Cognitive Profile and Depressive Symptoms in Patients With Epilepsy

Maarika Liik[1], Liina Vahter[2], Katrin Gross-Paju[2], Sulev Haldre[1]
[1]Department of Neurology and Neurosurgery, University of Tartu,
[2]Department of Neurology, West Tallinn Central Hospital, Estonia

Key Words: *cognitive functions; depression; epilepsy; neuropsychology.*

Summary. *Background and Objective. The aim of the present study was to describe the cognitive profile of patients with focal and generalized epilepsy syndrome in comparison with healthy control subjects and to investigate whether depression was related to neuropsychological functioning in these patients.*

Material and Methods. A total of 36 patients with focal epilepsy and 26 patients with generalized epilepsy were compared with the control group of healthy volunteers (n=53). A battery of neuropsychological tests assessing verbal and visual spatial memory and executive functioning was carried out in addition to the completion of the Beck Depression Inventory (BDI).

Results. The results indicated that patients with epilepsy performed significantly worse than controls on all verbal memory subscales and verbal fluency domains. The patients with focal epilepsy scored significantly worse than the patients with generalized epilepsy. The BDI scores were significantly correlated with several scores of the cognitive test in both patients' groups but not in the control group.

Conclusions. Our results suggest that patients with epilepsy, especially with focal-onset epilepsy, show cognitive disturbances predominantly in the verbal memory domain. In addition, depression was found to have a negative effect on cognitive functioning in patients with epilepsy.

Introduction

Cognitive and emotional disturbances are common in patients with all forms of epilepsy (1). The level of cognitive functioning is a critical aspect of quality of life in patients with epilepsy (2). The etiology of the disease and underlying neuropathology, frequency of epileptic seizures, side effects of antiepileptic drugs (AEDs), and psychosocial factors play significant roles in the cognitive functioning of patients with epilepsy (3). Research on cognitive functioning in patients with epilepsy has concentrated on the study of memory functions in adults with treatment-resistant temporal lobe epilepsy, and this has led to the concept of a complex of neuropsychological symptoms related to the syndrome of mesial temporal lobe epilepsy, with material-specific memory disturbances playing the leading role (4). A lower number of studies on patients with frontal lobe epilepsy have revealed a more widespread pattern of cognitive function disturbances (disturbances in psychomotor speed/attention, motor coordination, working memory, and response inhibition) (5). The possibility of using neuropsychological testing to differentiate between patients with frontal and temporal lobe epilepsy has been considered (6). There are even fewer studies addressing cognitive functioning in adults with idiopathic generalized epilepsies (7). The disturbances of prefrontal functions such as concept formation, abstract reasoning, mental flexibility, cognitive speed, planning, and organization have been described (8).

Previous research has indicated that there are several factors that influence cognitive functioning in epilepsy. Young age at seizure onset, long duration of epilepsy, a high number of lifetime tonic-clonic seizures, a history of status epilepticus, polytherapy, and symptomatic etiology of epilepsy are the variables that are linked to a greater risk for cognitive deficits (9, 10). Previous studies have found neuropsychological dysfunction to be present in patients with newly diagnosed generalized- and partial-onset seizures (11, 12), while memory functions have been shown to decline with a longer duration of the illness (13).

Depression is the most common psychiatric disorder among people with epilepsy and occurs at a higher rate among people with epilepsy compared to the general population (14). The lifetime prevalence of depression in patients with epilepsy has been shown to be as high as 40%–50% (15). Neuropsychological studies have reported that depression can affect a wide range of cognitive abilities including episodic memory and learning, verbal fluency, attention, and motor speed (16). The relationship between depression and cognitive functioning in epilepsy has not been well studied. Paradiso et al. (17) demonstrated that patients with temporal lobe epilepsy concurrent with depression performed significantly poorer on the measures of intelligence,

Correspondence to M. Liik, Department of Neurology and Neurosurgery, University of Tartu, L. Puusepp 8, 51014 Tartu, Estonia. E-mail: maarika.liik@kliinikum.ee

language, visual perceptual ability, memory, and executive function than patients with temporal lobe epilepsy without depression. In addition, these authors found that the effects of depression on cognition might be greater in patients with left temporal lobe epilepsy. Conversely, Tracy et al. (18) found no relationship between cognition and depression in patients with temporal lobe epilepsy. Helmstaedter and colleagues (19) found that depression and memory deficits were correlated only in patients with left lateral temporal focal epilepsy. Some studies, including our previous study (20), have found that the symptoms of depression affect subjective cognitive performance and also have some effect on objective cognitive functioning. As depression is known to cause several disturbances in cognitive functioning, patients with epilepsy could therefore be at a heightened risk of a double burden.

The aim of the current study was to describe the cognitive profile of an outpatient clinic population of patients with various forms of epilepsy, to investigate if cognitive performance of patients with epilepsy was different from that of control subjects' and whether the cognitive profile of patients with focal epilepsy was different from the cognitive profile of patients with generalized epilepsy syndrome, and to determine whether depression affected the neuropsychological functioning of patients with various forms of epilepsy compared with control subjects.

Material and Methods

Subjects. A total of 62 patients with epilepsy from the Outpatient Clinic, Department of Neurology and Neurosurgery, University of Tartu, were included into the study. Epilepsy was diagnosed based on clinical data supported by electroencephalography (EEG) and a magnetic resonance imaging (MRI) scan or a computerized tomography (CT) scan of the brain. The inclusion criteria were as follows: 1) age between 18 and 65 years; 2) absence of other neurological diseases; and 3) a native Estonian speaker. Based on a medical history, clinical data, and investigations, the patients were divided into the groups of focal and generalized epilepsy syndrome.

A total of 53 healthy volunteers matched for sex, age, or years of formal education served as a control group. The control volunteers had no history of seizures or other neurological disorders.

All the patients and control subjects gave their informed consent to participate before the inclusion in the study. The study was approved by the Ethics Committee of the University of Tartu.

Neuropsychological Screening. Neuropsychological status was assessed with a battery of tests based on the Brief Repeatable Battery of Neuropsychological Tests (21). The Buschke Selective Reminding Test (BSRT) was used to measure verbal learning and memory during a 6-trial list learning task (22).

Short-term and long-term components as well as the consistency of retrieval from long-term memory can be evaluated with this test.

Visual memory was assessed by the 10/36 Spatial Recall Test, which is an adapted version of the 7/24 test with a wider checkerboard (6×6) and 10 checkers. The 10/36 Spatial Recall Test assesses visual spatial learning and delayed recall (21).

Sustained attention and concentration were measured by the Symbol Digit Modalities Test (SDMT), which uses complex visual scanning and tracking. A series of 9 meaningless geometric symbols labeled from 1 to 9 were presented to the subject. The subject was then asked to substitute the symbols in a row with the corresponding number during a 90-second period. The score was calculated by the number of correct substitutions.

Verbal fluency was measured by the Word List Generation Test and the Verbal Fluency Test. The Word List Generation Test evaluates the spontaneous production of words from a given category within a limited amount of time. The subjects were asked to list as many names of animals as possible during 90 seconds. During the Verbal Fluency Test, the subjects were asked to list as many words beginning with a designated letter as possible within a 90-second period.

Visual search speed, scanning, speed of processing, mental flexibility, and executive functions were assessed with the Trail Making A and B Tests (23). Unlike in all other neuropsychological test measures used, in the Trail Making A and B Tests, a higher score is indicative of worse cognitive performance.

Depression Screening. Depressive symptoms were assessed with the Beck Depression Inventory (BDI) (24). A cutoff score of >11 was used to define the presence of depressive symptoms.

Data Analysis. Data were analyzed by the Statistica 7.0 software. Comparisons of neuropsychological test performance between the patients' groups of focal and generalized epilepsy and the control group were performed with one-way analysis of variance (ANOVA) followed by the Duncan's post-hoc test of pair-wise comparisons. Correlation analyses were used to study the relationship between the scores of neuropsychological tests, demographics- and epilepsy-related factors, and the BDI score in all study groups. A stepwise multiple linear regression analysis was carried out to evaluate the effects of demographics- and epilepsy-related factors and depression on neuropsychological test measures. Neuropsychological test measures were set as dependent variables and various demographics- and epilepsy-related factors and BDI score as independent variables. Significance was set at $P \leqslant 0.05$.

Results

Subjects. There were 87 patients with epilepsy screened for the study, 19 refused to participate,

and 6 did not meet the inclusion criteria. Of the 62 remaining patients, there were more women (n=37) than men (n=25) as indicated in Table 1 that summarizes all demographic and clinical characteristics of the patients and demographic characteristics of the control subjects. The mean age of the patients was 34.6 years (SD, 11.0), and the mean duration of epilepsy was 19.2 years (SD, 10.5) with a mean age of seizure onset being 15.4 years (SD, 12.1). All the patients had completed the first 9 years of regular primary and secondary education, and the mean number of formal years of education was 13.4 (SD, 4.0).

Thirty-six patients with epilepsy were diagnosed with focal epilepsy syndrome, and 26 were diagnosed with generalized epilepsy syndrome. There were no significant differences in demographic characteristics between the 2 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 receiving 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 the 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 2 patients; nonspecific white matter lesions, in 3; an arachnoid cyst, in 2; and old frontal contusional lesions, in 1 patient.

Cognitive Test Scores. The groups of patients with epilepsy performed significantly worse than the control group on all verbal memory test subscales (Table 2). The control group also scored significantly higher on the Verbal Fluency and Word List Generation Tests. While there was a trend for the patients with epilepsy to perform poorer than the controls in other tests of attention, concentration, mental flexibility, and nonverbal memory, none of these differences were significant comparing the groups.

The patients with focal epilepsy scored significantly worse than the patients with generalized epilepsy on the BSRT consistent long-term retrieval subscales and on the Word List Generation Test. There were no other significant differences between the 2 groups of patients with epilepsy, although there was a general trend to have lower scores on all tests of neuropsychological functioning for the patients with focal epilepsy.

Depression Score. The mean BDI score for the control subjects was 9.7 (SD, 8.0) compared with 11.6 (SD, 10.5) for the patients with generalized epilepsy and 14.1 (SD, 12.7) for the patients with focal epilepsy ($P > 0.05$). There were 17 patients (32%) with a BDI score of more than 11 in the control group, 14 patients (38.9%) with a BDI score of more than 11 in the focal epilepsy group, and 10 patients (38.5%) with a BDI score of more than 11 in the generalized epilepsy group.

Correlation of Demographic Variables, Depression, and Cognitive Test Scores. Correlation analysis revealed significant correlations between 2 subscales of BSRT and Trail Making Test B and years of education in the focal epilepsy syndrome group (Table 3), while education correlated significantly with most cognitive test measures among the patients

Table 1. Demographic Characteristics of Healthy Controls and Epilepsy Patients Along With Clinical Characteristics of Epilepsy Patients

Characteristic	Controls (n=53)	Focal Epilepsy (n=36)	Generalized Epilepsy (n=26)	All Patients With Epilepsy (n=62)	P Value
Age, years	38.2 (13.3)	36.3 (12.3)	32.2 (8.7)	34.6 (11.0)	0.13
Gender, n (%)					
Male	17 (32)	15 (42)	10 (38)	25 (40)	0.64
Female	36 (68)	21 (58)	16 (62)	37 (60)	
Education, years	14.8 (3.1)	12.9 (3.6)	14.2 (4.4)	13.4 (4.0)	0.06
Duration of epilepsy, years	NA	18.7 (12.0)	19.7 (8.1)	19.2 (10.5)	0.14
Age at seizure onset, years	NA	17.5 (15.1)	12.7 (4.7)	15.4 (12.1)	0.67
Seizure frequency for GTCS, n (%)					
Weekly	NA	10 (28)	3 (12)	13 (21)	
Monthly	NA	12 (38)	3 (12)	15 (24)	0.0007
A year	NA	5 (14)	19 (73)	24 (39)	
Medications, n (%)					
Monotherapy	NA	15 (42)	16 (61)	31 (50)	
Polytherapy	NA	18 (50)	8 (31)	26 (42)	0.30
No medication	NA	3 (8)	2 (8)	5 (8)	

Values are mean (standard deviation) unless otherwise stated.
NA, not applicable; GTCS, generalized tonic-clonic seizures.

Table 2. Comparison of Neuropsychological Test Scores in Healthy Controls and Patients With Epilepsy

	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 delayed recall	10.5 (2.0)	8.0 (2.8)	9.0 (3.4)	10.1	<0.001
Visual spatial 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 delayed 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

Values are expressed as mean (standard deviation).
SDMT, Symbol Digit Modalities Test; BSRT, Buschke Selective Reminding Test; BDI, Beck Depression Inventory;
NS, not significant.

with generalized epilepsy (Table 4). In the focal epilepsy group, the frequency of seizures correlated negatively with the scores of the Verbal Fluency Test, but in the generalized epilepsy group, in addition with the scores of visual memory test and Trail Making Tests A and B. Interestingly, epilepsy-related factors such as age at seizure onset and the duration of epilepsy did not have any significant correlations with neuropsychological test measures in the generalized epilepsy group, and in the focal epilepsy group, the duration of epilepsy was negatively correlated only with the scores of the Verbal Fluency Test. The BDI score was significantly correlated with a number of cognitive test scores, including verbal memory subtests, SDMT, Word List Generation Test, 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 the patients correlated significantly with the scores of 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, the number of AEDs correlated significantly only with the score of Word List Generation Test.

Unlike in the patients' groups, the 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 significantly correlated with the majority of test measures.

Multiple Linear Regression Analysis. Multiple linear 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). The BDI score was a significant factor together with age and years of education for the SDMT.

In the focal epilepsy group, the BDI score was a single predictive variable for the BSRT delayed recall subscale and SDMT, and it was also significant in combination with the number of AEDs for the

Table 3. Correlations Between Demographic Factors, Epilepsy-Related Factors, Depressive Symptoms, and Neuropsychological Test Scores in Patients With Focal Epilepsy Syndrome

	BSRT Long-Term Storage	BSRT Consistent Long-Term Retrieval	BSRT Delayed Recall	10/36 Total Score	10/36 Delayed Recall	SDMT	Word List Genera-tion	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 Patients With Generalized Epilepsy Syndrome

	BSRT Long-Term Storage	BSRT Consistent Long-Term Retrieval	BSRT Delayed Recall	10/36 Total Score	10/36 Delayed Recall	SDMT	Word List Genera-tion	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 the Control Group

	BSRT Long-Term Storage	BSRT Consistent Long-Term Retrieval	BSRT Delayed Recall	10/36 Total Score	10/36 Delayed Recall	SDMT	Word List Genera-tion	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.
*$P<0.05$.

Trail Making Test A. No other epilepsy-related factor, except the number of AEDs, was 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). The BDI score was predictive for the verbal fluency and verbal memory subscales (together with years of education). The duration of epilepsy and age at seizure onset were not significant factors in any of the models.

Discussion

The present study describes cognitive functioning and depression in the group of patients with fo-
cal and generalized epilepsy syndromes in comparison with healthy control subjects.

The main aim of the current study was to describe the cognitive profiles of the patients with various forms of epilepsy, to detect if depression was correlated with the neuropsychological functioning, and to evaluate the possible significant sociodemographic and disease-related predictors of performance on neuropsychological measures.

In agreement with previous reports in the literature (3), the overall neuropsychological performance of patients with epilepsy was somewhat worse than in the healthy volunteers, especially on the subscales of verbal memory and verbal fluency domains.

Of the 2 groups of patients with epilepsy, those with focal-onset epilepsy tended to perform worse

Table 6. Results of Multiple Linear Regression Analysis in Different Groups Indicating Significant Predictive Variables for Individual Neuropsychological Test Measures (Only Models With 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	0.40	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		0.30	0.09	0.07	4.87*
Age	−0.30				
SDMT		0.68	0.47	0.43	12.6*
Age	−0.50				
Years of education	0.31				
BDI score	−0.21				
Verbal fluency		0.50	0.23	0.23	16.7*
Years of education	0.50				
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				
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	−0.50				
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	0.40				
BDI score	−0.51				
BSRT delayed recall		0.71	0.50	0.45	10.2*
Years of education	0.42				
BDI score	−0.44				
10/36 spatial recall total score		0.55	0.30	0.27	10.4*
Frequency of seizures	−0.55				
Word list generation		0.63	0.40	0.38	16.2*
Years of education	0.64				
Verbal fluency		0.66	0.44	0.41	17.1*
BDI score	−0.66				
Trail making A		0.55	0.30	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.
*$P<0.05$.

on all tests of cognitive functioning compared with those with generalized epilepsy. However, the difference between the groups reached statistical significance only on verbal memory long-term retrieval subscales and word list generation.

While our results indicate that the performance on the 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 spectrum of affected domains in the population of these patients. Memory disturbances have previously been described in patients with generalized epilepsy, but the impairment of executive functioning has been emphasized in the majority of previous studies (7, 8, 25). Research on juvenile myoclonic epilepsy has found certain thalamo-frontal circuits as the possible cause of these disturbances (26). The present finding may 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 the patients with generalized epilepsy and the patients with focal epilepsy in our study.

Depression was more prevalent in both the groups of patients with epilepsy (38.9% in the focal epileptic group and 38.5% in the generalized epileptic group) as compared with 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 (27). Interestingly, the prevalence of depression in our control group was higher (32%) than in the general population and almost as high as in our patients' groups. This finding may be explained by a relatively small study sample and a relatively large proportion of female subjects in the control group. Since BDI is a subjective self-rating scale and we did not perform a thorough psychiatric assessment of 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 the symptoms of depression are clinically depressed and vice versa. This could change the prevalence rate of depression in our study sample and influence our results in both directions, but in this case, it would affect both the patients' and control groups, and we could still estimate the difference between the groups.

The scores of the depression scale showed negative associations with performance in the number of neuropsychological tests, and it appeared to be an important predictive factor for several neuropsychological test measures in both the patients' groups, but not in the control group. The influence of depressive symptoms on the neuropsychological status in patients with epilepsy has been previously reported (17, 20). However, another study (18) concluded that depression did not influence cognitive func-

tioning in patients with epilepsy. These authors proposed, however, that the overall level of depression found in their study was probably too mild to exert an effect on cognition. In a recent study of male patients with idiopathic epilepsy, the BDI score was not significantly correlated with performance on any cognitive scale (28), and these results were particularly surprising since the mean BDI scores in their patients' groups were extremely high.

In studies on depression, deficits in episodic memory, working memory, and more widely in various executive functions are commonly described (16). In our study, the scores of verbal memory, verbal fluency, and various tests of executive functioning were associated with the BDI score.

Depression in patients with epilepsy could be the result of interplay between several factors including stigma, and illness-related and psychosocial factors, but recent investigations addressing the comorbidity of epilepsy and depression have led to the concept of their common pathogenesis (29). This idea is supported by the fact that epilepsy is associated with an increased risk of depression, but depression could also be a risk factor for developing epilepsy (29). If this is true and both disorders are separately associated with an increased risk of cognitive dysfunction, it could mean that patients with epilepsy bear a double risk of neuropsychological disturbances. Our results, therefore, stress the importance of recognizing and treating depression in patients with epilepsy. The remission of depression symptoms could have positive effects on cognitive functioning, and patients with epilepsy could gain functionality in several factors influencing their quality of life.

Education was an important factor in determining neuropsychological test measures in the patients' groups (especially in the generalized epilepsy group) and in the control group. The correlation between education and neuropsychological measures has been previously noted (10). This again indicates that good education may give better reserves for people with epilepsy in coping with possible cognitive dysfunction.

There were surprisingly few strong associations between epilepsy-related factors and cognitive test measures. The frequency of seizures showed few correlations with the scores of tests of executive functioning in the generalized epilepsy group and the number of AEDs in the focal epilepsy group, but age at seizure onset and the duration of epilepsy did not show almost any associations with cognitive functioning. The latter are also considered important epilepsy-related factors in the development of cognitive dysfunction (3, 9, 30).

Our study has several limitations, including a small sample size, female preponderance, and heterogeneity of the patients' groups, as mentioned before. Moreover, a great number of correlations increase

the risk of alpha/type I error, although multiple regression analysis indicated compatible tendencies with correlation analysis in the current study.

Conclusions

The present study indicated that patients with epilepsy, especially with focal onset epilepsy, have cognitive disturbances that are most apparent in the verbal memory and verbal fluency domains compared with the healthy control subjects. Age and education were the main sociodemographic factors influencing neuropsychological test measures in both the groups of patients with epilepsy and control test subjects. The epilepsy-related factors showed surprisingly few associations with the cognitive test measures. As both patients' groups had a high proportion of subjects with depression symptoms and depression showed compounding negative effects on cognitive functioning only in the patients with epilepsy, it is therefore emphasized that depression needs to be adequately diagnosed and treated in this population.

Statement of Conflict of Interest

The authors state no conflict of interest.

References

1. Aldenkamp AP, Bodde N. Behaviour, cognition and epilepsy. Acta Neurol Scand 2005;112:19-25.
2. 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.
3. Kwan P, Brodie MJ. Neuropsychological effects of epilepsy and antiepileptic drugs. Lancet 2001;357:216-22.
4. Hermann BP, Seidenberg M, Schoenfeld J, Davies K. Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. Arch Neurol 1997;54:369-76.
5. Helmstaedter C, Kemper B, Elger CE. Neuropsychological aspects of frontal lobe epilepsy. Neuropsychologia 1996;34: 399-406.
6. 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.
7. Hommet C, Sauerwein HC, De Toffol B, Lassonde M. Idiopathic epileptic syndromes and cognition. Neurosci Biobehav Rev 2006;30:85-96.
8. Piazzini A, Turner K, Vignoli A, Canger R, Canevini MP. Frontal cognitive dysfunction in juvenile myoclonic epilepsy. Epilepsia 2008;49:657-62.
9. 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.
10. 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;40:1591-600.
11. 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.
12. 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: 20-7.
13. Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger C. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. Ann Neurol 2003;54:425-32.
14. Kanner A. Depression in epilepsy: a frequently neglected multifaceted disorder. Epilepsy Behav 2003;4:11-9.
15. Hermann BP, Seidenberg M, Bell B. Psychiatric comorbidity in chronic epilepsy: identification, consequences, and treatment of major depression. Epilepsia 2000;41:S31-41.
16. Murrough JW, Iacoviello B, Neumeister A, Charney DS, Iosifescu DV. Cognitive dysfunction in depression: neurocircuitry and new therapeutic strategies. Neurobiol Learn Mem 2011;96:553-63.
17. 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;70:180-5.
18. 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: 2327-35.
19. 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.
20. 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 Res 2009;84:194-200.
21. Boringa JB, Lazeron RHC, Reuling IEW, Ader HJ, Pfennings L, Lindeboom J, et al. The brief repeatable battery of neuropsychological tests: normative values allow application in multiple sclerosis clinical practice. Mult Scler 2001;7: 263-7.
22. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology 1974;24:1019-25.
23. Lezak, MD. Neuropsychological assessment. 4th ed. New York: Oxford University Press; 2004.
24. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
25. 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;77:834-40.
26. Pulsipher DT, Seidenberg M, Guidotti L, Tuchscherer VN, Morton J, Sheth RD, et al. Thalamocortical circuitry and executive dysfunction in recent-onset juvenile myoclonic epilepsy. Epilepsia 2009;50:1210-9.
27. Aluoja A, Leinsalu M, Shlik J, Vasar V, Luuk K. Symptoms of depression in the Estonian population: prevalence, sociodemographic correlates and social adjustment. J Affect Disord 2004;78:27-35.
28. Shehata GA, Bateh AEM. Cognitive function, mood, behavioural aspects, and personality traits of adult males with idiopathic epilepsy. Epilepsy Behav 2009;14:121-4.
29. Kanner AM. Psychiatric issues in epilepsy: the complex relation of mood, anxiety disorders, and epilepsy. Epilepsy Behav 2009;15:83-7.
30. 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.