health Survey. Eur Psychiatry 2010; 25: 485–490.

Kobow K, Auvin S, Jensen F, Löscher W, Mody I, Potschka H, Prince D, Sierra A, Simonato M, Pitkänen A, Nehlig A, Rho JM. Finding a better drug for epilepsy: Antiepileptogenesis targets. Epilepsia 2012; 53: 1868–1876.

Krishnamoorthy ES, Trimble MR, Blumer D. The classification of neuropsychiatric disorders in epilepsy: a proposal by the ILAE Commission on Psychobiology of Epilepsy. Epilepsy Behav 2007; 10: 349–353.

Kuzniecky R, Bilir E, Gilliam F, Faught E, Martin R, Hugg J. Quantitative MRI in temporal lobe epilepsy: evidence for fornix atrophy. Neurology 1999; 53: 496–501.

Kwan P, Brodie MJ. Neuropsychological effects of epilepsy and antiepileptic drugs. Lancet 2001; 357: 216–22.

Lannoo E, Colardyn F, Vandekerckhove T, De Deyne C, De Soete G, Jannes C. Subjective complaints versus neuropsychological test performance after moderate to severe head injury. Acta Neurochir 1998; 140: 245–253.

Lehto S, Tolmunen T, Joensuu M, Saarinen PI, Vanninen R, Ahola P, Tiihonen J, Kuikka J, Lehtonen J. Midbrain binding of [123I]nor-beta-CIT in atypical depression. Prog Neuropsychopharmacol Biol Psychiatry 2006; 30: 1251–1255.

Lespinet V, Bresson C, N'Kaoua B, Rougier A, Claverie B. Effect of age of onset of temporal lobe epilepsy on the severity and the nature of preoperative memory deficits. Neuropsychologia 2002; 40: 1591–1600.

Lezak, MD. Neuropsychological assessment, 4th Ed. Oxford University Press, New York; 2004

Lin JJ, Mula M, Hermann BP. Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. Lancet 2012; 380: 1180–1192.

Lin KJ, Liu CY, Wey SP, Hsiao IT, Wu J, Fu YK, Yen TC: Brain SPECT imaging and whole-body biodistribution with [(123)I]ADAM – a serotonin transporter radiotracer in healthy human subjects. Nucl Med Biol 2006, 33: 193–202.

Loring DW, Meador KJ, Lee GP. Determinants of quality of life in epilepsy. Epilepsy Behav 2004; 5: 976–980.
Lothe A, Didelot A, Hammers A, Costes N, Saoud M, Gilliam F, Ryvlin P. Comorbidity between temporal lobe epilepsy and depression: a [18F]MPPF PET study. Brain 2008; 131: 2765–2782.
Malison RT, Price LH, Berman R, van Dyck CH, Pelton GH, Carpenter L, Sanacora G, Owens MJ, Nemeroff CB, Rajeevan N, Baldwin RM, Seibyl JP, Innis RB, Charney DS. Reduced brain serotonin transporter availability in major depression as measured by [123I]-2 beta-carbomethoxy-3 beta-(4-iodophenyl)tropane and single photon emission computed tomography. Biol Psychiatry 1998; 44: 1090–1098.
Maor Y, Olmer L, Mozes B. The relation between objective and subjective impairment in cognitive function among multiple sclerosis patients – the role of depression. Multiple Sclerosis 2001; 7: 131–135.
Marino SE, Meador KJ, Loring DW, Okun MS, Fernandez HH, Fessler AJ, Kustra RP, Miller JM, Ray PG, Roy A, Schoenberg MR, Vahle VJ, Werz MA. Subjective perception of cognition is related to mood and not performance. Epilepsy Behav 2009; 14: 459–464.
Martinez A, Finegersh A, Cannon DM, Dustin I, Nugent A, Herscovitch P, Theodore WH. The 5-HT1A receptor and 5-HT transporter in temporal lobe epilepsy. Neurology 2013; 80: 1465–1471.
May TW. Assessment of adverse effects of antiepileptic drugs: The patient's view. Epileptology 2013; 1: 46–54.
Mazarati A, Siddarth P, Baldwin RA, Shin D, Caplan R, Sankar R. Depression after status epilepticus: behavioural and biochemical deficits and effects of fluoxetine. Brain 2008; 131: 2071–2083.
McAfee AT, Chilcott KE, Johannes CB, Hornbuckle K, Hauser WA, Walker AM. The incidence of first provoked and unprovoked seizure in pediatric patients with and without psychiatric diagnoses. Epilepsia 2007; 48: 1075–1082.
McCormic DA, Contreras D. On the cellular and network bases of epileptic seizures. Annu Rev Physiol 2001; 63: 815–846.
McDonald CR, Delis DC, Norman MA, Tecoma ES, Iragui VJ. Discriminating patients with frontal-lobe epilepsy and temporal-lobe epilepsy: utility of a multilevel design fluency test. Neuropsychology 2005; 19: 806–813.
McLaughlin DP, Pachana NA, McFarland K. Depression in a community-dwelling sample of older adults with late-onset or lifetime epilepsy. Epilepsy Behav 2008; 12: 281–285.
McLaughlin DP, Pachana NA, McFarland K. The impact of depression, seizure variables and locus of control on health related quality of life in a community dwelling sample of older adults. Seizure 2010; 19: 232–236.
McNamara JO. Emerging insights into the genesis of epilepsy. Nature 1999; 399: 15–22.
Meador K.J. Cognitive outcomes and predictive factors in epilepsy. Neurology 2002; 58: 21–26.
Meador KJ, Loring DW, Hulihan JF, Kamin M, Karim R; CAPSS-027 Study Group. Differential cognitive and behavioral effects of topiramate and valproate. Neurology 2003; 60: 1483–1488.
Meador KJ. Suicide in patients with epilepsy. Epilepsy Curr 2008; 8: 40–42.

Merlet I, Ostrowsky K, Costes N, Ryvlin P, Isnard J, Faillenot I, Lavenne F, Dufournel D, Le Bars D, Mauguière F. 5-HT1A receptor binding and intracerebral activity in temporal lobe epilepsy: an [18F]MPPF-PET study. Brain 2004; 127: 900–913.

Metternich B, Wagner K, Brandt A, Kraemer R, Buschmann F, Zentner J, Schulze-Bonhage A. Preoperative depressive symptoms predict postoperative seizure outcome in temporal and frontal lobe epilepsy. Epilepsy Behav 2009; 16: 622–628.

Meyer JH. Imaging the serotonin transporter during major depressive disorder and antidepressant treatment. J Psychiatry Neurosci 2007; 32: 86–102.

Moore PM, Baker GA. The neuropsychological and emotional consequences of living with intractable temporal lobe epilepsy: implications for clinical management. Seizure 2002; 11: 224–230.

Motamedi G, Meador K. Epilepsy and cognition. Epilepsy & Behav 2003; 25–38.

Mula M, Jauch R, Cavanna A, Collimedaglia L, Barbagli D, Gaus V, Kretz R, Viana M, Tota G, Israel H, Reuter U, Martus P, Cantello R, Monaco F, Schmitz B. Clinical and psychopathological definition of the interictal dysphoric disorder of epilepsy. Epilepsia 2008; 49: 650–656.

Mula M, Monaco F. Antiepileptic drugs and psychopathology of epilepsy: an update. Epileptic Disord 2009; 11: 1–9.

Mula M. The interictal dysphoric disorder. In: Trimble M, Schmitz B (eds). The neuropsychiatry of epilepsy. 2nd ed. Cambridge University Press: Cambridge, 2011, 80–89.

Murrough JW, Iacoviello B, Neumeister A, Charney DS, Iosifescu DV. Cognitive dysfunction in depression: neurocircuitry and new therapeutic strategies. Neurobiol Learn Mem 2011; 96: 553–563.

Natsume J, Bernasconi N, Andermann F, Bernasconi A. MRI volumetry of the thalamus in temporal, extratemporal, and idiopathic generalized epilepsy. Neurology 2003; 60: 1296–1300.

Newberg AB, Amsterdam JD, Wintering N, Ploessl K, Swanson RL, Shults J, Alavi A. 123I-ADAM binding to serotonin transporters in patients with major depression and healthy controls: a preliminary study. J Nucl Med 2005; 46: 973–977.

Newberg AB, Amsterdam JD, Wintering N, Shults J. Low brain serotonin transporter binding in major depressive disorder. Psychiatry Res 2012; 202: 161–167.

Nicolai J, Ebus S, Biemans DPLJJG, Arends J, Hendriksen J, Vles JSH, Aldenkamp AP. The cognitive effects of interictal epileptiform EEG discharges and short nonconvulsive epileptic seizures. Epilepsia 2012; 53: 1051–1059.

Nilsson L, Ahlbom A, Farahmand BY, Asberg M, Tomson T. Risk factors for suicide in epilepsy: a case control study. Epilepsia 2002; 43: 644–651.

O'Donoghue MF, Goodridge DM, Redhead K, Sander JW, Duncan JS. Assessing the psychosocial consequences of epilepsy: a community-based study. Br J Gen Pract 1999; 49: 211–214.

Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jönsson B; CDBE2010 study group; European Brain Council. The economic cost of brain disorders in Europe. Eur J Neurol 2012; 19:155–162.

O'Muircheartaigh J, Vollmar C, Barker GJ, Kumari V, Symms MR, Thompson P, Duncan JS, Koepp MJ, Richardson MP. Focal structural changes and cognitive dysfunction in juvenile myoclonic epilepsy. Neurology 2011; 76: 34–40.

Ööpik P, Aluoja A, Kalda R, Maaroos HI. Screening for depression in primary care. Fam Pract 2006; 23: 693–698.

Õun A, Haldre S, Mägi M. Incidence of adult epilepsy in Estonia. Acta Neurol Scand 2003a; 108: 245–251.
Õun A, Haldre S, Mägi M. Prevalence of adult epilepsy in Estonia. Epilepsy Research 2003b; 52: 233–242.
Oya S, Choi SR, Hou C, Mu M, Kung MP, Acton PD, Siciliano M, Kung HF. 2-((2-((dimethylamino)methyl)phenyl)thio)-5-iodophenylamine (ADAM): an improved serotonin transporter ligand. Nucl Med Biol 2000; 27: 249–254.
Oyegbile TO, Dow C, Jones J, Bell B, Rutecki P, Sheth R, Seidenberg M, Hermann BP. The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. Neurology 2004; 62: 1736–1742.
Paradiso S, Hermann BP, Blumer D, Davies K, Robinson RG. Impact of depressed mood on neuropsychological status in temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 2001; 70: 180–185.
Park SP, Kwon SH. Cognitive effects of antiepileptic drugs. J Clin Neurol 2008; 4: 99–106.
Parsey RV, Hastings RS, Oquendo MA, Huang YY, Simpson N, Arcement J, Huang Y, Ogden RT, Van Heertum RL, Arango V, Mann JJ. Lower serotonin transporter binding potential in the human brain during major depressive episodes. Am J Psychiatry 2006; 163: 52–58.
Pascalicchio TF, de Araujo Filho GM, da Silva Noffs MH, Lin K, Caboclo LO, Vidal-Dourado M, Ferreira Guilhoto LM, Yacubian EM. Neuropsychological profile of patients with juvenile myoclonic epilepsy: a controlled study of 50 patients. Epilepsy Behav 2007; 10: 263–267.
Patrikelis P, Angelakis E, Gatzonis S. Neurocognitive and behavioral functioning in frontal lobe epilepsy: a review. Epilepsy Behav 2009; 14: 19–26.
Perrine K, Hermann BP, Meador KJ, Vickrey BG, Cramer JA, Hays RD *et al.* The relationship of neuropsychological functioning to quality of life in epilepsy. Arch Neurol 1995; 52:997–1003.
Piazzini A, Turner K, Vignoli A, Canger R, Canevini MP. Frontal cognitive dysfunction in juvenile myoclonic epilepsy. Epilepsia. 2008; 49: 657–662.
Piazzini A, Canevini MP, Maggiori G, Canger R. The perception of memory failures in patients with epilepsy. European Journal of Neurology 2001; 8: 613–620.
Pitkänen A, Kharatishvili I, Karhunen H, Lukasiuk K, Immonen R, Nairismägi J, Gröhn O, Nissinen J. Epileptogenesis in experimental models. Epilepsia 2007; 48: 13–20.
Pitkänen A, Lukasiuk K. Mechanisms of epileptogenesis and potential treatment targets. Lancet Neurol 2011; 10: 173–186.
Pompili M, Girardi P, Ruberto A, Tatarelli R. Suicide in the epilepsies: a meta-analytic investigation of 29 cohorts. Epilepsy Behav 2005; 7: 305–310.
Powell HW, Richardson MP, Symms MR, Boulby PA, Thompson PJ, Duncan JS, Koepp MJ. Reorganization of verbal and nonverbal memory in temporal lobe epilepsy due to unilateral hippocampal sclerosis. Epilepsia 2007; 48: 1512–1525.
Prevey ML, Delaney RC, Cramer JA, Mattson H. Complex partial and secondarily generalized seizure patients: cognitive functioning prior to treatment with antiepileptic medication. Epilepsy Res 1998; 30: 1–9.
Pugliatti M, Beghi E, Forsgren L, Ekman M, Sobocki P. Estimating the cost of epilepsy in Europe: a review with economic modeling. Epilepsia 2007; 48: 2224–2233.
Pulliainen V, Kuikka P, Jokelainen M. Motor and cognitive functions in newly diagnosed adult seizure patients before antiepileptic medication. Acta Neurol Scand 2000; 101: 73–78.

Pulliainen V, Kuikka P, Kalska H. Are negative mood states associated with cognitive function in newly diagnosed patients with epilepsy? Epilepsia 2000; 41: 421–425.
Pulsipher DT, Seidenberg M, Guidotti L, Tuchscherer VN, Morton J, Sheth RD, Hermann B. Thalamocortical circuitry and executive dysfunction in recent-onset juvenile myoclonic epilepsy. Epilepsia 2009; 50: 1210–1219.
Quiske A, Helmstaedter C, Lux S, Elger CE. Depression in patients with temporal lobe epilepsy is related to mesial temporal sclerosis. Epilepsy Res 2000; 39: 121–125.
Rafnsson V, Olafsson E, Hauser WA, Gudmundsson G. Causespecific mortality in adults with unprovoked seizures. A populationbased incidence cohort study. Neuroepidemiology 2001; 20: 232–236.
Rätsepp M, Õun A, Haldre S, Kaasik AE. Felt stigma and impact of epilepsy on employment status among Estonian people: exploratory study. Seizure 2000; 9: 394–401.
Rayner G, Wrench JM, Wilson SJ. Differential contributions of objective memory and mood to subjective memory complaints in refractory focal epilepsy. Epilepsy Behav 2010; 19: 359–364.
Ruhé HG, Ooteman W, Booij J, Michel MC, Moeton M, Baas F, Schene AH: Serotonin transporter gene promoter polymorphisms modify the association between paroxetine serotonin transporter occupancy and clinical response in major depressive disorder. Pharmacogenet Genomics 2009, 19: 67–76.
Salgado PC, Yasuda CL, Cendes F. Neuroimaging changes in mesial temporal lobe epilepsy are magnified in the presence of depression. Epilepsy Behav 2010; 19: 422–427.
Saling MM. Verbal memory in mesial temporal lobe epilepsy: beyond material specificity. Brain 2009; 132: 570–582.
Salmenperä T, Kälviäinen R, Partanen K, Pitkänen A. Hippocampal and amygdaloid damage in partial epilepsy: a cross-sectional MRI study of 241 patients. Epilepsy Res 2001; 46: 69–82.
Sancho J, Iváñez V, Molins A, López Gómez V, Masramón X, Pérez M. Changes in seizure severity and quality of life in patients with refractory partial epilepsy. Epilepsy Behav 2010; 19: 409–413.
Sandok EK, O'Brien TJ, Jack CR, So EL. Significance of cerebellar atrophy in intractable temporal lobe epilepsy: a quantitative MRI study. Epilepsia 2000; 41: 1315–1320.
Sass KJ, Sass A, Westerveld M, Lencz T, Novelly RA, Kim JH, Spencer DD. Specificity in the correlation of verbal memory and hippocampal neuron loss: dissociation of memory, language, and verbal intellectual ability. J Clin Exp Neuropsychol 1992; 14: 662–672.
Sawrie SM, Martin RC, Kuzniecky R, Faught E, Morawetz R, Jamil F, Viikinsalo M, Gilliam F. Subjective versus objective memory change after temporal lobe epilepsy surgery. Neurology 1999; 53: 1511–1517.
Schenkel LC, Bragatti JA, Torres CM, Martin KC, Gus-Manfro G, Leistner-Segal S, Bianchin MM. Serotonin transporter gene (5HTT) polymorphisms and temporal lobe epilepsy. Epilepsy Res 2011; 95: 152–157.
Schmitz B, Yacubian EM, Feucht M, Hermann B, Trimble M. Neuropsychology and behavior in juvenile myoclonic epilepsy. Epilepsy Behav 2013; 28: 72–73.
Shamim S, Hasler G, Liew C, Sato S, Theodore WH. Temporal lobe epilepsy, depression, and hippocampal volume. Epilepsia 2009; 50: 1067–1071.

Shehata GA, Bateh AEM. Cognitive function, mood, behavioural aspects, and personality traits of adult males with idiopathic epilepsy. Epilepsy Behav 2009;14: 121–124.
Sonmez F, Atakli D, Sari H, Atay T, Arpaci B. Cognitive function in juvenile myoclonic epilepsy. Epilepsy Behav 2004; 5: 329–336.
Spencer SS. Neural networks in human epilepsy: Evidence of and implications for treatment. Epilepsia 2002; 43: 219–227.
Swinkels WA, van Emde Boas W, Kuyk J, van Dyck R, Spinhoven P. Interictal depression, anxiety, personality traits, and psychological dissociation in patients with temporal lobe epilepsy (TLE) and extra-TLE. Epilepsia 2006; 47: 2092–2103.
Szabó CA, Lancaster JL, Lee S, Xiong JH, Cook C, Mayes BN, Fox PT. MR imaging volumetry of subcortical structures and cerebellar hemispheres in temporal lobe epilepsy. AJNR Am J Neuroradiol 2006; 27: 2155–2160.
Tang WK, Lu J, Ungvari GS, Wong KS, Kwan P. Anxiety symptoms in patients with frontal lobe epilepsy versus generalized epilepsy. Seizure 2012; 21: 457–460.
Tatum WO 4th, French JA, Faught E, Morris GL 3rd, Liporace J, Kanner A, Goff SL, Winters L, Fix A; PADS Investigators. Post-marketing antiepileptic drug survey. Postmarketing experience with topiramate and cognition. Epilepsia 2001; 42: 1134–1140.
Taylor J, Baker GA. Newly diagnosed epilepsy: cognitive outcome at 5 years. Epilepsy Behav 2010; 18: 397–403.
Taylor J, Kolamunnage–Dona R, Marson AG, Smith PE, Aldenkamp AP, Baker GA; SANAD study group. Patients with epilepsy: cognitively compromised before the start of antiepileptic drug treatment? Epilepsia 2010; 51: 48–56.
Taylor RS, Sander JW, Taylor RJ, Baker GA. Predictors of health-related quality of life and costs in adults with epilepsy: a systematic review. Epilepsia 2011; 52: 2168–2180.
Tellez-Zenteno JF, Patten SB, Jetté N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia 2007; 48: 2336–2344.
Thompson PJ, Corcoran R. Everyday memory failures in people with epilepsy. Epilepsia 1992; 33: 18–20.
Toczek MT, Carson RE, Lang L, Ma Y, Spanaki MV, Der MG, Fazilat S, Kopylev L, Herscovitch P, Eckelman WC, Theodore WH. PET imaging of 5-HT1A receptor binding in patients with temporal lobe epilepsy. Neurology 2003; 60: 749–756.
Toomela A, Pulver A, Tomberg T, Orasson A, Tikk A, Asser T. Possible interpretation of subjective complaints in patients with spontaneous subarachnoid haemorrhage. J Rehabil Med 2004; 36: 63–69.
Tracy JI, Lippincott C, Mahmood T, Waldron B, Kanauss K, Glosser D, *et al.* Are depression and cognitive performance related in temporal lobe epilepsy? Epilepsia 2007; 48: 2327–2335.
Trenerry MR, Jack CR Jr, Ivnik RJ, Sharbrough FW, Cascino GD, Hirschorn KA, Marsh WR, Kelly PJ, Meyer FB. MRI hippocampal volumes and memory function before and after temporal lobectomy. Neurology 1993; 43: 1800–1805
Uijl SG, Uiterwaal CS, Aldenkamp AP, Carpay JA, Doelman JC, Keizer K, Vecht CJ, de Krom MC, van Donselaar CA. A cross-sectional study of subjective complaints in patients with epilepsy who seem to be well-controlled with anti-epileptic drugs. Seizure 2006; 15: 242–248.
Upton D, Thompson PJ. Age at onset and neuropsychological function in frontal lobe epilepsy. Epilepsia 1997; 38: 1103–1113.

Upton D, Thompson PJ. General neuropsychological characteristics of frontal lobe epilepsy. Epilepsy Res 1996; 23: 169–177.
Vahter L. Subjective complaints in different neurological diseases – correlations to the neuropsychological problems and implications for the everyday life. Dissertations on social sciences. Tallinn University 2009.
van de Giessen E, Booij J. The SPECT tracer [123I]ADAM binds selectively to serotonin transporters: a double-blind, placebo-controlled study in healthy young men. Eur J Nucl Med Mol Imaging 2010; 37: 1507–1511.
van Dyck CH, Malison RT, Staley JK, Jacobsen LK, Seibyl JP, Laruelle M, Baldwin RM, Innis RB, Gelernter J. Central serotonin transporter availability measured with [123I]beta-CIT SPECT in relation to serotonin transporter genotype. Am J Psychiatry 2004; 161: 525–531.
Vermeulen J, Aldenkamp AP, Alpherts WCJ. Memory complaints in epilepsy: correlations with cognitive performance and neuroticism. Epilepsy Res 1993; 15: 157–170.
Vermoesen K, Massie A, Smolders I, Clinckers R. The antidepressants citalopram and reboxetine reduce seizure frequency in rats with chronic epilepsy. Epilepsia 2012; 53: 870–878.
Wandschneider B, Thompson PJ, Vollmar C, Koepp MJ. Frontal lobe function and structure in juvenile myoclonic epilepsy: a comprehensive review of neuropsychological and imaging data. Epilepsia 2012; 53: 2091–2098.
World Health Organization. Epilepsy. Fact sheet 999. WHO, 2012. http://www.who.int/mediacentre/factsheets/fs999/en/

9. SUMMARY IN ESTONIAN

Kognitiivsed funktsioonid, tajutud kognitiivne toimimine, subjektiivsed kaebused ja depressiooni sümptomid epilepsiaga inimestel: neuropsühholoogiline hindamine ja SPET aju kuvamisuuring

Epilepsia on närvisüsteemi krooniline haigus, mida iseloomustab püsiv valmisolek epileptiliste hoogude tekkeks, millega kaasneb rida neurobioloogilisi, kognitiivseid, psühholoogilisi ja sotsiaalseid järelmeid (Fisher *et al.*, 2005). Epileptiline hoog on ülemäärasest ja sünkroonsest neuronite aktiivsusest tingitud mööduv sensoorne, motoorne, käitumise või teadvuse seisundi muutus.

Maailmas on epilepsiaga inimesi umbes 50 miljonit (WHO, 2012), Euroopas 6 miljonit (Pugliatti *et al.*, 2007; ILAE/IBE/WHO Global Campaign Against Epilepsy, 2010) ja Eestis hinnanguliselt umbes 6300 inimest (Haldre *et al.*, 2009). Epilepsiaga inimeste elu ja tervist mõjutavate tegurite seas on ühtedeks olulisemateks elukvaliteeti langetavateks faktoriteks neuropsühholoogilised, psühholoogilised ja psühhiaatrilised probleemid (Perrine *et al.*, 1995; Jehi *et al.*, 2011; Taylor *et al.*, 2011). Epilepsia on seotud märkimisväärse koormusega nii üksikisikule, perekonnale kui kogu ühiskonnale. Epilepsia on teiste ajuhaiguste seas nii otseste kui kaudsete kulude poolest üks kulukamaid (Olesen *et al.*, 2012).

Epilepsiaga inimestel on suurem risk kognitiivsete häirete esinemiseks (Meador, 2002). Varasem uurimistöö selles vallas on tõestanud, et epilepsiaga inimestel võib esineda muutusi erinevate kognitiivsete funktsioonide osas – psühhomotoorne kiirus, infotöötlus, mälu, keskendumise ja tähelepanu häired (Aldenkamp *et al.*, 2004). Kognitiivset funktsioneerimist epilepsia korral mõjutab rida tegureid: haiguse etioloogia, epileptilised hood, antiepileptilised ravimid ja psühhosotsiaalsed tegurid (Elger *et al.*, 2004).

On viiteid, et varasem haiguse algus, pikem epilepsia kestus, suurem hoogude arv ja polüteraapia omavad suuremat riski kognitiivse defitsiidi tekkeks. Suur osa kahjustusest on olemas epilepsia diagnoosimise hetkel (Äikiä *et al.*, 2000) ja pikaajalistes uurimistöödes on leidud, et vanuse kasvades langeb epilepsiaga inimeste sooritusvõime mälu osas kontrollgrupiga paralleelselt, kuid algselt kahjustunud mälufunktsioonide tõttu langeb epilepsiaga inimeste mälusooritus kriitilisele tasemele oluliselt varem (Helmstaedter ja Elger, 2009). Depressiooniga võivad kaasneda probleemid mitmete kognitiivsete funktsioonide osas (Murrough *et al.*, 2011). Kaasneva depressiooni mõju kognitiivsetele funktsioonidele epilepsia korral on suuresti teadmata. On töid, kus kirjeldatakse suuremat neuropsühholoogilist defitsiiti kaasuva depressiooni korral (Paradiso *et al.*, 2001) ja samas mitmeid töid, kus seda seost leitud ei ole (Tracy *et al.*, 2007; Taylor *et al.*, 2010). Arvestades, et depressioon iseenesest võib kognitiivsetele funktsioonidele negatiivset mõju avaldada, võivad epilepsiaga inimesed, kellel esineb depressioon olla ohustatud vähemalt kahe erineva kognitiivseid võimeid mõjutava riskiteguri poolt.

Lisaks objektiviseeritud kognitiivsete funktsioonide kahjustusele esitavad epilepsiaga patsiendid erinevaid subjektiivseid kognitiivseid kaebusi. Peamisteks kaebusteks on tähelepanu halvenemine, mõtlemise aeglus ja mälu halvenemine (Moore ja Baker, 2002). Paradoksaalsel kombel esineb tajutud mälufunktsiooni ja objektiivse mälufunktsiooni vahel minimaalne korrelatsioon (Hall *et al.*, 2009). Selle põhjuseks on sageli peetud kaasuva meeleoluhäire mõju tajutud kognitiivsele toimimisele, mille tõttu patsiendid hindavad oma mälufunktsioone vääralt (Marino *et al.*, 2009).

Meeleoluhäirete esinemissagedus epilepsiaga patsientidel on suur. On leitud, et üldrahvastikuga võrreldes esineb depressiooni epilepsiaga inimestel oluliselt sagedamini ja selle levimus ulatub kuni 50% (Hermann *et al.*, 2000). Psühhosotsiaalsete tegurite kõrval võib epilepsia puhul olla üheks depressiooni tekkepõhjuseks ka otsene meeleolu regulatsioonis osalevate ajupiirkondade düsfunktsioon (Kanner, 2005). On leitud, et psüühikahäirete esinemine on seotud suurenenud riskiga epilepsia tekkeks ja omakorda epilepsia diagnoos suurendab tõenäosust psüühikahäire esinemiseks (Hesdorffer *et al.*, 2012). See on uurijaid viinud hüpoteesini, et epilepsial ja depressioonil võib olla ühine patogeneetiline mehhanism ja üheks võimalikuks seoseks epilepsia ja depressiooni patogeneesis võib olla serotoniini metabolism. Positronemissioontomograafia uuringus temporaalsagara epilepsiaga patsientidel on kirjeldatud alanenud serotoniini retseptori ($5\text{-}HT_{1A)}$ sidumine mesiaalsetes temporaalsagara struktuurides hoo fookusega ipsilateraalselt (Toczek *et al.*, 2003) ja samuti negatiivne korrelatsioon suuremate depressiooni sümptomite ja $5\text{-}HT_{1A}$ retseptori sidumise vahel ipsilateraalses hipokampuses (Hasler *et al.*, 2007). Serotoniini transporteri (SERT) roll on epilepsia ja depressiooni seoste osas seni suuresti teadmata.

Uurimistöö eesmärgid

1. Kirjeldada epilepsiaga patsientide (fokaalse ja generaliseerunud epilepsiaga patsientide) kognitiivseid funktsioone võrrelduna tervete kontrollgrupi isikutega
2. Kirjeldada epilepsiaga seotud tegurite toimet kognitiivsele toimimisele
3. Hinnata depressiooni mõju kognitiivsetele funktsioonidele epilepsia korral
4. Võrrelda subjektiivseid kognitiivseid kaebusi objektiivsete neuropsühholoogiliste testide tulemustega
5. Hinnata depressiooni sümptomite mõju tajutud kognitiivsele toimimisele
6. Uurida serotoniini transporteri (SERT) sidumist epilepsiaga patsientide keskajus ja hinnata kaasuvate depressiooni sümptomite mõju SERT sidumisaktiivsusele

Uuritavad ja meetodid

Uurimistöö jaoks andis loa Tartu Ülikooli Inimuuringute Eetikakomitee ja kõik uuritavad allkirjastasid kirjaliku informeeritud nõusoleku uuringus osalemiseks.

Kognitiivsete funktsioonide ja subjektiivsete kaebuste uuringus osales 62 epilepsiaga patsienti. Uuringus osalemise kriteeriumiteks olid: vanus 18–65

aastat, teiste neuroloogiliste haiguste puudumine ja eesti keel emakeelena. 25 patsienti algsest valimist (n=87) keeldus või ei täitnud uuringusse kaasamise kriteeriume. Kontrollgrupi moodustasid 53 tervet vabatahtlikku, kes ei erinenud patsientide grupist sooliste, vanuseliste ja haridusega seotud tunnuste poolest. SERT kuvamisuuringus osales 12 epilepsiaga patsienti. Osalemise eelduseks oli teiste kaasuvate neuroloogiliste haiguste puudumine ja varasem serotoniini süsteemi toimivate antidepressantide mittekasutamine.

Kognitiivsete funktsioonide hindamiseks kasutati neuropsühholoogilisi teste, mis põhinesid testipatareil Brief Repeatable Battery of Neuropsychological Tests (Boringa *et al.*, 2001). See sisaldas teste mälufunktsiooni hindamiseks (Buschke Selective Reminding Test – verbaalne õppimine ja mälu; 10/36 Spatial Recall Test – nägemis-ruumiline mälu ja õppimine) ja erinevate täideviivate funktsioonide hindamiseks (Symbol Digit Modalities Test – püsiv tähelepanu ja infotöötlemise kiirus; Word List Generation and Verbal Fluency Test – verbaalsed võimed, kontsentreerumine; Trail Making A and B – tähelepanu, kontsentreerumine, paindlikkus). Depressioonisümptomite esinemist hinnati Beck'i depressiooniküsimustiku (BDI) ja emotsionaalse enesetunde küsimustiku (EEK-2) abil. Subjektiivsete kaebuste uurimiseks kasutatud subjektiivsete kaebuste küsimustikku, mis sisaldas 13 küsimust subjektiivsete kaebuste kohta 4-pallisel skaalal.

SERT kuvamisuuringus süstiti uuritavatele SERT ligandi ^{123}I-ADAM (*2-([2-([dimethylamino] methylphenoxyl]thio)-5-[123I]iodophenylamine*) ja hinnati SERT sidumisaktiivsust keskajus üksikfooton-emissioontomograafia (SPET) abil. Kuvamisuuringud teostati Põhja-Eesti Regionaalhaigla nukleaarmeditsiini osakonnas.

Uurimistöö tulemused ja arutelu

Patsientide sooritus oli kontrollgrupiga võrreldes statistiliselt olulisel halvem verbaalse mälu ja verbaalse voolavuse osas. Teistes testides olulisi erinevusi ei esinenud. Samas oli märgata halvem sooritus kõikides tähelepanu, kontsentreerumise, verbaalsete funktsioonide alatestides, kuid mitte statistiliselt olulisel määral. Fokaalse epilepsiaga patsientide tulemused olid statistiliselt oluliselt halvemad verbaalse püsimälu ja verbaalse voolavuse osas. Fokaalse epilepsiaga patsientide sooritus oli nõrgem kõikides alatestides, kuid muus osas statistiliselt mitteolulisel määral.

21 patsiendil oli BDI >11, mida interpreteeriti depressioonisümptomite esinemisena. Haridusaastate arv ja depressiooni sümptomite esinemine on peamised kognitiivset funktsioneerimist mõjutavad tegurid.

Varasemate uuringute valguses oli epilepsiaga patsientide, eriti fokaalse epilepsiaga patsientide mõnevõrra nõrgem sooritus oodatav tulemus. Generaliseerunud epilepsiaga patsientidel on kirjeldatud oluliselt laiemat kognitiivse kahjustuse profiili (Schmitz *et al.*, 2013), kuid meie uuringu tulemustes eristus siiski kahjustus verbaalse mälu ja verbaalse voolavuse osas. See võib tähendada, et erinevate epilepsia tüüpidega patsiente ei ole võimalik usaldusväärselt

neuropsühholoogilise profiili alusel eristada, mida on kirjeldatud ka varem (Exner *et al.*, 2002). Samas võib uuringu tulemusi mõjutada ka uuringugruppide suur heterogeensus.

Depressiooni sümptome esines suurel osal epilepsiaga patsientidest ja depressiooni sümptomite esinemine mõjutas oluliselt neuropsühholoogiliste testide tulemusi halvemuse suunas. Kirjeldatud negatiivne mõju puudus kontrollgrupi uuritavatel. Senistes teadustöödes on mitmel korral depressiooni negatiivset mõju kognitiivsetele võimetele epilepsiaga inimestel kirjeldatud (Dulay *et al.*, 2012), kuid paljudel juhtudel ei ole seda seost leitud (Taylor *et al.*, 2010). Arvestades, et depressioon võib muus osas tervete inimeste kognitiivsetele võimetele negatiivset mõju avaldada, oleks sarnase mõju esinemine epilepsiaga inimestel oodatav tulemus. Veelgi enam – epilepsia ja depressiooni koosesinemise korral võivad kombineeruda kaks kognitiivset toimimist ohustavat riskitegurit. See rõhutab depressiooni sümptomite uurimise ja nende ravimise vajadust epilepsia korral.

Subjektiivsete kaebuste uurimisel ilmnes vähene või puuduv korrelatsioon subjektiivsete kaebuste ja objektiivsete testitulemuste vahel. Samas esines negatiivse korrelatsiooni trend subjektiivsete kaebuste ja objektiivse leiu vahel – parema neuropsühholoogilise sooritusega patsientidel oli suurem subjektiivsete kaebuste määr ja vastupidi. Subjektiivsetel kaebustel oli tugev korrelatsioon BDI tulemusega. Lineaarne regressioonanalüüs näitas, et 36% subjektiivsetest kaebustest võis seostada depressioonisümptomite esinemisega. Kõrgema BDI skooriga patsientidel esines statistiliselt oluliselt enam subjektiivseid kaebusi küsimustiku kõikide alaosade osas, va kõne ja valu. Neuropsühholoogiliste testide osas esinesid samuti statistiliselt olulised erinevused verbaalse mälu hilise meenutamise alatestis, kus depressiooni sümptomitega patsientidel oli halvem sooritus.

Kuigi depressiooni sümptomite esinemine seostub tugevalt subjektiivsete kaebustega, lisandub sellele ilmselt veel tegureid, mis mõjutavad tajutud kognitiivset toimimist. Nende tuvastamine vajab täiendavaid uuringuid. Olulise järeldusena lähtub uuringu tulemustest, et patsiendi rohket subjektiivsete kognitiivsete kaebuste hulka ei tohiks kontrollimata seostada objektiivse neuropsühholoogilise toimetulekuga, vaid see võib olla märk kaasuvast meeleoluhäirest.

SERT kuvamisuuringus osalenud patsientidest oli 7 depressiooniskaala tulemus depressiooni sümptomite esinemisele viitav. Ei esinenud korrelatsiooni BDI ja SERT sidumise vahel keskajus. Samuti ei erinenud statistiliselt olulisel määral SERT sidumine depressiooni sümptomitega ja ilma depressiooni sümptomiteta patsientidel.

Ka varasemates uuringutes on SERT sidumisaktiivsus depressiooniga inimestel andnud erinevaid tulemusi. Kuigi suur osa uurimistöödest kirjeldab suurenenud SERT sidumist depressiooniga uuritavate taalamuses ja limbilistes piirkondades (Cannon *et al.*, 2007), on mitmeid teadustöid, kus SERT sidumisaktiivsus amügdala ja keskaju piirkonnas on depressiooniga uuritavatel

langenud (Lehto *et al.*, 2006). Seega oleks epilepsia ja kaasuva depressiooniga seotud SERT sidumisaktiivsuse muutuse suunda veelgi raskem ennustada.

Antud uurimistöös võib seoste puudumine SERT sidumisaktiivsuse ja depressiooni esinemise vahel olla seotud ka väikese uuritavate arvu ja uuritavate gruppide suure heterogeensusega. Serotoniini süsteemi, epilepsia ja depressiooni omavaheliste seoste hindamine vajab edasisi suurema uuritavate arvu ja homogeensemate gruppidega uuringuid.

Kokkuvõtvalt viitavad antud uurimistöö tulemused, et epilepsiaga inimestel on suurem risk kognitiivsete häirete tekkeks ja võimalikule kahjustusele lisab oma negatiivse toime depressiooni sümptomite kaasuv esinemine. Kuna subjektiivsed kaebused ei seostunud niivõrd objektiivsete testitulemuste, kuivõrd depressiooni sümptomite esinemisega, rõhutab see depressiooni hindamise vajalikkust epilepsiaga inimestel, eriti kui esineb rohkem subjektiivseid kaebusi. Lisaks näitavad tulemused hariduse olulisust võimalike kognitiivsete häirete ennetamisel epilepsiaga inimestel.

Uurimistöö järeldused

1. Uuringu tulemused viitavad, et epilepsiaga patsientidel, eriti fokaalse epilepsiaga patsientide grupis, esines kontrollgrupi katsealustega võrreldes enam kognitiivseid häireid, mis ilmnesid eelkõige verbaalse mälu ja verbaalse voolavuse osas. Uuritava vanus ja haridus olid peamised neuropsühholoogiliste testide tulemust mõjutavad sotsiodemograafilised tegurid nii patsientide kui kontrollgrupi uuritavate puhul.
2. Epilepsiaga seotud teguritel, nagu haiguse kestus, vanus haiguse alguses või hoogude sagedus, kognitiivsele toimimisele olulist mõju esile ei tulnud.
3. Nii fokaalse kui generaliseerunud epilepsiaga uuritavate grupis oli suur hulk depressiooni sümptomitega patsiente ja depressiooni sümptomite esinemisel oli üksnes patsientide, kuid mitte kontrollgrupi uuritavate neuropsühholoogilisele profiilile oluline negatiivne mõju. Sellest lähtub depressiooni hindamise ja ravimise vajalikkus epilepsiaga inimestel
4. Subjektiivsete kaebuste seos objektiivse neuropsühholoogilise leiuga oli epilepsiaga patsientidel nõrk. Uuringu tulemused rõhutavad vajadust uurida erinevaid subjektiivseid kaebusi, mitte ainult mäluga seotud probleeme.
5. Tajutud kognitiivne toimimine oli olulisel määral seotud depressiooni sümptomite esinemisega.
6. SERT SPET kuvamisuuringu tulemused ei näidanud muutusi SERT sidumises epilepsiaga patsientidel, kellel esines/ei esinenud viiteid kaasuvale depressioonile. SERT rolli ja laiemalt serotoniini süsteemi osa epilepsia ja depressiooni ühises patogeneesis vajab täiendavaid uuringuid.

10. ACKNOWLEDGEMENTS

The currents studies were carried out at the Department of Neurology and Neurosurgery, University of Tartu.

The research was supported by Estonian Science Foundation grant ETF6786.

My sincerest gratitude and deepest respect goes to my supervisor Associate Professor Sulev Haldre for his continuous guidance, support, and patients throughout my doctoral studies. His clinical expertise, scientific advice, and fruitful discussions have been crucial in the process of this research.

I would like to express my sincerest gratitude towards my co-authors Liina Vahter and Katrin Gross-Paju. I would like to thank them for introducing me the secrets of neuropsychological assessment, for helping to find subjects for the studies, and for helpful and useful comments in the process of manuscript preparations.

I would like to thank Malle Paris and her colleagues in the Radiology Centre of North Estonian Medical Centre for helping to plan, to perform, and to interpret the SERT imaging study.

I am extremely grateful to Professor Veiko Vasar and Associate Professor Janika Kõrv for reviewing the thesis and making several helpful suggestions and comments.

My warmest thanks belong to my colleagues in the Department of Neurology and Neurosurgery of University of Tartu for their help and support.

I am deeply thankful to all the patients who agreed to participate in the studies.

And last but not least I feel deeply indebted to my children, family, and closest ones. I am thankful for their continuous support and encouragement. This includes my grandmother to whom this thesis is dedicated to.

11. APPENDICES

APPENDIX A

SUBJECTIVE COMPLAINTS QUESTIONNAIRE
Which of the listed problems disturb your daily life and how often?

	Not at all	Rarely	Frequently	Very often
Low mood	1	2	3	4
Problems of memory retrieval	1	2	3	4
Forgetting	1	2	3	4
Difficulties concentrating	1	2	3	4
Dizziness	1	2	3	4
Problems with speech	1	2	3	4
Problems with coordination	1	2	3	4
Problems with balance	1	2	3	4
Problems with vision (foggy, double)	1	2	3	4
Hand tremor	1	2	3	4
Fatigue	1	2	3	4
Headache	1	2	3	4
Pain in other parts of the body	1	2	3	4

APPENDIX B

SUBJEKTIIVSETE KAEBUSTE KÜSIMUSTIK (*in Estonian*)
Millised allpoolnimetatud probleemidest häirivad Teie igapäevast elu ja kui tihti?

	Üldse mitte	Harva	Tihti	Väga sageli
Meeleolu langus	1	2	3	4
Mälu käepärasuse häired	1	2	3	4
Unustamine	1	2	3	4
Raske keskenduda	1	2	3	4
Pearinglus	1	2	3	4
Probleemid kõnega	1	2	3	4
Probleemid koordinatsiooniga	1	2	3	4
Tasakaaluhäired	1	2	3	4
Probleemid nägemisega (topelt, udune)	1	2	3	4
Käte värisemine	1	2	3	4
Väsimus	1	2	3	4
Peavalud	1	2	3	4
Valud mujal	1	2	3	4

12. PUBLICATIONS

CURRICULUM VITAE

Name: Maarika Liik
Date of birth: 4.09.1979
Citizenship: Estonian
Address: L.Puusepp Str. 8H, 51014, Tartu, Estonia
Phone: +372 731 8554
E-mail: maarika.liik@kliinikum.ee

Education:

2003–	University of Tartu, Faculty of Medicine, PhD studies in neurosciences
2007–2013	University of Tartu, Faculty of Medicine, residency in neurology
1997–2003	University of Tartu, Faculty of Medicine
1994–1997	Pärnu Sütevaka Private High School of Humanities
1985–1994	Are Primary School

Professional employment:

2013–	Tartu University Hospital, Department of Neurology, neurologist

Scientific work and professional organizations:

Fields: neurophysiology, epileptology
Publications: 6 international, 1 domestic
Membership: Estonian Society of Neurologists and Neurosurgeons, member
Estonian League Against Epilepsy, member
Estonian Society of Clinical Neurophysiology, member
Estonian Movement Disorder Society, member

Publications:

Liik M, Sema L, Haldre S. Neuropsychological changes in epilepsy. Eesti Arst 2005; 84(5): 322–326.

Liik M, Vahter L, Gross-Paju K, Haldre S. Subjective complaints compared to the results of neuropsychological assessment in patients with epilepsy: The influence of comorbid depression. Epilepsy Research 2009; 84: 194–200.

Talvik I, Vibo R, Liik M, Haldre S, Talvik T. Epileptic laughter: 2 case reports. Medicina 2012; 48: 359–363.

Liik M, Puksa L, Lüüs SM, Haldre S, Taba P. Fulminant inflammatory neuropathy mimicking cerebral death. BMJ Case Reports 2012; 20.

Rakitin A, Liik M, Õun A, Haldre S. Mortality risk in adults with newly diagnosed and chronic epilepsy: a population-based study. European Journal of Neurology 2011; 18: 465–470.
Liik M, Vahter L, Gross-Paju K, Haldre S. Cognitive profile and depressive symptoms in patients with epilepsy. Medicina (Kaunas) 2013; 49: 254–261.
Liik M, Paris M, Vahter L, Gross-Paju K, Haldre S. ^{123}I-ADAM SPET imaging of serotonin transporter in patients with epilepsy and comorbid depression. BMC Neurol 2013; 13: 204.

ELULOOKIRJELDUS

Nimi:	Maarika Liik
Sünniaeg:	4.09.1979
Kodakondsus:	Eesti
Aadress:	Puusepa 8H, 51014, Tartu
Telefon:	731 8554
E-post:	maarika.liik@kliinikum.ee

Hariduskäik

2003–	Tartu Ülikool, Arstiteaduskond, neuroteaduste doktorikool
2007–2013	Tartu Ülikool, Arstiteaduskond, neuroloogia residentuur
1997–2003	Tartu Ülikool, Arstiteaduskond, arstiteadus
1994–1997	Pärnu Sütevaka Humanitaargümnaasium
1985–1994	Are Põhikool

Teenistuskäik:

2013–	SA TÜK Närvikliinik, neuroloogia osakond, arsti-õppejõud

Teadus- ja erialane tegevus:

Valdkonnad:	neurofüsioloogia, epilepsia
Publikatsioonid:	6 rahvusvahelistes ja 1 kohalikes meditsiiniajakirjades
Liikmelisus:	L. Puusepa nim. Neuroloogide ja Neurokirurgide Seltsi liige
	Eesti Epilepsiavastase Liiga liige
	Eesti Kliinilise Neurofüsioloogia Seltsi liige
	Eesti Liigutushäirete Seltsi liige

Publikatsioonid:

Liik M, Sema L, Haldre S. Neuropsühholoogilised muutused epilepsia korral. Eesti Arst 2005; 84(5): 322–326.

Liik M, Vahter L, Gross-Paju K, Haldre S. Subjective complaints compared to the results of neuropsychological assessment in patients with epilepsy: The influence of comorbid depression. Epilepsy Research 2009; 84: 194–200.

Talvik I, Vibo R, Liik M, Haldre S, Talvik T. Epileptic laughter: 2 case reports. Medicina 2012; 48: 359–363.

Liik M, Puksa L, Lüüs SM, Haldre S, Taba P. Fulminant inflammatory neuropathy mimicking cerebral death. BMJ Case Reports 2012; 20.

Rakitin A, Liik M, Õun A, Haldre S. Mortality risk in adults with newly diagnosed and chronic epilepsy: a population-based study. European Journal of Neurology 2011; 18: 465–470.

Liik M, Vahter L, Gross-Paju K, Haldre S. Cognitive profile and depressive symptoms in patients with epilepsy. Medicina (Kaunas) 2013; 49: 254–261.
Liik M, Paris M, Vahter L, Gross-Paju K, Haldre S. ^{123}I-ADAM SPET imaging of serotonin transporter in patients with epilepsy and comorbid depression. BMC Neurol 2013; 13: 204.

DISSERTATIONES NEUROSCIENTIAE UNIVERSITATIS TARTUENSIS

1. **Sirli Raud.** Cholecystokinin$_2$ receptor deficient mice: changes in function of GABA-ergic system. Tartu, 2005.
2. **Kati Koido.** Single-nucleotide polymorphism profiling of 22 candidate genes in mood and anxiety disorders. Tartu, 2005.
3. **Dzhamilja Safiulina.** The studies of mitochondria in cultured cerebellar granule neurons: characterization of mitochondrial function, volume homeostasis and interaction with neurosteroids. Tartu, 2006.
4. **Tarmo Areda.** Behavioural and neurogenetic study of mechanisms related to cat odour induced anxiety in rodents. Tartu, 2006.
5. **Aleksei Nelovkov.** Behavioural and neurogenetic study of molecular mechanisms involved in regulation of exploratory behaviour in rodents. Tartu, 2006.
6. **Annika Vaarmann**. The studies on cystatin B deficient mice: neurochemical and behavioural alterations in animal model of progressive myoclonus epilepsy of Unverricht-Lundborg type. Tartu, 2007.
7. **Urho Abramov.** Sex and environmental factors determine the behavioural phenotype of mice lacking CCK_2 receptors: implications for the behavioural studies in transgenic lines. Tartu, 2008.
8. **Hendrik Luuk.** Distribution and behavioral effects of WFS1 protein in the central nervous system. Tartu, 2009.
9. **Anne Must.** Studies on molecular genetics of male completed suicide in Estonian population. Tartu, 2009.
10. **Kaido Kurrikoff**. Involvement of cholecystokinin in chronic pain mechanisms and endogenous antinociception. Tartu, 2009.
11. **Anu Aonurm-Helm.** Depression-like phenotype and altered intracellular signalling in neural cell adhesion molecule (NCAM)-deficient mice. Tartu, 2010.
12. **Silva Sütt.** Role of endocannabinoid system and *Wfs1* in regulation of emotional behaviour: behavioural, pharmacological and genetic studies. Tartu, 2010.
13. **Mari-Anne Philips.** Characterization of *Myg1* gene and protein: expression patterns, subcellular localization, gene deficient mouse and functional polymorphisms in human. Tartu, 2010.
14. **Ranno Rätsep.** Genetics of psoriasis and vitiligo, focus on IL10 family cytokines. Tartu, 2010.
15. **Kairit Joost.** Selective screening of metabolic diseases in Estonia: the application of new diagnostic methods. Tartu, 2012, 143 p.
16. **Monika Jürgenson.** A complex phenotype in mice with partial or complete deficiency of the NCAM protein. Tartu, 2012, 117 p.

17. **Ene Reimann.** Description of the cytokines and cutaneous neuroendocrine system in the development of vitiligo. Tartu, 2012, 117 p.
18. **Jürgen Innos.** Behavioural, pharmacological and neurochemical characterisation of limbic system-associated membrane protein (LSAMP) deficient mice. Tartu, 2013, 113 p.
19. **Kaili Anier.** The role of DNA methylation in the development of cocaine-induced behavioural sensitisation. Tartu, 2013, 147 p.