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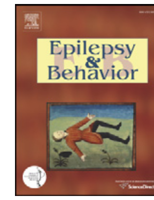

Memory in children with temporal lobe epilepsy is at least partially explained by executive dysfunction

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ABSTRACT

An association between memory and executive dysfunction (ED) has been demonstrated in patients with mixed neurological disorders. We aimed to investigate the impact of ED in memory tasks of children with temporal lobe epilepsy (TLE). We evaluated 36 children with TLE and 28 controls with tests for memory, learning, attention, mental flexibility, and mental tracking. Data analysis was composed of comparison between patients and controls in memory and executive function; correlation between memory and executive function tests; and comparison between patients with mild and severe ED in memory tests. Children with TLE had worse performance in focused attention, immediate and delayed recall, phonological memory, mental tracking, planning, and abstraction. Planning, abstraction, and mental tracking were correlated with visual and verbal memory. Children with severe ED had worse performance in verbal and visual memory and learning tests. This study showed that ED was related to memory performance in children with TLE.

1. Introduction

It is well established that patients with temporal lobe epilepsy (TLE), regardless of age, have memory impairment [1,2], especially in declarative memory. Helmstaedter [3] reviewed 1000 patients with drug/treatment-refractory TLE and showed that 70–80% had verbal or visual memory impairment. Nevertheless, there has been a growing interest in the literature regarding the relationship between neuropsychological performance and widespread neurodevelopmental brain abnormalities in TLE [4–8]. These studies are related to the need to better understand the frequent observation of a global developmental cognitive impairment, not originally expected in children with TLE [9].

Considering this scenario, there is robust evidence that, in addition to memory impairment, adults with TLE have executive dysfunction (ED) [1,10,11], characterized by a perseverative response, impaired abstraction, and problem-solving deficits [1,12]. In children and adolescents with TLE, this issue remains controversial. Although some authors have reported ED in children with TLE [12–14], others have shown that such impairment is not as severe as in other types of epilepsy [15,16]. In a previous study, using a comprehensive neuropsychological battery to evaluate children and adolescents with TLE [13], we found that there was some degree of ED in 90.32% of the patients evaluated.

The construct of executive function is heterogeneous including different conceptualizations, making it somewhat abstract and open to diverse interpretations. Here, we consider the executive functions as those metacognitive capacities that allow an individual to perceive stimuli from his or her environment, respond adaptively, flexibly change direction, anticipate future goals, consider consequences, and respond in an integrated manner, utilizing all these capacities to achieve a specific goal [17]. Thereafter, it requires the ability to plan and sequence behaviors, simultaneously attending to different sources of stimuli, problem solving, resisting distraction, control inhibition and sustaining behaviors for prolonged periods. Thus, it encompasses some aspects of perception, attention, and working memory.

Studies in primates have shown that permanent or transitory damage to the frontal cortex impairs learning abilities related to association and memory in recognition tasks [18]. In addition, studies in humans have demonstrated that integrity of frontal lobe structures results in good performance on tasks designed to evaluate the encoding phase of memory processing [19]. Although the classical patterns of amnesia are not typically seen in patients with frontal lobe lesions, such patients often fail on complex memory tasks, especially those that require temporal processing of spatial information with high levels of spatial interference or that involve contextual information [20]. Furthermore, it has been suggested that the frontal

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lobes play a role in control processes that regulate memory encoding and retrieval [21].

An association between verbal memory impairment and ED has been demonstrated in patients with distinct neurological or psychiatric disorders. Fossati et al. [22] noted a positive relationship between ED and verbal memory deficits in patients with schizophrenia. Vanderploeg et al. [23] found that some executive functions were related to verbal learning and memory in a sample of patients with neurological disorders of various etiologies. Duff et al. [24], in a similar study, demonstrated that executive functions, in general, were correlated with verbal and visual memory. Nevertheless, there have been few studies evaluating the association between executive function and memory in adults with TLE. To our knowledge, there is a lack of such studies in children and adolescents with TLE.

It is well known that integrity of executive and attentional functions is essential for memory consolidation. On the basis of this knowledge, we hypothesize that the memory impairment observed in patients with TLE is explained, in part, by ED. Up until the present time, the impact of ED in memory functioning has not been investigated in patients with TLE, especially in children and adolescents. Despite of that, Hermann et al. [25] showed that extratemporal cortices are affected in TLE, which could suggest that executive inefficiencies might not stem from temporal epileptogenic activity but rather possibly from anatomical changes in the frontal substrates related to chronic epilepsy or other factors.

In the present study, we aimed to evaluate the effect that executive function has on the memory performance of children with TLE. In addition, we attempted to determine whether individual aspects of memory are related to executive dysfunctions.

2. Material and methods

2.1. Studied population

Patients with TLE were recruited from among children and adolescents under treatment at a tertiary epilepsy center. Control subjects, composed of healthy volunteers was matched to the patients for age, sociodemographic profile, and educational background. Healthy volunteers were recruited from among students at a public school.

Exclusion criteria, applied for both patients and controls, were: an estimated IQ below 80 clinical signs of drug intoxication or systemic and metabolic disorders that could lead to cognitive impairment; alcohol or drug abuse; any neurosurgical procedure; and not currently attending school. Children with current or previous history of other neurological disorders, with moderate to severe learning disabilities, with attention deficit hyperactivity disorder, and those using psychoactive drugs that might impair neuropsychological performance were also excluded. A portion of the present sample was also examined in other already published studies [13,14].

Patients and controls, as well as their parents, were evaluated by a child psychiatrist with a structured psychiatric interview followed no more than six weeks later by the Portuguese validated version of Schedule for Affective Disorders and Schizophrenia for School-Age Children — Present and Lifetime Version (KSADS-PL) [26]. Therefore, children and adolescents with lifetime history of major psychiatric disorders (DSM-IV TR) [27] were excluded.

2.1.1. Patients

We prospectively evaluated 36 children and adolescents with TLE [47.22% males; mean age 11.78 ± 2.26 years (range, 8–16 years)]. Mean IQ, estimated on the basis of performance on the Block Design and Vocabulary subtests of the Wechsler Intelligence Scale for Children—Third Edition [28], was 99.53 ± 13.25 (range, 80–135).

Twenty-nine children (80.56%) had symptomatic TLE, defined as a lesion restricted to the mesial or lateral temporal lobe region, as demonstrated by 1.5-T MRI. The symptomatic TLE group was made up by (1) mesial TLE group with 22 children (75.86%) — 19 with hippocampal sclerosis, two with a tumor, and one with gliosis on the parahippocampal gyrus and by (2) lateral TLE group with seven children (24.14%) — three with dysplasia, one with cysts, two with a tuber, and one with a cavernoma.

Seven children (19.44%) had cryptogenic TLE determined by concordant interictal and ictal findings (VEEG). Children with extratemporal epileptiform discharges were excluded.

The mean age at epilepsy onset was 4.58 ± 3.34 years, and the mean duration was 6.70 ± 3.07 years. Nineteen children (52.78%) had drug/treatment-refractory TLE and, at the time of evaluation, 17 (47.22%) had TLE that was well controlled (seizure-free for at least six months prior to the cognitive assessment). There were 25 children (69.44%) under monotherapy, eight (22.22%) under polytherapy, and three (8.33%) with no pharmacotherapy. Demographic and clinical data are summarized in Table 1.

2.1.2. Controls

The control group was composed of 28 healthy children and adolescents (32.14% males). The mean age was 11.96 ± 2.30 years (range, 9–16 years). The mean IQ was 109.39 ± 13.95 (range, 83–135).

2.2. Methods

Children were included after a written consent was obtained with parents or caretakers. This protocol was approved by the Ethics Committee of the University of São Paulo and of the University of Campinas.

Neuropsychological evaluations were performed at least 48 h after the last seizure. Three patients had seizures during testing and were re-evaluated one week later. The tests were administered by two trained neuropsychologists in a quiet laboratory setting and in

Table 1
Clinical description of the temporal lobe epilepsy patient group.

Clinical variable	Values
Age at onset, mean (SD)	4.58 (3.34)
Epilepsy duration, mean (SD)	6.70 (3.07)
Lesion laterality[a]	
Right, n (%)	17 (58.62)
Left, n (%)	10 (34.48)
Bilateral, n (%)	2 (6.90)
Status epilepticus	
Present, n (%)	9 (25)
Absent, n (%)	27 (75)
Family history	
Present, n (%)	21 (58.33)
Absent, n (%)	15 (41.67)
Febrile seizures	
Present, n (%)	9 (25)
Absent, n (%)	27 (75)
Seizure frequency	
No seizures, n (%)	17 (47.22)
Daily, n (%)	9 (25)
Weekly, n (%)	7 (19.44)
Monthly, n (%)	2 (5.56)
Bi-annually, n (%)	1 (2.78)
Number of AEDs	
No medication, n (%)	3 (8.34)
Monotherapy, n (%)	25 (69.44)
Combination therapy, n (%)	8 (22.22)
Seizure type	
SPS, n (%)	3 (8.34)
CPS, n (%)	11 (30.56)
SPS, CPS, n (%)	13 (36.11)
CPS, GTC, n (%)	4 (11.11)
SPS, CPS, GTC, n (%)	5 (13.88)

AEDs: antiepileptic drugs; SPS: simple partial seizure; CPS: complex partial seizure; and GTC: generalized tonic clonic seizure.

[a] Laterality was defined on the basis of neuroimaging and neurophysiological data.

a standard sequence. Evaluations were conducted over the course of two sessions, in which a battery of executive and memory function tests were administered (for a review see [17,29,30]) (Fig. 1).

2.3. Statistical analysis

1. The homogeneity of samples was verified using Student's *t*-test or chi-square test, as appropriate. In order to compare performance on memory tests and executive function tests, we applied analysis of covariance (ANCOVA), using IQ and age as covariates. We used Pearson's correlation coefficient to identify correlations between memory test results and results of tests of specific executive functions in patients and controls.
2. Regression analysis was used to controlling for multiple comparisons in order to decrease the risk of type I error. Therefore, when correlation between two tests had statistical significance, we used a linear regression analysis with the dependent variables (memory test results) and independent variables (executive test results and IQ) entered simultaneously. Intelligence quotient was included as an independent variable in order to control for confounding factors.
3. Patients were divided into 2 groups, based on their performance on executive tests: mild to moderate ED and severe ED. Impaired performance on tests of executive function was defined as scoring lower than controls by at least 1 SD. Patients who were 1 SD below controls on no more than 4 executive function tests were categorized as being in the mild to moderate ED group, and those who were 1 SD below controls on 5 or more executive function tests were classified as being in the severe ED group. We used ANCOVA to compare the two groups in terms of their performance on memory function tests, again using IQ and age as covariates.
4. In order to evaluate the impact of IQ on executive function tests, two analyses were done: (i) IQ scores of patients with mild/moderate ED and severe ED were compared using the ANCOVA with age as a covariate, and (ii) a Pearson's correlation was used evaluating the association between IQ and each executive function test (for patients and controls separately), followed by a regression analysis of those pairs significantly correlated with the Pearson's correlation analysis, with the memory test as the dependent variable and executive function tests and IQ as the independent variables.
   Since Story Memory and Verbal Learning and Visual Learning subtests of Wide Range Assessment of Memory and Learning (WRAML) have different presentations for children under and above 9 years old, we excluded the data from those tests of two 8-year-old children [31].
   Raw scores of WRAML were used in all analyses since there is no normative data of this test for the Brazilian population. The level of significance was set at $\alpha = 0.05$ for all analyses with the exception of the correlation analysis, in which it was set at $\alpha = 0.01$ in order to correct for multiple comparisons [24].
5. In addition, a stepwise linear regression analysis with the dependent variables (memory function test results) and independent variables (executive function test results and IQ) was used to investigate which executive function test better predicted memory performance. This analysis was done separately for patients and controls.

Focused attention	
1. Digit Span (WISC-III)	Auditory attention for numbers and short-term retention capacity
2. Number /Letter (WRAML)	Auditory attention for numbers and letters and short-term retention capacity
3. Finger Windows (WRAML)	Visual attention and short-term retention capacity
Divided attention	
4. Trail Making Test (TMT), parts A and B for children	Complex visual scanning, visual scanning speed, visual attention, mental flexibility, and inhibitory control
Mental Flexibility and Concept Formation	
5. Wisconsin Card Sorting Test (WCST)	Abstract behavior, set shifting, response inhibition, and mental flexibility at the cognitive level
Selective Attention	
6. Matching Familiar Figures Test	Selective attention and impulse control
Mental tracking for Semantic Information	
7. Category Fluency	Verbal fluency in categories (animals and foods) in terms of semantics, initiation, and scanning for mental information
Episodic Memory	
8. Story Memory (WRAML)	Recall of two short but detailed stories immediately after hearing it (immediate recall) and 30 minutes later (delayed recall), as well as with a multiple-choice questionnaire (recognition)
9. Picture Memory (WRAML)	Identification of items that have been altered when a picture is compared with a very similar picture shown immediately before
10. Design Memory (WRAML)	The drawing of four cards designs from memory
Phonological Memory	
11. Sentence Memory (WRAML)	Performance on a sentence repetition task presenting sentences of increasing length and complexity
Learning	
12. Verbal Learning (WRAML)	Performance on a word list recall task with 4 immediate lists of 16 words each and after 30 minutes (delayed recall)
13. Visual Learning (WRAML)	Visuospatial placement of 14 simple designs in 4 immediate trials and after 30 minutes (delayed recall)

Fig. 1. Cognitive functions evaluated and respective neuropsychological tests used.

Table 2
Memory function test results.

Test	TLE Patients (n = 36)	Controls (n = 29)	F[a]	P	Cohen's d
Picture Memory	22.50 (5.58)	23.32 (5.91)	0.10	0.377	0.143
Design Memory	33.50 (9.66)	38.54 (8.64)	1.59	0.106**	0.550
Story Memory					
Immediate	23.68 (8.53)	29.61 (9.49)	**2.59**	**0.057***	**0.657**
Delayed	19.48 (8.74)	25.18 (10.65)	1.59	0.106	0.585
Sentence Memory	14.86 (5.37)	20.32 (6.25)	**10.11**	**0.001***	**0.937**
Verbal Learning					
Processing	37.06 (8.71)	38.61 (10.06)	0.183	0.336	0.165
Recall	1.39 (2.50)	0.86 (1.74)	0.172	0.340	0.246
Visual Learning					
Processing	24.48 (12.04)	28.11 (9.20)	0.148	0.351	0.339
Recall	0.75 (1.19)	0.15 (1.32)	**5.608**	**0.011***	**0.477**
Recognition	10.00 (3.53)	11.43 (1.99)	0.797	0.186	0.499

Results expressed as mean (SD).
TLE: temporal lobe epilepsy.
[a] IQ and age were used as covariates in the ANCOVA.
* refers to significant finding.
** refers to trend toward significance.

For statistical analysis, we used the Statistical Package for the Social Sciences, version 14.0 for Windows (SPSS Inc., Chicago, IL, USA), as well as the open-source software R.2.10.1.

3. Results

No statistical differences were observed between patients and controls regarding gender [$x^2 = 2.25$; p = 0.134], age [t = 0.33; p = 0.746], or years of formal education [t = 1.30; p = 0.199]. Mean IQ was significantly lower in the patient group [t = 2.89; p = 0.005].

When comparing patients with mild/moderate and severe ED, we observed that patients with severe ED were younger [t = 2.87; p = 0.007], had less formal education [t = 4.94; p < 0.001], had an earlier age of seizure onset [t = 4.75; p < 0.001], and a longer duration of epilepsy [t = −3.12; p = 0.004]. There were no differences between patients with mild/moderate and severe ED in gender [$x^2 = 0.89$; p = 0.345], history of *status epilepticus* [$x^2 = 0.02$; p = 0.886], family history of epilepsy [$x^2 = 1.08$; p = 0.298], history of febrile seizure [$x^2 = 0.02$; p = 0.886], frequency of seizures [$x^2 = 1.59$; p = 0.207], seizure control [$x^2 = 0.23$; p = 0.632], number of AEDs [$x^2 = 1.94$, p = 0.379], and secondary generalization of seizures [$x^2 = 0.09$; p = 0.763].

3.1. Memory tests

Children with TLE had a worse performance in terms of immediate recall of Story Memory (F = 3.24; p = 0.039) and WRAML Sentence Memory subtest (F = 10.11; p = 0.001), and in terms of delayed recall of Visual Learning (F = 5.61; p = 0.011). Therefore, patients had deficits in episodic memory for verbal and visual materials and in phonological memory.

There were no differences between the two groups in terms of episodic memory for visual material, learning, or recognition memory (Table 2).

3.2. Executive function tests

Children and adolescents with TLE had worse performance on the following executive tests: number of errors in TMT part B (F = 4.69; p = 0.018); WCST number of categories (F = 4.85; p = 0.016) and number of non-perseverative errors (F = 2.74; p = 0.052); Verbal Fluency for foods (F = 3.09; p = 0.042), and Number/Letter Memory (F = 6.83; p = 0.006). This indicates that the patients had deficits in attention (focused and divided), mental tracking for semantic information, and concept formation.

There were no differences between the two groups for mental control, selective attention, or mental flexibility (Table 3).

Table 3
Executive function test results.

Test	TLE patients (n = 36)	Controls (n = 29)	F[a]	P	Cohen's d
Digit Span Forward	6.86 (1.73)	7.79 (1.73)	1.88	0.088	0.538
Digit Span Backward	4.57 (1.96)	4.82 (1.19)	0.55	0.230	0.154
Matching Familiar Figures Test					
Errors	19.50 (10.59)	13.93 (8.19)	1.62	0.104	0.588
Time	223.77 (122.24)	238.14 (154.88)	0.01	0.489	0.103
Total	3416.15 (1904.03)	2582.96 (1539.89)	1.57	0.108	0.481
Trail Making Test					
Part A, time	35.64 (37.21)	26.36 (12.29)	0.36	0.276	0.335
Part A, errors	0.18 (0.47)	0.04 (0.19)	1.31	0.129	0.391
Part B, time	59.53 (25.09)	48.29 (27.44)	2.02	0.081	0.428
Part B, errors	0.50 (0.80)	0.11 (0.32)	**4.69**	**0.018***	**0.64**
Wisconsin Card Sorting Test					
Number of categories	4.43 (2.69)	6.67 (2.37)	**4.85**	**0.016***	**0.884**
Perseverative errors	26.11 (17.42)	19.44 (10.65)	0.18	0.328**	0.462
Non-perseverative errors	26.09 (16.74)	18.26 (10.10)	**2.74**	**0.052***	**0.566**
Perseverative responses	30.83 (23.94)	23.22 (13.16)	0.04	0.420	0.394
Failure to maintain set	1.23 (1.26)	0.74 (0.81)	2.01	0.081	0.464
Verbal Fluency					
Animals	13.00 (4.60)	14.61 (5.29)	0.38	0.271	0.325
Foods	11.17 (4.19)	13.86 (4.66)	**3.09**	**0.042***	**0.607**
Finger Windows	13.81 (4.97)	15.36 (4.16)	0.14	0.358	0.338
Number/Letter Memory	7.78 (3.19)	11.11 (4.86)	**6.83**	**0.006***	**0.810**

Results expressed as mean (SD).
TLE: temporal lobe epilepsy.
[a] IQ and age were used as covariates in the ANCOVA.
* refers to significant finding.
** refers to trend toward significance.

Table 4
Significant results of regression analysis.

		Memory Tests[a]											
		Picture Memory			Design Memory			Story Memory I			Sentence Memory		
		R^2	t	p	R^2	t	p	R^2	t	p	R^2	t	p
Executive tests	NL	0.234	2.87	**0.007***							0.424	4.42	<**0.001***
	DS back				0.487	4.14	<**0.001***	0.346	3.02	**0.005***	0.369	3.81	**0.001***
	MFFT e				0.437	3.50	**0.001***						
	TMTB				0.366	3.06	**0.006***						
	WCST PE				0.354	2.66	**0.012***						
	WCST RP				0.340	2.49	**0.018***						

NL: Number and Letter, DS back: Digit Span Backward; MFFT e: Matching Familiar Figures Test errors; TMT B: Trail Making Test part B; WCST PE: Wisconsin Card Sorting Test perseverative errors; and WCST PR: Wisconsin Card Sorting Test perseverative responses.
[a] IQ was used as an independent variable.

3.3. Association between memory processes and executive functions

Digit Span Backward was correlated with Design Memory ($t=4.14$; $p<0.001$); with Story Memory, immediate recall ($t=3.02$; $p=0.005$); and with Sentence Memory ($F=3.81$; $p=0.001$).

Number/Letter Memory was correlated with Picture Memory ($t=2.87$; $p=0.007$) and Semantic Memory ($t=4.42$; $p<0.001$).

Design Memory performance was determined by MFFT errors ($t=3.50$; $p=0.001$) and time to complete the TMT part B ($t=3.06$; $p=0.006$); number of perseverative errors ($t=2.66$; $p=0.012$); and number of perseverative responses ($t=2.49$; $p=0.018$) of Wisconsin Card Sorting Test.

Results of executive function tests were not significantly correlated with memory tests when we used $\alpha=0.01$ and corrected for differences in IQ. The significant results of the regression analysis are in Tables 4 and 5.

In the control group, Picture Memory was correlated with number of errors in TMT part B ($r=-0.51$, $R^2=0.30$, $t=2.54$, $p=0.019$). Design Memory was correlated with TMT part A ($r=-0.50$, $R^2=0.25$, $t=2.69$, $p=0.013$) and part B ($r=-0.51$ $R^2=0.27$, $t=2.82$, $p=0.010$). Verbal Learning was correlated with Verbal Fluency for foods ($r=0.71$, $R^2=0.52$, $t=5.14$, $p<0.001$). Immediate recall of Story Memory was correlated with Verbal Fluency for foods ($r=0.49$, $R^2=0.26$, $t=2.74$, $p=0.011$), and Sentence Memory was correlated with Number/Letter Memory ($r=0.61$, $R^2=0.40$, $t=3.99$, $p=0.001$).

Pearson's correlation between memory function tests and other executive function tests did not reach the α level of 0.010.

3.4. Relationship between executive functions and memory determined by Stepwise Regression Analysis

Stepwise Regression Analysis results of each memory test with executive functions are shown in Tables 1 and 2 (Supplemental material).

For patients, Trail Making Test part B (number of errors) and Verbal Fluency for foods were the tests that impacted the most memory performance (predicted the performance of three memory tests each). Some executive tests were not associated with memory tests: Digit Span Forward; Matching Familiar Figures Test time and Total score; Trail Making Test part A (time and number of errors) and part B (time); Wisconsin Card Sorting Test number of non-perseverative errors and number of perseverative responses; Verbal Fluency for animals; and Finger Windows Test.

As to controls, Verbal Fluency for foods was the test that impacted the most memory performance (predicted the performance of six memory tests). Some executive tests also were not associated with memory tests: Digit Span Forward; Trail Making Test part A (number of errors) and part B (time); all subtests of Wisconsin Card Sorting Test; Verbal Fluency for animals; and Finger Windows Test.

Table 5
Pearson's correlations between executive functions and memory test results in patients with temporal lobe epilepsy.

Variable	Picture M.	Design M.	Story M. I	Story M. II	Recogn	Sentence M.	Verbal L. I	Verbal L. II	Visual L. I	Visual L. II
DSF	0.246	0.405	0.095	−0.008	−0.361	0.312	0.156	0.400	0.115	0.256
DSB	0.397	**0.703**[a]	**0.519**[a]	0.474	0.004	**0.582**[a]	**0.497**[a]	−0.265	**0.602**[a]	0.010
F.Windows	0.309	**0.489**[a]	0.326	0.162	−0.127	**0.518**[a]	0.450	0.198	0.377	−0.060
N/Letter	**0.490**[a]	0.409	0.239	−0.005	−0.348	**0.540**[a]	0.298	0.435	0.218	0.404
MFFT errors	−0.220	**−0.631**[a]	−0.360	−0.466	0.068	−0.317	−0.372	0.087	**−0.542**[a]	−0.024
MFFT time	0.200	**0.613**[a]	0.292	0.322	−0.239	0.297	0.180	−0.170	**0.539**[a]	−0.163
MFFT total	−0.259	0.025	−0.071	−0.008	−0.314	−0.301	−0.148	−0.273	−0.134	−0.420
TM A time	−0.272	**−0.561**[a]	−0.314	−0.150	0.164	**−0.515**[a]	−0.403	−0.264	−0.292	−0.179
TM A errors	−0.308	−0.244	−0.264	−0.151	−0.190	−0.399	−0.107	−0.015	−0.386	0.037
TM B time	−0.166	**−0.576**[a]	−0.412	−0.333	0.197	−0.455	−0.395	−0.205	−0.212	0.092
TM B errors	−0.104	−0.187	−0.168	−0.040	0.355	0.178	−0.196	−0.218	0.121	−0.014
WCST (cat)	0.459	**0.518**[a]	0.411	0.359	−0.020	0.390	0.432	−0.068	**0.548**[a]	0.096
WCST (PE)	**−0.486**[a]	**−0.551**[a]	−0.329	−0.267	0.259	−0.214	−0.366	0.154	**−0.507**[a]	0.103
WCST (NPE)	−0.331	−0.181	−0.293	−0.226	−0.284	−0.348	−0.131	−0.223	−0.320	0.033
WCST (PR)	−0.472	**−0.541**[a]	−0.309	−0.258	0.288	−0.180	−0.352	0.173	−0.468	0.102
WCST (FS)	0.233	0.068	−0.024	−0.050	−0.068	−0.212	0.043	0.334	−0.029	−0.369
VF animal	0.211	**0.545**[a]	0.304	0.297	−0.005	**0.630**[a]	0.477	−0.122	**0.580**[a]	−0.066
VF foods	0.272	**0.579**[a]	**0.517**[a]	**0.486**[a]	−0.065	**0.649**[a]	**0.578**[a]	−0.233	0.471	0.285

DSF: Digit Span Forward; DSB: Digit Span Backward; MFFT: Matching Familiar Figures Test; TM: Trail Making Test; WCST: Wisconsin Card Sorting Test; WCST (cat): Wisconsin Card Sorting Test (number of categories); WCST (PE): Wisconsin Card Sorting Test (perseverative errors); WCST (NPE): Wisconsin Card Sorting Test (non-perseverative errors); WCST (PR): Wisconsin Card Sorting Test (perseverative responses); WCST (FS): Wisconsin Card Sorting Test (failure to maintain set); VF: Verbal Fluency Test; Picture M.: Picture Memory; Design M.: Design Memory; Story M I: Story Memory Immediate Recall; Story M II; Story Memory Delayed Recall; Recogn: Recognition; Sentence M: Sentence Memory; Verbal L I: Verbal Learning Immediate Recall; Verbal L II: Verbal Learning Delayed Recall; Visual L I: Visual Learning Immediate Recall; and Visual L. II: Visual Learning Delayed Recall.
[a] Refers to statistically significant differences

Table 6
Effects of executive dysfunction (mild/moderate vs. severe) on memory test results.

Test	Degree of dysfunction		F[a]	P	Cohen's d
	Mild/moderate (n=12)	Severe (n=24)			
Picture Memory	25.25 (4.09)	21.13 (5.78)	**3.64**	**0.034***	**0.82**
Design Memory	42.58 (5.88)	28.96 (7.81)	**11.62**	**0.001***	**1.97**
Story Memory					
Immediate	29.92 (5.07)	20.27 (8.15)	**9.410**	**0.002***	**1.43**
Delayed	25.17 (5.98)	16.24 (8.50)	**5.958**	**0.011***	**1.22**
Sentence Memory	19.58 (3.58)	12.39 (4.43)	**10.99**	**0.001***	**1.79**
Verbal Learning					
Processing	42.50 (7.15)	34.09 (8.14)	**8.627**	**0.003***	**1.10**
Recall	1.33 (1.83)	1.42 (2.89)	0.236	0.316	0.04
Visual Learning					
Processing	30.42 (11.41)	21.10 (11.28)	2.199	0.075	0.82
Recall	0.92 (1.16)	0.65 (1.23)	0.001	0.498	0.23
Recognition	10.00 (2.45)	10.00 (4.10)	0.186	0.335	0.00

Results expressed as mean (SD).
[a] IQ and age were used as covariates in the ANCOVA.

3.5. Severity of executive dysfunction and memory performance

Patients with severe ED had a worse performance than those with mild to moderate ED on Picture Memory (F = 3.64; p = 0.034); Design Memory (F = 11.62; p = 0.001); Story Memory, immediate recall (F = 5.76; p = 0.012); Story Memory, delayed recall (F = 3.56; p = 0.001); Sentence Memory (F = 10.99; p = 0.001); and Verbal Learning (F = 3.66; p = 0.033) (Table 6).

3.6. Association between IQ and executive function tests

Patients with mild and moderate ED (mean = 104.5, SD = 11.49) had a trend to a significantly higher IQ score than patients with severe ED (mean = 97.04, SD = 13.59; F = 4.03, p = 0.053).

In the patient group, IQ was significantly associated with WCST categories achieved (r = 0.60, R^2 = 0.41, t = 4.51, p < 0.001); number of perseverative errors (r = −0.51, R^2 = 0.28, t = 3.44, p = 0.002), and number of perseverative responses (r = −0.48, R^2 = 0.23, t = 3.10, p = 0.004).

Pearson's correlation between IQ and other executive function tests did not reach the α level of 0.010.

In the control group, IQ was not significantly associated with any executive function test when the α level was set to 0.010.

4. Discussion

This study demonstrated that some aspects of memory and executive functions are impaired in children and adolescents with TLE and that the presence of an executive dysfunction was highly associated with impaired performance on some memory tests.

Children with temporal lobe epilepsy exhibited deficits in immediate and delayed recall of episodic memory, for verbal stimuli and for phonological memory, in agreement with earlier studies that showed impaired immediate recall of verbal material [32] and impaired delayed recall, suggesting deficits in long-term memory storage [33,34]. However, these findings are in contrast with those showing that immediate recall is not impaired in children and adolescents with TLE [35] or that only delayed recall is compromised [33,34]. We attribute these distinct results to methodological differences between studies. Other studies involved samples with adults [3,33,34] and evaluated different groups in their comparison such as patients with temporal lobe and frontal lobe epilepsy [33,34]. In our work, we used a battery developed to study distinct aspects of memory, using 10 subtests that assess immediate and delayed recall for verbal and visual stimuli, besides including a test for phonological memory. In addition, we avoided the use of tests applied to adults, choosing only those designed specifically for childhood. The use of tests developed for children and adolescents, instead of those adapted from adults, avoids underachievement due to the difficulties of the test itself and not due to the cognitive impairment. Furthermore, our data that are related to deficits in episodic verbal memory and phonological memory corroborate those presented by Helmstaedter [3], although with different tests.

Some studies with TLE [3,32,36] showed more robust evidence of memory impairment than the ones observed in our group (three out of 12 memory indices). This may be related to distinct factors considering selection criteria and some clinical variables. Exclusion of patients with other comorbidities, such as psychiatric disorders, intellectual retardation, learning disabilities, and ADHD, was done in order to avoid the impact of these variables on executive functioning. The impact of psychiatric disorders in distinct aspects of executive and memory functions has been extensively demonstrated [37–39]. Therefore, the studied sample is a selected group of patients from a wider spectrum of patients with TLE and may represent a higher functioning group of children and adolescents with TLE. The use of some very restrictive selection criteria, which excluded psychiatric comorbidities, intellectual disabilities, learning disabilities, and attentional disorders, might explain some of the differences between previous studies [3,32,36] and ours.

The importance of controlling for differences in intelligence potential and excluding patients with a lower IQ (lower than 80) is related to the consensus that intelligence is associated with executive functions. In the Spearman's general factor model (factor g), there is an emphasis in the role of executive control for a higher intelligence potential [40,41]. By the same token, when considering the alternative intelligence framework [42,43], according to which the intelligence reflects the average or combined activity of many separate cognitive functions, executive functions also play a pivotal role [44].

Other evidence for the relevance of considering the effects of IQ on executive functions was also observed in our analysis, as we demonstrated that patients with severe ED had a trend of showing a lower IQ score compared with patients with mild/moderate ED. Nevertheless, we also revealed that IQ might have a different impact on some executive subfunctions than others.

Criteria for controls considered sociodemographic level, especially schools that had a similar curriculum. It is also relevant that, in opposition to series with adults [45] or surgical series with children [46], this study analyzed children with TLE irrespective of its control and etiology.

In a previous study, our group demonstrated that children with TLE present ED [13,14]. In addition, this ED was specific to certain executive functions, such as focused attention, selective attention, abstraction, and mental tracking for semantic information. Therefore, patients had worse performance than controls in some but not in all executive function tests used, which might reflect the fact that some aspects of executive functions were impaired and others were not. For a more detailed discussion of these findings, refer to Rzezak et al. [13,14]. These findings are in agreement with those of Igarashi et al. [12], using the WCST, who demonstrated deficits in planning and abstraction in a sample of children with TLE. Nevertheless, we used a more extensive battery with a broader model of executive functions that allowed us to evaluate executive functions other than planning and abstraction.

Some authors have not observe ED in children with TLE [15,16]. However, in these studies children with TLE were compared with children with other epilepsy syndromes, such as frontal lobe epilepsy, in which executive function is undoubtedly more impaired than in patients with TLE.

We analyzed the relationship between ED and memory from a unique perspective, evaluating a sample composed exclusively of children and adolescents with TLE. In addition, we used two different analyses to confirm our data — a simple regression analysis and a Stepwise Regression Analysis. The main finding was that executive functions have an effect on some aspects of verbal and visual memory in all analyses performed. Moreover, patients with TLE and controls showed a different pattern of associations between executive and memory functions, which also suggests that TLE pathology might alter the memory–executive function relationship in comparison with healthy individuals. To our knowledge, only a few studies that investigated this relationship have focused on neurological populations [23,24], and all of those involved mixed neurological samples with distinct neurological diseases. This relationship has not been demonstrated in patients with epilepsy though. Duff et al. [24] determined that executive functions have an impact on visual memory and, to a lesser degree, on verbal memory. Here, we have demonstrated the relationship between executive and memory functions in a homogeneous sample.

Laterality of TLE in adults usually has an impact on the type of memory impairment of those patients [3]. Although it would be interesting to investigate if the impact of ED in memory functions would be different in patients with left or right TLE, our sample size did not allow for this comparison. However, in a previous study [47] that included only patients with unilateral mesial temporal sclerosis, we could not demonstrate differences between children with left or right TLE in verbal or visual memory tests, which seems to favor a non-material-specific pattern of memory impairment in children with TLE, which has been demonstrated by others [48,49]. Future studies, with a larger sample with children and adolescents with unilateral TLE, are necessary to determine if there is a different impact of ED on verbal and visual memory of patients with left and right TLE.

Besides, in addition, we demonstrated that certain aspects of executive functions, but not all, had an impact on memory, thereby corroborating previous findings that demonstrated the importance of investigating different domains of executive functions and how some of them may be more related to memory than others [23]. Attention, mental tracking, and abstraction were the executive subfunctions that had a more substantial influence on memory functioning.

Our most remarkable finding was that all aspects of attention (focused attention, selective attention, and divided attention) were related to memory impairment. Focused attention is the most basic type of attention. It is a non-uniform cognitive function, related to the distribution of awareness of particular sensory stimuli, and is, therefore, essential for the acquisition of information that must be subsequently stored. Selective attention consists in directing attention resources to one stimulus among many and, thus, requires inhibition of interference in order to pay attention to a given source of information. Divided attention plays a role in memory functions because it implies the sharing of attentional resources between competing stimuli. Thus, our finding can be easily explained by the role that attention plays in memory consolidation. Attentional processes are crucial for good retention, because if the stimulus acquisition phase is inefficient, the information cannot be stored [29].

We observed that a deficit in working memory also had an impact on memory impairment. In fact, this relationship was expected because what has been previously shown is that short-term storage of verbal and/or visual information is correlated with certain aspects of working memory [50]. In addition, in daily life, individuals often have to retain and manipulate information before storing the final data.

It is well established that, even in samples of patients with the same syndrome, individual patients can respond differently to the same neurological insult. In an attempt to refine our analysis, we categorized patients according to the severity of ED and evaluated the impact that the degree of severity had on memory functions. Patients with severe ED performed more poorly on tests of episodic memory (visual and verbal), phonological memory, and learning (visual and verbal). Therefore, although memory dysfunction in children with TLE is related to hippocampal involvement, the severity of ED might play an important role in this cognitive domain.

Not surprisingly, when comparing children with mild/moderate to those with severe ED, differences in age, schooling, and age of epilepsy onset were evident. We previously demonstrated that earlier age of onset and longer epilepsy duration were more frequently observed in patients classified as having severe ED, which may represent an epiphenomenon of a diseased cortex [13]. Therefore, it would be impossible to match these groups for other variables. Although this is a limitation of this analysis, the categorization of children and adolescents according to their ED severity seemed necessary in order not to classify all patients under the same umbrella.

Our findings have clinical implications for programs aimed at the rehabilitation of patients with TLE, especially children and adolescents. Programs in which the neuropsychological evaluation is based solely on memory functioning and the cognitive rehabilitation designed to encompass this dysfunction can be less effective and have an undesirable impact on social functioning. However, TLE rehabilitation programs which take the extensive clinical neuropsychological profile into consideration can result in better patient quality of life. Seizure control is only one of the aspects that must be addressed, and there is a need for a more comprehensive approach to treating patients with epilepsy, especially those with TLE.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2012.09.043.

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