Title

Cognitive phenotypes in temporal lobe epilepsy are associated with distinct patterns of white matter network abnormalities.

Journal

Neurology, 92(17)

ISSN

0028-3878

Authors

Reyes, Anny
Kaestner, Erik
Bahrami, Naeim
et al.

Publication Date

2019-04-23

DOI

10.1212/wnl.0000000000007370

Peer reviewed

ARTICLE

Cognitive phenotypes in temporal lobe epilepsy are associated with distinct patterns of white matter network abnormalities

Anny Reyes, MS, Erik Kaestner, PhD, Naeim Bahrami, PhD, Akshara Balachandra, BS, Manu Hegde, MD, PhD, Brianna M. Paul, PhD, Bruce Hermann, PhD, and Carrie R. McDonald, PhD

Neurology® 2019;92:e1957-e1968. doi:10.1212/WNL.0000000000007370

Correspondence
Dr. McDonald
camcdonald@ucsd.edu

Abstract

Objective

To identify distinct cognitive phenotypes in temporal lobe epilepsy (TLE) and evaluate patterns of white matter (WM) network alterations associated with each phenotype.

Methods

Seventy patients with TLE were characterized into 4 distinct cognitive phenotypes based on patterns of impairment in language and verbal memory measures (language and memory impaired, memory impaired only, language impaired only, no impairment). Diffusion tensor imaging was obtained in all patients and in 46 healthy controls (HC). Fractional anisotropy (FA) and mean diffusivity (MD) of the WM directly beneath neocortex (i.e., superficial WM [SWM]) and of deep WM tracts associated with memory and language were calculated for each phenotype. Regional and network-based SWM analyses were performed across phenotypes.

Results

The language and memory impaired group and the memory impaired group showed distinct patterns of microstructural abnormalities in SWM relative to HC. In addition, the language and memory impaired group showed widespread alterations in WM tracts and altered global SWM network topology. Patients with isolated language impairment exhibited poor network structure within perisylvian cortex, despite relatively intact global SWM network structure, whereas patients with no impairment appeared similar to HC across all measures.

Conclusions

These findings demonstrate a differential pattern of WM microstructural abnormalities across distinct cognitive phenotypes in TLE that can be appreciated at both the regional and network levels. These findings not only help to unravel the underlying neurobiology associated with cognitive impairment in TLE, but they could also aid in establishing cognitive taxonomies or in the prediction of cognitive course in TLE.

From the San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology (A.R.); Center for Multimodal Imaging and Genetics (A.R., E.K., N.B., A.B., C.R.M.) and Department of Psychiatry (C.R.M.), University of California, San Diego; Department of Neurology (M.H., B.M.P.), University of California, San Francisco; UCSF Comprehensive Epilepsy Center (M.H., B.M.P.), San Francisco; Matthews Neuropsychology Section (B.H.), University of Wisconsin–Madison; and UCSD Comprehensive Epilepsy Center (C.R.M.), San Diego, CA.

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

AD = Alzheimer disease; **AED** = antiepileptic drug; **ANOVA** = analysis of variance; **ARC** = arcuate fasciculus; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FDR** = false discovery rate; **FOV** = field of view; **HC** = healthy control; **ILF** = inferior longitudinal fasciculus; **MD** = mean diffusivity; **MTS** = mesial temporal sclerosis; **ROI** = region of interest; **STG** = superior temporal gyrus; **SWM** = superficial white matter; **TE** = echo time; **TLE** = temporal lobe epilepsy; **TR** = repetition time; **UNC** = uncinate fasciculus; **WM** = white matter.

Cognitive dysfunction is a highly prevalent and debilitating comorbidity in patients with temporal lobe epilepsy (TLE).[1,2] Up to 80% of patients with TLE demonstrate impairments in at least one cognitive domain, most frequently in language or memory.[3–5] Despite the high prevalence of cognitive dysfunction in TLE, there is considerable variability in the nature and severity of impairments observed across patients, some demonstrating generalized impairment, some specific cognitive deficits, and others with normal cognition.[6]

Recently, studies have attempted to understand the heterogeneity in TLE by identifying cognitive phenotypes and examining the neuroanatomical correlates associated with each subtype.[7–9] These studies have revealed that patients with generalized cognitive impairment demonstrate widespread cortical thinning,[8] subcortical atrophy,[7] and diffuse white matter (WM) compromise,[9] whereas patients with normal cognitive profiles demonstrate minimal structural abnormalities. These studies revealed that the type and degree of cognitive impairment is associated with the extent of brain abnormalities in TLE. However, more precise characterization of patients according to domain-specific cognitive impairment is warranted and could provide new insights into the neuroanatomical substrates of cognitive dysfunction in TLE.

In this study, we identify unique cognitive phenotypes in TLE based on patterns of language and memory impairment and examine microstructural alterations associated with each phenotype. We accomplish this by evaluating patterns of WM disruption within deep, long-range association tracts and within the WM directly beneath the cortex, using both a regional and a network-based approach. We hypothesize that distinct cognitive phenotypes can be identified with unique patterns of network disruption that underlie the neuropsychological heterogeneity of TLE. Specifically, patients with isolated memory or language impairment will demonstrate significant mesial vs lateral temporal pathology, respectively, whereas those with impairment in both domains will demonstrate widespread frontotemporal pathology that is more pronounced within the left hemisphere. Finally, we anticipate patients with no impairment will show minimal regional or network-based pathology.

Methods

Participants

This study was approved by the institutional review boards at UC San Diego and UC San Francisco, and informed consent was collected from all participants. Seventy patients with TLE and 46 healthy controls (HC) met inclusion/exclusion criteria for the study. All patients were recruited through referral from the UC San Diego or UC San Francisco Epilepsy Centers. Inclusion criteria for patients included a TLE diagnosis by a board-certified neurologist with expertise in epileptology, in accordance with the criteria defined by the International League Against Epilepsy, and based on video-EEG telemetry, seizure semiology, and neuroimaging evaluation. The presence of mesial temporal sclerosis (MTS) was determined by inspection of MRI by a board-certified neuroradiologist. In 35 patients, MRI findings suggested the presence of ipsilateral MTS and the remaining patients demonstrated normal MRI. Patients were excluded if there was evidence on video-EEG of extratemporal seizure onset or the presence of a mass lesion on MRI. HC were included if they were between the ages of 18 and 65 and had no reported history of neurologic or psychiatric disease.

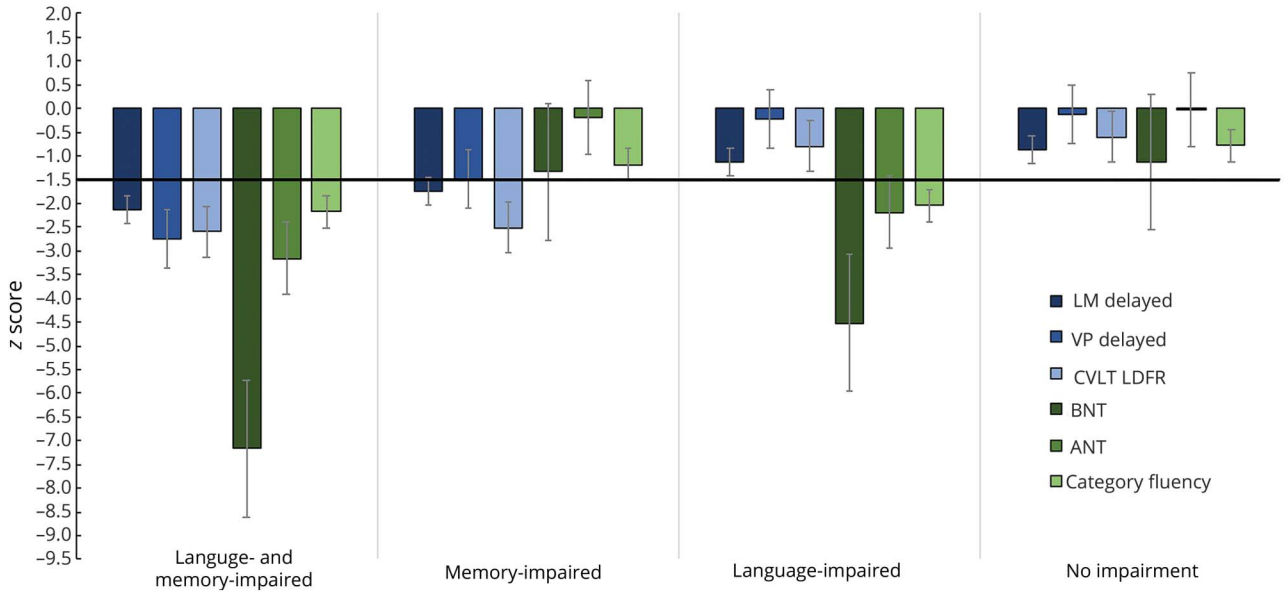
Neuropsychological measures

Neuropsychological data were available for all patients and HC. Verbal memory was evaluated with the California Verbal Learning Test–Second Edition[10] long delayed free recall and the Wechsler[11] Memory Scale–Third Edition logical memory delayed and verbal paired associates delayed. Language ability was also evaluated with the Boston Naming Test,[12] Auditory Naming Test,[13] and Category Fluency subtest of the Delis-Kaplan Executive Function System.[14]

Cognitive phenotyping

The cognitive phenotypes were derived using the 3 measures of verbal memory and 3 measures of language described above. Raw scores for all patients' neuropsychological data were converted into z scores based on the mean of the HC data. Impairment was defined as 1.5 SD below the mean of the HC. According to procedures outlined by Edmonds et al.,[15] patients were determined to be impaired in a given domain (i.e., memory or language) if 2 or more of the 3 cognitive tests fell within the impairment range. Four distinct cognitive phenotypes were derived: (1) patients impaired on both language and memory measures (language and memory impaired); (2) patients impaired on memory measures only (memory impaired); (3) patients impaired on language measures only (language impaired); and (4) patients with no evidence of impairment on language or memory measures (no impairment) (figure 1). Twenty-four percent of patients were impaired in both language and memory, 20% were impaired in memory only, 29% were

Figure 1 Distribution of language and memory performance across cognitive phenotypes



Mean *z* scores on measures of language and memory across cognitive phenotypes. Error bars represent SDs. Impairment was defined as 1.5 SD below the mean of healthy controls (represented as horizontal black line). ANT = Auditory Naming Test; BNT = Boston Naming Test; CVLT LDFR = California Verbal Learning Test Long Delayed Free Recall; LM = logical memory; VP = verbal paired associates.

impaired in language measures only, and 27% were not impaired in either domain.

MRI acquisition

MRI data were collected on a GE (Fairfield, CT) Discovery MR750 3T scanner with an 8-channel phased-array head coil at the Center for Functional MRI at UC San Diego or the Surbeck Laboratory for Advanced Imaging at UC San Francisco. Image acquisitions on the 3T scanner were identical at both centers and included a conventional 3-plane localizer, GE calibration scan, a T1-weighted 3D customized fast spoiled gradient-recalled echo structural sequence (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 1.2 mm), and for diffusion MRI, a single-shot pulse-field gradient spin-echo echoplanar imaging sequence (TR 8,000 ms, TE 82.9 ms, flip angle 90°, FOV 240 mm, matrix 96 × 96, slice thickness 2.5 mm, echo-spacing 588 ms). Diffusion data used for the diffusion tensor imaging (DTI) analysis were acquired with b-value = 0 and 1,000 s/mm^2 with 30 unique gradient directions. For use in nonlinear B_0 distortion correction, 2 additional b = 0 volumes were acquired with either forward or reverse phase-encode polarity.

DTI processing

Preprocessing of the diffusion 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 B0 distortion correction, a reverse gradient method was used.[16] A detailed description of the image processing is provided elsewhere.[17] DTI-derived fractional anisotropy (FA) and mean diffusivity (MD) were calculated based on a tensor fit to the b = 1,000 data.

Superficial WM (SWM) calculations

Individual T1-weighted MRIs were used for cortical surface reconstruction and parcellation using FreeSurfer, 5.3.0.[18] FA and MD for the SWM were calculated by sampling 1 mm below the pial surface normal at each vertex. To improve signal-to-noise ratio, all surface-based measures were smoothed on the average surface using a 20-mm full width at half maximum Gaussian kernel. Vertex-wise maps of FA and MD for the SWM were created for each individual and then averaged into a spherical representation to align sulcal and gyral features allowing for accurate matching of FA and MD measurement locations at the individual level, while minimizing metric distortion.[19]

Fiber tract calculations

Fiber tract FA and MD values were derived using a probabilistic diffusion tensor atlas that was developed using in-house software written in MATLAB, which has been validated in HC and patients with TLE.[20] For each participant, T1-weighted images were used to nonlinearly register the brain to a common space, and diffusion tensor orientation estimates were compared to the fiber tract atlas to obtain a map of the relative probability of a voxel belonging to a particular fiber tract, given the location and similarity of diffusion orientations. Voxels identified with FreeSurfer as CSF or cortical gray matter were excluded from the fiber regions of interest (ROIs). Fiber tracts were segmented in this way for each individual, and mean FA and MD values were calculated based on that participant's diffusion data. A

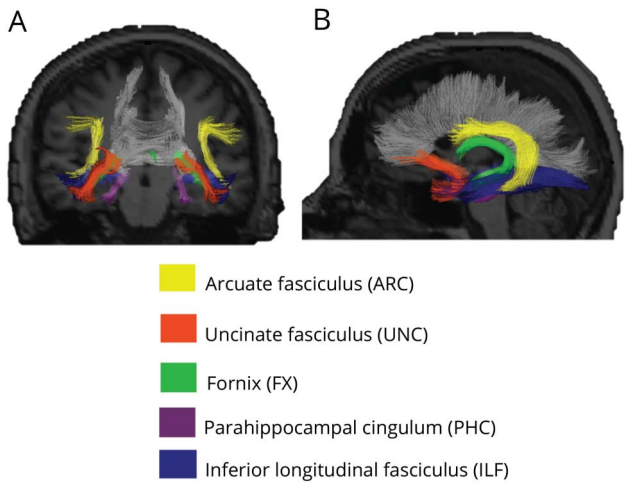
full description of the atlas is described elsewhere.[20] In the current study, the method described above was used to reconstruct the following tracts because they are among the most frequently implicated in verbal memory and language processing and are often reported to be compromised in TLE[21,22]: arcuate fasciculus (ARC), uncinate fasciculus (UNC), fornix, inferior longitudinal fasciculus (ILF), and parahippocampal cingulum (figure 2). Furthermore, decreases in FA and increases in MD within these tracts have been associated with impairment in language and memory in TLE and are sensitive to axonal loss and demyelination, respectively.[21–23]

Network analysis

Due to evidence that patients with TLE show less efficient network integration and oversegregation of cortical and subcortical networks relative to HC,[24] graph theoretical analysis was applied to the SWM data to determine whether cognitive phenotypes differ in their network microstructure covariance.[25–27] Estimates of FA were measured within 33 gyral-based ROIs per hemisphere[28] that were based on average estimates obtained from the unsmoothed data at each vertex within a given SWM ROI. A 66 × 66 symmetric-weighted matrix of the structural connectivity in the whole brain was constructed using Pearson correlations for each phenotype group and the HC as well as for the pooled group of all patients with TLE. Each correlation value in this matrix represents the covariance strength between 2 related nodes (i.e., ROIs).

For this study, we analyzed differences in 4 network-based measures: global efficiency, local efficiency, transitivity, and modularity, due to evidence that these measures are (1) sensitive to global and local network changes in TLE[24,25] or (2) implicated in cognitive functioning.[29,30] Group differences in each measure were tested over a wide range of network densities, $0.1 \leq S_{thr} \leq 0.5$, with the threshold incremented by 0.05, using the Brain Connectivity Toolbox.[31] Global efficiency is a measure of global network integration and is defined as the average inverse shortest path length.[32] Local efficiency is calculated using the global efficiency from the adjacent subgraph of the node and can be interpreted as local network connectivity representing regional topologic changes[31]; the local efficiencies across all nodes are then averaged to estimate the total network local efficiency. Transitivity is a measure of network segregation, such that greater transitivity indicates a tendency for nodes to be highly integrated within their local cluster.[33] This measure is similar to clustering coefficient. However, unlike clustering coefficient, transitivity is normalized collectively for all nodes and therefore is not influenced by the number of nodes in the network.[31] Finally, modularity describes the degree to which a network may be divided into nonoverlapping groups with a high number of within-module connections and a low number of between-module connections.[29,34] A detailed description of these graph theoretic measures, as well as the toolbox used to calculate them, are described in a review by Rubinov and Sporns.[31]

Figure 2 Deep white matter tracts of interest



(A) Coronal and (B) sagittal rendering of the arcuate fasciculus, uncinate fasciculus, fornix, parahippocampal cingulum, and inferior longitudinal fasciculus derived from AtlasTrack 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.

Statistical analysis

Independent *t* tests and Fisher tests were used to test differences in demographic variables between patients and HC. Analysis of variance (ANOVA) was conducted to compare clinical and demographic variables across the 4 cognitive phenotypes. Vertex-wise *t* tests were used for surface-based comparisons between each cognitive phenotype group and HC and corrected for multiple comparisons using a false discovery rate (FDR). ANOVA was conducted to compare FA and MD of fiber tracts across the 4 cognitive phenotypes and HC, correcting for multiple comparisons using FDR. When results from the ANOVA were significant, group contrasts were assessed using post hoc pairwise tests with Bonferroni correction.

For the graph theoretic measures, a subsampling methodology[26] was used to estimate a spread of values for the HC group for each measure at each network density level. Patient group values outside of the 0.0005 and 0.9995 percentile range (corresponding to a *p* value of 0.001) were considered significantly different from HC. Because the individual phenotype groups had fewer patients per group than the number of HC, to create the HC spread of values, a subsample of 18 HC, corresponding to the average size of the phenotype groups, was sampled 4,000 times.

Data availability statement

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

Demographics and patient clinical variables

There were no differences in age (t [114] = −0.020, p = 0.984) or sex distribution (Fisher exact = 0.383, p = 0.571) between patients with TLE and HC; however, as expected, HC had more years of education (t [114] = −5.715, p < 0.001) (table 1). There were no differences in age ($F_{3,66}$ = 0.869, p = 0.462), education ($F_{3,66}$ = 0.329, p = 0.805), sex distribution (Fisher exact 4.087, p = 0.699), handedness (Fisher exact 6.61, p = 0.083), duration of epilepsy ($F_{3,66}$ = 2.15, p = 0.102), seizure frequency ($F_{3,61}$ = 1.308, p = 0.280), number of antiepileptic drugs (AEDs; $F_{3,66}$ = 1.73, p = 0.169), MTS status (Fisher exact = 2.162, p = 0.533), or side of seizure onset (Fisher exact = 3.975, p = 0.707) across the 4 cognitive phenotype groups. However, there were differences in age at seizure onset ($F_{3,66}$ = 7.02, p < 0.001), with the memory impaired group demonstrating an older age at seizure onset relative to the language and memory (p = 0.023) and the language impaired (p < 0.001) groups.

Surface-based SWM abnormalities across cognitive phenotypes

The results of the surface maps for SWM FA and MD are presented in figure 3. Relative to HC, the language and memory group showed widespread reductions in FA in lateral temporal, parietal, frontocentral/cingulate, and lateral prefrontal regions bilaterally, coupled with highly left lateralized increases in MD that were pronounced within lateral temporal and orbitofrontal SWM. In the memory impaired group, higher MD was observed in the inferior and medial temporal lobe regions bilaterally, including parahippocampal, entorhinal, fusiform, and temporal pole, as well as the cingulate cortices (figure 3A). The language impaired and the no impairment group (not depicted) showed no differences in SWM FA or MD relative to HC that survived FDR correction. Post hoc comparisons across the cognitive subgroups revealed higher MD in the language and memory group compared to the no impairment group within left lateral temporo-parietal regions (figure 3B).

Differences in FA/MD of deep WM fiber tracts

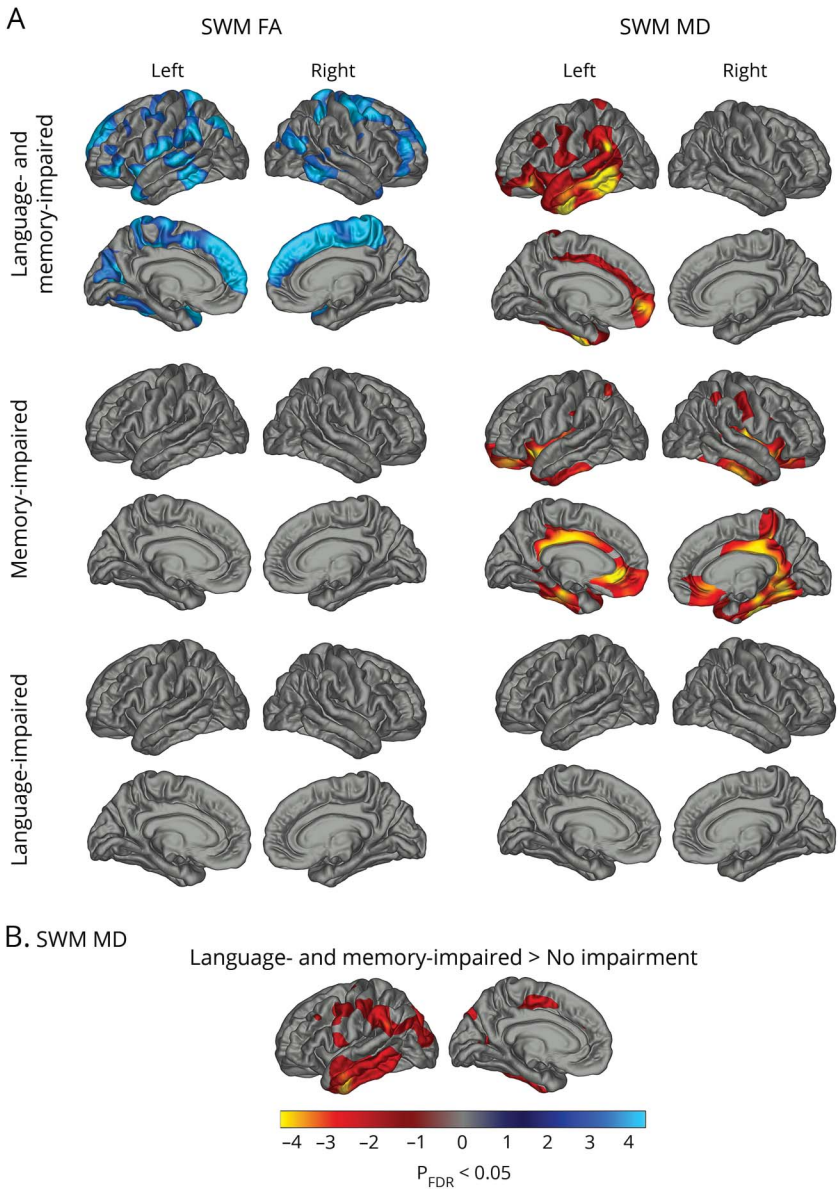
ANOVA revealed group differences in FA and MD of the ARC and ILF bilaterally and in FA of the left UNC (table 2). Pairwise comparisons revealed that the language and memory group had lower FA of the left and right ARC (left ARC: p = 0.004; right ARC: p = 0.018), the left and right ILF (left ILF: p = 0.005; right ILF: p = 0.011), and the left UNC (p < 0.01) relative to HC. They also showed higher MD of the left ILF relative to HC (p = 0.002). The memory impaired group showed higher MD of the right ILF relative to HC (p = 0.034) and the language impaired group demonstrated lower FA of right ILF relative to HC (p = 0.045).

Table 1 Demographics and clinical variables

	Temporal lobe epilepsy			Healthy controls
N	70			46
Age, y	36.14 (13.66)			36.19 (14.13)
Education	13.34 (2.26)			15.80 (2.33)
Sex: M/F	33/37			19/27
	Language and memory impaired	**Memory impaired**	**Language impaired**	**No impairment**
N	17	14	20	19
Age, y	36.06 (15.51)	40.14 (14.56)	32.60 (13.06)	37.00 (11.86)
Education, y	13.00 (2.85)	13.71 (2.19)	13.15 (2.28)	13.58 (1.57)
Sex: M/F	8/9	10/4	10/10	5/14
Handedness: L/R/A	2/14/1	2/11/1	1/19	2/17
MTS: yes/no	11/6	8/6	8/11	9/10
Side: L/R/bilateral	8/8/1	7/7	8/9/3	8/10
Age at onset, y	17.82 (12.08)	32.07 (16.50)	11.25 (12.12)	20.68 (14.17)
Duration, y	18.24 (19.22)	8.07 (8.87)	21.35 (13.47)	16.32 (16.89)
Number of AEDs	1.88 (0.857)	2.35 (0.633)	2.45 (0.887)	2.36 (0.83)
Seizure frequency[a]	6.10 (5.72)	6.83 (5.63)	4.47 (4.23)	4.05 (2.34)

Abbreviations: A = ambidextrous; AED = antiepileptic drug; MTS = mesial temporal sclerosis.
Standard deviations are presented inside the parentheses.
[a] Number of seizures per month. Patients with 2 standard deviations above the mean of the entire TLE group were removed from analysis.

Figure 3 Surface-based superficial white matter (SWM) abnormalities across cognitive phenotypes



(A) Surface-based mapping of SWM fractional anisotropy (FA) and mean diffusivity (MD) differences across cognitive phenotypes relative to healthy controls (HC) after correcting for multiple comparisons, $p_{FDR} < 0.05$. The color bar shows patients with either lower values than controls in blue/cyan or greater value than HC in red/yellow. (B) Post hoc comparison between the language and memory impaired group and the no impairment group in SWM MD. Increases in MD in the language and memory group are shown in red/yellow.

Post hoc comparisons across the patient subgroups showed that the language and memory group had lower FA of the left UNC relative to the language impaired group (p = 0.013). This group also showed higher MD of the left ARC relative to the no impairment group (p = 0.024), and a trend for higher MD of the left ILF relative to the no impairment group (p = 0.062). Given that patients in the memory impaired group had an older age at seizure onset and a trend for a longer duration of disease, we conducted a secondary analysis controlling for age at seizure onset and disease duration for WM tracts that were significant in the primary analysis. Similar results were obtained in this analysis, with the exception that the finding of higher MD of the left ARC in the language and memory impaired relative to the no impairment group only approached significance (p = 0.064). No other patient subgroup comparisons were significant.

Global and local network analysis

Whole-group analysis

When treated as a single group, patients with TLE showed decreased global efficiency across a consecutive range of network densities (10–35; $p < 0.001$), as well as increased transitivity (network densities: 15–50; $p < 0.001$) and decreased modularity (network densities: 10–20; $p < 0.001$) relative to HC (figure 4A).

Cognitive phenotypes analysis

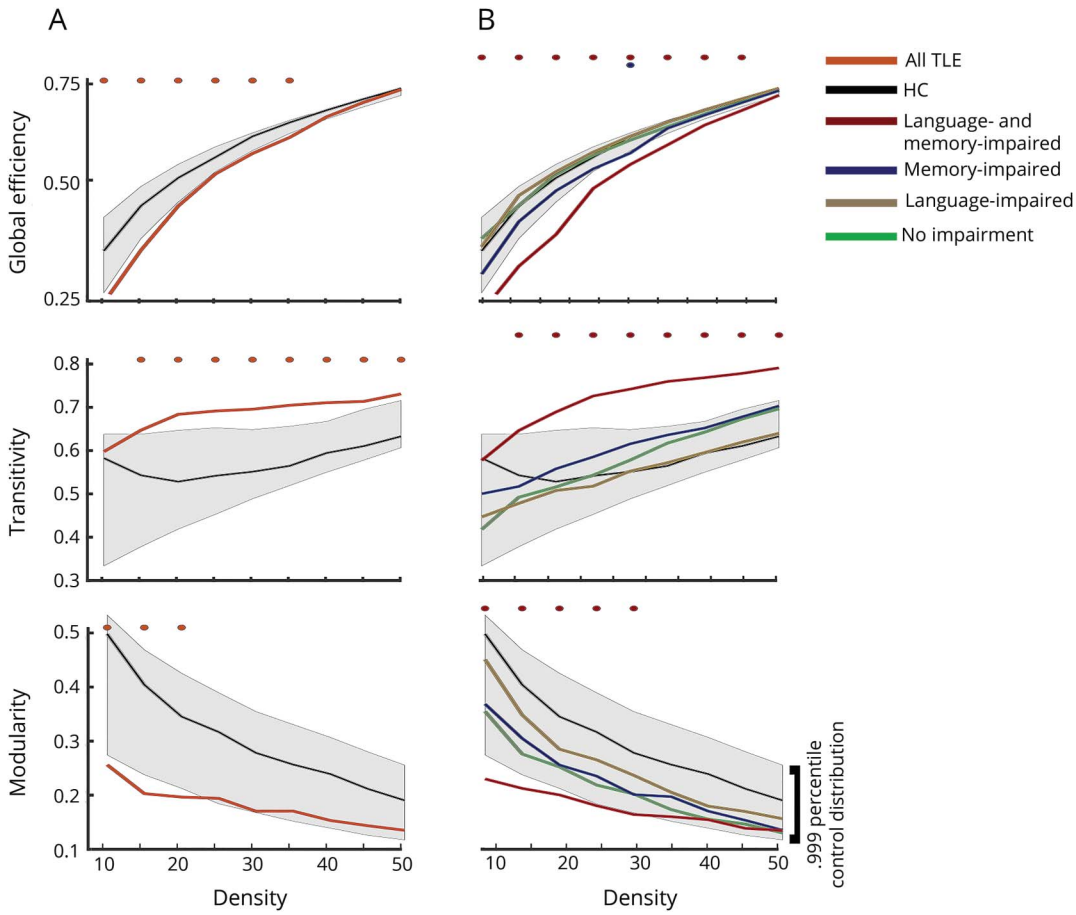
When analyzing the data separately for each cognitive phenotype, only the language and memory and memory impaired

Table 2 Fractional anisotropy (FA) and mean diffusivity (MD) group comparisons

	Language and memory impaired, mean (SD)	Memory impaired, mean (SD)	Language impaired, mean (SD)	No impairment, mean (SD)	HC, mean (SD)	ANOVA, *F* value	*p* Value
ARC							
Left							
FA	0.449 (0.044)[a]	0.473 (0.028)[a]	0.467 (0.031)[a]	0.466 (0.029)[a]	0.480 (0.024)[a]	3.600[a]	0.008[a]
MD	0.762 (0.030)[a]	0.757 (0.025)[a]	0.735 (0.025)[a]	0.720 (0.082)[a]	0.732 (0.025)[a]	3.478[a]	0.010[a]
Right							
FA	0.436 (0.033)[a]	0.459 (0.029)[a]	0.448 (0.039)[a]	0.448 (0.024)[a]	0.462 (0.023)[a]	3.147[a]	0.017[a]
MD	0.740 (0.049)	0.747 (0.036)	0.737 (0.040)	0.718 (0.089)	0.725 (0.030)	1.063	0.378
UNC							
Left							
FA	0.380 (0.062)[a]	0.416 (0.033)[a]	0.423 (0.031)[a]	0.408 (0.046)[a]	0.431 (0.028)[a]	5.663[a]	<0.001[a]
MD	0.832 (0.088)	0.815 (0.028)	0.795 (0.038)	0.793 (0.085)	0.779 (0.046)	2.858	0.027
Right							
FA	0.388 (0.049)	0.409 (0.027)	0.398 (0.030)	0.396 (0.039)	0.414 (0.255)	2.553	0.044
MD	0.778 (0.098)	0.816 (0.032)	0.793 (0.060)	0.787 (0.111)	0.777 (0.064)	0.821	0.515
FX							
Left							
FA	0.304 (0.037)	0.295 (0.037)	0.291 (0.039)	0.297 (0.043)	0.307 (0.030)	0.876	0.481
MD	1.216 (0.346)	1.33 (0.357)	1.259 (0.261)	1.212 (0.197)	1.187 (0.231)	0.964	0.430
Right							
FA	0.314 (0.080)	0.318 (0.037)	0.290 (0.050)	0.298 (0.032)	0.313 (0.033)	1.336	0.261
MD	1.147 (0.333)	1.332 (0.355)	1.233 (0.262)	1.226 (0.189)	1.234 (0.250)	0.902	0.466
PHC							
Left							
FA	0.326 (0.085)	0.347 (0.063)	0.342 (0.046)	0.327 (0.056)	0.367 (0.051)	2.488	0.047
MD	0.876 (0.241)	0.846 (0.062)	0.802 (0.088)	0.811 (0.121)	0.777 (0.111)	2.038	0.094
Right							
FA	0.332 (0.112)	0.330 (0.046)	0.337 (0.079)	0.327 (0.079)	0.370 (0.075)	1.597	0.180
MD	0.870 (0.265)	0.889 (0.067)	0.800 (0.146)	0.804 (0.185)	0.755 (0.173)	2.248	0.068
ILF							
Left							
FA	0.440 (0.029)[a]	0.459 (0.037)[a]	0.454 (0.034)[a]	0.462 (0.036)[a]	0.471 (0.022)[a]	3.623[a]	0.008[a]
MD	0.853 (0.050)[a]	0.847 (0.027)[a]	0.827 (0.044)[a]	0.805 (0.091)[a]	0.797 (0.056)[a]	5.361[a]	0.001[a]
Right							
FA	0.438 (0.027)[a]	0.451 (0.022)[a]	0.445 (0.029)[a]	0.449 (0.029)[a]	0.463 (0.022)[a]	3.703[a]	0.007[a]
MD	0.809 (0.066)[a]	0.840 (0.022)[a]	0.820 (0.076)[a]	0.784 (0.097)[a]	0.782 (0.044)[a]	3.196[a]	0.016[a]

Abbreviations: ARC = arcuate fasciculus; FX = fornix; HC = healthy control; ILF = inferior longitudinal fasciculus; PHC = parahippocampal cingulum; UNC = uncinate fasciculus.
[a] Significant at a false discovery rate correction of q* = 0.02.

Figure 4 Global network measures



(A) Plots show differences in global efficiency, transitivity, and modularity between healthy controls (HC) and the whole temporal lobe epilepsy (TLE) group across network densities. Shaded areas represent the upper and lower bounds of each measure in HC. (B) Differences in global efficiency, transitivity, and modularity between HC and each cognitive phenotype. Colored circles represent significant difference between HC and patients.

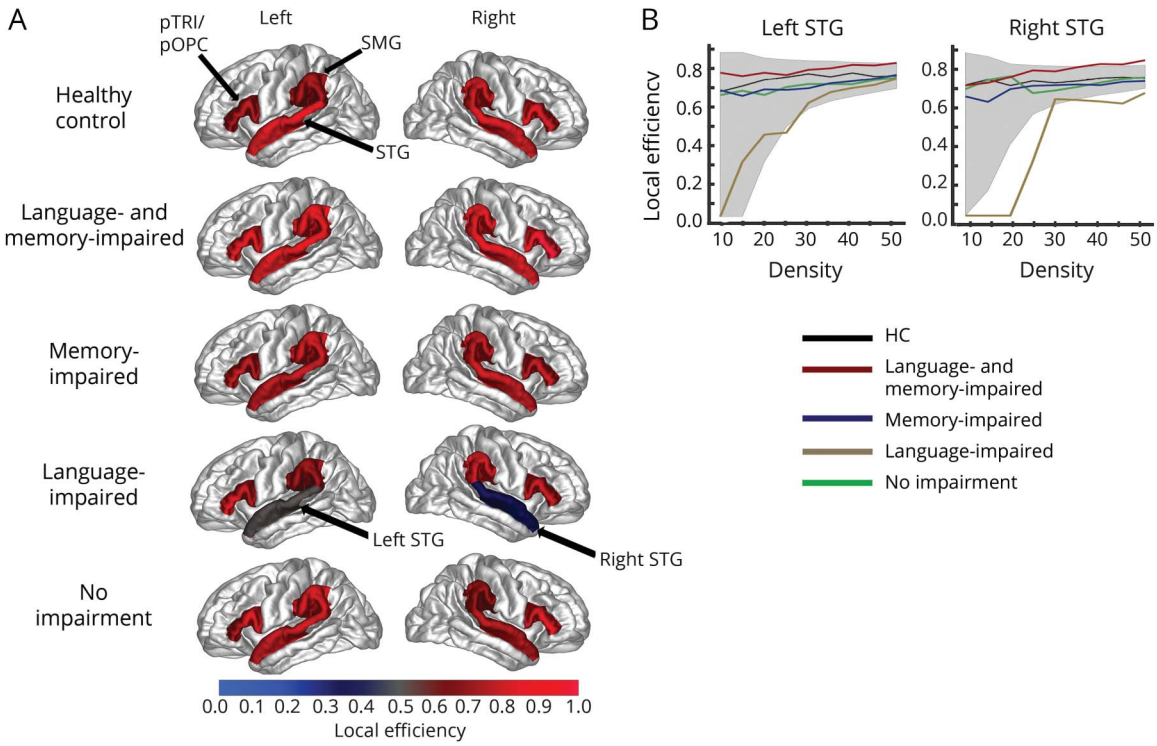
groups showed significant differences from HC. The language and memory group showed decreased global efficiency (network densities: 10–45; $p < 0.001$), increased transitivity (network densities: 15–50; $p < 0.001$), and decreased modularity (network densities: 10–30; $p < 0.001$). The memory impaired group demonstrated decreased global efficiency relative to HC at a network density of 30 ($p < 0.001$). Neither the no impairment nor the language impaired group displayed any significant differences in global network structure from HC.

Given that the language impaired group failed to show any differences in the regional or global network SWM analyses, a post hoc subnetwork analysis was performed to determine if the language impaired group differed in their network structure within classic language (i.e., perisylvian) regions. For this analysis, local efficiency was selected and tested within the pars triangularis/pars opercularis, superior temporal gyrus (STG), and supramarginal gyrus. One region, the STG, displayed significantly decreased local efficiency for the language impaired group, bilaterally ($p < 0.05$; figure 5, A and B). No other group differed from HC across perisylvian regions.

Discussion

In this study, we identify 4 distinct cognitive phenotypes within TLE and demonstrate that each phenotype is associated with a unique pattern of WM abnormalities. Specifically, we show that patients in the language and memory and memory impaired groups show pronounced microstructural changes within widespread SWM regions and deep WM association tracts implicated in language and memory.[21] These findings were particularly pronounced for those in the language and memory impaired group at both the regional and global network levels. Finally, we show that patients in the language impaired group show abnormal network structure within perisylvian SWM, despite relatively intact global network structure. Collectively, our findings suggest that distinct cognitive phenotypes exist in TLE that are not differentiated or explained by known clinical characteristics. Rather, these different phenotypes appear to be characterized by underlying neurobiological differences in their regional WM microstructure and network topology.

Figure 5 Local efficiency differences within perisylvian regions



(A) Local efficiency differences between healthy controls (HC) and each cognitive phenotype in pars triangularis (pTRI)/pars opercularis (pOPC), superior temporal gyrus (STG), and supramarginal gyrus (SMG). Significant differences from HC are depicted in gray/blue within each region of interest. (B) Differences in local efficiency within the left and right STG between HC and each cognitive phenotype across different network densities. Shaded areas represent the upper and lower bounds in local efficiency for HC.

Cognitive dysfunction is the most common comorbidity in TLE, with impairments in language and memory accounting for a majority of this comorbidity.[1,2,4,6,35] A number of factors have been identified as playing a pivotal role in the cognitive dysfunction observed in TLE, including the presence of MTS,[36] the type and frequency of seizures,[3] age at seizure onset,[37] duration of disease,[6] and the effects of AEDs.[38] Interestingly, not all patients with TLE demonstrate cognitive dysfunction, even when they share similar clinical characteristics to those who do. In our study, 1/4 of the patients were impaired in both language and memory, while approximately half of the sample had isolated memory or language impairment and the remaining patient sample demonstrated a relatively normal cognitive profile. In particular, patients who were impaired in both language and memory showed the poorest performance across all measures, indicating more pervasive cognitive dysfunction relative to those with domain-specific impairments (i.e., memory impaired and language impaired). This group of patients may reflect those described as having "generalized impairment" in Hermann et al.,[7] where approximately 29% of patients in their study demonstrated impairment in memory, language, executive function, and processing speed. Of interest, this patient group was at risk for cognitive progression over a 4-year interval, whereas their other groups (i.e., memory impaired, minimally impaired) showed minimal progression over time. In addition, we replicate their prior findings of a subgroup of patients with isolated memory deficits (20%) and of a sizable group with no significant impairments (27%). Importantly, we expand this literature by further characterizing cognitive profiles in a large cohort of patients using a priori neuropsychological criteria that have been shown to produce meaningful cognitive subtypes in other neurologic disorders.[15,39] By doing so, we were able to identify a unique group (language impaired) that constituted 29% of our sample and may be best described as harboring a significant anomia (figure 1). Despite the range in cognitive performances across the 4 phenotypes, our groups demonstrated relatively similar clinical features (table 1). Therefore, we purport that the nature and extent of cognitive dysfunction observed in TLE cannot be fully explained by common clinical characteristics (i.e., MTS, side of onset, AEDs), and that treating patients with TLE as a single group may obscure important cognitive and neuroanatomical variability across patient samples. In addition, given the evidence that different cognitive phenotypes may be at differential risk for cognitive progression,[7] the cognitive course of patients with normal cognitive profiles or with generalized impairments may not be fully appreciated when comparing these patients to the "average" cognitive profile described in the TLE literature. Therefore, a finer characterization of cognitive phenotypes is warranted and could aid in the prediction of individual cognitive trajectories.

The WM directly beneath the cortex (i.e., the SWM) has been shown to be particularly important for cognition given its key role in maintaining cortico–cortical connectivity.[40–42] Furthermore, there is evidence that the SWM is highly sensitive to TLE-related pathology and may be an important predictor of postoperative outcomes.[43] Here, we demonstrate a differential pattern of SWM alterations across unique cognitive phenotypes. Specifically, the language and memory impaired group showed decreases in FA throughout frontocentral and lateral temporal regions bilaterally, coupled with highly left lateralized increases in MD that were pronounced within lateral temporal and orbitofrontal SWM. Conversely, the memory impaired group showed increased MD that was particularly pronounced within the cingulate and medial temporal lobes, bilaterally. Notably, a dissociative pattern emerged between these groups, where impairments in both language and memory were associated with SWM alterations that encompassed perisylvian regions, whereas isolated memory impairments were associated with changes in SWM within medial temporal structures critical to memory.[44] An unexpected finding was the lack of regional changes in SWM microstructure in patients with isolated language impairment. Interestingly, this group did not differ from the other groups in the number of AEDs or other identifiable clinical characteristics. A post hoc analysis also demonstrated that this group of patients was not more likely to be bilingual (25%), nor were they more likely to be on topiramate (10%) or zonisamide (10%) (all χ^2 p values >0.05), all of which may contribute to language impairments in TLE.[45,46] Rather, results from a subnetwork analysis (discussed below) indicate that the language-impaired group may harbor subtle changes within perisylvian network structure that are not apparent in traditional regional analysis. As anticipated, we found no significant changes in SWM microstructure in patients with normal cognitive profiles. Despite a prolonged course of epilepsy and having a clinical profile known to affect cognition, the patients in the no impairment group showed a similar neuropsychological and microstructural profile to HC. Altogether, these findings further highlight the importance of the SWM to cognition and reveal that cognitive phenotypes in TLE have unique SWM signatures.

Alterations in deep WM tracts are often associated with impairments in memory and language in TLE.[21,22] In our study, patients demonstrating impairment in both language and memory showed reductions in FA of the ARC and ILF bilaterally, and left UNC, and increases in MD of the left ARC and ILF. These findings suggest that a worse cognitive phenotype is associated with widespread WM alterations in both short-range U-shaped fibers connecting adjacent gyri[42] and long-range association tracts connecting distal cortical regions. Interestingly, the memory impaired group showed minimal alterations in deep WM tracts relative to HC despite showing diffuse SWM MD changes within inferior and mesial temporal structures. Although several studies have found an association between compromise to our selected fronto-temporal and medial temporal lobe tracts and both language and memory impairment in TLE,[17,47] it is possible that microstructural loss restricted to the SWM within the medial temporal lobe is more likely to result in an isolated memory impairment. In particular, the SWM beneath the entorhinal cortex includes the perforant path, which provides afferent input to the hippocampus (CA3/dentate)[48] and is known to be critical to verbal memory, but not necessarily to language.[17,49] Therefore, while we found more restricted alterations in deep WM tracts in the domain-specific groups, it is possible that damage to multiple deep association tracts leads to impairment in both cognitive domains.

Given that TLE is now understood to represent a network disorder with alterations in whole-brain network topology,[24] we applied a graph theory approach to explore whether distinct cognitive phenotypes demonstrate unique SWM network organization. First, we replicate previous findings[24,25] demonstrating that patients with TLE display disrupted integration (i.e., lower global efficiency) and increased segregation (i.e., increased transitivity) at the whole group level. However, our subgroup analysis revealed that these topologic differences were primarily driven by the language and memory impaired group, with minimal differences observed in the other groups at the global network level. These findings mirror the regional analysis and indicate that more pervasive cognitive deficits are associated with pronounced alterations of SWM network structure.

Previous studies using network analyses in TLE have found consistent increases in path length and clustering coefficient,[24,25] suggesting a more regularized network configuration that may be less resilient to epilepsy-related pathology. In our study, we found decreases in global efficiency (i.e., increased path length) in patients with language and memory impairment, as well as increases in transitivity (i.e., increased coefficient). These alterations in global topology have been characterized as reflecting a lattice-like network configuration[25] that may lead to reduced efficiency in information transfer, contributing to the cognitive dysfunction in this clinical population. Thus, the broad cognitive impairment observed in the language and memory impaired group may, in part, be due to an altered global topology within SWM networks. We also found decreases in modularity and increases in transitivity in patients in the language and memory impaired group relative to HC. Modularity describes the extent to which networks are organized into smaller subgroups.[29,50] A highly modular brain may offer a high level of local specialization needed for the demands of different cognitive processes. In support of this, de Haan et al.[29] found decreases in modularity to be associated with poorer language and memory performances in patients with Alzheimer disease (AD). Decreases in modularity have also been linked to more advanced clinical status in AD.[30] Our results in the language and memory impaired group provide further evidence that decreases in modularity may result in disruption in intermodular communication and lead to pervasive cognitive deficits in TLE.

As described above, patients with isolated language impairment showed intact global network structure but decreased local efficiency within the left and right STG, suggesting less integration of the STG with other brain regions. Given that the STG is a critical node within the perisylvian network, a less well-integrated STG may lead to isolated language impairment in some patients in the absence of other cognitive or microstructural changes and suggests avenues for further inquiry. Collectively, these results demonstrate unique changes in network organization within specific cognitive phenotypes. Specifically, more pervasive language and memory impairments are associated with widespread WM pathology that leads to altered segregation and integration of WM networks, whereas isolated language impairment may be associated with disruption of local nodes within persylvian networks.

Our study has several important limitations that should be noted. First, we only included neuropsychological measures of language and memory. While impairments in language and memory account for the most pervasive and problematic cognitive comorbidities in patients with TLE,[2] impairments in executive function and processing speed are also present in some patients and could help to further subdivide our phenotypes. Future studies with a broader examination of different cognitive domains are warranted. Second, we used specific neuropsychological criteria to define impairment and to derive our phenotypes, whereas previous studies[7–9] in TLE have relied on a data-driven approach (i.e., cluster analysis). Defining cognitive phenotypes based on individual test performance has been widely used within the mild cognitive impairment and AD literature, given its clinical utility, interpretability, and comparability across different studies.[15,39] However, a comparison of clinically driven and data-driven methods is needed to test the utility and reproducibility of each method. Nonetheless, our study adds to an emerging literature demonstrating that TLE is associated with distinct cognitive phenotypes with unique underlying neuroanatomical signatures. Knowledge of these phenotypes not only helps to improve cognitive and neuroanatomical taxonomies in TLE, but it may also enhance individualized prediction of cognitive trajectories and yields a different perspective on the cognitive consequences of the TLE. Additional longitudinal studies such as Hermann et al.[7] will improve our understanding of whether these distinct phenotypes portend differential patterns of cognitive impairment progression and whether epilepsy-related clinical variables (e.g., seizure frequency, number and type of AEDs) affect such progression. Furthermore, knowledge about these phenotypes and their underlying neurobiology could be used in combination with clinical data to help predict risk for cognitive decline associated with aging or medical/surgical interventions in TLE. As the field of epilepsy is moving towards establishing more meaningful cognitive and neurobehavioral taxonomies, identifying syndrome-dependent and syndrome-independent phenotypes and understanding their accompanying neurobiology could improve our ability to match patients to treatments and improve a range of epilepsy-related outcomes.

Study funding

Supported by NIH (CRM R01 NS065838).

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* September 28, 2018. Accepted in final form December 31, 2018.

Appendix Authors

Name	Location	Role	Contribution
Anny Reyes, MS	University of California, San Diego	Author	Designed and conceptualized study, analyzed the data, drafted the manuscript for intellectual content
Erik Kaestner, PhD	University of California, San Diego	Author	Analyzed the data, drafted the manuscript for intellectual content
Naeim Bahrami, PhD	University of California, San Diego	Author	Interpreted the data, revised the manuscript for intellectual content
Akshara R. Balachandra, BS	University of California, San Diego	Author	Interpreted the data, revised the manuscript for intellectual content
Manu Hegde, MD, PhD	University of California, San Francisco	Author	Interpreted the data, revised the manuscript for intellectual content
Brianna M. Paul, PhD	University of California, San Francisco	Author	Interpreted the data, revised the manuscript for intellectual content
Bruce Hermann, PhD	Matthews Neuropsychology Section, University of Wisconsin	Author	Interpreted the data, revised the manuscript for intellectual content
Carrie R. McDonald, PhD	University of California, San Diego	Author	Designed and conceptualized study, analyzed the data, drafted the manuscript for intellectual content

References

1. Saling MM. Verbal memory in mesial temporal lobe epilepsy: beyond material specificity. Brain 2009;132:570–582.
2. Bell B, Lin JJ, Seidenberg M, Hermann B. The neurobiology of cognitive disorders in temporal lobe epilepsy. Nat Rev Neurol 2011;7:154–164.
3. Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. Ann Neurol 2003;54:425–432.
4. Hermann BP, Seidenberg M, Dow C, et al. Cognitive prognosis in chronic temporal lobe epilepsy. Ann Neurol 2006;60:80–87.
5. Helmstaedter C, Hermann B, Lassonde M, Kahane P, Arzimanoglou A. Neuropsychology in the Care of People with Epilepsy. Montrouge, France: John Libbey Eurotext; 2011.

6. Oyegbile TO, Dow C, Jones J, et al. The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. Neurology 2004;62:1736–1742.
7. Hermann B, Seidenberg M, Lee EJ, Chan F, Rutecki P. Cognitive phenotypes in temporal lobe epilepsy. J Int Neuropsychol Soc 2007;13:12–20.
8. Dabbs K, Jones J, Seidenberg M, Hermann B. Neuroanatomical correlates of cognitive phenotypes in temporal lobe epilepsy. Epilepsy Behav 2009;15:445–451.
9. Rodriguez-Cruces R, Velazquez-Perez L, Rodriguez-Leyva I, et al. Association of white matter diffusion characteristics and cognitive deficits in temporal lobe epilepsy. Epilepsy Behav 2018;79:138–145.
10. Delis DC, Kramer JH , Kaplan E, Ober BA. CVLT-II: California Verbal Learning Test: Adult Version. San Antonio: Psychological Corporation; 2000.
11. Wechsler D. WMS-III: Wechsler Memory Scale Administration and Scoring Manual. San Antonio: Psychological Corporation; 1997.
12. Kaplan E, Goodglass H, Weintraub S. Boston Naming Test. Austin: Pro-ed; 2001.
13. Hamberger MJ, Seidel WT. Auditory and visual naming tests: normative and patient data for accuracy, response time, and tip-of-the-tongue. J Int Neuropsychol Soc 2003; 9:479–489.
14. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan executive function system. London: Pearson; 2001.
15. Edmonds EC, Eppig J, Bondi MW, et al. Heterogeneous cortical atrophy patterns in MCI not captured by conventional diagnostic criteria. Neurology 2016;87: 2108–2116.
16. Holland D, Kuperman JM, Dale AM. Efficient correction of inhomogeneous static magnetic field-induced distortion in Echo Planar Imaging. Neuroimage 2010;50: 175–183.
17. McDonald CR, Leyden KM, Hagler DJ, et al. White matter microstructure complements morphometry for predicting verbal memory in epilepsy. Cortex 2014;58: 139–150.
18. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis: I: segmentation and surface reconstruction. Neuroimage 1999;9:179–194.
19. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis: II: inflation, flattening, and a surface-based coordinate system. Neuroimage 1999;9:195–207.
20. Hagler DJ Jr, Ahmadi ME, Kuperman J, et al. Automated white-matter tractography using a probabilistic diffusion tensor atlas: application to temporal lobe epilepsy. Hum Brain Mapp 2009;30:1535–1547.
21. Leyden KM, Kucukboyaci NE, Puckett OK, et al. What does diffusion tensor imaging (DTI) tell us about cognitive networks in temporal lobe epilepsy? Quant Imaging Med Surg 2015;5:247–263.
22. Allone C, Lo Buono V, Corallo F, et al. Neuroimaging and cognitive functions in temporal lobe epilepsy: a review of the literature. J Neurol Sci 2017;381:7–15.
23. Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage 2003;20:1714–1722.
24. Bernhardt BC, Bonilha L, Gross DW. Network analysis for a network disorder: the emerging role of graph theory in the study of epilepsy. Epilepsy Behav 2015;50: 162–170.
25. Bernhardt BC, Chen Z, He Y, Evans AC, Bernasconi N. Graph-theoretical analysis reveals disrupted small-world organization of cortical thickness correlation networks in temporal lobe epilepsy. Cereb Cortex 2011;21:2147–2157.
26. Bahrami N, Seibert TM, Karunamuni R, et al. Altered network topology in patients with primary brain tumors after fractionated radiotherapy. Brain Connect 2017;7: 299–308.
27. Carmeli C, Fornari E, Jalili M, Meuli R, Knyazeva MG. Structural covariance of superficial white matter in mild Alzheimer's disease compared to normal aging. Brain Behav 2014;4:721–737.
28. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006;31:968–980.
29. de Haan W, van der Flier WM, Koene T, Smits LL, Scheltens P, Stam CJ. Disrupted modular brain dynamics reflect cognitive dysfunction in Alzheimer's disease. Neuroimage 2012;59:3085–3093.
30. Brier MR, Thomas JB, Fagan AM, et al. Functional connectivity and graph theory in preclinical Alzheimer's disease. Neurobiol Aging 2014;35:757–768.
31. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 2010;52:1059–1069.
32. Latora V, Marchiori M. Efficient behavior of small-world networks. Phys Rev Lett 2001;87:198701.
33. Newman ME. The structure and function of complex networks. SIAM Rev 2003;45: 167–256.
34. Newman ME. Modularity and community structure in networks. Proc Natl Acad Sci USA 2006;103:8577–8582.
35. Stretton J, Thompson PJ. Frontal lobe function in temporal lobe epilepsy. Epilepsy Res 2012;98:1–13.
36. Wieser HG; Epilepsy ICoNo. ILAE Commission Report: mesial temporal lobe epilepsy with hippocampal sclerosis. Epilepsia 2004;45:695–714.
37. Hermann B, Seidenberg M, Bell B, et al. The neurodevelopmental impact of childhood-onset temporal lobe epilepsy on brain structure and function. Epilepsia 2002;43:1062–1071.
38. Meador KJ. Cognitive outcomes and predictive factors in epilepsy. Neurology 2002; 58:S21–S26.
39. Snowden JS, Stopford CL, Julien CL, et al. Cognitive phenotypes in Alzheimer's disease and genetic risk. Cortex 2007;43:835–845.
40. Nazeri A, Chakravarty MM, Felsky D, et al. Alterations of superficial white matter in schizophrenia and relationship to cognitive performance. Neuropsychopharmacology 2013;38:1954–1962.
41. Nazeri A, Chakravarty MM, Rajji TK, et al. Superficial white matter as a novel substrate of age-related cognitive decline. Neurobiol Aging 2015;36:2094–2106.
42. Ouyang M, Kang H, Detre JA, Roberts TPL, Huang H. Short-range connections in the developmental connectome during typical and atypical brain maturation. Neurosci Biobehav Rev 2017;83:109–122.
43. Liu M, Bernhardt BC, Hong SJ, Caldairou B, Bernasconi A, Bernasconi N. The superficial white matter in temporal lobe epilepsy: a key link between structural and functional network disruptions. Brain 2016;139:2431–2440.
44. Squire LR, Zola-Morgan S. The medial temporal lobe memory system. Science 1991; 253:1380–1386.
45. Gollan TH, Montoya RI, Fennema-Notestine C, Morris SK. Bilingualism affects picture naming but not picture classification. Mem Cognit 2005;33:1220–1234.
46. Ojemann LM, Ojemann GA, Dodrill CB, Crawford CA, Holmes MD, Dudley DL. Language disturbances as side effects of topiramate and zonisamide therapy. Epilepsy Behav 2001;2:579–584.
47. McDonald CR, Ahmadi ME, Hagler DJ, et al. Diffusion tensor imaging correlates of memory and language impairments in temporal lobe epilepsy. Neurology 2008;71: 1869–1876.
48. Witter MP. The perforant path: projections from the entorhinal cortex to the dentate gyrus. Prog Brain Res 2007;163:43–61.
49. Yassa MA, Mattfeld AT, Stark SM, Stark CE. Age-related memory deficits linked to circuit-specific disruptions in the hippocampus. Proc Natl Acad Sci USA 2011;108: 8873–8878.
50. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 2009;10:186–198.