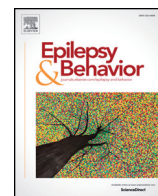




Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Development of verbal short-term memory and working memory in children with epilepsy: Developmental delay and impact of time-related variables. A cross-sectional study

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ARTICLE INFO

Article history:

Received 14 July 2017

Revised 12 October 2017

Accepted 12 October 2017

Available online xxxx

Keywords:

Short-term memory

Working memory

Typically developing children

Epilepsy in children

Age at onset in epilepsy

Development of memory

ABSTRACT

While short-term memory (STM) and working memory (WM) are understood as being crucial for learning, and children with epilepsy often experience learning difficulties, little is known about the age-related development of memory span tasks in children with epilepsy. Short-term memory and WM, operationalized as digit span forwards (DSF) or digit span backwards (DSB), respectively, were studied. Participants were 314 children with epilepsy and 327 typically developing children in ages between 5 and 15 years and full scale intelligence quotient (FS-IQ) ≥ 75 . Cross-sectional analyses of the data were done with analyses of variance and analyses of covariance ((M)ANCOVAs) and generalized linear analyses. The analyses revealed that STM problems in epilepsy were mediated by age-related gains in WM as well as by differences in IQ. Working memory developed at a quick pace in the younger children, the pace slowed down to some extent in the later primary school years and resumed again later on. Working memory problems prevailed in epilepsy, independent of IQ and development of STM. Timing of the epilepsy in terms of age at onset and duration determined memory development. The youngest children with epilepsy showed age-appropriate development in STM but were the most vulnerable in terms of WM development. Later in the course of the epilepsy, the WM problems of the young children attenuated. In later onset epilepsy, WM problems were smaller but persisted over time.

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1. Introduction

Although working memory (WM) is generally recognized to be a system essential for learning [1], and children with epilepsy are known to have cognitive and learning problems [2–4], studies on the development of WM in children in the context of epilepsy are still scarce. Also, little is known about the factors affecting WM development in children with epilepsy.

Verbal short-term memory (STM) is often regarded as a subcomponent of WM [5]. Short-term memory refers to the temporary storage of verbal information. Verbal WM refers to the simultaneous storage and processing of verbal information [6,7]. The difference between the two systems is that, beyond retention, WM implies mental manipulation of the information. In this sense, it is considered an executive function [8]. In contrast to the sheer limited capacity of long-term memory, the capacity of both STM and WM in man is limited.

Individual differences in both STM and WM are important for scholastic achievement like reading and mathematics [9–11]. With its higher

processing load, WM is more strongly associated with school learning than STM [1,12]; deficits are associated with learning disabilities [13]. Some evidence even suggests that WM is a more powerful predictor of academic success than IQ ([1], but see [14]). McGrew [15] discussed the possibility that WM may be one of the important abilities underlying general intelligence.

1.1. Development of verbal STM and WM

Studies on development of STM and WM in typically developing children and adolescents have found steady increases in capacity over time [11,16,17]. For children aged 6 to 15 years, this increase was found to be linear [11,17], but the rate of growth was likely to decrease from childhood toward late adolescence [18].

1.2. Brain areas involved in WM

A common measure for verbal STM is digit span forwards (DSF). The DSF task requires the repetition of a series of orally presented digits in the order of presentation. Digit span backwards (DSB) is often taken as a measure of WM. On this task, the series of orally presented digits have to be repeated in backward order [1,10,16,17,19]. Both span

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tasks are believed to recruit multiple brain areas. These areas show overlap for both tasks as well as distinct areas recruited only in DSB. Functional Magnetic Resonance Imaging (MRI) studies have shown that the right dorsolateral prefrontal cortex, the right parietal cortex (inferior parietal lobule), the anterior cingulate, as well as the medial occipital cortex are involved in DSF and DSB [20]. In DSB, bilateral involvement of the dorsolateral prefrontal cortex and involvement of the right inferior parietal lobule and Broca's area may also be seen [20]. Structural MRI studies have indicated involvement of the parietal lobe in DSF and involvement of frontal and prefrontal areas, as well as of the left anterior insular cortex in DSB [21]. Overall, the studies suggest involvement of more posterior areas, mainly the parietal areas, in digits forwards tasks and of anterior areas in the more demanding digit backwards tasks [8,18,20,21]. In addition, cortical changes in bilateral prefrontal and posterior parietal regions were seen as children grow older [18].

1.3. STM and WM in children with epilepsy

Children with epilepsy have been reported to have STM and WM problems. On the Wechsler Intelligence Scale for Children - IVth edition (WISC-IV), children with low full scale intelligence quotients (FS-IQs) performed worse on the WM factor, which contains both types of span tasks, than on the verbal or the perceptual factors [22]. Working memory problems were already present early in the course of the epilepsy and were seen to remain stable over time when children were retested several times within a year [23]. Deficits on memory span tasks have been found in children with benign epilepsy with centrotemporal spikes [24], as well as frontal and temporal lobe epilepsy [25,26]; no effect of seizure frequency has been reported [27]. The studies reviewed have included either separate or combined measures for DSF and DSB. Given the differences in STM and in WM, also in terms of brain areas involved, in the present study separate measures of STM and WM were included.

2. Present study

Given the importance of STM and particularly WM for scholastic achievement and given that children with epilepsy have learning disorders [3,4] and changing cognitive patterns over time [28], it is worthwhile to pursue a better understanding of the development of STM and WM in children with epilepsy. In addition to age-related changes, STM and WM were studied in relation to demographic and epilepsy variables. The study addressed the following three research questions:

1. Does the development of STM and WM follow the same pattern in children with epilepsy compared with typically developing children? The hypothesis in the present study was that children with epilepsy follow a similar – predominantly linear [11,18] – developmental pattern at a slower pace.
2. To what extent can development of WM be accounted for by the development of STM – and vice versa? Are individual differences the result of differences in intellectual development? While STM is thought of as being less complex than WM, both abilities develop alongside each other [5], and a mutual interaction between STM and WM is proposed in the model on WM [6,29]. Lower IQ in children with epilepsy is a general finding [3,28]. Working memory has been found to be correlated with IQ but could just as well be a factor underlying FS-IQ [15]. From this point of view, low WM would contribute to a low IQ. The hypotheses tested were that STM and WM influence each other's development and that STM and WM are compromised in children with epilepsy, beyond IQ differences.
3. Which demographic and epilepsy-related variables are associated with STM and WM in children with epilepsy? It is hypothesized that children with greater scholastic needs (i.e., children enrolled in

special education), from families with lower education [28], would have lower STM and WM capacity. Based on the literature, it was hypothesized that frontal or posterior epilepsy will be associated with STM proficiency and that frontal lobe involvement may negatively impact on WM, but that age-related differences may be seen [18,20]. Based on earlier findings highlighting the impact of time-related variables on cognitive development in children [28], it was also hypothesized that younger age at onset has a more detrimental impact on STM and WM than later onset of epilepsy.

3. Methods

3.1. Participants

Participants were 327 typically developing children and 314 children with epilepsy, between 5 and 15 years of age. The typically developing children had participated in a larger study that aimed to provide national norms for a variety of neuropsychological tests, including STM and WM. They had been tested in regular schools for primary and secondary education in The Netherlands. To ensure that the children belonged to the “typically developing children”, together with the informed consent form, parents filled in a query on their child's development; teachers were also consulted on this topic. The typically developing children were enrolled in regular primary and secondary schools and were hence assumed to have normal IQs.

The children with epilepsy were clinically referred for comprehensive neuropsychological evaluation to a tertiary epilepsy center (Epilepsy Institute in the Netherlands Foundation (SEIN)) or its associated school for children with epilepsy because of concerns about their cognitive development. They were included in the study if their FS-IQ on the Wechsler tests was equal or larger than 75 and if data on DSF and DSB were present. Data concerning only IQ patterns on part of these children have been reported earlier by the authors (i.e., [3]). Table 1 shows the numbers of children per age group, mean age, and percentages of boys for the typically developing group and the group with epilepsy.

Comparison of the group of typically developing children with the group of children with epilepsy indicated no difference with a *t*-test in mean age ($t = -0.17, p = 0.865$) and no differences in the proportions of children in each age group ($\chi^2(8633) = 10.3, p = 0.240$). A smaller proportion of boys was seen in the group with typically developing children compared with the group with epilepsy ($\chi^2(1,640) = 13.62, p < 0.001$). Therefore, sex was included as a covariate in the analyses.

3.2. Measures

3.2.1. Forward and backward span

The DSF and DSB were taken from the digit span subtest of the Dutch WISC-III^{NL} [30]. Digit span was given to all children. In the DSF task, the child is asked to repeat a series of orally presented digits in the order of presentation. If the child succeeds, the length of the series is progressively increased until the child fails the two presentations in a row of the same length. In DSB, the same procedure is followed, except that the series of digits have to be repeated in reverse order. The lengths of the longest series correctly reproduced forwards and backwards were the measures of interest in the present study. For the second part of the analyses, raw scores were converted into standardized scores for all children based on the normed data from the typically developing control group.

3.2.2. Intelligence

Intelligence was assessed with age-appropriate Wechsler scales, which included either the full Dutch Wechsler Preschool and Primary Scale for Intelligence- III edition (WPPSI-III^{NL}) [31], the full Dutch Wechsler Intelligence Scale for Children - III edition (WISC-III^{NL}) [30], or a 4-subtest short form of the WISC-III^{NL} [32]. The short form was developed for use for the screening of children attending the Child

Table 1

Characteristics of the samples. Age, sex, and sample sizes per age group. Uncorrected means and SDs on digit span backwards per age group, and *p*-values and effect size Cohen's *d* after independent samples two-sided *t*-test.

Group	N and percentage		Digit span forwards			ES	Digit span backwards			ES
	Typically developing children	Children with epilepsy	Typically developing children	Children with epilepsy	<i>p</i>		Typically developing children	Children with epilepsy	<i>p</i>	
N	327	314	327	314			327	314		
Age 5	16 (4.9)	10 (3.2)	3.94 (0.7)	4.00 (0.7)	0.820	−0.09	1.94 (1.2)	0.90 (1.2)	0.040	0.88
Age 6	43 (13.1)	36 (11.5)	4.30 (0.8)	3.89 (0.9)	0.033	0.51	2.95 (0.8)	1.94 (1.3)	<0.001	1.24
Age 7	37 (11.3)	44 (14.0)	4.49 (0.9)	4.34 (0.7)	0.420	0.16	3.27 (0.7)	2.70 (0.8)	0.001	0.77
Age 8	34 (10.4)	50 (15.9)	4.94 (1.0)	4.38 (0.8)	0.005	0.55	3.76 (0.8)	2.84 (0.8)	<0.001	1.18
Age 9	55 (16.8)	49 (15.6)	5.76 (1.1)	4.57 (0.9)	<0.001	1.06	3.84 (0.8)	3.39 (0.8)	0.007	0.55
Age 10	44 (13.5)	39 (12.4)	5.27 (0.9)	4.69 (1.0)	0.007	0.63	4.09 (0.7)	3.49 (0.8)	0.001	0.81
Age 11	34 (10.4)	19 (6.1)	5.68 (0.8)	4.58 (0.8)	<0.001	1.30	4.29 (1.1)	3.32 (1.1)	0.002	0.92
Ages 12 and 13	32 (9.8)	34 (10.8)	5.53 (1.0)	5.12 (0.9)	0.801	0.41	4.25 (1.0)	3.74 (1.1)	0.051	0.52
Ages 14 and 15	32 (9.8)	33 (10.5)	5.66 (0.9)	5.24 (0.9)	0.064	0.48	4.66 (1.0)	4.21 (1.3)	0.135	0.43

Note. Age in years. Typically developing children: N = 145 (44.3%) boys; Epilepsy N = 185 (58.9%) boys.

Epilepsy Centre (KEC) at SEIN for a 24-hour multidisciplinary evaluation. The validity of the short form was evaluated on a subset of children with focal epilepsy and found to be adequate [32]. It should be noted that while DSF and DSB scores were derived from a subtest of the intelligence scale, they were not included in the computation of FS-IQ.

3.2.3. Epilepsy-related measures

Information on epilepsy variables was collected from neurological reports and is shown in Table 2. These variables related firstly to time-related epilepsy variables as age at onset of epilepsy (AOE) and duration of epilepsy. Duration of epilepsy was calculated as the difference between age at onset and age at testing. Secondly, information of seizure type (focal or generalized), lateralization (left or right hemisphere, LH and RH), and localization (involvement of the frontal, temporal, parietal, occipital, or central cortex, in isolation, or in combination) was included. Thirdly, information was collected on the number of antiepileptic drugs (AEDs) taken at time of testing and AEDs tried during the course of the seizure condition, presence of lesions on MRI (MRI + if a lesion had been observed on MRI; MRI − if no lesion had been observed or no MRI was done), seizure freedom (taken as inactive epilepsy for a period of 12 months or more at the time of testing), and epilepsy syndrome severity [33]. Epilepsy syndrome severity was assessed with epilepsy syndrome severity scale of Dunn [33]. The scale ranges from 1 to 10, where higher values reflect increased severity.

3.2.4. Background characteristics

Demographic variables were provided by parents. Apart from sex and age at testing, the demographic variables included were enrollment in regular versus special education and parental education. Parental education was scored according to the Netherlands system (SOI) from the Central Bureau of Statistics [34]. Higher values indicate higher parental education. All children with epilepsy were clinically referred children, likely to have educational needs. Most had special provisions at their regular school; for some, placement in a school for special education was required. Therefore, enrollment in regular versus special education was taken as a measure for severity of educational needs. The characteristics of the children with epilepsy, including both epilepsy variables and demographic variables, are presented in Table 2.

3.3. Analyses

3.3.1. Control versus epilepsy: a cross-sectional developmental curve of DSF and DSB

Multivariate Analysis of Covariance (MANCOVA) was done, based on the raw scores of the two span tasks. The DSF and DSB tasks were the dependent variables, group and age were independent variables, and sex was a covariate.

Polynomial contrasts were done to study which model (linear or higher order) would best describe the developmental curve seen in children of increasing age. Repeated contrasts were done to study

Table 2

Characteristics of the sample with epilepsy.

Epilepsy	N (%)
N	314
Seizure type	
Generalized N (%)	81 (25.8)
Focal N (%)	
Left hemisphere LH	56 (17.8)
Right hemisphere RH	36 (11.5)
Bilateral/multifocal/uncertain	74 (23.6%)
Frontal	43 (13.7)
Temporal	67 (21.3)
Parietal	21 (6.7)
Occipital	22 (7.0)
Central	38 (12.1)
Uncertain/unknown	67 (21.3)
SE	27 (8.6)
MRI +	35 (11.1)
MRI + LH	13 (4.1)
MRI + RH	10 (3.2)
MRI −	279 (88.9)
CSWS/atypical LKS	18 (5.7)
AEDs taken = 0	64 (20.4)
AEDs taken = 1	138 (43.9)
AEDs taken = 2	82 (26.1)
AEDs taken ≥ 3	16 (5.1)
AEDs tried = 0	18 (5.7)
AEDs tried = 1	108 (34.4)
AEDs tried = 2	81 (25.7)
AEDs tried ≥ 3	93 (29.6)
AEDs taken/tried unknown	14 (4.5)
Inactive epilepsy, 12 months or longer	55 (17.5)
Active epilepsy after 2 of more AEDs	147 (49.0)
	Mean (SD)
Epilepsy syndrome severity (max = 10)	5.3 (1.7)
Age at epilepsy onset in years AOE	5.6 (3.1)
Duration of epilepsy to test, in years	4.1 (2.8)
Demographic (familial) variables and school	N (%)
Parental education level	4.3 (0.9)
Enrolled in special education	33 (10.5)

Note. Frontal/temporal/parietal/occipital/central denotes involvement of this hemisphere in the seizures and may be in combination with another hemisphere, as in centrottemporal. SE = status epilepticus reported in the child's history. MRI + = lesion seen on neuroimaging. MRI − = no lesion seen on imaging or no imaging available. CSWS/atypical LKS = continuous spike and wave during slow sleep with spike-wave index ≥ 50% recorded; alternatively, (atypical) Landau-Kleffner syndrome. Active epilepsy after two or more AEDs was based on *n* = 330; for two additional children with inactive epilepsy (seizure-free for 12 months or more), the number of AEDs was unknown. Epilepsy syndrome severity based on *n* = 287 children; range: 2 to 10. Parental education based on *n* = 232, range: 2 to 6.

whether significant gains were seen between subsequent age groups. Analyses of Covariance (ANCOVA's) were done for each span task, first adding the development of the other span task (interaction of the other span task * age) as a covariate; thereafter, adding FS-IQ as well. To study the development for each group separately, additional, separate ANCOVA's were done.

3.3.2. Epilepsy sample

The effect of demographic and epilepsy variables on STM and WM was analyzed applying generalized linear models, with normal probability distribution and identity link function. Separate analyses were done for STM and WM, following the same procedure, based on standardized, age-adjusted digit span scores. Digit span forwards (and then backwards) scores were the predicted variables. Each model was evaluated first without the "other" digit span task as a covariate. Thereafter, the standardized digit span task (backwards or forwards, respectively) was entered as a covariate and called a covariate model or c-Model. Consecutive analyses were performed, and the Akaike Information Criterion (AIC) was compared to establish whether the new model was superior to the previous one. Aikake Information Criterion is a commonly used goodness-of-fit measure. Lower values indicate better fit. When comparing two models, a difference of two or more points may be used as a cut-off. Aikake Information Criterion penalizes for model complexity and provides better values for parsimonious models [35]. For continuous variables (AEDs tried, epilepsy syndrome severity, parental education), missing data were replaced with the mean. Age at onset of epilepsy and duration of epilepsy were centered and expressed in years; FS-IQ was z-transformed (mean = 0, SD = 1). The remaining variables were scored 0 if absent and 1 if present (i.e., the variable frontal seizures was scored 0 if no frontal involvement was reported; the variable was scored 1 if frontal involvement had been seen on the EEG). For sex, boys were scored 1; for education, special education was scored 1.

In the first model (Model I), sex, FS-IQ, parental education, and type of education were entered as predictors. From the second model onward, epilepsy variables were entered. In the second model, the time-related variables, AOE, duration of epilepsy, and their interaction were added as predictors (Model II-a). In the third model, measures associated with epilepsy severity were entered. These variables were number of AEDs tried and epilepsy syndrome severity. Also, as dummy variables, presence of MRI abnormalities, presence of status epilepticus (SE) in the child's history, and presence of night time epileptic activity with a spike-wave index above ~50% ([partial]continuous spike and wave during slow sleep, [partial] CSWS) were entered. In the fourth model, seizure type (generalized seizures, focal seizures), hemispheric lateralization (LH), and hemispheric localization (frontal, temporal, parietal, occipital, central involvement) were all entered as dummy variables. Thereafter, for each hemispheric localization, the interactions with age (Model IV-a) and hemisphere (Model IV-b) were entered. The variables in the model were maintained if the variables were close to significance ($p \leq 0.10$), and the model was as good as or better than the previous model (AIC comparison). Otherwise, they were removed. The present study was based on norm data collected by students of educational psychology and observational data collected in a clinical neuropsychological setting. Parents signed an informed consent form.

4. Results

4.1. Preliminary analyses

Age was expressed in years (5 to 15 years). Given relatively small numbers at the older age ranges, age 12/13 years contained the pooled data for 12 and 13 years; age 14/15 years contained the pooled data for 14 and 15 year olds. Data on FS-IQ were present for $n = 113$ typically developing children up to age 13 years (mean FS-IQ = 102.26, SD = 12.1),

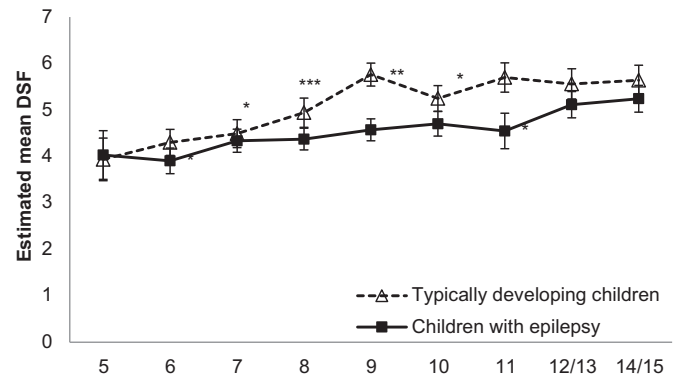


Fig. 1. Short-term memory development. Note. Two-tailed. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$. Means adjusted for sex.

for all 314 children with epilepsy (mean FS-IQ = 92.74, SD = 11.5), and for $n = 281$ children with epilepsy up to age 13 years (mean FS-IQ = 92.64, SD = 11.3). Comparison with two-sided t -tests for independent samples and $p \leq 0.05$ showed that typically developing children had higher scores than children with epilepsy on FS-IQ ($t(2452) = 7.44$, $p < 0.001$, 95% confidence interval (95% C.I.), [7.0; 12.0]) when only the 394 children with an IQ test up to age 13 years were selected ($t(2392) = 7.47$, $p < 0.001$, [7.1; 12.2]). Based on standardized scores for the span tasks, Pearson's product moment correlation with FS-IQ was significant for DSF ($r = 0.250$, $p < 0.001$) and DSB ($r = 0.233$, $p < 0.001$).

4.2. Comparison of typically developing control children and children with epilepsy

Means and standard deviations for DSF and DSB per age group are provided in Table 1 for the typically developing children and the children with epilepsy. The mean scores for the typically developing children may be interpreted as norm scores for Dutch children. Two-sided independent-samples t -tests ($p \leq 0.05$) to compare groups at each age level showed that higher scores were seen in typically developing children relative to children with epilepsy at almost all ages (Table 1). After correcting for sex, the mean values and the 95% C.I. for both groups are depicted in Fig. 1 for DSF and in Fig. 2 for DSB.

4.3. The role of group and age in the development of DSF and DSB

First, MANCOVA showed that for DSF, a significant effect of sex could be seen, suggesting a higher mean score for girls than boys. The effect of group was significant, meaning that typically developing children outperformed the children with epilepsy. There was a significant effect of age, indicating that abilities improved with increasing age. In addition, a group * age interaction was seen, suggesting that the developmental curves differed between the two groups (Table 3).

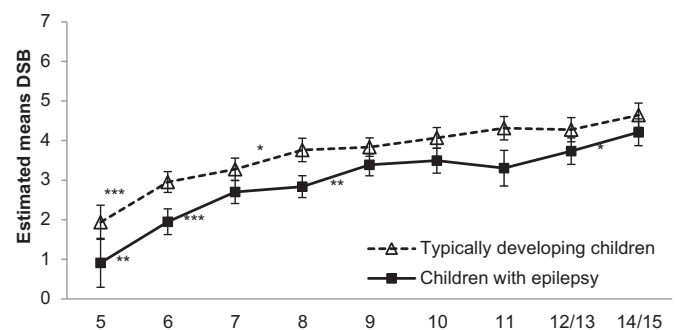


Fig. 2. Working memory development. Note. Two-tailed. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$. Means adjusted for sex.

Table 3

Comparison of typically developing children and children with epilepsy on digit span forwards and digit span backwards: development, effects of development of the other span task and effect of IQ.

	df	Digit span forwards			Digit span backwards		
		F	p	η_p^2	F	p	η_p^2
MANCOVA							
Sex	1	7.55	0.006	0.01	3.32	0.069	0.01
Group	1	41.57	<0.001	0.06	74.83	<0.001	0.11
Age	8	21.12	<0.001	0.21	42.30	<0.001	0.35
Group * age	8	3.45	0.001	0.04	1.21	0.291	0.02
Error	622						
ANCOVA with span task * age							
Sex	1	4.86	0.028	0.01	0.93	0.334	0.00
Span task DSB/DSF * age	1	63.89	<0.001	0.09	68.46	<0.001	0.10
Group	1	17.84	<0.001	0.03	44.79	<0.001	0.07
Age	8	3.52	0.001	0.04	6.54	<0.001	0.08
Group * age	8	3.63	<0.001	0.04	2.03	0.041	0.03
Error	621						
ANCOVA with span task * age^a							
Sex	1	7.25	0.007	0.01	0.24	0.627	<0.001
Span task DSB/DSF * age	1	52.69	<0.001	0.09	56.18	<0.001	0.10
Group	1	8.76	0.003	0.02	45.09	<0.001	0.08
Age	7	1.24	0.278	0.02	6.59	<0.001	0.08
Group * age	7	1.56	0.145	0.02	1.35	0.226	0.02
Error	519						
ANCOVA with IQ^a							
Sex	1	8.01	0.005	0.02	0.36	0.547	0.001
Span task * age	1	4.09	<0.001	0.08	46.57	<0.001	0.08
FS-IQ	1	14.23	<0.001	0.03	6.50	0.011	0.01
Group	1	2.21	0.137	0.00	29.01	<0.001	0.05
Age	7	1.62	0.126	0.02	6.57	<0.001	0.08
Group * age	7	1.50	0.164	0.02	1.44	0.187	0.02
Error	518						
Polynomial contrasts^a							
	Difference (SE)	p	95% C.I.	Difference (SE)	p	95% C.I.	
Linear	0.21 (0.2)	0.329	0.21; 0.64	0.70 (0.3)	0.013	0.15; 1.26	
Quadratic	-0.14 (0.1)	0.233	-0.39; 0.09	-0.79 (0.1)	<0.001	-1.06; -0.52	
Cubic	-0.21 (0.1)	0.071	-0.43; 0.02	0.39 (0.1)	<0.001	0.14; 0.64	

Note. DSF = digit span forwards, DSB = digit span backwards. Span task DSB/DSF * age: DSB * age is entered in the study on DSF, conversely, DSF * age was entered in the study on DSB.

^a 9-year old children were excluded from the analysis.

Polynomial contrasts revealed that the developmental curve could be described as linear; quadratic and “eighth order” (random) terms were also significant. For the combined group, significant age-related gains were seen on DSF between ages 6 and 7 years ($p = 0.030$) and between 8 and 9 years ($p < 0.001$).

For DSF, separate analyses for the *typically developing children* showed significant effects of sex, and an “atypical peak” at age 9 years – a significant increase between ages 8 and 9 years ($p < 0.001$) – was followed by a significant decrease at age 10 years ($p = 0.007$); significant changes were also seen between ages 7 and 8 years ($p = 0.043$), as well as between 10 and 11 years ($p = 0.36$). The scores of the *children with epilepsy*, on the other hand, increased gradually and showed significant gains between ages 6 to 7 years ($p = 0.022$) and ages 11 to 12/13 years ($p = 0.020$). No effects of sex were seen for the children with epilepsy. The results are depicted in Fig. 1. Given the unusual peak at age 9 years for the typically developing children, the subsequent analyses were done for the complete sample and repeated after removal of all 9-year-old children.

Second, an ANCOVA (Table 3) was done entering the interaction term “DSB * age” as a covariate. The results showed significant effects for sex, span task * age, group, and group * age. After removal of the 9 year olds, the effects of age and the interaction of group * age were no longer seen, suggesting that the different age effects for the two groups seen earlier were associated with this atypical peak. Without the 9 year olds, curves were largely similar between the groups. Typically developing children had higher scores. Also, the age-related development of the other span task (i.e., the changes of digits backwards over time) accounted for the

age-related development of digit forwards, and no significant effect of age was seen over and above this effect.

Third, missing IQ data for the typically developing children were replaced by the group mean (102.26), and IQ was added to the ANCOVA. Significant effects were seen for sex ($p = 0.018$), span task * age ($p < 0.001$), and FS-IQ ($p = 0.001$), as well as for group ($p = 0.006$), age ($p < 0.001$), and the group * age interaction ($p < 0.001$). Again, after removal of the 9 year olds (Table 3), no effects were seen any longer for group, age, or their interaction. This meant that changes in DSF were accounted for by differences in IQ and age-related changes in DSB; while there was no longer a separate effect of group or age. Polynomial contrasts showed no significant results for linear or higher order patterns (Table 3). This meant that, after taking into account the covariates, differences were no longer seen between the two groups. The results did not meaningfully change when the third analysis was redone with the smaller sample of children up to age 13 years who actually had taken the IQ-test.

For DSB, partly different results emerged. The Analyses of Variance and Analyses of Covariance (MANCOVAs) showed significant effects of group and age. Typically developing children scored higher than children with epilepsy, and scores increased as children grew older. The curve could be described as linear, quadratic, or cubic. Significant sex-corrected age-related gains were seen between the ages 5 to 6 years ($p < 0.001$), 6 to 7 years ($p < 0.001$), 7 to 8 years ($p = 0.035$), 8 to 9 years ($p = 0.024$), and 12/13 to 14/15 years ($p = 0.009$). This meant that largest gains were seen in the early primary school years, the rate of growth diminished in later primary school years and increased again in the secondary school years. Separate analyses for

typically developing children and children with epilepsy on DSB showed, for typically developing children, significant age-related gains from 5 to 6 years ($p < 0.001$) and 7 to 8 years ($p = 0.019$). For children with epilepsy, significant gains were seen for a somewhat more prolonged period of time. Significant age-related gains were seen from 5 to 6 years ($p = 0.004$), 6 to 7 years ($p = 0.001$), 8 to 9 years ($p = 0.006$), and between 12/13 years and 14/15 years ($p = 0.049$). For each of the two groups, developmental curves could be described as linear, quadratic, or cubic. The sex-corrected developmental curves, 95% C.I.s and significant changes between two consecutive ages are depicted in Fig. 2.

Again, based on the complete sample, the span task by age (DSF * age) was added as a covariate, and ANCOVA was done. Results showed significant effects for the span task * age; beyond this effect, group as well as age effects were seen. An interaction effect between group and age emerged, which disappeared when the 9-year-old children were removed.

Addition of FS-IQ as a covariate showed overall similar results, together with significant effects for FS-IQ. That is to say, there were significant effects of age-related changes of the other span task ($p < 0.001$) as well as of IQ ($p = 0.003$), while differences according to group ($p < 0.001$) and age ($p < 0.001$) were still present. An interaction effect was seen for group * age ($p = 0.035$), which disappeared after exclusion of the 9 year olds (Table 3). In this final analysis, the developmental curves could again be described as linear, quadratic, as well as cubic (Table 3), suggesting accelerations and decelerations over time in the development of WM.

In summary, some similarities and differences between the development of DSF and DSB could be seen. Typically developing children outperformed children with epilepsy on both span tasks. Both span tasks increased as children grow older. Scores on span tasks were influenced by scores on the age-related changes of the other span task, as well as by IQ. Both span tasks revealed an impact of the atypical peak of the 9 year olds. The peak was only seen in one group suggesting that typically developing Dutch children show a period of rapid but temporary increase of STM around age 9 years, not mirrored in children with a brain disorder.

For DSF, the differences between the two groups disappeared when the effects of the atypical peak in the 9 year olds were singled out and removed from the sample and when the effects of age-related changes in DSB and IQ were controlled. When the covariates were taken into account, the groups appeared to be largely similar, both in terms of shape of the curve as level of performance. This meant that the developmental gains of DSF could be explained by changes over time that occurred in DSB, as well as IQ-differences and sex differences. Sex was a predictor of DSF for the typically developing children only.

In contrast, for DSB, differences between the two groups could not be explained only by differences in STM or IQ and were thus likely to be associated with the epileptic condition. A developmental lag prevailed in children with epilepsy relative to typically developing children. Both groups showed a similar developmental curve, with gains that were largest in the early years, continued at a slower pace thereafter, and speeded up again.

4.4. Variables contributing to STM and WM in epilepsy

4.4.1. DSF

After applying generalized linear models, Model I (without the span task as covariate) and c-Model I (with DSB as a covariate) showed that sex and parental education were not significant predictors of DSF (see Table 4). Significant values were seen for special education and FS-IQ. Children in special education did worse on DSF than children in regular education. A higher FS-IQ was associated with higher digit span scores. Inclusion of DSB as a covariate indicated that DSB had a modulatory role on digits forwards (c-Model I). Model II (not shown in the table) added the time-related epilepsy variables, AOE and duration of epilepsy up to

testing. Age at onset of epilepsy had a significant negative relation with the span task, indicating that a somewhat younger age at onset was associated with higher DSF scores. Model fit was not improved relative to Model I. Inclusion of the covariate DSB (c-Model II) led to an improved model fit. Both AOE as well as duration of epilepsy were significant. Negative values suggested that younger AOE and shorter duration were associated with higher DSF scores. The interaction term AOE * duration was also entered, and the model was called Model II-a. Only AOE remained significant. Model fit of c-Model II-a was not significant better than c-Model II. Model III added variables related to severity of the epilepsy. None of these epilepsy variables were significant. Model IV included variables for seizure type, lateralization, and localization of seizures. Marginally significant values emerged for temporal ($p = 0.084$) and occipital ($p = 0.064$) lobe seizures, but the model fit was not improved, possibly suggesting a modest role for topographical localization of seizure onset. In the next step, the interactions of localization with age and with lateralization were included. Interactions of localization with age (Model IV-a) showed a significant interaction of occipital lobe with age. Again, the model was not improved. Interactions of localization with LH (Model IV-b) led to significant values for occipital with LH as well as central brain areas with LH and improved model fit both without and with the covariate backward span (Table 4). The negative values suggested that left occipital and, less clearly, left central involvement were associated with worse performance on DSF. In the Model IV-b, special education, lower FS-IQ, late onset of seizures, and left occipital and left central seizures were associated with lower scores on DSF. These results were modulated by the DSB task, such that in c-Model IV-b, later onset of seizures, left occipital onset seizures, and lower scores on DSB (but no longer special education, low FS-IQ, or left central seizures) were associated with lower scores on DSF.

Further inspection of the data suggested that five children had occipital left hemisphere involvement. Mean standardized DSF for this subsample was indeed particularly low. Given an overall mean on standardized DSF of 8.3 ($SD = 2.8$) for the 314 children with epilepsy, the sample with left occipital seizures had a mean = 3.8 ($SD = 3.8$). Such a deficiency was not seen on DSB (overall mean = 7.9, $SD = 3.0$; mean for left occipital seizures = 7.2, $SD = 4.3$). Central involvement was seen in 11 children (mean DSF = 6.6; $SD = 2.6$; mean DSB = 6.2 $SD = 3.4$).

4.4.2. DSB

The analogous procedure with generalized linear models for DSB is presented in Table 4. Model I and c-Model I showed significant values for special education and FS-IQ. The covariate also made a significant contribution, providing a better model fit. Model II added the time-related epilepsy variables. Improvement of Model fit was seen after inclusion of the interaction term (Model II-a); there was a positive association between AOE and DSB. Inclusion of the covariate (c-Model II) showed significant positive terms for AOE and duration of epilepsy. The positive terms suggested that older age at onset as well as longer duration would be associated with higher DSB. Inclusion of the interactive term (c-Model II-a), however, indicated that older AOE was associated with higher DSB and that there was also a significant interaction effect, while duration was no longer significant. The c-Model II provided better a fit than c-Model I; c-Model II-a had a better fit than c-Model II.

Beyond c-Model II-a (Table 4), no other epilepsy variable significantly predicted DSB. Model II-a and c-Model II-a were retained as the models providing the best fit for the data. Model II-a showed that special education, low FS-IQ, and the interaction AOE * duration of epilepsy were associated with low scores on DSB. After the inclusion of the forward span task (c-Model II-a), special education, FS-IQ, and AOE * duration were retained; in addition, early AOE and low DSF, were associated with lower DSB.

After inspection of the data (2 * 2 table of early versus late onset, short versus long duration, using means as cut-off values), the

Table 4

Results of generalized linear models on the sample with epilepsy. First, second and last models, with and without “other” digit span task as covariate.

		Digit span forwards				Digit span backwards			
		b	S.E.	p	95% C.I.	b	S.E.	p	95% C.I.
Model I	Intercept	7.59	0.90	<0.001	5.8; 9.4	7.34	0.99	<0.001	5.4; 9.3
	Sex (male)	−0.26	0.31	0.401	−0.9; 0.3	−0.15	0.34	0.650	−0.8; 0.5
	Special education	−1.49	0.49	0.003	−2.5; −0.5	−1.69	0.54	0.002	−2.7; −0.6
	Parental education	0.29	0.20	0.134	−0.1; 0.7	0.27	0.21	0.207	−0.2; 0.7
	FS-IQ	0.53	0.20	0.009	0.1; 0.9	0.68	0.22	0.002	0.2; 1.1
	Deviance	2223.8				2654.3			
c-Model I	AIC	1517.8				1573.3			
	Intercept	5.11	0.91	<0.001	3.3; 6.9	4.29	1.01	<0.001	2.3; 6.3
	Sex (male)	−0.21	0.29	0.469	−0.8; 0.4	−0.05	0.31	0.877	−0.7; 0.6
	Special education	−0.92	0.47	0.048	−1.8; 0.01	−1.09	0.51	0.032	−2.1; −0.1
	Parental education	0.20	0.18	0.267	−0.2; 0.6	0.15	0.20	0.447	0.2; 0.5
	FS-IQ	0.30	0.18	0.111	−0.1; 0.7	0.46	0.21	0.026	0.1; 0.9
Model II-a	Span task DSB/DSF	0.34	0.05	<0.001	0.2; 0.4	0.40	0.06	<0.001	0.3; 0.5
	Deviance	1922.6				2294.8			
	AIC	1474.1				1529.6			
	Intercept	8.86	0.28	<0.001	8.3; 9.4	8.19	0.30	<0.001	7.6; 8.8
	Sex (male)	−0.26	0.31	0.394	−0.9; 0.3	−0.08	0.33	0.798	−0.7; 0.6
	Special education	−1.58	0.49	0.001	−2.5; −0.6	−1.71	0.53	0.001	−2.8; −0.7
c-Model II-a	FS-IQ	0.62	0.20	0.002	0.2; 1.0	0.70	0.01	0.001	0.3; 1.1
	Age at onset	−0.13	0.06	0.039	−0.3; −0.01	0.10	0.01	0.164	−0.04; 0.2
	Duration of epilepsy	−0.11	0.08	0.151	−0.3; 0.04	0.005	0.08	0.957	−0.2; 0.2
	AOE * duration	0.01	0.02	0.557	−0.05; 0.03	−0.06	0.02	0.005	−0.1; −0.02
	Deviance	2209.4				2569.0			
	AIC	1519.7				1567.1			
Model IV-b	Intercept	5.91	0.47	<0.001	5.0; 6.8	4.47	0.57	<0.001	3.4; 5.6
	Sex (male)	−0.23	0.28	0.414	−0.8; 0.3	0.02	0.30	0.935	−0.6; 0.6
	Special education	−0.96	0.46	0.036	−1.9; −0.1	−1.05	0.50	0.035	−2.0; −0.1
	FS-IQ	0.37	0.19	0.051	−0.001; 0.7	0.44	0.2	0.031	0.04; 0.8
	Age at onset	−0.17	0.06	0.005	−0.03; −0.003	0.15	0.06	0.018	0.03; 0.3
	Duration of epilepsy	−0.11	0.07	0.114	−0.3; −0.1	0.05	0.08	0.507	−0.1; 0.2
c-Model IV-b	AOE * duration	0.01	0.02	0.589	0.03; 0.04	−0.05	0.02	0.005	−0.1; −0.02
	Span task DSB/DSF	0.36	0.05	<0.001	0.3; 0.5	0.42	0.06	<0.001	0.3; 0.5
	Deviance	1874.9				2180.0			
	AIC	1470.2				1517.5			
	Intercept	8.89	0.28	<0.001	8.3; 9.4				
	Sex (male)	−0.20	0.30	0.498	−0.8; 0.4				
Model IV-b	Special education	−1.41	0.49	0.004	−2.4; −0.5				
	FS-IQ	0.58	0.20	0.003	0.2; 1.0				
	Age at onset	−0.13	0.06	0.031	0.3; −0.01				
	Duration of epilepsy	−0.12	0.08	0.126	−0.3; 0.03				
	AOE * duration	−0.01	0.02	0.522	−0.05; 0.02				
	Frontal * LH	0.73	0.70	0.301	0.7; 2.1				
	Temporal * LH	−0.28	0.66	0.671	−1.6; 1.0				
	Parietal * LH	0.79	1.30	0.541	−1.8; 3.3				
	Occipital * LH	−4.01	1.19	0.001	−6.3; −1.7				
	Central * LH	−2.04	0.89	0.023	−3.8; −0.3				
c-Model IV-b	Deviance	2096.0							
	AIC	1513.2							
	Intercept	5.99	0.47	<0.001	5.1; 6.9				
	Sex (male)	0.16	0.28	0.559	−0.7; 0.4				
	Special education	−0.80	0.46	0.080	−1.7; 0.1				
	FS-IQ	0.34	0.18	0.063	−0.02; 0.7				
	Age at onset	−0.17	0.06	0.004	−0.3; 0.02				
	Duration of epilepsy	−0.12	0.07	0.095	−0.3; 0.02				
	AOE * duration	0.01	0.02	0.638	−0.03; 0.04				
	Frontal * LH	0.71	0.65	0.277	−0.6; 2.0				
Model IV-b	Temporal * LH	−0.44	0.61	0.473	−1.6; 0.8				
	Parietal * LH	0.55	1.20	0.647	−1.8; 2.9				
	Occipital * LH	−3.90	1.10	<0.001	−6.1; −1.8				
	Central * LH	−1.36	0.83	0.100	−3.0; 0.3				
	Span task DSB/DSF	0.35	0.05	<0.001	0.3; 0.4				
	Deviance	1781.8							
c-Model IV-b	AIC	1464.2							

Note. S.E. = standard error. Model: model without other span task as covariate. c-Model: model with other span task as covariate. Span task DSB/DSF digit span backwards as a covariate for digit span forwards; alternatively, digit span forwards as a covariate for digit span backwards. AIC = Akaike Information Criterion. FS-IQ: full scale IQ. AOE * duration = age at onset of epilepsy by duration of epilepsy to test. Frontal * LH = frontal left hemisphere seizures.

results suggest that early age at onset was associated with lower WM scores but was influenced by the duration of the seizure condition. Children who developed epilepsy at an early age and were tested after a short time interval were most prone to show low WM scores; those

tested after a longer time interval had slightly higher scores. Children who developed epilepsy at a later age did overall better, but scores decreased slightly with longer duration of epilepsy compared with short duration.

5. Discussion

Cross-sectional comparison of $n = 314$ children with epilepsy and $n = 327$ typically developing children in ages ranging from 5 to 15 years revealed age-related gains over time in STM and WM capacity. The study highlighted similar developmental trajectories for both groups; and prevailing WM difficulties in children with epilepsy.

5.1. The developmental trajectory

Short-term memory capacity was overall limited [29], and so was its growth over time. A relatively well-developed STM capacity was already seen in the youngest children; some moderate gains were seen over time in an overall linear trajectory, as described earlier [11,17]. Analysis of the effect of age-related increases in WM showed that the development of STM was influenced by the gains in WM capacity; beyond those effects, no clear age-related growth emerged in STM.

For WM, a linear development had been suggested earlier for typically developing children [11], followed by a deceleration in an older age range [18]. The present data also provided evidence for a linear progressive development, adding to the knowledge that it also applies to children with epilepsy. In addition, a development with a higher rate of growth in the younger ages, and leveling off later on (quadratic), was also seen in both groups, followed by an increased rate of growth later on up to age 15 years (cubic term).

5.2. WM and general abilities

Information processing models together with psychometric research indicate that WM and general cognitive abilities (i.e., general intelligence) are highly interrelated. Moreover, it has been proposed that WM potentially exerts a strong causal effect on general intelligence (see [15] for an overview). This may also be true for clinical samples. Indeed, a study comparing control children with children with temporal lobe epilepsy without learning problems indicated that while the samples did not differ in STM or WM regardless of IQ, a significant association between WM (but not STM) and IQ could be seen in the clinical sample [36]. The results of the present study confirmed that there was a significant (albeit small to moderate) correlation between WM and IQ. The finding that WM is impaired in children with epilepsy relative to control children beyond the differences in IQ suggested partial independence between the measure of IQ and the WM measure.

5.3. Epilepsy variables

Except for epilepsy from posterior brain areas, which was associated with lowered STM, the epilepsy variables studied were not significantly associated with memory span. In particular, and contrary to the hypothesis, frontal lobe involvement of the seizures, alone or in interaction with age or brain side, was not found to be preferentially associated with WM problems. This result lends additional support to studies indicating that WM, as operationalized in this study, engages multiple brain areas bilaterally [16,20] and that disruptions of normal brain activity in any brain area may lead to WM problems. In the same line of thought, the present results are also consistent with the notion that in epilepsy in children, focal frontal seizures seldom limit themselves to a single brain area but may impact distant interconnected brain areas [37].

5.4. Timing of epilepsy

Earlier studies have already recognized that the detrimental effect of early onset of epilepsy on cognitive functions may be mediated by other factors like response to AEDs, duration of the epilepsy, and type of cognitive area assessed [28,38,39]. In the present study, early AOE was associated with relatively well-preserved STM abilities, while at the same time it was associated with low WM abilities. This result suggests

an independent development of STM and WM in the early school years, with an age-appropriate development of STM and a disrupted development of WM.

The finding that STM and WM show different trajectories over time, confirms that the two tasks should be studied independently. The relationship between time-related epilepsy variables and memory span may be intricate and may depend on task, age at epilepsy onset, as well as duration of the seizure condition. The impact on WM was largest in the younger children with epilepsy in the early years of the seizure condition; in children with older age at onset, deficiencies in WM were smaller but remained stable or increased later on. These results imply that the timing of the epilepsy and its subsequent course may affect the trajectory of the cognitive development. An adult study on early versus late onset of the epilepsy validated this proposal [40]. These authors proposed a different mechanism in earlier onset of epilepsy, when brain-related changes may be at stake, versus epilepsy of later onset, when other factors, like adjustment to the seizure condition, may impact on cognitive measures. The time-related differences may be one of the factors contributing to the struggles young children experience in the early school years; but this may also partly explain secondary school failures as often experienced by adolescents with later onset of seizures [41]. Working memory deficiencies may decrease somewhat over time, possibly suggesting amelioration due to better seizure control over time, even if the epileptic condition persists, but this may be particularly true for the younger children, that is the children with younger onset of epilepsy.

5.5. Limitations and strengths of the study

The typically developing children showed an “atypical” peak at age 9 years in STM, suggesting a temporary developmental spurt, not associated with differences in sex or IQ. A group-by-age interaction was seen which disappeared when the 9-year-old children were removed from the sample. The peak was interpreted as a random fluctuation, as seen more often when data are collected from typically developing children [17], but its meaning is not fully understood.

The sample of children with epilepsy comprised a heterogeneous referred group, and results are limited to children with epilepsy and close to normal IQs for whom neuropsychological assessment was required. The sample may nevertheless be understood as being fairly representative for children with epilepsy, given that children with epilepsy are likely to be referred as they frequently experience developmental and scholastic difficulties [4].

The present study relied solely on DSF and DSB as measures of memory. Although commonly used, other measures have also been suggested [19]. Independent of the specific task materials used, however, verbal memory has been found compromised in children with learning difficulties [13]. The results, however, are limited to STM and WM as measured with a verbal-numerical task and need not generalize to tasks with other modes of presentation or higher memory loads.

A major strength of the study is that better insight is provided into the developmental aspects of STM and WM in children with epilepsy and typically developing children, as well as in the differential impact of timing in epilepsy. In addition, another strength of this study is that Dutch norm data on the development of DSF and DSB are presented – up to now lacking in the WISC-III^{NL} manual.

5.6. Implications

The developmental lag in WM of about 2 years should have consequences for provisions offered at school to children with epilepsy. Provisions could be similar to those suggested for children with specific learning disabilities [42]. To adjust WM load in school tasks, training to proficiency of lower-order subtasks should be pursued, in such a way that children can rely on them in an automatic manner when they turn to the next level of a task (e.g., sound blending should be mastered

at the time of initial reading; quadratic terms from multiplication tables should be mastered before Pythagorean Theorem comes up). Measures should be taken particularly in the early school years and in the early years of the epileptic conditions; close follow-up of older children with epilepsy is also recommended.

Ethical statement

The authors confirm having read the position of the Journal in issues involved in ethical publication and affirm that this paper is consistent with those guidelines.

Conflict of interest statement

The authors disclose no conflicts of interest. The authors did not receive financial support for the study.

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