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Patterns of verbal learning and memory in children with intractable temporal lobe or frontal lobe epilepsy

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ABSTRACT

Purpose: The objective of this study was to provide a better understanding of the verbal learning and memory (VLM) patterns that might differentiate children with frontal lobe epilepsy (FLE) from children with temporal lobe epilepsy (TLE) and to examine the impact of variables thought to influence outcomes (seizure laterality, age at seizure onset, age at assessment, epilepsy duration, number of antiepileptic drugs).
Methods: Retrospective analyses were carried out for children with intractable unilateral TLE ($n = 100$) and FLE ($n = 27$) who completed standardized measures of VLM entailing lists of single words or lists of word pairs.
Results: Mean intelligent quotients and VLM scores on single words fell within the average range for both groups, whereas scores fell within the low average to borderline range on word pairs. No significant overall differences in VLM were found between the group with TLE and the group with FLE.
Older age at assessment and older age at seizure onset were generally associated with better VLM in both groups but were related to better performance in a number of indices in the group with TLE and only fewer intrusions in the group with FLE.
Conclusions: The VLM profiles of children with TLE and FLE are generally similar. Older age at assessment and older age at seizure onset have a favorable impact on both groups but are related to better encoding, retrieval, and monitoring processes for the group with TLE and improved memory monitoring (i.e., as indicated by fewer intrusions) in the group with FLE.

1. Introduction

Research indicates that verbal learning and memory (VLM) is compromised in children with epilepsy (for review, see Menlove & Reilly [1]), which has deleterious consequences for school achievement [2] and health-related quality of life [3]. Children with intractable epilepsy are particularly at risk for VLM deficits, possibly because of hippocampal dendrite growth suppression that results from recurring seizures [4]. However, research examining VLM in children with temporal lobe epilepsy (TLE) remains somewhat limited (for review, see Rzezak et al. [5]), despite the well-known roles of the medial temporal lobe brain structures (i.e., hippocampus, entorhinal cortex, perirhinal cortex, parahippocampal cortex) in memory encoding (i.e., initial organization and processing of information) and consolidation (i.e., conversion of temporary, short-term memories into permanent, long-term storage) processes [6]. The studies that have investigated VLM in children with TLE generally indicate deficits relative to healthy controls [5]. Verbal learning and memory has remained an even more underresearched topic in the population with pediatric frontal lobe epilepsy (FLE) (the second most common localization-related epilepsy in childhood after TLE), with studies primarily focusing instead on the domains of attention and executive functioning (for review, see Braakman et al. [7]). This lack is a critical gap in the literature given the well-known role of the frontal cortex for attending to and organizing information during encoding and retrieval (i.e., recall of previously learned material) processes [6].

The few studies examining VLM profiles in children with FLE have produced somewhat inconsistent findings, with some reporting no VLM deficits [8,9] and others reporting impairment [10–13]. Of note, the small sample size ($n = 8$) in the former study [8] may have limited power to detect memory deficits. Closer inspection of the studies reporting significant differences between children with FLE and controls [10–13] revealed overall mean VLM scores falling within the low average to average range. Children with FLE have been found to display a global decrease in functional brain connectivity relative to controls, which is suggested to be one of the possible mechanisms underlying the deficits found in both "frontal lobe functions" (e.g., attention, executive functioning) and "extrafrontal functions" (e.g., memory) [14]. Questions remain, however, concerning whether or not there are distinguishing features to differentiate the VLM profiles of children with FLE from those with TLE. In adults, the verbal Selective Reminding Test (i.e., list learning

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measure whereby the examiner repeats only those words not previously recalled on the immediate previous trial) was recently found to be useful in distinguishing patients with FLE from patients with TLE in that those with FLE performed worse, suggesting that the group with FLE struggled with the organizational and monitoring aspects of VLM [15]. However, the generalizability of these findings to the pediatric population remains unclear. Conflicting findings have been found in studies comparing the VLM profiles of children with TLE and FLE, with some researchers not finding group differences [11], others reporting greater deficits in children with TLE [13], and still others reporting greater deficits in children with FLE [12]. Hernandez et al. [10] observed that children with FLE were more prone to interference and intrusion errors on the California Verbal Learning Test compared to children with TLE and generalized absence seizures (GAE), but the groups did not differ in terms of the amount of information learned and retained, number of repetitions, or use of semantic clustering. Of note, these findings are difficult to interpret because of the small sample size (TLE = 8, FLE = 16, GAE = 8) and the fact that the sample consisted primarily of children with well-controlled seizures (e.g., half of the sample had been seizure-free for more than a year and the remaining experienced only occasional seizures).

Further research is also required in order to shed light on predictors of VLM impairment in children with epilepsy. The systematic review conducted by Menlove and Reilly [1] identified greater number of antiepileptic drugs (AEDs), younger age at seizure onset, increased seizure frequency, longer duration of epilepsy, and younger age at assessment as predictors of memory impairment in children with epilepsy; however, the evidence remained mixed, with 76% of studies reporting no impact for the number of AEDs, 69% reporting no impact of age at onset, only 25% reporting an increased risk for longer duration of epilepsy, and 37% reporting no impact of age at assessment. Research regarding laterality effects in the memory functioning of children with epilepsy is even more discordant. Kibby et al. [16] reported slight laterality effects for VLM in a large sample ($n = 143$) of children with focal epilepsy, with children with left hemisphere focus performing worse than controls on immediate and delayed recall on a paired-associates task; however, performance between children with left versus right hemisphere focus was not significantly different. Studies addressing laterality effects, specifically in children with TLE, have produced conflicting findings, with some linking left hemisphere involvement with impaired VLM and right hemisphere involvement with impaired visual memory, and conversely, others reporting no such associations (for review, see Rzezak et al. [5]). A recent longitudinal study conducted by Gonzalez et al. [17] indicates that these contrary findings may be explained by developmental factors, as laterality effects in VLM were found to emerge in children with TLE over time. Specifically, in contrast to the baseline assessment (M age = 11.76 years), laterality effects were detected at follow-up (M age = 16.10 years), with children with left hemisphere involvement performing worse on verbal paired-associative learning compared to children with right hemisphere involvement [17]. In one of the few studies to date to address laterality effects specifically in children with FLE, Riva et al. [8] documented worse performance on long-term free recall of words in children with left frontal focus relative to those with right frontal focus. Moreover, it is noteworthy that reduced hippocampal volume has been documented in both children with TLE and children with FLE and that reduced left hippocampal head volume has been specifically linked with reduced VLM in those with left lateralized epilepsy [10].

The objectives of this study were twofold. The *primary* objective was to compare the VLM profiles of children with TLE versus FLE. The *secondary* objective was to examine the clinical and demographic variables thought to influence VLM, namely, seizure laterality, age at seizure onset, age at assessment, number of AEDs, and epilepsy duration. The VLM profiles of children with TLE and FLE were assessed using measures of single-word list learning and paired-associate learning, thus allowing for a comprehensive characterization of VLM, namely, rate of encoding, retention, retrieval, effect of interference, monitoring, response inhibition, and sequencing. According to Golden, Espe-Pfeifer, and Wachsler-Felder [18], comparison of performance on single-word list learning and paired-associate learning can give rise to the following clinical interpretations: (1) poor performance on both indicates impairments in rote learning; (2) stronger performance on paired-associate learning indicates enhanced performance with cueing and/or external organization; and (3) stronger performance on single-word list learning indicates enhanced performance with reduced organizational/association demands.

Based on prior findings documenting memory impairment in both children with TLE and children with FLE [1,5,10–13], it was hypothesized that VLM performance would fall below normal limits. Although the research concerning the VLM patterns characterizing children with TLE versus children with FLE is limited based on previous literature [9] and what is known about the neuroanatomical substrates of memory (e.g., [6]), it was anticipated that the group with FLE would display more difficulties with the organizational and monitoring aspects of VLM, as evinced by an increased number of intrusion and repetition errors and vulnerability to interference. With respect to the impact of clinical and demographic variables on VLM, it was hypothesized that younger age at seizure onset, younger age at assessment, longer epilepsy duration, and increased number of AEDs would be associated with more impairment (as noted in the systematic review by Menlove & Reilly [1]). Finally, based on the literature reviewed [8,10,16], it was hypothesized that children with left hemisphere seizure focus would demonstrate worse VLM performance compared to children with right hemisphere focus.

2. Material and methods

2.1. Participants

The participants were patients who received neuropsychological assessments at the Hospital for Sick Children between 1993 and 2014 as part of their evaluation to determine their candidacy for epilepsy surgery. All were considered to have intractable epilepsy because achieve seizure control was not obtained after trials of two or more antiepileptic drugs (AEDs). Inclusion criteria included the following: (1) completion of at least one of the verbal learning measures included in the study; (2) unilateral seizure focus; (3) between the ages of 5 and 18 years; and (4) fluency in English. Exclusion criteria included the following: (1) epileptogenic focus outside of the frontal or temporal regions; (2) prior epilepsy surgery; (3) bilateral seizure foci; and (4) Full Scale Intelligence Quotient (FSIQ) ≤ 70. These criteria yielded a sample of 100 children with intractable TLE and 27 children with intractable FLE. The participant demographic characteristics are summarized in Table 1.

2.2. Procedure

The study was approved by the Research Ethics Board of the Hospital for Sick Children. Data were obtained through a retrospective chart review. All testing was completed at the hospital and was conducted by experienced psychometrists. Children completed a comprehensive neuropsychological assessment as part of their presurgical evaluations; however, only tests pertaining to the current study are reported.

2.3. Measures

Measures were chosen to assess verbal learning and memory, as well as overall intelligence. Table 2 provides a summary of the measures used and the specific abilities assessed.

2.3.1. Single-word list — Children's Auditory Verbal Learning Test, Second Edition (CAVLT-2)/California Verbal Learning Test, Second Edition (CVLT-II)

Participants were administered either the CAVLT-2 [19] or the CVLT-II [20] as a measure of single-word list learning, depending on their age. The CAVLT-2 is a standardized list learning measure for children and adolescents ranging in age from 6 to 17 years. The child is required to memorize a Learning List of 16 items orally presented by the examiner