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CLINICAL ARTICLE

Preoperative white matter network organization and memory decline after epilepsy surgery

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OBJECTIVE Risk for memory decline is a common concern for individuals with temporal lobe epilepsy (TLE) undergoing surgery. Global and local network abnormalities are well documented in TLE. However, it is less known whether network abnormalities predict postsurgical memory decline. The authors examined the role of preoperative global and local white matter network organization and risk of postoperative memory decline in TLE.

METHODS One hundred one individuals with TLE (n = 51 with left TLE and 50 with right TLE) underwent preoperative T1-weighted MRI, diffusion MRI, and neuropsychological memory testing in a prospective longitudinal study. Fifty-six age- and sex-matched controls completed the same protocol. Forty-four patients (22 with left TLE and 22 with right TLE) subsequently underwent temporal lobe surgery and postoperative memory testing. Preoperative structural connectomes were generated via diffusion tractography and analyzed using measures of global and local (i.e., medial temporal lobe [MTL]) network organization. Global metrics measured network integration and specialization. The local metric was calculated as an asymmetry of the mean local efficiency between the ipsilateral and contralateral MTLs (i.e., MTL network asymmetry).

RESULTS Higher preoperative global network integration and specialization were associated with higher preoperative verbal memory function in patients with left TLE. Higher preoperative global network integration and specialization, as well as greater leftward MTL network asymmetry, predicted greater postoperative verbal memory decline for patients with left TLE. No significant effects were observed in right TLE. Accounting for preoperative memory score and hippocampal volume asymmetry, MTL network asymmetry uniquely explained 25%–33% of the variance in verbal memory decline for left TLE and outperformed hippocampal volume asymmetry and global network metrics. MTL network asymmetry alone produced good diagnostic classification of memory decline in left TLE (i.e., an area under the receiver operating characteristic curve of 0.80–0.84 and correct classification of 65%–76% of cases with cross-validation).

CONCLUSIONS These preliminary data suggest that global white matter network disruption contributes to verbal memory impairment preoperatively and predicts postsurgical verbal memory outcomes in left TLE. However, a leftward asymmetry of MTL white matter network organization may confer the highest risk for verbal memory decline. Although this requires replication in a larger sample, the authors demonstrate the importance of characterizing preoperative local white matter network properties within the to-be-operated hemisphere and the reserve capacity of the contralateral MTL network, which may eventually be useful in presurgical planning.

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KEYWORDS epilepsy; neurosurgery; memory; connectome; white matter; diffusion MRI

Temporal lobe surgery is effective for seizure reduction in individuals with pharmaco-resistant temporal lobe epilepsy (TLE) but confers a substantial risk of memory decline.[1,2] Although clinical and demographic variables are traditionally used to predict decline,[2] investigation of neuroimaging biomarkers is important for further improvement in risk stratification given wide heterogeneity of memory outcomes in TLE[1] and variable gray

ABBREVIATIONS ATL = anterior temporal lobectomy; AUC = area under the ROC curve; BIC = Bayesian information criterion; BVMT-R = Brief Visuospatial Memory Test–Revised; CVLT-II = California Verbal Learning Test–Second Edition; DWI = diffusion-weighted imaging; FDR = false discovery rate; fMRI = functional MRI; HCV = hippocampal volume; LDFR = Long Delay Free Recall; MD = mean difference; MTL = medial temporal lobe; MTS = mesial temporal sclerosis; RCI-PE = reliable change indices that account for practice effect; ROC = receiver operating characteristic; SelAH = selective amygdalohippocampectomy; SLAH = selective laser amygdalohippocampotomy; TLE = temporal lobe epilepsy; UCSD = University of California, San Diego; UCSF = University of California, San Francisco; WTAR = Wechsler Test of Adult Reading.

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and white matter pathology across individuals,[3] coupled with the noninvasive and available nature of neuroimaging. The integrity of the hippocampus and surrounding medial temporal lobe (MTL) structures are the most commonly investigated imaging markers of memory decline,[4,5] which are functionally assessed presurgically using the intracarotid amobarbital procedure (Wada test) or functional MRI (fMRI).[6] However, converging studies have also suggested an important role of white matter connectivity for memory function in TLE, revealing associations between both MTL (i.e., local) and extratemporal or whole-brain (i.e., global) white matter integrity and memory impairment.[7,8]

Epilepsy causes widespread structural and functional network disruption beyond the MTL.[9–11] A variety of functional and structural connectome approaches demonstrated that network disruption is related to cognition preoperatively.[3,12–20] Here, we chose two of the most universally examined metrics of white matter network organization[21] shown to be disrupted in TLE:[22] integration, the brain's ability to rapidly process information from distal and distributed regions, and specialization, the ability for specialized processing to occur within densely interconnected groups of brain regions. To our knowledge, it is unknown whether these common network metrics are related to memory in epilepsy. As network metrics have predictive utility for postsurgical seizure outcome and seizure localization,[23–26] they may also aid in prediction of postoperative memory decline. It is also unknown whether local network organization of the MTL (i.e., structures directly impacted by surgical disruption) predicts memory outcomes. This question is timely, as there is limited empirical support for the clinical translation of network-based measures in epilepsy.[27,28]

Our main objective was to examine whether global and local preoperative white matter network organization predicts risk for postoperative memory decline in TLE. We hypothesized that more optimal network organization will be related to higher memory performance preoperatively. It is not clear how global measures of network organization relate to postoperative outcomes. It is conceivable that more efficient global network organization increases brain reserve, protecting against postsurgical decline. Alternatively, more efficient network organization could be a risk factor for decline due to surgery-driven whole-brain network disruption.[29] Second, as we previously found that left-lateralized MTL white matter integrity at a local level was predictive of memory decline after left anterior temporal lobectomy (ATL),[30] we hypothesized that a greater ipsilateral than contralateral bias of local MTL network organization may lead to greater memory decline after temporal lobe surgery.

Methods

Participants

Before exclusion, our initial sample had 135 patients with drug-resistant TLE and 86 healthy controls recruited between 2005 and 2022 in an IRB-approved study at the University of California, San Diego (UCSD), or University of California, San Francisco (UCSF). Inclusion criteria were 1) age 18–65 years, 2) English speaking, 3) estimated premorbid IQ ≥ 70, 4) at least one memory score available, and 5) preoperative T1-weighted MRI and diffusion-weighted imaging (DWI) that passed quality inspection. TLE diagnosis was established by an epileptologist based on video-EEG, seizure semiology, and neuroimaging. A neuroradiologist inspected MR images for mesial temporal sclerosis (MTS). Patients were included postoperatively if they underwent temporal lobe resection (i.e., ATL or selective amygdalohippocampectomy [SelAH]) or selective laser amygdalohippocampotomy (SLAH) and had at least one memory score obtained 1 year postsurgery (mean 15.9 [SD 9.6] months), in addition to aforementioned criteria. ATL included resection of medial temporal structures, extending into the hippocampal tail until roughly the level of the tectal plate including the entorhinal cortex. SelAH included selective transcortical resection of the amygdala and hippocampus. SLAH consisted of a stereotactic transparietal/occipital to medial temporal insertion of a temperature-controlled catheter, targeting the amygdala as well as the hippocampus from the head to the posterior body. Excluded participants had missing preoperative cognitive or demographic data (n = 36), DWI data with artifacts (n = 19), bilateral seizure focus (n = 6), age greater than 65 years (n = 2), presence of tumor (n = 2), different surgical procedure (n = 3), or missing postoperative memory scores (n = 13). Figure S1 shows a detailed flowchart.

Neuropsychological Outcomes

Estimated intelligence was measured by the Wechsler Test of Adult Reading (WTAR).[46] Verbal learning and memory were assessed by the California Verbal Learning Test–Second Edition (CVLT-II) Learning and Long Delay Free Recall (LDFR).[47] Visuospatial learning and memory were assessed with the Brief Visuospatial Memory Test–Revised (BVMT-R) Learning and Delayed Recall.[33] Preoperative to postoperative memory change was calculated by subtracting preoperative from postoperative raw scores.

Characterization of Individual-Level Decline

Preoperative to postoperative change was binarized into decline versus no decline using reliable change indices accounting for test measurement error and practice effects (RCI-PEs), allowing for more clinically meaningful characterization[31,32] using established test-retest normative data[33,34] and a formula incorporating the standard error of the difference between test and retest. This formula provided by Iverson enables a more accurate estimate, as it additionally takes into account variability in retest scores.[32] We used a 90% confidence interval (i.e., Z score ≤ −1.65) as a cutoff, corresponding to a decline of 6 and 3 points on CVLT-II Learning and LDFR, respectively, and 3 and 1 points on BVMT-R Learning and Delayed Recall, respectively.

Image Acquisition

Imaging at UCSD (49 patients with TLE and 45 healthy controls) and UCSF (28 patients with TLE) was performed on a 3T MR750 Discovery scanner (GE) with identical protocols, head coils (8-channel phased-array), imaging sequences, and software versions, which were prospectively

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harmonized. Acquisitions included a conventional 3-plane localizer, GE calibration scan, T1-weighted 3D structural scan (TR 8.08 msec, TE 3.16 msec, flip angle 8°, FOV 256 mm, slice thickness 1 mm), and for DWI, a single-shot pulsed field-gradient spin-echo EPI sequence (TE 96 msec, TR 17 seconds, FOV 24 cm, matrix 128 × 128 × 48). We also included 24 patients with TLE and 11 healthy controls who underwent scanning at UCSD prior to the 3T upgrade on a 1.5T EXCITE HD scanner (GE) with an 8-channel head coil, which included a conventional 3-plane localizer, GE calibration scan, Tl-weighted 3D structural scan (TR 10.7 msec, TE 3.8 msec, flip angle 8°, FOV 256 mm, slice thickness 1 mm), and single-shot echo-planar imaging (TR 12.3 seconds, TE 75.6 msec, flip angle 90°, FOV 240 mm, matrix 96 × 96, slice thickness 2.5 mm). All DWI scans were acquired with 30 diffusion gradient directions using a b-value = 1000 mm^2/sec. For use in nonlinear B0 distortion correction, two additional b = 0 volumes were acquired with either forward or reverse phase-encode polarity. Field strength was not associated with graph metrics (all $p > 0.05$) and the distributions of graph metrics did not differ across sites or field strength (all $p > 0.05$; Figure S2). Additional steps were taken to ensure results were not influenced by field strength (see *Sensitivity Analyses*).

DWI Processing and Connectome Generation

Detailed methods are provided in Supplemental Material. Imaging was preprocessed using the Multi-Modal Imaging pipeline.[35] Automatic segmentation of the hippocampus was performed with FreeSurfer (version 7.1.1) using T1-weighted scans. Hippocampal volume (HCV) was divided by the total intracranial volume. DWI data were corrected for head motion, geometrical susceptibility-induced distortions, and eddy current–induced artifacts. The reverse gradient method was used to correct B0 distortion. Seven participants did not have a B0 but were visually inspected and found to be free of significant distortion. These participants were not outliers in graph metrics (see Figure S3). All main analyses were run with and without these 7 participants, and the results remained consistent. Postprocessing was performed using MRtrix3. Probabilistic tractography was performed using the default iFOD2 algorithm, based on fiber orientation distributions and convolved using constrained spherical deconvolution. Tractography was performed using QSIprep. Streamlines were refined using anatomically constrained tractography using the T1-weighted image. Streamlines were continuously seeded until 10 million valid streamlines were produced through the iFOD2 algorithm for each participant. Per-streamline cross-section streamline weights were computed using the SIFT2 algorithm. Cortical and subcortical parcellations derived from FreeSurfer's Desikan-Killiany atlas were used to determine connectome edge weights and defined as the sum of SIFT2 weights of all streamlines connecting a pair of nodes. Connectome edges were scaled by the inverse of two node volumes. Undirected, binary graph matrices were created at multiple density levels, with each density level defined as the threshold at which the number of edges in the graph equaled 10%–65% of the total possible edges, in concordance with similar methods.[18,36] We used 55 different density levels to calculate a single summary area under the receiver operating characteristic (ROC) curve (AUC) for each participant. Connectivity matrices were analyzed with the Brain Connectivity Toolbox.[21]

Graph Theory Metrics

Global Metrics

Because a recent meta-analysis found that path length and clustering coefficient differed in TLE versus controls,[22] we chose path length as a measure of global integration (i.e., the minimum number of intermediate nodes needed to connect any two nodes [lower = higher capacity for exchanging information across the network]) and transitivity (i.e., a normalized clustering coefficient) as a measure of global specialization instead of clustering coefficient, because clustering coefficient is normalized individually for each node and may be disproportionately influenced by nodes with a low degree (Fig. 1A).[21] Transitivity (i.e., ratio of the number of estimated connections among a node's first-degree neighbors to the number of all possible connections) reflects the degree to which nodes cluster together (higher = neighbors of a node are more densely interconnected).

Local Metric

As a measure of local network organization, we computed asymmetry of the mean local efficiency for an a priori defined MTL subnetwork, henceforth, MTL network asymmetry, defined as the average global efficiency constrained to only the local neighbors of a specific node and averaged for bilateral parahippocampal, hippocampal, and entorhinal nodes (Fig. 1B). This was used to create a laterality index between the mean local efficiency of the two hemispheres, with ipsilateral corresponding to the hemisphere with seizures (laterality index = [ipsilateral − contralateral]/[ipsilateral + contralateral] × 100). Positive asymmetry indicates a greater ipsilateral than contralateral MTL network efficiency.

Statistical Analysis

We tested for group differences in demographic and clinical variables using ANOVAs and chi-square tests. Partial correlations (bootstrapped with 1000 samples with robust 95% confidence intervals) examined associations between network metrics and memory, controlling for 1) age and WTAR score in preoperative analyses and 2) preoperative score in postoperative analyses. We determined the best predictors of memory decline in regressions using the Bayesian information criterion (BIC). All interpreted p values survived a 5% false discovery rate (FDR) correction (Benjamini-Hochberg). A secondary discriminant function analysis with leave-one-out cross-validation accounting for unbalanced sample sizes and ROC curve analyses tested individual-level prediction of memory decline.

Results

Demographic and Clinical Variables

Our preoperative sample included 101 patients with TLE and 56 healthy controls (Table 1). Patients with TLE

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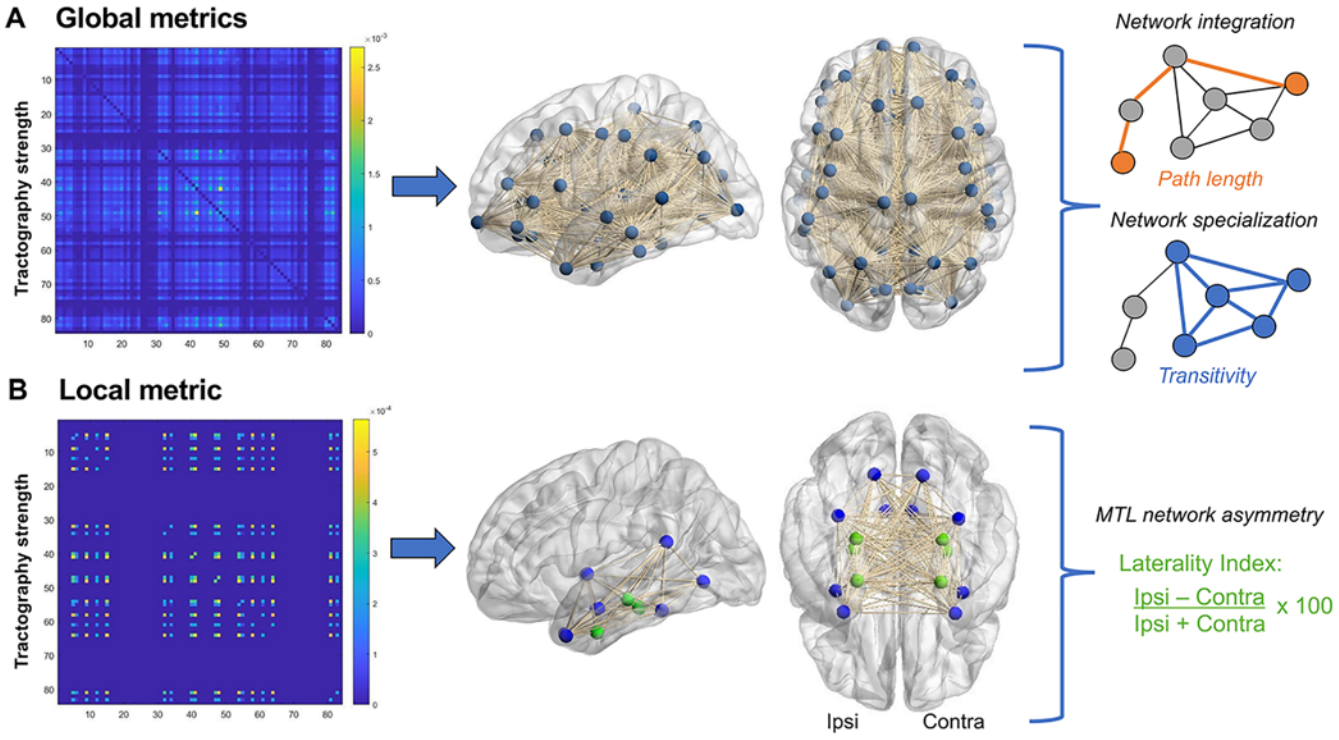

FIG. 1. Generation of the white matter structural connectome and graph theory analysis for global (i.e., whole-brain) (**A**) and local (i.e., MTL) (**B**) metrics. White matter connectivity matrices were generated by assessing pairwise connections between each pair of brain regions (i.e., nodes) and input into a 2D matrix where each *row* and *column* represent an ROI from the Desikan-Killiany atlas and the corresponding color is the strength of the structural connectivity (i.e., edges) between that pair of ROIs. For visualization purposes, a matrix averaged across participants was imposed on a standard brain template using the BrainNet Viewer. Connectivity matrices were analyzed with graph theory analysis to extract two global metrics of interest that reflect whole-brain network integration (measured by path length) and specialization (measured by transitivity, a normalized clustering coefficient) (A) and a local metric that reflects network organization of the MTL (i.e., average local efficiency of the parahippocampal, hippocampal, and entorhinal nodes) (B). A laterality index (referred to as MTL network asymmetry) was computed by subtracting the local efficiency of the contralateral (contra) from the local efficiency of the ipsilateral (ipsi) hemisphere and dividing by the sum. Figure is available in color online only.

had lower education level and WTAR scores than healthy controls (all $p < 0.001$), and patients with right TLE had higher WTAR scores than those with left TLE ($p = 0.03$). The healthy control group had a higher proportion of non-White and non-Hispanic participants. Although the left TLE group had a higher proportion of patients with MTS than the right TLE group, the groups did not differ in ipsilateral HCV. Our postoperative TLE sample included 22 patients with left TLE and 22 patients with right TLE matched on demographic and epilepsy-related variables, including seizure outcome and surgery type (Table 1).

Preoperative Network Organization

A multivariate ANCOVA comparing TLE patients versus healthy controls and controlling for age and WTAR score revealed a significant medium-sized effect of group on global metrics [$F(4,152) = 5.33$; $p = 0.006$; partial $\eta^2 = 0.07$]. Compared with healthy controls, both TLE groups had higher path length (left TLE vs HC: mean difference [MD] = −0.38 [95% CI −0.75 to −0.02], $p = 0.041$; right TLE vs HC: MD = −0.35 [95% CI −0.68 to −0.01], $p = 0.046$) and lower transitivity (left TLE vs HC: MD = 0.55 [95% CI 0.21 to 0.90], $p = 0.002$; right TLE vs HC: MD = 0.38 [95% CI 0.06 to 0.70], $p = 0.020$), with no difference between left TLE and right TLE (all $p > 0.05$). Figure S4 plots individual data.

Postoperative Memory Outcomes

Postoperatively, the left TLE group experienced a greater memory decline than the right TLE group (i.e., significant interactions between time and group) on CVLT-II Learning [$F(1,41) = 7.23$; $p = 0.010$; partial $\eta^2 = 0.15$] and LDFR [$F(1,409) = 6.18$; $p = 0.017$; partial $\eta^2 = 0.13$]. No effects were significant for BVMT-R (all $p > 0.05$), although numerically the right TLE group showed a steeper decline than the left TLE group. Table 2 presents postoperative decline on an individual patient level, consistent with the analyses above. Table S1 presents pre- and postoperative means, and Figure S5 visualizes individual-level decline.

Association Between Preoperative Network Organization and Preoperative Memory

Table 3 shows bootstrapped partial correlations, adjusted for age and WTAR, which are plotted in Figures S6 and S7.

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TABLE 1. Demographic and clinical characteristics of the pre- and postoperative samples

	Preop Sample				Postop Sample		
	Lt TLE	Rt TLE	HC	p Value	Lt TLE	Rt TLE	p Value
No. of pts	51	50	56		22	22	
Age, yrs	36.12 (13.06)	34.97 (11.66)	36.62 (12.65)	0.789	33.36 (12.05)	35.14 (12.51)	0.635
Education, yrs	13.31 (1.93)	13.88 (2.20)	15.73 (2.14)	**<0.001**	13.05 (1.56)	13.82 (2.56)	0.223
WTAR, standard score	95.39 (13.66)	100.74 (14.05)	116.36 (8.63)	**<0.001**	92.27 (12.32)	99.59 (13.22)	0.108
Sex				0.536			0.761
Female	26	30	34		12	13	
Male	25	20	22		10	9	
Handedness				0.603			0.234
Rt	45	46	52		18	20	
Lt	6	3	3		4	1	
Ambidextrous	0	1	1		0	1	
Race				**0.004**			0.552
White	35	29	45		14	13	
>1 race	11	8	0		4	4	
Black or African American	1	7	2		1	3	
Asian	4	1	6		3	1	
American Indian or Alaska Native	0	2	2		0	1	
Native Hawaiian/Other Pacific Islander	0	1	0		0	0	
Unknown	0	2	1		0	0	
Ethnicity				**0.040**			0.216
Non-Hispanic	38	37	51		20	17	
Hispanic	13	13	5		2	5	
Age at seizure onset, yrs	20.20 (14.54)	20.98 (13.88)	—	0.782	18.23 (12.96)	22.59 (15.01)	0.308
Duration of epilepsy, yrs	15.92 (14.42)	14.00 (11.36)	—	0.459	15.14 (13.20)	12.55 (8.10)	0.437
No. of ASMs	2.29 (0.90)	2.20 (0.88)	—	0.597	2.59 (0.96)	2.36 (1.00)	0.447
MTS			—	**0.021**			0.060
Yes	36	26	—		17	11	
No	15	24	—		5	11	
Ipsilat hippocampal vol*	0.0024 (0.0005)	0.0025 (0.0005)	—	0.282	0.0024 (0.0005)	0.0025 (0.0006)	0.625
Op type							0.240
ATL	—	—	—	—	20	16	
SLAH	—	—	—	—	2	5	
SelAH	—	—	—	—	0	1	
Seizure outcome							0.747
Engel class I (seizure free)	—	—	—	—	14	16	
Engel class ≥II (not seizure free)	—	—	—	—	8	6	

ASM = antiseizure medications; HC = healthy control; pt = patient.
Values represent the number of patients or mean (SD) unless stated otherwise. Boldface type indicates statistical significance.
* Ipsilateral HCV is divided by intracranial volume.

Path Length

In left TLE patients, a shorter path length was associated with higher CVLT-II scores. No significant correlations were observed in patients with right TLE, healthy controls, or for BVMT-R.

Transitivity

In left TLE patients, higher transitivity was associated with higher CVLT-II scores. No significant correlations were observed in right TLE, healthy controls, or for BVMT-R.

MTL Network Asymmetry

In left TLE patients, greater ipsilateral (i.e., leftward) asymmetry of MTL network organization was associated with higher CVLT-II Learning, although this did not survive FDR correction. No associations were observed in right TLE patients or BVMT-R.

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TABLE 2. Number of individuals who showed postoperative memory decline based on RCI-PE

	Lt TLE, n		Rt TLE, n			
	Decline	No Decline	Decline	No Decline	Fisher's Z-Test	p Value
CVLT-II Learning	14	7	6	16	(1,43) = 6.70	**0.015**
CVLT-II LDFR	8	12	2	20	(1,42) = 5.52	**0.030**
BVMT-R Learning	5	9	10	8	(1,32) = 1.25	0.308
BVMT-R Delayed Recall	7	8	12	6	(1,33) = 1.34	0.304

Boldface type indicates statistical significance. The cutoff for clinically meaningful decline was based on a 90% confidence interval (i.e., Z score ≤ –1.65) corresponding to 6 and 3 points on CVLT-II Learning and CVLT-II LDFR, respectively, and 3 and 1 points on BVMT-R Learning and BVMT-R Delayed Recall, respectively. See *Methods* for details on calculations and normative data used and Figure S2 for individual data points.

Association Between Preoperative Network Organization and Pre- to Postoperative Memory Decline

Table 3 and Fig. 2 show bootstrapped partial correlations, adjusted for preoperative score. Scatterplots for visual memory are shown in Figure S8.

Path Length

In left TLE patients, shorter path length predicted greater CVLT-II Learning decline. No associations were observed in right TLE patients or for BVMT-R.

Transitivity

In left TLE patients, higher transitivity predicted greater CVLT-II Learning decline, with a similar but weaker association for CVLT-II LDFR. No associations were observed in right TLE patients or for BVMT-R.

MTL Network Asymmetry

In left TLE patients, greater ipsilateral MTL network asymmetry predicted greater CVLT-II Learning and LDFR decline. Although greater ipsilateral asymmetry predicted greater BVMT-R Learning decline in right TLE patients, this did not survive FDR correction.

Multivariate Predictors of Verbal Memory Decline

For left TLE patients, in a multivariate regression model with all three network predictors and controlling for preoperative memory score, only MTL network asymmetry uniquely predicted CVLT-II decline (Learning: $\beta = -0.54$; $p = 0.002$; B = –5.93 [95% CI –9.43 to –2.43]; LDFR: $\beta = -0.52$; $p = 0.016$; B = –2.82 [95% CI –5.03 to –0.61]). Compared with each global metric, MTL network asymmetry explained more variance and had the lowest BIC (i.e., 8–10 points lower). Including all three metrics did not improve model fit relative to MTL network asymmetry alone (Table S2). These same models were not significant in right TLE patients (all $p > 0.05$).

We next examined whether network metrics explained unique variance above and beyond established predictors of memory decline using hierarchical regressions with preoperative memory score and HCV asymmetry in block 1 and MTL network asymmetry in block 2 (Table 4). MTL network asymmetry explained an additional 33% and 25% of the variance in CVLT-II Learning and LDFR scores, respectively, improving model fit and outperforming HCV asymmetry. Preoperative score, MTL network asymmetry, and HCV asymmetry together explained 67% and 53% of the variance in CVLT-II Learning and LDFR outcomes, respectively. Replacing HCV asymmetry with binary MTS status, a negative MTS status was a weak but nonsignificant predictor of greater decline (CVLT-II Learning: $\beta = 0.24$; $p = 0.078$; CVLT-II LDFR: $\beta = 0.30$; $p = 0.057$).

Secondary Analysis: Individual-Level Prediction of Memory Decline in Left TLE Patients

A follow-up discriminant function and ROC analysis tested whether network metrics and established predictors of decline correctly classified verbal memory decline at the individual patient level in left TLE based on RCI-PEs. To avoid overfitting, we assessed only one predictor per model using leave-one-out cross-validation for unbalanced samples. Figure 3 shows ROCs and AUCs, and Table 5 presents classification results.

CVLT-II Learning

Classification models and the AUC were significant for network metrics but not for preoperative score or HCV asymmetry (Table 5 and Fig. 3). MTL network asymmetry correctly classified 76% (cross-validated) of 21 patients, with an AUC of 0.84 and a cutoff score > –0.124 corresponding to 86% sensitivity and 71% specificity (Figure S9). Models with path length and transitivity each correctly classified 67% and 62% of cases (cross-validated), with AUCs of 0.79 and 0.79, respectively. A cutoff score of 71.16 for path length produced 71% sensitivity and 86% specificity. A cutoff score of 45.54 for transitivity produced 71% sensitivity and 100% specificity.

CVLT-II LDFR

Only the model with MTL network asymmetry was significant, correctly classifying 65% of the 20 patients, with an AUC of 0.80. A cutoff score of –0.124 produced 100% sensitivity and 58% specificity (Figure S9).

Sensitivity Analyses

Three-Tesla Only

To evaluate whether differences in magnetic field strength impacted results, we reanalyzed the primary analyses in two ways: 1) including only individuals who underwent 3T MRI scanning and 2) including field strength as a covariate. Results from the main preoperative and postoperative analyses remained significant and of a similar

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TABLE 3. Partial correlations between preoperative network organization and preoperative learning and memory and pre- to postoperative learning and memory change

Time Point & Network Metric	Memory Outcome	Lt TLE			Rt TLE			HC		
		No. of Pts	Pearson's r	95% CI	No. of Pts	Pearson's r	95% CI	No. of Pts	Pearson's r	95% CI
Preop†										
Path length	CVLT-II Learning	51	**−0.31****	−0.58 to −0.02	46	0.18	−0.13 to 0.46	52	−0.07	−0.36 to 0.20
	CVLT-II LDFR	49	**−0.41*****	−0.66 to −0.10	45	0.18	−0.11 to 0.46	52	−0.21	−0.52 to 0.13
	BVMT-R Learning	35	−0.15	−0.51 to 0.21	35	−0.24	−0.50 to 0.11	32	0.23	−0.06 to 0.51
	BVMT-R Delay	35	−0.20	−0.55 to 0.16	35	−0.28	−0.56 to 0.06	32	0.12	−0.22 to 0.45
Transitivity	CVLT-II Learning	51	**0.33****	0.05 to 0.60	46	−0.24	−0.50 to 0.08	52	0.09	−0.15 to 0.33
	CVLT-II LDFR	49	**0.38*****	0.09 to 0.62	45	−0.20	−0.48 to 0.11	52	0.19	−0.08 to 0.43
	BVMT-R Learning	35	0.18	−0.20 to 0.53	35	0.07	−0.26 to 0.36	32	−0.02	−0.28 to 0.29
	BVMT-R Delay	35	0.21	−0.15 to 0.53	35	0.19	−0.12 to 0.47	32	0.04	−0.26 to 0.39
MTL network asymmetry	CVLT-II Learning	51	0.29**	−0.04 to 0.58	46	0.16	−0.12 to 0.41	—	—	—
	CVLT-II LDFR	49	0.21	−0.14 to 0.51	45	0.11	−0.12 to 0.35	—	—	—
	BVMT-R Learning	35	0.16	−0.14 to 0.48	35	−0.19	−0.48 to 0.18	—	—	—
	BVMT-R Delay	35	0.28	−0.02 to 0.59	35	−0.06	−0.37 to 0.31	—	—	—
Pre- to postop change‡										
Path length	CVLT-II Learning	21	**0.53****	0.22 to 0.75	22	−0.19	−0.48 to 0.17	—	—	—
	CVLT-II LDFR	20	0.33	−0.17 to 0.75	22	0.00	−0.32 to 0.27	—	—	—
	BVMT-R Learning	15	0.01	−0.46 to 0.58	18	−0.16	−0.51 to 0.28	—	—	—
	BVMT-R Delay	15	−0.15	−0.59 to 0.49	18	−0.01	−0.45 to 0.50	—	—	—
Transitivity	CVLT-II Learning	21	**−0.54****	−0.81 to −0.18	22	0.13	−0.28 to 0.46	—	—	—
	CVLT-II LDFR	20	−0.41*	−0.80 to 0.02	22	0.13	−0.20 to 0.45	—	—	—
	BVMT-R Learning	15	−0.08	−0.66 to 0.39	18	0.16	−0.30 to 0.54	—	—	—
	BVMT-R Delay	15	−0.07	−0.71 to 0.41	18	0.01	−0.47 to 0.48	—	—	—
MTL network asymmetry	CVLT-II Learning	21	**−0.74******	−0.92 to −0.48	22	0.16	−0.13 to 0.50	—	—	—
	CVLT-II LDFR	20	**−0.66*****	−0.86 to −0.34	22	0.31	−0.01 to 0.57	—	—	—
	BVMT-R Learning	15	−0.39	−0.72 to 0.08	18	−0.48**	−0.80 to 0.17	—	—	—
	BVMT-R Delay	15	−0.36	−0.64 to −0.01	18	−0.37	−0.72 to 0.09	—	—	—

*p < 0.1; **p < 0.05; ***p < 0.01; ****p < 0.001. Pearson's r values in boldface type had associated p values that survived a 5% FDR correction (corrected separately by group and by verbal vs visual memory). Confidence intervals were derived from bootstrapping using 1000 samples.
† Partial correlations control for age and WTAR score.
‡ Partial correlations control for preoperative score.

effect size in the left TLE group and nonsignificant in the right TLE group (Table S3).

ATL Only

We repeated our primary analyses within ATL only given that memory decline and postsurgical network disruption may be greater in this group. All previously significant effects remained significant and were of the same effect size or larger for the left TLE group and nonsignificant for the right TLE group (Table S4).

Dominant Versus Nondominant Surgeries

We repeated our main postoperative analyses classifying patients into dominant versus nondominant surgeries based on available Wada, fMRI, and/or handedness. Although the associations with global metrics were weaker in dominant surgeries, MTL network asymmetry was a robust predictor of verbal memory outcomes in dominant but not in nondominant surgeries (Table S5).

Discussion

Temporal lobe surgery results in seizure freedom for many patients but places them at risk for significant memory decline, negatively impacting quality of life and functional outcomes.[37] Memory depends on a complex and distributed network of structures including and beyond the hippocampus. Therefore, we investigated whether white matter network organization predicts postsurgical memory outcomes in TLE. Our main finding was that although both global and local white matter network organization were important for verbal memory abilities preoperatively

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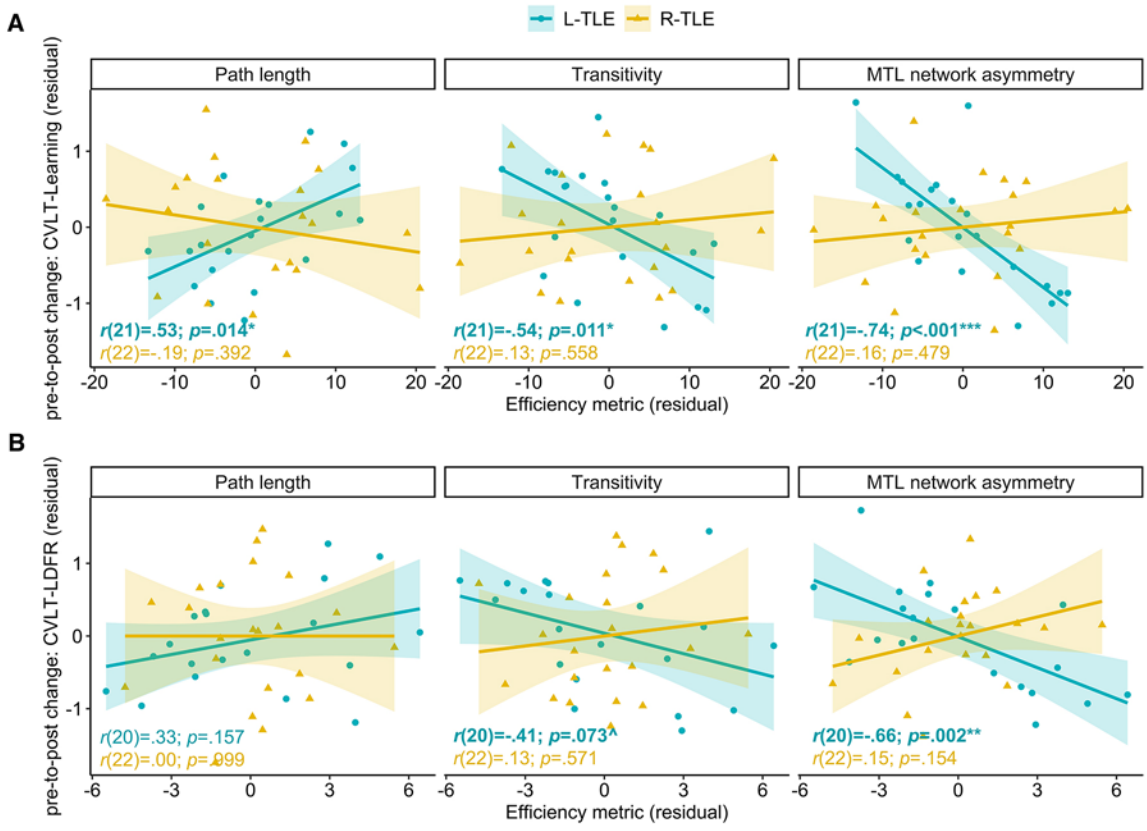

FIG. 2. Associations between preoperative network organization and pre- to postoperative verbal learning and memory change. Scatterplots of partial correlations between preoperative network organization (path length, transitivity, and MTL network asymmetry) and pre- to postoperative verbal memory change for CVLT-II Learning (**A**) and CVLT-II LDFR (**B**) are shown. Residuals are plotted, as these are partial correlations that control for preoperative score. *Ribbons* represent 95% confidence intervals. Patients with left TLE are depicted as *circles* and patients with right TLE as *triangles*. Figure is available in color online only.

TABLE 4. Hierarchical multiple regression output for left TLE with pre- to postoperative verbal learning and memory change scores as dependent variables

	β	B (95% CI)	p Value	Adjusted R^2	F Change	BIC	p Value
CVLT-II Learning (n = 21)							
Block 1: baseline variables				0.34	6.25	150.65	**0.009**
Preop score	−0.63	−0.48 (−0.79 to −0.18)	**0.004**				
HCV asymmetry	−0.40	−0.34 (−0.68 to 0.00)	0.051				
Block 2: add network metric				0.67	18.71	138.11	**<0.001**
Preop score	−0.60	−0.47 (−0.68 to −0.25)	**<0.001**				
HCV asymmetry	−0.24	−0.20 (−0.45 to 0.05)	0.104				
MTL network asymmetry	−0.58	−6.34 (−9.43 to −3.25)	**<0.001**				
CVLT-II LDFR (n = 20)							
Block 1: baseline variables				0.28	4.63	113.87	**0.025**
Preop score	−0.57	−0.55 (−0.96 to −0.15)	**0.010**				
HCV asymmetry	−0.27	−0.10 (−0.26 to 0.06)	0.196				
Block 2: add network metric				0.53	10.06	107.11	**0.006**
Preop score	−0.58	−0.56 (−0.89 to −0.23)	**0.002**				
HCV asymmetry	−0.11	−0.04 (−0.17 to 0.09)	0.535				
MTL network asymmetry	−0.53	−2.86 (−4.78 to −0.95)	**0.006**				

B = unstandardized coefficient estimate; HCV asymmetry = as above.
Dependent variables are measured by the pre- to postoperative change in raw scores. Boldface type indicates statistical significance and denotes that the p value survived a 5% FDR (Benjamini-Hochberg) correction. HCV asymmetry is based on the laterality index using the same formula as for MTL network asymmetry.

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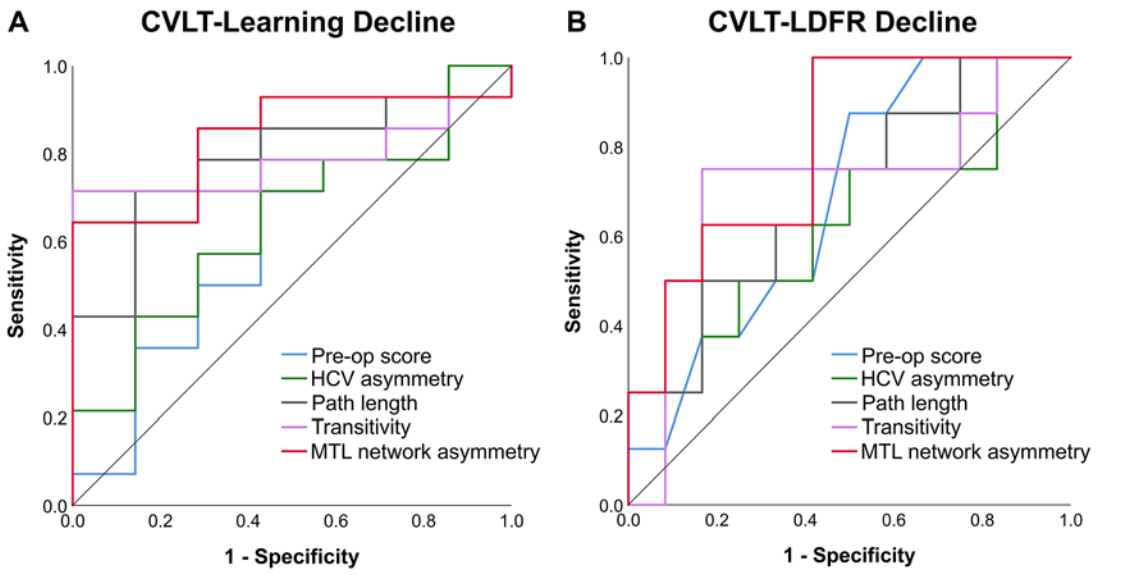

Predictor	*AUC*	*95% CI*	*p*
Pre-op score	.67	[.40, .95]	.205
HCV asymmetry	.64	[.40, .89]	.296
Path length	.79	[.59, .99]	**.037***
Transitivity	.79	[.59, .99]	**.037***
MTL network asymmetry	.84	[.66, 1.00]	**.014***

Predictor	*AUC*	*95% CI*	*p*
Pre-op score	.68	[.45, .92]	.177
HCV asymmetry	.63	[.36, .89]	.355
Path length	.68	[.44, .92]	.190
Transitivity	.73	[.47, .97]	.105
MTL network asymmetry	.80	[.61, 1.00]	**.025***

FIG. 3. Predictors of individual-level verbal learning and memory decline in patients with left TLE. ROC curves for classifying pre- to postoperative decline in CVLT-II Learning (**A**) and CVLT-II LDFR (**B**) for each individual predictor of interest. AUCs along with 95% confidence intervals of the AUC, and p values are reported below. Figure is available in color online only.

and predicted postoperative decline, asymmetry of local MTL network organization was the most important predictor of postoperative verbal memory decline in left TLE. These preliminary data drive home the importance of understanding not only the integrity of white matter MTL networks ipsilateral to the seizure focus but also the integrity of contralateral networks when assessing surgical risk. Second, our findings support the idea that development of preoperative memory impairment in TLE may arise from broad decreases in network communication at the whole-brain level, rather than from localized disruption only, which is in line with widespread evidence of global white matter network abnormalities in TLE.[11,38]

Although preliminary, a clinical application of the observed link between networks and cognition in TLE is the predictive utility of whole-brain and local white matter network organization for postoperative memory decline. With further replication, this may assist in presurgical planning or tailored neurosurgery and is relevant in the era of precision medicine. Although graph theoretical measures from preoperative resting-state fMRI previously showed predictive utility at a group level across various cognitive domains,[39] to our knowledge, our study is the first investigation of postsurgical memory outcomes using whole-brain DWI connectomes, with initial evidence of individual-level predictive utility. We found that although

TABLE 5. Results of a discriminant function analysis for classification of verbal memory decline in left TLE

	CVLT-II Learning					CVLT-II LDFR				
	Wilks' Lambda	Chi-Square	Canonical Correlation	% Correctly Classified*	p Value	Wilks' Lambda	Chi-Square	Canonical Correlation	% Correctly Classified*	p Value
Preop memory score	0.89	2.09	0.33	71.4	0.148	0.88	2.16	0.34	60.0	0.142
HCV asymmetry	0.93	1.27	0.26	57.1	0.260	0.95	0.84	0.22	45.0	0.359
Path length	0.80	4.11	0.45	66.7	**0.043**	0.93	1.36	0.27	60.0	0.243
Transitivity	0.79	4.33	0.46	61.9	**0.037**	0.91	1.66	0.30	70.0	0.197
MTL network asymmetry	0.75	5.41	0.50	76.2	**0.020**	0.73	5.52	0.52	65.0	**0.019**

* Based on cross-validation with leave-one-out.

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higher integration and specialization of preoperative global white matter was associated with higher preoperative memory function in left TLE, it also increased the risk of verbal learning decline. This is commensurate with studies suggesting that having a healthier network presurgically confers greater risk of decline. That is, temporal lobe surgery may induce damage to the relatively intact communication of information transfer at the whole-brain level.[29] This provides support for the adequacy model rather than a reserve model, but at a whole-brain structural level.[40] An alternative scenario is that healthier global network organization would assist in compensatory postsurgical reorganization and adaptation of function, and therefore would be associated with lower decline (i.e., opposite of what was observed). However, it is difficult to draw firm conclusions from the global findings, as a more specific network may be driving the results. For this reason, we additionally investigated local MTL network organization.

The local MTL network organization of the hippocampal, parahippocampal, and entorhinal regions was the most robust predictor, uniquely accounting for 25%–33% of the variance in verbal learning and memory outcomes in left TLE, outperforming HCV, and showing good diagnostic classification of individual-level decline. That is, a greater left than right lateralized MTL network asymmetry predicted greater decline in verbal memory in left TLE. Interestingly, greater leftward MTL network asymmetry was only weakly correlated with higher preoperative verbal learning. Together with our knowledge of the distributed memory network, this suggests that episodic verbal memory may be more dependent on global rather than local network properties preoperatively. However, that the left MTL network plays a more critical role to memory function is evident only after a surgically induced lesion. Our findings of a higher predictive value of local compared with global metrics postoperatively is in line with studies in which abnormalities in network connectivity of MTL regions (rather than whole-brain metrics) led to improved prediction of postsurgical seizure freedom.[24,41]

Consideration of the asymmetry of the MTL network is important because it takes into account both integrity of the ipsilateral network (structural adequacy) and integrity or presumed functionality of the contralateral network (structural reserve) to predict memory outcomes. We previously found that risk for associative memory decline following left ATL was greater with more leftward asymmetry of MTL white matter integrity, or the health of specific deep white matter tracts and adjoining superficial white matter.[30] We expand upon this to show that beyond integrity, greater leftward MTL network organization produced greater risk for verbal memory decline. A previous fMRI graph theory study reported that better integration of the contralateral hippocampus with the rest of the brain was important for cognitive outcomes, suggestive of functional reserve.[39] Our novel results support an extension of both the reserve and adequacy models to MTL network efficiency.

Finally, asymmetry of network organization within the MTL and preoperative verbal learning and memory score were the most important predictors of memory outcomes for left TLE. It has long been understood that the higher one's preoperative memory score, the greater the risk for postoperative memory decline. Because network analysis is more complex and costly than neuropsychological testing, it is important to consider whether it adds additional value. We found that including MTL network asymmetry explained additional variance above and beyond presurgical memory performance, and in individual-level analyses MTL network asymmetry was a more robust predictor. In addition, greater HCV and/or absence of MTS are traditionally associated with greater risk for memory decline. However, in our data, neither HCV asymmetry nor MTS uniquely contributed to memory decline. This may be due to lower sensitivity of structural MRI compared with microstructural measures (i.e., DWI) or related to the growing number of individuals with TLE with no visible hippocampal pathology on MRI for whom probing MTL network integrity and its associations to memory function may be particularly useful.

Our study has several limitations. Our postoperative sample was limited and requires replication in a larger sample. Network metrics were not predictive of memory function in controls or memory decline in right TLE, except for an expected but weak association between rightward MTL network asymmetry and visual memory decline in right TLE. Whereas null associations in controls could be related to a restricted range of values, in right TLE this could be related to more adaptive memory reorganization. In addition, we did not observe robust correlations between visual memory and network measures, possibly because visual memory tests are less sensitive to temporal lobe dysfunction,[42] the material specificity hypothesis may not be applicable,[43] and/or because of lower power given fewer data points for visual compared with verbal memory. The mean interval between surgery and postoperative memory testing was slightly over a year and varied across patients. Although the interval did not moderate associations between network metrics and memory decline (all $p > 0.05$), it is important for future studies to examine whether testing at a longer interval may capture additional damage or reorganization given evidence of both postoperative decreases and increases in white matter integrity.[44] Our network metrics reflected structural (i.e., anatomical) connectivity, an indirect measure of function. It is unclear how functional network alterations[39] compare with structural alterations in prediction of memory, which is important to investigate given that fMRI is routinely used to predict postoperative decline,[6] although most commonly for language outcomes. As is common in cognitive and neuroimaging studies, our enrollment criteria required an estimated IQ > 70, limiting the generalizability of results to individuals with lower intellectual functioning, and may represent a disparity for patients with lower developmental abilities.[45]

Our postoperative sample was heterogeneous and included ATL, SelAH, and SLAH. All three surgeries disrupt MTL networks, but ATL may cause the most disruption. Although our main network findings replicated (and were slightly stronger) in ATL only, a head-to-head comparison of memory and network associations by surgery group in a larger and more-powered study is a fruitful future goal. Specifically, determining whether a more intact preoperative global network organization and/or greater ipsilateral

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asymmetry poses greater risk for memory decline in ATL versus SLAH may eventually aid in risk stratifying patients when weighing the costs and benefits of resection. For example, a left TLE patient with a more preserved global network organization may be a better candidate for SLAH over ATL to minimize the risk of memory decline related to whole-brain network disruption and maximize adaptive network reorganization postsurgery. Conversely, a patient with greater ipsilateral MTL network asymmetry may be at risk for memory decline from either surgery.

It is noteworthy that we did not have postoperative imaging available. Therefore, we could not characterize how network organization changes postoperatively, how these changes relate to memory outcomes, or how this varies by surgery type. This is an important future avenue given evidence of atrophy and adaptive neuroplasticity months[44] and potentially years after surgery. We hypothesize that adaptive contralateral or whole-brain network reorganization postsurgery may drive improvements in memory outcomes.

Conclusions

Although more work remains to link graph theoretical measures more strongly to neurobiology, our study represents a first step to revealing the mechanisms underlying memory impairment and postsurgical decline. Although ATL remains the most efficacious surgical intervention for seizure freedom, the emergence of other less-invasive surgical options (e.g., SLAH, deep brain stimulation, and responsive neurostimulation) necessitates a clear understanding of the memory risks associated with surgery for individual patients. It is important to move beyond comparisons of patients with TLE versus controls in network metrics to capture what those group differences mean for functional outcomes.[23,27] Our preliminary findings may have important clinical implications for individuals undergoing surgical consideration who are at risk for memory decline. After further replication, we suggest that incorporating MTL white matter network organization may be an important future personalized biomarker for memory prognosis.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: McDonald, Stasenko, Kaestner, Ben-Haim. Acquisition of data: Shih, Ben-Haim. Analysis and interpretation of data: Stasenko, Kaestner, Arienzo, Schadler, Helm. Drafting the article: Stasenko. Critically revising the article: McDonald, Kaestner, Shih, Ben-Haim. Reviewed submitted version of manuscript: McDonald, Kaestner, Ben-Haim. Approved the final version of the manuscript on behalf of all authors: McDonald. Statistical analysis: Helm.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

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