

INCIDENTAL MEMORY OUTCOME IN CHILDHOOD-ONSET EPILEPSY

Long-Term Effects of Childhood-Onset Epilepsy on Incidental Memory in Aging Individuals

Viktor Gestranius, 40602
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Supervisor: Mira Karrasch
Faculty of Arts, Psychology and Theology
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Subject: Psychology	
Author: Viktor Gestranius	
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Abstract: <p>While the short-term effects of childhood-onset epilepsy on cognitive functions have been extensively studied, the cognitive trajectory of the affected individuals in late middle age is still relatively unknown. Utilizing data from the TACOE-project, which has mapped the long-term outcome of childhood-onset epilepsy, this study investigated whether childhood-onset epilepsy is connected to abnormal incidental memory deterioration as individuals reach retirement age. The sample consisted of 36 adults with childhood-onset epilepsy (COE) and 39 healthy controls (HC). The participants with COE were categorized as having active epilepsy (PWE-A, $n = 8$) or remitted epilepsy (PWE-R, $n = 28$). A baseline assessment, which included tests of incidental and intentional memory, was conducted in 2012, and a follow-up assessment was conducted in 2017. Incidental memory was measured with memo-BNT and intentional memory with the Logical Memory (LM) subtest of the Wechsler Memory Scale-Revised. A mixed-model ANOVA showed a significant interaction between time and group on incidental memory performance. The interaction arose due to the performance of PWE-A worsening over time, while the performance of PWE-R and HC improved over time. There was no significant interaction between time and group on LM. The results indicate that chronic childhood-onset epilepsy can have an adverse effect on incidental memory as individuals reach retirement age. Furthermore, since memo-BNT is sensitive to early signs of Alzheimer's disease (AD), the results may indicate that PWE-A are exhibiting signs of underlying AD pathology. However, the small sample size may affect the results of the study, which underscores the relevance of future research in this area to corroborate these findings.</p>	
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Författare: Viktor Gestranius	
Arbetets titel: Långtidseffekter av barndomsepilepsi på incidentellt minne hos åldrande individer	
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Abstrakt: De effekter som barndomsepilepsi på kort sikt har på kognitiva funktioner har blivit utförligt undersökta, medan sjukdomens effekter på den kognitiva utvecklingen senare i livet fortfarande är ett relativt utforskat område. Genom att använda data från TACOE-projektet, som har kartlagt utfallet av barndomsepilepsi på lång sikt, har denna studie undersökt huruvida barndomsepilepsi har ett samband med en avvikande försämring i incidentellt minne då personer når pensionsåldern. Samplet bestod av 36 vuxna med barndomsepilepsi (COE) och 39 friska kontroller (HC). Av deltagarna med COE hade 8 aktiv epilepsi (PWE-A) och 28 remitterad epilepsi (PWE-R). År 2012 genomfördes ett utförligt testningsprogram som inkluderade test av incidentellt och intentionellt minne. En uppföljning gjordes år 2017. Incidentellt minne mättes med memo-BNT och intentionellt minne med Logiskt Minne (LM), som är ett deltest av Wechsler Memory Scale-Revised. En blandad variansanalys visade en signifikant interaktion mellan tid och grupp på den incidentella minnesprestationen. Interaktionen uppstod som en följd av att PWE-A:s prestation försämrades över tid, medan PWE-R:s och HC:s prestationer förbättrades över tid. Det fanns ingen signifikant interaktion mellan tid och grupp på LM. Resultaten indikerar att kronisk barndomsepilepsi medför en avvikande försämring i incidentellt minne då personerna når pensionsåldern. Eftersom memo-BNT är sensitivt för tidiga tecken på Alzheimers sjukdom (AD) kan resultaten indikera att PWE-A visar tecken på en underliggande AD-patologi. Dock bör det tas i beaktande att resultaten i denna studie kan påverkas av att samplet var relativt litet. Således vore fortsatt forskning inom området motiverad för att bekräfta dessa fynd.	
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Introduction

Epilepsy is a neurological condition characterized by aberrant electrical activity in the brain causing seizures associated with change in behavior (Schoenberg & Scott, 2011; World Health Organization [WHO], 2019). Epilepsy can also be described as a persisting tendency of the brain to generate seizures (Fisher et al., 2005). The diagnostic process of epilepsy includes identification of the type of seizure as well as its etiology, and there are many distinct epilepsy syndromes (Schoenberg & Scott, 2011). An epilepsy syndrome with a debut in early childhood is referred to as childhood-onset epilepsy. Treatment of the disorder may include antiepileptic drugs, diet therapies, behavioral therapies, and surgery (Schoenberg & Scott, 2011; Shorvon et al., 2015). Epilepsy does not necessarily last a lifetime but can be considered resolved if a person is seizure-free for 10 years, with at least the last 5 years off antiepileptic medication (Fisher et al., 2014).

Epilepsy is one of the most common neurological disorders, with a lifetime prevalence rate between 0.7% (Fiest et al., 2017) and 3% (Schoenberg & Scott, 2011). The disorder is a significant global health issue, accounting for 0.5% of the global disease burden (WHO, 2019). With over 5 million new cases annually, epilepsy is a condition that is on the rise. The WHO speculates that this is due to rising life expectancy and increased survivability of epilepsy-provoking insults, including birth injury, head trauma, brain infection and stroke.

Epilepsy is connected to an exacerbated risk of premature mortality compared with the general population (Neligan et al., 2011; Sillanpää & Shinnar, 2010; Sillanpää et al., 1998; WHO, 2019). The disorder is also associated with a vast array of comorbid physical and psychiatric conditions (Berg et al., 2011; Keezer et al., 2016; WHO, 2019). According to the WHO, the most common psychiatric comorbidities are depression, anxiety, and intellectual disability. In children with epilepsy, elevated levels of psychiatric comorbidities such as depression, anxiety and attention deficit hyperactivity disorder have been observed (Jones et al., 2007).

The disorder is also accompanied by challenges in psychosocial functioning (Fisher et al., 2000; Hermann & Jacoby, 2009). Fisher et al. (2000) found that persons with epilepsy experience limitations in lifestyle, school, and employment, and that the uncertainty and fear of having a seizure is considered the most unpleasant aspect of having epilepsy. Cognitive impairment is also regarded as a major problem by persons with epilepsy (Fisher et al., 2000). In addition, Fisher et al. (2000) found that younger patients are more concerned about academic performance and the social stigma of having epilepsy, while older patients worry

about cognitive problems, and unfavorable effects on work, driving and relationships. Furthermore, the social stigma that is associated with epilepsy contributes to poor physical and mental health in individuals affected by the disorder (WHO, 2019). Across the globe, affected persons may face discrimination and human rights violations, decreasing their quality of life, possibility of social inclusion and proneness of seeking treatment. The WHO (2019) suggests that epilepsy should be made a public health priority.

The long-term prognosis of childhood-onset epilepsy is relatively favorable, with most children reaching complete remission (Berg & Rychlik, 2015; Berg et al. 2014; Geerts et al., 2010). Epilepsy patients with a good prognosis may even show social outcomes comparable to healthy controls (Puka et al., 2019). However, even in those who are seizure free for several years childhood-onset epilepsy may still affect their psychosocial functioning (Sillanpää et al. 1998, 2004). For instance, individuals with childhood-onset epilepsy are less likely to be employed (Sillanpää & Schmidt, 2010). Long-term quality of life in childhood-onset epilepsy is strongly connected to psychiatric comorbidities (Baca et al., 2011) and affected individuals are at elevated risks of encountering challenges such as cognitive difficulties, behavioral disorders, and depression (Berg, 2011). Not only seizures, but also these cognitive detriments and comorbid psychiatric disorders should be considered important when it comes to treating epilepsy patients (Rudzinski & Meador, 2013).

Childhood-onset epilepsy and neurocognitive development

Epilepsy can have an adverse effect on cognitive functioning (Arslan & Demir, 2022; Berg et al., 2008; Breuer et al., 2016; Hermann et al., 2006; Kim & Ko, 2016; Schoenberg & Scott, 2011), which may predispose for long-term risk of learning problems (Bailet & Turk, 2000) and academic difficulties (Kim & Ko, 2016). The continuation versus discontinuation of seizures is an important predictor of long-term cognitive outcome in childhood-onset epilepsy (Karrasch et al., 2017). Onset at early age may also predispose for poorer cognitive outcomes (Korman et al., 2013). In children and adolescents with epilepsy, normal cognitive development is affected by a multitude of influences, including anti-epileptic drugs and recurring seizures (Berg et al., 2012; Besag & Vasey, 2021; Kellogg & Meador, 2017; Ortinski & Meador, 2004). Ortinski & Meador (2004) further assessed that children and the elderly are especially vulnerable to cognitive side effects of antiepileptic medication. Findings from another study indicate that recurring seizures may induce neural alteration and predispose for cognitive and behavioral problems later in life (Pitkänen & Sutula, 2002). In addition, abnormalities in cognitive development and functioning have been observed at or

near the time of diagnosis in children with new-onset epilepsy (Hermann et al., 2006; Rathouz et al., 2014). Rathouz et. al. (2014) further assessed that the cognitive development of children with epilepsy lags behind that of children without epilepsy.

Indications of abnormal patterns of brain development (Helmstaedter & Elger, 2009; Hermann et.al, 2010) have been found in persons with epilepsy. Structural abnormalities in the brain exist early in the course of childhood-onset epilepsy (Lin et al., 2014). Many studies suggest that the strain the disorder puts on the developing brain accelerates brain aging and predisposes for cognitive deterioration later in life (Breuer et al., 2016; Dabbs et al., 2012; Helmstaedter & Elger, 2009; Joutsa et al., 2017). Some of these studies suggest that the interference on early brain development that childhood-onset epilepsy causes has a detrimental effect on cognitive reserve capacity in older age (Breuer et al., 2016; Helmstaedter & Elger, 2009). The reduced reserve capacity may accelerate cognitive decline later in life when processes of normal or pathological aging take place.

Incidental memory

As has been presented so far, there is ample evidence that childhood-onset epilepsy is associated with abnormal cognitive and neural development, which may in turn predispose for accelerated cognitive deterioration as individuals age. In this study, the effects of childhood-onset epilepsy on the neuropsychological function incidental memory will be examined.

Episodic memory traces can be encoded and consolidated either intentionally, when learning and remembering information is done with the intent to retain that information, or incidentally, when the information is automatically and unintentionally acquired. In a typical test of intentional episodic memory, the test subject is asked to remember the presented information and may dedicate attention and effort to the task. Most episodic memory tests used in neuropsychological assessments are of the intentional type. In an incidental memory test, the test subject is not asked to remember the information and is thus unaware that he must later recall or recognize the information that was presented. In an everyday life setting, episodic memory traces are mostly encoded unintentionally, and thus measurements of incidentally encoded memory traces may be more ecologically valid in comparison to measurements of intentional memory (Vingerhoets et al., 2005). Measurements of incidental memory have also proven to be accurate in separating normal aging or mild cognitive impairment from Alzheimer's disease (AD; Grönholm-Nyman et al., 2010; Karrasch et al., 2010; Kontaxopoulou et al., 2018).

The current study

In the current study, data was taken from a population-based cohort of individuals with childhood-onset epilepsy and matched controls followed up in 2012 and 2017, over fifty years after the cohort was formed. The recruitment and data collection process will be more extensively described in the methods section.

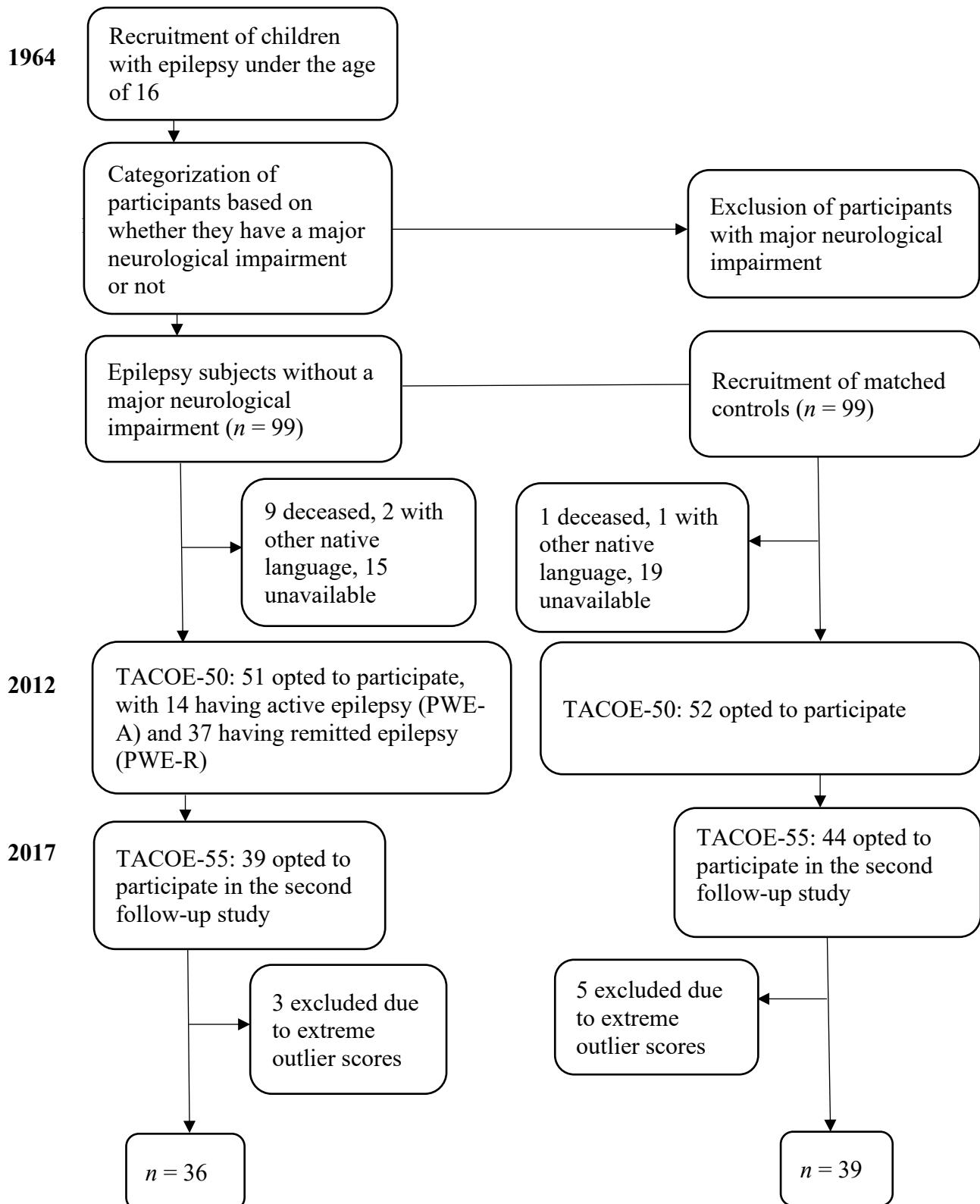
Since there are indications that childhood-onset epilepsy may predispose for cognitive deterioration as individuals reach older age, the aim of this study is to further examine this notion by utilizing measurements of incidental memory. As has been previously presented, this memory function may provide early indications of approaching cognitive deterioration. In the current study, the performance on tests of incidental and intentional memory will be analyzed. The analysis will encompass differences in test performance over a five-year interval, differences between groups, and possible interactions between group and time. While there are many tests available for measuring intentional memory, the number of incidental memory tests is low. In the current study, the results of an incidental memory modification, memo-BNT (Karrasch et al., 2010), of the Boston Naming Test (BNT; Kaplan et al., 1983) will be examined. The groups and tests will be more thoroughly described in the methods section.

While the short-term effects of childhood-onset epilepsy have been extensively studied, there have not been many opportunities to examine the long-term effects over an entire lifetime. This cohort offers a unique opportunity to study the effects of the disorder on cognitive functioning over 50 years later. To the author's knowledge, there have been no previous studies on the long-term effects of childhood-onset epilepsy on incidental memory.

Methods

The current study draws its data from a population-based cohort of children under 16 years of age, living in the catchment area of the University of Turku Hospital, Turku, Finland, in 1964. At the time, the participants met the criteria for epilepsy as in two or more unprovoked seizures (Commission on Revised Classification of Seizures, 1981). Identification of participants was made based on hospital records and National Health Service records. The recruitment process and data collection has been extensively described elsewhere (Sillanpää et al. 2015; Sillanpää et al., 1998; Sillanpää, 1973), and will also be illustrated in Figure 1.

In 1992, the group of participants was subdivided into those who had major neurological impairment at the onset of their epilepsy, and those who had no major neurological impairment at onset. The group with no neurological impairment at onset was defined as having uncomplicated epilepsy ($n = 99$). A group of healthy controls ($n = 99$) was subsequently recruited from the population registry. These matched the demographic characteristics of the group with uncomplicated epilepsy (Sillanpää et al., 1998). In 2012, the group that was classified as having uncomplicated epilepsy in 1992 and their matched controls were invited to participate in the TACOE-50-study (Turku Aging in Childhood-Onset Epilepsy). Of the original 99 participants with uncomplicated epilepsy, 26 were excluded based on being deceased ($n = 9$), having a mother tongue other than Finnish ($n = 2$), or for unspecified reasons ($n = 15$; Sillanpää et al., 2015). Of the remaining 73 who met the criteria, 51 opted to participate. Of the original 99 controls, 21 were excluded based on being deceased ($n = 1$), having a native language other than Finnish ($n = 1$) or for unspecified reasons ($n = 19$). Of the remaining 78 controls, 52 opted to participate and subsequently served as the control group. No differences in neither seizure variables nor demographic characteristics were found between participants and non-participants with epilepsy. In the TACOE-50-study, the group with uncomplicated epilepsy was further divided into two groups depending on whether they had had continuing seizure activity or had taken anti-epileptic drugs within the last five years. If they met either of these criteria they were classified as participants with active (chronic) epilepsy (PWE-A, $n = 14$), whereas those who did not were classified as participants with remitted epilepsy (PWE-R, $n = 37$). The cohort underwent a two-day investigation program, which included comprehensive neuropsychological testing. Finnish versions of well-established and validated neuropsychological tests were utilized. The assessment covered numerous cognitive domains, including incidental and intentional memory. In 2017, the cohort was invited to participate in a second follow-up study, TACOE-55. Of the 51 participants with epilepsy, 39 opted to participate. Of the 52 controls, 44 opted to participate. In addition, three participants with epilepsy and five controls were excluded from analyses due to extreme outlier scores, leaving a total of 36 participants with epilepsy and 39 controls. The 2012 investigation program, including neuropsychological assessment, was repeated.

Figure 1.*Recruitment process*

Instruments

Memo-BNT

The memo-BNT (Karrasch et al., 2010) is an incidental memory modification of the Boston Naming Test (BNT; Kaplan et al., 1983). In the neuropsychological assessments conducted at baseline and follow-up, the second edition of the BNT in Finnish (Laine et al., 1997) was used. Memo-BNT can be accurate in differentiating between mild Alzheimer's disease (AD) and normal aging. The test includes three tasks, but only the free recall task was used in the TACOE study, since this task is the most clinically valid. Utilizing a sample of AD patients as well as old controls without AD, Karrasch et al. (2010) found that the memo-BNT free recall task correctly classified 94 % of participants. Memo-BNT is initiated by having participants perform the naming task of the BNT. In this task, the participants are shown pictures of objects and asked to name these. The participant is unaware that he will then be asked to recall from memory as many as of the presented objects as possible within a time window of 120 seconds. This is the free recall task of the memo-BNT. If the participant knows the name of the object or can describe it, the item is scored as correct.

WMS-R Logical Memory

The Logical Memory subtest of the Wechsler Memory Scale-Revised (Wechsler, 1996) assesses intentional episodic memory. It consists of one immediate recall task (LM-I), and one delayed recall task (LM-II). Initially, the examiner presents a short story orally and the participant is subsequently asked to recall the story as precisely as possible (LM-I). Roughly 30 minutes later the participant is asked to recall the story once more (LM-II). The tasks are scored based on how many details of the story the participant recalls. The data used in this study is based on the Finnish version of the WMS-R subtest Logical Memory part A.

Ethical statement

All actions contributing to this study are in line with the ethical standards established by national and institutional committees on human experimentation, as well as the Declaration of Helsinki. The study design was approved by the Institutional Review Board of the Hospital District of Southwest Finland (Diary No. 120/2008/26.1.2009 §454). Written informed consent to participate in the study and to allow access to medical records was also acquired from all participants.

Data analysis

The statistical analyses were conducted with IBM SPSS Statistics 24.0 for Windows. In the present study, possible changes in scores between the testing conducted in 2012 and the testing conducted in 2017, and how these changes compared between the groups, were of interest. The groups in question were, in addition to the control group, participants with active epilepsy (PWE-A) and participants with remitted epilepsy (PWE-R). A two-way mixed model ANOVA was performed for each of the tests (memo-BNT, LM-I, and LM-II) in order to examine possible changes over the five-year interval, with group and time as the independent variables and test score as the dependent variable. The descriptive statistics of the background variables were analyzed both for the within-group measures (baseline versus follow-up) and the between-group measures (control versus remitted versus active).

Table 1

Demographic characteristics of healthy controls (HC), participants with remitted epilepsy (PWE-R), participants with active epilepsy (PWE-A), and all participants with epilepsy (PWE).

	HC (n = 39)	PWE-R (n = 28)	PWE-A (n = 8)	PWE (n = 36)	Stat. sign.
	M (SD, min-max)	M (SD, min-max)	M (SD, min-max)	M (SD, min-max)	
Age	62.69 (4.2, 56-70)	62.71 (4.4, 55-70)	66.75 (3.0, 63-71)	63.62 (4.7, 55-71)	PWE-A > HC <i>p</i> = .014 PWE-A > PWE-R <i>p</i> = .018
Age at epilepsy onset		4.4 (4.1, 0-13)	9.0 (4.1, 3-14)	5.4 (4.4, 0-14)	PWE-A > PWE-R <i>p</i> = .009
Cumulative seizure duration (years)		3.7 (2.1, 1-11)	25.8 (11.7, 5-40)	8.6 (10.8, 1-40)	PWE-A > PWE-R <i>p</i> = .001
Sex	19m/22f	14m/14f	2m/6f	16m/20f	n.s.
Education in 2012*					PWE-A < HC <i>p</i> = .004 PWE-R < HC <i>p</i> = .033
Low	9 (22%)	10 (36%)	5 (62%)	15 (42%)	
Medium	20 (49%)	16 (57%)	2 (25%)	18 (50%)	
High	12 (29%)	2 (7%)	1 (13%)	3 (8%)	

*Low education = less than or only primary school with or without at least 1 years 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

Results

Descriptive statistics

The mean scores and standard deviations for memo-BNT, LM-I and LM-II for the three groups are presented in Table 1.

Table 2.

Means and Standard Deviations for Memo-BNT and Logical Memory Scores

Measure	HC				PWE-R				PWE-A			
	(n = 39)				(n = 28)				(n = 8)			
	Baseline	Follow up	M	SD	M	SD						
mBNT	9.31	3.70	10.57	2.64	8.91	3.03	9.39	3.22	8.86	3.67	6.14	3.63
LM-I	10.87	4.03	10.97	3.57	10.26	4.64	9.22	3.92	10.13	3.91	7.63	3.16
LM-II	9.03	3.56	9.92	3.98	8.44	5.31	8.07	3.96	7.50	4.31	5.25	2.82

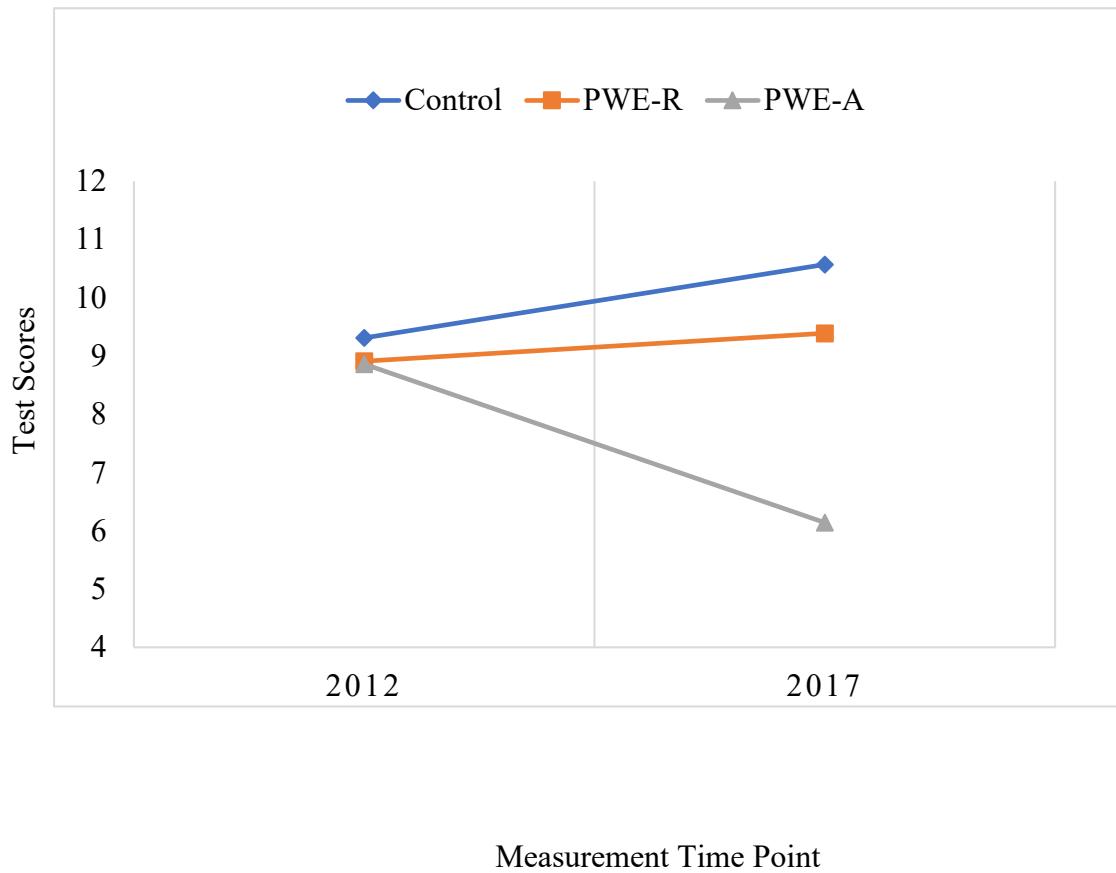
Main analyses

Memo-BNT

The two-way mixed ANOVA for memo-BNT showed no significant main effect of measurement time point ($F[1,62] = .499; p = .483, \eta_p^2 = .008$). The interaction between change in performance over time and group was however significant ($F[2,62] = 5.161, p = .008, \eta_p^2 = .143$). The interaction probably arose due to the performance of the PWE-A group declining over time (Figure 2). The analysis did not show a significant main effect of group ($F[2,62] = 2.262, p = .113, \eta_p^2 = .068$).

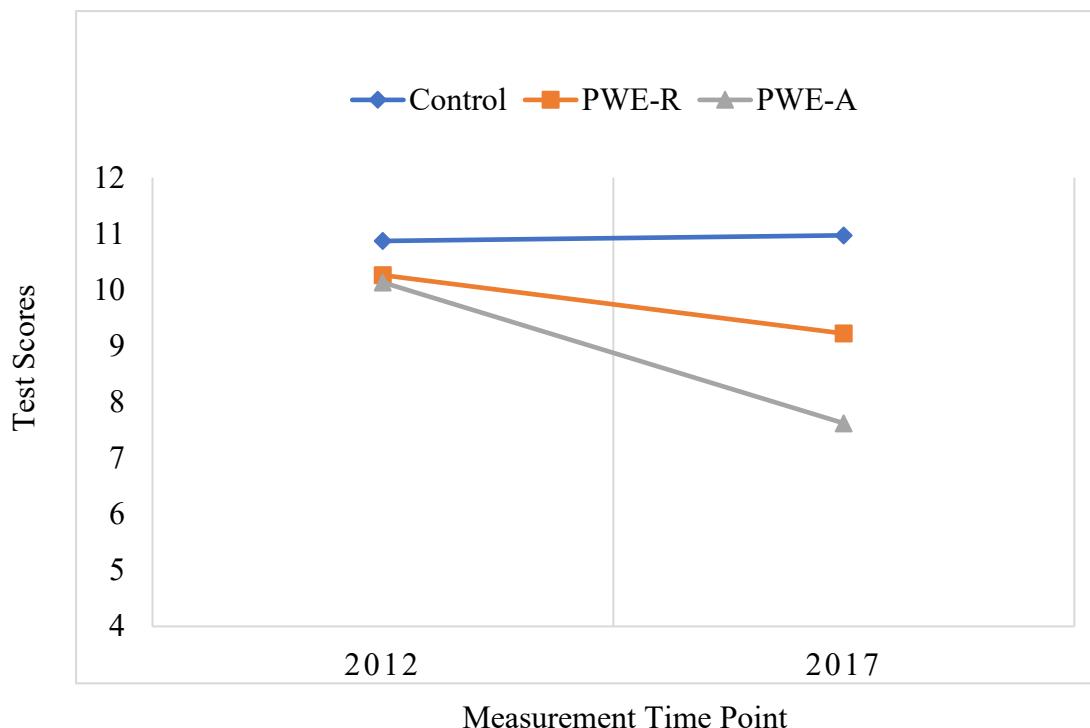
Figure 2

Baseline and Follow-up memo-BNT Scores for the Three Groups



Logical Memory

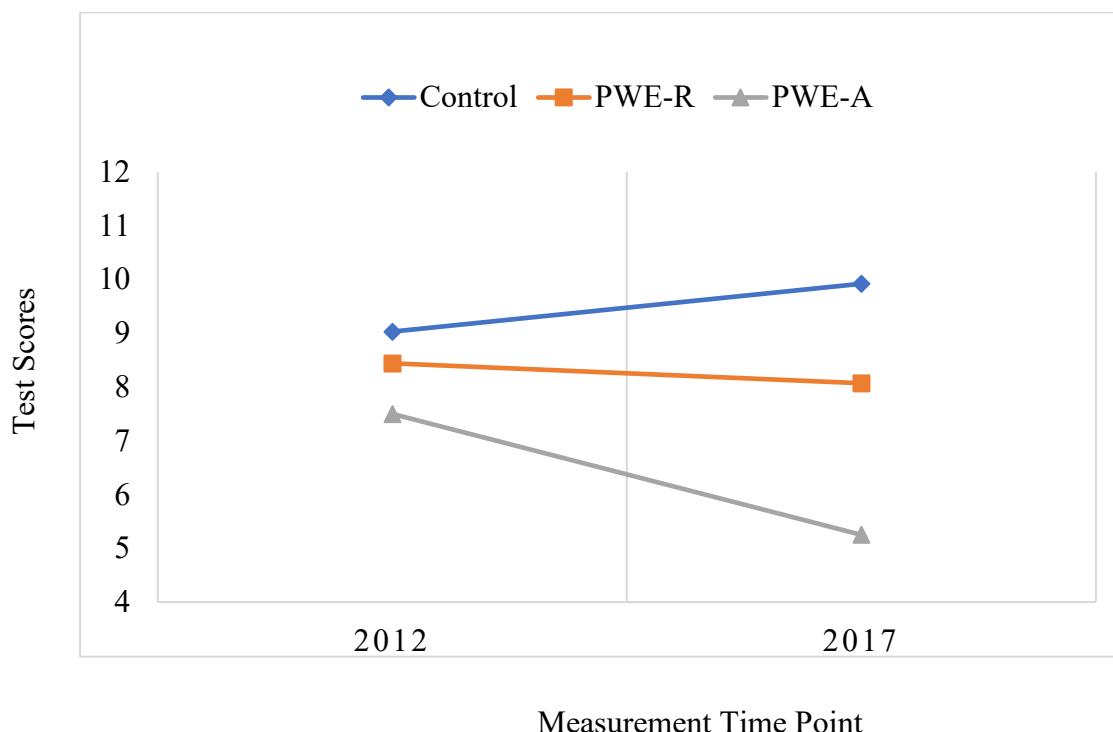
The two-way mixed ANOVA for LM-I showed a significant main effect of measurement time point ($F[1,71] = 4.617, p = .035, \eta_p^2 = .061$), as the scores declined over time (Figure 3). There was no significant interaction between change in performance over time and group ($F[2,71] = 1.957, p = .149, \eta_p^2 = .052$). The analysis did not show a significant main effect of group ($F[2,71] = 1.613, p = .207, \eta_p^2 = .043$).

Figure 3*Baseline and Follow-up LM-I Scores for the Three Groups*

The analysis of LM-II did not show a significant main effect of measurement time point ($F[1,71] = 1,056, p = .308, \eta_p^2 = .015$), nor of group ($F[2,71] = 2,720, p = .073, \eta_p^2 = .071$). There was no significant interaction between time and group ($F[2,71] = 2,052, p = .089, \eta_p^2 = .066$).

Figure 4

Baseline and Follow-up LM-II Scores for the Three Groups



Discussion

A multitude of studies suggest that childhood-onset epilepsy may predispose for cognitive deterioration and accelerated brain aging (Breuer et al., 2016; Dabbs et al., 2012; Helmstaedter & Elger, 2009; Joutsa et al., 2017). The brain development of persons with childhood-onset epilepsy is affected by an array of factors such as recurring seizures, antiepileptic drugs, and comorbid psychiatric disorders (Kellogg & Meador, 2017; Berg et al., 2012; Besag & Vasey, 2021, Ortinski & Meador, 2004). There are also indications that chronic epilepsy with recurring seizures and/or antiepileptic medication is associated with poorer long-term cognitive outcomes, whereas the remission of the disorder may yield outcomes similar to those of unaffected individuals (Karrasch et al., 2017). Considering these statements, it is reasonable to assume that chronic childhood-onset epilepsy puts a strain on the brain that may affect cognitive functioning in the long-term.

While the cognitive functioning of patients with childhood-onset epilepsy has been extensively studied early in their lifespan, less is known about the effects of the disorder as individuals reach old age. The aim of this study was to examine the long-term effects of

childhood-onset epilepsy on incidental memory. Measurements of incidental memory have been shown to be accurate in separating Alzheimer's disease (AD) from normal aging or mild cognitive impairment (Grönholm-Nyman, 2010; Karrasch et al., 2010, Kontaxopoulou et al., 2018) and the incidental memory test utilized in this study, memo-BNT, is sensitive to early signs of AD (Karrasch et al., 2010). Therefore, by examining incidental memory performance it is possible to detect early signs of abnormal cognitive decline. Furthermore, the results may provide indications of whether chronic epilepsy increases the risk of developing AD compared to remitted epilepsy or healthy controls. To assess whether chronic epilepsy affects episodic memory in general, measurements of intentional memory were included in this study.

In this study, the participants with epilepsy were categorized as having active (i.e. chronic) epilepsy (PWE-A) or epilepsy in remission (PWE-R). The epilepsy groups were compared with healthy controls (HC) as well as with each other on their performance on tests of incidental and intentional memory. Baseline measurements were conducted five years prior to the follow-up measurements, and the change in performance over time were of interest in this study. The participants were in late middle age at the time of these measurements.

Main findings

A significant interaction with a large effect size between group and time was found on the incidental memory measure. The interaction arose due to the performance in the group with chronic childhood-onset epilepsy (PWE-A) deteriorating between baseline and follow-up, while there seemed to be a small test-retest effect, i.e. improvement, in the patients with remitted epilepsy and controls. In the intentional memory measures, similar results were not found. In the immediate recall measure of the intentional memory task (LM-I), a significant main effect of time was found. The effect size of this main effect was moderate. Mean scores show that the main effect of time was driven by the performance in both epilepsy groups, which declined over time. The mean performance of the controls improved minimally over time. The interaction between time and group was, however, not significant and the effect size of the non-significant interaction was small. As for the measure of delayed recall in the intentional memory task, no significant main effect was found and the effect size was small, indicating no overall change in performance over time. While the main effect of group did not reach the threshold of statistical significance, it did show a trend level significance with a moderate effect size. A similar trend was observed for the interaction term between time and

group. The mean scores indicate that the trend level main effect of group and interaction between group and time were due to a test-retest effect of the controls (i.e. improvement), while a minimal decline was observed in the patients with remitted epilepsy, and a rather marked decline in the patients with chronic, active epilepsy.

The decline in incidental memory performance over time observed in the patients with active childhood-onset epilepsy indicates that chronic epilepsy has an adverse effect on incidental memory as individuals reach retirement age. Since memo-BNT can be predictive of AD, the results could indicate that the PWE-A group are showing signs of early AD. The fact that there was a trend level significance and moderate effect size on the interaction between time and group on the delayed recall measure in an intentional memory task (LM-II), which also is accurate in identifying early AD (Graham et al., 2004; Rabin et al., 2009), corroborates this suggestion. These findings could thus imply that the strain chronic epilepsy puts on the brain exacerbates the risk of developing AD. However, it is also possible that chronic epilepsy could affect automatic episodic memory functions independently of the pathological processes associated with AD.

Strengths and limitations

The population-based sample has provided a unique opportunity to examine the truly long-term effects of childhood-onset epilepsy as the participants reach older age. It is the only population-based childhood-onset epilepsy sample in the world that has been continually followed over such a long time span. Unfortunately, the fact that data has been gathered over an entire lifetime also provides some limitations. For instance, many confounding variables are likely to arise during a person's life. Furthermore, drop-outs have contributed to the fact that the remaining sample is small, especially the group with chronic epilepsy (PWE-A). The small sample was a limitation of this study. With this in mind, the trend level significance on the delayed recall measure in an intentional memory task (LM-II) is noteworthy, especially since there was a moderate effect size. A larger sample size could possibly have provided statistically significant results, which would further contribute to the suggestion that chronic epilepsy patients carry a higher risk of developing AD.

The tests themselves carry some limitations. The nature of incidental memory makes it difficult to assess over time, since the task is revealed to participants at the baseline measurement, and they may thus remember the task at the follow-up and are able to dedicate intentional effort to the task. Interestingly enough, the PWE-A group did not seem to benefit from this, even though the task had been revealed to them. It is possible that they did not

remember the task, whereas the other groups may have remembered and used intentional strategies at the follow-up assessment. Furthermore, the tests differed from each other in other ways than purely intentionality. For instance, while performance on LM is dependent on auditory-verbal memory ability, memo-BNT performance is dependent on visuo-verbal memory ability.

Conclusions and future suggestions

The results show an abnormal decline in incidental memory function in individuals with chronic childhood-onset epilepsy as they reach retirement age. This may be a sign of early AD, and could thus indicate that persons with chronic childhood-onset epilepsy carry a higher risk of developing AD. Another possible interpretation is that epilepsy could affect automatic episodic memory function independently of the pathological processes associated with AD. To determine which of these statements is true it would be necessary to do another follow-up study utilizing the same sample to see whether the participants with chronic epilepsy are diagnosed with AD later in life. Unfortunately, since the PWE-A group is already so small this may be unattainable using the same sample.

The first suggestion for future research derived from these findings is that the study should be replicated using a larger sample. A larger sample may yield statistical significance on the effects that in this study showed trends and moderate effect sizes. The second suggestion is that the prevalence of AD in a chronic epilepsy population older than the participants of this study should be investigated, since AD usually has an onset after the age of 65 (Schoenberg & Scott, 2011) and both the epilepsy group ($M = 63.62$, $SD = 4.7$) as well as the control group ($M = 62.69$, $SD = 4.2$) were still quite young. The third and final suggestion is that the connection between AD biomarkers and childhood-onset epilepsy should be studied, to further investigate the connection between chronic childhood-onset epilepsy and AD.

Summary in Swedish – Svensk sammanfattning

Långtidseffekterna av barndomsepilepsi på incidentellt minne hos åldrande individer

Introduktion

Epilepsi är en neurologisk sjukdom som kännetecknas av avvikande elektrisk aktivitet i hjärnan som orsakar krampfall (Schoenberg och Scott, 2011; Världshälsoorganisationen [WHO], 2019). Det finns många typer av epilepsisyndrom. Ett epilepsisyndrom med debut i tidig barndom kallas för barndomsepilepsi. Epilepsi är en av de vanligaste neurologiska sjukdomarna, med en livstidprevalens mellan 0,7 % (Fiest m.fl., 2017) och 3 % (Schoenberg och Scott, 2011). Årligen uppdagas över fem miljoner nya epilepsifall och sjukdomen står för 0,5 % av den globala sjukdomsbördan (WHO, 2019). Epilepsi medför också en ökad risk för att dö i förtid (Neligan m.fl., 2011; Sillanpää och Shinnar, 2010; Sillanpää m.fl., 1998; WHO, 2019). Sjukdomen är även förknippad med samexisterande psykiatriska störningar (Berg m.fl., 2011; Keezer m.fl., 2015; WHO, 2019) och psykosociala utmaningar (Fisher et al., 2000; Hermann och Jacoby, 2009). För många epileptiker är ändå prognosen relativt god. En majoritet av de barn som drabbats av epilepsi når fullständig remission (Berg och Rychlik, 2015; Berg m.fl., 2014; Geerts m.fl., 2010). Dock kan barndomsepilepsi medföra komplikationer i psykosocialt fungerande även hos dem som friskförklaras (Sillanpää m.fl., 1998, 2004).

Epilepsi är kopplat till kognitiva nedsättningar (Arslan och Demir, 2022; Berg m.fl., 2008; Breuer m.fl., 2016; Hermann m.fl., 2006; Kim och Ko, 2016; Schoenberg och Scott, 2011). Den kognitiva utvecklingen hos barn och unga med epilepsi påverkas av bland annat antiepileptiska läkemedel och återkommande krampfall (Berg m.fl., 2012; Besag och Vasey, 2021; Kellogg och Meador, 2017; Ortinski och Meador, 2004). Det finns indikationer på att den kognitiva utvecklingen hos barn med epilepsi blir på efterkälken jämfört med barn utan epilepsi (Rathouz m.fl., 2014). I hjärnan har strukturella avvikelse observerats tidigt i förloppet av barndomsepilepsi (Lin m.fl., 2014). Man har även observerat avvikande mönster i hjärnans utveckling hos barn med epilepsi (Hermann m.fl., 2010). Det finns indikationer på att den belastning som sjukdomen utsätter hjärnan för påskyndar hjärnans åldrande och ökar risken för kognitiva försämringar senare i livet (Breuer m. fl., 2016; Dabbs m.fl., 2012; Helmstaedter och Elger, 2009; Joutsa m.fl., 2017)

Enligt vad som hittills presenterats finns det belägg för att barndomsepilepsi är kopplat till avvikande kognitiv och neural utveckling, som i sin tur kan medföra försnabbad

kognitiv försämring i takt med att individen åldras. I denna studie kommer sjukdomens effekter på den neuropsykologiska funktionen incidentellt minne att undersökas.

Episodiska minnesspår kan kodas och konsolideras antingen intentionellt, då ihågkommandet av information sker med medveten ansträngning, eller incidentellt då ihågkommandet sker automatiskt och omedvetet. I ett typiskt test av intentionellt minne ber testledaren en testperson att komma ihåg den information som presenteras, vilket innebär att testpersonen kan göra en medveten ansträngning för att komma ihåg informationen. I ett test av incidentellt minne är testpersonen dock inte medveten om att den senare kommer att ombes att återkalla informationen. I en vardagsmiljö sker kodning och lagring av episodiska minnesspår vanligtvis incidentellt, och därför kan sådana minnesmått vara mer ekologiskt valida än mått på intentionellt minne (Vingerhoets m.fl., 2005). Mått på incidentellt minne har också visat sig kunna skilja på Alzheimers sjukdom (AD) och normalt åldrande eller mild kognitiv svikt. (Grönholm- Nyman m.fl., 2010; Karrasch m.fl., 2010; Kontaxopoulou m.fl., 2018).

Metoder

I denna studie används data från en populationsbaserad kohort av barn under 16 års ålder som år 1964 bodde i upptagningsområdet för Åbo Universitetscentralsjukhus, som är beläget i Åbo, Finland. Vid denna tidpunkt uppfyllde deltagarna kriterierna för epilepsi. Utförliga beskrivningar av rekryterings- och datainsamlingsprocessen finns annanstans (Sillanpää m.fl., 2015; Sillanpää m.fl., 1998; Sillanpää, 1973). År 1992 delades deltagarna in i två grupper beroende på om de hade någon omfattande neurologisk nedsättning eller inte. De deltagare som inte hade någon neurologisk nedsättning definierades som deltagare med okomplicerad epilepsi ($n = 99$). Därefter rekryterades en frisk kontrollgrupp ($n = 99$) som matchade epilepsigruppens demografiska profil (Sillanpää m.fl., 1998). År 2012 bjöds gruppen med okomplicerad epilepsi och deras matchade kontrollgrupp att delta i TACOE-50-projektet (Turku Aging in Childhood-Onset Epilepsy). I epilepsigruppen exkluderades 26 av de ursprungliga 99 deltagarna, och av de återstående 73 personerna valde 51 att delta. I kontrollgruppen exkluderades 21 av de ursprungliga 99 deltagarna, och av de återstående 78 personerna valde 52 att delta. Inom TACOE-50-projektet delades epilepsigruppen in i två grupper beroende på om de hade haft kontinuerliga krampfall och/eller hade tagit antiepileptiska läkemedel de senaste fem åren. Om de uppfyllde något av dessa kriterier, kategoriseras de som deltagare med aktiv (kronisk) epilepsi (PWE-A, $n = 14$), medan de som inte uppfyllde något av dessa kriterier definierades som deltagare med remitterad

epilepsi (PWE-R, $n = 37$). Kohorten genomgick ett utförligt undersökningsprogram som innehållade neuropsykologisk testning. Den neuropsykologiska testningen omfattade flertalet kognitiva domäner, inklusive incidentellt och intentionellt minne. År 2017 bjöds kohorten att delta i en andra uppföljningsstudie, TACOE-55. Av epilepsigruppen (PWE) deltog 36 personer och av kontrollgruppen (HC) deltog 39 personer. Samma undersökningsprogram som 2012 genomfördes, inklusive neuropsykologisk testning.

I denna studie undersöks resultaten av test på incidentellt och intentionellt minne som var en del av det omfattande testbatteriet som deltagarna gjorde. Memo-BNT (Karrasch m.fl., 2010) är en modifikation av Boston Naming Test (BNT; Kaplan m.fl., 1983) som möjliggör mätande av incidentellt minne. Logiskt Minne är ett deltest av Wechsler Memory Scale-Revised (Wechsler, 1996) som bedömer intentionellt minne. Logiskt Minne består både av omedelbar (LM-I) och födröjd (LM-II) återkallning. I denna studie var förändringen i prestation på memo-BNT, LM-I och LM-II från mättillfället 2012 till mättillfället 2017 av intresse. Skillnader mellan PWE-A, PWE-R och HC analyserades.

Resultat

En blandad variansanalys för memo-BNT visade ingen signifikant huvudeffekt av mättidpunkt ($F[1,62] = 0,499, p = 0,483, \eta_p^2 = 0,008$). Interaktionen mellan förändring i prestation över tid och grupp tillhörighet var dock signifikant ($F[2,62] = 5,161, p = 0,008, \eta_p^2 = 0,143$). Analysen visade ingen signifikant huvudeffekt av grupp tillhörighet ($F[2,62] = 2,262, p = 0,113, \eta_p^2 = 0,068$). Interaktionen uppstod som en följd av att PWE-A:s prestation försämrades mellan de bågge mättillfällena.

Analysen av LM-I visade en signifikant huvudeffekt av mättidpunkt ($F[1,71] = 4,617, p = 0,035, \eta_p^2 = 0,061$), men ingen signifikant interaktion mellan tid och grupp ($F[2,71] = 1,957, p = 0,149, \eta_p^2 = 0,052$). Det fanns inte heller någon signifikant huvudeffekt av grupp ($F[2,71] = 1,613, p = 0,207, \eta_p^2 = 0,043$).

Analysen av LM-II visade ingen signifikant huvudeffekt av mättidpunkt ($F[1,71] = 1,056, p = 0,308, \eta_p^2 = 0,015$) eller grupp ($F[2,71] = 2,720, p = 0,073, \eta_p^2 = 0,071$). Det fanns ingen signifikant interaktion mellan tid och grupp ($F[2,71] = 2,052, p = 0,089, \eta_p^2 = 0,066$).

Diskussion

Det finns belägg för att barndomsepilepsi medför en större risk för kognitiva nedsättningar och verkar påskynda hjärnans åldrande (Breuer m.fl., 2016; Dabbs m.fl., 2012; Helmstaedter och Elger, 2009; Joutsa m.fl., 2017). Dessutom påverkas hjärnans utveckling hos epileptiker av bland annat krampfall, medicinering och psykiatrisk samsjuklighet (Berg

m.fl., 2012; Besag och Vasey, 2021; Kellogg och Meador, 2017; Ortinski och Meador, 2004). Med detta i åtanke är det rimligt att anta att kronisk barndomsepilepsi medför en påfrestning på hjärnan som kan påverka kognitiva funktioner på lång sikt.

Syftet med denna studie var att undersöka långtidseffekterna av barndomsepilepsi på incidentellt minne. Mått på incidentellt minne har visat sig vara träffsäkra i att skilja Alzheimers sjukdom (AD) från normalt åldrande eller mild kognitiv svikt (Grönholm-Nyman m.fl., 2010; Karrasch m.fl., 2010; Kontaxopoulou m.fl., 2018). Det incidentella minnestestet som användes i denna studie, memo-BNT, är känsligt för tidiga tecken på AD (Karrasch m.fl., 2010). Genom att undersöka incidentellt minne är det således möjligt att upptäcka tidiga tecken på avvikande kognitiva försämringar. Dessutom kan resultaten ge indikationer på om kronisk epilepsi ökar risken för AD. För att undersöka om det episodiska minnet i allmänhet är påverkat inkluderades mått på intentionellt minne i denna studie.

I denna studie undersöktes förändring i prestation på minnestest under en femårsperiod hos individer i sen medelålder. Skillnaderna mellan deltagare med aktiv epilepsi, deltagare med remitterad epilepsi och friska kontrollpersoner analyserades. Analyserna visade att det incidentella minnet försämrades under femårsperioden hos gruppen med aktiv epilepsi. Hos deltagarna med remitterad epilepsi och kontrollpersonerna noterades ingen försämring. Det intentionella minnestestet visade ingen statistiskt signifikant interaktion mellan grupp och mätidspunkt.

Resultaten indikerar att kronisk epilepsi medför en avvikande försämring i incidentellt minne då personer närmar sig pensionsåldern. Detta kan tyda på att de har en förhöjd risk att utveckla AD. En annan förklaring är att det automatiska episodiska minnet är påverkat oberoende av den patologiska processen som associeras med AD.

Till författarens kännedom är detta den enda studie som gjorts om långtidseffekterna av barndomsepilepsi på incidentellt minne. Samplet är unikt i det avseendet att deltagarna har följs under hela sin livstid ända upp i övre medelåldern. Dock bör det tas i beaktande att det stora bortfallet som skett över en så lång tidsrymd har lett till att det som återstod av samplet var relativt litet. Resultaten indikerar dock att det vore motiverat att i framtiden replikera studien med ett större sampel. Det vore också fördelaktigt att undersöka ett äldre sampel, eftersom AD oftast diagnostiseras hos individer som är ännu äldre än i denna (Schoenberg & Scott, 2011).

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PRESSMEDDELANDE

Långtidseffekterna av barndomsepilepsi på incidentellt minne hos åldrande individer

Pro-gradu avhandling i psykologi

Fakulteten för humaniora, psykologi och teologi Åbo Akademi

Resultaten från en pro-gradu avhandling i psykologi vid Åbo Akademi tyder på att det finns ett samband mellan kronisk barndomsepilepsi och avvikande försämring av incidentellt minne då personer närmar sig pensionsåldern. Det incidentella minnet är den del av våra minnesfunktioner som sköter automatisk och omedveten inlärning och ihågkommande av information, vilket är typiskt för hur minnet fungerar i en vardagsmiljö. Till författarens kändedom är detta den enda studie som har gjorts om sambandet mellan barndomsepilepsi och incidentellt minne hos åldrande individer. Resultaten bygger dock på tidigare forskningsfynd som visat att barndomsepilepsi innebär en påfrestning för hjärnan som kan öka risken för kognitiva försämringar senare i livet. Denna studie är en del av TACOE-projektet, som undersöker långtidseffekter av barndomsepilepsi i ett finskt populationsbaserat sampel. Deltagarna har genomgått utförliga neurologiska och neuropsykologiska undersökningar, inklusive testning av incidentellt minne. Samplet i studien bestod av 36 personer med epilepsi och 39 friska kontrollpersoner. Studien undersökte förändringar i incidentellt minne från en baslinjemätning år 2012 till en uppföljningsmätning år 2017. Resultaten tyder på att det incidentella minnet försämrar hos personer med kronisk barndomsepilepsi då de närmar sig pensionsåldern, medan det hålls intakt hos personer med remitterad barndomsepilepsi och hos friska kontrollpersoner. Eftersom det incidentella minnestestet som användes i denna studie har visat sig kunna identifiera tidiga tecken på Alzheimers sjukdom kan en tolkning av resultaten vara att kronisk barndomsepilepsi ökar risken för denna demenssjukdom. Dock bör det tas i beaktande att samplet på grund av stort bortfall var relativt litet och framtida forskning behövs för att bekräfta dessa resultat.

Avhandlingen utfördes av Viktor Gestranius under handledning av Mira Karrasch, Docent i neuropsykologi.

Ytterligare information fås av: Viktor Gestranius

Tel. 050 599 1525

Epost: viktor.gestranius@abo.fi