Received: 29 August 2024 | Revised: 21 January 2025 | Accepted: 21 January 2025

DOI: 10.1111/epi.18298

Epilepsia®

RESEARCH ARTICLE

Left parietal structural connectivity mediates typical and atypical language laterality in temporal lobe epilepsy

Salvatore Citro[1] | **Sam S. Javidi**[2] | **Ankeeta Ankeeta**[2] | **Xiaosong He**[3] | **Qirui Zhang**[2] | **Yolanda Kry**[2] | **Michael R. Sperling**[2] | **Joseph I. Tracy**[2]

[1]IRCCS SYNLAB SDN, Naples, Italy

[2]Department of Neurology, Farber Institute for Neuroscience, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

[3]Department of Psychology, University of Science and Technology of China, Hefei, China

Correspondence
Joseph I. Tracy, Department of Neurology, Vickie and Jack Farber Institute for Neuroscience, Thomas Jefferson University, 901 Walnut Street, Health Sciences Building, Philadelphia, PA 19107, USA.
Email: joseph.tracy@jefferson.edu

Funding information
National Institutes of Health, Grant/Award Number: R01 NS106611, R01 NS112816-01 and U01 NS113198

Abstract

Objective: Subjects with left temporal lobe epilepsy may either show altered hemispheric language lateralization or retain typical, left lateralization. Examining the integrity of white matter pathways involved in the adaptation or maintenance of language lateralization in these patients could have important clinical implications for preserving or potentiating compensatory language mechanisms.

Methods: We combined task functional magnetic resonance imaging and structural diffusion metrics to determine the dependency of lobe-based language laterality on white matter integrity in healthy participants and left temporal lobe epilepsy (TLE) patients. We tested for differences between individuals who expressed typical, left hemisphere laterality compared to those with atypical laterality patterns (bilateral or right hemisphere biased).

Results: A total of 41 left TLE patients and 51 sex- and age-matched healthy participants (HPs) were enrolled. In left temporal lobe epilepsy, typical patterns of frontal and temporal lateralities were less conditioned by the language-related white matter connections of the left temporal lobe. In typically organized epilepsy subjects, temporal lobe language laterality was dependent upon the structural connectivities of the left parietal lobe. Among atypically organized individuals, compared to HPs, TLE patients displayed frontal and parietal language lateralities mediated by the structural connectivities of the left parietal lobe.

Significance: Language-related left parietal lobe connections were critical both for maintaining typical left hemisphere-biased language processing in the temporal lobe and for the formation of noncanonical, potentially adaptive language processing asymmetries in the frontal and parietal lobes. Assessments of the laterality and integrity of language skills in left temporal lobe epilepsy will require modeling white matter structural influences.

KEYWORDS

compensatory structural networks in epilepsy, fMRI language laterality, hemispheric language organization, structural–functional connectivity

1 | INTRODUCTION

Language functions are implemented by a complex network of bihemispheric regions,[1] extending through the temporal, parietal, and frontal lobes.[2,3] The integrity of language processing is highly dependent upon the integrity of the white matter (WM) pathways underlying the language regions of the brain.[4] Temporal lobe epilepsy (TLE) is a structural and functional network disorder,[5] involving changes to WM microstructure[6,7] and reductions in functional connectivity[8] leading to verbally mediated deficits.[4]

Brain surgery on the language-dominant hemisphere increases the risk for postoperative language dysfunction. Thus, before surgical treatment, the intracarotid amobarbital procedure (IAP) or task functional magnetic resonance imaging (fMRI) is utilized to lateralize language processors.[9] Language processing is typically left-lateralized in the general population[10] (rate of 95%[11]), but is not "ubiquitous in the general population," with atypical dominance present in both dextral and adextral populations (higher in the latter).[12] In contrast, 24.5%–29% of epilepsy patients exhibit atypical patterns.[13] Such bilateral or right hemisphere dominance[14–17] patterns reflect hemispheric reorganization that has clinical implications for seizure-related neurocognitive impacts and the prediction of postsurgical outcomes.[18–20]

Verb generation (VG) fMRI is commonly used to stimulate language processing in multiple perisylvian language regions[21,22] and is a reliable tool for investigating language lateralization.[23] Based upon prior work,[23–25] however, there is evidence that hemispheric shifts in language representation are not monolithic, as different regional components of language processing may be independent, and, therefore, not shift their brain topography as a unit.

Prior studies utilizing a variety of WM diffusion indices along with fMRI tasks have demonstrated language network reorganization in left TLE (LTLE).[18,26,27] However, these studies focused on interlobar WM connections and hemispheric fMRI laterality indices (LIs) rather than regional or lobe-specific language activation patterns. Notably, these studies did not examine the WM structural bases of typical and atypical language asymmetries in both healthy participants (HPs) and TLE patients. Language organization exists on a spectrum influenced by individual histories and brain pathology. To isolate pathology-driven changes in language hemispheric organization, it is critical to characterize atypical language asymmetries in healthy individuals.

Accordingly, here we addressed the following two questions: (1) Are lobe-based measures of functional language laterality influenced by the integrity of underlying structural WM pathways? and (2) Do any such influences differ between TLE patients and HPs with "typical" or "atypical" language laterality patterns? We answered these questions by quantifying WM streamline counts among language-processing regions and testing for differences in the association between these structural metrics and fMRI-based measures of lobe-specific and hemispheric language asymmetry.

Key points

- White matter integrity provided crucial structural support for language lateralization patterns in both healthy participants and epilepsy patients.
- Left temporal lobe epilepsy altered the structural substrates of both typical and atypical hemisphere language lateralization.
- Combining task fMRI and diffusion metrics revealed crucial insights into language network organization and the functional adaptations or maladaptations caused by temporal lobe epilepsy.
- In left temporal lobe epilepsy, typical patterns of frontal and temporal language laterality are less conditioned by temporal lobe structural connections. Instead, abnormal left parietal structural connections are critical for maintaining typical language laterality patterns.
- In left temporal lobe epilepsy, atypical language lateralization involves areas of frontal and parietal cortex mediated by left parietal structural connectivity.

2 | MATERIALS AND METHODS

2.1 | Participants

Forty-one patients with drug-resistant LTLE (age = 40.76 ± 15.37 years) were recruited from the Thomas Jefferson University Comprehensive Epilepsy Center. All patients were surgical candidates for either a standard anterior temporal lobectomy or thermal ablation of the ictal mesial temporal lobe. A multimodal evaluation (e.g., neurologic history/examination, scalp video-electroencephalography [video-EEG], MRI, positron emission tomography [PET], neuropsychological testing) was used to lateralize the side of seizure focus.[28] All participants met the following criteria: unilateral temporal lobe seizure onset through surface video-EEG recordings, normal MRI or MRI evidence of pathology located in the epileptogenic temporal lobe, and concordant PET findings. Participants were excluded for the following reasons:

previous brain surgery, medical illness with central nervous system impact other than epilepsy, extratemporal or multifocal epilepsy, contraindications to MRI, and an Axis I psychiatric diagnosis listed in the Diagnostic and Statistical Manual of Mental Disorders V. Depressive disorders were allowed, given the high comorbidity of depression and epilepsy.[29] All patients were verified to have adequate verbal intellectual capacity to complete the VG fMRI task (Wechsler Adult Intelligence Scale III or IV verbal or full-scale verbal intelligence quotient of 70 or greater).

Fifty-one HPs were recruited to match LTLE participants in age, gender, and handedness. HPs were free of psychiatric or neurological disorders based on health screening measures. This study was approved by the Thomas Jefferson University Board for Human Subjects Research. All participants provided written informed consent.

2.2 | Imaging acquisition

All participants underwent scanning on a 3-T X-series Philips Achieva clinical MRI scanner equipped with an eight-channel head coil. The VG task[21,23] and diffusion images[30,31] were collected during the same scanning session. During the VG task, participants viewed single nouns, one by one, and were instructed to covertly generate an action word they associated with the noun. VG data were collected as described He et al.[23]

The diffusion data were obtained using a single-shot spin-echo echo planar imaging pulse sequence (echo time = 90 ms, repetition time = 8609 ms, Sensitivity Encoding (SENSE) factor = 2.5, 5-min acquisition) with 32 diffusion-weighted directions (b-factor = 850 s/mm^2, anterior–posterior fold-over direction) and three volumes without diffusion gradient (b-factor = 0 s/mm^2; averaged in the scanner to a single B_0 volume). Each volume comprised 66 slices (thickness = 2 mm, gap = 0 mm) acquired in the axial plane, with a reconstructed matrix size of 128 × 128 and field of view of 230 mm, resulting in a voxel size of 1.8 × 1.8 × 2 mm. To gain higher signal-to-noise ratio, the sequence was done twice for each participant, and the datasets were averaged. Regarding the tractography, based on an acquired high angular resolution diffusion imaging dataset, for each subject, 10^7 streamlines with a length in the range of 30–250 mm and Fiber Orientation Distribution (FOD) power of .33 were reconstructed. The structural connectome matrix was estimated using weights for each streamline determined using a spherical deconvolution-informed filtering of tractograms (SIFT2).[32] We chose the Automated Anatomical Labeling (AAL) atlas parcellation scheme including $n = 90$ cortical and subcortical parcels to build the structural network. This parcellation was then inversely warped onto the native space of the T1 weighted (T1w) reference and resampled at 2-mm^3 voxel resolution. We built a 90 by 90 undirected adjacency matrix for each participant with the SIFT-weighted streamline counts representing interregional structural connectivity (see Appendix S1 and prior publication with the same methodology[33]).

2.3 | VG task processing

The VG task data were preprocessed through the fMRIPREP pipeline (see Appendix S1 for details).[34,35] Further details on the VG task preprocessing can be found in our prior publications.[19,23]

2.4 | Construction and calculation of Statistical Parametric Mapping lobe-based functional laterality indices

An LI was computed to capture the asymmetry in VG task activation separately for the temporal, frontal, and parietal lobes (hemisphere LI was also computed) for each participant utilizing the Statistical Parametric Mapping 12 (SPM12) Toolbox.[36] The voxel values (t-maps) were taken from both sides of a given lobe (excluding 5 mm of the interhemispheric fissure).[37] To compute the LI, we used the following formula:

$$\mathrm{LI} = \frac{\text{Left ROI activation} - \text{Right ROI activation}}{\text{Left ROI activation} + \text{Right ROI activation}}$$

Lobe- and hemisphere-based regions of interest (ROIs) were constructed following AAL atlas anatomical landmarks. Activation encompassed by those masks were utilized in the LI calculation (exclusive mask of midline ±5 mm). The LI calculation averaged the fMRI signal within each ROI (lobe), followed by subtraction of the activation in the right from the left-sided ROI. The final step was to divide by the summation of activation in the left and the right ROIs. The LI ranged from +1 (maximum left-sided asymmetry) to −1 (maximum right-sided asymmetry). Three lobe-based LIs (frontal, temporal, and parietal) and one hemispheric LI (calculated by combining the activation data of the three lobes using the SPM toolbox) were computed.

There is no standardized LI value defining laterality as typical or atypical.[26,38] In this study, participants were classified as typical (Typ) if their LI values were above the 75th percentile of HPs or atypical (Atyp) if their values were at or below this percentile. The 75th percentile LI values for HPs were .52 (frontal), .28 (temporal), .50 (parietal), and .53 (hemisphere). Mean LI values for these subgroups are presented in Table 1.

TABLE 1 Sample demographic and clinical characteristics.

Characteristic	Left TLE, $n = 41$	HPs, $n = 51$	$t/U/\chi^2$	p
Age, years (range)	40.76 ± 15.37 (20–69)	36.08 ± 11.07 (24–61)	884.0	.206
Gender, M/F	22/19	27/24	.100	.906
Years of education, years	**14.78 ± 2.33**	**16.51 ± 2.55**	**666**	**.002**
Handedness, R/L	35/6	45/6	.180	.836
Edinburgh handedness	69.65 ± 65.53	75.00 ± 60.24	1025	.827
Verbal IQ[a]	94.76 ± 21.05	NA		
Number typical/atypical for each laterality index considered				
Frontal	26/15	40/11		
Temporal	30/11	39/12		
Parietal	28/13	38/13		
Hemisphere	24/17	39/12		
Verb generation laterality index				
Whole sample				
Frontal	.483 ± .388	.575 ± .289	961.5	.512
Temporal	.418 ± .394	.473 ± .289	1037	.949
Parietal	.502 ± .326	.540 ± .299	971.5	.564
Hemisphere	.465 ± .380	.598 ± .275	819.0	.075
Typical subgroups				
Frontal	.714 ± .063	.700 ± .072	439.5	.460
Temporal	.625 ± .146	.690 ± .075	332.0	.268
Parietal	.667 ± .069	.683 ± .067	.929	.357
Hemisphere	.706 ± .066	.705 ± .081	453.0	.836
Atypical subgroups				
Frontal	.083 ± .392	.208 ± .369	75.0	.310
Temporal	**−.145 ± .284**	**.251 ± .259**	**4.100**	**<.001**
Parietal	.144 ± .376	.225 ± .366	88.0	.495
Hemisphere	.124 + .380	.248 ± .385	78.0	.298
Age at epilepsy onset, years	23.76 ± 16.7	NA		
Duration of epilepsy, years	17.00 ± 18.25	NA		
Interictal spike, ipsilateral/bilateral	35/6	NA		
Temporal pathology, NB/HS/TT/TD/E	11/20/3/4/3	NA		
Seizure type				
FIAS	10	NA		
FAS + FIAS	4			
FAS + FBTCS	1			
FIAS + FBTCS	18			
FAS + FIAS + FBTCS	8			
Antiepileptic drugs				
VGNC[b]	26	NA		
$GABA_A$ agonist[c]	2			
$SV2_A$ receptor mediated[d]	14			
CRMP2 receptor mediated[e]	17			
Multiaction[f]	2			

Note: Continuous variables are presented as mean ± SD. Temporal pathology was diagnosed by neuroradiologists specializing in epilepsy based upon presurgical magnetic resonance imaging scans. Independent sample *t*-tests and χ^2 tests were carried out for continuous and categorical variables, respectively.

Abbreviations: CRMP2, collapsin response mediator protein 2; E, encephalomalacia; F, female; FAS, focal onset aware; FBTCS, focal to bilateral tonic–clonic; FIAS, focal onset impaired awareness; $GABA_A$, γ-aminobutyric acid type A; HP, healthy participant; HS, hippocampal sclerosis; IQ, intelligence quotient; L, left; M, male; NA, not applicable; NB, normal brain; R, right; $SV2_A$, synaptic vesicle protein $SV2_A$; TD, temporal dysplasia; TLE, temporal lobe epilepsy; TT, temporal tumor; VGNC, voltage-gated Na^+ channel blockage. Bold values indicate a statistically significant difference between the left TLE and HP groups.

[a]Measured by Wechsler Adult Intelligence Scale version III or IV.

[b]Examples include phenytoin, carbamazepine, oxcarbazepine, lamotrigine (plus T type Ca^{2+} channel blockage).

[c]Examples include diazepam, clonazepam, clobazam, lorazepam, tranxene, phenobarbital.

[d]Examples include levetiracetam.

[e]Examples include lacosamide (plus VGNC blockage).

[f]Examples include Na^+ valproate (VGNC + $GABA_A$ agonist), topiramate (VGNC + $GABA_A$ agonist + α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate receptor blockage + carbonic anhydrase inhibitor).

2.5 | Construction and calculation of lobe-based structural WM measures

To construct WM structural measures related to language processing that would, in addition, align with our lobe-based measures of language laterality, we focused on regions reported in the literature to be hubs for language processing.[23,39] These regions were identified in the AAL atlas (see Figure 1; 38 [19×2] regions: left frontal = 10 regions, right frontal = 10, left temporal = 6, right temporal = 6, left parietal = 3, right parietal = 3, left hemisphere total = 19, right hemisphere homologs = 19). For each ROI, we computed a streamline count measure (STL) derived from the sum of streamlines connecting that ROI to all other ROIs within that same lobe. This procedure was carried out separately for the 19 ROIs of each hemisphere. We note that prior to these ROI-specific STL calculations for each participant we normalized each ROI STL measure by the total number of streamlines in the participant's brain. Thus, we utilized structural measures of language laterality that corresponded to the lobe-based functional measures of language laterality described above. Our

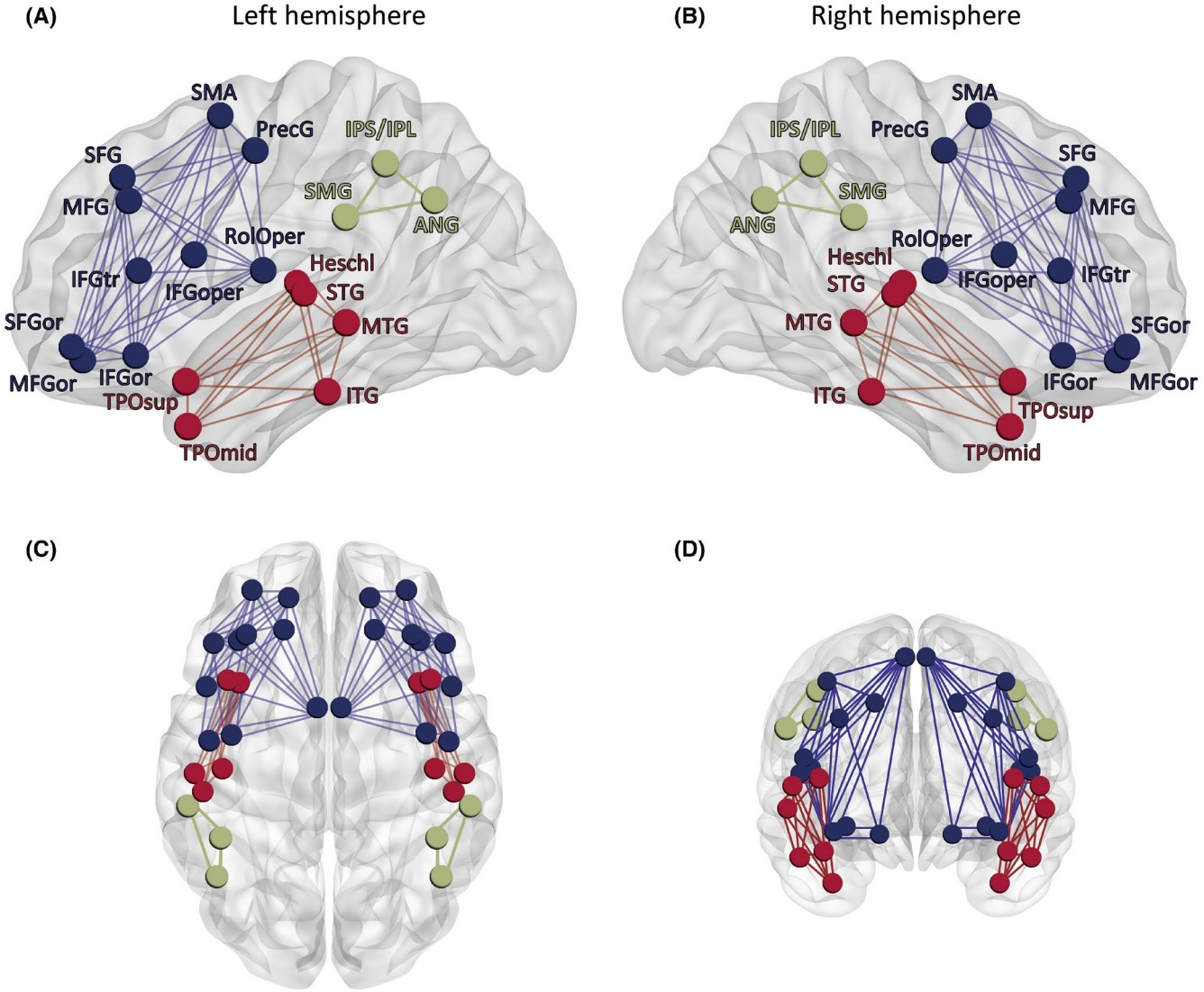

FIGURE 1 Representation of the streamline count measures for construction of intralobar measures. Each sphere represents a language region as captured by the Automated Anatomical Labeling atlas (blue = frontal lobe, green = parietal, red = temporal). (A) Lateral view of the left hemisphere showing the streamline count measures for each lobe considered. (B) Lateral view of the right hemisphere. (C) Transversal plane of the brain. (D) Anterior view of the brain. ANG, angular gyrus; Heschl, Heschl's gyrus; IFGoper, inferior frontal gyrus, pars opercularis; IFGor, inferior frontal gyrus, pars orbitalis; IFGtr, inferior frontal gyrus, pars triangularis; IPL, inferior parietal lobule; IPS, intraparietal sulcus; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; MFGor, middle frontal gyrus, orbital; MTG, middle temporal gyrus; PrecG, precentral gyrus; RolOper, Rolandic operculum; SFG, superior frontal gyrus; SFGor, superior frontal gyrus, orbital; SMA, supplementary motor area; SMG, supramarginal gyrus; STG, superior temporal gyrus; TPOmid, temporal pole, middle; TPOsup, temporal pole, superior.

statistical analyses focused on these 38 WM-derived structural (STL) measures, along with the lobe and hemisphere language LIs and relevant subgroups described above.

2.6 | Statistical analyses

Statistical analyses included χ^2 tests, independent samples *t*-tests, or Mann–Whitney *U*-tests, as appropriate, to test for group differences in sample demographic and clinical epilepsy parameters (IBM SPSS v29; Table 1). Independent sample *t*-tests compared HP and LTLE groups on lobe and hemisphere functional LIs and each ROI structural (STL) measure.

We performed Partial Least Squares Multi-Group Analyses (PLS-MGA, SmartPLS 4[40]) to examine whether LIs were influenced by the integrity of structural WM pathways (intralobar STL measures) and whether these influences differed between Typ and Atyp subgroups of LTLE patients and HPs. PLS-MGA models (groups permutation, 1000 bootstrapped samples) provided means of modeling and quantifying relationships between multiple independent variables (STL measures) and a dependent variable (each lobe or hemisphere LI), allowing for both direct and indirect (mediated) effects on the dependent variable. The measured streamline counts associated with each separate lobe (intralobar STL measures referred to in this context as indicators: 10 frontal, 6 temporal, 3 parietal) were decomposed to form three lobe-specific latent factor (LF) measures of WM structure (referred to as frontal STL LF [FLF], temporal STL LF [TLF], or parietal STL LF [PLF], with separate left and right hemisphere forms of each). These STL LFs were modeled as predictors of the VG-based lobe (or hemisphere) LI measures with PLS-MGA models run separately for each LI. The PLS-MGA models tested for group differences in the following metrics: (1) weighted coefficients ($\beta 1 - \beta 2$) quantifying the direct effect of the lobe (FLF, TLF, PLF) on each lobe-based language LI and (2) weighted coefficients ($\beta 1 - \beta 2$) quantifying the indirect (mediated) effects of the lobe STL LFs on each lobe-based language LI. A significant group difference in the direct or indirect coefficient (permutation Bonferroni [perm bonf]-$p < .05$) indicated a reliable impact of the LF on the LI, with a positive value indicating that a unit change in the independent variable (LF) was associated with a unit change in the dependent variable (the LI). The direct coefficients tested the LF direct influence on lobe or hemisphere LI, whereas indirect coefficients captured sequenced relationships among the LFs in their influence on the LI. Together, these coefficients clarified the causal chain from LF to LI, highlighting the impact of WM structure on the lobe or hemisphere LI. In each LI model, the direct effects of the epileptogenic left temporal lobe (TLF), the left frontal lobe (FLF), and the left parietal lobe (PLF) on the LI were analyzed in the presence of two mediating influences (left TLF → left FLF → LI; left TLF → left PLF → LI). HPs and patients differed by years of education ($p < .002$). Accordingly, all PLS-MGA models were executed with years of education modeled as a weighted (covariate) vector, yielding coefficients accounting for this factor.

3 | RESULTS

The demographic and clinical epilepsy characteristics of the sample are shown in Table 1. HPs and the LTLE group did not statistically differ on any of the lobe or hemisphere functional LIs. A comparison of the three language LI measures between the subgroups revealed that the lobe or hemisphere LI values did not differ across the Typ LTLE

TABLE 2 PLS-MGA model results comparing HP/LTLE, typical/atypical groups for the prediction of lobe-based frontal language LI.

	Typ HPs vs. Typ LTLE		Atyp HPs vs. Atyp LTLE	
	$\beta 1 - \beta 2$	Permutation *p*	$\beta 1 - \beta 2$	Permutation *p*
Frontal LI model, based on R^2 adjusted	.011	.943	.378	.236
Direct path coefficients				
Frontal left STL → frontal LI	−.333	−.185	−.263	.757
Parietal left STL → frontal LI	.096	.161	−.374	.385
Temporal left STL → frontal LI	**.791**	**<.001**	.069	.920
Indirect path coefficients				
Parietal left STL → frontal left STL → frontal LI	−.076	.411	−.214	.214
Temporal left STL → parietal left STL → frontal LI	−.003	.952	**−.720**	**.001**
Temporal left STL → frontal left STL → frontal LI	−.135	.377	.060	.918
Temporal left STL → parietal left STL → frontal left STL → frontal LI	.011	.427	−.130	.127

Note: Bolded values indicate a statistically significant difference in the beta values of the two groups.

Abbreviations: Atyp, atypical; HP, healthy participant; LI, laterality index; LTLE, left temporal lobe epilepsy; STL, streamline count measure; Typ, typical.

and HP subgroups. The LI values did significantly differ between the Atyp LTLE and HP subgroups on the temporal lobe LI ($t_{11}=4.10$, perm bonf-$p<.001$; see Figure S1).

Regarding the streamline measures, the HP group possessed higher STL counts than the LTLE group (Table S1) for the left superior temporal pole ROI (HPs $=1.12\times10^3$, LTLE $=.83\times10^3$, $t=2.73$, perm bonf-$p=.007$) and the left middle temporal pole ROI (HPs $=.89\times10^3$, LTLE $=.54\times10^3$, $t=3.63$, perm bonf-$p<.001$).

We ran correlations between age at epilepsy onset and duration of epilepsy, and intralobar and hemisphere LI measures. Only one emerged as significant, involving weaker frontal LI left-sided laterality in association with longer duration ($p=.036$).

4 | PLS-MGA RESULTS

4.1 | Frontal LI model

In the PLS-MGA frontal LI model, a significant difference was observed between the typical HP and LTLE

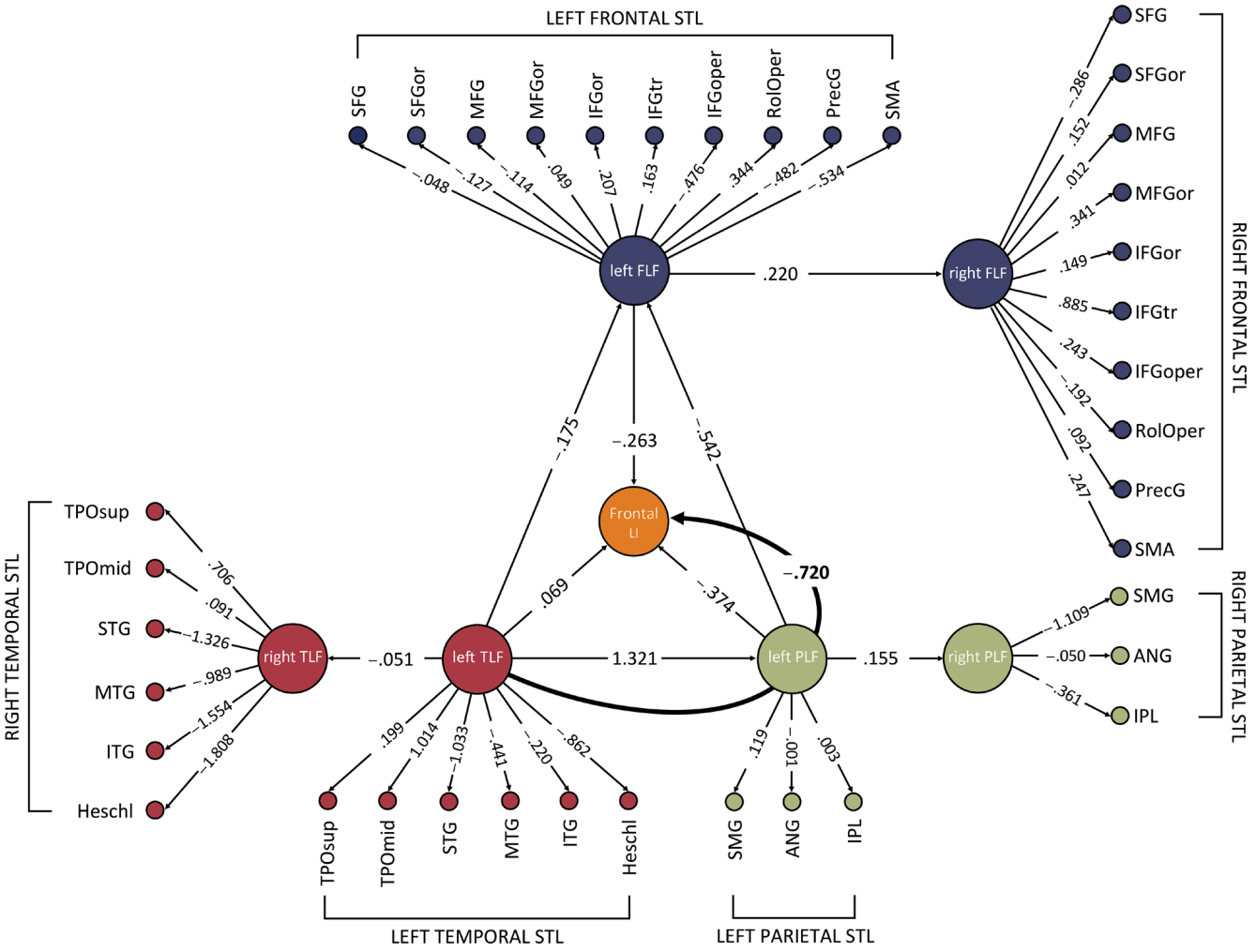

FIGURE 2 PLS-MGA path diagram representing differences between the atypical groups for the frontal lobe laterality index (LI) model. The large circles represent the streamline count measure (STL) latent factors, one for each lobe (frontal, temporal, parietal) for both the right and left hemispheres. Each STL latent factor is derived from its corresponding outer loadings, represented by the small circles. These outer loadings were obtained from the decomposition of observed region of interest streamlines used to construct the latent factors. On each arrow connecting a latent factor to its corresponding outer loadings, the difference in that outer loading between healthy participants and left temporal lobe epilepsy is indicated. Arrows connecting the STL latent factors display the associated coefficients ($\beta1-\beta2$, with significant coefficients in bold; see Table 2 for permutation Bonferroni p-values). ANG, angular gyrus; FLF, frontal latent factor; Heschl, Heschl's gyrus; IFGoper, inferior frontal gyrus, pars opercularis; IFGor, inferior frontal gyrus, pars orbitalis; IFGtr, inferior frontal gyrus, pars triangularis; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; MFGor, middle frontal gyrus, orbital; MTG, middle temporal gyrus; PLF, parietal latent factor; PrecG, precentral gyrus; RolOper, Rolandic operculum; SFG, superior frontal gyrus; SFGor, superior frontal gyrus, orbital; SMA, supplementary motor area; SMG, supramarginal gyrus; STG, superior temporal gyrus; TLF, temporal latent factor; TPOmid, temporal pole, middle; TPOsup, temporal pole, superior.

subgroups in the direct path coefficient from the left temporal STL LF to the frontal LI (Table 2). The value associated with HPs was significantly higher than in the LTLE group (perm bonf-$p < .001$, $\beta1 - \beta2 = .791$), indicating that the frontal LI is influenced by the temporal left STL LF to a greater extent in typical HPs than the typical LTLE group.

Regarding the frontal LI model differences between the atypical subgroups, no direct path coefficients were significant. A significant difference, however, in the indirect path coefficient emerged, indicating that the influence of the left temporal STL LF on the frontal LI was mediated by the left parietal STL LF (Figure 2). The HP value was smaller than in LTLE (perm bonf-$p = .001$: $\beta1 - \beta2 = -.72$), indicating that this more complex set of effects on the frontal LI was stronger in atypical LTLE patients compared to atypical HPs.

4.2 | Temporal LI model

In the PLS-MGA temporal lobe LI model, a significant difference between the typical groups was found in two direct path coefficients (Table 3). The first reflected a stronger influence for the left parietal STL LF on the temporal LI in the LTLE group. The value for HPs was smaller than in LTLE (Figure 3; perm bonf-$p = .034$, $\beta1 - \beta2 = -.615$), suggesting that the influence or predictive strength of the left parietal STL LF on the temporal LI was significantly higher in typical LTLE patients compared to typical HPs. The second significant direct path coefficient for the temporal lobe LI model involved prediction by the left temporal STL LF (Table 3). This coefficient was significantly higher in HPs than LTLE, indicating that the left temporal STL LF's influence on the temporal lobe LI was stronger in HPs (perm bonf-$p = .019$, $\beta1 - \beta2 = .657$).

4.3 | Parietal LI model

In the PLS-MGA parietal lobe LI model comparing the atypical groups, a significant direct path coefficient emerged involving prediction of the parietal lobe LI by the left parietal STL LF, with the coefficient significantly higher in the HPs than LTLE (Table 4; perm bonf-$p = .40$, $\beta1 - \beta2 = .729$).

The comparison of the atypical groups also demonstrated a significant indirect path coefficient, revealing that the influence of the left temporal STL LF on the parietal LI was mediated by the left parietal STL LF. This mediating effect was stronger in the atypical LTLE group (Figure 4; perm bonf-$p = .029$, $\beta1 - \beta2 = -.438$).

4.4 | Hemisphere LI model

Lastly, in the PLS-MGA hemisphere LI model, a significant difference between the typical groups was found in the direct path coefficient from the left temporal STL LF to the hemisphere LI (Table 5). The value in HPs was higher than for the LTLE subgroup (perm bonf-$p = .001$, $\beta1 - \beta2 = .850$).

The comparison of the atypical groups also demonstrated a significant indirect path coefficient, indicating that the influence of the left temporal STL LF on the hemisphere LI was mediated by the left parietal STL LF. This mediating effect was stronger in the atypical LTLE than HP group (Table 5; perm bonf-$p = .027$, $\beta1 - \beta2 = -.439$).

TABLE 3 PLS-MGA model results comparing HP/LTLE, typical/atypical groups for the prediction of lobe-based temporal language LI.

	Typ HPs vs. Typ LTLE		Atyp HPs vs. Atyp LTLE	
	$\beta1 - \beta2$	Permutation p	$\beta1 - \beta2$	Permutation p
Temporal LI model, based on R^2 adjusted	**−.287**	**.008**	−.339	.403
Direct path coefficients				
Frontal left STL → temporal LI	.102	.773	−.275	.629
Parietal left STL → temporal LI	**−.615**	**.034**	.231	.682
Temporal left STL → temporal LI	**.657**	**.019**	−.545	.411
Indirect path coefficients				
Parietal left STL → frontal left STL → temporal LI	.045	.576	−.027	.954
Temporal left STL → parietal left STL → temporal LI	.035	.194	−.122	.704
Temporal left STL → frontal left STL → temporal LI	.064	.712	−.261	.738
Temporal left STL → parietal left STL → frontal left STL → temporal LI	−.009	.260	.096	.674

Note: Bolded values indicate a statistically significant difference in the beta values of the two groups.

Abbreviations: Atyp, atypical; HP, healthy participant; LI, laterality index; LTLE, left temporal lobe epilepsy; STL, streamline count measure; Typ, typical.

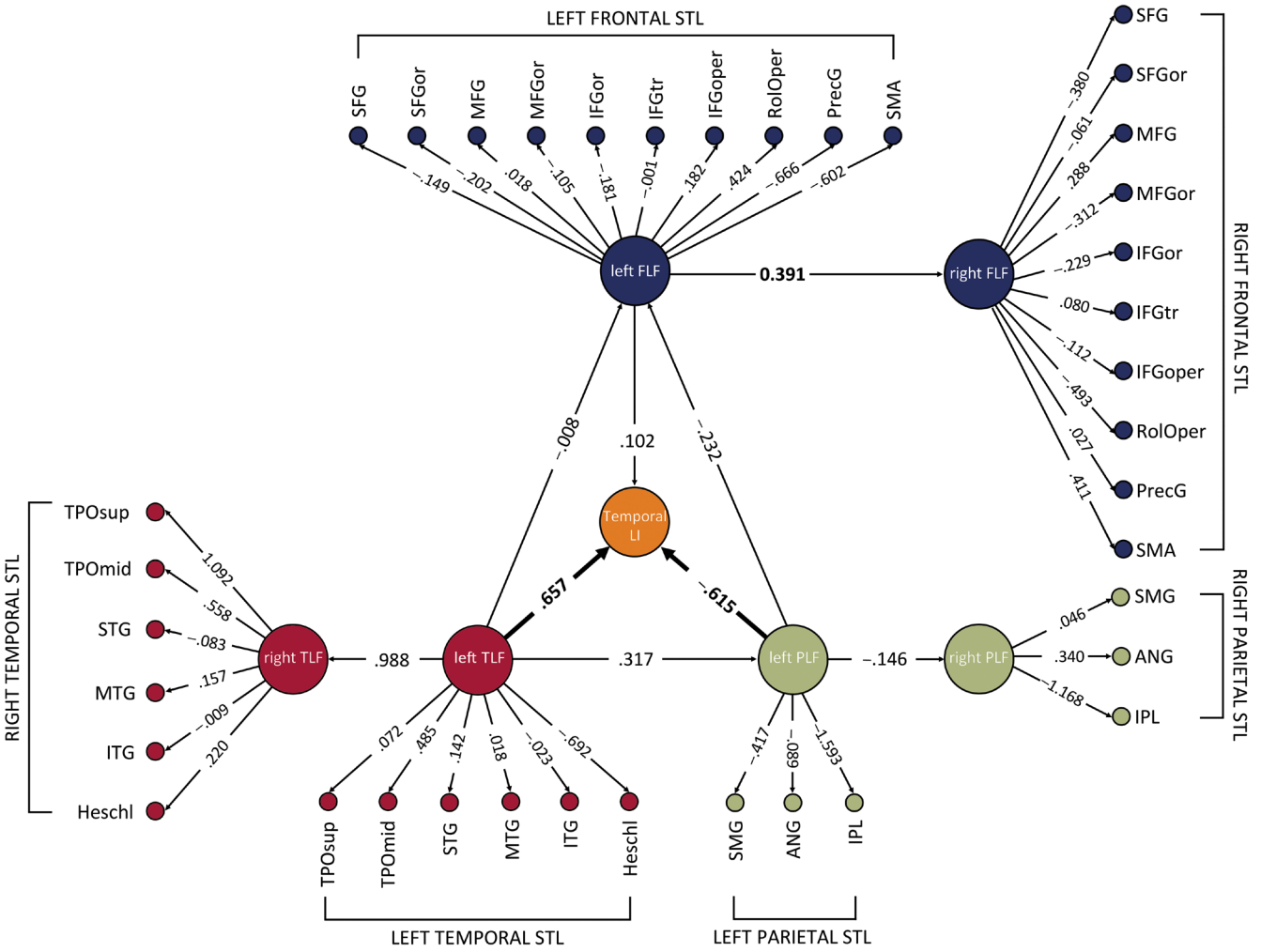

FIGURE 3 PLS-MGA path diagram representing differences between the typical groups for the temporal lobe laterality index (LI) model. Figure 2 serves as a reference for the description of the path model. ANG, angular gyrus; FLF, frontal latent factor; Heschl, Heschl's gyrus; IFGoper, inferior frontal gyrus, pars opercularis; IFGor, inferior frontal gyrus, pars orbitalis; IFGtr, inferior frontal gyrus, pars triangularis; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; MFGor, middle frontal gyrus, orbital; MTG, middle temporal gyrus; PLF, parietal latent factor; PrecG, precentral gyrus; RolOper, Rolandic operculum; SFG, superior frontal gyrus; SFGor, superior frontal gyrus, orbital; SMA, supplementary motor area; SMG, supramarginal gyrus; STG, superior temporal gyrus; STL, streamline count measure; TLF, temporal latent factor; TPOmid, temporal pole, middle; TPOsup, temporal pole, superior.

5 | DISCUSSION

We combined task fMRI and structural diffusion metrics to determine the influence of WM integrity on functional measures of lobe-based and hemispheric language laterality. In the setting of left temporal lobe pathology, the present results implicated the structural connectivities of language regions in the left parietal lobe as key mediators of adaptive alterations in both typical and atypical patterns of language laterality. Among typically organized LTLE patients, these adaptive left parietal connectivities helped maintain canonical left temporal-biased language processing asymmetries. In contrast, in atypically organized LTLE patients these parietal structural connectivities helped support bilateral or right hemisphere-biased language processing in the frontal and parietal lobes.

Functional language representations may exhibit distinct distributions across the two hemispheres, and tasks such as verb generation, even in the absence of pathology, may produce individual differences in the distribution of activation patterns (lateralities) across the hemisphere of each lobe of the brain.[1] Accordingly, we did not assume that language asymmetries in healthy individuals would necessarily follow the canonical left hemisphere dominance pattern,[41] nor that their structural basis would be identical to typically organized LTLE patients. This led us to compare the WM structural basis of typical and atypical language laterality patterns in LTLE patients as well as HPs. We used frequency distributions in HPs to identify

TABLE 4 PLS-MGA model results comparing HP/LTLE, typical/atypical groups for the prediction of lobe-based parietal language LI.

	Typ HPs vs. Typ LTLE		Atyp HPs vs. Atyp LTLE	
	$\beta 1 - \beta 2$	Permutation *p*	$\beta 1 - \beta 2$	Permutation *p*
Parietal LI model, based on R^2 adjusted	−.084	.221	−.441	.087
Direct path coefficients				
Frontal left STL → parietal LI	−.428	.280	−.113	.904
Parietal left STL → parietal LI	.194	.513	**.729**	**.040**
Temporal left STL → parietal LI	.004	.995	.009	.981
Indirect path coefficients				
Parietal left STL → frontal left STL → parietal LI	−.124	.250	.018	.852
Temporal left STL → parietal left STL → parietal LI	−.034	.303	**−.438**	**.029**
Temporal left STL → frontal left STL → parietal LI	−.156	.350	−.049	.856
Temporal left STL → parietal left STL → frontal left STL → parietal LI	.022	.151	−.003	.913

Note: Bolded values indicate a statistically significant difference in the beta values of the two groups.

Abbreviations: Atyp, atypical; HP, healthy participant; LI, laterality index; LTLE, left temporal lobe epilepsy; STL, streamline count measure; Typ, typical.

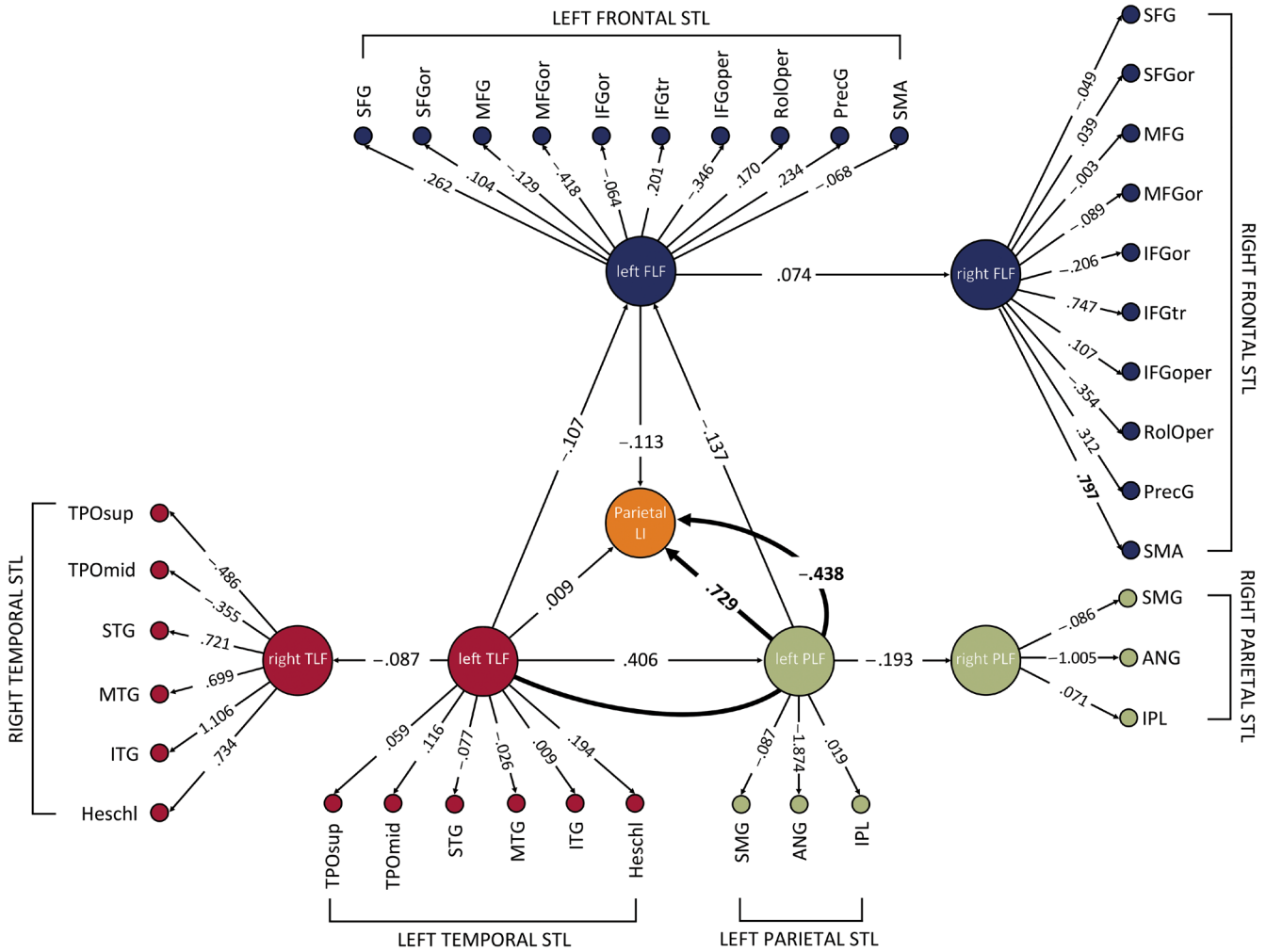

FIGURE 4 PLS-MGA path diagram representing the atypical groups for the parietal lobe laterality index (LI) model. Figure 2 serves as a reference for the description of the path model. ANG, angular gyrus; FLF, frontal latent factor; Heschl, Heschl's gyrus; IFGoper, inferior frontal gyrus, pars opercularis; IFGor, inferior frontal gyrus, pars orbitalis; IFGtr, inferior frontal gyrus, pars triangularis; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; MFGor, middle frontal gyrus, orbital; MTG, middle temporal gyrus; PLF, parietal latent factor; PrecG, precentral gyrus; RolOper, Rolandic operculum; SFG, superior frontal gyrus; SFGor, superior frontal gyrus, orbital; SMA, supplementary motor area; SMG, supramarginal gyrus; STG, superior temporal gyrus; STL, streamline count measure; TLF, temporal latent factor; TPOmid, temporal pole, middle; TPOsup, temporal pole, superior.

TABLE 5 PLS-MGA model results comparing HP/LTLE, typical/atypical groups for the prediction of lobe-based hemisphere language LI.

	Typ HPs vs. Typ LTLE		Atyp HPs vs. Atyp LTLE	
	$\beta 1 - \beta 2$	Permutation p	$\beta 1 - \beta 2$	Permutation p
Hemisphere LI model, based on R^2 adjusted	−.039	.822	.401	.159
Direct path coefficients				
Frontal left STL → hemisphere LI	−.004	.996	−.717	.304
Parietal left STL → hemisphere LI	−.359	.218	−.159	.609
Temporal left STL → hemisphere LI	**.850**	**.001**	.305	.798
Indirect path coefficients				
Parietal left STL → frontal left STL → hemisphere LI	−.016	.874	−.103	.387
Temporal left STL → parietal left STL → hemisphere LI	.083	.166	**−.439**	**.027**
Temporal left STL → frontal left STL → hemisphere LI	.025	.904	−.363	.249
Temporal left STL → parietal left STL → frontal left STL → hemisphere LI	.007	.634	−.067	.179

Note: Bolded values indicate a statistically significant difference in the beta values of the two groups.

Abbreviations: Atyp, atypical; HP, healthy participant; LI, laterality index; LTLE, left temporal lobe epilepsy; STL, streamline count measure; Typ, typical.

atypical patterns of lobe- (and hemisphere)-based language activation asymmetries. Mean VG LIs for each lobe showed no reliable differences between HPs and LTLE patients. Subgroup analysis, however, revealed a higher percentage of atypical language asymmetries in LTLE compared to HPs across all three lobe-based LI measures. This is consistent with prior reports from language-based fMRI studies.[42–44] We reported the relative differences in lateralities among the lobes for typically and atypically organized HPs and LTLE patients. Only for the temporal lobe LI in atypical patients was an HP/LTLE difference observed, with the atypical patients appearing more bilateral and right hemisphere biased.

We used PLS-MGA modeling to examine subgroup differences in the degree to which lobe-based functional LIs depended on the structural integrity of language-related, lobe-based WM tracts (as indexed by WM diffusion streamlines). Our PLS-MGA models revealed that frontal, temporal, parietal, and hemispheric language asymmetries in our HP/LTLE subgroups were conditioned by different WM structural influences.

Our findings for typically organized LTLE patients demonstrate that literature reports on normative functional laterality indices may obscure significant differences between LTLE/HP groups in the underlying WM structural support for language laterality. In the setting of left temporal lobe seizure pathology, frontal, temporal, and hemisphere LIs are less conditioned by left temporal lobe WM connections. Moreover, temporal lobe LIs in typically organized LTLE patients were subject to an additional structural connectivity influence that did not appear strong in HPs. Namely, temporal lobe language asymmetries were mediated by the structural connectivities of the language ROIs of the left parietal lobe. In the setting of a dysfunctional left temporal lobe, this report of an adaptive role for left parietal language-related structural connections depicts an important structural reorganization in typically organized LTLE patients. These data indicated that these left parietal lobe structural connections are working to maintain the typical left hemisphere-biased language processing in the temporal lobes. It is important to note that typical left hemisphere-biased language processing in the frontal and parietal lobes as reflected in their LIs (also in the hemisphere LI) was not subject to this left parietal lobe structural mediation. Given that the typically organized LTLE and HP groups showed no differences in any of the lobe and hemisphere LIs, these data suggest that in LTLE this left parietal mediation is adaptive and crucial to maintaining a left-biased language processing in the temporal lobe but is not needed to maintain left-biased processing in the frontal lobe or the hemispheres as a whole.

Regarding individuals with atypically organized language, in LTLE but not HPs both the frontal and parietal functional LIs appeared to be dependent upon left temporal lobe structural connectivities that were mediated by the structural connectivities of the language regions in the left parietal lobe. In the setting of a dysfunctional, epileptogenic temporal lobe, these data indicate that the structural connections of the ipsilateral, left parietal lobe play a critical role in the redistribution of language processing across the frontal and parietal lobes, providing the structural support for potentially adaptive functional reorganization.

This is the first report highlighting the significant role of left parietal lobe structural mediation for the

distribution of language processing across the hemispheres in both typical and atypical LTLE patients. The importance of the parietal lobe in language processing was initially emphasized by Geschwind,[45] and later confirmed by diffusion and fMRI studies. For instance, the inferior parietal lobule is part of an extended network involving many language functions.[46–48] Our findings regarding the influential role of parietal streamlines in the formation of language laterality clarified that in the setting of LTLE, left parietal structural pathways play a role in both typically organized and reorganized, atypical forms of language processing. This involvement of the left parietal lobe in typically organized LTLE may be part of the adaptive plasticity that allows for the maintenance of cognitive functions, such as language.[49] As the left parietal lobe may be a region less affected by temporal lobe seizures, it may possess the WM structural reserve that drives adaptive language reorganization. Moreover, our data indicate that in LTLE, left parietal lobe WM pathways provide abnormal structural support for atypical language processing, implicating their role in forming noncanonical language asymmetries (bilateral or right hemisphere biased). Therefore, our data add to the literature showing that microstructural changes in WM pathways are not only limited in the ictal temporal lobe[50] in left TLE but also extend to other cerebral lobes.[51]

In summary, we have demonstrated the dependency of LTLE language representations on specific WM structural connectivities, with this dependency varying by lobe and the pattern of language laterality (typical or atypical). Among typically organized LTLE patients, the frontal LI showed an abnormal direct dependence on left temporal structural connectivities, but the parietal LI showed no abnormal direct or indirect structural dependence. Among atypically organized LTLE patients, the frontal, parietal, and hemisphere LIs were influenced by left parietal structural effects, but the temporal LI was not. Accordingly, our data confirm that language organization shifts are not monolithic, as different relationships between structure and function were observed for each lobe. Our data highlight that disease-specific pressures influence the structural basis of both typical and atypical language lateralization. The clinical implication is that it is important to know whether the specific structural WM substrates, upon which language dominance depends, are targeted by the surgical procedure. At many epilepsy centers, patients may be excluded from left TL surgery due to perceived risks to language related to the presence of typical left hemisphere dominance for language. Our data demonstrated that when lobe-based functional measures are used in conjunction with lobe-based diffusion measures, evidence can be obtained to show not just that cortical reorganization of language has occurred (e.g., involving strong left parietal mediation of language), but that there are also structural supports for such reorganization. With such evidence in hand, epilepsy centers can show that risks from surgery are mitigated, thereby opening up the surgical procedure to individuals who might otherwise refuse or be denied the procedure.

Our study has limitations. The use of specific language-related ROIs may have missed potentially relevant WM structural changes outside these areas. We only focused on intralobar WM, not interlobar WM streamlines. The sample included only LTLE patients, lacking generalizability to right TLE and other epilepsy types. Future studies need to focus on the structure/function relationships in other types of epilepsy. The small sample size and the absence of genetic/familial data on left-handedness (e.g., influences of language laterality[12]) may have limited our findings' applicability. We did not assess neurocognitive language competencies. Thus, the compensatory benefit of the structural influences on language that we describe need to be clarified. Lastly, our results speak more to understanding the structural supports for different forms of language organization, and do not address the likelihood of postsurgical deficits.

6 | CONCLUSIONS

The failure to account for the status of extratemporal structural connectivities may help explain why the techniques used to establish hemispheric language dominance (IAP, fMRI)[24] demonstrate a weak ability to predict language outcomes following epilepsy surgery. We are the first to report that key structural connectivity involving the left parietal lobe (n.b., untouched by TLE surgery) has a fundamental influence on the maintenance of normal language laterality patterns, as well as the formation of atypical and potentially adaptive language lateralities. Successful prognosis of language skills after temporal lobe surgery will require modeling these structural influences. Longitudinal studies are needed to test whether the structural influences we report here can reliably predict language outcomes after TLE surgery.

AUTHOR CONTRIBUTIONS

Joseph I. Tracy, Salvatore Citro, and Sam S. Javidi contributed to the conception and design of the study. Joseph I. Tracy, Yolanda Kry, Xiaosong He, and Michael R. Sperling contributed to participant recruitment. Sam S. Javidi, Ankeeta A, Xiaosong He, Qirui Zhang, and Yolanda Kry contributed to the acquisition and analysis of data. Joseph

I. Tracy, Salvatore Citro, Sam S. Javidi, and Michael R. Sperling contributed to drafting the manuscript and preparing the figures. Joseph I. Tracy and Salvatore Citro contributed to final editing and review of manuscript, tables, and figures.

ACKNOWLEDGMENTS

We would like to thank the epilepsy patients and the healthy participants for contributing to this study. J.I.T. acknowledges funding support for this project from the National Institutes of Health (R01 NS112816-01). M.R.S. acknowledges funding support from the National Institutes of Health (R01 NS106611 and U01 NS113198).

CONFLICT OF INTEREST STATEMENT

The authors report no competing interests. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Data are available upon request from a qualified investigator and approval from the Thomas Jefferson University Department of Neurology, and the Thomas Jefferson University Human Subjects Research Committee.

ETHICS STATEMENT

This study was approved by the Institutional Review Board for Research with Human Subjects at Thomas Jefferson University. All participants provided written informed consent.

ORCID

Salvatore Citro https://orcid.org/0000-0001-5222-6501
Xiaosong He https://orcid.org/0000-0002-7941-2918
Michael R. Sperling https://orcid.org/0000-0003-0708-6006
Joseph I. Tracy https://orcid.org/0000-0001-5260-3290

REFERENCES

1. Hickok G, Poeppel D. The cortical organization of speech processing. Nat Rev Neurosci. 2007;8(5):393–402.
2. Fedorenko E, Thompson-Schill SL. Reworking the language network. Trends Cogn Sci. 2014;18(3):120–6.
3. Labache L, Joliot M, Saracco J, Jobard G, Hesling I, Zago L, et al. A SENtence Supramodal Areas AtlaS (SENSAAS) based on multiple task-induced activation mapping and graph analysis of intrinsic connectivity in 144 healthy right-handers. Brain Struct Funct. 2019;224(2):859–82.
4. Binding LP, Dasgupta D, Giampiccolo D, Duncan JS, Vos SB. Structure and function of language networks in temporal lobe epilepsy. Epilepsia. 2022;63(5):1025–40.
5. Bourel-Ponchel E, Mahmoudzadeh M, Adebimpe A, Wallois F. Functional and structural network disorganizations in typical epilepsy with centro-temporal spikes and impact on cognitive neurodevelopment. Front Neurol. 2019;10:809.
6. Concha L, Beaulieu C, Gross DW. Bilateral limbic diffusion abnormalities in unilateral temporal lobe epilepsy. Ann Neurol. 2005;57(2):188–96.
7. McDonald CR, Ahmadi ME, Hagler DJ, Tecoma ES, Iragui VJ, Gharapetian L, et al. Diffusion tensor imaging correlates of memory and language impairments in temporal lobe epilepsy. Neurology. 2008;71(23):1869–76.
8. Tracy JI, Doucet GE. Resting-state functional connectivity in epilepsy: growing relevance for clinical decision making. Curr Opin Neurol. 2015;28(2):158–65.
9. Dym RJ, Burns J, Freeman K, Lipton ML. Is functional MR imaging assessment of hemispheric language dominance as good as the Wada test?: a meta-analysis. Radiology. 2011;261(2):446–55.
10. Jäncke L, Steinmetz H. Anatomical brain asymmetries and their relevance for functional asymmetries. In: Davidson RJ, Hugdahl K, editors. The asymmetrical brain. Cambridge: The MIT Press; 2002. p. 187–229.
11. Springer JA, Binder JR, Hammeke TA, Swanson SJ, Frost JA, Bellgowan PS, et al. Language dominance in neurologically normal and epilepsy subjects: a functional MRI study. Brain. 1999;122(Pt 11):2033–46.
12. Labache L, Ge T, Yeo BTT, Holmes AJ. Language network lateralization is reflected throughout the macroscale functional organization of cortex. Nat Commun. 2023;14(1):3405.
13. Carey, DP, Johnstone, LT. Quantifying cerebral asymmetries for language in dextrals and adextrals with random-effects meta analysis. Frontiers in Psychology. 2014;5:1128.
14. Berl MM, Zimmaro LA, Khan OI, Dustin I, Ritzl E, Duke ES, et al. Characterization of atypical language activation patterns in focal epilepsy. Ann Neurol. 2014;75(1):33–42.
15. Gaillard WD, Berl MM, Moore EN, Ritzl EK, Rosenberger LR, Weinstein SL, et al. Atypical language in lesional and nonlesional complex partial epilepsy. Neurology. 2007;69(18):1761–71.
16. Adcock JE, Wise RG, Oxbury JM, Oxbury SM, Matthews PM. Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. Neuroimage. 2003;18(2):423–38.
17. Branch C, Milner B, Rasmussen T. Intracarotid sodium amytal for the lateralization of cerebral speech dominance: observations in 123 patients. J Neurosurg. 1964;21:399–405.
18. Chang YA, Kemmotsu N, Leyden KM, Kucukboyaci NE, Iragui VJ, Tecoma ES, et al. Multimodal imaging of language reorganization in patients with left temporal lobe epilepsy. Brain Lang. 2017;170:82–92.
19. Crow AJD, Thomas A, Rao Y, Beloor-Suresh A, Weinstein D, Hinds WA, et al. Task-based functional magnetic resonance imaging prediction of postsurgical cognitive outcomes in temporal lobe epilepsy: a systematic review, meta-analysis, and new data. Epilepsia. 2023;64(2):266–83.
20. Gross WL, Helfand AI, Swanson SJ, Conant LL, Humphries CJ, Raghavan M, et al. Prediction of naming outcome with fMRI language lateralization in left temporal epilepsy surgery. Neurology. 2022;98(23):e2337–e2346.
21. Doucet GE, He X, Sperling MR, Sharan A, Tracy JI. From "rest" to language task: task activation selects and prunes from broader resting-state network. Hum Brain Mapp. 2017;38(5):2540–52.
22. Caciagli L, Paquola C, He X, Vollmar C, Centeno M, Wandschneider B, et al. Disorganization of language and

working memory systems in frontal versus temporal lobe epilepsy. Brain. 2023;146(3):935–53.
23. He X, Bassett DS, Chaitanya G, Sperling MR, Kozlowski L, Tracy JI. Disrupted dynamic network reconfiguration of the language system in temporal lobe epilepsy. Brain. 2018;141(5):1375–89.
24. Modi S, He X, Chaudhary K, Hinds W, Crow A, Beloor-Suresh A, et al. Multiple-brain systems dynamically interact during tonic and phasic states to support language integrity in temporal lobe epilepsy. Neuroimage Clin. 2021;32:102861.
25. Tracy JI, Waldron B, Glosser D, Sharan A, Mintzer S, Zangaladze A, et al. Hemispheric lateralization and language skill coherence in temporal lobe epilepsy. Cortex. 2009;45(10):1178–89.
26. Briellmann RS, Mitchell LA, Waites AB, Abbott DF, Pell GS, Saling MM, et al. Correlation between language organization and diffusion tensor abnormalities in refractory partial epilepsy. Epilepsia. 2003;44(12):1541–5.
27. Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, et al. Abnormalities of language networks in temporal lobe epilepsy. Neuroimage. 2007;36(1):209–21.
28. Sperling MR, O'Connor MJ, Saykin AJ, Plummer C. Temporal lobectomy for refractory epilepsy. JAMA. 1996;276(6):470–5.
29. Tracy JI, Dechant V, Sperling MR, Cho R, Glosser D. The association of mood with quality of life ratings in epilepsy. Neurology. 2007;68(14):1101–7.
30. Pustina D, Avants B, Sperling M, Gorniak R, He X, Doucet G, et al. Predicting the laterality of temporal lobe epilepsy from PET, MRI, and DTI: a multimodal study. Neuroimage Clin. 2015;9:20–31.
31. Osipowicz K, Sperling MR, Sharan AD, Tracy JI. Functional MRI, resting state fMRI, and DTI for predicting verbal fluency outcome following resective surgery for temporal lobe epilepsy. J Neurosurg. 2016;124(4):929–37.
32. Smith RE, Tournier JD, Calamante F, Connelly A. SIFT2: enabling dense quantitative assessment of brain white matter connectivity using streamlines tractography. Neuroimage. 2015;119:338–51.
33. Javidi SS, He X, Ankeeta A, Zhang Q, Citro S, Sperling MR, et al. Edge-wise analysis reveals white matter connectivity associated with focal to bilateral tonic-clonic seizures. Epilepsia. 2024;65(6):1756–67.
34. Esteban O, Markiewicz CJ, Blair RW, Moodie CA, Isik AI, Erramuzpe A, et al. fMRIPrep: a robust preprocessing pipeline for functional MRI. Nat Methods. 2019;16(1):111–6.
35. Esteban O, Markiewicz CJ, Burns C, Goncalves M, Jarecka D, Ziegler E, et al. nipy/nipype: 1.8.3. Zenodo. 2022. https://doi.org/10.5281/zenodo.6834519
36. SPM12. [cited 2022 July 12]. Available from: http://www.fil.ion.ucl.ac.uk/spm/software/spm12/
37. Wilke M, Lidzba K. Li-tool: a new toolbox to assess lateralization in functional MR-data. J Neurosci Methods. 2007;163(1):128–36.
38. Abbott DF, Waites AB, Lillywhite LM, Jackson GD. fMRI assessment of language lateralization: an objective approach. Neuroimage. 2010;50(4):1446–55.
39. Fedorenko E, Hsieh PJ, Nieto-Castañón A, Whitfield-Gabrieli S, Kanwisher N. New method for fMRI investigations of language: defining ROIs functionally in individual subjects. J Neurophysiol. 2010;104(2):1177–94.
40. Ringle CM, Wende S, Becker J-M. SmartPLS 4. Monheim am Rhein: SmartPLS; 2024 [cited 2020 Jan 13]. Available from: https://www.smartpls.com
41. Kroliczak G, Buchwald M, Kleka P, Klichowski M, Potok W, Nowik AM, et al. Manual praxis and language-production networks, and their links to handedness. Cortex. 2021;140:110–27.
42. Hamberger MJ, Cole J. Language organization and reorganization in epilepsy. Neuropsychol Rev. 2011;21(3):240–51.
43. Neudorf J, Kress S, Gould L, Gibb K, Mickleborough M, Borowsky R. Language lateralization differences between left and right temporal lobe epilepsy as measured by overt word reading fMRI activation and DTI structural connectivity. Epilepsy Behav. 2020;112:107467.
44. Rosenberger LR, Zeck J, Berl MM, Moore EN, Ritzl EK, Shamim S, et al. Interhemispheric and intrahemispheric language reorganization in complex partial epilepsy. Neurology. 2009;72(21):1830–6.
45. Geschwind N. Disconnexion syndromes in animals and man. I. Brain. 1965;88(2):237–94.
46. Forkel SJ, Rogalski E, Drossinos Sancho N, D'Anna L, Luque Laguna P, Sridhar J, et al. Anatomical evidence of an indirect pathway for word repetition. Neurology. 2020;94(6):e594–e606.
47. Vilberg KL, Rugg MD. Memory retrieval and the parietal cortex: a review of evidence from a dual-process perspective. Neuropsychologia. 2008;46(7):1787–99.
48. Martín-Loeches M, Casado P, Hernández-Tamames JA, Alvarez-Linera J. Brain activation in discourse comprehension: a 3t fMRI study. Neuroimage. 2008;41(2):614–22.
49. Tracy JI, Pustina D, Doucet G, Osipowicz K. Seizure-induced neuroplasticity and cognitive network reorganization in epilepsy. In: Tracy JI, Hampstead BM, Sathian K, editors. Cognitive plasticity in neurologic disorders. Oxford: Oxford University Press; 2014. p. 29–60.
50. Hammen T, Reisert M, Juschkat W, Egger K, Urbach H, Zentner J, et al. Alterations of intracerebral connectivity in epilepsy patients with secondary bilateral synchrony. Epilepsy Res. 2020;166:106402.
51. Liu M, Chen Z, Beaulieu C, Gross DW. Disrupted anatomic white matter network in left mesial temporal lobe epilepsy. Epilepsia. 2014;55(5):674–82.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Citro S, Javidi SS, Ankeeta Ankeeta, He X, Zhang Q, Kry Y, et al. Left parietal structural connectivity mediates typical and atypical language laterality in temporal lobe epilepsy. Epilepsia. 2025;66:1599–1612. https://doi.org/10.1111/epi.18298