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Review

Neuropsychology of frontal lobe epilepsy in children and adults: Systematic review and meta-analysis☆

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ABSTRACT

Frontal lobe epilepsy (FLE) is associated with cognitive problems, especially in areas related to frontal lobe functioning as executive functions, attention, and motor skills, but with impact on memory and psychosocial adaptation. Deficits are similar in both adults and children with FLE, although no studies have compared adult and pediatric performance in the same study. The aim of this research was to analyze the existing evidence concerning the cognition in adults and children with FLE. A random effect meta-analysis was used using Cohen's *d*, and the confidence interval for each cognitive factor was calculated. The results in the meta-analysis show a general pattern of cognitive dysfunction in FLE, especially in functions related to the frontal lobe, with an influence of the duration and the age at onset of epilepsy, as well as the age of the sample used. In addition, researches in this type of epilepsy are heterogeneous, with too many different sampling and methodological characteristics, which is not a standard format for reporting clinical sample characterization, making it difficult to study FLE in depth.

1. Introduction

Frontal lobe epilepsy (FLE) is the second most common focal epilepsy behind temporal lobe epilepsy [1], accounting for 15–20% of all focal epilepsies. Frontal lobe epilepsy is characterized by seizures that tend to spread, with a wide variability in behavioral and neuroimaging manifestations and a complex electroencephalographic record, which makes its differential diagnosis difficult [2]. Patients with epilepsy have a high risk of presenting cognitive alterations [3]. However, few studies examine the neuropsychological alterations associated with FLE [1].

The cognitive alterations in FLE are related to dysfunctions in areas related to the functioning of the frontal lobe. In this sense, it has been found that these patients have problems in programming and motor coordination and response inhibition [4], inhibition and cognitive flexibility [5], social cognition [6], and phonetic fluency [7]. The possible amnesic alteration in FLE is not exempted from debate but is not supported by conclusive results [8].

Pediatric patients with FLE show a cognitive alteration pattern equivalent to that of adults [1]. Children with FLE have problems in executive functioning [9], sustained attention [10], motor skills [11], the recovery of information, and the use of recall strategies [12,13].

In general, adults and children with FLE present a series of similar cognitive problems; however, no studies, longitudinal or transversal, compare adult and child performances within the same investigation. The objective of this research is to systematically review and analyze the neuropsychological alterations in child and adult patients with FLE as presented in various studies and to identify the variables that may moderate this performance.

2. Material and methods

The systematic review and meta-analysis were carried out following the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guide [14] for observational meta-analysis studies in epidemiology.

2.1. Search strategy

The search process for eligible studies was conducted in the Academic Search Complete, ERIC, Medline, Psychinfo, and Psycharticles databases. The search was restricted to articles published between 1989, the publication year of the ILAE=International League Against Epilepsy review of epileptic syndromes, and 2015 to avoid a possible

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change of diagnostic criteria. The search was conducted between May 19, 2015 and June 16, 2015. Articles were screened according to their title and summary, duplicates were eliminated, and then, an additional search was carried out in eligible articles' list of references. Finally, the complete list of eligible articles was obtained on June 19, 2015. The keywords are in Appendix.

2.2. Selection criteria

The studies had to meet the following inclusion criteria:

1. Peer-reviewed publications written in Spanish or English from 1989 to 2015.
2. Studies comparing at least one presurgical group (>2 patients) of patients with FLE with a group of healthy controls and/or another group of patients with epilepsy.
3. Studies with results that include some domain of cognitive functioning measured by neuropsychological instruments with proven validity and reliability.
4. Studies with summary and full text available.

The exclusion criteria were:

1. Studies without a comparison group.
2. Studies in which the results of the group with FLE are different from other forms of epilepsy.
3. Studies for which the article's full text was not available.

2.3. Coding of studies

The moderator variables were coded by age group (children vs. adults), the average frequency of epileptic seizures in the group with FLE, the mean duration in years of epilepsy in the group with FLE, and the average age in years at the onset of epilepsy in the group with FLE.

A coding book was made of each study's moderating variables. The book was initially debugged by a group of experts, and then, to ensure the reliability of the book and the judgments during the coding, two independent researchers coded a random sample of 24% of the studies. The agreement index was calculated using the average Kappa index, which was 0.81. Manifest errors in the coding book were corrected, and inconsistencies were resolved by consensus.

2.4. Summary measures and calculation of effect size

The reviewed studies included a wide variety of cognitive tests. To draw a coherent and valid comparison between them, each neuropsychological test was classified under one of the cognitive factors of the Cattell–Horn–Carroll (CHC) model [15]. This model has been used in other meta-analyses of epilepsy [16] and as a conceptual framework in other pathologies [17–20]. The tests used in the selected studies were classified under six of the CHC model's broad stratum abilities: general cognitive ability (G), comprehensive knowledge (Gc), fluid reasoning (Gf), long-term memory (Glr), cognitive processing speed (Gs), and span and working memory (Gsm). A definition of each factor based on the Woodcock–Johnson III Test of Cognitive Ability [21] is provided in Table 1.

The test results were assigned to one or the other factor according to each test's description as reflected in its manual and in the literature. Because of the studies' variability, not all of them included results for all factors. Also, several studies used different tests for the same factor. In such cases, each test was counted separately, and a standardized mean was calculated between the various tests for the factor. When a study included several results for the same test, only the most representative result was included.

Also, in addition to the CHC factors, and given its theoretical and empirical interest, the executive function factor was added. This classification included results that the manuals, the authors, and the literature define as instruments of evaluation of executive function [22].

Table 1
Description of CHC broad stratum abilities [21].

Factor	Description
General cognitive ability (G)	Aggregate of all cognitive abilities
Comprehensive knowledge (Gc)	Breadth and depth knowledge and verbal comprehension
Fluid reasoning (Gf)	Ability to solve problems, form concepts and reason using novel information
Long-term memory (Glr)	Ability to store and retrieve information efficiently
Cognitive processing speed (Gs)	Speed and efficiency in performing automatic or simple cognitive tasks
Span and working memory (Gsm)	Ability to hold information and use it within several seconds

Using the means and standard deviations of the cognitive tests of each group in the studies, the effect size was calculated from the difference of standardized means between the group with FLE and the comparison group (control or with temporal lobe epilepsy) using Cohen's *d*. If a study compared FLE with TLE and controls, the effect size was calculated with each comparison, and the combined effect was used. The effect size was classified as small, medium, or large according to the values of 0.2, 0.5, and 0.8, respectively [23]. For each *d* value, the 95% confidence interval was calculated to determine when the effect size obtained was statistically different from zero.

2.5. Meta-analysis procedure

The mean sizes and confidence intervals of all the studies for each of the analyzed variables were determined using a random effects statistical model. For each analysis, a forest plot was made, and the Q index of homogeneity and I^2 were calculated. The quantitative moderating variables were analyzed through a meta-regression, and the qualitative moderating variables were analyzed by means of an analysis of variance (ANOVA). In addition, the publication bias for each analysis was calculated with a funnel plot and the fail-safe number. Version 3 of the comprehensive meta-analysis program was used.

3. Results

3.1. Selection of studies and characteristics

A total of 21 studies met the inclusion criteria (Fig. 1). Table 2 shows a summary of the characteristics of the studies considered in the meta-analysis.

3.2. Process

The analysis of all the studies jointly (Fig. 2) gave an average effect size of 0.32 (95% CI: −0.47; −0.17), which was of small-medium magnitude and significant ($Z = -4, 19$; $p \leq 0.001$). The heterogeneity is low ($I^2 = 36.48$) and significant ($Q(20) = 31.48$, $p \leq 0.05$). Table 3 shows the overall results of the analyses by factor.

3.3. Summary of the results

In general, there is an effect on the group with FLE in the cognitive profile. In-depth analysis of this effect revealed that it has a medium negative affect on the group with FLE in the factors of Gf, Gs, working memory, and executive function. It oscillates between 0.37–0.63. It has no effect on G, Glr, or Gc. The heterogeneity among all the factors is significant and medium, with values ranging from 54.53% to 66.85%.

3.4. Moderating variables

The analysis of the four moderating variables was conducted for each variable's factor: whether the sample consisted of children (up to

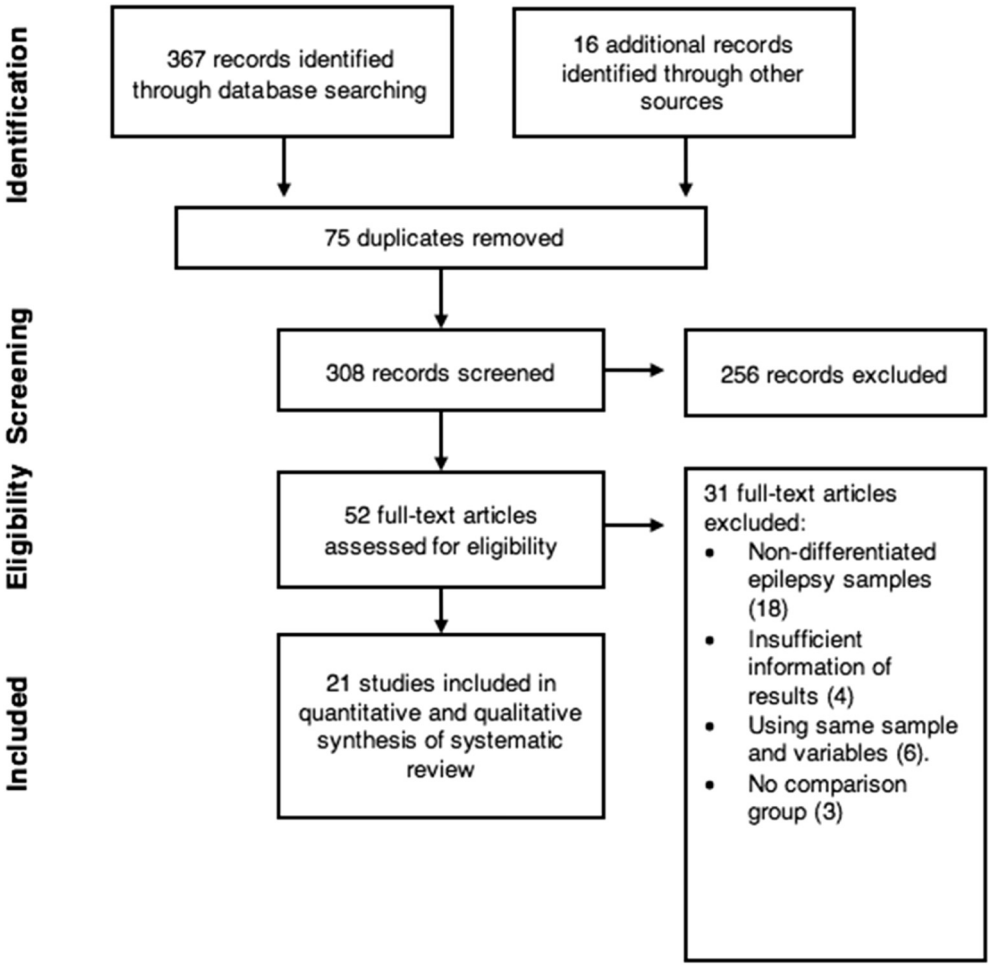

Fig. 1. Flow diagram of the process of selected studies.

Table 2
Characteristics of the included studies.

Study	Sample size	FLE sample size	Average age (years)	Sample type	Foci localization	Age at onset (years)	Duration of epilepsy (years)	Seizures frequency/ year	Type of seizures	Etiology	Medication
Auclair et al. (2005) [24]	27	8	9.58	Children	2R, 1L, 5BI	5.80	6.00	Not reported	8FO	3SM, 5GN	8P
Braakman et al. (2015) [25]	75	34	10–77	Children	7R, 8L, 19BI	4.80	6.10	Not reported	6FO, 5FEB, 23GE	Not reported	1WM, 21M, 12P
Culhane-Shelburne et al. (2002) [9]	27	12	12.28	Adults	5R, 5L, 2B	6.83	6.20	0.61	3FO, 9FEB	Not reported	10M, 2P
Drane et al. (2006) [7]	29	9	32.54	Adults	5R, 4L	20.60	Not reported	Not reported	Not reported	Not reported	Not reported
Exner et al. (2002) [26]	47	16	38.94	Adults	5R, 11L	27.00	14.00	Not reported	Not reported	7SM, 9U	Not reported
Farrant et al. (2005) [6]	28	14	35.08	Adults	5R, 8L, 1BI	11.80	Not reported	Not reported	Not reported	9SM, 5U	Not reported
Giovagnoli et al. (2005) [27]	159	40	51.96	Adults	15R, 25L	20.22	20.53	2.75	Not reported	27SM, 13U	Not reported
Helmstaedter et al. (1998) [28]	61	33	29.60	Adults	16R, 17L	14.96	15.25	Not reported	Not reported	31SM, 2U	Not reported
Helmstaedter et al. (1996) [4]	32	23	22.75	Adults	17R, 6L	13.00	17.00	9.25	Not reported	13SM, 10U	Not reported
Hernandez et al. (2002) [29]	32	16	11.57	Children	4R, 4L, 8BI	7.77	3.82	Not reported	16FO	3SM, 13U	6M, 10P
Hernandez et al. (2003) [12]	32	16	11.57	Children	4R, 4L, 8BI	7.77	3.82	Not reported	16FO	3SM, 13U	6M, 10P
Jocic-Jakubi & Jovic (2006) [13]	160	44	11.00	Children	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Lendt et al. (2002) [11]	24	12	11.55	Children	6R, 6L	6.30	Not reported	11.25	15FO, 7FEB	12SM	Not reported
Longo et al. (2013) [10]	66	19	13.25	Children	9R, 8L, 2BI	6.03	Not reported	Not reported	Not reported	10sM, 9u	6M, 13P
Luton et al. (2010) [30]	40	20	12.55	Children	2R, 6L, 9BI	7.20	Not reported	2.66	20FO	Not reported	10M, 10P
McDonald et al. (2008) [31]	65	22	37.88	Adults	11R, 10L, 1BI	17.40	21.50	1.38	Not reported	15SM, 7U	Not reported
McDonald et al. (2005) [5]	65	22	37.17	Adults	11R, 10L, 1BI	17.40	21.50	1.38	12FO, 10FEB, 0GE	15SM, 7U	Not reported
Rayner et al. (2015) [32]	33	9	38.11[a]	Adults	6R, 1L, 2BI	14.56	24.67	9.19	Not reported	9SM	1M, 8P
Upton & Thompson (1996) [33]	131	74	28.82	Adults	32R, 42L	10.20	17.26	Not reported	Not reported	60SM, 14U	6M, 58P
Vanasse et al. (2005) [34]	60	10	10.12[a]	Children	2R, 8L	3.94	6.40	1.02	10FO	1SM, 9U	7M, 3P
Wang et al. (2011) [35]	38	18	31.64	Adults	9R, 7L, 2BI	12.17	Not reported	Not reported	Not reported	Not reported	2WM, 12M, 4P

R: right; L: left: BI: bilateral; FO: focal seizures; FEB: focal seizures to bilateral; GE: generalized seizures; SM: structural-metabolic; GN: genetics; U: unknown; WM: without medication; M: monotherapy; P: polytherapy.

[a] Only the average age of the group with FLE is specified.

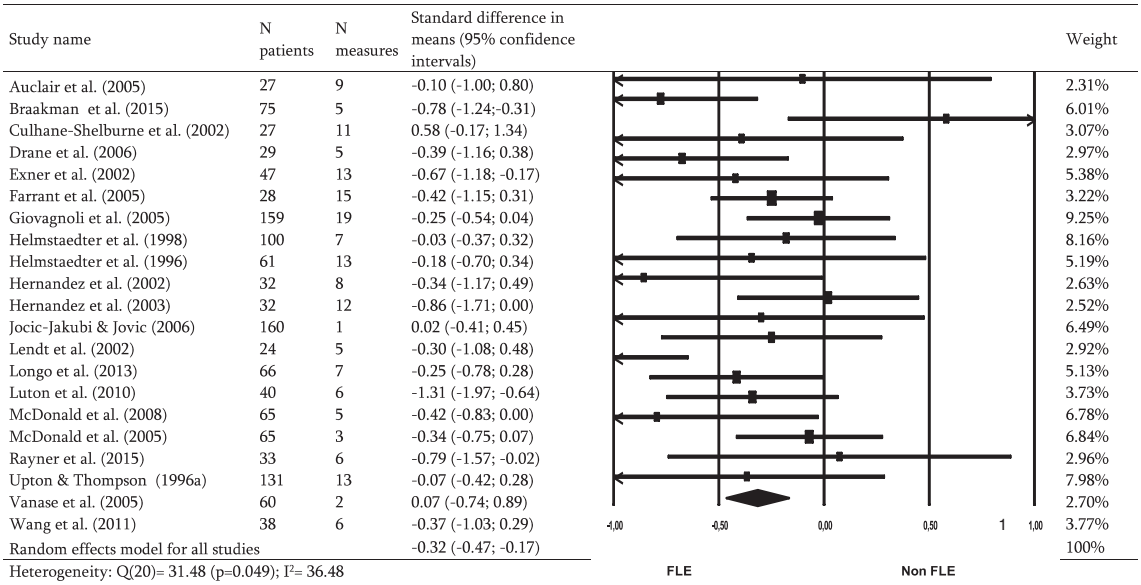

Fig. 2. Mean effect size and 95% confidence interval corresponding to all studies combining individual size effects.

Table 3
Summary of the analysis of each cognitive factor.*

Factor	Number of studies	Effect size (95% confidence interval)	Global effect (Z)	Q value	I^2
General cognitive ability	11	−0.09 (−0.42; 0.23)	−0.57	32.10***	66.85
Comprehensive knowledge	12	−0.22 (−0.45; 0.01)	−1.88	25.53**	56.91
Fluid reasoning	11	−0.47 (−0.75; −0.18)	−3.25**	29.56***	66.16
Long-term memory	9	−0.13 (−0.43; 0.18)	−0.80	18.92**	57.72
Cognitive processing speed	18	−0.40 (−0.59; −0.21)	−4.07***	39.31***	56.75
Span and working memory	11	−0.63 (−0.90; −0.36)	−4.58***	21.91**	54.37
Executive function	17	−0.37 (−0.56; −0.18)	−3.80***	35.19**	54.53

* $p \le 0.05$.
** $p \le 0.01$.
*** $p \le 0.001$.

18 years old) or adults, the age at onset of epilepsy, the duration of epilepsy, and the frequency of seizures.

Table 4 shows the results for the moderator variable of sample type, with important effect sizes found in Gs, working memory, and executive function. The adult sample also shows a significant effect on Gf and Gc.

Table 4
Results of the random effect analyses performed with the moderator variable of sample type in the studies.

Factor	Sample	Number of studies	Effect size (95% confidence interval)	Z
G	Children	5	0.13 (−0.31; 0.57)	0.58
	Adults	6	−0.32 (−0.73; 0.08)	−1.57
Gc	Children	8	−0.03 (−0.45; 0.39)	−0.13
	Adults	4	−0.29 (−0.57; −0.02)	−2.08
Gf	Children	5	−0.31 (−0.80; 0.17)	−1.26
	Adults	6	−0.56 (−0.93; −0.19)	−2.95
Glr	Children	5	0.12 (−0.28; 0.51)	0.57
	Adults	4	−0.37 (−0.76; 0.02)	−1.84
Gs	Children	8	−0.66 (−0.96; −0.36)	−4.27
	Adults	10	−0.26 (−0.48; −0.04)	−2.33
Gsm	Children	5	−0.64 (−1.09; −0.20)	−2.84
	Adults	6	−0.63 (−1.00; −0.25)	−3.28
EF	Children	8	−0.56 (−0.86; −0.25)	−3.55
	Adults	9	−0.26 (−0.49; −0.03)	−2.24

Note: G: general cognitive ability; Gc: comprehensive knowledge; Gf: fluid reasoning; Glr: long-term memory; Gs: cognitive processing speed; Gsm: span and working memory; EF: executive function.

The age at onset of epilepsy was significant only in the G factor ($Z = -2.80$, $p \le 0.01$). The duration of epilepsy has a significant influence on the factors of Glr ($Z = -2.69$, $p \le 0.01$) and Gs ($Z = 1.96$, $p \le 0.05$). The frequency of seizures was not significant in any cognitive factor.

3.5. Risk of bias

The risk of bias in this study is marked by three possible sources. First, the variability of the epileptic population can be a source of bias. However, the fact that not all studies report on these clinical variables has hindered optimal control of heterogeneity. Second, one must consider the great variety of neuropsychological tests used. To address this risk, measures reported in the studies were reduced to a representative measure and to add the measures to a factor whenever they assessed the same neuropsychological construct. Finally, to control for publication bias, the classic fail-safe number (Ns = 134, $z = -5.31$, $p \le 0.001$) and Orwin's fail-safe number (Ns = 124) were calculated, indicating the nonexistence of bias.

4. Discussion

This systematic review and meta-analysis presents the cognitive effects of FLE in adult and pediatric patients in publications since 1989. To our knowledge, this review is the first attempt to evaluate cognitive effects in FLE and constitutes a global approach to neuropsychological problems in this population, bringing together various

preoperative studies conducted with adults and children separately. Patrikelis et al. [1] claimed that cognitive problems in adults and children with FLE are similar but no study has ever been carried out analyzing the pattern of cognitive deficits in both populations. Therefore, this paper highlights (a) the clinical utility of a cognitive model to explain neuropsychological findings, (b) which cognitive deficits affect patients with FLE, (c) differences in neuropsychological disturbances in FLE according to age, (d) clinical variables that influence the cognitive profile in FLE, and (e) heterogeneity across studies on the neuropsychology of FLE.

The use of the CHC model for the interpretation of neuropsychological assessment implies a functional approach to cognitive dysfunctions because a single test score frequently does not reflect cognitive deficits. In addition, several tests may involve various cognitive domains, or several tests may be used with divergent results but they assess the same function. For this reason, cognitive assessments to differentiate diagnoses should be based on theories and models that cover multiple cognitive domains. In this way, the CHC theory constitutes an explanatory model of normal and pathological cognitive functioning that allows for the analysis of various cognitive domains in a parsimonious and valid way. Factor analysis studies show that the CHC model provides a parsimonious interpretation of cognitive functioning [15], and it has been used as a conceptual framework and support for differential diagnosis and cognitive description in various pathologies, such as epilepsy [16], Alzheimer's disease [17], pediatric oncology [18], learning disabilities [19], autism [20], acquired brain injury [20], and attention-deficit hyperactivity disorder [20].

The studies analyzed in this meta-analysis show that patients with FLE obtain lower scores than their comparison groups. This fact indicates that FLE in and of itself constitutes a significant risk of developing neuropsychological deficits. These cognitive alterations are evidenced with a medium effect in the factors of Gs, problem solving (Gf), short-term memory (Gsm), and executive function, all deficits associated with FLE [1]. These are the functions most directly associated with the operation of the frontal lobe [36]. Deficits shown in FLE are normally related to disturbances in various stages of brain maturation, but they cannot be ascribed to specific abnormalities in the frontal lobe [37].

However, in verbal comprehension (Gc), Glr, and G, no effects were found. As Glr is a function generally associated with alterations related to temporal lobe epilepsy, it has not often been considered in FLE studies; therefore, only nine of the studies analyzed here included Glr assessment. The amnestic problems observed in FLE are more due to retrieval and access to information dysfunctions than to encoding deficits, in which attention and language play an important role [8]. A complete review can be found in Centeno et al. [8,38]. In this sense, the very structure of the frontal lobes and the great variability in the location of the frontal epileptic focus explain why hardly any mnesic effects exist or why those that do appear are much milder and more difficult to measure, unlike the great amnestic deficits observed in patients with temporomedial epilepsy damage.

Regarding the age of participants in FLE research, studies with adults address alterations in more functions than studies with children. Both types of studies show that patients with FLE have similar deficits, but adults also show problems in concept formation, problem solving, and verbal comprehension. Frontal lobe epilepsy in adults is more severe at the neuropsychological level than FLE in children because the shorter duration of the children's epilepsy and the infant brain's adaptive capacity make children more resistant to the damage caused by epilepsy [39].

Neuropsychological well-being and functioning are crucial features in epilepsy. People with epilepsy are at risk of developing learning problems, having low self-esteem, or lack of social skills because of cognitive deficits, as well as depression and anxiety [40]. To ensure an effective intervention and according to this study, neuropsychological assessment in FLE should cover multiple cognitive domains but especially executive functions processing speed, memory, and verbal comprehension, the main cognitive areas that can be affected by FLE and that impact daily life. Therefore, the impairments found in FLE have an important impact in patients' daily lives and long-term social and labor integration, similar to patients with TLE [41]. Considering the results of this meta-analysis, neuropsychological interventions in patients with FLE should focus on processing speed and executive functions, mainly problem solving and working memory. However, in adults, because of the duration of epilepsy, cognitive treatment should also include verbal comprehension and concept formation. As with any other neuropsychological treatment, in the case of FLE, one should consider the patient's educational level, social environment, and perception of cognitive interference in his/her daily life [42].

On the other hand, the results indicate the influence of clinical variables of epilepsy on the cognitive profile. Shulman [43] summarized three potential factors mediating cognitive deficits in epilepsy: (a) neurobiological factors, such as etiology, seizure semiology, age at onset, laterality of onset, interictal activity, and seizure control; (b) iatrogenic factors, such as medication effects, metabolic effects, and mono/polytherapy; and (c) psychosocial factors, such as demographics, chronic illness factors, and developmental issues. Duration of epilepsy is related with a cognitive decline in epilepsy from 3 to 4 years of onset in children and adults [44]. In this study, a longer duration of epilepsy is related to differences in processing speed and Glr. On the other hand, late onset of epilepsy has repercussions only in a low outcome in G because structural/metabolic epilepsies can begin at any age and cause worse cognitive prognoses [45]. Frequency of seizures normally has a great impact on cognitive functioning [8]. However, no effects were found in this review, perhaps because of difficulties in reporting frequency of seizures and because not all studies report on these and other important variables in epilepsy.

Finally, the studies analyzed show an average heterogeneity of approximately 55%. This result also demonstrates the influence of the moderator variables discussed. In this study, we determined how the cognitive effect of FLE is conditioned by variables such as the age at onset of seizures, the duration of the epilepsy, and participants' ages. The lack of a systematic information protocol for this type of clinical variable in epilepsy studies makes it difficult to collect the data because not all studies include the same variables, nor do they address the variables in the same way or at least in some way that can be transformed into a common metric. Studies concerning cognition in epilepsy, especially in focal epilepsies, should always report age at onset, seizure frequency, duration of the epilepsy, etiology, types of seizure, and medication. These are critical variables that affect the cognitive profile in epilepsy and should always be considered in any neuropsychological study of epilepsy. They also make the development of cognitive prognostic models and prediction of which patients are at risk of developing more cognitive deficits difficult [46].

This study has two limitations. On the one hand are the reduction of the results to seven cognitive factors and the synthesis of several scores into a single outcome variable for each factor. This simplification was preferred to the use of a multivariate meta-analysis because the latter methodology is still in the exploratory phase [47]. On the other hand, the studies' variability and heterogeneity and the heterogeneous samples represent another limitation associated with a meta-analysis of epilepsy.

5. Conclusions

In summary, the results obtained show a general pattern of cognitive dysfunction in FLE, especially in the functions related to the frontal lobe, which are influenced by the duration of and age at onset of epilepsy, as well as the patient's age. Neuropsychological interventions in FLE should be administered differently based on whether the patient is an adult or a child and the epilepsy's clinical characteristics. In addition, it has been found that research on this type of epilepsy consists of heterogeneous studies, with varied samples and methodological characteristics, which do not always report certain basic clinical variables

in a standard format that would permit an in-depth study of FLE. Efforts to solve these methodological discrepancies across studies should be made to improve the quality of the research in the neuropsychology of epilepsy.

Conflict of interest

There is no conflict of interest.

Annex 1. List of meta-analysis search terms

Terms used in the meta-analysis search with two types of keywords: some on epilepsy and others on cognition.

Search terms for meta-analysis			
Databases	Keywords "epilepsy"	Boolean	Keywords "cognition"
EBSCO	(KEY ("frontal lobe epilepsy") OR KEY or key ("focal epilepsy") or key ("frontal seizures") or key ("focal seizures") and not key ("temporal lobe epilepsy"))	and	(KEY ("cognition") or key ("cognitive function") or key ("neuropsychology") or key ("memory") or key ("executive function"))

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