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Research Article

Cognitive decline over 7 years in aging patients with childhood-onset epilepsy: A population-based prospective follow-up study

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Abstract

Objective: The cognitive trajectory of aging individuals with childhood-onset epilepsy is poorly understood. Our aim was to examine cognitive change over a 7-year period in aging individuals with epilepsy, originally recruited for prospective follow up in the early 1960's. **Method:** 36 participants with childhood-onset epilepsy from a prospective population-based cohort and 39 controls participated in the 50-year and 57-year follow-up data collections. Eight participants had active epilepsy, 28 were in remission. Eleven neuropsychological tests were used to measure language/semantic function, episodic memory and learning, executive function, visuomotor function, and working memory. Regression-based standardized change scores were used to control for sources of error in test-retest assessments. **Results:** Participants with epilepsy lacked a test-retest effect in language functions. A significant decline was found in participants with active epilepsy in episodic memory functions overall, and in those with remitted epilepsy in learning, immediate recall and set-shifting. The risk of clinically significant general cognitive decline was higher in participants with active epilepsy (OR 61.25, 95% CI 5.92–633.81, $p = .0006$). Among those with remitted epilepsy the risk was lower and non-significant (OR 2.19, 95% CI 0.58–8.23, $p = .24$). **Conclusions:** Our results demonstrate poorer cognitive trajectories in participants with childhood-onset epilepsy compared to controls, particularly in those with active epilepsy. The risk of general cognitive decline was lower in participants with remitted epilepsy, but a decline in episodic memory functions was observed. Our findings likely reflect faster brain aging in childhood-onset epilepsy, even in individuals with early remission.

Keywords: Childhood-onset epilepsy; cognitive impairment; cognitive decline; aging; memory; learning

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Statement of Research Significance

Research Question:

- Is childhood-onset epilepsy associated with an adverse cognitive trajectory in later life?

Main Findings:

- Relative to the control group, substantial decline in cognitive function over seven years was observed in participants with chronic epilepsy, with memory being most affected. Cognitive decline was less pronounced in participants with remitted epilepsy, but significant decline was observed in learning and recall.

Study Contributions:

- The results demonstrate a progressively worsening cognitive trajectory in participants with childhood-onset epilepsy, particularly in those with chronic active epilepsy, more than 55 years after the onset of epilepsy. This finding may indicate faster brain aging and/or initiation of a preclinical dementing process in childhood-onset epilepsy, possibly affecting even individuals with early remission.

Introduction

The course of cognition in chronic epilepsy has been a longstanding clinical concern, the first empirical study appearing in the English literature in 1924 (Fox, 1924), with the issue revisited frequently over the decades up to the present time (Choi et al., 2021, 2022b). Most often the question has been addressed by cross-sectional examinations of the association between epilepsy duration and some aspect of cognition (Baxendale et al., 2010; Helmstaedter & Elger, 2009), while a more limited number of investigations tracked cognition prospectively (Baker et al., 2011; Piazzini et al., 2006; Thompson & Duncan, 2005). The limitations

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of a cross-sectional approach to a fundamentally longitudinal issue are appreciated. But even in existing longitudinal studies, with few exceptions (Johnson et al., 2020), the overwhelming majority of reports were not population-based, focused on active cases only, contained modest test-retest intervals, with variable thoroughness of cognitive assessments, and minimal relevant lifespan information other than that related to epilepsy (Dodrill, 2004; Kesselmayer et al., 2019).

This concern about the cognitive course of epilepsy has recently intersected with sharply increased global awareness of the exponential growth of the aging population and its attendant risk of cognitive disorders of aging and their linked fiscal, social, and personal implications (Sen et al., 2020). Recent studies have found that vascular and genetic risk factors (APOE ε4) increase the risk of cognitive impairment and also accelerate cognitive decline in aging patients with epilepsy (Choi et al., 2021, 2022a; Hermann et al., 2017; Reyes et al., 2021; Tai et al., 2023), thus rendering vascular health as one important factor for slowing or preventing cognitive decline. Another recent age-related issue is the fact that de novo onset of epilepsy in later life is related to an increased risk of a progressive neurodegenerative process (Johnson et al., 2020; Keret et al., 2020; Tang et al., 2022). But one critical question that still remains to be clarified is the *cognitive aging process* in chronic childhood-onset epilepsy over the longer term—a related but distinctly different issue. In clinical settings, neuropsychologists working with the elderly population will benefit from knowing the potential impact of epilepsy on brain aging and insight into potential adverse trajectories can guide preventive interventions.

Here the focus is on the cognitive aging process in longstanding established epilepsy (Sen et al., 2018) where we address the issue in unique ways. First, we benefit from a population-based cohort of persons with childhood onset epilepsy (COE) initially recruited when younger than 16 years of age, subsequently followed for 5+ decades, the sample consisting of both remitted and active epilepsy cases—a rarely considered comparison. Second, a closely matched control population is available for comparison to the epilepsy cohort. Third, all participants presented for prior face-to-face comprehensive cognitive evaluation which characterized their neuropsychological status 50 years after diagnosis. Here we report the prospective cognitive course in the participants with epilepsy almost seven years later, when participants are entering their early 60's, using the cognitive change in the control population as a comparison point. The results provide the ability to characterize both static and potentially longstanding cognitive anomalies versus problematic progressive changes with further aging. Finally, the prospective data are analyzed not only at a group level but also with a focus on characteristics of cognitive change across individual epilepsy participants.

Our hypotheses included the following: First, despite the extended 7-year test-retest interval practice effects will be more likely to be observed in the control than the COE cohort. Second, prospective cognitive abnormalities will be more likely to be observed in the active epilepsy than remitted group. Third, among the remitted epilepsy group, modest cognitive declines will nonetheless be observed compared to the control cohort.

Methods

Baseline study participants

The core investigation from which these participants were obtained originated from a population-based cohort of 245 children under 16 years of age, living in the catchment area of Turku University Hospital, Turku, Finland at the end of 1964 (Sillanpää, 1973). All participants met the criteria for epilepsy at the time, with two or more unprovoked seizures (Commission on Revised Classification of Seizures, 1981), and were identified based on hospital and primary healthcare records, as well as a review of the National Health Service (NHS) records, a registry of all patients living in Finland. A review of the NHS records was important since, by rule, all Finnish children with seizures were (and still are) referred to hospitals for evaluation. The recruitment and data collection processes have been described in detail previously (Sillanpää et al., 1998, 2015). The participants were enrolled in a prospective, longitudinal study examining the natural history and diverse outcomes (eg, social function, epilepsy remission, mortality) of childhood onset epilepsy whose medical records were reviewed continuously. In 1992 a follow-up with an in-person structured interview and a clinical examination was conducted. Participants with no neurological impairment were regarded as subjects with *uncomplicated epilepsy*. The 100 participants with uncomplicated epilepsy were paired with matched controls, selected from the Central Statistical Office of Finland. The control subjects were chosen with a stratified random sampling, in which each study participant had four potential control subjects, all matched for age, sex, and place of birth. In the end, one of the 100 control subjects was excluded due to a technical error, after which 99 pairs of epilepsy participants and control subjects remained.

Turku adult childhood-onset epilepsy (TACOE) studies

In 2012–2013, 50 years after the baseline measurements, participants with complicated epilepsy were excluded from further analyses. All initial 99 childhood-onset epilepsy (COE) subjects with uncomplicated epilepsy and their matched controls were invited to participate in a new study (TACOE-50) (Figure 1). Of the 99 COE subjects, 26 were not available, and of the 99 controls, 21 were not available. In the end, 51 COE subjects and 52 controls gave their written consent and underwent an extensive investigation program for two days, which included a neuropsychological assessment conducted at Turku University Hospital. Comprehensive clinical and neurological examinations were performed by the designated neurologist. Although the subject-control pairs were no longer complete, the controls effectively continued to serve as a control group. In the TACOE-50 study, the epilepsy group was further divided into two groups: participants with continuing seizure activity (PWE-A, seizure activity within the past 5 years and/or use of anti-seizure drugs (ASD) and participants with epilepsy in remission (PWE-R, no seizure activity within the last 5 years and no ASD use). The TACOE-50 study has been described in detail previously (Sillanpää et al., 2015).

A second follow-up investigation, the current (TACOE-55) study, was initiated in 2017. Of the 51 COE subjects, 12 declined to participate, which resulted in a total of 39 COE participants. In the control group, eight declined, leaving the group with 44 controls. An additional eight participants (three COE subjects and five controls) were excluded from data analyses due to extreme outlier scores, which resulted in a total of 36 COE subjects and 39 controls in the final analyses. None of the COE or control participants died between the years 2012–2013 and 2017–2019 (Figure 1). The cohort underwent the same neuropsychological assessment and other procedures as in 2012–2013 (Table 1). The clinical and neurological examination followed the same protocol in TACOE-50 and TACOE-55. Due to practical challenges in data collection

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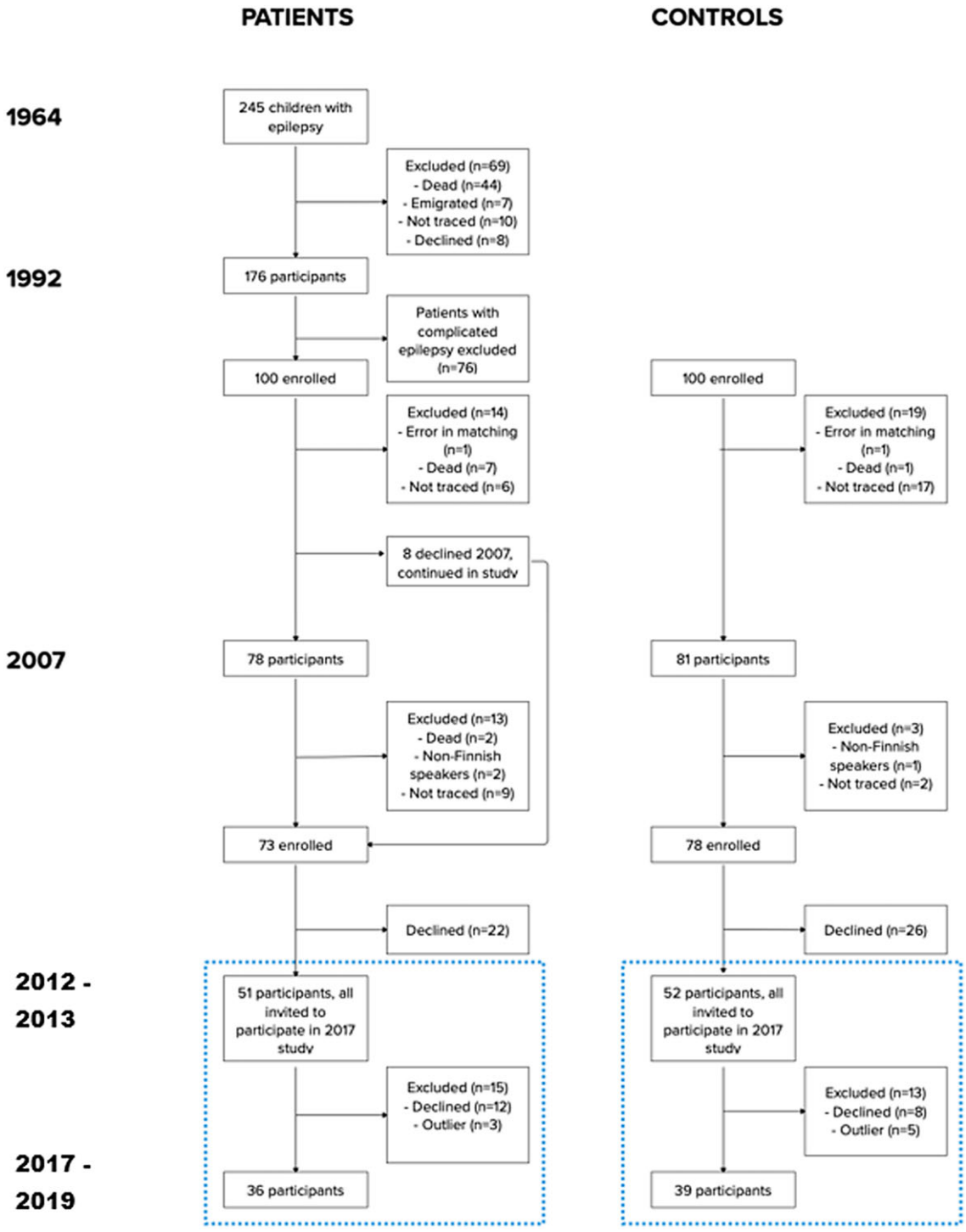

Figure 1. Flow chart of study participants and exclusions.

procedures, the final time lag between the TACOE-50 baseline and TACOE-55 follow-up was almost seven years.

Attrition rates have been previously reported from the TACOE-50 follow-up study (Sillanpää et al., 2015). The attrition rates were low and without differential dropouts. In the present study, the attrition rate from TACOE-50 to TACOE-55 was also low with a non-significant difference between COE subjects and controls (12% vs. 20%, $p = .289$). Dropouts were more often female than male (23% vs. 3%, $p = .004$) for unknown reasons; dropouts were more frequent among those with no or less than weekly versus weekly alcohol consumption (22% vs. 4%, $p = .015$); the effects did not differ significantly between the COE and control subgroups. Dropouts were also more often cognitively impaired in the TACOE-50 study (48% vs. 26%, $p = .049$); but there were no differential group effects. We also examined possible differences in the number of impaired tests at the TACOE-50 baseline between dropouts vs. non-dropouts, and no differences were found in the controls ($t = 1.116$, $p = .135$), in the PWE-R ($t = .795$, $p = 216$)

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Table 1. Cognitive functions and tests administered

Cognitive function	Test administered
Language/semantic function	
Naming	Boston Naming Test, items 30–60 (Laine et al., 1997)
Semantic processing	COWAT Semantic fluency, animals, 60 s (Benton & Hamsher, 1976)
Verbal concept formation	WAIS-R Similarities (Wechsler, 1992)
Episodic memory and learning	
Learning	RAVLT Sum of learning trials 1–5 (Schmidt,1996)
Immediate recall	WMS-R Logical memory immediate free recall, part A (Wechsler, 1996)
Delayed recall	WMS-R Logical memory delayed free recall, part A, (Wechsler, 1996)
Visuomotor function	
Visual-motor coordination	WAIS-R Digit symbol (Wechsler, 1992)
Visual scanning	Trail Making Test A, time to completion (Poutiainen et al., 2010) [a]
Executive function	
Set-shifting	Trail Making Test B, time to completion (Poutiainen et al., 2010)
Production	COWAT Phonemic fluency, letter S, 60 s (Benton & Hamsher, 1976)
Working memory	
Auditory working memory	WAIS-R Digit span, sum score of span forward and backward (Wechsler, 1992)

[a]*The test administrator corrected errors in both Trail Making Test A and B.*

group or PWE-A group ($t = .443$, $p = .334$), and again the effects did not differ between the groups. No other significant differences were found between the participants and nonparticipants. The reasons for dropouts are presented in Figure 1. Out of the 12 participants that declined, seven reported other diseases (eg, multiple sclerosis, cancer, hearing problems), one suffered from claustrophobia associated with neuroimaging scanners and four did not present any particular reason for not participating. One control person had intensive cancer treatments, and the remaining seven did not express any reason for refusal.

Neuropsychological assessment

During the neuropsychological assessment, Finnish versions of validated neuropsychological tests were used (Table 1) (Lezak et al., 2012). The tests covered several cognitive domains, including episodic memory and learning, language and semantic function, working memory, executive function, and visuomotor function. Finnish norms for the tests used are based on different normative samples and standardized scores are not available for all tests. Hence, raw scores were deemed to be more valid and were used in the study in 2012 (Karrasch et al., 2017a), as well as in the present study. The assessments in TACOE-50 were conducted by a licensed psychologist (P.T.) and a research assistant with a BA in psychology (J.P.) under the supervision of a clinical neuropsychologist (M.K.). In TACOE-55 all assessments were conducted by a licensed psychologist (P.T.) under the supervision of a clinical neuropsychologist (M.K.). The tests were administered in the same order for all participants. All assessments were conducted during a single visit ranging between 1.5–2.5 hours.

Data analysis

In order to estimate the age-appropriate test-retest change in cognitive test performance over the course of almost 7 years (TACOE-50 to TACOE-55), regression-based methods were used (Duff, 2012; Durant et al., 2019; Hermann et al., 2006; Sawrie et al., 1996). Using the test-retest data of the controls, the baseline test scores (TACOE-50) were entered as predictors for follow-up (TACOE-55) test scores. The resulting equations were used to calculate predicted follow-up scores for each test and each participant:

$$\mathrm{Y(predicted)} = [\mathrm{Constant} + (\mathrm{Beta\ for\ test\ at\ follow\text{-}up\ x\ ,\ test\ at\ baseline})]$$

Thereafter, differences between the predicted and actual performance, again in each test and each participant at the TACOE-55 measurement were calculated. These difference scores were finally transformed into standardized Z-scores:

$$\mathrm{Z-(score)} = [\mathrm{Y(observed\ at\ follow)} - \mathrm{Y\ (predicted)/SE\ of\ the\ estimate}]$$

The resulting metric reflects how much the test scores for each test, for each participant at the TACOE-55 measurement, differed from what would be expected based on aging alone as informed by control group performance.

Clinically significant decline was defined using a regression-based standardized cognitive test performance of $Z \leq -1.5$. The number and percentages of participants in each group having a declined performance in each cognitive test were calculated. In addition, the number of declined tests (0–11) was calculated and differences between the groups were analyzed. Overall cognitive decline was defined as below normal ($Z \leq -1.5$ SD) performance in 4 or more out of 11 cognitive tests (≥36%). Cognitive decline was defined this way to reduce the likelihood of false positives. When using –1.5 SD as the criterion for decline on 11 different cognitive tests, the likelihood of obtaining at least four impaired scores by chance alone is less than 5% (Ingraham & Aiken, 1996). These are the same procedures as reported in the TACOE-50 investigation (Karrasch et al., 2017), with the exception of WMS-R Logical memory consolidation (savings%) being substituted with the raw score in WMS-R Logical memory delayed recall and RAVLT also now being included, the number of tests thus now being 11 instead of 10. Also, in the TACOE-50 investigation the cut off for cognitive impairment in the cross-sectional comparison was 3/10 (Karrasch et al, 2017).

The statistical analyses were conducted using IBM SPSS Statistics 26.0. For the clinical, demographic, and background variables, data was analyzed using one-way analyses of variance (ANOVA's), t-tests, Kruskal-Wallis tests, χ^2 (Fisher's exact test, two-tailed), Cohen's D as appropriate. Odds ratios (OR) with 95% confidence intervals for having general cognitive decline were also calculated for the PWE-R and PWE-A groups.

Ethical statement

All actions contributing to this work are in line with the ethical standards established by national and institutional committees on

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Table 2. Demographic and clinical data on the participants with continuing seizures (PWE-A), participants with epilepsy in remission (PWE-R), all participants with diagnosed epilepsy (PWE), and healthy controls (HC), $\alpha < .05$

	PWE-A ($n = 8$)	PWE-R ($n = 28$)	PWE ($n = 36$)	HC ($n = 39$)	
	M (SD, min-max)	*M* (SD, min-max)	*M* (SD, min-max)	*M* (SD, min-max)	Stat. sign.
Age at epilepsy onset	9.00 (4.1, 3–14)	4.4 (4.1, 0–13)			$p < .01$
Type of epilepsy					
Generalized	3 (37.5%)	14 (50%)			n.s.
Focal	5 (62.5%)	14 (50%)			
ASD use	8 (100%)	0 (0%)		0 (0%)	
Age at follow-up	66.75 (3.0, 63–71)	62.71 (4.4, 55–70)	63.62 (4.7, 55–71)	62.69 (4.2, 56–70)	PWE-A > HC $p = .014$ PWE-A > PWE-R $p = .018$
CAIDE score at baseline**	10.3 (2.9)	9.6 (2.9)	9.76 (2.9)	8.15 (2.9)	PWE > HC, $p = .023$
Sex	2m/6f	14m/14f	16m/20f	19m/22f	n.s.
APOE ε4 carrier	3 (38%)	7 (25%)	10 (27%)	11 (28%)	n.s.
Vascular pathology at baseline (Wahlund >0)	3 (38%)	7 (25%)	10 (27%)	4 (10%)	PWE-A > HC, $p = .005$, PWE > HC, *trend* $p = .052$
Mild hippocampal atrophy at baseline (Scheltens = 1)	0 (0%)	2 (7%)	2 (5%)	4 (10%)	n.s.
Vascular pathology at follow-up (Wahlund >0)	4 (50%)	16 (57%)	20 (55%)	23 (59%)	n.s.
Hippocampal atrophy at follow-up (Scheltens ≥1)	1 (12.5%)	3 (10%)	4 (11%)	4 (10.5%)	n.s.
Education*					PWE-A < HC $p = .004$ PWE-R < HC $p = .033$
Low	5 (62%)	10 (36%)	15 (42%)	9 (22%)	
Medium	2 (25%)	16 (57%)	18 (50%)	20 (49%)	
High	1 (13%)	2 (7%)	3 (8%)	12 (29%)	
Occupational status at follow-up					
Working full- or part-time	2 (25%)	16 (57%)	18 (50%)	24 (61.5%)	n.s.
Retired	6 (75%)	12 (43%)	18 (50%)	15 (38.5%)	

*Low education = less than or only primary school with or without at least 1 year of professional education, Medium education = middle school or comprehensive school with or without at least 1 year of professional education, High education = high school, college, or university.**The CAIDE score is calculated using the following vascular risk factors: age (> or = 47 years), low education (< 10 years), sex, systolic blood pressure, obesity (BMI ≥30), any physical activity, and total cholesterol, with greater points associated with higher dementia risk (Kivipelto et al., 2006)

human experimentation, as well as the Declaration of Helsinki. The study design was approved by the Joint Institutional Review Board of the University of Turku and the Turku University Hospital (Diary No. 120/2008/26.1.2009 §454). Written informed consent and access to medical records were also acquired from all participants.

Results

The epilepsy group consisted of 8 (22%) subjects who continued to have active epilepsy (PWE-A) and 28 (78%) subjects that were in remission for 5 or more years (PWE-R). There was a significant difference in age between the PWE-A group and the HC group, as well as between the PWE-A group and the PWE-R group. Participants who continued to have seizures (PWE-A) were on average 3 years older than participants in the other two groups. The controls had higher education than both the PWE-groups as expected. At baseline, the PWE group had significantly higher CAIDE-scores than the controls. The PWE group overall and particularly the PWE-A group also had more vascular brain changes as indicated by the Wahlund-score than the controls. At follow-up, the incidence of vascular brain changes had increased markedly and to a similar degree in all groups. No differences in the incidence of hippocampal atrophy was observed between the groups, either at baseline or follow-up. The percentage of APOE ε4 carriers was also similar in all groups. There were no significant differences between the three groups (HC, PWE-R, PWE-A) in sex distribution. Despite the fact that some participants had low cognitive test performances, none showed significant impairment in everyday functioning, and none were diagnosed with a clinical dementia syndrome. The demographic data are presented in Table 2.

Group-level analyses of cognitive change

The mean performances in the control group improved slightly during the 5-year interval in eight out of eleven neuropsychological tests, but the improvement was statistically significant only on the tests measuring naming ($p < .001$), learning ($p < .01$) and delayed recall ($p < .05$). There was also a trend level improvement ($p = .072$) on the test measuring verbal concept formation. On three tests (visual scanning, production, auditory working memory) performances declined minimally, but none of the declines were statistically significant (means at both measurement time-points in the control group, as well as the test-retest correlations, constants, betas and standard errors of estimates are provided in supplemental material).

Table 3 summarizes the regression-based Z-score results for the participants with remitted epilepsy (PWE-R). The observed changes in raw scores from baseline to follow-up were relatively modest, but when the observed 7-year follow-up score was compared to the regression-based predicted score, unfavorable results emerged. Significantly lower than expected performances were observed across six of eleven tests, particularly in the domain of language/semantic function. While this effect was systematic, it did not reach the threshold of clinical significance (all Z-scores > -0.6). Significantly lower than expected performances were also observed in free immediate recall and set-shifting. The standardized difference in these tests was larger, but still below the level of clinical significance ($Z > -1.5$).

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Table 3. Mean raw scores at TACOE-50 and TACOE-55, predicted scores and difference between observed and predicted scores, as well as mean standardized change scores for PWE-R ($n = 28$)

Test	Observed 50 Mean (SD)	Observed 55 Mean (SD)	Predicted 55 Mean (SD)	Observed vs predicted score, mean difference	Mean *Z*-score	*p*	Cohen's D
Language/semantic function							
Naming	25.9 (3.0)	26.4 (3.9)	27.6 (1.9)	−1.2	−0.56	**0.010**	0.387
Semantic processing	20.9 (5.4)	20.6 (4.5)	22.0 (3.4)	−1.4	−0.53	**0.028**	0.354
Verbal concept formation	25.6 (3.6)	25.9 (3.1)	26.9 (2.0)	−1	−0.24	**0.049**	0.377
Episodic memory							
Learning	39.6 (9.6)	37.9 (10.6)	44.9 (6.0)	−7	−1.34	**0.001**	**0.810**
Immediate recall	10.1 (4.6)	9.1 (3.9)	10.5 (2.9)	−1.4	−1.1	**0.026**	0.409
Delayed recall	8.3 (5.3)	7.9 (4.0)	8.8 (3.3)	−0.9	−0.62	0.103	0.245
Visuomotor function							
Visual-motor coordination	41.8 (11.8)	41.7 (10.7)	42.9 (10.1)	−1.2	−0.26	0.106	0.114
Visual scanning*	58.9 (29.5)	60.9 (25.8)	56.6 (21.5)	4.3	−0.60	0.174	0.181
Executive function							
Set-shifting*	96.2 (28.3)	106.7 (45.3)	93.1 (20.5)	13.6	−1.25	**0.027**	0.387
Production	13.8 (5.3)	13.5 (4.2)	13.8 (2.5)	−0.3	−0.17	0.272	0.072
Working memory							
Auditory working-memory	12.0 (3.4)	11.2 (2.8)	11.6 (2.8)	−0.4	−0.32	0.132	0.128

*= lower scores indicate better (faster) performance.

Table 4. Mean raw scores at TACOE-50 and TACOE-55, predicted scores and difference between observed and predicted scores, as well as mean standardized change scores for PWE-A ($n = 8$)

Test	Observed 50 Mean (SD)	Observed 55 Mean (SD)	Predicted 55 Mean (SD)	Observed vs predicted score, mean difference	Mean *Z*-score	*p*	Cohen's D
Language/semantic function							
Naming	24.1 (4.4)	24.9 (4.4)	26.5 (2.8)	−1.6	−0.72	**0.047**	0.438
Semantic processing	14.0 (3.2)	14.6 (5.9)	17.1 (1.9)	−2.5	−0.92	0.101	**0.567**
Verbal concept formation	23.6 (4.2)	23.8 (3.2)	25.7 (2.4)	−1.9	−0.51	**0.042**	**0.674**
Episodic memory							
Learning	33.4 (3.6)	35.4 (8.4)	41.1 (2.9)	−5.7	−1.08**	**0.046**	**0.903**
Immediate recall	10.1 (3.9)	7.6 (3.2)	10.5 (2.4)	−2.9	−2.28	**0.009**	**1.027**
Delayed recall	7.5 (4.3)	5.3 (2.8)	8.3 (2.7)	3	−2.20	**0.005**	**1.090**
Visuomotor function							
Visual−motor coordination	33.3 (11.1)	32.3 (10.5)	35.6 (9.5)	−3.3	−0.69	0.075	0.329
Visual scanning*	78.3 (25.5)	89.0 (43.1)	70.5 (18.6)	−18.5	−2.60	0.076	**0.557**
Executive function							
Set−shifting*	128.6 (58.3)	133.1 (62.9)	116.8 (42.2)	−16.3	−1.49	0.259	0.304
Production	11.1 (6.2)	11.4 (4.2)	12.5 (2.9)	−1.1	−0.56	0.152	0.226
Working memory							
Auditory working−memory	9.9 (1.4)	9.4 (2.1)	9.9 (1.1)	−0.5	−0.38	0.171	0.400

*= lower scores indicate better (faster) performance, ** = lower education associated with lower *Z*-score.

Table 4 summarizes the regression-based Z-score results for the participants with active epilepsy (PWE-A). The changes in raw scores from baseline to follow-up were, again, relatively modest, but when the observed score was compared to the predicted score, the pattern of unfavorable results differed somewhat from that of the PWE-R group. Significantly lower than expected performances were observed in five out of eleven tests, particularly in the domain of episodic memory, including learning, immediate free recall and consolidation. This effect was quite pronounced and of likely clinical significance (Z-scores -2.20 and -2.28). Significantly lower than expected performances were also observed on two measures of language/semantic function, but the decline was clearly milder compared to the quite massive lack of test-retest effect or stark decline observed in episodic memory tests. A significant negative correlation with education was observed for the test measuring learning ($r = .770$, $p < .05$). No associations between age and cognitive measures were observed.

Individual analyses of clinically significant cognitive decline over seven years

The number of tests showing clinically significant decline over the seven-year follow-up ($Z < -1.5$) was calculated for all three groups (Figure 2). A Kruskal-Wallis test showed that the distributions differed significantly, $\chi 2 = 15{,}395(2)$, $p < .001$. Pairwise comparisons showed a significant difference between the PWE-A and HC groups ($\chi^2 = 31{,}644$, $p < .001$) as well as a significant difference between the PWE-A and PWE-R groups ($\chi^2 = 21{,}214$, $p < .041$), with the PWE-A group having more tests showing clinically significant decline than the two other groups. The difference between the PWE-R and HC groups

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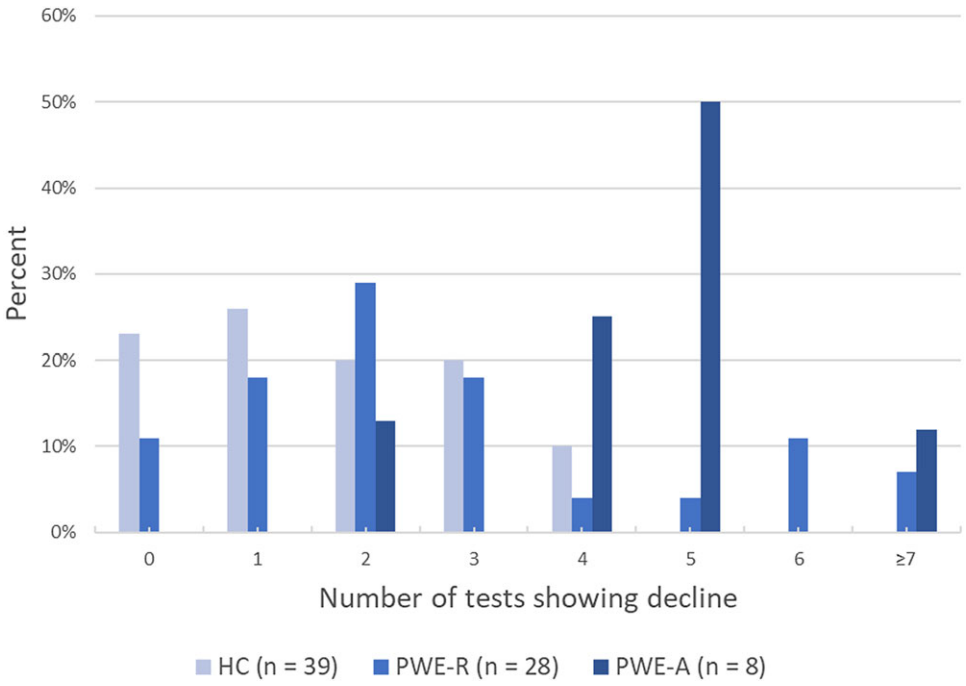

Figure 2. Number of tests showing decline over the 7-year follow-up in the three groups (PWE-A, PWE-R, HC) shown as percentages for respective groups.

was borderline statistically significant ($\chi^2 = 10{,}430$, $p = .050$). For the controls, age ($r = .336$, $p < .05$), but not educational background was associated with the number of tests showing decline. For the PWE-R and PWE-A groups, neither age nor educational background was associated with the number of tests showing decline.

General cognitive decline was defined as having four or more tests showing clinically significant decline (i.e. a below -1.5 change-based Z-score). In the PWE-A group, seven out of eight (88%) participants met the criterion for general cognitive decline. Statistical comparisons between declined and non-declined PWE-A participants in age and educational background were not meaningful due to only one participant being non-declined, but the non-impaired participant was the youngest (63 years) in the PWE-A group (range 63-71 years), while also having low education. Meanwhile, the corresponding number for the PWE-R group was 7 out of 28 (25%) participants. There were no differences in educational background between the declined vs. non-declined PWE-R participants, but a significant difference in age ($t = -1.098$ (26), $p < .037$), with the declined participants being older. In the control group, 4 out of 39 (10%) participants met the criterion for general cognitive decline (Figure 3). No significant differences in age or education were found between the declined vs. non-declined controls. For the PWE-A group, the OR for having general cognitive decline (decline in ≥ 4/11 tests) was 61.25 (95% CI 5.92 – 633.81 $p = .0006$), meanwhile, for the PWE-R group the OR was 2.19 (95% CI 0.58 – 8.23, $p = .24$.)[1].

Across all three groups, the percentage of individuals with clinically significant decline in Z-transformed scores ($Z < -1.5$ SD) was also calculated for each cognitive test (Figure 4). Significant

[1]In the PWE-R group, one individual had performances below −1.5 SD in 7 of the cognitive tests and therefore stood out from the other participants in the group. A follow-up detailed case analysis was conducted for this participant, and s/he was found to have several factors in the anamnesis likely contributing to the declined cognitive test performances. Besides childhood-onset epilepsy, this individual had a genetic risk for Alzheimer's disease (APOE e4 carrier), was morbidly obese, had cerebrovascular risk factors, and had previously suffered a traumatic brain injury

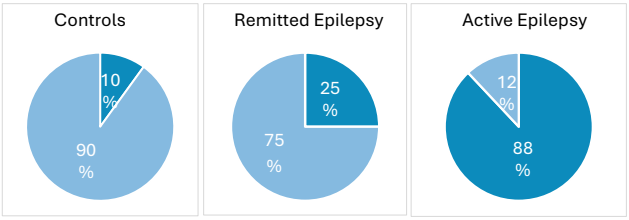

Figure 3. Percentage of participants with general cognitive decline in the three groups (darker blue area = declined).

pair-wise differences were observed in five tests between the PWE-A group and controls, as the percentage of individuals with clinical decline was markedly larger in the PWE-A group in all three memory tests, as well as in one test of language function and one test of visual scanning. For the PWE-R group, a larger than expected percentage of individuals with clinically significant decline was observed in the test measuring learning.

Discussion

Attempts to characterize the broad course of *life span* cognition in epilepsy have necessarily been cross-sectional in nature and focused on participants with active epilepsy from specialized tertiary clinics (Baxendale et al., 2010; Helmstaedter & Elger, 2009). The TACOE-study provides us a possibility to examine the cognitive trajectory over a seven year follow-up period of a population-based cohort of aging persons with childhood onset epilepsy, the sample consisting of both remitted and active epilepsy cases.

Previously, in the TACOE-50 study, we showed that participants with active epilepsy in late middle-age had a very high risk of being cognitively impaired when compared to matched controls (Karrasch et al., 2017). The cognitive outcome in participants with remitted epilepsy, on the other hand, was essentially commensurate with controls. The cognitive domains affected in the participants with active epilepsy were language/

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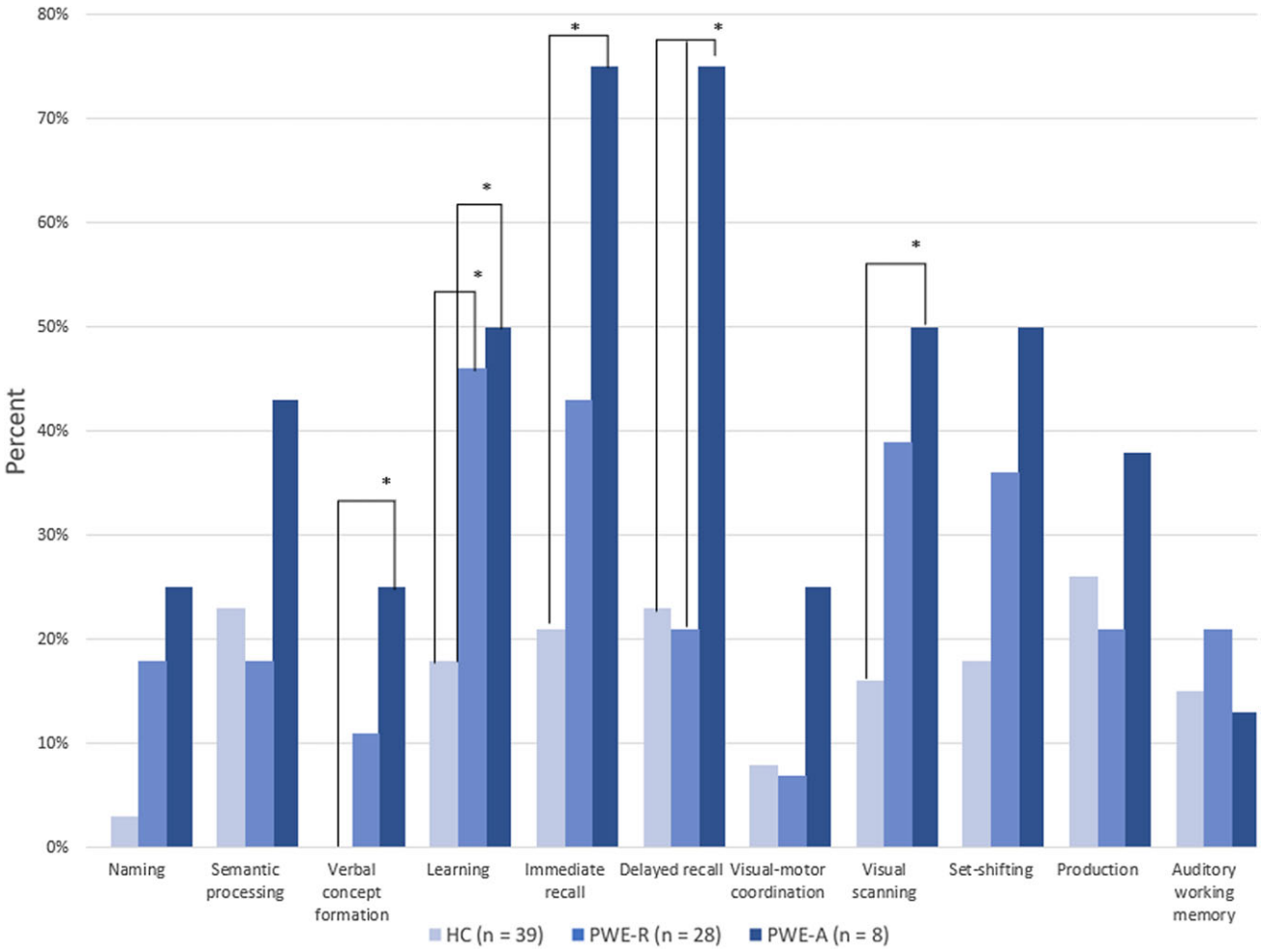

Figure 4. Amount (%) of participants with significant decline (≥ −1.5 SD) in the neuropsychological tests measuring various cognitive functions. Percentages are shown for respective groups. Statistically significant ($p < .05$) pairwise differences are marked with *.

semantic function, learning, visuomotor functioning and executive functions, whereas no effects were observed in episodic memory encoding and consolidation. Here we examined the subsequent prospective status of cognitive change in the same population-based cohort over seven years, with a mean age now of 63 years (TACOE-55).

First, we found that the prospective cognitive trajectory during the seven-year period in both the participants with remitted and active epilepsy differed from that of the normally aging controls. While there were test-retest effects (i.e. some improvement) for the control group in some tests, as hypothesized, the same did not hold true for the two patient groups. The absence of test-retest practice effects in longitudinal settings is now recognized as a relevant cognitive marker that has been found to be associated with a more problematic cognitive course, conversion to preclinical or clinical AD (Jutten et al., 2020; Machulda et al., 2013), and found by some to be associated with biomarkers (Duff et al., 2011, 2012).

The domain-wise patterns of lack of improvement/decline differed in the two patient groups as well. In the participants with remitted epilepsy, a somewhat unfavorable cognitive trajectory was found particularly for multiple tests assessing language and semantic functions, but particularly affecting episodic memory (learning and immediate verbal recall) as well as executive function (set shifting). The largest difference between observed and expected scores was found in a test measuring learning (RAVLT). In the participants with active epilepsy a similar lack of test-retest effects was observed in most language-related tests, with more prominent decline observed for tests measuring episodic memory (both learning, immediate free recall and delayed recall). Taken together, our results indicate that childhood-onset epilepsy, even when remitted, seems to be associated with slightly accelerated cognitive decline in aging individuals when reaching ~ 60 years of age. Interestingly, while episodic memory performances (encoding and consolidation) in the participants with active epilepsy were minimally affected in the cross-sectional group-comparison in the TACOE-50 baseline study, the group now shows marked decline in memory functions. The fact that this pattern has emerged over time indicates that it is less likely to be related to chronic epilepsy (e.g., ASD use, seizure activity) per se, but would likely indicate faster brain aging or progressive brain processes.

Second, when turning from examination of overall group trends to a focus on the rate of clinically significant cognitive decline over time across individuals in the two patient groups, additional insights emerge. In the baseline-study (TACOE-50) we found that the risk of general cognitive impairment was very high for participants with active epilepsy (OR 11.7), while the risk was slightly elevated, but not significant in the participants with remitted epilepsy (OR 2.6) (Karrasch et al., 2017). In line with our hypotheses, a similar trend was now observed regarding the cognitive trajectory going forward. The risk of a clinically

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significant general cognitive *decline* was clearly more pronounced in the participants with active epilepsy (OR 61.2) than in the group with remitted epilepsy (OR 2.2). Thus, participants with active childhood-onset epilepsy showed clinically significant cognitive impairment relative to controls already in late middle-age (TACOE-50) and now also signs of progressively worsening general cognitive functioning (particularly affecting episodic memory) when entering old age. Unfortunately, the number of participants with active epilepsy retained in the study up to the TACOE-55 follow-up was small, thus the results for the subgroup need to be interpreted with caution. It is also noteworthy that the group-level decline in learning in the participants with remitted epilepsy was clinically significant in almost 50% of the individuals in the group. This finding is particularly troublesome, as learning over several trials have been found to significantly predict conversion from MCI to AD (Dawidowicz et al., 2021; Tabatabaei-Jafari et al., 2020). Further follow-up will elucidate the trajectory going forward and show whether the incidence of neurogenerative disorders will be elevated in the participants with remitted epilepsy.

The progressive decline both in general cognitive functioning but particularly in episodic memory and learning in the participants with epilepsy raises some concerns. The participants with active and remitted epilepsy did not differ from the controls in terms of the percentage of APOE ε4 carriers, which is a known risk factor for Alzheimer pathology. The participants with epilepsy did, however, have significantly higher CAIDE vascular risk scores at baseline compared to the controls. At baseline, there was also a trend-level difference in MRI vascular brain changes between the PWE and control groups, and the difference was significant between the PWE-A group and controls. The prevalence of white-matter vascular brain changes increased quite markedly in all groups over the follow-up period, and at follow-up were as frequently found in controls. Taken together, the findings could indicate that age-related vascular brain changes develop earlier in people affected by epilepsy and vascular factors could thus contribute to the unfavorable cognitive trajectory. Hermann et al (2017) showed that vascular, inflammatory and metabolic health markers were associated with cognitive functioning cross-sectionally in a middle-aged sample of patients with chronic epilepsy. Multifactorial pathways in the brain aging process are likely and further studies are needed to elucidate possible associations between vascular brain changes, amyloid buildup, cortical atrophy and cognitive decline in epilepsy.

Strengths, limitations and future directions

While this unique population-based cohort offers a window into the aging processes of persons with childhood onset epilepsy (including remitted epilepsy, a population rarely included in long-term studies), it does have limitations. The sample size in this ultra-long follow-up study is understandably limited and offers low statistical power for group-analyses. Especially the number of participants with active epilepsy remaining at the TACOE-55 follow-up was small. Considering the very long time span and the heavy two-day investigation schedule, the participation rate still remained high, with 73% of the participants from the TACOE-50 study returned for the TACOE-55 follow-up. Establishing thresholds for abnormal or impaired performances is not unproblematic, it always entails a balancing act between false negatives and false positives. We deemed our choices of a the test-wise cut off of Z −1.5 and an battery-wise cut off of ≥ 4/11 (36%) tests to provide an optimal balance between the two error-risks. The choice of tests included in the battery can also be discussed. While we feel that the test-battery provides a good coverage of central cognitive domains, we did add two tests in the TACOE-55 battery that were not included in the TACOE-50 battery, namely WAIS-R Block design and Stroop. Prospective change in these tests will be addressed in the future, when examining change from TACOE-55 to TACOE-60. In the broader aging, preclinical and clinical dementia literature there is a distinct focus on identification of potentially modifiable health and lifestyle factors with an eye to determining ways to maintain cognitive and brain health and potentially delay the onset of later-life cognitive disorders (Livingston et al., 2024). The lifelong registry of information regarding epilepsy, general health and lifestyle information in this cohort will allow similar work for epilepsy. In the future, the role of biomarkers (both cognitive and laboratory/imaging) in the prediction of abnormal cognitive aging will be addressed.

Summary and conclusions

This ultra-long-term follow showed unfavorable cognitive trajectories from late middle-age to old age in a population-based sample of participants with childhood-onset epilepsy. Progressive decline in several cognitive domains was observed in participants with active, chronic epilepsy. In participants with remitted epilepsy, larger than age-appropriate decline was observed in memory, especially in learning.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1355617725101021.

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Competing interests. Dr Karrasch serves as Associate Editor for Nordic Psychology. Dr Joutsa has received conference travel support from Insightec, Abbvie and Abbott; lecturer honoraria from Lundbeck, Novartis, Addiktum and Nordic Infucare; consultancy fees from Teva Finland, Summaryx and Adamant Health; acts as an advisory board member for Teva Finland; and owns stock of Neurologic Finland and Suomen Neurolaboratorio. Dr Rinne serves as a neurology consultant for CRST Oy (Clinical Research Services Turku), Global Expert Panel for NOVO Nordisk and Data Monitoring Committee for Lundbeck. Other authors declare no conflicts of interest.

References

Baker, G. A., Taylor, J., & Aldenkamp, A. P. (2011). Newly diagnosed epilepsy: Cognitive outcome after 12 months. *Epilepsia*, *52*(6), 1084–1091.

Baxendale, S., Heaney, D., Thompson, P. J., & Duncan, J. S. (2010). Cognitive consequences of childhood-onset temporal lobe epilepsy across the adult lifespan. *Neurology*, *75*(8), 705–711.

Benton, A. L., & Hamsher, K. (1976). *Multilingual aphasia examination*. University of Iowa.

Choi, H., Elkind, M. S. V., Longstreth, W. T., Boehme, A. K., Hafen, R., Hoyt, E. J., & Thacker, E. L. (2022a). Epilepsy, vascular risk factors, and cognitive decline in older adults. *Neurology*, *99*(21), e2346–e2358.

Choi, H., Elkind, M. S. V., Longstreth, W. T., Boehme, A. K., Hafen, R., Hoyt, E. J., & Thacker, E. L. (2022b). Epilepsy, vascular risk factors, and cognitive decline in older adults: The cardiovascular health study. *Neurology*, *99*(21), E2346–E2358.

Choi, H., Thacker, E. L., Longstreth, W. T., Elkind, M. S. V., & Boehme, A. K. (2021). Cognitive decline in older adults with epilepsy: The cardiovascular health study. *Epilepsia*, *62*(1), 85–97.

Commission on Revised Classification of Seizures. (1981). Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the commission on classification and terminology of the International League Against Epilepsy. *Epilepsia*, *22*, 489–501.

Dawidowicz, L. L., Ash, E., Korczyn, A. D., Andelman, F., Levy, S., & Elkana, O. (2021). Can the RAVLT predict deterioration from MCI to Dementia? Data from long term follow up. *Experimental Aging Research*, *47*(4), 347–356.

Dodrill, C. B. (2004). Neuropsychological effects of seizures. *Epilepsy & Behavior : E& B*, *5 Suppl 1*, S21–4.

Duff, K. (2012). Current topics in science and practice evidence-based indicators of neuropsychological change in the individual patient: Relevant concepts and methods. *Archives of Clinical Neuropsychology*, *27*(3), 248–261.

Duff, K., Callister, C., Dennett, K., & Tometich, D. (2012). Practice effects: A unique cognitive variable. *Clinical Neuropsychologist*, *26*(7), 1117–1127.

Duff, K., Lyketsos, C. G., Beglinger, L. J., Chelune, G., Moser, D. J., Arndt, S., Schultz, S. K., Paulsen, J. S., Petersen, R. C., & McCaffrey, R. J. (2011). Practice effects predict cognitive outcome in amnestic mild cognitive impairment. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry*, *19*(11), 932–939.

Durant, J., Duff, K., & Miller, J. B. (2019). Regression-based formulas for predicting change in memory test scores in healthy older adults: Comparing use of raw versus standardized scores. *Journal of Clinical and Experimental Neuropsychology*, *41*(5), 460–468.

Fox, J. T. (1924). The response of epileptic children to mental and educational tests. *British Journal of Medical Psychology*, *4*(3), 235–248.

Helmstaedter, C., & Elger, C. E. (2009). Chronic temporal lobe epilepsy: A neurodevelopmental or progressively dementing disease? *Brain : A Journal of Neurology*, *132*(Pt 10), 2822–2830.

Hermann, B. P., Sager, M. A., Koscik, R. L., Young, K., & Nakamura, K. (2017). Vascular, inflammatory, and metabolic factors associated with cognition in aging persons with chronic epilepsy. *Epilepsia*, *58*(11), e152–e156.

Hermann, B. P., Seidenberg, M., Dow, C., Jones, J., Rutecki, P., Bhattacharya, A., & Bell, B. (2006). Cognitive prognosis in chronic temporal lobe epilepsy. *Annals of Neurology*, *60*(1), 80–87.

Ingraham, L. J., & Aiken, C. B. (1996). An empirical approach to determining criteria foabnormality in test batteries with multiple measures. *Neuropsychology*, *10*(1), 120–124.

Johnson, E. L., Krauss, G. L., Walker, K. A., Brandt, J., Kucharska-Newton, A., Mosley, T. H., Yasar, S., & Gottesman, R. F. (2020). Late-onset epilepsy and 25-year cognitive change: The atherosclerosis risk in communities (ARIC) study. *Epilepsia*, *61*(8), 1764–1773.

Jutten, R. J., Grandoit, E., Foldi, N. S., Sikkes, S. A. M., Jones, R. N., Choi, S. E., Lamar, M. L., Louden, D. K. N., Rich, J., Tommet, D., Crane, P. K., & Rabin, L. A. (2020). Lower practice effects as a marker of cognitive performance and dementia risk: A literature review. *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring*, *12*(1), e12055.

Karrasch, M., Tiitta, P., Hermann, B., Joutsa, J., Shinnar, S., Rinne, J., Anttinen, A., & Sillanpää, M. (2017). Cognitive outcome in childhood-onset epilepsy: A five decade prospective cohort study. *Journal of the International Neuropsychological Society*, *23*(4), 332–340.

Keret, O., Hoang, T. D., Xia, F., Rosen, H. J., & Yaffe, K. (2020). Association of late-onset unprovoked seizures of unknown etiology with the risk of developing Dementia in older veterans. *JAMA Neurology*, *77*(6), 710–715.

Kesselmayer, R. F., Morel, G. M., Bordnave, J. M., & Jones, J. E. (2019). Epilepsy and cognition. In *The Comorbidities of Epilepsy* (pp. 245–271). Academic Press.

Kivipelto, M., Ngandu, T., Laatikainen, T., Winblad, B., Soininen, H., & Tuomilehto, J. (2006). Risk score for the prediction of dementia risk in 20 years among middle aged people: A longitudinal, population-based study. *Lancet Neurology*, *5*(9), 735–741.

Laine, M., Koivuselkä-Sallinen, P., Hänninen, R., & Niemi, J. (1997). *Bostonin nimentätestin suomenkielinen versio [Finnish version of the Boston Naming Test]*. Psykologien kustannus.

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012), Neuropsychological Assessment. Oxford University Press.

Livingston, G., Huntley, J., Liu, K. Y., Costafreda, S. G., Selbæk, G., Alladi, S., Ames, D., Banerjee, S., Burns, A., Brayne, C., Fox, N. C., Ferri, C. P., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., Nakasujja, N., Rockwood, K. . . . Mukadam, N. (2024). Dementia prevention, intervention, and care: 2024 report of the lancet standing commission. *The Lancet*, *404*(10452), 572–628.

Machulda, M. M., Pankratz, V. S., Christianson, T. J., Ivnik, R. J., Mielke, M. M., Roberts, R. O., Knopman, D. S., Boeve, B. F., & Petersen, R. C. (2013). Practice effects and longitudinal cognitive change in normal aging vs. Incident mild cognitive impairment and Dementia in the mayo clinic study of aging. *The Clinical Neuropsychologist*, *27*(8), 1247–1264.

Piazzini, A., Turner, K., Chifari, R., Morabito, A., Canger, R., & Canevini, M. P. (2006). Attention and psychomotor speed decline in patients with temporal lobe epilepsy: A longitudinal study. *Epilepsy Research*, *72*(2-3), 89–96.

Poutiainen, E., Kalska, H., & Laasonen, M. (2010). *Trail making test [Finnish manual for the Trail Making Test]*. Hogrefe Psykologien kustannus.

Reyes, A., Kaestner, E., Edmonds, E. C., Christina Macari, A., Wang, Z. I., Drane, D. L., Punia, V., Busch, R. M., Hermann, B. P., & McDonald, C. R. (2021). Diagnosing cognitive disorders in older adults with epilepsy. *Epilepsia*, *62*(2), 460–471.

Sawrie, S. M., Chelune, G. J., Naugle, R. I., & Lüders, H. O. (1996). Empirical methods for assessing meaningful neuropsychological change following epilepsy surgery. *Journal of the International Neuropsychological Society*, *2*(6), 556–564.

Sen, A., Capelli, V., & Husain, M. (2018). Cognition and dementia in older patients with epilepsy. *Brain*, *141*(6), 1592–1608.

Sen, A., Jette, N., Husain, M., & Sander, J. W. (2020). Epilepsy in older people. In *The Lancet*. (vol. *395*, Issue 10225, p. 735–748). Lancet Publishing Group, https://doi.org/10.1016/S0140-6736(19)33064-8,

Sillanpää, M. (1973). Medico-social prognosis of children with epilepsy. Epidemiological study and analysis of 245 patients. *Acta Paediatrica Scandinavica Supplement*, *237*, 3–104.

Sillanpää, M., Anttinen, A., Rinne, J. O., Joutsa, J., Sonninen, P., Erkinjuntti, M., Hermann, B., Karrasch, M., Saarinen, M., Tiitta, P., & Shinnar, S. (2015). Childhood-onset epilepsy five decades later. A prospective population-based cohort study. *Epilepsia*, *56*(11), 1774–1783.

Sillanpää, M., Jalava, M., Kaleva, O., & Shinnar, S. (1998). Long-term prognosis of seizures with onset in childhood. *The New England Journal of Medicine*, *338*(24), 1715–1722.

Tabatabaei-Jafari, H., Shaw, M. E., Walsh, E., & Cherbuin, N. (2020). Cognitive/functional measures predict alzheimer's disease, dependent on hippocampal volume. *Journals of Gerontology - Series B Psychological Sciences and Social Sciences*, *75*(7), 1393–1402.

Tai, X. Y., Torzillo, E., Lyall, D. M., Manohar, S., Husain, M., & Sen, A. (2023). Association of Dementia risk with focal epilepsy and modifiable cardiovascular risk factors. *JAMA Neurology*, *80*(5), 445.

Tang, T., Zhang, R., & Pan, X. (2022). Meta-analysis of the risk of dementia in elderly patients with late-onset epilepsy. *Clinical Neurology and Neurosurgery*, *223*, 107499.

Thompson, P. J., & Duncan, J. S. (2005). Cognitive decline in severe intractable epilepsy. *Epilepsia*, *46*(11), 1780–1787.

Wechsler, D. (1992). *WAIS-R käsikirja [Manual of the Finnish version of WAIS-R]*. Psykologien kustannus.

Wechsler, D. (1996). *WMS-R käsikirja [Manual of the Finnish version of WMS-R]*. Psykologien kustannus.

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