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Age-Dependent Mesial Temporal Lobe Lateralization in Language fMRI

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Abstract

Objective—fMRI activation of the mesial temporal lobe (MTL) may be important for epilepsy surgical planning. We examined MTL activation and lateralization during language fMRI in children and adults with focal epilepsy.

Methods—142 controls and patients with left hemisphere focal epilepsy (Pediatric: epilepsy, $n = 17$, mean age = 9.9 ± 2.0 ; controls, $n = 48$; mean age = 9.1 ± 2.6 ; Adult: epilepsy, $n = 20$, mean age = 26.7 ± 5.8 ; controls, $n = 57$, mean age = 26.2 ± 7.5) underwent 3T fMRI using a language task (auditory description decision task). Image processing and analyses were conducted in SPM8; ROIs included MTL, Broca's area, and Wernicke's area. We assessed group and individual MTL activation, and examined degree of lateralization.

Results—Patients and controls (pediatric and adult) demonstrated group and individual MTL activation during language fMRI. MTL activation was left lateralized for adults but less so in children (p 's < 0.005). Patients did not differ from controls in either age group. Stronger left-lateralized MTL activation was related to older age ($p = 0.02$). Language lateralization (Broca's and Wernicke's) predicted 19% of the variance in MTL lateralization for adults ($p = 0.001$), but not children.

Significance—Language fMRI may be used to elicit group and individual MTL activation. The developmental difference in MTL lateralization and its association with language lateralization suggests a developmental shift in lateralization of MTL function, with increased left lateralization across the age span. This shift may help explain why children have better memory outcomes following resection compared to adults.

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We confirm that we have read *Epilepsia*'s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure of Conflicts of Interest

The remaining authors have no conflicts of interest to report.

Keywords

Functional neuroimaging; Seizures; Neuropsychological Assessment

Presurgical language and memory assessment help to minimize adverse effects of epilepsy surgery. Neuropsychological assessment and the intracarotid amobarbital procedure are used for this purpose. In children, however, the former is not highly predictive of post-operative outcome¹; the latter is invasive and difficult to perform. Functional magnetic resonance imaging (fMRI) provides reliable, noninvasive language mapping for adults and children²; however, using fMRI to directly probe *memory* function in epilepsy is a nascent technique, with published studies only for adults³⁻⁶.

Memory fMRI can be methodologically challenging; therefore, we explored an indirect method of eliciting hippocampal/parahippocampal or mesial temporal lobe (MTL) activation in epilepsy. We used an established pre-operative fMRI task conventionally used for language mapping to glean information regarding MTL functioning^{7,8}. Our rationale for this approach is based on previous data showing that language fMRI predicts post-operative memory outcome in adults with temporal lobe epilepsy (TLE)^{8,9} and that the MTL supports language functioning¹⁰⁻¹⁷. Numerous studies have demonstrated the MTL's role in language processing, including evidence that confrontation naming depends on hippocampal integrity, and left hippocampal volume and degree of perirhinal cortex asymmetry in TLE predict language and memory performance¹⁰. Hippocampal pathology also affects language lateralization^{13,14,16,17}, intrahemispheric language reorganization¹⁵, and pre- and post-operative language functioning¹².

We address gaps in understanding the MTL's role in language by determining if 1) language fMRI reliably elicits MTL activation on group and individual bases, 2) MTL lateralization differs between children and adults with and without epilepsy, and 3) MTL lateralization parallels anterior (Broca's) and posterior (Wernicke's) language lateralization. We hypothesized that language fMRI would elicit MTL activation on group and individual bases due to evidence that the MTL supports language¹⁰⁻¹⁷. Second, as memory encoding in typically developing (TD) adults produces material-specific lateralization (verbal-left MTL, visual-right MTL)^{4,18,19}, we predicted left-lateralized MTL activation during language fMRI in TD adults. Adults with TLE demonstrate greater MTL activation contralateral to seizure foci^{4,6}; in left TLE verbal encoding yields right activation and in right TLE nonverbal encoding yields left activation⁴. Therefore, we expected reduced left lateralization in left focal epilepsy patients compared to controls. Although there is ongoing strengthening of the lateralization of fronto-temporal language regions across development^{20,21}, the language network itself is fundamentally established by age four²⁰. Children also have demonstrated left parahippocampal activation during language fMRI²², thus we expected similar results for adults and children. Finally, TD adults show material-specific memory lateralization related to language lateralization during memory fMRI²³; thus, we predicted MTL lateralization would correlate with Broca's and Wernicke's lateralization during language fMRI for adults and children. Overall, children would show a similar pattern to adults with less pronounced lateralization.

METHODS

Participants

This cross-sectional, retrospective review of data from a prospectively acquired study included adult and pediatric participants:

Adult—Seventy-seven native English speaking, right-handed adults participated; all evaluated between 2003–2011 at a tertiary referral epilepsy center. Twenty patients had left-hemisphere focal epilepsy and normal MRI (mean age = 26.7 years, range = 17.0–40.8, SD = 5.8 years; 12 female); 57 were TD controls (mean age = 26.2 years, range = 20.1–56.3, SD = 7.5 years; 29 female).

Pediatric—Sixty-five native English-speaking, right-handed children aged 6–13 participated. Seventeen had left-hemisphere focal epilepsy (mean age = 9.9 years, range = 6.8–12.8 SD = 2.0 years); 48 were TD controls (mean age = 9.1 years, range = 4.2–13.0, SD = 2.6 years). See Supplemental Materials for more information about pediatric and adult participants.

For all patients, clinical features, neurologic examination, ictal video-EEG, and high-resolution epilepsy protocol MRI were used to localize seizure foci. In both groups (adult and pediatric), we included only patients with left hemisphere foci (based on clinical evaluation and ictal video-EEG) who had normal MRI to limit confounding factors and volume averaging effects in patients with sclerotic MTL (see Table 1 for seizure characteristics). The patients were on various AEDs. Detailed AED information was available for 12 of the adult patients, with 11 out of the 12 adult patients on more than one medication (Table 1 for AEDs). AED information was available for all 17 pediatric patients, with 1 patient not taking any AEDs and 6 on more than one medication. Controls had IQ > 70 and no history of developmental, learning, neurological, or psychiatric disorders.

The study was approved by the Combined Neurosciences Institutional Review Board of National Institutes of Health and the Institutional Review Board of Children's National Medical Center. Adult participants and parents of pediatric participants provided informed consent; all minors provided assent.

MRI

Pediatric patients and TD controls were scanned on a 3.0 Tesla Siemens Magnetom Trio scanner (Erlangen, Germany), and adult patients and TD controls were scanned on a 3.0 Tesla General Electric scanner (General Electric Medical Systems, Milwaukee, WI) using echoplanar imaging (EPI) blood oxygen level dependent (BOLD) techniques. All participants underwent EPI BOLD fMRI during an age-adjusted language task (auditory description decision task) known to activate inferior frontal gyrus (Broca's area). Details of acquisition methods and experimental paradigm were previously described^{2,20}, and acquisition methods are reviewed in Supplemental Materials.

We used a block design composed of five epoch cycles; each cycle consisted of an experimental condition that alternated with a control condition and each hemicycle lasted 30

seconds. Total scan time was five minutes. Individual stimuli were presented every three seconds (pediatric) or two second (adults) for a total of 10 per block (pediatric) and 15 per block (adult). Our previous analyses show no differences between scanners using these paradigms and acquisition parameters^{24,25}. Tasks were presented via E-Prime software version 1.1 (Psychology Software Tools, Inc., Pittsburgh, PA). Auditory stimuli were digitized and presented via pneumatic earphones. Responses were performed via fiber-optic push button (MRA, Inc., Washington, PA) response recorded by PC in E-Prime.

Experimental Paradigm

Auditory description decision task—For the experimental condition, the participant hears an auditory clue (5–6 word sentences) that describes and names an object (*e.g.*, “A long yellow fruit is a banana”) and pushes a button when the description accurately describes the object. Seventy percent of items are correct targets and 30% are foils. The task is designed to provide in-scanner monitoring of performance by requiring a semantic decision identified by button press response. Task performance was evaluated by the overall accuracy for the task (true positives divided by the sum of the number of correct answers possible and the number of commissions, multiplied by 100); these data were only available for the pediatric groups (Table 1). The control condition consists of reverse speech with tone identification where the participant pushes a button when the tone follows reverse speech (70% have tones, 30% are foils). The task was adjusted by age-level with different versions of the tasks developed based on word frequency normative data derived from children’s reading materials²⁶.

Image processing and Regions of Interest

Preprocessing and group analyses were performed in SPM8 (Wellcome Department of Cognitive Neurology, London, UK) using MATLAB (Version 8.1 Mathworks, Inc., Sherborn, MA). Regions of interest (ROIs) for bilateral MTL included hippocampi and parahippocampal gyri^{4,18}, based on the Anatomical Atlas Library in the Wake Forest PickAtlas (Wake Forest University School of Medicine, Winston-Salem, NC). To categorize each subject’s language patterns traditional language regions were used as ROIs: Broca’s area (inferior frontal gyrus) and Wernicke’s area (Brodmann’s areas: 21, 22, 39, dilated) using the Wake Forest PickAtlas²⁷. All images were temporally filtered (high-pass filter: 128s).

The MTL is a small region subject to artifact, signal loss, and field distortion²⁸. To improve detection of MTL activation we reduced smoothing to 5mm full width at half maximum Gaussian kernel after functional images were spatially normalized to MNI standard anatomical space; we used the same amount of smoothing for bilateral MTL ROIs to ensure accurate matching with underlying voxels. Data for language analysis (Broca’s and Wernicke’s) were smoothed using the typical 8 mm kernel. We were conservative in ROI application; rather than applying ROIs at design level, which improves ROI activation by restricting first-level statistical analysis to that area (but interferes with smoothness estimation), we applied ROIs (MTL, Broca’s, or Wernicke’s) to whole brain activation t-maps calculated without restrictions. As we planned to compare MTL and language

(Broca's, Wernicke's) lateralization, this allowed for application of ROIs at the same analysis point.

As the small size and location of the MTL increase motion vulnerability we employed an individualized approach to explaining motion-related variance (motion fingerprint)²⁹. This motion fingerprint (6 total traces: 3 traces plus their shifted versions) was entered into first-level statistical analyses as covariates of no interest. Participants were excluded if movement exceeded 3 mm (~1 voxel size) total displacement (TotD; common criterion). To be rigorous, we examined results with and without participants demonstrating TotD < 3, but scan-to-scan (STS) displacement < 1 mm. See Supplemental Materials for more specifics about TotD and STS.

Determination of Language Lateralization and MTL Lateralization

Lateralization indices (LIs) were calculated for each participant's MTL and language areas (Broca's, Wernicke's). We categorized lateralization as left, right, or bilateral based on a commonly-used value of 0.20³⁰. Using the LI Toolbox bootstrap method (implemented in SPM8)³¹ ROIs were individually categorized as left lateralized if $LI \geq 0.20$, bilateral if $LI < |0.20|$, or right if $LI \leq -0.20$. Only individuals with activation clusters of 5 voxels or greater ($k \geq 5$) were used in MTL lateralization analyses.

Data analyses

Overall, we examined MTL activation during a language task and then investigated if MTL lateralization differed by clinical (epilepsy vs. controls) or age group (adult vs. pediatric). When appropriate, age was examined as a linear variable. We explored relationships between MTL and language lateralization categorically (left, bilateral, right) and linearly (using individual LIs). Categorical analyses allow for characterization of lateralization based on common, clinically useful thresholds; linear analyses may be differentially sensitive due to increased variance providing better understanding of variable relationships.

We first established group level MTL activation, then individual level activation. As individual level activation is less robust, particularly for the MTL, we examined activation rates within bilateral MTL ROIs at various thresholds (0.05, FDR; 0.001, 0.01, 0.05, uncorrected). We used ANOVA to determine if average MTL LI values differed by those thresholds. Categorical agreement (left, right, bilateral) between MTL and language (Broca's, Wernicke's) lateralization for each age group was tested using Cohen's kappa coefficient. Linear MTL lateralization was assessed using two ANCOVA models with clinical (epilepsy vs. controls) and age group (adult vs. pediatric) as between-group factors. One ANCOVA had Broca's LI as the covariate and the other Wernicke's LI, to separately examine impacts of each language area LI on MTL LI. We examined age linearly with Pearson's correlation to investigate the relationship between age and MTL LI, and linear regression models to predict MTL LI from Wernicke's and Broca's LI for each age group.

RESULTS

MTL Activation on a Group Level

Adult—The combined activation map for controls and patients demonstrated MTL activation ($p = 0.05$, FWE; $k = 5$ voxels). Controls showed MTL activation ($p = 0.05$, FWE; $k = 5$ voxels), but patients only at more liberal thresholds. No activation clusters were evident when comparing patients and controls ($p = 0.05$, FWE).

Pediatric—Controls and patients displayed MTL activation ($p = 0.05$, FWE; $k = 5$ voxels), with no activation differences between groups ($p = 0.05$, FWE). Controls demonstrated MTL activation ($p = 0.05$, FWE; $k = 5$ voxels), but patients only showed MTL activation at more liberal thresholds.

MTL Activation on an Individual Level

The majority of adult and pediatric controls and patients demonstrated individual MTL activation ($k = 5$) at the most lenient threshold (0.05, uncorrected); however, rates decreased at more stringent thresholds (Table 2). Despite different proportions of individual MTL activation by threshold, MTL LIs were not significantly affected by activation thresholds for either age or clinical group (Table 2). To account for possible movement effects, we examined results with more stringent exclusion criteria (excluding scan-to-scan displacement ≥ 1 mm); results were stable (Table 2). As a result, for the remaining analyses participants were only excluded if movement exceeded 3 mm (~ 1 voxel size) total displacement.

MTL Lateralization

As MTL LIs were similar regardless of activation thresholds, we included all individuals demonstrating MTL activation ($k = 5$) at the most lenient threshold (0.05, uncorrected) for the following LI analyses.

We found a main effect of age group for both ANCOVAs (covariate Wernicke's LI: $F(1,124) = 8.67, p < 0.001$; covariate Broca's LI: $F(1,124) = 6.80, p = 0.004$) demonstrating more left-lateralized LI in adults than children (Figure 1). No significant differences were found between controls and patients with epilepsy and there was no clinical by age group interaction. For adults, MTL LI was left lateralized overall (control mean MTL LI = 0.42, SD = 0.39; epilepsy mean MTL LI = 0.35, SD = 0.50; Figure 2). Categorically, 25% (17 of 67) of adults had right or bilateral MTL lateralization. For children, MTL LI was bilateral overall (control mean MTL LI = 0.18, SD=0.35; epilepsy mean MTL LI = 0.09, SD = 0.42; Figure 2). Categorically, 45% (28 of 62) had right or bilateral MTL lateralization. Each individual's peak voxel within the bilateral MTL ROIs illustrates that adults have more left-lateralized activation than children (Figure 1). Greater MTL LI was positively correlated with age for the pediatric and adult samples combined ($r = 0.21, p = 0.02$).

MTL Lateralization related to Language Lateralization: Categorical Analysis

As expected, language lateralization was primarily left lateralized for adults and children in both temporal (Wernicke's) and frontal (Broca's) areas; however, the relationship with MTL lateralization varied by age group.

Adult—Patients and controls with left-lateralized temporal (Wernicke's) language showed mostly left-lateralized MTL activation; those with right/bilateral Wernicke's lateralization ($n = 5$) had variable MTL activation patterns (Figure 3). Similarly, those with left-lateralized frontal (Broca's) language showed left lateralized MTL activation, while those with right/bilateral Broca's lateralization ($n=6$) had variable MTL activation (Figure 3). We found agreement between categorical lateralization of Wernicke's and MTL ROIs ($p = 0.005$; Cohen's kappa = 0.21), and between Broca's and MTL ROIs ($p < 0.001$, Cohen's kappa = 0.32).

Pediatric—Patients and controls showed variable MTL lateralization patterns across categories of Wernicke's and Broca's language lateralization; we did not find significant agreement between categorical lateralization of Wernicke's and MTL (Figure 3) nor Broca's and MTL using Cohen's kappa.

MTL Lateralization related to Language Lateralization: Linear Analysis

Overall, Wernicke's and Broca's LI were both related to MTL LI across age and clinical groups [covariate Wernicke's LI: $F(1,124) = 8.72, p = 0.004$; covariate Broca's LI: $F(1,124) = 12.92, p < 0.001$]; however, the relationship between language LI and MTL LI varied by age group.

Adult—The linear regression model including Wernicke's LI and Broca's LI accounted for 18.7% of the variance in MTL LI, $F(2,64) = 7.34, p = 0.001$ (Table 3).

Pediatric—The linear regression model including Wernicke's LI and Broca's LI was not significant (Table 3).

DISCUSSION

We found group and individual MTL activation during language fMRI in adults and children with epilepsy, as well as controls. MTL activation was more left lateralized with increasing age. Our results suggest a developmental shift in the relationship between MTL and language lateralization. Adults showed relatively homogeneous left-lateralized MTL activation that was related to language lateralization, consonant with the concept of material specificity of memory function in adulthood. Our study is the first to provide neuroimaging evidence showing that children have a more variable distribution of MTL lateralization, which is unrelated to language LI. Our results offer important insight into MTL lateralization across development. Overall, MTL activation becomes more left lateralized with age, eventually mirroring language lateralization.

Our results reinforce other empirical evidence of the MTL's role in language processing. Specifically, studies suggest MTL functioning affects language ability^{10,11} and hippocampal

pathology affects language lateralization^{13,14,17}, intrahemispheric reorganization of language¹⁵, and pre- and post-operative language functioning¹². Further, approximately 25% of patients with mesial temporal sclerosis have atypical language dominance¹⁴.

We found that language lateralization predicted MTL lateralization for adults, which parallels another fMRI study where patients with left-lateralized language showed increased left MTL lateralization for a verbal memory task and increased right MTL lateralization for visual memory, while the opposite occurred for patients with right-dominant language²³. In contrast, for children in our study, neither posterior nor anterior language lateralization was predictive of MTL lateralization.

Our results suggest less lateralization of MTL function in children than adults. The majority of neuropsychological studies suggest children with epilepsy do not show pre-surgical lateralizing memory impairments^{33,34}. One TLE study demonstrated adults and adolescents, but not children, showed laterality differences in memory performance³⁵. The decreased MTL lateralization we found in children may explain the lack of material-specific memory deficits in TLE children compared to adults. We propose that children initially engage both MTLs, with specialization for specific types of material (verbal-left MTL, visual-right MTL) occurring later in development. This follows research demonstrating increased left lateralization for language²⁰ and right lateralization for visuospatial functions with age³⁶.

In typical development, structural and functional changes occur along the hippocampal longitudinal axis^{37,38}. Functionally, episodic recall is associated with posterior hippocampal activity in children, and anteriorly in adults³⁸. Our results suggest this hippocampal/parahippocampal activation may also be lateralized differently across development. This lateralization difference may result from neuroanatomical changes throughout development, different processing strategies (*e.g.*, decreased visual imagery) across the age span, or a combination of both factors. Future studies are necessary to evaluate these hypotheses.

Our results have implications for improving assessment of surgical risk. Selective anterior temporal resection is the most effective treatment for intractable TLE³⁹, but given the MTL's critical role in language and memory, resection can have negative cognitive effects. Dominant temporal resections may lead to post-operative naming and verbal memory decline in adults⁴⁰. Post-operative memory outcomes may be predicted by activation in the hippocampus to be resected (*hippocampal adequacy*) or activation in the non-resected hippocampus (*hippocampal reserve*)⁵. TLE adults with greater ipsilateral than contralateral MTL activation on pre-operative fMRI memory demonstrate greater memory decline following temporal resection, supporting *hippocampal adequacy*^{3,5}. Language fMRI also helps predict post-operative memory outcome in TLE adults^{8,9}, with outcomes correlating better with fMRI language lateralization than hippocampal lateralization during scene-encoding⁹. Our results may explain the utility of language fMRI to predict post-operative verbal memory outcome, suggesting it represents MTL activation during language tasks.

Children with epilepsy do not show material-specific memory impairments pre-^{33,34} or post-surgery¹, suggesting children, unlike adults, are less reliant on the dominant MTL for memory functioning. Although we used an indirect measure (language fMRI), our results

support this hypothesis; children with epilepsy may have less post-operative memory deficit risk due to contralateral MTL activation. These findings posit a developmental shift in lateralization of MTL function, and thus a switch in prediction of post-operative outcome from *hippocampal reserve* to *hippocampal adequacy* across development.

We found that adults with left focal epilepsy demonstrated left-lateralized MTL activation similar to TD adults, which is discrepant from previous memory fMRI studies showing greater activation in the MTL contralateral to seizure foci in TLE^{4,6}. One language fMRI study (using a single-word category decision task) also found that individuals with right TLE displayed stronger contralateral hippocampal, parahippocampal, and collateral sulcus activation compared to left TLE⁷. Discrepant findings may be due to use of fMRI tasks which burden language/memory networks differently; for example, we did not use an explicit memory task and our language task (auditory description decision) varies from the single-word category decision task previously described⁷. Alternatively, our sample of left focal epilepsy was not limited to TLE; 81% of adult patients and 24% of pediatric patients had TLE. Adult patients in our sample had TLE without evidence of hippocampal atrophy, which could also account for the discrepancies from previous memory fMRI studies. However, different TLE distributions in our sample are not a likely factor as developmental MTL lateralization differences were also evident in TD adult and pediatric samples.

Limitations

The MTL is small and subject to artifact; therefore, accurate activation estimation is difficult. Decreased activation may be due to reduced MTL function or acquisition difficulty. The number of activated voxels in the MTL may be low, making it difficult to accurately assess lateralization. However, our methods—adjusting smoothing level for MTL activation data and ROIs, and stringent movement criteria—improved activation assessment. New acquisition methods, such as fieldmaps, fast image acquisition, thin slices, and reversing phase encoding direction may reduce MTL distortion and signal loss²⁸. Further, due to our hypothesis regarding MTL activation during language fMRI, we employed an ROI approach as opposed to an exploratory whole-brain search. As memory and language functioning involves a distributed network of brain regions, this limits our ability to comment on other brain regions that might be involved in these cognitive processes.

All children were scanned on a 3.0 Tesla Siemens Magnetom and adults on a 3.0 Tesla GE scanner using slightly different parameters. Previous analyses showed no differences between scanners using these paradigms and acquisition parameters^{24,25}. The Siemens scanner has potential for better spatial resolution, while the GE may allow for greater MTL activation given better temporal resolution. However, neither variable should affect MTL LI. Task accuracy was only available for pediatric participants and not adults. While it is theoretically possible that task accuracy differences between the age groups may explain some of the developmental MTL lateralization differences, we have previously shown that accuracy on this auditory description decision task does not correlate with lateralization in children²⁰. We do not have a reason to suspect this would be different for adults. Further, the two age groups (adult vs. pediatric) have different seizure foci, with more TLE in the adult compared to the pediatric group. The difference in seizure foci may explain some of

the discrepancy in results between age groups; however, given that the majority of adults had left TLE and we expect greater MTL activation contralateral to seizure foci^{4,6}, our results showing greater left-lateralized MTL activation in the left focus adult group further supports our hypothesis. This study involved patients with left focal epilepsy due to the clinical selection bias; future studies should include patients with right focal epilepsy.

A pragmatic objective of this study was to ascertain if a single fMRI task could yield presurgical MTL activation helpful in understanding both language and memory function. Thus, future research will examine if this MTL lateralization during language fMRI predicts post-operative language and memory ability. Finally, we expect stronger individual MTL activation with explicit memory paradigms, where MTL activation can be measured directly. Thus, our results need to be confirmed by memory fMRI paradigms.

Conclusions

Differences exist between children and adults for the effects of epilepsy and temporal resection on memory networks. Our results provide insight into understanding MTL lateralization across development. Adults demonstrated homogeneous left-lateralized MTL activation during a language task, while children were more heterogeneous in their MTL lateralization patterns. Developmental differences in MTL lateralization and relationships with language lateralization may represent a shift in MTL lateralization across development. Contralateral MTL activation may explain better memory performance following surgery in children compared to adults, supporting *hippocampal reserve* in pediatric epilepsy. Better understanding of MTL function and development will minimize potential adverse effects of temporal resection by helping to establish the optimal developmental window for surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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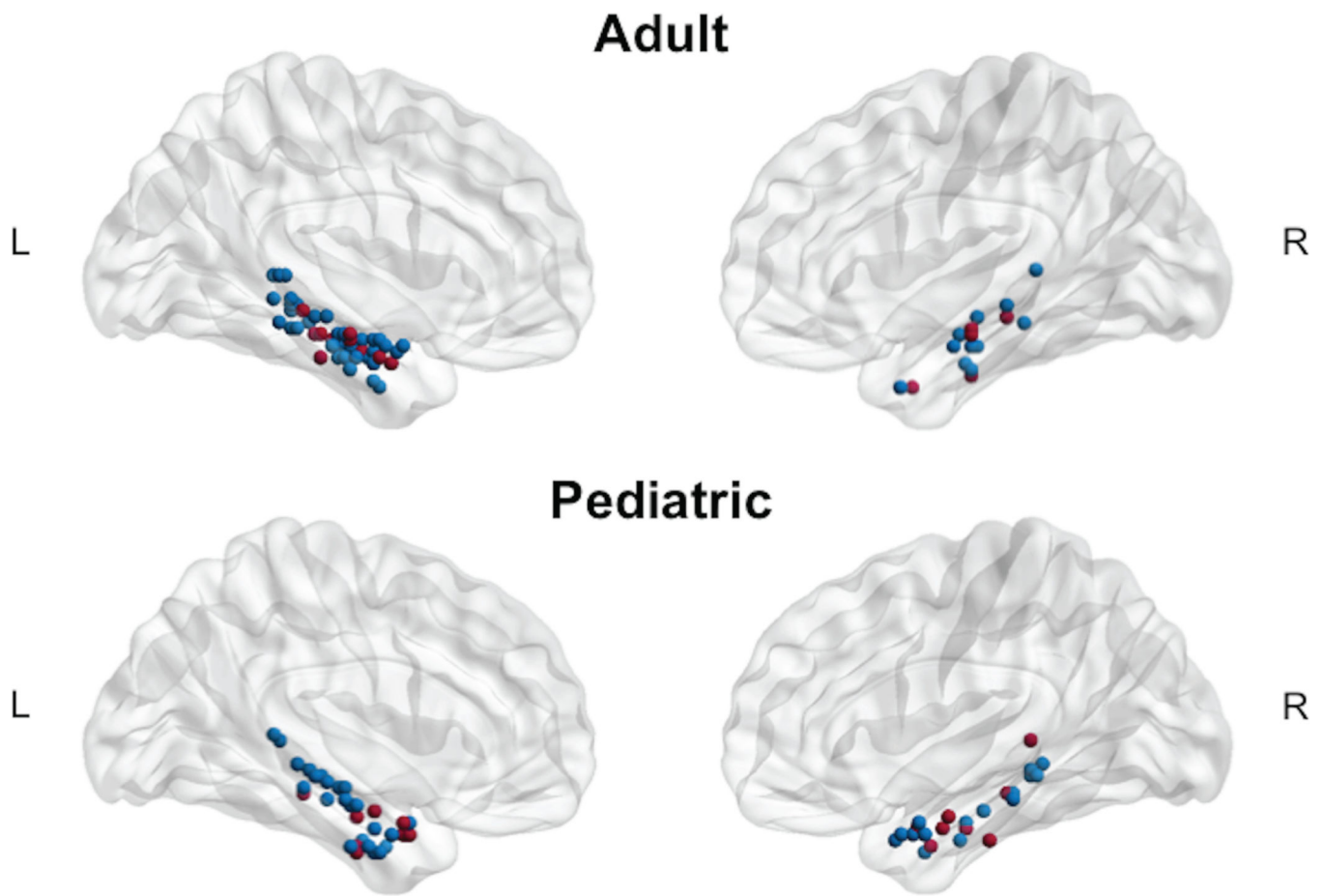
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KEY POINTS

- Language fMRI may be used to elicit group and individual MTL activation.
- Adults demonstrated homogeneous left-lateralized MTL activation during language fMRI, while children were more heterogeneous.
- Our results suggest a developmental shift in lateralization of MTL function, with increased left lateralization across the age span.
- Contralateral MTL activation may explain why children have better memory outcomes following resection compared to adults.

**Figure 1. Peak MTL Activation**

The peak voxel in the MTL is depicted for each individual in each age group (adult and pediatric) if cluster size was 5 voxels or greater ($k = 5$). Activation peaks depicted in blue represent TD Controls and red represent Epilepsy. MTL, mesial temporal lobe.

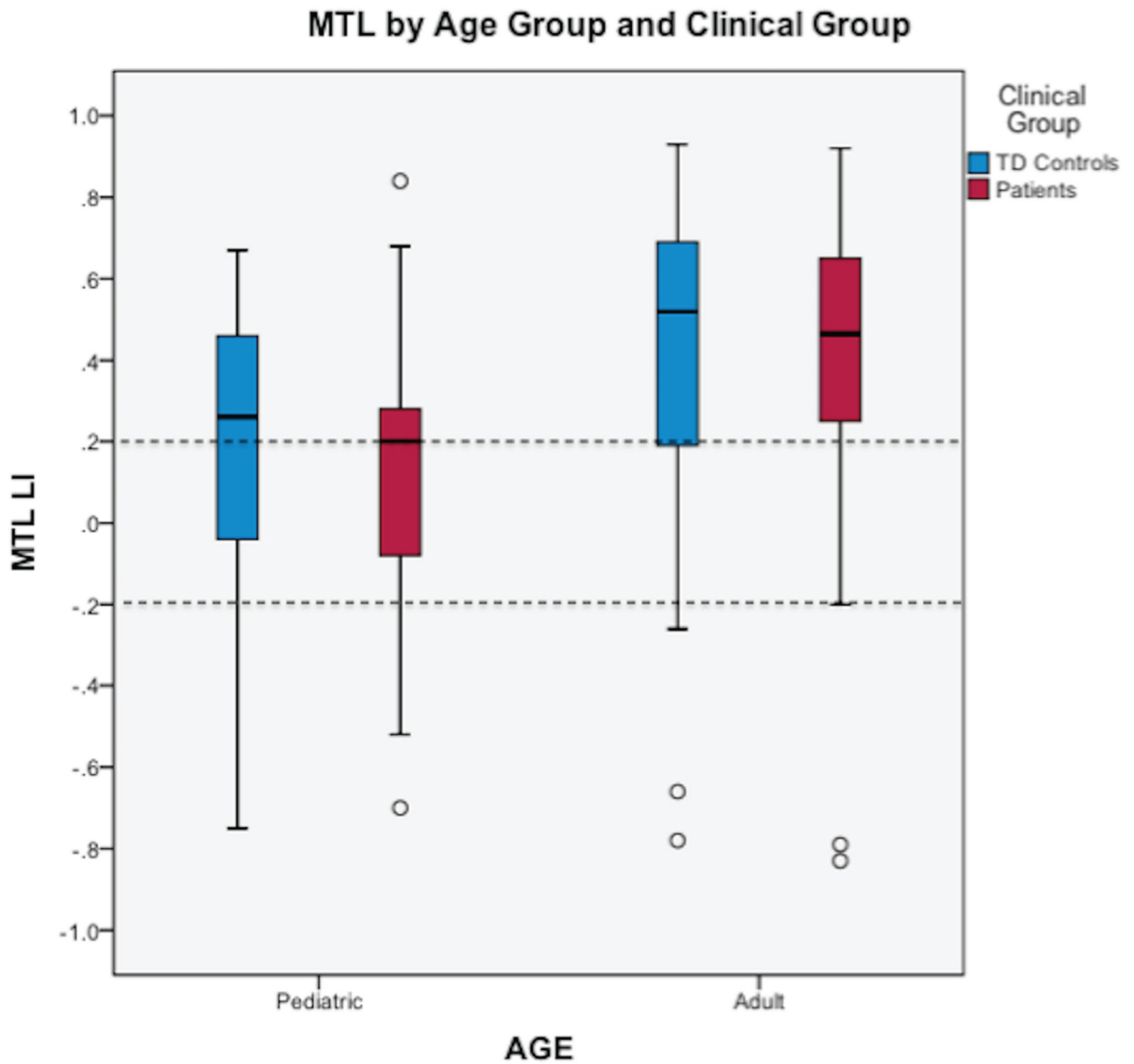


Figure 2. MTL Lateralization Index

Graph of MTL lateralization in the pediatric and adult samples by clinical group. Dotted lines signify common a priori cut-offs of 0.20 and -0.20 that correspond to lateralization categories (left if $LI \geq 0.20$, bilateral if $LI < |0.20|$, or right if $LI \leq -0.20$). MTL, mesial temporal lobe; LI, lateralization index.

Adult

Pediatric

		MTL Lateralization		
		Left (n=50)	Right (n=5)	Bilateral (n=12)
WA Lateralization	Left (n=62)	49	3	10
	Right (n=3)	1	1	1
	Bilateral (n=2)	0	1	1

		MTL Lateralization		
		Left (n=34)	Right (n=11)	Bilateral (n=17)
WA Lateralization	Left (n=52)	29	9	14
	Right (n=3)	2	0	1
	Bilateral (n=7)	3	2	2

		MTL Lateralization		
		Left (n=50)	Right (n=5)	Bilateral (n=12)
Broca's Lateralization	Left (n=61)	49	4	8
	Right (n=2)	0	1	1
	Bilateral (n=4)	1	0	3

		MTL Lateralization		
		Left (n=34)	Right (n=11)	Bilateral (n=17)
Broca's Lateralization	Left (n=50)	29	9	12
	Right (n=5)	3	0	2
	Bilateral (n=7)	2	2	3

Figure 3. MTL LI related to Wernicke's (WA) and Broca's lateralization for pediatric and adult samples

Areas colored in orange represent consistent lateralization between WA or Broca's and MTL; areas in yellow are inconsistent. As seen in these tables, language LI (WA and Broca's) and MTL lateralization was more consistent for adults than children.

Table 1

Seizure Characteristics and fMRI Task Performance.

Epilepsy Characteristics	AGE GROUPS	
	ADULT	PEDIATRIC
Localization (left focus)	15 temporal, 3 frontal, and 2 fronto-temporal (1 temporal and parasagittal)	4 temporal, 3 frontal, 1 fronto-temporal, 2 parietal, 2 temporo-parietal, 1 occipital, and 4 lobe undetermined
Seizure Duration (mean)	11.1 years (± 7.1 ; range=3–33 years)	3.4 years (± 2.8 ; range=0.4–10.4 years)
Age of Onset	15.0 years of age (± 5.1 ; range=5–24 years)	6.5 years (± 2.2 ; range=1.0–9.0 years)
AEDs*	Carbamazepine: n=2, clonazepam: n=1, gabapentin: n=2, lamotrigine: n=5, levetiracetam: n=6, lorazepam: n=1, oxcarbazepine: n=3, phenytoin: n=2, pregabalin: n=1, topiramate: n=3, valproate: n=1, zonisamide: n=2	Carbamazepine: n=2, clonazepam: n=1, diazepam: n=2, lamotrigine: n=4, levetiracetam: n=3, lorazepam: n=1, oxcarbazepine: n=7, phenobarbital: n=1, topiramate: n=1, valproate: n=2, zonisamide: n=1
		PEDIATRIC
fMRI Task Performance	Patients	Controls
Overall Accuracy (Percent)*	61% (± 28) (n=17)	76% (± 23) (n=48)

Seizure characteristics for pediatric and adult groups. Mean and standard deviations of fMRI Task Performance for the pediatric group only.

* Overall accuracy was different between groups ($p=0.04$), but was not related to MTL lateralization [overall or for either group (patients, controls) separately].

Table 2

MTL Activation and Lateralization.

AGE GROUPS	MTL: Thresholds (k 5)											
	0.05, FDR		0.001*		0.01*		0.05*					
	Activation	Mean LI	Activation	Mean LI	Activation	Mean LI	Activation	Mean LI	Activation	Mean LI	Activation	Mean LI
ADULT:												
Control (n=57)	46% (26)	0.49 (±0.29)	44% (25)	0.49 (±0.30)	68% (39)	0.41 (±0.35)	86% (49)	0.42 (±0.39)				
Control (STS<1) (n=54)	46% (25)	0.49 (±0.30)	44% (24)	0.49 (±0.30)	69% (37)	0.42 (±0.35)	85% (46)	0.42 (±0.39)				
Patients (n=20)	55% (11)	0.44 (±0.25)	35% (7)	0.39 (±0.30)	75% (15)	0.42 (±0.43)	90% (18)	0.35 (±0.50)				
Patients (STS<1) (n=17)	59% (10)	0.51 (±0.14)	35% (6)	0.49 (±0.16)	82% (14)	0.46 (±0.41)	94% (16)	0.40 (±0.51)				
PEDIATRIC:												
Controls (n=48)	25% (12)	0.22 (±0.40)	31% (15)	0.27 (±0.37)	60% (29)	0.27 (±0.33)	94% (45)	0.18 (±0.35)				
Control (STS<1) (n=28)	25% (7)	0.28 (±0.42)	25% (7)	0.28 (±0.42)	57% (16)	0.29 (±0.33)	93% (26)	0.18 (±0.37)				
Patients (n=17)	24% (4)	0.21 (±0.06)	18% (3)	0.20 (±0.08)	77% (13)	0.16 (±0.42)	100% (17)	0.09 (±0.42)				
Patients (STS<1) (n=9)	33% (3)	0.19 (±0.05)	22% (2)	0.17 (±0.05)	67% (6)	0.26 (±0.22)	100% (9)	0.11 (±0.35)				

* Thresholds are uncorrected

Percentages of participants demonstrating MTL activation at different thresholds and mean LIs for each activation threshold for adult and pediatric groups.

MTL, mesial temporal lobe; STS, scan-to-scan displacement; k, cluster size; LI, lateralization index.

Table 3

Regression Analyses Predicting MTL LI.

ADULT: MTLLI						
Predictor	<i>b</i>	SE <i>B</i>	β	<i>t</i>	<i>F</i>	<i>R</i> ²
					7.34***	0.19
Wernicke's LI	0.34	0.20	0.27	1.74		
Broca's LI	0.25	0.20	0.20	1.28		
PEDIATRIC: MTLLI						
Predictor	<i>b</i>	SE <i>B</i>	β	<i>t</i>	<i>F</i>	<i>R</i> ²
					1.47	0.05
Wernicke's LI	-0.09	0.17	-0.08	-0.52		
Broca's LI	0.26	0.16	0.25	1.65		

* *p* .05,

** *p* .01,

*** *p* .001

Results of the linear regression models predicting MTL LI from language LI (Wernicke's and Broca's) for adults and children. Both models presented passed tests for multicollinearity.