Paper IV

Executive functions and seizure-related factors in children with epilepsy in western Norway

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Executive functions (EFs), seizure-related factors, and school performance were studied in a population-based sample of children with epilepsy (*n*=117; 71 males, 46 females; mean age 10y 5mo [SD 2y]; range 6y–12y 11mo) and a comparison group (*n*=124; 71 males, 53 females; mean age 10y 1mo [SD 2y 1mo]; range 6y–12y 11mo). EF, cognitive function, depression, socioeconomic status, and school performance were examined. Patients with epilepsy performed significantly lower than the comparison group on all EF measures except incidental memory. Intellectual dysfunction and depression accounted for 43% of EF problems. All epilepsy syndrome groups (except Rolandic epilepsy) were associated with decreased EF in addition to early epilepsy onset, high seizure frequency, and polytherapy. Patients had more school performance problems than comparison children which were attributed partly to EF difficulties. All aspects of EF were affected in children with epilepsy and all epilepsy syndrome groups, except Rolandic epilepsy, influenced EF negatively. EF problems contributed to patients' school difficulties beyond intellectual dysfunction.

See end of paper for list of abbreviations.

Cognitive problems are frequent in children with epilepsy (Besag 2002). Various neuropsychological tests have been used to study impaired learning in children with epilepsy, although traditional intelligence testing may not give sufficient insight into cognitive problems. Executive function (EF) is defined as the ability to maintain a set of appropriate problem-solving strategies for attainment of future goals. EF is considered to be one of the major roles of the frontal cortex. Opinions differ in the literature with regard to which functions should be included in the EF concept.

EF domains mature at different rates from infancy to adulthood (Anderson 2002). According to Alexander and Stuss (2000), neural systems underlying EF are numerous, complex, and interrelated, with the prefrontal cortex dependent on efferent and afferent connections to almost all brain regions, including the brain stem, occipital, temporal, and parietal lobes, and the limbic and subcortical regions. Disturbed EF may be associated with prefrontal pathology or with network disconnections, such as white-matter damage or impairment in other brain regions (Alexander and Stuss 2000). Therefore, integrity of the prefrontal cortex is necessary, but not sufficient, for effective EF (Della Sala et al. 1998). The current view in neuropsychology is that the frontal lobes are important for executive or supervisory aspects of problem solving (Anderson 2002).

Variables other than epilepsy might also have an impact on EFs. Elixhauser et al. (1999) reported that aspects of memory were influenced by depressed mood. Socioeconomic and family characteristics may be significantly associated with neuropsychological status and should be controlled for when neuropsychological dysfunctions are studied (Fastenau et al. 2004). To the current authors' knowledge, population-based studies of EF in children with epilepsy have not been presented previously.

The aims of the present study were to investigate EF in a population-based sample of children with epilepsy and matched comparisons and to examine possible relationships between: (1) EF and seizure-related factors; (2) EF and learning problems; and (3) EF problems and IQ, depression, and/or low socioeconomic status (SES).

Methods

STUDY AREA AND POPULATION

The study was conducted in Hordaland County in western Norway. The study population has been described previously (Waaler et al. 2000, Høie et al. 2005). As of 1 January 1995, 38 593 of the inhabitants in Hordaland were born from 1 January 1982 to 31 December 1988. Demographic characteristics of the county are similar to those of Norway as a whole, and relatively small differences exist with regard to socioeconomic conditions and public access to official health services.

DEFINITIONS

Epileptic seizures were defined as clinically-identified abnormal and excessive discharge of neurons in the brain. Such seizures might be motor, sensory, and/or involve disturbed consciousness. Epilepsy was defined as two or more epileptic seizures occurring at least 24 hours apart that were unprovoked by a transient disruption, such as fever, acute metabolic changes, or drug intoxication, and regardless of antiepileptic drug (AED) treatment. Epilepsy was described as active if at least one seizure had occurred during the previous 4 years.

Classifications of epileptic seizures and epileptic syndromes were based on clinical picture, electroencephalogram (EEG), and the International League Against Epilepsy classification system (ILAE; Commission on Classification and Terminology of the ILAE 1989). Seizure type was classified according to the type that most accurately described the clinical condition. The term 'remote symptomatic etiology' was reserved for cases where obvious etiological factors were responsible for the seizures. A model for EF is proposed by Anderson (2002) dividing EF into different cognitive functions: cognitive flexibility, attention control, goal setting, and information processing; tests to measure these functions are discussed below under 'psychological examinations'.

INCLUSION AND EXCLUSION CRITERIA

Children in Hordaland who have had at least two epileptic seizures are generally referred to the University Hospital of Bergen for EEG and/or paediatric examination. The following identification methods were used: (1) review of hospital files of all 6- to 12-year-old patients with seizure disorders who had been examined in the paediatric department; (2) review of EEG files of all 6- to 12-year-old children registered at the EEG laboratory within the last 5 years; and (3) contact with the county's general practitioners, departments of child psychiatry, special institutions for children with disabilities, and other hospitals.

The selection procedure of patients is shown in Figure 1. One hundred and ninety-eight children were identified with active epilepsy born between 1 January 1982 and 31 December 1988 living in Hordaland during the prevalence period (1 October 1994–31 March 1996). Children with severe cognitive deficits were excluded as assessment with the selected instruments would not have been possible. One hundred and seventeen children with epilepsy and full psychological reports were included (71 males, 46 females; mean age 10y 5mo [SD2y]; range 6y–12y 11mo).

Table I: Demographic characteristics of children with epilepsy and comparison children[a]

Variable	*Epilepsy group*	*Comparison group*	*p*[b]
n	133	139	
Age, y:m			
Mean	10:5	10:1	0.21
SD	2:0	2:1	
Sex (males/females)			
Number	79/54	82/57	0.95
Percent	59/41	59/41	
SES (score)			
Mean	4.4	4.7	0.06
SD	1.6	1.4	

[a]Of the 133 eligible children with epilepsy, 117 (88%) responded, and of the 139 comparisons, 124 (89%) performed at least three of the 14 tests of executive function. [b]Independent samples *t*-test. SES, socioeconomic status.

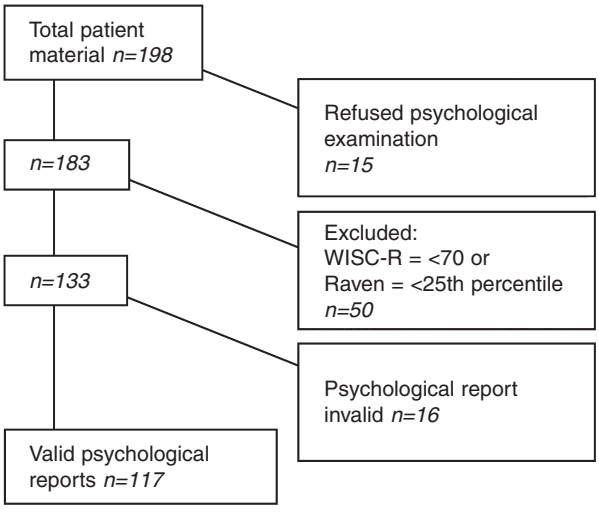

Figure 1: *Flow chart of patient selection. WISC-R, Weschler Intelligence Scale for Children-Revised (Weschler 1949).*

COMPARISON PARTICIPANTS

Comparison children living in Hordaland were randomly selected from the Norwegian birth registry. For each patient a comparison child was identified and matched with children from the epilepsy group according to sex and birth month and year. Comparison children from the general population were preferred because the primary research goal was to describe the picture of various psychological problems encountered by school children with epilepsy. Comparison children underwent the same psychological examinations as patients. Valid data were obtained from 124 of the comparison children (71 males, 53 females; mean age 10y 1mo [SD 2y 1mo]; range 6y–12y 11mo).

PSYCHOLOGICAL EXAMINATIONS

Psychological investigations were performed by one of the authors (BH) and a test technician. While patients and comparisons were examined, the mothers completed the Child Behaviour Checklist (CBCL; Achenbach and Edelbrock 1983) and questions regarding SES (Sommerfelt 1997). Investigators were not blinded to study group conditions.

Children's cognitive function was measured using Raven Matrices (Raven 1965). Due to time restrictions, a non-verbal problem-solving test was chosen. School performance was evaluated using information from the CBCL (mean level of school performance in Norwegian language, English language, mathematics, history, and natural sciences). Scores were registered on a 4-point Likert scale.

There is a lack of consistency regarding a single definition of EF in the literature and there is no single test to measure it (Pennington and Ozonoff 1996). Therefore, a composite set of tests to cover a broad EF definition was used and, among these tests, three of the 'traditional EF tests' were selected to cover a narrow EF definition (Alexander and Stuss 2000).

The following examination methods were included to cover a broad definition of the EF concept: (1) visual short-term memory from Illinois Test of Psycholinguistic Abilities (ITPA; Gjessing and Nygaard 1995) to assess immediate visual short-term memory; (2) visual–motor function using the Developmental Test of Visual–Motor Integration (VMI; Beery 1989); and (3) Verbal learning (VL) and immediate recall (IR) were tested using 10 unrelated common words adapted from Luria (1966). The list was read aloud and the child was invited to

recall as many words as possible in any preferred order. The list was repeated with similar recall-trials until the child remembered all words or had been given 10 trials; (4) Word fluency test (WF; Halperin et al. 1989): requiring the child to say as many words as possible starting with a specific letter(s) in 60 seconds (WF [letter]); and to name as many animals as possible in another 60 seconds (WF [animals]). These tests are sensitive to diffuse reduction in cognitive efficiency, working memory function, and/or EF; (5) The Wisconsin Card Sorting Test (WCST) computerized version (Nyman 1996) was used to evaluate the ability to form abstract concepts, deduce abstract categories, and to shift and maintain cognitive set. The WCST is reported to be sensitive to frontal-lobe dysfunction and diffuse brain damage (Robinson et al. 1980). Seven different scores were obtained: (a) number of trials administered, (b) total correct responses, (c) total errors, (d) perseverative responses, (e) perseverative errors, (f) non-perseverative errors, (g) categories completed: failure to maintain set/learning to learn; (6) Copying from the Wechsler Intelligence Scale for Children-Revised (WISC-R; Wechsler 1949) was used to tap visual working memory. No instruction was given to remember the task; and (7) A measure of incidental memory using a sheet that was covered. Children were asked to fill in all numbers remembered

Table II: Executive functions (EFs) in children with epilepsy and comparison group

EF measure	*Epilepsy group*			*Comparison group*			*p*[a]	*Difference of means, (95% CI)*[b]	
	n	*Mean*	*SD*	*n*	*Mean*	*SD*			
ITPA	115	23.0	5.3	124	25.3	5.5	0.002	–2.2	(–3.6 to –0.8)
VMI (drawing)	114	9.5	3.2	123	10.4	3.3	0.037	–0.9	(–1.7 to –0.1)
VL	97	6.3	3.1	113	4.6	2.1	0.000	1.7	(1.0 to 2.4)
WF (letter)	117	9.0	4.4	124	11.1	4.2	0.000	–2.1	(–3.2 to –1.0)
WF (animals)	117	13.8	4.8	124	15.8	4.6	0.001	–2.0	(–3.2 to –0.9)
WCST trials administered	99	69.2	16.8	106	78.4	13.5	0.000	–9.2	(–13.4 to –5.0)
WCST correct responses	100	52.8	22.4	106	40.0	18.8	0.000	12.7	(7.1 to 18.4)
WCST total errors	100	28.0	17.7	106	21.5	13.4	0.003	6.6	(2.3 to 10.9)
WCST perseverative responses	100	24.8	14.3	106	19.3	11.5	0.002	5.6	(2.0 to 9.1)
WCST perseverative errors	100	28.5	15.7	106	21.8	13.2	0.001	6.8	(2.8 to 10.7)
WCST non-perseverative errors	100	3.6	1.8	106	4.6	1.7	0.000	–1.0	(–1.5 to –0.5)
WCST categories completed	100	1.3	1.2	105	1.8	1.6	0.010	–0.5	(–0.9 to –0.1)
WISC-R coding	112	25.7	11.3	120	32.5	12.0	0.000	–6.8	(–9.8 to –3.8)
Incidental memory	107	5.3	2.8	119	6.0	2.6	0.054	–0.7	(–1.4 to 0.0)

[a]Independent sample *t*-test of means, epilepsy vs comparison. [b]Epilepsy vs comparison. CI, confidence interval; ITPA, Illinois Test of Psycholinguistic Abilities for visual short-term memory (Gjessing and Nygaard 1995); VMI, Developmental Test of Visual–Motor Integration (Beery 1989); VL, Verbal learning (adapted from Luria 1966); WF, Word fluency test (Halperin et al. 1989): specific letter(s) (WF [letter]), animals (WF [animals]); WCST, Wisconsin Card Sorting Test (Nyman 1996); WISC-R, Wechsler Intelligence Scale for Children – Revised (Weschler 1949).

Table III: Executive functions (EFs) according to linear regression analyses and reported as standardized regression coefficients, with separate adjustments for cognitive function (Raven 1965), depression (Birleson et al. 1987), and socioeconomic status (SES) in children with epilepsy and comparison group

EF measures	*Crude effect (p)*	*Adj for Raven (p)*	*Adj for depression (p)*	*Adj for SES (p)*	*Total adj (p)*
ITPA	0.20 (0.002)	0.13 (0.053)	0.19 (0.015)	0.17 (0.006)	0.10 (0.177)
VMI (drawing)	0.32 (0.000)	0.25 (0.001)	0.31 (0.000)	0.29 (0.000)	0.22 (0.008)
VL	0.24 (0.000)	0.21 (0.002)	0.25 (0.001)	0.23 (0.000)	0.20 (0.011)
WF (letter)	0.21 (0.001)	0.19 (0.006)	0.22 (0.004)	0.19 (0.002)	0.18 (0.027)
WF (animals)	0.29 (0.000)	0.23 (0.002)	0.22 (0.005)	0.29 (0.000)	0.12 (0.122)
WCST trials administered	0.30 (0.000)	0.23 (0.002)	0.22 (0.004)	0.29 (0.000)	0.12 (0.129)
WCST total correct responses	0.21 (0.003)	0.16 (0.035)	0.13 (0.111)	0.20 (0.004)	0.09 (0.298)
WCST total errors	0.21 (0.002)	0.16 (0.035)	0.12 (0.127)	0.21 (0.003)	0.06 (0.446)
WCST perseverative responses	0.23 (0.001)	0.20 (0.007)	0.20 (0.008)	0.22 (0.001)	0.09 (0.229)
WCST perseverative errors	0.27 (0.000)	0.21 (0.003)	0.17 (0.030)	0.27 (0.000)	0.07 (0.361)
WCST nonperseverative errors	0.18 (0.010)	0.12 (0.101)	0.16 (0.051)	0.18 (0.012)	0.10 (0.235)
WCST categories completed	0.14 (0.037)	0.08 (0.264)	0.15 (0.051)	0.13 (0.044)	0.06 (0.459)
WISC-R coding	0.28 (0.000)	0.27 (0.000)	0.33 (0.000)	0.27 (0.000)	0.30 (0.000)
Incidental memory	0.13 (0.054)	0.09 (0.209)	0.16 (0.032)	0.11 (0.103)	0.12 (0.152)
Mean EF*	0.23	0.18	0.20	0.22	0.13

*Mean of the 14 scores given above. Adj, adjustment; ITPA, Illinois Test of Psycholinguistic Abilities for visual short-term memory (Gjessing and Nygaard 1995); VMI, Developmental Test of Visual–Motor Integration (Beery 1989); VL, Verbal learning (adapted from Luria 1966); WF, Word fluency test (Halperin et al. 1989): specific letter(s) (WF [letter]), animals (WF [animals]); WCST, Wisconsin Card Sorting Test (Nyman 1996); WISC-R, Wechsler Intelligence Scale for Children – Revised (Wechsler 1949).

Table IV: Seizure-related factors and executive functions (EFs) index in children with epilepsy

Seizure-related factors (n)	*Standardized mean in narrow EF score*[a]	*95% CI*	*Partial Eta squared (p)*	*Standardized mean in broad EF score*[a]	*95% CI*	*Partial Eta squared (p)*
Remote symptomatic aetiology			<0.001 (0.849)			0.005 (0.457)
Not present (123)	0.55	0.35 – 0.76		0.61	0.38 to 0.83	
Present (10)	0.48	–0.18 to 1.15		0.89	0.17 to 1.62	
Epileptic syndrome			0.139 (0.011)			0.171 (0.002)
Localization-related idiopathic (33)	0.04	–0.32 to 0.41		–0.06	–0.45 to 0.33	
Localization-related sympt. (17)	0.68	0.18 to 1.18		0.97	0.44 to 1.51	
Localization-related crypt. (29)	0.71	0.29 to 1.14		0.86	0.41 to 1.32	
Generalized idiopathic (24)	0.39	–0.05 to 0.84		0.52	0.04 to 1	
Generalized crypt./sympt. (15)	0.62	0.07 to 1.18		0.75	0.16 to 1.34	
Generalized symptomatic (8)	1.34	0.58 to 2.1		1.33	0.52 to 2.13	
Undetermined (7)	1.33	0.58 to 2.09		1.48	0.67 to 2.29	
Main seizure type			0.032 (0.832)			0.033 (0.819)
Simple partial (21)	0.46	–0.05 to 0.96		0.57	0.02 to 1.12	
Complex partial (41)	0.55	0.18 to 0.92		0.56	0.16 to 0.96	
Secondary generalized (18)	0.28	–0.24 to 0.8		0.39	–0.17 to 0.95	
Absences (18)	0.54	–0.01 to 1.09		0.57	–0.03 to 1.17	
Atypical absences (15)	0.98	0.41 to 1.55		1.11	0.49 to 1.73	
Myoclonic (4)	0.43	–0.64 to 1.5		0.59	–0.57 to 1.75	
Tonic–clonic (14)	0.60	–0.05 to 1.24		0.76	0.06 to 1.46	
Others (2)	0.42	–1.09 to 1.93		0.97	–0.67 to 2.61	
Age at onset, y (*n*)			0.151 (0.003)			0.168 (0.001)
0–1 (18)	0.89	0.41 to 1.37		1.02	0.50 to 1.54	
2–3 (24)	0.96	0.54 to 1.38		1.25	0.80 to 1.71	
4–5 (20)	0.83	0.40 to 1.25		0.81	0.36 to 1.27	
6–7 (20)	0.07	–0.39 to 0.54		0.13	–0.38 to 0.63	
8–9 (25)	0.38	–0.01 to 0.77		0.37	–0.05 to 0.79	
>9 (10)	–0.29	–0.91 to 0.33		–0.22	–0.90 to 0.45	
Seizure frequency last year (*n*)			0.06 (0.032)			0.081 (0.009)
No seizures (33)	0.28	–0.05 to 0.6		0.25	–0.1 to 0.61	
1–12 seizures a year (54)	0.5	0.19 to 0.81		0.63	0.29 to 0.96	
>12 seizures a year (46)	0.92	0.57 to 1.28		1.08	0.70 to 1.47	
AED treatment last year (*n*)			0.017 (0.373)			0.050 (0.012)
No drugs (34)	0.3	–0.09 to 0.7		0.41	–0.03 to 0.84	
One drug (88)	0.61	0.37 to 0.86		0.7	0.44 to 0.97	
Two or three drugs (11)	0.69	0.05 to 1.32		0.72	0.02 to 1.41	
AED treatment past and/or present (*n*)			0.075 (0.034)			0.117 (0.003)
No drugs (16)	0.14	–0.41 to 0.69		0.05	–0.53 to 0.63	
One drug (56)	0.32	0.01 to 0.62		0.35	0.03 to 0.67	
Two drugs (42)	0.89	0.55 to 1.22		1.13	0.77 to 1.48	
Three or more drugs (19)	0.71	0.23 to 1.2		0.74	0.23 to 1.26	
AEA[b] (*n*)			0.086 (0.138)			0.07 (0.233)
Frontal right (58)	0.71	0.42 to 0.99		0.91	–0.43 to 2.25	
Frontal left (51)	0.54	0.23 to 0.86		–0.22	–1.86 to 1.43	
Middle right (80)	0.59	0.34 to 0.83		0.34	–0.39 to 1.08	
Middle left (77)	0.53	0.28 to 0.78		0.04	–0.48 to 0.56	
Posterior right (71)	0.71	0.45 to 0.97		0.57	–0.05 to 1.19	
Posterior left (55)	0.72	0.43 to 1.01		0.77	0.44 to 1.10	
Number of AEAs (*n*)			0.033 (0.286)			0.065 (0.058)
No area (22)	0.79	0.28 to 1.30		1.20	0.66 to 1.74	
One area (33)	0.23	–0.16 to 0.62		0.25	–0.17 to 0.66	
Two to five areas (33)	0.61	0.23 to 0.99		0.64	0.23 to 1.05	
Generalized (45)	0.62	0.29 to 0.96		0.66	0.30 to 1.02	

Numbers were obtained from Univariate Analyses of Variance (ANOVA) which comprised epilepsy group only. [a]Standardized mean *z*-score of index comprising eight standardized measures of EF. Comparison group mean 0 (SD 1), reversed (positive) values indicating EF problems. [b]Subgroups not mutually exclusive. CI, confidence interval; Sympt, symptomatic, Crypt, cryptogenic; AED, antiepileptic drug; AEA, areas of epileptic activity located with electroencephalogram.

under the correct symbols on a new similar sheet allowing 1.5 minutes. The following tests were used to cover a narrow EF definition: WCST perseverative responses, WF (letter), and WF (animals).

Based on a broad definition of the EF concept, a composite broad EF index was computed as a standardized sum of *z*-scores of eight subtests (mean 0 [SD 1]): ITPA, VMI, VL, WF (letter), WF (animals), WCST perseverative responses, WISC-R, coding, and incidental memory. This composite EF index had good internal consistency (Cronbach's alpha=0.83). Principal component analysis identified only one factor with eigenvalue above 1, explaining 50% of the variance in the original items. Based on a narrow definition of EF, a narrow EF index was computed in the same way using WCST perseverative responses, WF (letter), and WF (animals).

Depression was measured using the Birleson Depression Scale (Birleson et al. 1987), which consists of 23 questions to be answered on a 5-point Likert scale. The test was administered to children ≥9 years of age (n=89).

NEUROPAEDIATRIC EXAMINATIONS

Children with epilepsy were examined by a neuropaediatrician (PEW). All EEGs were interpreted by one neurophysiologist (HS). Six brain areas of epileptic activity were evaluated regarding past and/or present epileptogenic activity: right and left frontal, right and left middle, and right and left posterior areas. Epileptogenic activity (spikes and spike-and-slow-wave discharges) was regarded as present in an area if observed in at least one EEG recording.

The following seizure-related variables were registered in each child with epilepsy: remote symptomatic aetiology (present or absent); epileptic syndrome; main seizure type; age at epilepsy onset; seizure frequency last year; AED treatment last year; AED treatment past and/or present; area of epileptic activity (AEA) located with EEG; and number of AEAs.

SOCIOECONOMIC STATUS

SES was assessed using a summary score based on parents' income level, present occupation, and educational level (Cronbach's alpha=0.63). For two-parent households, the SES score was calculated as the mean score for both parents. Families were categorized as low, average, or high SES.

STATISTICS

Independent sample *t*-tests and χ^2 tests were used to investigate possible differences between epilepsy and comparison groups regarding age, sex, and SES (Table I). EF in children with epilepsy and comparisons was compared using means and SDs, and tested with independent sample *t*-tests. Mean differences with 95% confidence intervals (CI) were also calculated (Table II). Linear regression analyses were used calculating a composite score by sums of *z*-scores from all EF tests. Results were given as standardized regression coefficients before adjustment for covariates, with separate adjustments for IQ, depression (Birleson Depression Scale), and SES as well as a fully adjusted model (Table III).

Analysis of variance (ANOVA) was used to examine associations between seizure-related factors and the composite EF index. These tests were performed within the epilepsy group. To compare the various EF groups to comparisons, the composite score was scaled as a *z*-score in the comparison group.

Table V: Level of school performance[a] in children with epilepsy compared with comparison children[b]

	Model 1	*Model 2*	*Model 3*	*Model 4*	*Model 5*
Epilepsy[c]					
B	**–0.68**	**–0.50**	**–0.32**	**–0.32**	**–0.26**
95% CI	–0.38 to –0.99	–0.19 to –0.8	–0.04 to –0.61	–0.03 to –0.61	0.02 to –0.55
Significance	<0.001	0.002	0.028	0.028	0.069
Raven Matrices centile score[d]					
B		**0.29**	**0.16**	**0.16**	**0.16**
95% CI		0.14 to 0.44	0.01 to 0.3	0.01 to 0.31	0.01 to 0.31
Significance		<0.001	0.038	0.038	0.032
EF broad index[d]					
B			**–0.47**	**–0.47**	**–0.45**
95% CI			–0.64 to –0.29	–0.64 to –0.29	–0.62 to –0.28
Significance			<0.001	<0.001	<0.001
SES[d]					
B				**0.01**	**–0.01**
95% CI				–0.13 to 0.15	–0.15 to 0.13
Significance				0.898	0.859
Depression[d]					
B					**–0.20**
95% CI					–0.05 to –0.36
Significance					0.011

[a]Mean level of school performance recorded as standardized mean group differences according to Child Behavior Checklist (CBCL; Achenbach and Edelbrock 1983) information about children's skills in Norwegian language, English language, mathematics, history, and natural sciences, 4-point Likert-scale. [b]Children in school (with valid CBCL parent scheme completed) included, epilepsy group n=117, comparison group n=124. Results were obtained from linear regression analyses. [c]Negative values indicate more problems in children with epilepsy compared with comparison group. [d]Level of school performance, cognitive function (Raven 1965), Executive function (EF) index, socioeconomic status, and depression (Birleson et al. 1987) are continuous variables encoded as *z*-scores. Significance at ≤0.05%. CI, confidence interval; B, unstandardized regression coefficient.

Patient groups whose 95% CI did not comprise zero were considered different from the comparison group. All values were scaled: positive figures indicated more EF problems. Tests of significance were based on multiple group comparisons (within the subgroups of each seizure-related factor), as was level of explained variance according to ANOVA (Table IV). A step-wise linear regression analysis was used to examine school performance in patients but not comparisons. Additional adjustments to models were introduced for cognitive function (Raven Matrices), EF, SES, and depression (Table V). The study was approved by the Norwegian Data Inspectorate and by the Regional Committee on Medical Research Ethics. Written informed consent was obtained from all parents in both study groups.

Results

Epilepsy and comparison groups were comparable with regard to age, sex distribution, and SES (Table I). Distributions of the various epilepsy syndromes and main seizure types are shown in Table IV.

Children with epilepsy scored significantly lower than comparison children in all EF tests except incidental memory (Table II). EF according to the broad definition was reported as standardized regression coefficients. Adjustments for cognitive function (Raven Matrices), depression, and SES showed that about one-fifth of the effect on the EF measure could be attributed to cognitive function, less to depression, and hardly anything to SES. The total model explained nearly half of the patients' EF problems (Table III).

There was a strong correlation between the broad EF index and the narrow EF index (Pearson's $r=0.89$, $p<0.001$). As shown in Table IV, there were significant relationships between the broad EF index and the following seizure-related factors: epilepsy syndrome, age at onset, AED treatment past and/or present, seizure frequency, and AED treatment last year; these factors explained 17%, 17%, 12%, 8%, and 5% of patients' EF problems respectively. Within each of these categories there were subgroups that were not significantly related to EF problems: localization-related idiopathic epilepsy syndrome, epilepsy onset 6 years and older, seizure freedom, and no drug treatment. Three seizure-related factors (epilepsy aetiology, main seizure type, and EEG) were not significantly related to EF problems. The relationships between narrow EF index and seizure-related factors showed a similar pattern to the broad EF index (Table IV). There were two exceptions that were not significantly related to EF problems: AED treatment last year and generalized idiopathic epileptic syndromes.

The epilepsy group's school performance was 0.68 SD poorer than comparisons (Table V, Model 1). Separate adjustments for candidate mechanisms were used to identify this group difference. Adjustment for EF (broad definition) explained most of the poorer school performance, followed by cognitive function (Raven Matrices centile scores), and depression. SES did not explain this difference.

Discussion

The major findings were as follows: (1) Children with epilepsy without severe cognitive deficits had more EF problems than comparisons; (2) EF problems could be partly explained by cognitive function and depression; (3) EF problems were related to epileptic syndrome, age at epilepsy onset, seizure frequency, and AED treatment; and (4) Level of school performance was lower in children with epilepsy than in comparisons: this could be partially explained by cognitive problems, EF problems, and depression, whereas SES did not show any significant effect.

As there was a highly significant correlation between results based on a broad versus a narrow definition of EF, the discussion will be based on the broad EF definition. In this population-based study, children with epilepsy had more problems than comparison children in all but one EF measure (incidental memory), indicating problems with visual and auditory working short memory, retrieval of verbal material, visual–motor speed, and perseveration. With the exception of idiopathic localization-related epilepsies, all epilepsy syndrome groups were associated with EF deficits.

Memory problems have been reported in children with frontal lobe, temporal lobe, and absence epilepsies (Nolan et al. 2004). Subtle EF deficits have been reported in benign occipital lobe epilepsies (Gulgonen et al. 2000). Farwell et al. (1985) performed detailed neuropsychological testing of 118 children with epilepsy and found that 70% of children with epilepsy and 29% of comparisons had various degrees of impaired neuropsychological functions.

No significant difference in EF was found between children with remote symptomatic aetiology and those who had epilepsy of other aetiology. In a 10-year follow-up study of 69 heterogeneous patients with epilepsy, Kalska (1991) reported no difference in long-term neuropsychological performance between patients with unknown and known aetiology.

In the current study, early-onset of epilepsy was significantly associated with EF problems. Riva et al. (2002) found that onset of frontal epilepsy before 6 years of age was associated with more perseverative errors (WCST) than later onset of epilepsy. Hermann et al. (2002) found problem solving in patients with early onset was worse than in those with late onset temporal lobe epilepsy, but no difference was found in processing speed.

More EF problems were identified in children with a high frequency of seizures. Kalska (1991) found that participants with no seizures during a 10-year follow-up period had the highest levels of improvement in neuropsychological functioning, while participants whose last seizure occurred during the previous 24 hours showed a decline, particularly in visual–spatial reasoning and motor tasks.

Use of one or more AEDs and having seizures at present were both associated with more EF problems in the current study. These two factors reflect the present activity of epilepsy. Kalska (1991) reported that polypharmacy appeared to maximize the detrimental effect of structural brain pathology in motor speed and memory of patients with epilepsy (Riva et al. 2002).

There was a significant difference in school performance between children with epilepsy and comparisons: children with epilepsy showed poorer function. School performance information was obtained from the CBCL form (Achenbach 1991). No school performance information was provided from teachers, therefore acting as a limitation of the study. Lower levels of EF in the epilepsy group accounted for the major part of poorer school performance. Fastenau et al. (2004) also found a direct effect of neuropsychological function on academic achievement in children with chronic epilepsy.

High frequency of depression has been reported in childhood epilepsy (Thome-Souza et al. 2004). Depression has been

found to have a negative influence on memory function of patients with epilepsy (Elixhauser et al. 1999). Such findings are supported in the current study as depression appeared to influence EF measures including attention and memory functions. SES was not found to influence EF significantly. The relatively homogeneous population in the Scandinavian countries might explain this conclusion. However, the conclusion cannot be generalized to other populations with greater SES variations.

As the study was conducted in a hospital setting, it was not possible to perform psychological examinations blinded to group, which represents a limitation of the study.

Conclusion

This population-based study showed an increased frequency of EF problems in all epilepsy syndromes (except Rolandic epilepsy), early epilepsy onset, high seizure frequency, and polytherapy. EF problems partly explained poorer school performance in children with epilepsy, in addition to cognitive problems and depression, but not SES. In patients with EF problems, special educational procedures should be initiated. The need for therapeutic efforts regarding depression should also be considered.

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List of abbreviations

CBCL	Child Behavior Checklist
EF	Executive function
IR	Immediate recall
ITPA	Illinois Test of Psycholinguistic Abilities
VL	Verbal learning
VMI	Developmental Test of Visual–Motor Integration
WCST	Wisconsin Card Sorting Test
WF	Word fluency test
WF (animals)	Word fluency test naming animals
WF (letter)	Word fluency test starting with specific letter