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Verbal associative memory outcomes in pediatric surgical temporal lobe epilepsy: Exploring the impact of mesial structures

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ABSTRACT

Objective: We examined verbal associative memory outcomes in children with left- or right-sided temporal lobe epilepsy (TLE) who received combined lateral and mesial resections versus lateral resections sparing mesial structures. We hypothesized that children who underwent left-sided resections including mesial structures would show the greatest verbal associative memory declines following surgery.
Method: We retrospectively analyzed neuropsychology assessment results from a sample of 65 children with TLE who completed pre- and postoperative evaluation at the Hospital for Sick Children in Toronto, Canada. We examined verbal associative memory score changes between groups by laterality (left versus right) and resection type (lateral only versus lateral and mesial resection). We also explored potential associations between certain epilepsy-related characteristics and verbal associative memory changes.
Results: Postoperative decline was found in children with left-sided resections, but not those with right-sided resections. In children who received left-sided resections, there was some suggestion of verbal associative memory decline in those who had both lateral and mesial tissues excised, but not in those with lateral resections only. Notably, there was also a language dominance (typical versus atypical) by resection type interaction. Specifically, for the typical language group, children with left lateral plus mesial resections (but not mesial sparing resections) showed postoperative verbal associative memory declines, whereas the opposite was true for the atypical language group.
Significance: These data contribute to our growing understanding of verbal memory outcomes following TLE in childhood, with consideration of the extent of resection to mesial structures. Our findings also highlight the importance of language laterality when interpreting neuropsychological assessment findings and making predictions regarding risk of functional loss following surgery.

1. Introduction

1.1. Overview of verbal memory research in pediatric epilepsy

Verbal memory dysfunction is a known cognitive morbidity in temporal lobe epilepsy (TLE) [1–3], although the nature of and extent of these difficulties are better understood in adults compared to children. According to a recent systematic review of 88 epilepsy memory studies [4], the majority of investigations indicated that children with epilepsy have poorer memory (across a range of measures) compared to both healthy controls and population norms. Parents and teachers of children who undergo epilepsy surgery often want to know what cognitive changes to expect, with potential memory declines being of particular concern. Not surprisingly, verbal memory difficulties are known to be associated with academic problems [5] and health-related quality of life [6]. Therefore, assessment of verbal memory in children with epilepsy is critical for making surgical candidacy decisions, as the need to treat seizures must be considered alongside potential cognitive risks such as memory declines.

Several studies suggest that children generally experience similar, but less pronounced verbal memory deficits than adults [1,7–9]. Interestingly, there is also growing evidence of distinct adult and pediatric findings, including different patterns of cognitive outcome following temporal resective surgery. For example, children appear to experience higher rates of gain in their overall intellectual functioning than adults [10]. Similarly, Gleissner et al. [11] found that the children in their sample returned to preoperative verbal learning capacity at one-year postsurgery, whereas the adults did not. Such findings provide evidence of better functional recovery for children than adults following temporal

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resection, which may be attributed to the increased plasticity of the developing brain. However, the results of a systematic review indicate that while most young people have stable or improved cognitive functioning postsurgery, we do not yet fully understand the surgical risk factors underlying deterioration following surgery in some children [12].

1.2. Impact of resection type and seizure laterality on verbal memory outcomes

If it has been determined that a child with TLE is an appropriate surgical candidate, a critical treatment decision involves the extent of resection, and whether or not mesial structures should also be excised. The process by which this decision is made is extremely complex, and requires consideration of multiple factors to minimize the risk of poor surgical and quality-of-life outcomes; such factors include the extent and nature of underlying pathology, localization of the epileptogenic zone, postsurgical seizure prognosis, developmental stage, and risk of memory and language declines. To best inform medical teams about the potential risks of memory loss following various resection types, it is vital that neuropsychologists are able to sensitively and accurately measure various levels of memory ability, including more nuanced or subtle forms of memory dysfunction.

Despite the intricacies of the surgical decision-making process, there are only a few studies within the pediatric epilepsy literature that can aid in informing patients and their families regarding the potential functional risks of various resection options (e.g., selective amygdalohippocampectomy, partial lateral resection including the hippocampus, combined lateral and mesial resections). There is evidence that preserving the hippocampus in children undergoing temporal excisions can result in excellent seizure outcome [13]. However, the findings of several other pediatric studies show that more extensive resections result in better seizure control [14–17]. Examinations of verbal memory outcomes following hippocampal resections in children are still in their infancy, with some studies focusing on outcomes related to semantic memory (i.e., recall of factual information, naming) and others on episodic memory (i.e., recall of life events, often evaluated in research and clinical settings by having a patient remember new spoken information). The current study focused on a particular aspect of verbal episodic memory, and thus we briefly review previous investigations that have looked at verbal episodic memory outcomes related to different resection types. As might be expected, some have identified associations between greater hippocampal resections and poorer episodic verbal memory outcomes [18–21]. In contrast, Lah and Smith [22] did not find evidence of increased episodic or semantic verbal memory decline for children with temporal excisions that included the hippocampus.

Of particular relevance to the present study is a recent investigation by Law et al. [21] that examined verbal memory changes in children who underwent left or right temporal lobe resection that either included or preserved mesial structures. The authors measured verbal memory by having children learn a list of single words over multiple trials, with recall tested after a delay. The data indicated postsurgical verbal memory declines for children who received left temporal excisions including mesial structures, but not for those with left excisions sparing mesial structures or right-sided excisions. Poorer verbal memory outcomes were also observed for those with left hemisphere language dominance and intact preoperative verbal memory. Critically, understanding how the extent of resection impacts verbal memory changes helps to inform epilepsy treatment teams regarding the risks of functional memory loss following surgical interventions. Therefore, using a similar approach to that used by Law et al. [21], we examined a different aspect of verbal memory in children with TLE who had lateral or combined lateral and mesial resections.

1.3. Verbal associative memory

Verbal associative memory (also referred to as verbal relational memory) is an aspect of verbal episodic memory that refers to our ability to remember relations amongst spoken items/words that were presented together during initial learning. This skill is important for everyday life given that our understanding of concepts develops partly as a result of continued associations that we make between spoken words and ideas. Verbal associative memory is known to involve the hippocampus in adults [23–26], with the degree of impairment being associated with severity of hippocampal sclerosis [27–29]. From this literature, it has been theorized that one key function of the hippocampus is to bind arbitrary information [30], and that the degree to which verbal memory tasks can measure left hippocampal dysfunction depends on the semantic relatedness of the material to be learned. Thus, memory tasks involving learning of unrelated/arbitrary word pairs should capture left mesial effects, whereas learning of related word pairs would not [31]. Similarly, other commonly used verbal memory tasks that do not involve learning of novel associations (e.g., list learning, story memory) are also not expected to be particularly sensitive to left mesial temporal dysfunction. The use of a verbal associative memory paradigm in the present study allows for continued examination of this 'arbitrary binding' model of hippocampal functioning in a pediatric sample. Similar to the pattern observed with adults, there is emerging evidence that hippocampal pathology is also associated with deficits in associative memory in children with TLE. For example, the findings of Gonzalez et al. [32] indicated greater deficits in verbal associative memory for those with mesial (as compared to lateral) seizure involvement. Similarly, Cormack et al. [33] found that children with hippocampal sclerosis showed poorer performance on a verbal associative memory task compared with children with temporal lobe dysembryoplastic neuroepithelial tumor (DNET). Interestingly, both of these studies suggested that verbal associative memory deficits occurred for patients with both left and right-sided pathology. However, neither of these studies analyzed pre- versus postsurgical verbal associative memory outcomes, which is the main objective of the current study. Furthermore, we specifically examined whether verbal associative memory tasks appear to be useful for lateralizing seizure involvement. This information is important given that verbal associative memory tasks are often given for this purpose in presurgical assessments. Thus, for the present study, an associative memory task was thought to be particularly useful to detect differences in verbal memory functioning in children who underwent temporal resections that spared or included mesial structures.

1.4. Impact of other factors on verbal memory outcomes

In the course of treatment decision-making for patients with epilepsy, medical teams also consider how various potential risk factors may impact surgical recovery and outcomes. For example, in adults, there are several risk factors known to be associated with postoperative verbal memory decline including: dominant temporal lobe resection [10,34,35], younger age at seizure onset [36,37], higher/intact preoperative memory abilities [38,39], preoperative hippocampal volume and integrity [38], and low mood [40]. Ipsilesional language dominance has also been identified as a risk factor for verbal memory decline [36,41], and a significant association between language dominance and medial temporal verbal memory abilities has been found [41]. Currently, research on verbal memory outcomes following left temporal resection in children is more limited but continues to grow. According to a recent long-term follow-up study in children [42], lower baseline memory scores and older age at surgery were associated with improvements in verbal memory at follow-up assessment 4–11 years after surgery. The latter finding is particularly interesting as older age at surgery has been found to be associated with postoperative verbal memory declines in adults [39,43]. Specific to pediatric TLE, younger age at seizure onset

and longer duration of epilepsy have been associated with verbal memory declines after surgery for those who had both lateral and mesial tissues resected [21]. Along these lines, we also evaluated the associations between several presurgical factors and verbal memory changes that may contribute to our understanding of who is most at risk of memory decline following temporal lobe resection in childhood.

1.5. Current study objectives

The primary objective of this study was to examine verbal associative memory in children with TLE who received lateral versus combined lateral and mesial resections. We considered resection type alongside laterality of resection (left versus right). We hypothesized that those who received left-sided resections including mesial structures would show the greatest decline in verbal associative memory from baseline (preoperative) to follow-up (postoperative) assessment. At an individual level, we also examined the number of patients between groups whose scores declined at least 1.5 standard deviations between baseline and follow-up assessment. Further, we wanted to investigate whether the baseline verbal associative memory scores effectively lateralized patients who went on to receive left versus right temporal resections. In this regard, we hypothesized that those who had left-sided resections would have poorer baseline memory scores than the patients who had right-sided resections. Within the left resection group only, we also anticipated that those with typical language dominance and persistent postoperative seizures would also have greater memory declines.

As a secondary objective, we sought to better understand the association between certain clinical/epilepsy characteristics and verbal memory changes. Therefore, we conducted a series of exploratory correlation analyses and hypothesized that longer duration of epilepsy at baseline assessment, younger age at seizure onset, persistent postoperative seizures, greater number of antiepileptic drugs (AEDs) at follow-up assessment, and younger age at surgery would be associated with poorer verbal associative memory outcomes.

2. Methods

This was a retrospective study that used a pretest–posttest design to evaluate potential changes in verbal associative memory approximately one year after unilateral TLE surgery in childhood. This study was approved by the research ethics board at the Hospital for Sick Children in Toronto, Canada.

2.1. Participants

We retrospectively analyzed clinical data from 66 consecutive cases of children with focal TLE who completed a verbal associative memory task as part of a neuropsychology assessment completed through the comprehensive epilepsy program at the Hospital for Sick Children (Toronto, Canada) between April 1998 and May 2018. All patients had drug-resistant epilepsy (as defined by failure to achieve seizure control after at least two trials of AEDs). All patients in our sample completed a baseline neuropsychological assessment to aid in determining candidacy for surgery, as well as a follow-up assessment approximately one year after surgery (on average) to determine the extent of potential cognitive changes. Exclusion criteria included overall intellectual functioning less than two standard deviations below the population mean at baseline assessment, as patients with lower intellectual function would be expected to have less variability in their profile of scores, thus reducing the potential to detect postoperative changes. One case was identified as an extreme outlier and excluded due to having a very large difference between baseline and follow-up verbal memory outcome scores. Our final sample included 65 children with focal TLE ranging in age from 6 to 18 years at baseline. There were 21 children who had left-sided resections sparing mesial structures (group with left TL), 7 children who had right-sided resections sparing mesial structures (group with right TL), 19 children who had left-sided resections including mesial structures (group with left TL + M), and 18 children who had right-sided resections including mesial structures (group with right TL + M).

2.2. Neuropsychological measures

We used a word pair learning and memory task as our measure of verbal associative memory. For children less than 16 years of age, the Word Pairs subtest of the Children's Memory Scale (CMS) [44] was used, and older children were given the Verbal Paired Associates subtest from the Wechsler Memory Scale (WMS-III/IV) [45,46]. Both tasks are very similar in terms of requirements; the patient is presented with 14 word pairs (read aloud) over several learning trials. Memory for the word pairs is tested using a cued recall procedure after each learning trial, for which the examiner reads the first word of each pair, and the patient is instructed to provide the word that went with it. After a 20- to 30-minute delay, memory for the word pairs is tested again, producing a delayed recall score. On the CMS, the patient is asked to freely recall the word pairs, whereas on the WMS the patient is provided with the first word and asked to provide the accompanying word. For both tasks, most of the word pairs are comprised of semantically unrelated words; on the CMS, 12 of 14 word pairs are unrelated, and on the WMS, 10 of 14 word pairs are unrelated.

Given that our hypotheses were focused on verbal associative *memory* (as opposed to learning) outcomes, we restricted our analyses to the delayed recall scores produced by the tasks described above. The standardized scores generated for both of these measures are scaled scores, with a normative mean of 10 and a standard deviation of 3. Estimates of global intellectual functioning were collected using the age-appropriate version of the Wechsler Scales of Intelligence; these data were used to characterize the overall cognitive functioning of our sample.

2.3. Language dominance

As part of their presurgical investigations, most patients within our left temporal group underwent assessment of language dominance using intracarotid amobarbital procedure/etomidate speech and memory testing or functional magnetic resonance imaging (fMRI). Based on these results, patients were classified as having typical (left-sided) language dominance or atypical (right or bilateral) language dominance.

2.4. Statistical approach

Prior to the main statistical analyses, between-group differences on several demographic and epilepsy-related variables were examined using analyses of variance (ANOVA), independent samples t-tests or chi-squared (χ^2) tests, as appropriate. To address our primary research objectives, we investigated group differences in verbal associative memory change scores using univariate ANOVAs. Change scores were calculated by subtracting baseline from follow-up memory scores for each participant; thus, negative values would index declines following surgery. We then analyzed data from the left resection group only to explore the potential impact of language dominance, postoperative seizure outcome, and level of preoperative verbal associative memory functioning. To examine stability/improvement or decline of scores across groups, we used Fisher's exact test to explore the potential impact of seizure laterality and resection type on memory score stability/improvement versus decline. Pearson's product–moment correlations were calculated to examine the relationships between verbal memory change scores and age at seizure onset, duration of epilepsy at baseline assessment, age at surgery, and number of AEDs at follow-up assessment. An alpha level of 0.05 was used to determine statistical significance.

3. Results

3.1. Patient characteristics

As can be seen in Table 1, the groups with TL and TL + M were comparable on several relevant characteristics including sex, handedness, age at baseline assessment, age at follow-up assessment, age at seizure onset, duration of epilepsy, age at surgery, time between surgery and follow-up assessment, number of AEDs at baseline and follow-up assessment, postoperative seizure status, and overall intellectual functioning (Full Scale IQ; FSIQ) at baseline and follow-up assessment. The group with TL had a significantly longer mean time interval between their baseline and follow-up assessments than the group with TL + M, which was largely driven by the patients with right TL.

Within the group with left TL + M, there were a higher number of patients with nontumor pathology whereas tumor and other pathologies were relatively evenly distributed amongst the other groups. Given this difference, for the left-sided resection groups, we examined whether there were differences related to pathology. For these analyses, the patients with nontumor pathologies were collectively compared with those with tumors. For the group with left TL, no statistically significant differences were found at baseline, follow-up, or in their pre-post difference scores. Similarly, there were no differences in these scores within the group with left TL + M, although it should be recognized that the tumor subset was very small within this group (n = 3).

Table 1
Demographic and epilepsy-related characteristics of our sample.

	Temporal lobe		Temporal lobe + mesial		*p*
	Left (n = 21)	Right (n = 7)	Left (n = 19)	Right (n = 18)	
Sex (male/female)	11/10	4/3	7/12	12/6	.34
Handedness (right/left)	20/1	7/0	17/2	15/2	.67
Age at baseline (mean in years, SD)	13.0 (3.2)	12.7 (3.9)	14.2 (2.8)	12.8 (3.5)	.40
Age at follow-up (mean in years, SD)	14.8 (3.2)	15.0 (4.1)	16.1 (2.6)	14.3 (3.6)	.27
Age at seizure onset (mean, SD)	8.8 (4.6)	5.2 (4.5)	8.5 (5.1)	7.1 (4.2)	.40
Duration of epilepsy at baseline (mean in years, SD)	4.2 (3.9)	7.5 (5.3)	5.7 (4.4)	5.7 (5.0)	.19
Age at surgery (mean, SD)	13.7 (3.2)	13.9 (4.0)	15.0 (2.7)	13.3 (3.6)	.28
Time between baseline and follow-up (mean in years, SD)	1.8 (0.46)	2.3 (1.5)	1.9 (0.74)	1.5 (0.47)	.03
Time between surgery and follow-up (mean in years, SD)	1.1 (0.44)	1.1 (0.11)	1.1 (0.16)	1.0 (0.30)	.91
Number of AEDs					
Mean pre-op	1.7	1.4	1.7	1.5	.81
Mean post-op	1.9	1.3	1.8	1.5	.44
# Seizure-free post-op	12	4	12	12	.93
Full Scale IQ					
Mean pre-op (SD)	91.7 (8.8)	95.1 (20.2)	89.8 (11.3)	91.4 (10.2)	.77
Mean post-op (SD)	93.1 (11.6)	101.3 (20.5)	87.9 (11.3)	93.2 (8.5)	.66
Pathology (n)					N/A
Tumor	10	4	3	7	
Dual pathology	2	3	5	4	
Gliosis	5	0	4	2	
Malformation of cortical development	3	0	2	2	
Mesial temporal sclerosis	0	0	3	1	
Vascular malformation	1	0	1	1	
Other	0	0	0	1	
No discernable pathology	0	0	1	0	

3.2. Effect of test version

Depending on the age of the child at baseline and follow-up assessment, as well as adaptations to different test batteries over time, patients may have received different versions of the verbal associative memory task over the course of the study. Nine out of the 65 children in our sample received different memory test versions between baseline and follow-up assessment. As this presents a potential confound in our data, we examined the impact of memory test version on verbal associative memory scores at baseline and follow-up. Memory test version was found to significantly impact verbal associative memory scores at baseline assessment ($p = .03$), but not at follow-up ($p = .27$). Given that the significant impact of different test versions could conceivably influence verbal associative memory change scores, we compared change scores between patients who received each baseline memory measure; there we no significant group differences ($p = .97$). Because it can be difficult to reliably capture memory changes when different measures are administered at baseline and follow-up, we also compared change scores between those who received the same versus different memory tasks at both time points; change scores were very similar between groups ($p = .85$).

3.3. Primary analyses

3.3.1. Baseline memory performance

The left and right resection groups performed similarly at baseline assessment; that is, there was no significant main effect of laterality ($F_{1,61} = 0.05$, $p = .82$, partial $\eta^2 = 0.001$). The main effect of resection type trended toward (but did not reach) statistical significance ($F_{1,61} = 3.56$, $p = .064$, partial $\eta^2 = 0.06$), with the group with TL + M producing marginally poorer memory scores than the group with TL. There was no significant interaction ($F_{1,61} = 0.27$, $p = .61$, partial $\eta^2 = 0.004$).

3.3.2. Effect of seizure laterality and resection type

Table 2 shows the mean baseline and follow-up delayed recall scores for each group, and Fig. 1 depicts mean change scores. There was a significant main effect of laterality, with greater verbal associative memory declines observed in patients with left compared to right-sided resections ($F_{1,61} = 7.16$, $p = .01$, partial $\eta^2 = 0.11$). There was no significant effect of resection type ($F_{1,61} = 0.05$, $p = .82$, partial $\eta^2 = 0.001$), and no laterality by resection type interaction ($F_{1,61} = 1.39$, $p = .24$, partial $\eta^2 = 0.02$).

Despite the nonsignificant interaction effect, it is apparent from the data shown in Table 2 and Fig. 1 that the group with left TL + M experienced greater decline in their verbal associative memory scores compared with the other groups. Therefore, to further investigate potential group differences, we conducted paired t-tests for each group comparing mean baseline and follow-up memory scores. As these were post hoc analyses, we employed a Bonferroni correction and adopted an adjusted alpha level of 0.0125. There were no significant differences between baseline and follow-up memory scores for the groups with left TL ($p = .099$), right TL ($p = .69$), or right TL + M ($p = .18$). However, there was a trend observed ($p = .019$) for the group with left TL + M, with means providing emerging evidence of decline in verbal associative memory following surgery.

Table 2
Mean baseline and follow-up verbal associative memory scores.

Resection type	Laterality	n	Mean baseline Scores (SD)	Mean follow-up Scores (SD)
TL	Left	21	9.67 (2.71)	8.48 (3.36)
	Right	7	9.00 (4.76)	9.29 (4.31)
TL + M	Left	19	7.53 (3.47)	4.95 (3.55)
	Right	18	7.78 (2.96)	9.00 (2.00)

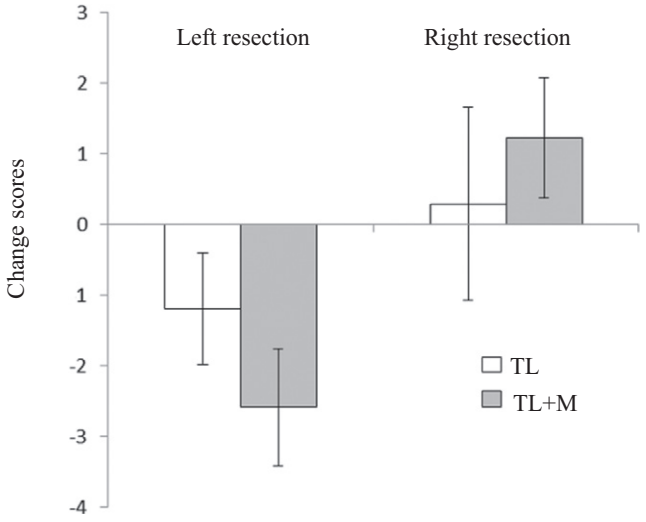

Fig. 1. Verbal associative memory change (scaled) scores by resection type and laterality. Error bars represent standard deviation.

3.3.3. Stability of verbal memory scores

As can be seen in Table 3, verbal associative memory scores remained stable (within 1.5 standard deviations; SD) following surgery for most patients across groups. We used Fisher's exact test to compare outcomes of verbal associative memory scores (decline of at least one SD versus stable or improved) between the left and right-sided resection groups. Although decline occurred more often in patients with left-sided resections (10 of the 13 who declined), this was not found to be statistically significant ($p = .34$). Within the left resection group, those who had mesial structures excised were not more likely to experience score decline than those with lateral resections only ($p = .47$). These results should be interpreted cautiously, however, given that sample sizes were small.

Given that the previous analyses were likely underpowered, we also wanted to describe the characteristics of the 13 children (6 males, 7 females) in our sample who showed a decline in verbal associative memory scores of at least 1.5 SDs. Most of the patients (10 out of 13) who declined underwent left-sided resections, with the majority of these having combined lateral and mesial tissue excised (6 out of 10). Similarly, all three patients from the right-sided resection group who declined had combined lateral and mesial resections. Most of those with verbal associative memory decline had typical (left hemisphere) language dominance (10 out of 13) and were almost exclusively right-handed (12 out of 13). Mean duration of epilepsy at the time of baseline assessment was 6.50 years (range = 1.06–14.83 years), with a mean age at surgery of 15.19 years (range = 10.42–18.33 years).

3.4. Exploratory analyses

Given that the left (but not right) resection group experienced statistically significant verbal associative memory declines, we investigated the impact of several epilepsy-related variables on verbal associative memory change scores within the two left resection subgroups only. This exploratory approach reflects that used by Law et al. [21].

3.4.1. Language dominance

A two-way ANOVA was conducted on the change scores with resection type and language dominance as independent variables producing four groups: left TL-typical language dominance, left TL + M-typical language dominance, left TL-atypical language dominance, and left TL + M-atypical language dominance. See Table 4 for mean verbal associative memory change scores by resection type and language dominance. There was no main effect of resection type ($F_{1,34} = 0.079$, $p = .78$, partial $\eta^2 = 0.002$) or language dominance ($F_{1,34} = 0.44$, $p = .51$, partial $\eta^2 = 0.01$). However, there was a significant interaction ($F_{1,34} = 10.90$, $p = .002$, partial $\eta^2 = 0.24$). Post hoc comparisons indicated that for those with typical language, the group with TL + M showed greater memory score declines than the group with TL ($p = .008$). However, for those with atypical language dominance, the group with TL trended toward greater score declines than the group with TL + M ($p = .058$).

3.4.2. Level of preoperative verbal memory

To examine the impact of intact versus impaired baseline verbal associative memory on change scores, the left resection group was divided into those who scored at least within 1 standard deviation of the normative mean at baseline assessment and those who scored below 1 standard deviation of the normative mean. In typical clinical neuropsychological practice, scores that are less than 1 standard deviation of the age-normative mean indicate a mild degree of dysfunction. Given the importance of the presurgical neuropsychological evaluation to detect even subtle deficits, using this threshold was believed to be appropriate. We performed a two-way ANOVA with resection type and baseline memory ability (intact versus below average) as independent variables. There was no significant main effect of resection type ($F_{1,36} = 1.20$, $p = .28$, partial $\eta^2 = 0.03$) or preoperative verbal memory functioning ($F_{1,36} = 2.74$, $p = .11$, partial $\eta^2 = 0.07$), and the interaction was also nonsignificant ($F_{1,36} = 0.035$, $p = .85$, partial $\eta^2 = 0.001$). However, these results should be interpreted with caution as subgroup (cell) sizes were very unequal, with only 2 patients with left TL (out of 21) and 6 patients with left TL + M (out of 19) having poor preoperative memory scores.

3.4.3. Postoperative seizure outcome

For this analysis, we divided patients within the left resection group into those who were seizure-free following surgery and those that reported continued seizures. We conducted a two-way ANOVA with resection type and seizure outcome (seizure-free versus persistent seizures postoperatively) as independent variables. There was no main effect of seizure outcome ($F_{1,36} = 0.23$, $p = .64$, partial $\eta^2 = 0.01$) or resection type ($F_{1,36} = 1.21$, $p = .28$, partial $\eta^2 = 0.03$), and there was no significant interaction ($F_{1,34} = 0.01$, $p = .92$, partial $\eta^2 < 0.001$).

3.4.4. Association of verbal memory change scores, age at seizure onset, age at surgery, duration of epilepsy, and number of AEDs

For the group with left TL, there were no significant correlations between verbal associative memory change scores and duration of epilepsy, age at seizure onset, number of AEDs at follow-up assessment,

Table 3
Number of patients in each group who declined, remained stable, or improved in their verbal associative memory scores from baseline to follow-up assessment.

Laterality	Resection type	n	Declined by at least 1.5 SD	Stable	Improved by at least 1.5 SD
Left	TL	21	4	17	0
	TL + M	19	6	12	1
Right	TL	7	0	7	0
	TL + M	18	3	9	6

Table 4
Mean verbal associative memory change (scaled) scores by resection type and language dominance in the left resection group.

Language dominance	Resection type	n	Mean memory change scores (SD)
Typical	TL	13	−0.15 (2.48)
	TL + M	12	−4.25 (4.37)
Atypical	TL	6	−3.17 (3.31)
	TL + M	7	0.29 (2.56)

and age at surgery (p values > .52). Results were largely similar for the group with left TL + M, except that improvements in verbal associative memory scores were correlated with a higher number of AEDs at the time of follow-up assessment ($r = 0.55$, $p = .02$).

4. Discussion

The primary objective of this study was to examine verbal associative memory outcomes in a pediatric surgical TLE sample, while taking into account both the laterality and extent of resection (including or sparing mesial structures). In keeping with a recent investigation by Law et al. [21] conducted through our center, we hypothesized that those with left-sided resections including mesial structures would have particularly poor verbal memory outcomes.

Our data showed that patients who underwent left-sided resections experienced greater declines than those who had right-sided resections. Within the left resection group, there is also some suggestion that additional excision of mesial structures may be a risk factor for verbal associative memory decline. This conclusion is stated with some reserve, as it is based on a statistical trend using a conservative (Bonferroni-corrected) alpha value. However, low statistical power was likely an issue given our relatively small sample size. It should also be noted that the pattern of results in our primary analyses was consistent with that of Law et al. [21] using a word list learning task. Specifically, declines in verbal memory were documented for patients with left lateral and mesial temporal resections, but not other resection types (i.e., left lateral temporal, right lateral temporal, right lateral temporal plus mesial structures). This previous finding, in conjunction with the similar pattern found in our data, suggests that children who receive left temporal resections including mesial structures may be at particular risk for verbal memory declines following surgery compared to those who have preserved mesial structures.

We did not find an effect of baseline verbal associative memory performance on postoperative performance in the patients who had undergone left resections. This finding is in contrast to the Law et al. [21] study which found that memory scores tended to decline for patients with intact baseline memory, but improve for patients with baseline verbal memory difficulties. Furthermore, for those with below average baseline verbal memory scores, those who underwent combined left-sided lateral and mesial resections declined postsurgery, whereas those with left lateral resections improved postsurgery. However, it should be noted that the lack of similar findings in the current study may be due to very unequal sample sizes between groups. Thus, the impact of baseline verbal associative memory performance requires further study.

The ability of verbal memory tasks normed on children to detect dysfunction in brain structures contralateral or ipsilesional to the site of seizure onset is vital to the presurgical neuropsychological evaluation and predictions of potential functional loss postsurgery. As such, an additional goal of this study was to examine whether baseline verbal associative memory scores would differentiate those who received left versus right-sided resections. In our sample, verbal associative memory performance was similar for children with left or right-sided resections, suggesting limited utility of this particular verbal memory task for informing seizure lateralization. It is important to note that others have also failed to find lateralized memory deficits in pediatric TLE, with the exception of facial recognition [32,47]. Moreover, Cormack et al. [33] compared children with hippocampal sclerosis (HS) and those with temporal lobe DNET pathology and found that memory scores on a verbal associative memory task were more impaired in the group with HS, regardless of laterality. Indeed, there was also a trend in our data indicating marginally poorer verbal associative memory performance for those with combined lateral plus mesial resections compared to those with only lateral resections. The finding that children with left or right TLE seem to be at risk for verbal memory difficulties may be explained by interference with the developing connectivity of the hippocampus with surrounding cortical regions.

Overall, verbal associative memory scores remained stable for the majority of patients across groups following surgery, which has consistently been found in postoperative outcome studies in pediatric TLE (see Flint et al. [12] for a recent review). This finding provides some reassurance on a group-level as most patients, regardless of resection type, would not be expected to experience verbal memory decline. However, in 20% of our sample there was a decline (of at least 1.5 standard deviations) in scores between baseline and follow-up assessment. Although this smaller subsample was too small to conduct statistical analyses, it should be noted that most of the patients who declined in their verbal associative memory functioning had left-sided resections. The majority also had mesial structures excised, was right-handed, and had typical (left hemisphere) language dominance.

Examination of the impact of language representation on verbal memory change scores (within the left resection group only) yielded particularly interesting results. Our data indicated that in children with typical language dominance, those with combined lateral and mesial resections had mean verbal memory declines of more than a standard deviation, whereas little overall memory change was observed in the lateral group. This finding points to the expected localization of language/verbal skills (including memory) within the left hemisphere in those with typical language dominance, and the importance of mesial structures to verbal memory. However, within the existing literature, language laterality has not consistently been found to impact verbal memory functioning in pediatric patients with TLE [18,21,41], which can be partially attributed to factors such as small sample sizes and variable pathologies. However, when significant effects have been found, atypical language dominance has been associated with better verbal memory outcomes [41]. In contrast, within our atypical language group, a statistical trend suggested that those with lateral resections may be at particular risk for verbal associative memory decline following surgery, unlike the combined lateral and mesial group who appear to remain stable. Although this interaction effect should be interpreted with caution given small sample sizes, the effect size was medium to large. Notably, the overall pattern of our language dominance and memory change score data was similar to that of Law et al. [21], albeit with slight differences in statistically significant findings.

An unexpected finding was that positive verbal associative memory change scores were associated with a greater number of AEDs at postoperative assessment for the left lateral plus mesial group. To our knowledge, this relationship has not been documented previously. It should be noted that 17 out of 19 children in this group were on one or two AEDs at follow-up assessment. The two remaining children were on more than two AEDs and had stable or improved verbal associative memory performance. Thus, this correlation appears to be driven by these two participants. Future research using larger sample sizes will be helpful for informing whether this is a reliable memory finding in pediatric surgical TLE.

4.1. Limitations

We acknowledge that our study is limited by several factors, and we highlight what we view as the most critical ones here. To start, despite the extended period of time over which our sample was collected, our overall sample size was relatively small. Thus, several of our statistical comparisons were likely underpowered when our sample was subdivided, which may have led to type II errors. Along these lines, we did not explore the impact of certain epilepsy variables that might impact verbal associative memory outcomes following surgery. For example, compared to adults, children with TLE have a greater range of underlying pathologies, and this was reflected in our sample. However, sample size limitations precluded statistical analyses including pathology as an independent variable. Perhaps more critically, within our left lateral plus mesial resection group, there were more patients

with nontumor pathology than the other groups. More careful consideration of the relationship between pathology and memory outcomes is warranted with a larger sample size to disentangle the impact of resection type, pathology, and other relevant variables such as language dominance on memory outcomes.

Moreover, there are likely other cognitive factors that could impact memory outcomes postoperatively. For example, executive dysfunction has been found to impact memory performance in children with TLE [48], and one pediatric study found that 84% of their TLE sample had at least moderate executive functioning impairment [49]. Based on these findings, one might hypothesize memory performance differences between children with TLE and frontal lobe epilepsy (FLE), given that the frontal lobes are known to subserve executive functions (reviewed, e.g., Alvarez & Emory [50]). However, Fuentes and Smith [51] recently found statistically comparable verbal associative memory performance between children with TLE and FLE.

Unfortunately, separate age-normed scores were not available for the related and unrelated word pairs included in the commonly used verbal associative memory tasks we considered. Although the majority of word pairs on both the CMS and WMS are unrelated, it is possible that potential stronger effects shown by the unrelated word pairs were somewhat attenuated by null or weaker effects of the related word pairs. In keeping with this interpretation, the results of one pediatric study indicated that memory for unrelated word pairs effectively differentiated between children with lateral versus mesial temporal lesions [32].

Another limitation of our study is that surgical volumetric data for the resections were not available; this would allow us to analyze the extent to which excised brain tissue impacts memory outcomes. Along these lines, such an approach has been useful in another study, for which greater postsurgical residual hippocampal volumes were associated with better verbal memory outcomes at follow-up [18].

4.2. Conclusions

Based on our cohort of pediatric patients with temporal lobe epilepsy that was evaluated at our center over a 20-year period, poorer postoperative verbal associative memory outcomes were observed in those who underwent left compared to right-sided resections. Within the left resection group, we provide emerging evidence that children who underwent combined lateral and mesial resections showed poorer verbal associative memory outcomes following surgery compared with those who had mesial structures spared. Our data also highlight the importance of language dominance for those with left-sided seizure foci. For those with typical language dominance, children with left lateral plus mesial resections showed greater postoperative verbal associative memory declines compared with those with lateral resections sparing mesial structures. However, the opposite pattern was observed in the atypical language group, as those who underwent lateral resections were at somewhat elevated risk for verbal associative memory decline.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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