Noninvasive identification of seizure lateralization in children

Name that thing

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Abstract

Objective

With this prospective, observational study, we aimed to determine whether noninvasive language tasks, developed specifically for children, could reliably identify the hemisphere of seizure onset in pediatric epilepsy.

Methods

Seventy-eight children with unilateral epilepsy (44 left), aged 6–15 years (mean age = 11.8, SD = 2.6), completed the Children's Auditory Naming and Visual Naming Tests, the Boston Naming Test, and other verbal and nonverbal tasks. Multivariate analysis of variance was used to compare test performance between left and right hemisphere epilepsy groups, and χ^2 analyses and odds ratios were used to examine classification of left vs right hemisphere epilepsy for individual patients based on test performance.

Results

Group comparisons revealed poorer auditory naming in children with left hemisphere epilepsy ($p = 0.02$), yet no significant differences on measures of visual naming, general intelligence, or other cognitive functions. Moreover, χ^2 analyses using auditory naming cutoff scores to define intact vs impaired performance correctly classified seizure laterality in a significant proportion of children ($p = 0.004$). The odds of left hemisphere epilepsy were 4.2 times higher (95% confidence interval 1.4–11.7) than the odds of right hemisphere epilepsy with poor auditory naming performance. In the subset of patients with temporal lobe epilepsy (TLE), the odds of left TLE were 11.3 times higher (95% confidence interval 2.00–63.17) than the odds of right TLE with poor auditory naming performance.

Conclusion

Contrary to previous findings, naming performance can lateralize hemisphere of seizure onset in children with epilepsy, thereby assisting in the preoperative workup for pediatric epilepsy surgery.

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Editorial

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Glossary

ANT = Auditory Naming Test; BNT = Boston Naming Test; CI = confidence interval; FSIQ = Full Scale IQ; PPV = positive predictive value; TLE = temporal lobe epilepsy; TOT = tip-of-the-tongue; VNT = Visual Naming Test; WIAT = Wechsler Individual Achievement Test.

Individuals with refractory epilepsy who are candidates for surgical treatment undergo multiple procedures that aim to lateralize and localize the epileptogenic region. In clinical practice, consistencies in the brain areas implicated across components of the workup, including EEG, neuroimaging, and neuropsychological evaluation, are taken as evidence for lateralization or localization of seizure onset. Nevertheless, despite decades of experience and numerous technological advances, localization, and sometimes even lateralization, of the epileptogenic region can be difficult to discern.

In adult epilepsy, one of the most reliable, noninvasive indicators of left (i.e., dominant) temporal lobe epilepsy (TLE) is word-finding or “naming” difficulty.^{1,2} Naming is traditionally assessed using visual object naming tests³; however, more recent work has shown auditory description naming to be particularly sensitive to dysfunction associated with left TLE. Specifically, impaired auditory naming, but not visual naming performance, has been shown to significantly classify laterality of seizure onset in individual adult patients with TLE.⁴

By contrast, naming has not shown similar utility in children.^{5–7} This has been interpreted to reflect less lateralized, more diffuse language representation in children.^{8–14} However, it is critical to consider that pediatric naming assessment has been hampered by widespread use of a measure with serious inherent limitations that was, in fact, designed for use with adults.¹⁵ Given the recent development of auditory and visual naming tests specifically for children, we investigated whether these noninvasive measures would yield clinically relevant laterality results in children with epilepsy. Because TLE is less prevalent in children,¹⁶ we broadened inclusion to unilateral left or right hemisphere epilepsy.

Methods

Patients

Participants comprised 78 children, aged 6 through 15 years, with unilateral epilepsy (44 left) who were recruited from 2011 through 2017 from the epilepsy programs at The Hospital for Sick Children (n = 39), Columbia University Medical Center (n = 17), New York University Medical Center (n = 13), Florida Hospital for Children (2014–2015; n = 5), and Cleveland Clinic (2016–17; n = 4). Consecutive patients were included in the study if they were classified by the attending epileptologist as having unilateral seizure onset based on scalp EEG and MRI. Patients were excluded if MRI showed evidence of contralateral structural abnormalities. Children with past or present head injury or neurologic disorders other than

epilepsy were excluded. Children were required to be left hemisphere language-dominant, native English speakers or to have learned English by age 5, and to have been fully educated in English. Language dominance was identified by fMRI (n = 39), postictal speech disturbance consistent with left hemisphere language dominance and right-handed (n = 25),¹⁷ memory test results consistent with left hemisphere language dominance and right-handed (n = 11; i.e., verbal and visual memory patterns that would not be inconsistent with left hemisphere language dominance), or Wada testing (n = 3).

Standard protocol approvals, registrations, and patient consents

Institutional review boards approved the study at each site. Parents provided written informed consent and minor participants provided written assent.

Materials and procedures

Naming assessment

The Children’s Visual Naming Test (VNT) consists of 36 color photographs of familiar items, each on a white background (i.e., without contextual cues), and the Children’s Auditory Naming Test (ANT) consists of 36 descriptions of familiar items (e.g., “where birds lay their eggs”). For ages 6 and 7, the tests are each 28 items, selected from the 36-item test for older children based on item analysis from the normative sample.¹⁸ Order of naming tasks was counterbalanced across participants. Tests were administered according to standardized instructions.³

Naming performance measures for the Children’s ANT and VNT include the following: total correct responses within 20 seconds, total correct responses in <2 seconds, total correct responses in 2 to 20 seconds, and tip-of-the-tongue (TOT) responses (defined as the sum of items named accurately in 2 to 20 seconds plus items not named by 20 seconds, yet named accurately following a phonemic cue [e.g., “ha” for hammer]). Both delayed (i.e., ≥2 seconds) and cued responses represent instances in which the word is clearly within the individual’s mental lexicon, but additional time or a phonemic cue was necessary to retrieve the word. Two summary scores were calculated as well: (1) Summary Score–All, which uses best performance as its base, with a penalty for TOT responses: total correct responses <2 seconds – TOT responses; and (2) Summary Score–Time, a purely time-based summary score: total correct responses in <2 seconds – total correct responses in ≥2 seconds.

The Boston Naming Test (BNT) is a widely used measure of visual object naming that was developed for adults, consisting

of 60 line-drawn objects. Patients are permitted up to 20 seconds to name each object, presented one at a time. Items that are named spontaneously or with a stimulus cue (e.g., “a musical instrument”) are awarded 1 point for a total of 60 points. Number of items named correctly constitutes the sole performance measure for the BNT. Sixty children were administered the BNT as part of their clinical neuropsychological evaluation; otherwise, the dataset was complete.

Additional cognitive measures

Full Scale IQ (FSIQ) was obtained from either the Wechsler Intelligence Scale for Children–IV/V ($n = 61$) or the 2-subtest Wechsler Abbreviated Scale of Intelligence ($n = 17$),¹⁹ comprised of Vocabulary (i.e., word definitions) and Matrix Reasoning (i.e., spatial puzzles). Participants also completed the Word Reading subtest of the Wechsler²⁰ Individual Achievement Test (WIAT-II/III, $n = 78$).

Statistical analyses

Raw scores were converted to z scores based on age-stratified normative data.¹⁸ Multivariate, 1-way (group: left vs right hemisphere epilepsy) analysis of variance was used for the primary analysis of performance data and to compare demographic and clinical data between groups. Chi square analyses were used to examine classification for left vs right hemisphere epilepsy based on naming performance. Odds ratio and confidence intervals (CIs) as well as sensitivity, specificity, and positive predictive value (PPV) were calculated based on 2×2 tables.

Power analysis was performed prospectively to determine the necessary sample sizes to detect differences between groups. Effect size was based on results from an earlier pilot study.

Data availability

For any data not published within this article, anonymized data will be shared by request from any qualified investigator.

Results

Demographic and clinical information is presented in table 1 for the left and right hemisphere groups.

Left hemisphere vs right hemisphere: Group comparisons

There were no differences between left and right hemisphere groups for age, age at epilepsy onset, number of antiepilepsy drugs, FSIQ, Vocabulary, Matrix Reasoning, or WIAT Word Reading (all $p > 0.18$), thereby reducing potential sources of bias.

Multivariate analysis of variance comparing naming performance in children with left vs right hemisphere seizures revealed significant group differences in several ANT scores; patients with left hemisphere seizures showed poorer performance on 3 of the 4 measures (figure and table 2). By contrast, there were no significant group differences in performance on any of the measures for the VNT or BNT.

Age was analyzed as a categorical variable, using the 2-year age groups from the normative data (6–7, 8–9, 10–11, 12–13, 14–15). There were no significant effects of age group (all $p > 0.40$), and no significant interactions between age group and laterality (all $p > 0.12$) for ANT or VNT performance.

Left hemisphere vs right hemisphere: Patient classification

To assess potential clinical utility, we tested whether ANT performance could predict seizure-onset laterality in individual patients. We operationally defined poor performance as a score of ≤ 1.5 SD below the age-stratified mean (i.e., z score -1.5 or lower) for either of the 2 summary scores. For comparative purposes, we examined patient classification using visual naming as well (i.e., VNT and BNT). For BNT, normative data for z score calculations are available only for untimed accuracy.^{21,22}

The 2×2 tables (table 3) show left vs right hemisphere classification results for ANT, VNT, and BNT performance. Results of χ^2 analyses assessing classification of individual patients were significant for ANT performance ($\chi^2 = 8.13$, $p = 0.004$). Odds ratio calculation indicated that the odds of left hemisphere epilepsy were 4.2 times higher than the odds of right hemisphere epilepsy with ANT summary score ≤ 1.5 SD below the mean (95% CI 1.4–13.4, sensitivity 52.3%, specificity 79.4%, PPV 76.7%). By contrast, classification results were not significant for VNT ($\chi^2 = 0.79$, $p = 0.37$) or BNT ($\chi^2 = 1.41$, $p = 0.23$) performance.

TLE subgroup

Given the known role of the dominant temporal lobe in naming, together with the significant laterality findings reported for adults with TLE, we analyzed naming performance separately in the subset of children with a clear diagnosis of unilateral TLE (23 left TLE, 14 right TLE). There were no group differences in age, age at epilepsy onset, number of antiepilepsy drugs, FSIQ, Vocabulary, Matrix Reasoning, or WIAT Word Reading (all $p > 0.10$; table 4). In addition, there were no group differences in BNT performance. However, despite the relatively small group, children with left TLE demonstrated significantly poorer performances on the time-based summary score, and 2 other measures approached significance of the ANT (table 5). Several laterality comparisons using VNT performance approached but did not reach significance. Laterality comparison of BNT performance was not significant (table 5).

As with the full sample, we assessed laterality classification of children with TLE using z scores of -1.5 or lower to define poor naming performance. Chi-square analyses assessing classification based on auditory naming was again significant, but more robust, primarily attributable to a higher proportion of patients with left TLE who had poor ANT performance and patients with right TLE who had intact performance ($\chi^2 = 9.09$, $p = 0.003$). Odds ratio calculation indicated that the odds of left TLE epilepsy were 11.3 times higher than the odds of right TLE with ANT summary score ≤ 1.5 SD below

Table 1 Demographic and clinical information

	Left hemisphere (n = 44)	Right hemisphere (n = 34)
Age, y	11.8 (2.6)	11.8 (2.5)
Girls/boys	21/23	18/16
Onset age, y	6.7 (3.8)	7.5 (3.6)
FSIQ	91.6 (11.6)	95.6 (14.2)
No. of AEDs	1.7 (0.8)	1.7 (0.7)
WIAT-II or -III Word Reading scaled score	93.4 (16.7)	96.8 (14.4)
WISC or WASI Vocabulary t score	46.2 (9.8)	48.4 (10.3)
WISC or WASI Matrix Reasoning t score	49.4 (10.5)	47.1 (12.9)
MRI findings	Normal MRI: 16, tumor: 7, vascular lesion: 7, white matter abnormality: 6, dysplasia: 5, DNET: 1, migrational defect: 1, unavailable (no contralateral EEG abnormalities): 1	Normal MRI: 11, dysplasia: 6, white matter abnormality: 4, tumor: 3, encephalomalacia: 3, vascular lesion: 2, cortical thinning: 1, choroid cyst: 1, mild atrophy: 1, polymicroglia: 1, unavailable (no contralateral EEG abnormalities): 1

Abbreviations: AED = antiepilepsy drug; DNET = dysembryoplastic neuroepithelial tumor; FSIQ = Full Scale IQ; WASI = Wechsler Abbreviated Scale of Intelligence; WIAT = Wechsler Individual Achievement Test; WISC = Wechsler Intelligence Scale for Children. Data represent count or mean (SD).

the mean (95% CI 2.00–63.17, sensitivity 65.2%, specificity 85.7%, PPV 88.2%). By contrast, neither VNT ($\chi^2 = -0.18$, $p = 0.43$) nor BNT ($\chi^2 = -0.18$, $p = 0.43$) classification of individual patients was significant (table 6).

Discussion

In adult epilepsy, there is an established history of using cognitive test results to draw inferences regarding the functional integrity of lateralized and focal brain regions. However,

utilization of cognitive test results in this way has been considerably less reliable in pediatric epilepsy. While this has been assumed to reflect a more diffuse representation of verbal functions in children, we speculated that for naming, the nature of the tests used with children might account, at least in part, for this discrepancy. That is, naming in children with epilepsy has been primarily assessed using an adult-level measure that assesses naming only in the visual modality, and only via untimed accuracy. In this study, we administered auditory naming and visual naming tests developed

Figure Auditory and visual naming performance in children with left vs right hemisphere epilepsy

(A) TOT scores; (B) Summary Score-All; (C) Summary Score-Time. For TOT: higher score indicates poorer performance. TOT = tip-of-the-tongue.

Table 2 ANT and VNT performance: Comparison between children with left and right hemisphere epilepsy

	Left hemisphere (n = 44)	Right hemisphere (n = 34)	F; p value
ANT			
Total correct responses	−1.16 (2.91)	−0.61 (2.04)	0.87; 0.433
TOT^a	1.50 (1.73)	0.69 (1.38)	4.99; 0.028 ^b
Summary Score–All	−1.57 (1.86)	−0.72 (1.43)	4.69; 0.033 ^b
Summary Score–Time	−1.55 (1.78)	−0.68 (1.33)	5.65; 0.020 ^b
VNT			
Total correct responses	−0.76 (3.01)	−0.15 (1.16)	1.27; 0.262
TOT^a	0.37 (1.25)	0.18 (1.16)	0.48; 0.487
Summary Score–All	−0.40 (1.39)	−0.11 (1.19)	0.90; 0.345
Summary Score–Time	0.34 (1.29)	0.09 (1.21)	0.77; 0.383
BNT	−1.71 (1.92)	−1.21 (1.66)	1.69; 0.198

Abbreviations: ANT = Auditory Naming Test; BNT = Boston Naming Test; TOT = tip-of-the-tongue; VNT = Visual Naming Test.

z scores: mean (SD).

^a TOT higher scores reflect poorer performance.

^b $p < 0.05$.

specifically for use with children and examined time-based efficiency as well as response accuracy, in an attempt to identify hemisphere of seizure onset.

Group comparisons between children with left vs right hemisphere epilepsy revealed no significant differences in age, age at epilepsy onset, number of seizure medications, FSIQ, or Word Reading. Although there were no group differences in visual naming performance, children with left hemisphere seizures exhibited significantly poorer performance on the time- and cue-based performance measures of the auditory naming task. In fact, ANT summary score cutoffs defining intact vs poor performance correctly classified seizure

laterality in a significant proportion of patients. Specifically, children with poor ANT performance were 4 times more likely to have left than right hemisphere epilepsy. Given the integral role of the dominant temporal lobe in naming,^{23,24} as well as our previous adult TLE findings,⁴ we also examined laterality effects in the subgroup of children with a clear diagnosis of TLE. Despite the smaller sample size, lateralization was both more sensitive and more specific than that in the full group; the odds of left TLE were 11 times greater than the odds of right TLE with poor auditory naming performance.

Table 3 Laterality classification by naming test

Summary score	Left hemisphere	Right hemisphere	<i>p</i> Value
ANT			
≤ −1.5 SD	23	7	0.004
> −1.5 SD	21	27	
VNT			
≤ −1.5 SD	10	5	0.37
> −1.5 SD	34	29	
BNT			
≤ −1.5 SD	15	10	0.23
> −1.5 SD	17	21	

Abbreviations: ANT = Auditory Naming Test; BNT = Boston Naming Test; VNT = Visual Naming Test.

Table 4 Demographic and clinical information for TLE subgroup

	Left TLE (n = 23)	Right TLE (n = 14)
Age, y	11.8 (2.9)	11.1 (2.6)
Girls/boys	9/14	8/6
Onset age, y	7.1 (3.7)	6.1 (3.6)
FSIQ	92.8 (10.0)	98.1 (15.2)
No. of AEDs	1.7 (0.8)	1.5 (0.8)
WIAT-II or -III Word Reading scaled score	91.5 (18.2)	100.1 (12.4)
WISC or WASI Vocabulary t score	45.0 (8.9)	50.0 (12.3)
WISC or WASI Matrix Reasoning t score	51.4 (11.6)	49.0 (15.5)

Abbreviations: AED = antiepilepsy drug; FSIQ = Full Scale IQ; TLE = temporal lobe epilepsy; WASI = Wechsler Abbreviated Scale of Intelligence; WIAT = Wechsler Individual Achievement Test; WISC = Wechsler Intelligence Scale for Children. Data represent count or mean (SD).

Table 5 ANT and VNT performance: Comparison between children with left and right TLE

	Left TLE (n = 23)	Right TLE (n = 14)	F; p Value
ANT			
Total correct responses	-1.72 (3.78)	-0.82 (3.06)	0.52; 0.451
TOT^a	1.77 (1.73)	0.59 (1.74)	3.83; 0.058
Summary Score-All	-1.89 (1.98)	-0.58 (1.87)	3.98; 0.054
Summary Score-Time	-1.80 (1.75)	-0.49 (1.64)	5.06; 0.031 ^b
VNT			
Total correct responses	-1.27 (4.01)	0.25 (0.22)	1.99; 0.167
TOT^a	0.74 (1.43)	-0.07 (1.09)	3.42; 0.073
Summary Score-All	-0.79 (1.54)	0.08 (1.06)	3.56; 0.067
Summary Score-Time	-0.79 (1.40)	0.07 (1.06)	4.03; 0.052
BNT	-1.25 (1.77)	-1.14 (2.1)	0.027 0.871

Abbreviations: ANT = Auditory Naming Test; BNT = Boston Naming Test; TLE = temporal lobe epilepsy; TOT = tip-of-the-tongue; VNT = Visual Naming Test. z scores: mean (SD).

^a TOT higher scores reflect poorer performance.

^b $p < 0.05$.

The sensitivity of auditory naming in particular to dominant hemisphere dysfunction does not appear to be attributable to the vocabulary level of the target words on the tests, as ANT and VNT item names are matched by spoken word frequency. In addition, vocabulary level did not differ between children with left and right hemisphere epilepsy. We speculate that the key difference between tasks lies in the processing of the naming cues, i.e., the verbal description vs the pictured object. Both tasks require access to the semantic system, inhibition of semantically and phonemically related words, and honing in on the unique target word. However, the verbal demands of the auditory naming task require rapid semantic and syntactic

processing of the description. This heavier verbal load likely underlies the laterality effect.

Laterality effects appeared more robust in the TLE subgroup, although it is important to note that the TLE group was relatively small, and along with the higher odds ratio, the CI around the odds ratio for patients with TLE was quite wide. Nevertheless, results could be considered consistent with the other findings suggesting that auditory naming is particularly dependent on the functional integrity of the dominant temporal lobe. Electroconvulsive stimulation mapping in adults has shown that visual naming is primarily disrupted with stimulation in the mid to posterior temporal region, whereas auditory naming is disrupted with both anterior and posterior temporal stimulation.^{25,26} This could reflect a general vulnerability of auditory naming processes to virtually any temporal lobe abnormalities associated with temporal lobe seizures. However, temporal lobe seizures and interictal discharges, at least those arising from mesial temporal structures, tend to propagate anteriorly rather than posteriorly.²⁷ Thus, auditory naming might be more adversely affected than visual naming due to the predominant support of auditory naming by the anterior temporal cortex. Either of these possibilities would render auditory naming more vulnerable to the abnormalities associated with TLE. Of course, these speculations are based on adult findings, and it remains to be determined whether these same neurophysiologic and anatomical findings would apply to children with epilepsy.

Although results suggest that incorporation of auditory naming increases the sensitivity of naming assessment in children with epilepsy, it is also important to note that neither auditory- nor visual-naming untimed accuracy scores differed between right

Table 6 Laterality classification by naming test in TLE subgroup

Summary score	Left TLE	Right TLE	p Value
ANT			
≤ -1.5 SD	15	2	0.003
> -1.5 SD	8	12	
VNT			
≤ -1.5 SD	7	2	0.43
> -1.5 SD	16	12	
BNT			
≤ -1.5 SD	7	3	0.43
> -1.5 SD	9	10	

Abbreviations: ANT = Auditory Naming Test; BNT = Boston Naming Test; TLE = temporal lobe epilepsy; VNT = Visual Naming Test.

and left hemisphere (or TLE) patients. Rather, response latency best reflected word-finding difficulty, suggesting that epilepsy-related abnormalities may disrupt the efficiency by which words are selected and retrieved, rather than cause degradation to the words or concepts themselves. Thus, it seems that time-based scores better capture the dysfunction that underlies word-finding difficulty in epilepsy, thereby providing more useful information regarding lateralization of seizure onset.

With reference to limitations, our sample of children with TLE permitted laterality analysis within this subgroup, but other subgroups (e.g., frontal or parietal seizure onset) were not sufficiently represented to examine potential differences related to laterality or to intrahemispheric localization of seizure onset. In addition, children with left and right hemisphere epilepsy were, overall, comparable in age; however, the age range was relatively wide, without a sufficient number of children in each age group to explore potential age-related differences in auditory and visual naming. Given these initial findings, future studies should aim for larger samples that would permit analysis of naming in epilepsy by age and intrahemispheric location of seizure onset. Also, because participants were all clinical patients, examiners were not consistently blinded to lateralization of seizure onset, potentially introducing some degree of bias. Finally, our sensitivity, specificity, and PPVs should be replicated in an independent sample to further assess clinical applicability.

These results, which are strikingly similar to those found previously in adults,⁴ are somewhat counter to the notion that lateralization of dysfunction is less reliable in children because of their more diffuse cerebral organization of language. While it is very likely the case that language functions are overall less lateralized in children, it does appear that the cognitive mechanisms that support naming are lateralized earlier than had been assumed and possibly earlier than other language functions. Nevertheless, as with any findings based on a clinical sample, generalizations regarding normal development must be made cautiously.

Clinically, the current results underscore that naming assessment in children is markedly improved with the addition of auditory naming, by minimizing the influence of vocabulary and by incorporating response time into performance measures. In the context of epilepsy surgery, results suggest that these children's naming tests promise utility in lateralization of dysfunction associated with the region of seizure onset. Just as important, these measures can also be used to identify intact naming function that would be critical to preserve. Although the current study centered on focal epilepsy, it is reasonable to anticipate these tests, designed specifically for children, may have both clinical and investigative utility in other pediatric conditions that affect brain areas that support language.

Author contributions

M.J. Hamberger: design and conceptualization of study, data acquisition and supervision, analysis and interpretation of

data, drafting/revising the manuscript for intellectual content, study supervision and coordination. W.S. MacAllister: design of study, study supervision and coordination, interpretation of data, drafting/revising the manuscript for intellectual content. W.T. Seidel: design and conceptualization of study, analysis and interpretation of data, drafting/revising the manuscript for intellectual content. R.M. Busch: study supervision and coordination, interpretation of data, revising the manuscript for intellectual content. C.M. Salinas: study supervision and coordination, interpretation of data, revising the manuscript for intellectual content. P. Klaas: study supervision and coordination, interpretation of data, revising the manuscript for intellectual content. M.L. Smith: design and conceptualization of study, study supervision and coordination, interpretation of data, revising the manuscript for intellectual content.

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