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RESEARCH ARTICLE

Association Between Microstructural Asymmetry of Temporal Lobe White Matter and Memory Decline After Anterior Temporal Lobectomy

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Abstract

Background and Objectives

Risk for memory decline is a substantial concern in patients with temporal lobe epilepsy (TLE) undergoing anterior temporal lobectomy (ATL). Although prior studies have identified associations between memory and integrity of white matter (WM) networks within the medial temporal lobe (MTL) preoperatively, we contribute a study examining whether microstructural asymmetry of deep and superficial WM networks within the MTL predicts postoperative memory decline.

Methods

Patients with drug-resistant TLE were recruited from 2 epilepsy centers in a prospective longitudinal study. All patients completed preoperative T1 and diffusion-weighted MRI (DWI) as well as preoperative and postoperative neuropsychological testing. Preoperative fractional anisotropy (FA) of the WM directly beneath the neocortex (i.e., superficial WM [SWM]) and of deep WM tracts associated with memory were calculated. Asymmetry was calculated for hippocampal volume and FA of each WM tract or region and examined in linear and logistic regressions with preoperative to postoperative memory change as the primary outcome.

Results

Data were analyzed from 42 patients with TLE (19 left TLE [LTLE], 23 right TLE [RTLE]) who underwent ATL. Leftward FA asymmetry of the entorhinal SWM was associated with decline on prose and associative recall in LTLE, whereas leftward FA asymmetry of the uncinate fasciculus (UNC) was associated with decline on prose recall only. After controlling for preoperative memory score and hippocampal volume, leftward FA asymmetry of the entorhinal SWM uniquely contributed to decline in both prose and associative recall ($\beta = -0.46$; SE 0.14 and $\beta = -0.68$; SE 0.22, respectively) and leftward FA asymmetry of the UNC uniquely contributed to decline in prose recall ($\beta = -0.31$; SE 0.14). A model combining asymmetry of hippocampal volume and entorhinal FA correctly classified memory outcomes in 79% of patients with LTLE for prose (area under the curve [AUC] 0.89; sensitivity 82%; specificity 75%) and 81% of patients for associative (AUC 0.79; sensitivity 83%; specificity 80%) recall. Entorhinal SWM asymmetry was the strongest predictor in both models.

Discussion

Preoperative asymmetry of deep WM and SWM integrity within the MTL is a strong predictor of postoperative memory decline in TLE, suggesting that surgical decision-making may benefit from considering each patient's WM network adequacy and reserve in addition to hippocampal integrity.

Classification of Evidence

This study provides Class II evidence that preoperative asymmetry of deep WM and SWM integrity within the MTL is a predictor of postoperative memory decline.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ATL = anterior temporal lobectomy; **AUC** = area under the curve; **BVMT-R** = Brief Visuospatial Memory Test–Revised; **DWI** = diffusion-weighted imaging; **FA** = fractional anisotropy; **FDR** = false discovery rate; **FOV** = field of view; **ILF** = inferior longitudinal fasciculus; **LI** = laterality index (left – right/left + right); **LM** = Logical Memory; **LTLE** = left temporal lobe epilepsy; **MTS** = mesial temporal sclerosis; **NPV** = negative predictive value; **OR** = odds ratio; **PPV** = positive predictive value; **RCI-PE** = reliable change indices that account for practice effects; **ROI** = region of interest; **RTLE** = right temporal lobe epilepsy; **SLAH** = stereotactic laser amygdalohippocampotomy; **SWM** = superficial white matter; **TE** = echo time; **TLE** = temporal lobe epilepsy; **TR** = repetition time; **UCSD** = University of California, San Diego; **UCSF** = University of California, San Francisco; **UNC** = uncinate fasciculus; **VPA** = Verbal Paired Associates; **WM** = white matter.

Anterior temporal lobectomy (ATL)[1] is an effective treatment for drug-resistant temporal lobe epilepsy (TLE)[2] but leads to memory impairment in 30%–60% of patients, decreasing quality of life and functional outcomes.[3] Risk factors for memory decline include surgery on the language-dominant hemisphere, higher preoperative memory performance, lower education, older age at seizure onset, and older age at surgery.[4,5] In addition, mesial temporal sclerosis (MTS) or hippocampal volume loss have been identified as reliable imaging markers of memory decline.[6-8] However, these variables only account for a modest portion of the variance,[9-11] indicating that other underlying neuroanatomical factors may be important predictors of memory decline following ATL.

To understand the neuroanatomical correlates associated with cognitive outcomes, studies assessed both integrity of the ipsilateral hippocampus (functional adequacy) and integrity or presumed "functionality" of the contralateral hippocampus (hippocampal reserve).[12] Beyond hippocampal volume, the integrity of white matter (WM) association tracts projecting through the bilateral medial temporal lobes (MTLs) as well as the WM subadjacent to the neocortex (superficial white matter [SWM]) are associated with preoperative memory performance in TLE.[13-16] In particular, the entorhinal SWM, which includes major afferent input to the hippocampus via the perforant path,[17] has been implicated in memory performance.[13] However, whether the concepts of adequacy and reserve also apply to WM integrity of the MTL and whether this predicts memory decline following ATL is unknown.

We investigated whether preoperative MTL network microstructure predicts verbal and nonverbal memory decline following ATL. We hypothesized that deep WM and SWM microstructural asymmetry, a within-subject index of reserve and adequacy, will predict risk for memory decline, even after accounting for hippocampal volume.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Institutional Review Boards at the University of California, San Diego (UCSD) and University of California, San Francisco (UCSF) under a joint IRB plan. All participants provided informed consent according to the Declaration of Helsinki.

Classification of Evidence

This prospective, longitudinal study provides Class II data for investigating the ability of white matter asymmetry to predict memory outcomes in TLE following ATL.

Participants

Fifty-nine patients with drug-resistant TLE were enrolled. A diagnosis of TLE was established by a board-certified neurologist with expertise in epileptology, based on video-EEG telemetry, seizure semiology, and neuroimaging. MRIs were inspected by a board-certified neuroradiologist for detection of MTS. Patients were included if they met the following criteria: (1) age 18–65; (2) English-speaking; (3) estimated premorbid IQ >70; (4) underwent standard ATL; (5) no evidence of large structural lesions or visible extrahippocampal pathology on MRI; (6) completed preoperative and postoperative neuropsychological evaluations that included at least 1 memory test; and (7) had structural and diffusion-weighted imaging (DWI) that passed quality inspection. Participants were excluded if they did not have postsurgical memory scores (n = 6), were missing DWI data (n = 3), had DWI data with artifacts (n = 3), or underwent a non-ATL surgical procedure (n = 5). All ATLs included resection of mesial temporal structures, with resection extending into the hippocampal tail until roughly the level of the tectal plate and including the entorhinal cortex. Although there was some variability in the extent of the lateral superior temporal neocortex resected based on an individual's pathology, this did not affect medial temporal structures of interest. Hemispheric dominance was determined based on language lateralization from presurgical fMRI or Wada testing. Seven right-handed individuals (4 left TLE [LTLE]) without available language lateralization were coded as left-hemisphere dominant.

Primary Outcome: Preoperative to Postoperative Memory Change

Verbal memory was assessed using measures of prose (i.e., stories) and associative (i.e., word-pair) delayed recall using 2 subtests from the Wechsler Memory Scale III—Logical Memory Delayed Recall (LM II) and Verbal Paired Associates Delayed Recall (VPA II)—for prose and

associative recall, respectively. Visuospatial memory was assessed with the Brief Visuospatial Memory Test–Revised (BVMT-R)[18] delayed recall.

Participants had preoperative and postoperative memory scores on at least one measure, obtained prior to and approximately 1 year following ATL (mean 15.5 months; SD 9.9; range 6–68). Preoperative to postoperative memory change was calculated by subtracting preoperative from postoperative age-adjusted scaled (LM II and VPA II) or raw scores (BVMT) (i.e., negative values correspond to decline). This continuous measure of change was used in all correlations and multiple regression analyses. Decline at an individual patient level was determined by reliable change indices that account for practice effects (RCI-PEs[19,20]), which allows for more clinically meaningful characterization, with 80% CIs (i.e., a z score of ≤−1.28 suggests decline). This allowed us to classify patients as "decliners" or "nondecliners" as a binary outcome for logistic regressions and mixed analysis of variance and to evaluate the number of patients who remained stable, improved, or declined on memory tests.

Image Acquisition

Participants completed their imaging visit within a year prior to their surgery (mean 4.3 months; SD 5.4). Imaging was performed on a General Electric Discovery MR750 3T scanner with an 8-channel phased-array head coil at UCSD (n = 20) or UCSF (n = 22). Image acquisitions were identical at both centers and included a conventional 3-plane localizer, GE calibration scan, a T1-weighted 3D structural scan (repetition time [TR] 8.08 ms, echo time [TE] 3.16 ms, inversion time 600 ms, flip angle 8°, field of view [FOV] 256 mm, matrix 256 × 192, slice thickness = 1 mm isotropic), and a single-shot pulsed-field gradient spin-echo echoplanar imaging sequence (TE/TR 96 ms/17 s; FOV 24 cm, matrix 128 × 128 × 48; axial). Diffusion-weighted images were acquired with b = 0 and b = 1000 mm2/s with 30 diffusion gradient directions. Two additional b = 0 volumes were acquired with either forward or reverse phase-encode polarity for use in B_0 correction.

Image Processing

Structural MRI

Automatic segmentation of the hippocampus was performed with Freesurfer (v5.3) using the T1-weighted images. The segmentations were visually inspected to ensure correct labeling of the hippocampus. In order to control for differences in brain size, hippocampal volume was divided by total intracranial volume.

Diffusion-Weighted Imaging

Preprocessing of the DWI data included corrections for distortions due to magnetic susceptibility (B_0), eddy currents, and gradient nonlinearities, head motion correction, and registration to the T1-weighted structural image. For B_0 distortion correction, a reverse gradient method was used.[21] A detailed description of the image processing is provided elsewhere.[14] DWI-derived fractional anisotropy (FA) was calculated based on a tensor fit to the b = 1,000 data.

Fiber Tract Calculations

Fiber tract FA values were derived using a probabilistic diffusion tensor atlas (i.e., AtlasTrack) previously validated in healthy controls and patients with TLE.[22] AtlasTrack is a fully automated method for labeling fiber tracts in individuals based on DWI, T1-weighted images, and a probabilistic atlas of fiber tract locations and orientations. A full description of the atlas and detailed steps used to create the atlas are provided elsewhere.[22]

SWM Calculations

Cortical surface reconstruction and parcellation was determined using FreeSurfer (v5.3) and the Desikan-Killiany atlas. FA for SWM was calculated by sampling the white matter directly below the pial surface at each vertex at a constant distance of 1 mm to ensure that measures are obtained from neighboring voxels. Average FA was measured in the white matter directly beneath 2 gray matter regions of interest (ROIs) (parahippocampal and entorhinal) in each individual's native space (a methodologic description is provided elsewhere[23]).

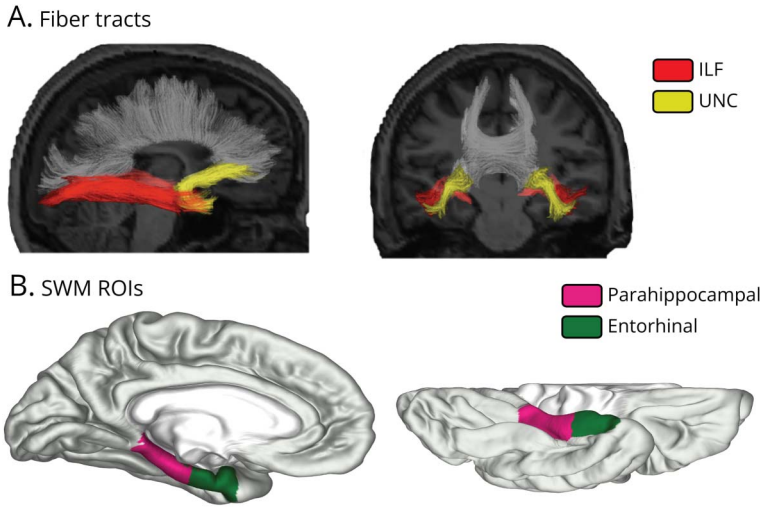
Selection of Tracts and ROIs

The uncinate fasciculus (UNC) and inferior longitudinal fasciculus (ILF) were selected due to evidence that they are often affected in TLE,[24] contribute to preoperative memory in TLE,[14-16,25] and are injured or transected during ATL[26,27] (Figure 1A). The UNC is a long-range WM tract that connects lateral orbitofrontal cortex and Brodmann area 10 with the anterior temporal lobe. The ILF is a long-range associative WM tract that connects the lingual and fusiform areas in the temporo-occipital junction to the anterior temporal cortex. Parahippocampal and entorhinal ROIs were selected based on their strong association with memory,[28] associations with preoperative verbal memory in TLE specifically,[14,29] and with verbal memory decline following ATL[30] (Figure 1B).

Laterality Indices as an Index of Asymmetry

Asymmetry of preoperative imaging measures was calculated using laterality indices [LI = (left − right)/(left + right)] between the 2 hemispheres. Positive LI indicates a leftward asymmetry of hippocampal volume or ROI/tract FA (i.e., higher FA within left hemisphere tracts/ROIs suggestive of more preserved WM integrity), whereas negative LI indicates a rightward asymmetry (i.e., higher FA within right hemisphere tracts/ROIs). LIs have been used extensively with hippocampal volumes,[31] presurgical fMRI,[32] and WM asymmetry,[33] and were robust predictors of language and memory decline following ATL.[34] These measures provide a single measure that takes into account both integrity of the ipsilateral MTL network (structural adequacy) as well as integrity or presumed "functionality" of the contralateral MTL network (structural reserve). LIs provide powerful estimates because

Figure 1 Deep White Matter Tracts and Superficial White Matter ROIs



(A) Sagittal and coronal views of the uncinate fasciculus (UNC) and inferior longitudinal fasciculus (ILF) derived from AtlasTrack and projected onto a T1-weighted image for a single individual. The corpus callosum is portrayed in light gray in order to provide additional spatial information. (B) Medial and ventral views of superficial white matter (SWM) regions of interest (ROIs) of the entorhinal and parahippocampal regions derived from the Desikan-Killiany Atlas.

they allow for within-subject normalization, controlling for variance across individuals and scanners.

The research team responsible for adjudicating the diagnostic test results and calculating the asymmetry indices of WM integrity and hippocampal volume was blinded to memory outcomes.

Statistical Analysis

Mann-Whitney *U* and Fisher exact tests examined differences among demographic and clinical variables between LTLE and right TLE (RTLE). One-sample *t* tests tested group-level change on memory measures using RCI-PEs. Fisher exact and independent samples *t* tests tested group differences in memory decline. Pearson bivariate correlations examined associations between memory change and clinical, demographic, and imaging variables. The Tables indicate *p* values that survived 5% false discovery rate (FDR) correction. We examined correlations separately for LTLE and RTLE to assess the differential effect of left vs right ATL on memory performance. Although memory outcomes were normally distributed (Shapiro-Wilk test $ps \geq 0.42$), there were several outliers in the standardized residuals (i.e., >2). For this reason, and given a smaller sample size, we used robust linear regressions with memory change scores (continuous) as dependent variables and preoperative memory score, hippocampal volume LI, and WM LIs that were significant or marginally significant in bivariate associations. Model comparisons evaluated the unique contribution of WM LIs to memory change using the Wald test of goodness-of-fit. We used the robustbase package in R with latest recommended defaults, with an M-estimator with iteratively reweighted least squares estimation. In a final analysis, binary logistic regressions and receiver operating characteristic (ROC) curves evaluated the ability of imaging LIs to correctly classify patients with TLE as decliners or nondecliners based on RCI-PEs. To avoid overfitting these models, and due to our primary interest in imaging LIs, we included only hippocampal volume LI and 1 WM LI predictor in each model.

Data Availability

The authors have full access to all study data and participant consent forms and take full responsibility for the data, the conduct of the research, the analysis and interpretation of the data, and the right to publish all data.

Results

Patient Demographics and Clinical Variables

The final sample consisted of 42 patients with drug-resistant TLE (19 LTLE; 23 RTLE). Table 1 presents demographic and epilepsy-related variables for LTLE and RTLE. Groups did not significantly differ on variables previously linked to memory outcomes, including education, age at seizure onset, age at surgery, sex, and presence of MTS. However, patients with LTLE were more likely to undergo a language-dominant resection ($p < 0.001$) and tended to have a greater number of generalized tonic-clonic seizures ($p < 0.05$).

Preoperative to Postoperative Memory Performance

Table 2 shows mean preoperative and postoperative scores as well as preoperative to postoperative change and percentage of patients who declined, improved, or remained stable on delayed recall measures based on RCI-PEs (see Table 2 footnote). eFigure 1 (links.lww.com/WNL/B778) plots individual data. As a group, patients with LTLE declined on both verbal delayed recall measures based on RCIs (LM II: $t[18] = -4.9$, $p < 0.001$ [FDR-corrected], Cohen $d = -1.1$; VPA II: $t[15] = -2.4$, $p < 0.05$ [FDR-corrected], $d = -0.6$). In contrast, RTLEs exhibited a groupwise decline on LM II only ($t[19] = -2.2$, $p < 0.05$, $d = -0.5$), although this did not survive

Table 1 Clinical and Demographic Characteristics of Patients With LTLE and Patients With RTLE Who Underwent ATL

	LTLE (n = 19), mean (SD)	RTLE (n = 23), mean (SD)	LTLE vs RTLE	
			U or OR	*p* Value
Age at surgery, y	34.1 (13.2)	34.0 (12.6)	218.0	0.990
Education, y	13.5 (1.7)	13.7 (2.4)	215.0	0.928
Sex, F/M	12/7	15/8	0.9	1.0
Handedness, R/L	15/4	22/1	5.6	0.158
Race				0.450
White	11	14		
>1 Race	4	5		
Black	1	2		
Asian	3	0		
NH	0	1		
Unknown	0	1		
Ethnicity				0.330
Non-Hispanic	17	16		
Hispanic	2	6		
Unknown	0	1		
Premorbid estimated IQ, WTAR	95.9 (13.5)	99.1 (13.5)	184.5	0.390
Age at seizure onset, y	19.2 (12.5)	18.7 (14.4)	206.0	0.752
Duration of epilepsy, y	14.9 (13.5)	15.3 (12.5)	201.5	0.667
No. of ASMs	2.6 (1.0)	2.4 (0.9)	185.0	0.368
MTS, Y/N	12/7	11/12	0.5	0.366
Resection side, dominant/nondominant[a]	15/4	2/21	34.2	<0.001[b]
Seizure frequency	6.2 (7.0)	3.6 (3.1)	164.5	0.238
Lifetime GTC frequency				0.031[b]
0–1	4	9		
2–9	4	10		
10–39	9	2		
>40	2	2		
Engel outcome, I/II+	14/5	17/6	1.0	1.0

Abbreviations: ASM = antiseizure medication; ATL = anterior temporal lobectomy; GTC = generalized tonic-clonic seizure; LTLE = left temporal lobe epilepsy; MTS = mesial temporal sclerosis; NH = Native Hawaiian/Other Pacific Islander; OR = odds ratio; RTLE = right temporal lobe epilepsy; WTAR = Wechsler Test of Adult Reading.
Engel Outcome (year 1): I = seizure-free; II+ = not seizure-free.
[a] This was determined based on language lateralization from available presurgical fMRI or Wada findings.
[b] Significant group differences ($p < 0.05$).

FDR correction. Decline on LM II trended to be greater for LTLE compared to RTLE ($p = 0.05$). Examining decline at an individual level, 42% and 44% of LTLEs declined on verbal memory measures compared to 25% and 29% of RTLEs (for LM II and VPA II, respectively). Although RTLEs did not exhibit group-level decline on BVMT, a greater percentage of RTLEs declined on BVMT than on either verbal memory measure (i.e., 56% vs 25% and 56% vs 29%).

Predictors of Postoperative Memory Change

Table 3 shows correlations between memory change scores and demographic, clinical, and imaging variables for LTLE and RTLE.

Table 2 Preoperative and Postoperative Memory Scores as Well as Change Scores and Percent of Patients Who Declined, Remained Stable, or Improved on Standard Neuropsychological Memory Tests

	LTLE, mean ± SD or n (%)	RTLE, mean ± SD or n (%)	LTLE vs RTLE			
			Mean difference	*t* or OR	95% CI	*p* Value
LM II	n = 19	n = 20				
Preoperative	8.0 ± 2.8	8.4 ± 2.5				
Postoperative	6.9 ± 3.1	9.2 ± 2.7				
Postoperative minus preoperative	−1.1 ± 3.0	0.9 ± 3.0				
Change (RCI-PE)[a]	−1.6 ± 1.4*,[b]	−0.7 ± 1.4‡	0.92	2.00	−0.02, 1.86	0.054§
Declined	8 (42)	5 (25)	—	2.14	0.46, 10.84	0.320
Improved	0 (0)	2 (10)				
Stable	11 (58)	13 (65)				
VPA II	n = 16	n = 17				
Preoperative	9.1 ± 3.3	10.4 ± 2.2				
Postoperative	8.4 ± 4.1	10.4 ± 3.1				
Postoperative minus preoperative	−0.7 ± 2.2	−0.1 ± 2.9				
Change (RCI-PE)[a]	−0.7 ± 1.2‡,[b]	−0.4 ± 1.5	0.36	0.75	−0.61, 1.32	0.456
Declined	7 (44)	5 (29)	—	1.83	0.36, 10.09	0.481
Improved	1 (6)	3 (18)				
Stable	8 (50)	9 (53)				
BVMT-R Delayed Recall	n = 15	n = 18				
Preoperative	8.2 ± 2.7	9.0 ± 2.9				
Postoperative	7.9 ± 3.4	8.3 ± 3.0				
Postoperative minus preopoperative	−0.3 ± 2.7	−0.7 ± 3.5				
Change (RCI-PE)[a]	−1.0 ± 2.6	−1.4 ± 3.4	−0.33	−0.31	−2.53, 1.87	0.762
Declined	6 (40)	10 (56)	—	0.54	0.11, 2.61	0.491
Improved	4 (27)	5 (28)				
Stable	5 (33)	3 (17)				

Abbreviations: BVMT-R = Brief Visuospatial Memory Test–Revised; LM = Logical Memory; LTLE = left temporal lobe epilepsy; OR = odds ratio; RCI-PE = reliable change indices (*z* scores) that account for practice effects; RTLE = right temporal lobe epilepsy; VPA = Verbal Paired Associates.
Group-level change and % declined or improved are based on RCI-PE with an 80% CI ($z \leq -1.28$ or $z \geq 1.28$). Test-retest data required to calculate RCI-PE were obtained in each measure's technical manual and a formula for calculating the *z* score was obtained from Iverson (2001).[20] Statistically significant decline corresponds to an age-adjusted scaled score decline of 1 or more points on LM II, an age-adjusted scaled score decline of 2 or more points on VPA II, and a raw score decline of 1 or more points on BVMT-R (these thresholds are lower because practice effects are expected and thus memory decline is characterized not only by decline on tests, but also the absence of expected practice effects).
[a] Significance of group-level change is based on a 1-sample *t* test vs 0 using RCI-PE.
[b] Significant effects that survive 5% false discovery rate correction. *$p < 0.001$; ‡$p < 0.05$; §$p < 0.10$.

Clinical and Demographic Variables and Postoperative Memory Change

For LTLE, the association between higher preoperative memory score and greater LM II decline approached significance ($p = 0.06$). Higher education was associated with less decline on VPA II ($p < 0.05$). For RTLE, higher preoperative memory scores were associated with greater memory decline on LM II and BVMT Delay (*p*s <0.05, respectively). Higher education was (unexpectedly) associated with greater decline on VPA II ($p < 0.05$).

Neither age at seizure onset nor age at surgery was significantly associated with memory decline in either group. There was no significant relationship between memory change and length of postsurgical interval in LTLEs or RTLEs (all *p*s ≥ 0.16).

Hippocampal Volume LI and Postoperative Memory Change

For LTLE, a more leftward hippocampal volume LI (i.e., greater left-lateralized volume) was marginally associated

Table 3 Pearson Bivariate Correlations Between Memory Change (i.e., Postoperative Minus Preoperative Score) and Clinical Variables and Imaging Laterality Indices

	LM II	VPA II	BVMT delay
LTLE	n = 19	n = 16	n = 15
Preoperative score	–0.44§	0.08	–0.19
Education	–0.03	0.52‡	0.40
Age at seizure onset	–0.23	0.15	–0.39
Age at surgery	–0.07	–0.07	–0.31
Hippocampal volume LI	–0.44§	–0.31	–0.06
UNC FA LI	–0.60†,[b]	0.03[a]	0.27
ILF FA LI	–0.07	–0.04	0.28
Parahippocampal SWM FA LI	–0.01	0.08	0.31
Entorhinal SWM FA LI	–0.64†,[b]	–0.47§	0.09
RTLE	n = 20	n = 17	n = 18
Preoperative score	–0.54‡	–0.24	–0.58‡
Education	–0.24	–0.57‡	0.08
Age at seizure onset	0.36	–0.03	–0.10
Age at surgery	0.18	–0.08	–0.11
Hippocampal volume LI	0.13	0.23	0.36
UNC FA LI	–0.23	–0.24	–0.38
ILF FA LI	0.13	–0.20	0.11
Parahippocampal SWM FA LI	–0.03	–0.14	0.15
Entorhinal SWM FA LI	0.10	0.40	0.18

Abbreviations: BVMT = Brief Visuospatial Memory Test; FA = fractional anisotropy; ILF = inferior longitudinal fasciculus; LI = laterality index (left – right/left + right); LM = Logical Memory; LTLE = left temporal lobe epilepsy; RTLE = right temporal lobe epilepsy; SWM = superficial white matter; UNC = uncinate fasciculus; VPA = Verbal Paired Associates;
[a] When one visual outlier was removed, this correlation became $r = -0.348$.
[b] p Values of correlations that survive a 5% false discovery rate (Benjamini-Hochberg) correction (these were corrected separately by clinical and imaging variables per temporal lobe epilepsy group). †$p < 0.01$; ‡$p < 0.05$; §$p < 0.10$.

with greater LM II decline ($p = 0.06$). For RTLE, hippocampal volume LI was not associated with memory change in RTLE ($ps \geq 0.13$).

WM LIs and Postoperative Memory Change

For LTLE, more leftward LIs of the UNC and entorhinal SWM FA were associated with greater decline in LM II ($ps = 0.008$ and 0.003; FDR-corrected). The association between entorhinal SWM FA and VPA II decline approached significance ($p = 0.06$). For RTLE, WM LIs were not significantly associated with memory decline ($ps \geq 0.12$). Figure 2 shows scatterplots depicting these relationships.

Left and Right Hemisphere WM Contributions to Memory Change in LTLE

To determine whether ipsilateral or contralateral WM FA was driving the significant associations reported above for LTLE, we examined correlations between left and right hemisphere FA values with memory change. Higher right entorhinal FA was associated with better outcomes (i.e., less memory decline) on LM II and VPA II ($r = 0.58$, $p = 0.01$; $r = 0.70$, $p = 0.002$, respectively). Left entorhinal FA was not significantly associated with memory outcomes ($ps \geq 0.60$). Higher right UNC FA was associated with better outcomes for LM II, although this only approached significance ($r = 0.39$; $p = 0.07$). eFigure 2 (links.lww.com/WNL/B778) presents scatterplots of these effects.

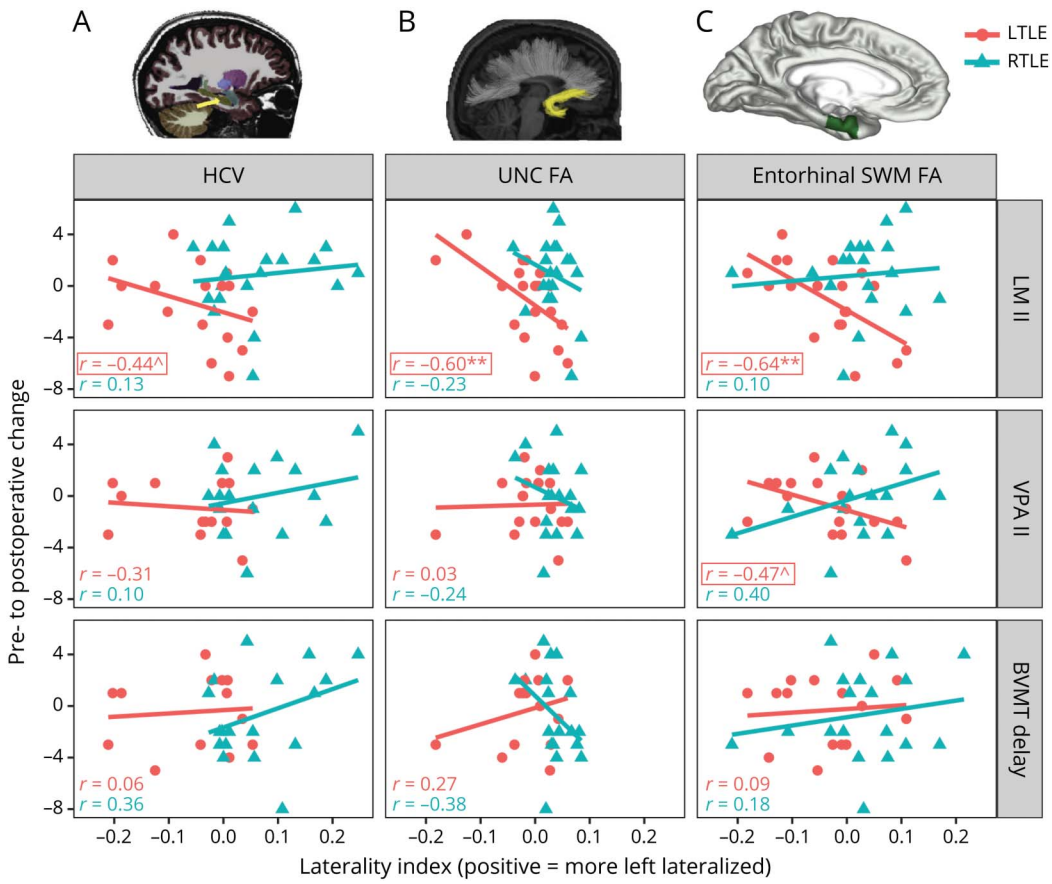
In a secondary analysis, we examined differences in preoperative FA of the entorhinal and UNC between decliners and nondecliners using a mixed analysis of variance (Figure 3). For entorhinal FA, there was a significant 2-way interaction between group and hemisphere ($p = 0.01$), such that decliners had significantly lower FA in the right hemisphere compared to nondecliners ($p = 0.04$). For UNC FA, there was a crossover 2-way interaction ($p = 0.04$) such that decliners tended to have lower FA in the right hemisphere and higher FA in the left hemisphere compared to nondecliners. We also examined left vs right hemisphere FA differences between patients with LTLE and age-matched healthy controls (see eAppendix 1 and eFigure 3, links.lww.com/WNL/B778). Briefly, controls tended to have higher FA in the left hemisphere relative to LTLE.

Multivariate Predictors of Postoperative Memory Change in LTLE

To determine whether WM asymmetry uniquely predicts verbal memory outcome in LTLE after controlling for important clinical predictors, we conducted a series of hierarchical robust linear regressions with preoperative memory score and hippocampal volume asymmetry in block 1 and entorhinal and UNC asymmetry in block 2 (Table 4).

Preoperative memory score and hippocampal volume LI together accounted for 29% and 3% (R^2_{adj}) of the variance in postoperative memory change on LM II and VPA II, respectively. Adding UNC and entorhinal LIs significantly improved model prediction (LM II: χ^2 [2] = 36.5; $p < 0.001$; VPA II: χ^2 [2] = 9.4; $p < 0.01$), accounting for an additional 45% and 49% of variance in LM II and VPA II, respectively. A combined model of preoperative memory score, hippocampal volume, UNC, and entorhinal LIs together accounted for 74% and 52% of the variance in LM II and VPA II change, respectively. For LM II, entorhinal LI made an independent, and the strongest, contribution to decline ($\beta = -0.46$), followed by baseline score ($\beta = -0.39$), hippocampal volume LI ($\beta = -0.37$), and UNC LI ($\beta = -0.31$). All 4 predictors survived FDR correction. For VPA II, entorhinal LI made an independent and the strongest contribution to decline

Figure 2 Associations Between Laterality Indices and Pre- to Postoperative Memory Change



Scatterplots depict the relationship between laterality indices (i.e., asymmetry) of hippocampal volume (HCV) (A), uncinate fasciculus (UNC) fractional anisotropy (FA) (B), and entorhinal superficial white matter (SWM) FA (C) and memory change (i.e., postoperative minus preoperative score) on Logical Memory Delayed Recall (LM II), Verbal Paired Associates Delayed Recall (VPA II), and Brief Visuospatial Memory Test (BVMT), plotted separately for left temporal lobe epilepsy (LTLE) and right temporal lobe epilepsy (RTLE). Significant or marginally significant effects are displayed within a box. $^{**}p < 0.01$; $^{\wedge}p < 0.10$.

(β = −0.68), followed by hippocampal volume LI (β = −0.67). These 2 predictors survived FDR correction. Standard linear regressions showed similar results (eTable 1, links.lww.com/WNL/B778).

Individual Prediction of Memory Decline in LTLE

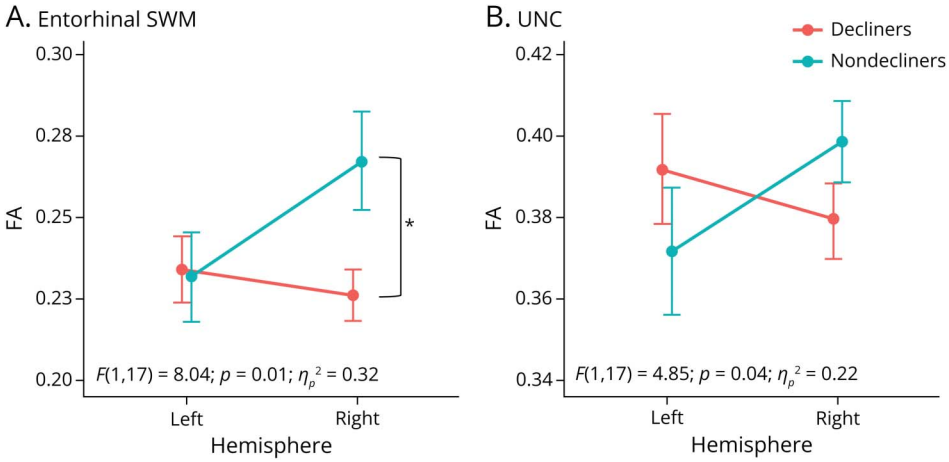
To examine the sensitivity of the imaging LIs at the patient level, we evaluated individual prediction of memory decline in LTLE using binary logistic regressions, focusing on the combination of hippocampal volume and each WM predictor examined in multiple regression models. For LM II, a combined model of hippocampal volume and entorhinal LI correctly classified 79% of patients (area under the curve [AUC] 0.89; $p < 0.01$; 95% CI [0.73, 1.0]; χ^2 [2] = 10.1; $p = 0.006$; sensitivity 82%, specificity 75%, positive predictive value [PPV] 82%, negative predictive value [NPV] 75%). The entorhinal LI contributed the most in terms of predictive power (Wald χ^2 [1] = 3.63; odds ratio [OR] 1.3; 95% CI [0.99, 1.61]; $p = 0.057$). A combined model of hippocampal volume and UNC LI correctly classified 68% of patients (AUC 0.83; $p < 0.05$; 95% CI [0.63, 1.0]; χ^2 [2] = 7.9; $p = 0.02$; sensitivity 63%, specificity 73%, PPV 63%, NPV 73%). The UNC LI contributed the most in terms of predictive power (Wald χ^2 [1] = 2.42; OR 1.3; 95% CI [0.93, 1.90]; $p = 0.12$). The Hosmer and Lemeshow test indicated good model fit for entorhinal and UNC models, respectively (ps = 0.82 and 0.25).

For VPA II, a combined model of hippocampal volume and entorhinal LIs approached significance (χ^2[2] = 4.8; $p = 0.09$) and correctly classified 81% of the patients (AUC 0.79; p = 0.05; 95% CI [0.56, 1.0]; sensitivity 83%, specificity 80%, PPV 71%, NPV 89%), with good model fit ($p = 0.36$). The entorhinal LI contributed the most predictive power (Wald χ^2[1] = 2.16; OR 1.13; 95% CI [0.96, 1.34]; $p = 0.14$). A combined model of hippocampal volume and UNC LI was not significant (classification accuracy 56%; $p = 0.344$). eFigure 4 (links.lww.com/WNL/B778) shows ROC curves for these models.

Discussion

The primary goal of this study was to examine asymmetry of deep WM and SWM networks in TLE in order to evaluate

Figure 3 Preoperative White Matter Integrity by Hemisphere in Decliners vs Nondecliners in LTLE



Significant 2-way interactions between hemisphere (left vs right) and group (decliners vs nondecliners) in left temporal lobe epilepsy (LTLE) with fractional anisotropy (FA) as the dependent variable, plotted separately for (A) entorhinal superficial white matter (SWM) and (B) uncinate fasciculus (UNC).

how radiographic markers of structural adequacy of the ipsilateral WM and structural reserve of the contralateral WM relate to postsurgical memory decline. These measures are akin to the concepts of functional adequacy and reserve[12] derived from studies of functional integrity of the hippocampus, but focus on the microstructural integrity of the underlying networks derived from DWI. Our most robust finding was that for individuals who underwent left ATL, leftward asymmetry (i.e., more left-lateralized FA) of the SWM adjacent to the entorhinal cortex was associated with greater decline in prose and associative memory and was the strongest predictor. A model that included entorhinal LI together with hippocampal volume LI correctly classified 79% and 81% of patients with LTLE declining in prose and associative memory, respectively. In addition, leftward asymmetry of the UNC was uniquely associated with postoperative change in prose recall in LTLE, independent of presurgical score, hippocampal volume, and entorhinal SWM asymmetry. These data suggest that presurgical integrity of the MTL WM network is important to the prediction of memory decline, above and beyond volume of the hippocampus.

The importance of the hippocampus to presurgical memory functioning and risk for postoperative decline is well documented; however, the network of extrahippocampal structures

Table 4 Results of Robust Linear Regression Analyses for Left Temporal Lobe Epilepsy With Preoperative to Postoperative Memory Change Scores as Dependent Variables

	β	B	SE (B)	*t*	95% CI	*p* Value
LM II (n = 19)[a]						
Preoperative score	−0.39	−0.41	0.13	−3.18	−0.69, −0.13	0.007[c]
Hippocampal volume LI	−0.37	−0.08	0.03	−3.09	−0.14, −0.02	0.008[c]
UNC FA LI	−0.31	−0.16	0.07	−2.27	−0.31, −0.01	0.039[c]
Entorhinal SWM FA LI	−0.46	−0.17	0.05	−3.42	−0.28, −0.06	0.004[c]
VPA II (n = 16)[b]						
Preoperative score	−0.52	−0.34	0.16	−2.09	−0.71, 0.02	0.061
Hippocampal volume LI	−0.67	−0.10	0.04	−2.70	−0.17, −0.02	0.021[c]
UNC FA LI	0.38	0.15	0.08	1.79	−0.03, 0.33	0.102
Entorhinal SWM FA LI	−0.68	−0.17	0.06	−3.02	−0.30, −0.05	0.012[c]

Abbreviations: B = unstandardized coefficient estimate; FA = fractional anisotropy; LI = laterality index (left – right/left + right) * 100; LM = Logical Memory; SWM = superficial white matter; UNC = uncinate fasciculus; VPA = Verbal Paired Associates.
CI for B estimates is provided. Dependent variables represent the difference between preoperative and postoperative age-adjusted scaled scores on LM II and VPA II.
[a] Full model: R^2 = 0.80; adjusted R^2 = 0.74.
[b] Full model: R^2 = 0.65; adjusted R^2 = 0.52.
[c] *p* Values that survive 5% false discovery rate (Benjamini-Hochberg) correction within each model.

is increasingly recognized as important to memory performance in TLE.[9] In our study, asymmetry of the WM microstructure beneath the entorhinal cortex was the strongest independent predictor of prose memory decline. Microstructural integrity of the entorhinal SWM includes the perforant path, which provides major afferent connections from the entorhinal cortex to CA3 and the dentate gyrus of the hippocampus, and is important to memory performance.[17,35] Surgery-induced damage to this white matter path would disrupt communication between the entorhinal cortex and the hippocampus, contributing to worsening memory impairments. This may also explain why some patients with normal hippocampal volume harbor verbal memory impairments before surgery,[36] and underscores the importance of a broader MTL network to memory impairment in TLE. Likewise, our data suggest that presurgical structural integrity of both the hippocampus and entorhinal SWM are important to the prediction of prose and associative memory decline after ATL.

We also found that integrity of the UNC was an independent predictor of prose memory decline, even after controlling for entorhinal WM integrity and hippocampal volume. The UNC is a long-range WM tract with bidirectional connections between the anterior temporal lobes and frontal cortices (Figure 1) and is often severed during ATL.[27] Our finding that higher left lateralization of the UNC FA was associated with greater prose memory decline is consistent with preoperative studies linking reduced WM integrity of the UNC to verbal memory impairment.[14,15,24] Whereas the UNC has been previously implicated in object naming and semantic memory retrieval,[27] it may also be important for accurate prose recall, which relies on retrieval of semantically associated information mediated by frontal and anteriolateral temporal cortex.[27] Unlike previous studies,[14,25] we did not find any association between microstructural asymmetry of the ILF and memory decline in LTLE or RTLE. Although the reason for this is unclear, it may be that the memory tasks employed herein depend more on frontotemporal network integrity than connections between anterior and posterior temporo-occipital cortex. Nevertheless, our work builds upon prior studies by demonstrating the importance of the UNC to the MTL memory network in TLE, whose integrity is a key risk factor for postoperative memory decline.

Risk for episodic memory decline is believed to depend on both the integrity of the tissue removed (functional adequacy model) and the integrity of contralateral networks (functional reserve).[12] Although both models have good empirical support, they have been mainly applied in the context of hippocampal structure or function using fMRI[32,37] or the intracarotid amobarbital procedure[38] (i.e., Wada procedure). Our findings support an extension of these models to consider the microstructural adequacy and reserve of surrounding MTL WM networks using DWI. Although our primary analyses focused on microstructural asymmetry, when we examined left and right hemisphere WM integrity separately, better verbal memory outcomes following left ATL were associated with higher integrity of right hemisphere WM, particularly of the entorhinal SWM. Furthermore, the group of LTLEs that showed decline had lower preoperative right hemisphere FA than the group that did not decline, particularly in the entorhinal WM FA. Our finding of contralateral hemisphere associations with postoperative memory decline extends the functional reserve model to reflect importance of not just the contralateral hippocampus but also the integrity of the broader contralateral memory network. Although our findings suggest a structural reserve correlate, it is unclear how much this reflects preservation of WM integrity of the contralateral hemisphere (i.e., brain reserve) vs functional reorganization to that hemisphere. Although previous studies found that preoperative interhemispheric language reorganization in LTLE (measured with fMRI) was associated with alterations to perisylvian white matter (i.e., a rightward shift),[39] future inclusion of an fMRI memory task would address this question directly.

Our findings have important clinical implications for patients with TLE undergoing surgical consideration because of the debilitating effects that memory decline can have on quality of life. Although much of the literature has focused on hippocampal volume, patients with hippocampal sparing surgery can still experience significant memory decline if surrounding structures are removed.[40] For example, tailored ATLs that spare the hippocampus can result in verbal memory decline when entorhinal and perirhinal cortices are included in the resection.[41] Furthermore, there is evidence that a greater extent of entorhinal resection predicts greater memory decline after ATL.[30] Despite an increased understanding of the importance of deep WM and SWM networks to successful memory performance in TLE,[13-16] the relationship between integrity of these networks and risk for postoperative memory decline has been vastly understudied. A few studies reported associations between WM and postoperative language deficits,[42,43] but to our knowledge similar studies do not exist for memory outcomes. Our data suggest that integrity of the UNC and WM beneath the entorhinal cortex may be important biomarkers for memory decline, potentially augmenting knowledge of the hippocampal network during presurgical planning. This is especially important because many patients with TLE with normal-appearing MRIs harbor increased risk for memory decline, and for these patients, WM integrity and brain reserve may be critical predictors of outcomes. Understanding how different MTL structures and WM networks contribute to memory is becoming increasingly important as we move toward more targeted surgeries[45] (e.g., stereotactic laser amygdalohippocampotomy [SLAH]) that mainly target the basal amygdala and hippocampus, but may also include a portion of the entorhinal cortex and collateral WM. In fact, existing studies have observed less semantic (e.g., naming) decline after SLAH than ATL,[46] and this has largely been attributed to the sparing of adjacent WM networks. However, the data on effects of SLAH on episodic memory are more variable.[47] Whether sparing key WM structures (e.g., entorhinal SWM) during

SLAH will lead to improved memory outcomes relative to ATL will require additional head-to-head comparisons.

Our study has several limitations. Our sample size was modest, which may have limited statistical power and prevented us from examining more complex models with a broader range of clinical and imaging variables. Despite this, we were still able to explain 52%–74% in verbal memory change, and our WM predictors survived stringent multiple comparison correction. We also took a rigorous approach to reduce the likelihood of spurious findings, including (1) choosing a priori defined regions that have been previously linked to verbal memory in TLE, (2) hierarchical robust regression analyses that use model comparison to evaluate the contribution of laterality indices, and (3) inclusion of 2 verbal memory measures that showed consistent patterns. Nonetheless, these findings are preliminary and should be replicated in a larger sample. We did not have memory fMRI to evaluate functional reorganization of memory in our sample. Thus, whether our WM findings truly reflect the functionality of underlying WM networks will require future studies that combine DWI with fMRI or other functional imaging modalities. We focused on 2 forms of verbal memory—associative and prose memory. Prose memory is known to moderately correlate with hippocampal volume in TLE,[48] but it may rely more on extrahippocampal regions (e.g., lateral temporal and frontal cortex) than, for example, measures of associative memory or list-learning. Consistent with this idea, our findings revealed larger effects of WM contributions to prose than to associative memory. It is possible that we did not observe an association between WM asymmetry and visual memory decline due to psychometric limitations of visual memory tests, including the BVMT.[49] Despite the known importance of the fornix to memory and its connections to the hippocampus, we did not include it in our analysis because the fornix is challenging to reliably reconstruct due to its narrow size and high bending angle, and is subject to significant partial voluming.[50] Advanced diffusion sequences with HARDI models are better suited to reliably reconstruct the fornix and evaluate its contribution to postoperative memory decline. Although we evaluated the contribution of MTL WM to memory outcomes, these fibers may also be important predictors of decline in other cognitive domains such as executive function. In particular, understanding how preoperative WM network patterns contribute to risk for combinations of cognitive impairments post-ATL (i.e., cognitive phenotypes[16]) is of interest, but necessitate a larger sample size than the present study. Finally, our sample was predominantly White. Future studies with more racially and ethnically diverse samples would help to increase the generalizability of our results.

Taken together, our findings add to a growing literature demonstrating the importance of deep WM and SWM to memory performance in TLE. We highlight the ability of microstructural asymmetry of the MTL network to predict verbal memory decline following ATL at the individual patient level. These findings may eventually help to guide more tailored surgical approaches in TLE with the combined goal of maximizing the likelihood of seizure freedom while minimizing memory decline.

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Disclosure

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Appendix Authors

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Erik Kaestner, PhD	University of California, San Diego	Analyzed the data; drafted the manuscript for intellectual content
Anny Reyes, MS	University of California, San Diego	Interpreted the data; revised the manuscript for intellectual content
Sanam Lalani, PhD	University of California, San Diego	Interpreted the data; revised the manuscript for intellectual content
Brianna M. Paul, PhD	University of California, San Francisco	Interpreted the data; revised the manuscript for intellectual content
Manu Hegde, MD, PhD	University of California, San Francisco	Interpreted the data; revised the manuscript for intellectual content
Jonathan L. Helm, PhD	San Diego State University	Statistical consultation; revised the manuscript for statistical content
Sharona Ben-Haim, MD	University of California, San Diego	Interpreted the data; revised the manuscript for intellectual content
Carrie R. McDonald, PhD	University of California, San Diego	Designed and conceptualized study; analyzed the data; drafted the manuscript for intellectual content

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