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REVIEW

Quantitative Meta-Analyses: Lateralization of Memory Functions Before and After Surgery in Children with Temporal Lobe Epilepsy

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Abstract

Rationale Memory deficits in children with epilepsy have been reported in some but not all studies assessing the effects of side of seizures and resection from the temporal lobe on cognitive performance. This meta-analysis provides a quantitative systematic review of previous studies on this issue.

Method A critical review and meta-analysis of the literature on memory performance in children with Temporal Lobe Epilepsy (TLE) was conducted. Search identified 25 studies, 13 of which compared children with TLE to healthy age-matched controls and 12 of which compared children with TLE before and after surgery.

Results Heterogeneity of the comparisons of children with TLE to healthy controls impeded drawing definitive conclusions. However, in 55% of the studies, verbal memory in children with left TLE (LTLE) was impaired as compared to healthy controls. Verbal memory performance slightly declines after pediatric LTLE surgery, but nonverbal memory tasks are not affected. By contrast, verbal memory performance is not affected by pediatric right TLE (RTLE) surgery.

Conclusions The findings suggest that side of the epileptogenic zone and resection from the temporal lobe affect verbal memory in children with LTLE. Right resection seems to be safe with respect to verbal memory performance.

Keywords Meta-analysis · Memory · Children · TLE · Surgery · Epilepsy

Introduction

According to Milner's (1966) early description of the dual "material-based" model, if seizure onset originates in the left language dominant temporal lobe, verbal learning and memory are adversely affected (i.e. lateralization of verbal memory; Saghafi et al., 2018; Sherman et al., 2011; Witt, Elger, & Helmstaedter., 2015; Witt et al., 2019). Although the data is somewhat less robust (Vaz, 2004), if onset derives from the right non-dominant temporal lobe, learning and memory for non-verbal materials such as designs, or faces is affected. More than 50 years later, there is still strong pre-operative and post-operative empirical support for the relationship between verbal memory impairment and dysfunction in the left mesial temporal lobe in adults with TLE (Saghafi et al., 2018; Sherman et al., 2011; Witt et al., 2015; Witt et al., 2019), but a lack of consensus with regard to lateralization and localization of nonverbal memory (Kennepohl, Sziklas, Garver, Wagner, & Jones-Gotman, 2007; Vaz, 2004).

Furthermore, although research suggests there is an increased risk of cognitive impairment in children with temporal lobe epilepsy (TLE) and that the memory domain is most likely to be affected (Flint et al., 2017; Menlove & Reilly, 2015), it is unclear whether children with TLE exhibit patterns of material-specific memory lateralization that are similar to those described for adults. Some researchers have suggested that children with temporal lobe epilepsy may have less localization than adults and thus exhibit a broad pattern of cognitive deficits, beyond those considered to subserved by the epileptogenic region (Hermann

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et al., 2008; Jambaqué, Dellatolas, Dulac, Ponsot, & Signoret, 1993; MacAllister & Schaffer, 2007; Pulsipher et al., 2009). For example, Stefanatos (2015) only found minor differences between the neuropsychological profile of children with frontal and temporal lobe epilepsies. In contrast, Gonzalez, Anderson, Wood, Mitchell, and Harvey (2007) reported higher levels of memory problems in children with mesial TLE (MTLE) than lateral TLE, but no lateralization of verbal or non-verbal memory, suggesting that memory in children with TLE is localized but not lateralized (Stefanatos, 2015). However, these studies typically have small sample sizes (e.g. Pulsipher et al., 2009), with heterogeneous participants and pathologies (e.g. Jambaqué et al., 1993), making it difficult to draw a robust conclusion regarding lateralization and localization of the memory domain in children with epilepsy.

The question of localization and lateralization of memory in children with TLE is particularly critical in clinical practice, in cases of intractable epilepsy, when resection of the epileptogenic zone is considered as a proactive treatment for seizure relief (Loring, 2010). Patients with intractable TLE typically undergo comprehensive monitoring and assessment to help localize the epileptogenic focus. Such assessments include EEG monitoring, neuroimaging and functional mapping (fMRI). The neuropsychological assessment is also part of the pre-operative routine which is used to detect subtle cognitive dysfunctions (Baxendale & Thompson, 2010) and predict, at least with some certainty, the risk of post-operative memory decline, following temporal lobe surgery (Helmstaedter & Witt, 2017). Although post-operative neuropsychological impairments, especially in the memory domain, have been widely documented in adults with TLE (Lee, Yip & Jones-Gotman, 2002; Witt et al., 2019), the effects of such surgery in childhood have been less extensively studied. Vulnerability of the verbal memory function to left temporal lobe resection in children has been reported in some studies (Dlugos et al., 1999; Jambaqué et al., 2007; Meekes et al., 2013; Szabó et al., 1998), but not in others (Gonzalez, Mahdavi, Anderson, & Harvey, 2012; Mabbott & Smith, 2003; Oitment et al., 2013; Williams Griebel, M. L., & Dykman, 1998). In a longitudinal study, Gleissner, Sassen, Schramm, Elger, and Helmstaedter (2005) reported cognitive decline three months post operation, in both children and adults. While the children showed recovery after nine months, the adults remained impaired. Skirrow et al. (2015) found long-term improvement of verbal memory following resection of the non-dominant right hemisphere in children. In a recent systematic qualitative review, Flint et al. (2017) concluded that after temporal lobe surgery, there was some evidence of material-specific memory deficits based on the resection side, namely verbal memory decline after left resection. Nevertheless, heterogeneity in sample sizes, methods, memory measures and outcomes, make it difficult to draw firm conclusions from a qualitative review. The inconsistent finding in pediatric TLE patients' memory function can be explained in a developmental perspective (Helmstaedter and Elger, 2009). Several authors have suggested that specific difficulties can manifest throughout childhood (Culhane-Shelburne, Chapieski, Hiscock, & Glaze, 2002; Helmstaedter & Elger, 2009; Gonzalez et al., 2012; Smith, 2016). For example, in Gonzalez et al. (2012) the participants were children at baseline and adolescents or young adults at follow-up. Verbal memory deficits were apparent in left TLE patients, only at follow-up, suggesting that verbal-specific memory deficits emerge over time. Researchers have claimed that there is a critical developmental period for verbal memory lateralization. Helmstaedter and Elger (2009) indicated that memory impairment in children with TLE becomes most pronounced in the decade after puberty, in contrast to Gonzalez et al. (2012) who posited that the critical developmental period for verbal memory lateralization occurs earlier, in mid-childhood when language function is strongly lateralized and the capacity for the reorganization of memory diminishes (Everts et al., 2010).

The purpose of the current study was to conduct a quantitative meta-analysis of studies investigating the effect of lateralization (right childhood TLE versus left childhood TLE), material-type (verbal versus nonverbal) and age (age of onset, duration of epilepsy and age at surgery), on memory functions in children with TLE. The crucial advantage of a quantitative meta-analysis over a qualitative review is that it provides quantitative data on the between-study heterogeneity (Miller et al., 1994), thus enabling more accurate conclusions.

Specifically, the current study investigates (a) whether memory functions are impaired in children with TLE compared to healthy controls, (b) whether memory functions are lateralized in children with TLE compared to healthy controls, (c) whether memory functions decline following temporal lobe surgery, and finally (d) whether earlier surgery leads to better memory outcomes.

Based on the literature, it was hypothesized that children with TLE would show impaired memory function compared to healthy controls and further, they would have material-specific memory deficits involving verbal memory. That is, it was assumed that verbal memory would manifest a lateralization effect. Specifically, verbal memory was predicted to be impaired in children with left TLE (LTLE), but preserved in children with a right focus and it was also expected to be better before than after childhood temporal lobe surgery. Finally, we hypothesized that earlier surgery would lead to better memory outcomes based on the notion that brain plasticity occurs mainly in the developing brain (e.g. Berl, 2014; Cross et al., 2006).

Methods

Data Sources

Review material was drawn from the PsycINFO, Medline, and Google Scholar databases for the years 1990-2019. An existing optimized child search strategy described by Boluyt et al. (2008) was used to select child studies. The key search terms were: *TLE* OR "temporal lobe epilepsy" OR "HS*" OR "hippocam*" OR "MTS*" OR "mesial temporal sclerosis*" AND "Surgical*" OR "Operati*" OR "Resecti*" OR "Temporal lobectomy" AND "child*" OR "pediatric*" OR "Paediatric*" OR "Paediatric*" OR "school age*" OR "schoolchild*" OR "school*" OR "kid*" OR "adolescent*" OR "teen*" OR "boy*" OR "girl*" OR "Junior*" AND "memory*" OR "learning and memory" OR "recall*".

Inclusion Criteria

Based on the PRISMA systematic review guidelines (Moher et al. 2015), the inclusion criteria for the studies were 1. fll-length, English language studies published between 1990 and October 2019, 2. contained samples of pediatric patients (aged 6-16) with RTLE or LTLE, 3. reported statistics for the comparison of memory data, or when not available, contained images that enable data extraction, and 4. had eight participants or more.

Data Extraction

The statistics extracted included verbal and nonverbal memory performance comparisons between patients and healthy age-matched control groups, or verbal and nonverbal memory performance comparisons pre- and post-surgery.

The quantitative analysis focused on delayed memory outcome, which is considered the gold standard for assessing memory integrity in TLE patients (Witt et al., 2019) and is also the most consistently reported. Other measures may have limited efficacy in differentiating paediatric epilepsy patients from healthy children or pre- to post-surgical patients. For example, children with epilepsy scored lower than the norm on long not short delay memory tasks, which were within the normal range (Hershey, Craft, Glauser, & Hale, 1998). The statistical data included the standardized means, and Standard Deviation (*SD*) of the delayed recall outcomes per group and memory material type. If the mean or the standard deviation values were not reported, these were calculated based on the reported confidence intervals (CI) or p-values. If the standard error (SE) was reported, this was converted to the standard deviation. Several studies reported more than one result for the same group of participants (e.g. multiple memory results for a single memory paradigm or multiple paradigms in a single memory domain). However, since inclusion of non-independent observations risks underestimating the error variance associated with each effect size (Borenstein et al. 2011) in cases of multiple results of a single measure, the results for delayed recall were used. More than 90% of the studies compared multiple independent experimental groups (RTLE and LTLE) with a single control group or multiple results for different memory domains (i.e., verbal and nonverbal domains) within the same sample. Since calculating an average effect size that collapses over the observations would result in the omission of important moderator data and therefore is not appropriate (see Higgins & Green 2011), effect sizes for each of these non-independent comparisons were included as separate datasets. Nevertheless, to avoid underestimating the error variance associated with each effect size, the sample sizes used to calculate the standard errors for each group were divided by the number of inclusions (see Higgins & Green, 2011; Webb et al., 2012).

Statistical Analyses: Meta-Analyses

The effect size was calculated using the standardized delayed memory scores for patients compared to controls (Higgins & Green, 2011). For before and after studies, the effect size was calculated as the change in memory performance from baseline. As recommended in the Cochrane Handbook for Systematic Review of Interventions and others (Follmann, Elliott, Suh, & Cutler, 1992), imputed correlation coefficients of 0.50 were used to impute the change from the baseline standard deviation required to calculate an effect size. Effect sizes were calculated in a multi-stage process. The first stage involved calculating effect sizes for each test that was included from each individual study. A higher memory test score indicated better performance. Therefore, a negative effect size indicates that patients performed worse than controls, or patients' scores decreased after surgery. To correct for small sample sizes, Hedges' g effect size computation was used: $g = d[1 - (3/4\ N) - 9]$, where N represents the cumulative sample size for both patients and control groups (Hedges & Olkin, 2014). The magnitude of Hedges' g coefficient is equivalent to Cohen's d effect sizes. Effect sizes of 0.2 were considered small, effect sizes of 0.5 were considered medium, and effect sizes of 0.8 were considered large (Cohen, 1988). The calculation of effect size for each outcome, the pooling of effect sizes and tests of heterogeneity were conducted using Meta-Essentials version 1.4 (Suurmond, van Rhee & Hak, 2017). Two-tailed significance tests were employed at a p value of 0.05. Given that the studies included in the meta-analyses differed in terms of several variables (e.g., memory test type, participants' characteristics, etc.), a random effects model was used to calculate the

between or within group comparison pooled effect. As noted by Borenstein, Hedges, Higgins, and Rothstein (2011), the random effects model is often the most appropriate model to use in a quantitative synthesis of existing literature because the random-effects model allows for the true effect size to vary from study to study unlike the fixed-effect model which is based on the assumption that all studies in the meta-analysis share a common (true) effect size. The effect sizes were calculated to the 95% confidence intervals.

Heterogeneity in effect sizes was tested using the Q statistic (Chi^2), I^2 and $tau - squared(\tau^2)$, for each comparison. Q provides significance testing for heterogeneity, with $p < 0.05$ indicating significant heterogeneity. I^2 represents the ratio of the variance in the true effect compared to the variance due to sampling errors and was reported for descriptive purposes (Borenstein, Higgins, Hedges, & Rothstein 2017), where 25%= low, 50%= moderate, and 75%= high heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). τ^2 estimates the between-study variance of the effect sizes, which is an indication of absolute variance (Borenstein, Higgins, Hedges, & Rothstein, 2011).

To explore heterogeneity, the effects of several moderator variables were investigated including the side of the epileptogenic foci (LTLE or RTLE), and the memory test material type (non-verbal or verbal). In addition, meta-regressions were used to investigate the roles of duration of epilepsy and age at onset. In addition, Forest plots were generated to visualize integrated size effects and heterogeneity.

Two quantitative meta-analyses were conducted. The first meta-analysis examined heterogeneity and estimated the effect sizes for differences in memory performance between children with TLE and healthy controls. The second meta-analysis examined the heterogeneity of the results and estimated effect sizes with regard to memory performance differences in children with TLE before and after temporal lobe surgery.

Each analysis first examined whether there were memory outcomes present in both the right and left foci, by assessing the heterogeneity of the findings of both groups as a whole. Then, in order to investigate the source of variation across studies, memory performance and heterogeneity in children with RTLE and LTLE were analyzed separately. Under the assumption that learning, and retention of verbal materials is associated with the left temporal memory system, tests were run on the RTLE and LTLE subgroups separately to determine whether the pooled estimate of memory outcomes and heterogeneity were influenced by specific differences in material. Finally, to investigate the potential influence of age parameters (age at onset, duration of seizures and age at surgery) on memory performance, moderator analyses was conducted to determine whether age moderated the memory performance in children with TLE and whether earlier surgery leads to better memory outcomes.

Results

Retrieval The literature search yielded 158 references of which 33 (21%) were duplicates and 98 (62%) did not meet inclusion criteria. After their removal, 27 studies met the inclusion criteria. Of these 27 studies, four studies were by the same research group and had identical numerical outcomes (Guimarães et al., 2007; Guimarães et al., 2014; Rzezak, Guimarães, Fuentes, Guerreiro, & Valente, 2011; Rzezak et al., 2012) therefore only the earlier version of the studies (Guimarães et al., 2007; Rzezak et al., 2011) were included, resulting in 25 remaining studies. A flow chart of the systematic review phases is presented in Fig 1**.**

The studies and their characteristics are presented in Tables 1-2.

11 studies compared patients to controls, 12 compared preoperative and post-operative results of the patient groups and two had both experimental designs (Beardsworth & Zaidel, 1994; Lendt, Helmstaedter, & Elger, 1999). However, in these two studies, only the between groups comparison data was available for numerical calculations. Two studies with a pre-post design measured post-operative memory twice, at three- and 12-months post-op (Gleissner et al., 2005; Lendt et al., 1999). Only the 12-month assessment outcomes were included in the current analyses. Five studies had a single patient group containing both RTLE and LTLE patients (Bailey, 2013; Guimarães et al., 2007; Mankinen et al., 2014; Rzezak, Guimarães, Guerreiro, & Valente, 2017; Smith, Elliott & Lach, 2006). The rest of the studies ($n = 19$) were composed of two patient groups of children with either LTLE or RTLE. All of the studies except two (Beardsworth & Zaidel, 1994; Martins et al., 2015), used a verbal memory paradigm, 16 of which (64%) also used a nonverbal paradigm whereas the remainder only used a verbal memory paradigm (Gleissner et al., 2002; Jambaqué et al., 2009; Lah & Smith, 2015;Law, Benifla, Rutka, & Smith, 2017; Mankinen et al., 2014; Szabó et al., 1998). Three studies used a memory of faces paradigm (Beardsworth & Zaidel, 1994; Gonzalez et al., 2012; Mabbott & Smith, 2003; Smith et al., 2006). As shown in Table 3, the children were older in the pre-post studies compared to the between groups studies, with respect to both the age at onset ($p < .05$) and the age at assessment ($p < .01$), but no differences were found between the pre-operative and post-operative studies and patient-control studies, with regard to the duration of epilepsy.

Quality assessment The following criteria were employed to assess study quality: (1) randomization, (2) double blinding and (3) proper treatment of withdrawals or dropouts (Jadad et al., 1996). The first two criteria were not applicable because the groups were divided by disease status and had apparent behavioral differences. The dropout criterion was not reported in any of the studies. Never-

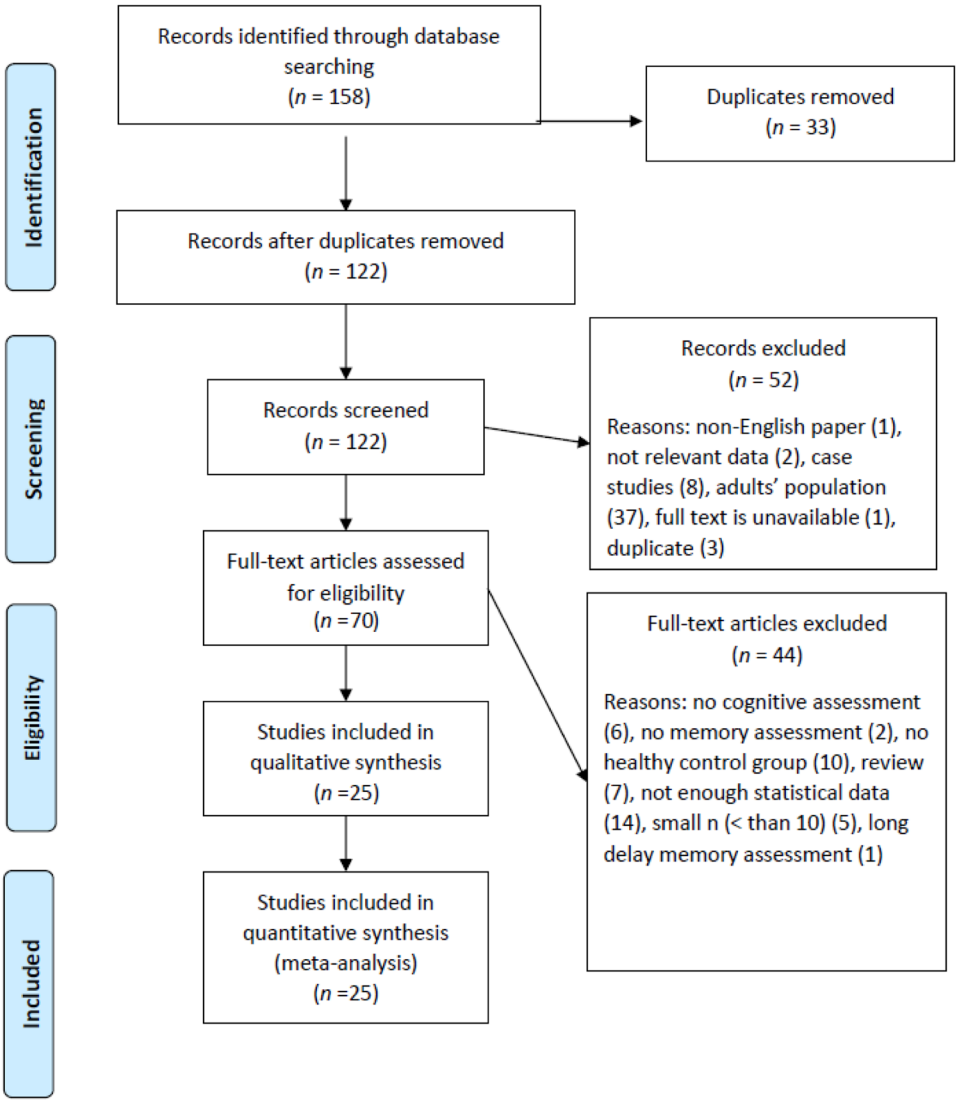

Fig. 1 A four-phase flow diagram of the systematic review (adapted from Moher, Liberati, Tetzlaff, & Altman, 2009)

theless, patients' withdrawal was reported in five studies: Bailey (2013), 31 patients at the post-operative assessment, Gascoigne et al. (2014), two patients and two controls, Gonzalez et al. (2012), 19 patients at the post-operative assessment, Mankinen et al. (2014), 11 patients, Smith et al. (2006), three patients and five controls. Effects of publication bias were examined with Egger's tests (Egger, Smith, Schneider, & Minder, 1997) and were also inspected visually by a funnel plot.

Quantitative Analysis (Meta-analysis)

Patients Versus Controls Differences

Thirteen studies compared memory performance in children with TLE and healthy children, with age-matched controls using either verbal, nonverbal or both paradigms (Table 4).

The 13 studies included 39 comparisons of children with either LTLE (18 comparison), RTLE (18 comparisons) or both (three comparisons) to controls. The first stage of the meta-analysis covered 38 effect sizes that were derived from the verbal and nonverbal paradigms for children with LTLE-RTLE groups in total. The magnitude of the differences was relatively moderate (df = 37, Hedges' g = −.48, $p < .0001$, 95% CI [−.75, -.22]). A statistical examination of the funnel plot using Egger's regression test resulted in a non-significant model, suggestive of a lack of significant publication bias ($t(38) = -.56$, $p > .05$). Q value indicated heterogeneity ($Q = 184.6$, $p < .01$, $\tau^2 = 0.51$, $I^2 = 80.5\%$) and therefore the presence of potential moderators (Sánchez-Meca & Marín-Martínez, 1997). Accordingly, in the second stage of analysis, the group type was entered as a moderator. For LTLE patients the magnitude of the differences was relatively small (df = 17, Hedges' g = −.41, $p < .01$,

Table 1 Summary of studies ($n = 13$) that compared children with TLE to controls

ID	Article	Participants (group, n, age)	Experimental Design	Seizure onset (years)
1	Cohen, 1992	LTLE: 12, 9.96 ± 3 RTLE: 12, 12.08 ± 2.78 C: 70, Range 6-12 (years)*	BGC	LTLE: 4.40 ± 2.69 RTLE: 5.08 ± 3.67
2	Jambaqué et al., 1993	LTLE: 12 RTLE: 6 TLE Age: 10.9 ± 2 (Range 7.5-14.5), (calculated for n=60). C: 60, 11 ± 1.9 (Range 7.5-14.5)	BGC	7.08 ± 3 (Range 1.25-12.9), (calculated for n=60)
3	Beardsworth & Zaidel, 1994	LTLE: Pre: 13, 14 ± 0.59 Post: 11 RTLE: Pre 16, 12.9 ± 0.59 Post: 10 C: 18, 12.6 (Range 12-13)	BGC, pre-post	LTLE: 5.1 ± 0.65 RTLE: 5.3 ± 0.65
4	Hershey et al., 1998	LTLE: 15, 11.24 ± 2.6 RTLE: 13, 11.16 ± 2.4 C: 19, 11.53 ± 2.7	BGC	LTLE: 5.6 ± 2.9 RTLE: 5.7 ± 3.7
5	Lendt et al., 1999	LTLE: 10, (Range 10-16)* RTLE: 10, (Range 10-16)* C-I (healthy children): 30, 13.6 (Range 10-16)* C-II (non- surgical children with epilepsy): 38, 13.5 (Range 9-16)*	BGC, pre-post	LTLE: 6.8 ± 3.6 (Range 1-12) RTLE: 9.7 ± 3.8 (Range 2-15)
6	Guimarães et al., 2007	TLE: 25 (LTLE: 14 / RTLE: 9 / Bilateral: 2) C: 25	BGC	TLE: 4.6 ± 2.9
7	Jambaqué et al., 2009	LTLE: 10, 13 ± 1.3 (Range 11-15) RTLE: 10, 13.2 ± 1.1 (Range 11-15) C: 40, 13 ± 1.2 (Range 11-15)	BGC	LTLE: 4.9 ± 2.2 RTLE:5.3 ± 2.3
8	Leunen et al., 2009	LTLE: 8, 12.7 ± 2.6 RTLE: 8, 11.1 ± 3.2 C: 16, 13.2 ± 2.3	BGC	LTLE: 6.3 ± 3.7 RTLE: 5.7 ± 3.2
9	Rzezak et al., 2011	LTLE: 10 RTLE: 17 MTS: 11.46 ± 2.06 (Range 8-16), (calculated for n=19)** C: 28, 11.96 ± 2.3 (Range 9-16)	BGC	TLE: 4.58 ± 3.3**
10	Gascoigne et al., 2014	LTLE: 15, 14 ± 5.9 RTLE: 6, 11.3 ± 5.2 C: 58, 11.4 ± 2.8	BGC	LTLE: 5.0 ± 6.1 RTLE: 7.0 ± 4.7 (Age diagnosed)
11	Mankinen et al., 2014	TLE: 21, 11.7 ± 2.1 (Range 8 - 15)** C: 21, (Range 8 - 15)*	BGC	TLE: 9.15 ± 3.1
12	Martins et al., 2015	LTLE: 11, 13 ± 2.75 RTLE: 10, 13 ± 2.75 C: 42	BGC	LTLE: 6.6 ± 4.2 RTLE: 6.8 ± 4.5
13	Rzezak et al., 2017	TLE: 38, 11.92 ± 2.28 (Range 8-16)** C: 28, 11.96 ± 2.30 (Range, 9-16)	BGC	TLE: 4.49 ± 3.30

*No Mean and/or SD and/or Range were documented

**No side discrimination

TLE temporal lobe epilepsy, *LTLE* left temporal lobe epilepsy, *RTLE* right temporal lobe epilepsy, *C* control group, *BGC* between group comparison, *RT* right temporal, *LT* left temporal, *MTS* mesial temporal sclerosis, *CAE* childhood absence epilepsy, *FLE* frontal lobe epilepsy, *ATL* anterior temporal lobectomy, *AH* amygdalo-hippocampectomy, *ATR a*nterior temporl resection, *TR* temporal resection, *AMTL* anteromesial temporal resection

95% CI [−.74, -.09]; $Q = 56.44$, $p < 0.05$, $\tau^2 = 0.31$, $I^2 = 71.65\%$). For RTLE patients the magnitude of the differences was also relatively small (df = 17, Hedges' g = −.34, $p < .01$, 95% CI [−.78, .10]; $Q = 83.71$, $p < .01$, $\tau^2 = 0.64$, $I^2 = 82.08\%$, see Fig. 2a). For both groups, the Q values indicated effect size heterogeneity and therefore the presence of additional moderator(s). Accordingly, in the third stage, paradigm type was entered as a moderator in each of the two patient groups: LTLE patients, verbal memory paradigm, df = 8, Hedges' g = −.76, $p < .01$,

Table 2 Summary of studies ($n = 14$) that compared children with TLE before and after epilepsy surgery on memory paradigms

ID	Article	Participants (group, n, age)	Experimental Design	Seizure onset (years)	Age at surgery (years)	Type of surgery	Seizure outcome after surgery	Time intervals of follow up tests after surgery (months)
1	Beardsworth & Zaidel, 1994	LTLE: Pre: 13, 14 ± 0.59 Post: 11 RTLE: Pre 16, 12.9 ± 0.59 Post: 10 C: 18, 12.6 (Range 12-13)	BGC, pre-post	LTLE: 5.1 ± 0.65 RTLE: 5.3 ± 0.65	LTLE: 14 ± 0.59 RTLE: 12.9 ± 0.59	ATL (27) AH (2)	N/A	6
2	Szabo et al., 1998	LTLE: 7* RTLE: 7*	Pre-post	LTLE: 3.7 ± 2.4 RTLE: 3.4 ± 2.1 (Range 0.2 - 8)	LTLE: 8.7 ± 1.2 RTLE: 10.1 ± 1.7 (Range 7-12)	TR (14): 7 LT, 7 RT Patients with MTS or mesial temporal tumors had more limited anterior and mesial temporal resections, whereas patients with neocortical tumors, cortical dysplasia, or temporal lobe atrophy had more extensive resections involving the lateral neocortex.	13 patients (93%) had no seizures or less than one seizure a year at follow-up 23-48 months (mean 34 months) after operation. 10 patients (71%) were completely seizure-free, 3 patients (21%) had rare seizures, less than one a year, and 1 patient had recurrences of her seizures within 6 months of her surgery; they were more frequent but milder than the pre-operative seizures.	6-9 (mean 7) for 13 patients. 32 (after the first operation) and 36 (after first testing) for 1 patient who underwent two-stage resection of a tumor.
3	Lendt et al., 1999	LTLE: 10, (Range 10-16)* RTLE: 10, (Range 10-16)* C-I (healthy children): 30, 13.6 (Range 10-16)* C-II (non- surgical children with epilepsy): 38, 13.5 (Range 9-16)*	BGC, pre-post	LTLE: 6.8 ± 3.6 (Range 1-12) RTLE: 9.7 ± 3.8 (Range 2-15)	LTLE: 12.5 ± 1.9 (Range 10-16) RTLE: 15.1 ± 1.4 (Range 12-16)	ATR (16): 9 RT, 7 LT Selective AH (4): 1 RT, 3 LT	Postoperative seizure outcome at the first-year follow-up was equally good in children with RTLE (70% seizure free since surgery) and LTLE (70%).	3 and 12

Table 2 (continued)

ID	Article	Participants (group, n, age)	Experimental Design	Seizure onset (years)	Age at surgery (years)	Type of surgery	Seizure outcome after surgery	Time intervals of follow up tests after surgery (months)
4	Robinson, 2000	Pre-22 / Post-21 LTLE: 14 * RTLE: 8 *	Pre-post	5.2 (Range 0.67 -12.4), (calculated for n=22)* **	15.4 (Range 9.4-21.7), (calculated for n=22)* **	TSA (22)	In 17 patients, follow-up lasted at least 2 years and 65% of these patients became seizure free. Seizure control was achieved in 71% of the 21 patients with at least 1 year of follow-up.	37.2 (Range 14-66)
5	Gleissner et al., 2002	LTLE: 26* RTLE: 29* (Range 6 - 17)	Pre-post	LTLE: 7.8 ± 4.7 (Range 1-16) RTLE: 6.8 ± 4.3 (Range 1-15)	LTLE: 13.1 ± 3.1 (Range 7-17) RTLE: 13.5 ± 2.7 (Range 6-17)	LPTR (26) RPTR (29) AH (14) LX) (14) LX+ (9) Standard ATR (18)	The surgical intervention led to complete seizure control in about 70% of the patients.	3, 12

Table 2 (continued)

ID	Article	Participants (group, n, age)	Experimental Design	Seizure onset (years)	Age at surgery (years)	Type of surgery	Seizure outcome after surgery	Time intervals of follow up tests after surgery (months)
6	Kuehn et al., 2002	LTLE: 13 * RTLE: 7 *	Pre-post	N/A	LTLE: 12.9 ± 2.8 RTLE: 13.1 ± 4	TR (20): 13 LT, 7 RT LTLE: In 5 patients the surgery included removal of the hippocampus and the amygdala. Sic patients only had o the amygdala removed. RTLE: In all patients, the surgery included removal of the hippocampus and the amygdala.	11 patients (55%) were seizure free postoperatively. 5 (25%) were not free of seizures but had more than 75% reduction in their seizure frequency. In 4 (20%), the seizure frequency was unchanged. LTLE: 8 patients (61.5%) were seizure- free postoperatively. 2 (15.4%) still had seizures but had more than 75% reduction in seizure frequency. In 3 (23.1%), the seizure frequency was unchanged. RTLE: 3 patients (42.9%) were seizure free postoperatively. 3 (42.9%) were not free of seizures but had morethan 75% reduction in seizure frequency. In 1 (14.3%), the seizure frequency was unchanged.	Range 5–15

Table 2 (continued)

ID	Article	Participants (group, n, age)	Experimental Design	Seizure onset (years)	Age at surgery (years)	Type of surgery	Seizure outcome after surgery	Time intervals of follow up tests after surgery (months)
7	Mabbott and Smith, 2003	LTLE: 17, 12.9 ± 3 (Range 7.6-17) RTLE: 18, 12.2 ± 3.3 (Range 5.5-16.7)	Pre-post	LTLE: 7.5 ± 4.3 RTLE: 6 ± 4.6	N/A	LTR (17) RTR (18) 9 children with extra-temporal excisions were included as a comparison group.	LTLE: at least 4 children with left-hemisphere lesions had post-operative seizures. RTLE: more the half of the children in the right-temporal group had post-operative seizures.	LTLE: 14.9 ± 12.7 RTLE: 16.1 ± 16.1
8	Gleissner et al., 2005	Pediatric: LTLE: 19* RTLE: 11* Adult: LTLE: 19* RTLE: 11*	Pre-post	Pediatric: LTLE: 8.3 ± 4.7** RTLE: 7.6 ± 4.7** Adult: LTLE: 8.7 ± 5.1** RTLE: 7.6 ± 5.1** (SD was calculated for n=30 for each group)	Pediatric: LTLE: 12.7 ± 2.9** RTLE: 13.6 ± 2.9** (Range 7-17) Adult: LTLE: 30.4 ± 6.6** RTLE: 30.7 ± 6.6** (Range 21-46) (SD was calculated for n=30 for each group)	TR (60): 11 RT, 19 LT Pediatrics: LTLE: AH (2), AL (10), LX (7) RTLE: AH (0), AL (7), LX (4) Adults: LTLE: AH (2), AL (12), LX (5) RTLE: AH (0), AL (8), LX (3)	Pediatric: 80% (24 of 30) were seizure-free 3 months and 1 year after surgery. Adults: 70% (21 of 30) were seizure-free at the short-term follow-up and 63.3% (19 of 30) were seizure free 1 year after surgery.	3, 12
9	Smith, Elliott & Lach, 2006	Pre-op TLE: 30, 13.3 ± 2.7 (Range 8 - 15)** Post-op TLE: 27, 1 * **	Pre-post (note that, surgical candidate patients were compared to non-surgical patient data obtained from different samples)	TLE: 6.4 ± 3.5	N/A	N/A	13 children became seizure- free	The first follow-up took place on average 12 months after surgery (range 10.8–14.4), and the second follow-up was conducted on average 28.8 months (range 21.6–40.8) after surgery. Since no differences were found between the first and the second follow-ups, the first follow-up was used for the current analysis

Table 2 (continued)

ID	Article	Participants (group, n, age)	Experimental Design	Seizure onset (years)	Age at surgery (years)	Type of surgery	Seizure outcome after surgery	Time intervals of follow up tests after surgery (months)
10	Jambaqué et al., 2007	LTLE: 12, 10.8 ± 2.5 RTLE: 8, 12.8 ± 1.7 (Range 7-14)	Pre-post	LTLE: 4.4 ± 3.7 RTLE: 6.7 ± 3.2	LTLE: 11.1 ± 2.5 RTLE: 13.3 ± 1.2	Surgery resection involved the temporal pole, the hippocampus, the parahippocampal gyrus and the amygdala in 17 patients. The resection was extended further to the more posterior part of temporal lobe in 3 of these (1 left, 2 right). The 3 remaining patients had more circumscribed resections: LX+ in 1 patient and AH in 2 patients in the LT group.	All patients were seizure- free following surgery.	LTLE: 14.4 ± 7.2 RTLE: 9.6 ± 4.8
11	Leunen et al., 2009	LTLE: 8, 12.7 ± 2.6 RTLE: 8, 11.1 ± 3.2 C: 16, 13.2 ± 2.3	BGC	LTLE: 6.3 ± 3.7 RTLE: 5.7 ± 3.2	LTLE: 11.5 ± 2.5 RTLE: 11.1 ± 3.2	AMTL (16)	All patients had been seizure free for at least at 6 months post-surgery.	N/A
12	Gonzalez et al., 2012	Pre-43 / Post-24 LTLE: Pre 22, Post 11 RTLE: Pre 21, Post 13 TLE age: 11.76 ± 3.17** (Range 8-23) (Age was calculated for n=24)	Pre-post	TLE: 6.31 ± 4.13** (Age was calculated for n=24)	TLE: 12.43 ± 4.74** (Age was calculated for n=24)	RTR (9) LTR (5) LX (8) ATR, including hippo-campecto-mies (6)	64% (9) of the surgical group were seizure- free	32.76 ± 13 (minimum of 12–month interval from surgery (range 1.17–4.75 years))

Table 2 (continued)

ID	Article	Participants (group, n, age)	Experimental Design	Seizure onset (years)	Age at surgery (years)	Type of surgery	Seizure outcome after surgery	Time intervals of follow up tests after surgery (months)
13	Bailey, 2013	Pre - 74 / Post - 47	Pre-post The groups compared were patients undergoing TLE surgery in the iMRI and the standard operating suites (those without imaging capabilities).	4.95 (Range 0-17.21)* (Calculated for n=74)	12.09 (Range 1.10-21.82)* (Calculated for n=74)	Right (30) Left (36) Bilateral (8) ATL (56) FTL (2) PTL (1) Modified ATL (2) TL (5) Multiple Lobes [>2] (2) Tumor Excision (6)	At least 75% of patients were considered to have made significant seizure improvement (i.e., greater than 90% seizure reduction); with over half of the subjects reporting complete freedom from disabling seizures at each time point.	47 patients at T1 (11.71 ± 6.06, Range 2.07-31.05) 14 patients at T2 (26.27 ± 9.10, Range 16.03 - 49.77) 11 patients at T3 (51.99 ± 24.31)
14	Lah and Smith, 2015	LTLE: 22, 13.64 ± 2.89 RTLE: 18, 13.01 ± 3.74	Pre-post	LTLE: 9 ± 4.65 RTLE: 7.15 ± 3.76	LTLE: 14.79 ± 2.99 RTLE: 13.66 ± 3.77	TR (40) The hippocampus was spared in 10 patients and was resected in 30 patients. The resection of the hippocampus was complete in 25 patients and incomplete in 4 patients. In 1 patient, it was impossible to determine whether the hippocampal resection was complete or not.	1-year post-TL, 60% of the children became seizure-free. LTLE: 14 were seizure- free, 8 were not. RTLE: 10 were seizure- free, 8 were not.	12

Table 2 (continued)

ID	Article	Participants (group, n, age)	Experimental Design	Seizure onset (years)	Age at surgery (years)	Type of surgery	Seizure outcome after surgery	Time intervals of follow up tests after surgery (months)
12	Law et al., 2017	TL: LTLE: 13, 13.72 ± 2.89 (Range 7.53-17.24) RTLE: 10, 12.92 ± 4.42 (Range 5.42-18.7) TL+M: LTLE: 22, 13.66 ± 3.17 (Range 6.83-18.27) RTLE: 18, 13.84 ± 3.16 (Range 8.04-17.76)	Pre-post	TL: LTLE: 9.4 ± 4.21 (Range 2-15.92) RTLE: 7.17 ± 5.57 (Range 0.67-16.17) TL+M: LTLE: 7.85 ± 5.2 (Range 0.75-16) RTLE: 7.16 ± 4.75 (Range 0.25-16)	TL: LTLE: 14.37 ± 2.85 (Range 8.79-18.54) RTLE: 13.92 ± 4.28 (Range 5.94-18.29) TL+M: LTLE: 14.52 ± 2.9 (Range 8.49-18.33) RTLE: 14.39 ± 3.36 (Range 8.11-18.09)	TL (23): 13 LT, 10 RT TL+M (40): 22 LT, 18 RT	TL seizure- free (7), TL continuing seizures (6). TL+M seizure- free (15), TL+M with seizures (7).	TL: LTLE: 11.4 ± 3.2 (Range 2.9-15.2) RTLE: 12.8 ± 1 (Range 10.6-14.2) TL+M: LTLE: 14 ± 4.2 (Range 10.6-30.9) RTLE: 12.7 ± 3.2 (Range 4.6-21.3)

*No Mean and/or SD and/or Range were documented

**No side discrimination

TLE Temporal lobe epilepsy, *LTLE* Left temporal lobe epilepsy, *RTLE* Right temporal lobe epilepsy, *MTS* Mesial temporal sclerosis, *LT* Left temporal, *TR* Temporal resection, *LTR* Left temporal lobe resection, *RTR* Right temporal lobe resection, *LPTR* Left partial temporal lobe resection, *RPTR* Right partial temporal lobe; resection, *ATR* Anterior Temporal Resection, *AL* Lobectomy or Lesionectomy including the Hippocampus, *ATL* Anterior temporal lobectomy, *AH* Amygdalo-Hippocampectomy, *LX* Lesionectomy, *LX+* Lesionectomy or partial resection including the Hippocampus, *TSA* Transparahippocampal variation of selective amygdalohippocampectomy, *FTL* Frontotemporal Lobectomy, *PTL* Parietotemporal Lobectomy, *TL* Temporal Lobectomy, *TL+M* patients who underwent temporal lobectomy that included resection of mesial structures

Table 3 Summary of cognitive measures and outcomes in studies ($n = 13$) that compared children with TLE to controls

ID	Article	Memory measures	Othercognitive measures	IQ Results	Main Memory Results	Cohen's D for memory row scores performance on delayed recall
1	Cohen, 1992	Comprehensive Children's Memory Scale (Experimental Edition); (Cohen, Holmes, Campbell, Smith, & Flanigin, 1990): Verbal: digit span, sentence repetition, passage recall, verbal learning with selective reminding, auditory paired associate learning test. Nonverbal**:** memory for designs (motor-free), Nonverbal Sequential Memory Test, Sequential Hand Movements, Sequential Touch Test, Non-verbal Paired Associate Learning, delayed tactile/kinesthetic recall.	WISC-R (Wechsler, 1974). Otis-Lennon Mental Ability Test (Otis & Lennon, 1988).	LTLE = RTLE; LTLE < Controls; RTLE < Controls (FSIQ; Measured by the Otis-Lennon for Controls and by WISC-R for patients).	Auditory/Verbal memory subtests: On all five subtests (immediate and 10-min delay): Controls>LTLE. Selective Reminding subtest (learning and 5-min delay): RTLE>LTLE. Visual/Spatialmemory subtests: On two of the six subtests (Visual Sequential Memory and Sequential Hand Movements): Controls>LTLE & Controls>RTLE / RTLE=LTLE.	LTLE - C Verbal delayed recall -1.2, RTLE - C Verbal delayed recall -0.17, LTLE - C Visual delayed recall -0.68, RTLE - C Non-verbal delayed recall -0.31.

Table 3 (continued)

ID	Article	Memory measures	Othercognitive measures	IQ Results	Main Memory Results	Cohen's D for memory row scores performance on delayed recall
2	Jambaqué et al., 1993	B.E.M 144 (Signoret, 1991): Verbal: immediate story recall, delayed story recall, word list learning, delayed word list recall, sentence recognition, word associated pairs. Nonverbal: immediate geometric figure recall, delayed geometric figure recall, design list learning, delayed design list recall, figure recognition, figure associated pairs.	WISC-R (Wechsler, 1974).	LTLE = RTLE (FIQ).	Verbal and non-verbal memory: [Control vs. Patients (no side descrimination)] On all memory tasks: Controls>TLE. [Control vs. Patients] On all verbal and non-verbal memory tasks (immediate and 10-min delay; except for Figure Recognition): Controls>LTLE. [Control vs. Patients] On Word list recall (immediate and 10-min delay) and on all non-verbal memory tasks: Controls>RTLE. Comparison between groups: [LTLE vs. RTLE] On the story recall task (immediate and 10-min delay) and for the calculated Verbal Memory Score: RTLE>LTLE. [LTLE vs. RTLE] For the calculated Non-verbal Memory Scores (except for Associated Pairs): LTLE>RTLE.	LTLE - C Verbal delayed recall -1, RTLE - C Verbal delayed recall -1.11, LTLE - C Non-verbal delayed recall -0.56, RTLE - C Non-verbal delayed recall -1.73
3	Beardsworth and Zaidel, 1994	Nonverbal: BMCFT (Beardsworth & Zaidel, 1994).	WISC-R (Wechsler, 1974).	LTLE = RTLE (PIQ, VIQ and FSIQ).	Non-verbal memory, preoperatively: Delayed memory trial (30-min): LTLE>RTLE. On all six trials (immediate and 30-min delay): Controls>RTLE. Non-verbal memory, postoperatively: Delayed memory trial (30-min): LTLE>RTLE.	RTLE -C pre Delayed recall -0.63 RTLE pre-post Delayed recall 0.71 RTLE-C Post Delayed recall -0.66

Table 3 (continued)

ID	Article	Memory measures	Othercognitive measures	IQ Results	Main Memory Results	Cohen's D for memory row scores performance on delayed recall
4	Hershey et al., 1998	Verbal: Immediate and delayed story recall (Craft, Zallen, & Baker, 1992;. Verbal span (digit span): with and without an interference condition (Hale, Myerson, Rhee, Weiss, & Abrams, 1996; Baddeley, 1992). Nonverbal: SDR (Luciana, Depue, Arbisi, & Leon, 1992). Pattern recall task (Craft et al., 1992). DMS; (different stimuli were used to make the task more challenging). Spatial span: with and without an interference condition (Hale et al., 1996; Baddeley, 1992).	WISC-III (Wechsler, 1991): information and block design subtests. The Stroop color and word test (the authors developed a similar task to the standardized version).	LTLE = RTLE; LTLE < Controls; RTLE < Controls (Information and Block Design subtests from WISC-III).	Nonverbal: [Control vs. Patients] On the SDR task (60-sec delay): Controls>LTLE & Controls>RTLE.	LTLE - C Verbal delayed recall -0.4, RTLE - C Verbal delayed recall -2, LTLE - C Non-verbal delayed recall -0.91, RTLE - C Non-verbal delayed recall -1.43
5	Lendt et al., 1999	Verbal: VLMT (Helmstaedter & Durwen, 1990): a German version of the RAVLT (Rey, 1964; Schmidt, 1996). Nonverbal: DCS-R (Weidlich & Lamberti, 1980).	D2 test (Brickenkamp, 1962). The token test (Orgass, 1982) and subtest 6 of the "Leistungspruf-system" written word fluency. Subtests 3-6 of the block-design test from the German Wechsler Intelligence Scale for Adults (HAWIE; Wechsler, 1964).	N/A	No significant differences were found between groups in verbal or figural memory performance.	LTLE - C Verbal delayed recall -0.79, RTLE - C Verbal delayed recall -0.21, LTLE - C Non-verbal delayed recall -0.43, RTLE - C Non-verbal delayed recall -0.61

Table 3 (continued)

ID	Article	Memory measures	Othercognitive measures	IQ Results	Main Memory Results	Cohen's D for memory row scores performance on delayed recall
6	Guimarães et al., 2007	Verbal & Nonverbal: WRAML (Sheslow & Adams, 1990).	WISC-III: subtests of block design and vocabulary (Wechsler, 1991). Verbal fluency test (Spreen & Strauss, 1998). BNT (Kaplan, Goodglass & Weintraub, 1983). Digit span (subtest of WISC-III; Wechsler, 1991). Perception of shapes and colors (Spreen & Strauss, 1998). Wisconsin card sorting test (Heaton, Chelune, Talley, et al., 1993). Trail making test for children A and B (Spreen & Strauss, 1998). Block design (subtest of WISC-III; Wechsler, 1991).	TLE < Controls (Estimated IQ based on Block Design and Vocabulary subtests from WISC-III).	Group differences: [Control vs. Patients (no side discrimination)] On WRAML subtests - delayed recall of verbal learning, delayed recall for stories (verbal) and recognition of stories (verbal)): Controls>Patients.	
7	Jambaqué et al., 2009	Verbal: Story recall (B.E.M 144; Signoret, 1991). Recall of words lists: learning and recall of two lists of words (12 common words and 12 emotional words).	WISC-III (Wechsler, 1991).	LTLE = RTLE (PIQ, VIQ and FIQ).	Verbal: [Controls vs. Patients] On Story Recall (immediate and 10-min delay): Controls>LTLE. [LTLE vs. RTLE] On Story Recall (immediate and 10-min delay): RTLE>LTLE.	LTLE - C Verbal delayed recall -0.13, RTLE - C Verbal delayed recall 0.31

Table 3 (continued)

ID	Article	Memory measures	Othercognitive measures	IQ Results	Main Memory Results	Cohen's D for memory row scores performance on delayed recall
8	Leunen et al., 2009	Verbal: The material included 16 words belonging to 16 different semantic categories selected from the Novlex lexical database (Lambert & Chesnet, 2001). Nonverbal: Spatial learning task: the material included 16 familiar pictures from Bonin et al. (Bonin, Peereman, Malardier, Méot & Chalard, 2003), belonging to 16 different semantic categories.	WISC-R (Wechsler, 1974).	N/A	Verbal: [Controls vs Patients] Verbal recall (learning and 15-min delay): Controls>LTLE. [LTLE vs. RTLE] Verbal recall (learning and 15-min delay): RTLE>LTLE.	LTLE - C Verbal delayed recall -2.09, RTLE - C Verbal delayed recall -0.71, LTLE - C Non-verbal delayed recall -0.57. RTLE - C Non-verbal delayed recall -0.73
9	Rzezak et al., 2011	Verbal: Episodic memory: story memory and verbal learning subtests from WRAML (Sheslow & Adams, 1990). Semantic memory: sentence memory subtest from WRAML; vocabulary subtest from WISC-III (Wechsler, 1991); verbal fluency (animals and foods): subjects were instructed to orally generate a list of animals and foods; BNT (Kaplan, Goodglass & Weintraub, 1983). Nonverbal: Episodic memory: picture memory, design memory and non-verbal learning subtests from WRAML.	WISC-III: block design and vocabulary subtests (Wechsler, 1991).	N/A	Non-verbal : [Control vs. Patients (no side discrimination)] Non-verbal learning recall (30-min delay): Control > TLE	LTLE post-pre-Verbal delayed recall 0.08, RTLE post-pre Verbal delayed recall 0.60, LTLE post-pre Non-verbal delayed recall 0.41, RTLE post-pre Non-verbal delayed recall 0.24

Table 3 (continued)

ID	Article	Memory measures	Othercognitive measures	IQ Results	Main Memory Results	Cohen's D for memory row scores performance on delayed recall
10	Gascoigne et al., 2014	Verbal: Story memory subtest from WRAML (Second edition; Sheslow & Adams, 1990). Word recall: word lists from CVLT-C (Delis, Kramer, Kaplan, & Ober, 1994). Nonverbal: Dot location subtest from CMS (Cohen, 1997). Design location task (Hepworth and Smith, 2002).	Vocabulary and matrix reasoning subtests from WASI (Wechsler, 1999).	LTLE < Controls; RTLE = Controls (FSIQ).	Verbal: [Control vs. Patients] On Story Memory (immediate and 30-min delay) and Word Recall task (2-min and 7-day delay): Control>LTLE. Non-verbal : [Control vs. Patients] On CMS: Dot Location (30-min delay): Control>LTLE.	TLE - C Verbal delayed recall -0.52, TLE - C Non-verbal delayed recall -0.69 * for LTLE and RTLE only median (QRL) scores are available
11	Mankinen et al., 2014	Verbal: Episodic memory: memory for names, narrative memory, sentence repetition and list learning, from NEPSY (Korkman, Kirk, Kemp, 1998).	WISC-III (Wechsler, 1991). Phonological processing, design copying, verbal fluency and comprehension of instructions subtests from NEPSY (Korkman, Kirk, Kemp, 1998).	LTLE = RTLE.	No significant differences were found between groups in verbal or figural memory performance.	TLE -C Delayed recall for names -0.62 TLE -C Delayed recall for narrative memory -0.52
12	Martins et al., 2015	The WHAT–WHERE–WHEN procedure (Martins et al., 2015): The WHAT investigated factual associations, The WHERE investigated spatial associations, The WHEN investigated sequential associative memory.	WISC-IV (Wechsler & Schelini, 2006).	N/A	Nonverbal: [Controls vs. Patients] Spatial recollection: Controls>LTLE and Controls>RTLE.	LTLE - C Non-verbal delayed recall -0.80. RTLE - C Non-verbal delayed recall -0.77

Table 3 (continued)

ID	Article	Memory measures	Othercognitive measures	IQ Results	Main Memory Results	Cohen's D for memory row scores performance on delayed recall
13	Rzezak et al., 2017	Verbal: Story memory, verbal learning and sentence memory subtests from WRAML (Sheslow & Adams, 1990). Nonverbal: Scene memory, design memory and non-verbal learning subtest from WRAML.	Block design and vocabulary subtests from WISC-III (Wechsler, 1991). Digit span subtest from WISC-III (Wechsler, 1991). Number & Letter subtest from WRAML (Sheslow & Adams, 1990). Finger windows subtest from WRAML (Sheslow & Adams, 1990). MFFT (Kagan, Rosman, Day, Albert & Phillips, 1964) Trail making test (Reitan & Wolfson, 1985). Wisconsin card sorting test (Heaton, Chelune, Talley, et al., 1993). Verbal fluency (for foods and animals).	TLE < Controls (Estimated IQ based on Block Design and Vocabulary subtests from WISC-III).	Group comparison with no IQ correction: [Control vs. Patients (no side discrimination)] On Story Memory (verbal) (immediate and 30-min delay): Controls>TLE.	

B.E.M 144 Signoret's Memory Battery, *BMCFT* The Beardsworth Memory for Children's Faces Test, *BNT* Boston Naming Test, *CAVLT* Children's Auditory Verbal Learning Test, *CMS* Children's Memory Scale, *CVLT* California Verbal Learning Test, *CVLT-C* California Verbal Learning Test – Children's Version, *DCS-R* Diagnosticurn fur Cerebralschaden, *DMS* Delayed Match to Sample, *FIQ* Full Scale Intelligence Quotient, *FSIQ* Full Scale Intelligence Quotient, *IQ* Intelligence Quotient, *MFFT* Matching Familiar Figures Test, *NEPSY* A Developmental Neuropsychological Assessment, *PIQ* Performance Intelligence Quotient, *RAVLT* Rey Auditory Verbal Learning Test, *SDR* Spatial Delayed Response Task, *VIQ* Verbal Intelligence Quotient, *VLMT* Verbal Learning and Memory Test, *WASI* Wechsler Abbreviated Scale of Intelligence, *WIAT* Wechsler Individual Achievement Test, *WIAT-II* Wechsler Individual Achievement Test: Second edition, *WISC-III* Wechsler Intelligence Scale for children: Third edition, *WISC-IV* Wechsler Intelligence Scale for Children: Forth edition, *WISC-R* Wechsler Intelligence Scale for children: Revised, *WRAML* Wide Range Assessment of Memory and Learning, *WRAT-III* Wide Range Achievement Test: Third edition

Table 4 Summary of cognitive measures and outcomes in studies ($n = 12$) that compared children with TLE before and after surgery

ID	Article	Memory measures	Other cognitive measures	IQ Results	Main Results	Cohen's D for memory row scores performance on delayed recall
1	Szabo et al., 1998	Verbal: CAVLT-2 (Talley, 1993).	WISC-R (Wechsler, 1974) or WISC-III (Wechsler, 1991).	Pre = Post (PIQ, VIQ and FIQ)	Verbal: [Pre vs. Post (no side discrimination)] For delayed verbal memory recall (30-min delay): Pre>Post.	LTLE post- pre-Verbal delayed recall -0.90, RTLE post-pre Verbal delayed recall -0.06
2	Robinson, 2000	Verbal: BNT (Kaplan, Goodglass, Weintraub, 1983). WRAML (Sheslow & Adams, 1990). WMS-R (Wechsler, 1987). CVLT-C or CVLT-A (Delis, Kramer, Kaplan, & Ober, 1994). Nonverbal: WRAML or the Rey Complex Figure (Rey, 1964).	WISC-III (Wechsler, 1991) or WAIS-R (Wechsler, 1981).	LTLE = RTLE both Pre and Post, Pre = Post (PIQ, VIQ and FIQ) *Although no group differences were found, there was an improvement in postoperative VIQ and FIQ scores in the seizure-free patients, compared to patients who had persistent seizures.	Pre-Post: [Pre vs. Post] Rote verbal memory (delayed recall): Post>Pre (only for patients who underwent TSA on the right side).	LTLE post-pre Verbal delayed recall -0.25, RTLE post-pre Verbal delayed recall 1.06, LTLE post-pre Non-verbal delayed recall -0.01, RTLE post-pre Non-verbal delayed recall -0.17
3	Gleissner et al., 2002	Verbal: VLMT (Helmstaedter et al., 2000; a recently standardized German version of the AVLT (Rey, 1964; Schmidt, 1996)).	WISC. Colored Progressive Matrices or Standard Progressive Matrices. K-ABC. Vocabulary estimate, similar to the widely used NART. Attention functions were assessed pre and post-operatively with a letter cancellation test measuring psychomotor speed (Brickenkamp, 1978).	LTLE = RTLE (Preoperative IQ).	Pre-Post findings: [Pre vs. .Post] In learning capacity and loss after delay: Pre>Post (for the LTLE group and only 3 month after surgery). [Pre vs. Post] In recognition (30-min delay): Pre>Post (for the RTLE group and only 3 month after surgery). Group Comparison: [LTLE vs. RTLE] In learning capacity and loss after delay (3 month after surgery): RTLE>LTLE.	LTLE post- pre Verbal delayed recall -0.24, RTLE post-pre Verbal delayed recall -0.24
4	Kuehn et al., 2002	WRAML (Sheslow & Adams, 1990).	WPPSI-R (Wechsler, 1989), WISC-III (Wechsler, 1991), WAIS-R (Wechsler, 1981), or WAIS-III (Wechsler, 1997).	LTLE = RTLE; Pre = Post (PIQ, VIQ and FIQ).	*No significant differences relevant to delayed recall were reported.	LTLE post- pre Verbal delayed recall -0.05, LTLE post-pre Non-verbal delayed recall 0.15

Table 4 (continued)

ID	Article	Memory measures	Other cognitive measures	IQ Results	Main Results	Cohen's D for memory row scores performance on delayed recall
5	Mabbott and Smith, 2003	Verbal: Story Recall: Denman neuropsychology memory scale (Denman, 1984) and Children's stories for testing long-term memory (Kimura & McGlone, 1979). CAVLT (Talley, 1993). Nonverbal: Recall of a complex geometric figure design (The test of copying a complex figure; Osterrieth, 1944 and The psychological examination in cases of traumatic encephalopathy; Rey, 1964). Face recognition (Denman neuropsychology memory scale; Denman, 1984).	WISC-III (Wechsler, 1991).	LTLE = RTLE both Pre and Post, Pre = Post (FIQ)	Nonverbal memory: [Pre vs. Post (no side discrimination)] Recognition of unfamiliar faces (90-sec delay): Post>Pre. [LTLE.vs.RTLE] Recognition of unfamiliar faces (90-sec delay): LTLE>RTLE (only post-operatively).	LTLE post-pre Verbal delayed recall -0.30, RTLE post-pre Verbal delayed recall 0.41, LTLE post-pre Non-verbal delayed recall -0.27, RTLE post-pre Non-verbal delayed recall 0.31, LTLE post-pre faces delayed recall 0.83, RTLE post-pre faces delayed recall 0.96

Table 4 (continued)

ID	Article	Memory measures	Other cognitive measures	IQ Results	Main Results	Cohen's D for memory row scores performance on delayed recall
6	Gleissner et al., 2005	Verbal: Parallel test versions of the VLMT (Helmstaedter et al., 2000; a recently standardized German version of the AVLT (Rey, 1964; Schmidt, 1996)). Nonverbal: Parallel test versions of a revised version of the DCS-R (Helmstaedter et al., 1991).	Adults - Vocabulary test: 'MWT-B'. This test is similar to the widely used NART test (Nelson, 1982). Pediatrics - MWT-B, Raven's Standard Progressive Matrices (SPM) and a German version of the Wechsler intelligence test for children (HAWIK-III; Tewes et al., 1999). Trail-making test for children, coding (HAWIK); Simple and choice reaction time. D2- test (letter cancellation). C.I.-test (receptive speed and response inhibition). Trail-making test for adults. Semantic Fluency, Vocabulary (HAWIK), Similarities (HAWIK), Boston Naming Test, Token-Test. Phonemic Fluency (COWA, letters: FAS). Naming (Subtest of the Aachener Aphasie Test) or Boston Naming Test Written Phonemic Fluency (Subtest 6 of the LPS, letters: LPS or FRK). Block Design (HAWIK) or Triangles (K-ABC). Mental rotation (Subtest 7 or 8 of the LPS). Chapuis–Mazes.	LTLE = RTLE (Preoperative IQ).	*No significant differences relevant to delayed recall were reported.	LTLE post-pre Verbal delayed recall -0.22, RTLE post-pre Verbal delayed recall -0.70, LTLE post-pre Non-verbal delayed recall 0.13. RTLE post-pre Non-verbal delayed recall 0.14

Table 4 (continued)

ID	Article	Memory measures	Other cognitive measures	IQ Results	Main Results	Cohen's D for memory row scores performance on delayed recall
7	Smith, Elliott & Lach, 2006	Verbal: Story Memory subtest of the CMS or WMS (Cohen, 1997). Nonverbal: Immediate recognition of faces task from the Denman Neuropsychology Memory Scale (Denman, 1987).	N/A	Pre = Post.	*No significant differences relevant to delayed recall were reported.	Pre-post for verbal memory -0.25 Pre-post for nonverbal memory 0.40
8	Jambaqué et al., 2007	Verbal and Nonverbal: B.E.M 144 (Signoret, 1991). RBMT (Wilson, Ivani-Chalian, & Aldrich, 1991; Wilson, Ivani-Chalian, Besag, & Bryant, 1993). *An age-appropriate version was used. Nonverbal: The Rey complex figure (Rey, 1964).	WISC-III (Wechsler, 1991). Coding subtest and the digit span composite score from WISC-III (Wechsler, 1991). Short-term visuospatial span on Corsi's block-tapping test (Nichelli, Bulgheroni, & Riva, 2001). The information (acquisition of general knowledge) and vocabulary (word memory) subtests from WISC-III (Wechsler, 1991) A naming test and a category verbal fluency test (Jambaque & Dellatolas, 2000).	LTLE = RTLE; Pre = Post (PIQ, VIQ and FIQ).	Signoret Memory Battery: [LTLE vs. RTLE] On immediate and delayed figure recall: LTLE>RTLE (only post-operation). Rivermead Behavioral Memory Test: [LTLE.vs.RTLE] On delayed story recall: RTLE>LTLE (only post-operation). Pre and post-surgery differences: [Pre vs. .Post (no side discrimination)] For immediate story recall, immediate word list recall, sentence recognition, and Verbal Memory Score: Post>Pre.	LTLE post-pre Verbal delayed recall -0.18, RTLE post-pre Verbal delayed recall -0.32, LTLE post-pre Non-verbal delayed recall 0.25, RTLE post-pre Non-verbal delayed recall 0.20
9	Gonzalez et al., 2012	Verbal: VPA and WMS-R (Wechsler, 1987). Nonverbal: NBMT-CV (Pentland et al., 2003; adapted from Abrahams et al., 1997). Faces subtest from CMS (Cohen, 1992) or WMS-III; Wechsler, 1997).*Test used was age appropriate.	Block Design and Vocabulary subtest from the WISC-III (Wechsler, 1991) or WASI (Wechsler, 1999).	LTLE = RTLE; Pre = Post (FIQ).	Verbal: [LTLE.vs.RTLE] For VPA hard pairs recalled on delay (30-min delay): RTLE>LTLE. * *Only when age at seizure onset was allowed to covary.	LTLE post-pre Verbal delayed recall 0.28, RTLE post-pre Verbal delayed recall 0.74, LTLE post-pre Non-verbal delayed recall -0.22, RTLE post-pre Non-verbal delayed recall 0.74, LTLE post-pre faces delayed recall 0.04, RTLE post-pre faces delayed recall 0.66

Table 4 (continued)

ID	Article	Memory measures	Other cognitive measures	IQ Results	Main Results	Cohen's D for memory row scores performance on delayed recall
10	Bailey, 2013	Verbal and Nonverbal: WRAML (Sheslow & Adams, 1990).	WISC-III or WISC-IV (Wechsler,1991; 2003). WAIS-III or WAIS-IV (Wechsler, 1997; 2008). WPSSI (Wechsler, 2002). CPT-II (Conners, 2000). WIAT (Wilkinson, 1993).	Pre > Post (only at T1 and only for VIQ); Pre = Post (at times T2 and T3 for FIQ). At baseline, subjects with early onset of epilepsy received significantly lower scores on FSIQ than their late onset counterparts.	Baseline-Post (T1): [Pre vs. Post (no side discrimination)] Verbal memory score: Pre>Post. [Pre vs. .Post (no side discrimination)] Working memory index: Post>Pre (p = .080)*. Baseline-Post (T2): [Pre vs. Post (no side discrimination)] For verbal recognition and working memory: Post>Pre (p = .055 for verbal recognition and p = .067 for working memory)*. *Alpha coefficients of $p < .10$ were considered marginally significant in this study.	TLE post-pre Verbal memory (T1- baseline) -0.35 TLE post-pre Non-verbal memory (T1- baseline) 0.03
11	Lah and Smith, 2015	Verbal: WISC-III (Wechsler, 1991), WISC-IV (Wechsler, 2003), WISC-IV, WAIS-III (Wechsler, 1997), WPPSI-III (Wechsler, 2002), WASI (Wechsler, 1999). EOWPVT, BNT (Kaplan, Goodglass & Weintraub, 1976), EVT (Williams, 1997). CAVLT (Talley, 1993), CVLT-A (Delis, Kramer, Kaplan & Ober, 1987).	WIAT or WIAT-II (Wechsler, 1992; 2002) or the WRAT-III (Jastak & Jastak, 1976). WJ-III (Woodcock, McGrew, & Mather, 2001).	LTLE < RTLE both Pre and Post; Pre = Post (PIQ).	Verbal: -[Controls vs. .Patients] On delayed recall (20-min delay): Mean norm scores > Patient's scores (only for the LTLE group and only post-operation).	LTLE post- pre Verbal delayed recall -1.20, RTLE post-pre Verbal delayed recall 0.2

Table 4 (continued)

ID	Article	Memory measures	Other cognitive measures	IQ Results	Main Results	Cohen's D for memory row scores performance on delayed recall
12	Law et al., 2017	Verbal: CAVLT-II was administered to children ages 17 or younger. CVLT-II was administered to those age 18 or older.	WISC-IV (Wechsler, 2003). WAIS-IV (Wechsler, 2008).	LTLE = RTLE both Pre and Post, Pre = Post (PIQ, VIQ and FIQ).	Delayed Recall: [Pre vs. Post] In delayed recall (20-min delay): Pre>Post for the left TLE+M group only.**Differences weren't significant when a two-way ANOVA was performed, but reached significance when a paired t-test was performed for each group. Impact of preoperative verbal memory: [Pre vs. .Post (no side discrimination)] Mean delayed recall change scores: Pre>Post (for patients with normative (standard score of ≥85) preoperative scores) and Post>Pre (for patients with below-average (standard score <85) preoperative scores). [Pre vs..Post] Mean delayed recall change scores (for patients with below-average preoperative scores): Pre>Post (for the TL+M group) and Post>Pre (for the TL group).	LTLE post- pre Verbal delayed recall -0.30, RTLE post-pre Verbal delayed recall -0.08, LMTS post- pre Verbal delayed recall -0.70, RMTS post-pre Verbal delayed recall 0.18

AVLT Auditory Verbal Learning Test, *BNT* Boston Naming Test, *CAVLT-2* Children's Auditory Verbal Learning Test: Second edition, *CAVLT* Children's Auditory Verbal Learning Test, *CMS* Children's Memory Scale, *CPT-II* Conners' Continuous Performance Test, *CVALT* Children's Auditory Verbal Learning Test, *CVLT-A* California; Verbal Learning Test – Adult's Version, *CVLT-C* California Verbal Learning Test – Children's Version, *DCS-R* Diagnosticum fu¨r Zerebralscha¨digung, *EOWPVT* Expressive One-Word Picture Vocabulary Test, *EVT* Expressive Vocabulary Test, *NART* New Adult Reading Test, *NBMT-CV* Nine Box Maze Test: Child Version, *RBMT* The Rivermead Behavioural Memory Test, *VLMT* Verbal Learning and Memory Test, *VPA* Verbal Paired Associate, *WAIS-III* Wechsler Adult Intelligence Scale: Third Edition, *WAIS-IV* Wechsler Adult Intelligence Scale: Forth Edition, *WAIS-R* Wechsler Adult Intelligence Scale: Revised, *WASI* Wechsler Abbreviated Scale of Intelligence, *WIAT* The Wechsler Individual Achievement Test, *WIAT* The Wechsler Individual Achievement Test: Second edition, *WISC-III* Wechsler Intelligence Scale for children: Third edition, *WISC-IV* Wechsler Intelligence Scale for children: Forth edition, *WISC-R* Wechsler Intelligence Scale for children: Revised, *WJ-III* Woodcock-Johnson: Third Edition, *WMS-III* Wechsler Memory Scale: Third edition, *WMS-R* Wechsler Memory Scale, *WMS-R* Wechsler Memory Scale: Revised, *WPPSI-III* Wechsler Preschool and Primary Scale of Intelligence: Third Edition, *WPPSI-R* Wechsler Preschool and Primary Scale of Intelligence: Revised, *WRAML* Wide Range Assessment of Memory and Learning, *WRAT-III* Wide Range Achievement Test: Third edition

#	Study name / Subgroup name	Hedges' g	CI Lower limit	CI Upper limit
1	Robinson et al., 2000	-0.24	-1.06	0.58
2	Robinson et al., 2000	-0.02	-0.84	0.79
3	Gleissner et al., 2002	-0.24	-0.79	0.31
4	Kuehn et al., 2002	-0.06	-0.84	0.72
5	Kuehn et al., 2002	0.14	-0.64	0.93
6	Mabbott and Smith, 2003	-0.29	-1.19	0.62
7	Mabbott and Smith, 2003	-0.27	-0.98	0.44
8	Mabbott and Smith, 2003	0.80	-0.09	1.69
9	Gleissner et al., 2005	-0.04	-0.69	0.60
10	Gleissner et al., 2005	0.13	-0.52	0.77
11	Jambaqué et al., 2007	-0.17	-0.99	0.64
12	Jambaqué et al., 2007	0.25	-0.57	1.07
13	Gonzalez et al., 2012	0.27	-0.59	1.13
14	Gonzalez et al., 2012	-0.21	-1.07	0.64
15	Gonzalez et al., 2012	0.05	-0.81	0.90
16	Lah and Smith, 2015	-1.18	-1.82	-0.53
17	Law et al., 2017	-0.32	-1.11	0.47
18	Law et al., 2017	-0.69	-1.30	-0.07
19	**LTLE**	**-0.15**	**-0.35**	**0.04**
20	Robinson et al., 2000	1.03	-0.06	2.11
21	Robinson et al., 2000	-0.16	-1.18	0.85
22	Gleissner et al., 2002	-0.24	-0.76	0.28
23	Mabbott and Smith, 2003	0.40	-0.63	1.42
24	Mabbott and Smith, 2003	0.30	-0.43	1.03
25	Mabbott and Smith, 2003	0.93	0.10	1.76
26	Gleissner et al., 2005	-0.74	-1.62	0.15
27	Gleissner et al., 2005	0.14	-0.72	1.00
28	Jambaqué et al., 2007	-0.31	-1.33	0.71
29	Jambaqué et al., 2007	0.19	-0.82	1.21
30	Gonzalez et al., 2012	0.80	-0.14	1.74
31	Gonzalez et al., 2012	0.63	-0.29	1.56
32	Gonzalez et al., 2012	0.66	-0.27	1.59
33	Lah and Smith, 2015	0.20	-0.47	0.86
34	Law et al., 2017	-0.08	-0.98	0.82
35	Law et al., 2017	0.18	-0.48	0.85
36	**RTLE**	**0.21**	**-0.02**	**0.44**
37	Szabó et al., 1998	-0.84	-1.99	0.30
38	Szabó et al., 1998	-0.06	-1.15	1.03
39	Smith, Elliott & Lach, 2006	-0.25	-0.78	0.27
40	Smith, Elliott & Lach, 2006	0.40	-0.15	0.94
41	Bailey et al., 2013	-0.34	-0.82	0.13
42	Bailey et al., 2013	0.03	-0.45	0.52
43	**TLE**	**-0.11**	**-0.40**	**0.18**
44	**Combined Effect Size**	**-0.02**	**-1.45**	**1.41**

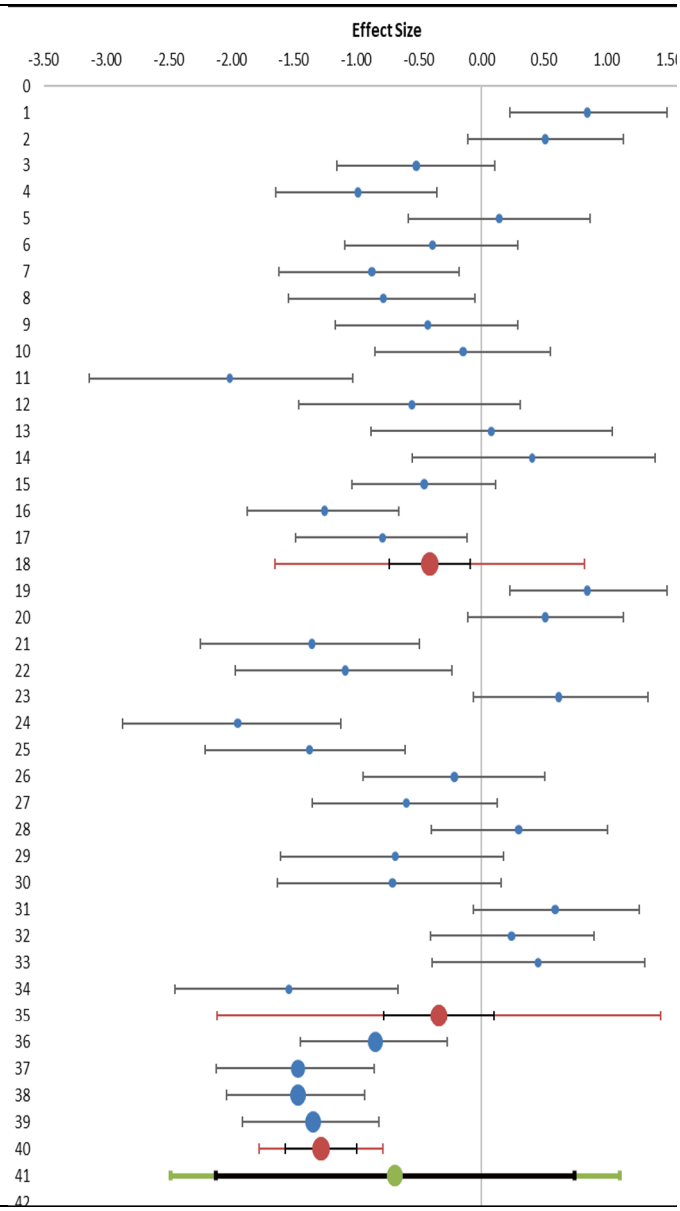

Fig. 2 **a-b** Forest plot of standardized effect sizes and confidence intervals for verbal memory and nonverbal memory in children with TLE compared to controls (2a) and in children TLE pre- compared to post-operative status (2b). Study name are in year of publication order

95% CI [−1.9, .47]; $Q = 45.60$, $p < 0.01$; LTLE patients, nonverbal memory paradigm, df = 8, Hedges' g = −.51, $p < .01$, 95% CI [−1.52, .28]; $Q = 30.72$, $p < 0.01$; RTLE patients, verbal memory paradigm, df = 8, Hedges' g = −.32, $p < .01$, 95% CI [−1.6, 1.07]; $Q = 54.93$, $p < 0.01$; RTLE patients, nonverbal memory paradigm, df = 8, Hedges' g = −.87, $p < .01$, 95% CI [−2.3, .61]; $Q = 63.87$. Therefore, with regard to patients and controls differences, since the Q value still indicated heterogeneity, the mean effect size was not considered a reliable estimation for the data.

Pre-operative versus post-operative differences Twelve studies compared the memory performance of children with TLE before and after surgery, using either verbal, nonverbal or both paradigms (Table 5).

The 12 studies included 39 comparisons of children with either LTLE (18 comparisons), RTLE (16 comparisons) or both (five comparisons). Verbal memory paradigms were used in 21 comparisons and nonverbal paradigms were used in 17 comparisons. In line with the between-groups analyses, the first stage of the meta-analysis included 39 effect sizes that were derived from the verbal and nonverbal paradigms for children with LTLE-RTLE groups in total. The magnitude of the differences was minimal (df = 38, Hedges' g = −.02, $p > .05$, 95% CI [−.16, .13]). A statistical examination of the funnel plot using Egger's regression test resulted in

Study name / Subgroup name	Hedges' g	CI Lower limit	CI Upper limit
Cohen, 1992	0.85	0.22	1.48
Cohen, 1992	0.51	-0.11	1.13
Jambaqué et al., 1993	-0.52	-1.15	0.11
Jambaqué et al., 1993	-0.99	-1.63	-0.34
Beardsworth and Zaidel, 1994	0.14	-0.59	0.86
Hershey et al., 1998	-0.39	-1.08	0.30
Hershey et al., 1998	-0.88	-1.60	-0.16
Lendt et al., 1999	-0.78	-1.53	-0.04
Lendt et al., 1999	-0.43	-1.16	0.30
Jambaqué et al., 2009	-0.15	-0.85	0.55
Leunen et al., 2009	-2.01	-3.07	-0.96
Leunen et al., 2009	-0.56	-1.44	0.33
Rzezak et al., 2011	0.08	-0.89	1.04
Rzezak et al., 2011	0.41	-0.57	1.38
Gascoigne et al., 2014	-0.46	-1.03	0.12
Gascoigne et al., 2014	-1.25	-1.86	-0.65
Martins et al., 2015	-0.79	-1.48	-0.10
LTLE	**-0.41**	**-0.74**	**-0.09**
Cohen, 1992	0.85	0.22	1.48
Cohen, 1992	0.51	-0.11	1.13
Jambaqué et al., 1993	-1.36	-2.23	-0.48
Jambaqué et al., 1993	-1.09	-1.95	-0.22
Beardsworth and Zaidel, 1994	0.62	-0.08	1.32
Hershey et al., 1998	-1.95	-2.82	-1.08
Hershey et al., 1998	-1.37	-2.17	-0.58
Lendt et al., 1999	-0.22	-0.94	0.51
Lendt et al., 1999	-0.60	-1.34	0.14
Jambaqué et al., 2009	0.30	-0.40	1.00
Leunen et al., 2009	-0.69	-1.58	0.20
Leunen et al., 2009	-0.71	-1.61	0.18
Rzezak et al., 2011	0.59	-0.07	1.25
Rzezak et al., 2011	0.24	-0.41	0.89
Gascoigne et al., 2014	0.45	-0.40	1.30
Gascoigne et al., 2014	-1.54	-2.43	-0.65
RTLE	**-0.34**	**-0.78**	**0.10**
Guimarães et al., 2007	-0.85	-1.43	-0.26
Guimarães et al., 2007	-1.47	-2.10	-0.83
Rzezak et al., 2017	-1.47	-2.02	-0.91
Rzezak et al., 2017	-1.35	-1.89	-0.80
TLE	**-1.28**	**-1.57**	**-1.00**
Combined Effect Size	**-0.69**	**-2.13**	**0.74**

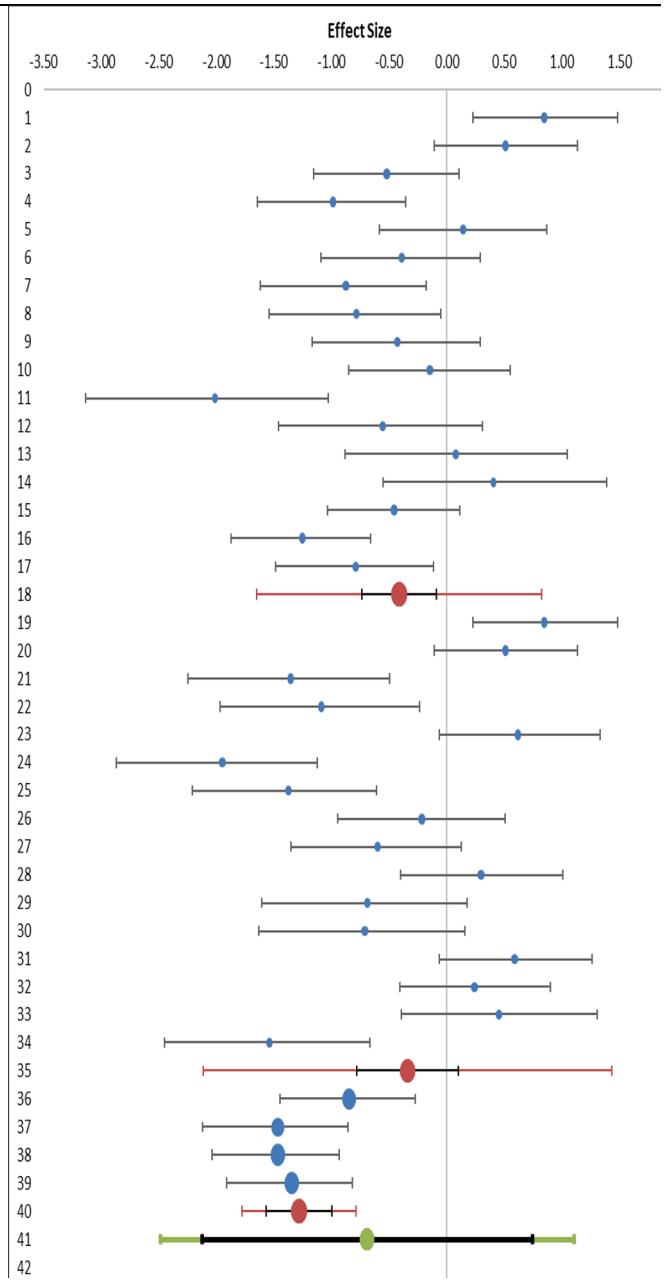

Fig. 2 (continued)

a non-significant model, suggestive of a lack of significant publication bias ($t(38) = 1.82$, $p = .07$). The Q value indicated heterogeneity ($Q = 57.60$, df = 38, $p < .05$, $\tau^2 = .06$, $I^2 = 32.28\%$) and therefore the presence of potential moderators (Sánchez-Meca & Marín-Martínez 1997). Accordingly, in the second stage of analysis, the group type was entered as a moderator: LTLE patients, $n = 18$, $Q = 22.70$, df = 17, $p > .05$, $\tau^2 = .04$, $I^2 = 25.12\%$; RTLE patients, $n = 16$, $Q = 20.00$, df = 15, $p > .05$, $\tau^2 = .05$, $I^2 = 25\%$ (Fig. 2b). The Q value indicated homogeneity and therefore the mean effect size was considered the best estimation for the data. The overall magnitude of the differences was small. In the LTLE studies Hedges' g = -.16, SE: .14, CI [-.36, .03] and in RTLE studies Hedges' g = .21, SE: .09, CI [-.30 , .73].

Finally, paradigm type (verbal, nonverbal) was added as a moderator for each of the two patients groups: LTLE patients, verbal memory paradigm, $n = 10$, $Q = 12.03$, df = 9, $p > .05$; LTLE patients, nonverbal memory paradigm, $n = 8$, $Q = 11.93$, df = 7 $p > .05$; RTLE patients, verbal memory paradigm, $n = 9$, $Q = 18.93$, df = 8, $p > .01$; RTLE patients, nonverbal memory paradigm, $n = 7$, $Q = 22.18$, df = 6, $p < .01$. Homogeneity of the estimated mean effect size

Table 5 Means in years (SD) of age at onset, age at assessment, and duration with epilepsy in pre-post studies compare to control-patient studies

	Age (SD)	Age at Onset (SD)	Duration (SD)
Pre-post studies (*N* pre = 483, *N* post = 450)	13.30 (1.05)	6.91 (1.40)	7.25 (2.66)
Control -patient studies (*N* patients = 358, *N* controls = 1106)	12.00 (1.51)	5.74 (1.54)	6.23 (1.60)

was found in LTLE patients for both the verbal (Hedges' g = -.38, SE: .13, CI [-0.71, -.06]) and nonverbal (Hedges' g = .09, SE: .16, CI [-.46, .65]) paradigms and in RTLE patients for the verbal paradigm (Hedges' g = .06, SE: .16, CI [-.76, .89]) but not for the nonverbal paradigm.

Covariance of age at onset and age at assessment Regression analysis revealed that age at onset, duration of epilepsy and age at assessment did not serve as moderators of the Hedges' g effect sizes for patients versus controls (age at onset, β = -.29, p = .08; duration of epilepsy; β = .21, p > .05; age at assessment , β = -.06, p > .05). This was also true with regard to pre-operative versus post-operative effect sizes, neither for the age parameters (age at onset, β = -.22 , p > .05; duration of epilepsy, β = -0.3, p > .05; age at assessment, β = -.12, p > .05).

Discussion

The purpose of this quantitative meta-analyses was to examine the role of lateralization, material type and age, on memory functions in children with TLE, both before and after surgery. It was hypothesized that there would be evidence of material-specific memory deficits, but only with regard to verbal memory in LTLE patients, in control-patient comparisons and in pre-post-surgery comparisons. The hypotheses were partly confirmed. In control-patient comparisons, in contrast to our predictions, heterogeneity indicated inconsistent results, It is difficult to draw conclusions based on the studies that reported memory differences between controls and pediatric TLE patients.

Control-Patient Findings

Although most studies that compared patients to controls have revealed a significant verbal or nonverbal memory impairment in children with TLE compared to controls (for example; Cohen, 1992; Jambaqué et al., 1993; Guimarães et al., 2007; Jambaqué et al., 2009; Leunen et al., 2009) the current meta-analysis failed to reveal consistent differences between groups. The main explanation is related to the substantial methodological differences across studies. The small sample sizes, within group variability, different measuring methods and outcome measures all increased the heterogeneity value, and hampered efforts to draw integrative conclusions. Although it is challenging to identify test measures that are common across the world, the establishment of an international uniform neuropsychological assessment protocol would constitute a valuable first step which would increase the homogeneity in results across studies and enable a coordinated international approach to neuropsychological assessment in epilepsy (Baxendale et al., 2019). Additionally, the idea that TLE might be regarded as a wider brain network disorder affecting brain areas beyond the temporal lobes, as opposed to the 'domain specificity' model, raises the question of whether memory function alone is the most appropriate cognitive measure to evaluate TLE cognitive dysfunctions (Hermann, Loring, & Wilson, 2017). Further studies should examine whether children with TLE exhibit impairment in other cognitive areas such as attention and language (Mankinen et al., 2014; Hermann et al., 2016; Lah & Smith, 2014).

Memory Decline Following TLE Surgery in Children

The results suggest that the side of the epilepsy foci (RTLE versus LTLE), alongside the material type (verbal versus non-verbal) may serve as a moderator for children with TLE memory changes after epilepsy surgery. These analyses revealed a mild effect size in children with LTLE for decline in post-operative verbal memory as compared to their pre-operative verbal memory performance. In addition, with regard to post-operative compared to pre-operative nonverbal memory performances, there was practically a zero-effect size which indicates stability. Similarly, in children with RTLE, a virtually zero effect size was revealed, indicating stability in verbal memory performance before and after epilepsy surgery.

Memory Decline Following Left TLE Surgery in Children

The main finding indicates that delayed verbal memory becomes impaired in children after left temporal lobe surgery. This result is in line with the literature on adult TLE, that has reported relatively consistent rates of verbal memory decline after left-sided surgery (Lee et al., 2002; Sherman et al., 2011). These results suggest that in children, as in adults, verbal memory is lateralized to the left hemisphere and that verbal memory tasks are sensitive to LTLE surgery (Flint et al., 2017). The data regarding lateralization of the nonverbal memory to the right hemisphere or demonstrating sensitivity of nonverbal tasks to RTLE surgery

were not confirmed. Hence, better post-operative cognitive outcomes might be expected with seizure freedom. One possible interpretation of these results is that seizure frequencies and seizure control might not serve as the main contributor with regard to memory function in children with TLE (Smith et al., 2006). Rather, the findings support the notion that an underlying neurological impairment may influence memory, not the seizures themselves. Note that seizure control was not included in the current analysis since not all studies provide data on this. Further research should include seizure control and seizure frequency as covariates when measuring memory function after pediatric TLE surgery.

Age at Onset: Developmental Considerations

Several authors have suggested that specific difficulties emerge throughout childhood (Culhane-Shelburne et al., 2002; Helmstaedter & Elger, 2009; Gonzalez et al., 2012; Smith, 2016). The current meta-analysis failed to show a similar association between age and effect size. Nevertheless, the patients versus controls effect sizes were marginally negatively associated with age at onset ($p = .08$). These findings may hint that early onset is related to better memory performance in children with TLE compared to controls, and therefore indirectly supports the notion that the vulnerability of memory in children with TLE has a developmental basis. The findings on adults which support a material-specific pattern of impairment (Saling, 2009) is consistent with the notion that the nature of verbal memory impairment changes over time. The most widespread explanation for these results is based on the concept of brain plasticity that occurs mainly in the developing brain (Berl, 2014). Further prospective longitudinal research is needed to fully explore the influence of age on memory performance in children with TLE. Another important issue which requires further investigation is whether earlier surgery leads to better memory outcomes. The current results show no association between patients' age at surgery and memory decline after surgery. Nevertheless, the possibility that memory functions becomes localized over the developmental period could indirectly suggest that earlier surgery might be more beneficial, given that the greater plasticity of the developing brain enables greater reorganization of cognitive functions and minimizes the functional impact of removal brain tissue (Cross et al., 2006). In contrast, the crowding hypothesis argues that lesion (removal of tissue) induced reorganization of cognitive function to the unimpaired hemisphere results in compromises in cognitive processing due to limited computational capacity (Strauss, Satz, & Wada, 1990). Interestingly, the crowding hypothesis has recently received support in a study on pediatric TLE (Danguecan & Smith, 2019).Future longitudinal studies could shed light on the issue of the recovery abilities of the developing brain with regard to memory function after TLE surgery.

Limitations and Future Directions

The results of this quantitative meta-analysis differ partially from the results of the preliminary qualitative analysis, which suggested that verbal memory is not affected after LTLE surgery. The results also partially counter the Menlove and Reilly (2015) systematic review results which suggested, although cautiously, that there was improved memory performance after left surgery in children with TLE.

As presented in Table 5, most studies that compared pre-surgery to post-surgery verbal memory in children with LTLE, did show a trend toward verbal memory decline, even though this was not always significant. The quantitative statistical analysis revealed that this trend was consistent. This difference between analyses highlights the advantages of performing a quantitative meta-analysis over other non-quantitative methods when the goal is to generate conclusions based on a literature review. Most of the pediatric studies that were included in the Menlove and Reilly (2015) qualitative review were excluded here, because they included small sample sizes, combined scores from different tests or test versions or measured change in ways that precluded the calculation of the estimated mean which is required for a quantitative analysis. Nevertheless, larger sample sizes in pre-surgery to post-surgery studies with longer follow-up periods and comprehensive memory batteries are needed to establish more robust conclusions.

Another limitation that needs to be considered is that some of the excluded studies did not match the inclusion criteria but still make an important contribution to the literature. For example, the Skirrow et al. (2015) study was excluded because the pre-post assessment interval was outside the delay frame and certain statistical data, namely SD, was missing. The authors reported that nine years post-operation, patients who underwent surgery in childhood tended to show a hemisphere-dependent material-specific improvement in memory functions in the intact temporal lobe (i.e. verbal memory improvement at the follow-up after right temporal lobe surgery and non-verbal memory improvement after left temporal lobe surgery). These results can be interpreted as the release of reserve capacities which were suppressed or damaged by epilepsy (Helmstaedter et al., 2003), i.e., the release of memory function in the non-operated temporal lobe. As mentioned in the Method section, we limited the scope of the studies in the current meta-analysis to either patients vs. controls or pre-surgery – post-surgery comparisons. Since most of the studies used standardized

memory scores, a future meta-analysis might consider the inclusion of studies without a control group, in order to prevent the exclusion of valuable data from the meta-analysis. Furthermore, other factors might also influence memory functions in children with TLE, such as intelligence, medical treatment, seizure control, seizure frequency and presence of comorbid conditions. These could not all be controlled for since the data was not always presented in the studies. Future studies could also address the question of whether other factors influence pediatric epilepsy patients' memory scores, and in particular the characteristics of memory paradigms, which are shown to have major influence on memory outcomes in the adult literature (Saling, 2009). The choice of method for handling non-independent effect sizes is a topic of ongoing debate (Borenstein et al. 2009) and the applicability of newly developed methods (Cheung, 2019) should be considered in future meta-analyses. Finally, for obvious ethical reasons none of the studies reviewed here conducted randomized clinical trials on the effect of surgery on memory performance and the conclusions cannot be extrapolated to frontal lobe or other extratemporal epilepsies.

Conclusions

The results of the current meta-analysis showed that studies have consistently found evidence for a mild verbal memory decline after LTLE surgery, whereas nonverbal memory performance stayed the same after either LTLE or RTLE surgery. The results also imply a better memory outcome at an earlier age. While further longitudinal investigation is needed, these results clarify to some extent the ambiguous findings on memory performance in children with TLE, before and after surgery. The results highlight the need for a coordinated international approach to neuropsychological studies of childhood TLE utilizing some common data elements. Special Acknowledgement should be referred to the latest ILAE guidelines regarding the role of neuropsychological assessment in epilepsy.

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Compliance with Ethical Standards

Conflict of interest All authors have no conflict of interest to disclose.

Consent for Publication All authors have approved the manuscript and agree with its submission to " Neuropsychology Review".

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