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BRIEF COMMUNICATION

Epilepsia®

Topological alterations in older adults with temporal lobe epilepsy are distinct from amnestic mild cognitive impairment

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Abstract

Epilepsy incidence and prevalence peaks in older adults, yet systematic studies of brain aging and epilepsy remain limited. We investigated topological network disruption in older adults with temporal lobe epilepsy (TLE; age > 55 years). Additionally, we examined the potential network disruption overlap between TLE and amnestic mild cognitive impairment (aMCI), the prodromal stage of Alzheimer disease. Measures of network integration ("global path efficiency") and segregation ("transitivity" and "modularity") were calculated from cortical thickness covariance from 73 TLE subjects, 79 aMCI subjects, and 70 healthy controls. Compared to controls, TLE patients demonstrated abnormal measures of segregation (increased transitivity and decreased modularity) and integration (decreased global path efficiency). aMCI patients also displayed increased transitivity and decreased global path efficiency, but these differences were less pronounced than in TLE. At the local level, TLE patients demonstrated decreased local path efficiency focused in the bilateral temporal lobes, whereas aMCI patients had a more frontal-parietal distribution. These results suggest that network disruption at the global and local level is present in both disorders, but global disruption may be a particularly salient feature in older adults with TLE. These findings motivate further research into whether these network changes have distinct cognitive correlates or are progressive in older adults with epilepsy.

KEYWORDS

amnestic mild cognitive impairment, graph theory, older adults, temporal lobe epilepsy

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1 | INTRODUCTION

Older adults represent the most rapidly growing segment of patients with epilepsy, with an incidence that peaks after 65 years and a prevalence of 5-6 per 100 individuals.[1] This older cohort presents with increased risk for cognitive impairment,[2] pathological brain aging,[3] and development of progressive neurodegenerative disorders such as Alzheimer disease (AD).[4] In particular, the similarity in clinical presentation between AD's prodromal stage, amnestic mild cognitive impairment (aMCI), and temporal lobe epilepsy (TLE) has drawn interest.[5–7] Combined with evidence of shared histopathology,[6] these similarities have led to theories of a bidirectional relationship between AD and TLE.[5]

Progressive atrophy, especially within the medial temporal lobe (MTL), has been reported in older adults with TLE.[3] Complementing regional analyses, TLE is characterized as a network disorder.[8] The subset of patients who display disrupted MTL network organization are associated with poor seizure outcomes following surgery[9] and worse cognitive dysfunction.[10] aMCI/AD is also associated with MTL atrophy[6] and network disruption, the latter of which has been associated with progressive cortical atrophy and cognitive decline.[11–13] Despite similarities in MTL regional atrophy, whether the network alterations observed in TLE and aMCI are similar has not been explored.

In this study, we compared both regional atrophy and gray matter topological network alterations of older patients (55-80 years old) with TLE and aMCI to older healthy controls (HC) to determine whether these two patient cohorts show similar patterns of structural network disruption.

2 | MATERIALS AND METHODS

2.1 | Participants

Institutional review boards (IRBs) at University of California, San Diego (UCSD), Emory University, Cleveland Clinic, and University of Wisconsin-Madison (UWM) approved this study. Written informed consent was obtained from all TLE patients at UCSD, Emory, and UWM; at Cleveland Clinic, data were collected as part of an IRB-approved data registry. Seventy-three older adults with TLE met inclusion criteria. Patients were diagnosed with TLE by an epileptologist in accordance with the criteria defined by the International League Against Epilepsy.[14] All TLE patients were drug-resistant, and all patients were older than 55 years at the time of the preoperative magnetic resonance imaging (MRI). Seventy-two percent (n = 53) of the patients subsequently underwent epilepsy surgery. Seventy-nine patients with aMCI and 70 older healthy controls were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Full details of ADNI, including inclusion criteria, can be found at adni.loni.usc.edu. Patient demographics are presented in Figure 1A, and TLE patient clinical characteristics are presented in Figure 1B. Measures of episodic memory included Logical Memory Immediate (LM1) and Logical

A

	TLE	aMCI	HC
N	73	79	70
Age	61.2 (4.86) 55-77	63.7 (3.59) 55-76	68.1 (4.07) 55-72
Education	13.4 (2.5)	16.4 (2.8)	16.3 (2.7)
Sex: M/F	30/43	39/40	27/43
LM1	43.7 (1.21)	43.0 (1.23)	65.5 (1.22)
LM2	43.5 (1.17)	33.5 (1.18)	63.5 (1.29)

B

	TLE
Age of Onset (years)	34.7 (19.7)
Duration (years)	26.5 (19.8)
MTS: Y/N	34/37
Onset Side: L/R/Bilateral	42/20/10
Family History of Epilepsy: Y/N	11/62
Number of failed ASMs	5.4 (2.5)

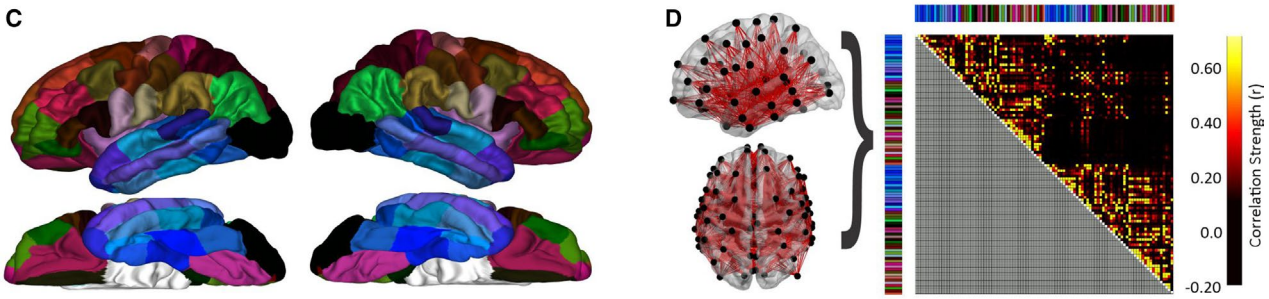

FIGURE 1 Neuroanatomical measures of topological networks derived from cortical thickness covariance. A, Patient and control demographics. Numbers represent means or counts, with parentheses displaying standard deviation. aMCI, amnestic mild cognitive impairment; F, female; HC, healthy controls; LM1, Logical Memory Immediate from WMS-III; LM2, Logical Memory Delayed from WMS-III; M, male; TLE, temporal lobe epilepsy; WMS-III, Wechsler Memory Scale-Third Edition. B, TLE clinical and demographic characteristics. Numbers represent means or counts, with parentheses displaying standard deviation. ASM, antiseizure medication; L, left; MTS, mesial temporal sclerosis; N, no; R, right; Y, yes. C, An illustration on an average brain of the regions of interest from the modified Desikan atlas. D, Average brain displaying the region-region correlations used in this study. On the right is a sample graded connectivity matrix representing correlation values for the TLE group. At each density, correlation thresholds are used to binarize this matrix (eg, a density of 0.10 means that the top 10% of correlations are "connected")

Memory Delayed (LM2) from the Wechsler Memory Scale-Third Edition.

2.2 | MRI data acquisition and processing

All T1-weighted MRI data for the TLE patients were obtained preoperatively using a specialized epilepsy imaging sequence at one of the four epilepsy centers. Data from aMCI subjects and HC were obtained from the ADNI database. All image processing and analyses occurred at the Center for Multimodal Imaging and Genetics Laboratory at UCSD using the exact same imaging analysis pipeline. In total, scanner strengths in each group were TLE (22/51 1.5T/3T), aMCI (42/37), and HC (25/45). Scanner strength was included as a covariate in analyses (see Section 2.5).

2.3 | Cortical surface reconstruction

FreeSurfer v5.3 software was used to obtain cortical thickness estimates.[15] For surface-based analyses, group maps were created by resampling individual surfaces into a common spherical coordinate system that aligned cortical folding patterns across participants and were smoothed with a 16-mm Gaussian kernel. For network regions of interest (ROIs), a modified Desikan-Killiany atlas was used in which long gyri were split into thirds to increase anatomical precision (Figure 1C). Visual inspection was performed on all images to identify topological defects, which were subsequently corrected with manual editing using established software guidelines (http://surfer.nmr.mgh.harvard.edu).

2.4 | Network analysis

A 98 × 98 symmetrically weighted matrix of whole-brain cortical thickness covariance was constructed for each group (Figure 1D). Because age differed between groups (see Section 3.1), prior to the correlation analysis, a linear regression was performed at every ROI to remove the effects of age. Residuals of this regression were then substituted for the raw cortical thickness values.[16] Each value represents Pearson correlation strength between two ROIs within each group (TLE, aMCI, HC). Graph theoretical analyses were applied to the structural covariance matrix. We analyzed four graph theory–based measures that are sensitive to network changes

TABLE 1 Network measures description and results

	Short description[17]	TLE significant differences from HC (density ranges)	aMCI significant differences from HC (density ranges)
Global path efficiency	Measure of global network integration. Integration reflects the brain's ability to rapidly combine specialized information from distributed brain regions. Decreased global efficiency reflects a decreased potential for information integration.	TLE < HC (0.10-0.30 & 0.50)	aMCI < HC (0.25-0.50)
Local path efficiency	Measure of local network integration for each ROI, interpreted as representing regional topological changes.	TLE < HC, clustered in temporal regions	aMCI < HC, clustered in frontal-parietal regions
Transitivity	Measure of network segregation. Segregation reflects the brain's ability for specialized processing to occur within interconnected groups of brain regions. Greater transitivity indicates a tendency for ROIs to be highly integrated within their local cluster.	TLE > HC (0.10-0.50)	aMCI > HC (0.30-0.50)
Modularity	Degree to which a network may be subdivided into clearly delineated and nonoverlapping groups. Decreased modularity reflects a network less organized into cohesive subdivisions.	TLE < HC (0.10-0.35 & 0.45-0.50)	No significant differences

in TLE[8] (Table 1): "global path efficiency," "local path efficiency," "transitivity," and "modularity."[17] Group differences in each measure were tested using the Brain Connectivity Toolbox[17] for network densities, $0.1 \leq$ threshold ≤ 0.5, with a threshold increment of 0.05. Densities refer to correlation thresholds to determine connectivity (eg, a density of 0.10 means that the top 10% of correlations are "connected"). Global path efficiency is a measure of global network integration and is defined as the average inverse shortest path length. Local path efficiency is calculated using the global efficiency from the adjacent subgraph of the ROI. Transitivity is a measure of network segregation, such that greater transitivity indicates a tendency for ROIs to be highly integrated within their local cluster. Transitivity is similar to clustering coefficient, but is normalized collectively for all ROIs so that the total number of ROIs does not influence measurement. 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.

2.5 | Statistical analysis

For demographic variables, analysis of variance and Fisher exact tests were used. Surface maps were compared between each patient group and HC using vertexwise analysis of covariance (ANCOVA) that included the covariates age, sex, education, and field strength (see Section 3.1). Statistical correction was applied using cluster-based thresholding[18] (cluster-corrected $P < .05$). For the graph theoretic measures, a subsampling methodology[10] was used to estimate a spread of values for the HC group by using nonparametric permutation tests with 1000 permutations for each measure at each network density level. At each density, patient group values outside of the 0.0005 and 0.9995 percentile range (corresponding to a P value of .001) were considered significantly different from HCs. This conservative approach was selected to protect against type 1 errors.

3 | RESULTS

3.1 | Group demographics

Groups differed in age ($F_{2, 219} = 50.3$, $P < .001$) and education ($F_{2, 219} = 27.7$, $P < .001$) but not sex (Fisher exact = 1.95, $P = .38$). Follow-up tests for age demonstrated HC (68.1 years) were older relative to TLE (61.2 years; $P < .001$) and aMCI (63.7 years; $P < .001$) patients. Follow-up tests for education demonstrated HC (16.3 years) had more education relative to TLE (13.4 years; $P < .001$), but not aMCI (16.4 years; $P > .05$) patients. For memory, significant ANCOVAs were observed across both cognitive measures (LM1: $F_{2, 209} = 63.85$, $P < .001$; LM2: $F_{2, 209} = 117.95$, $P < .001$). Follow-up analyses revealed that patients with either TLE or aMCI showed significantly worse performance across both tests relative to HC (all $P < .001$). On LM1 and LM2, 41% of TLE patients were classified as impaired.

3.2 | Cortical thickness

There were no differences in average thickness in either hemisphere across the epilepsy centers in an ANCOVA with the covariates age, sex, education, and field strength (left: $F_{3, 66} = 1.16$, $P = .33$; right: $F_{3, 66} = 1.20$, $P = .31$). Both TLE and aMCI groups showed prominent cortical thinning in bilateral MTL and inferotemporal regions (Figure 2A)

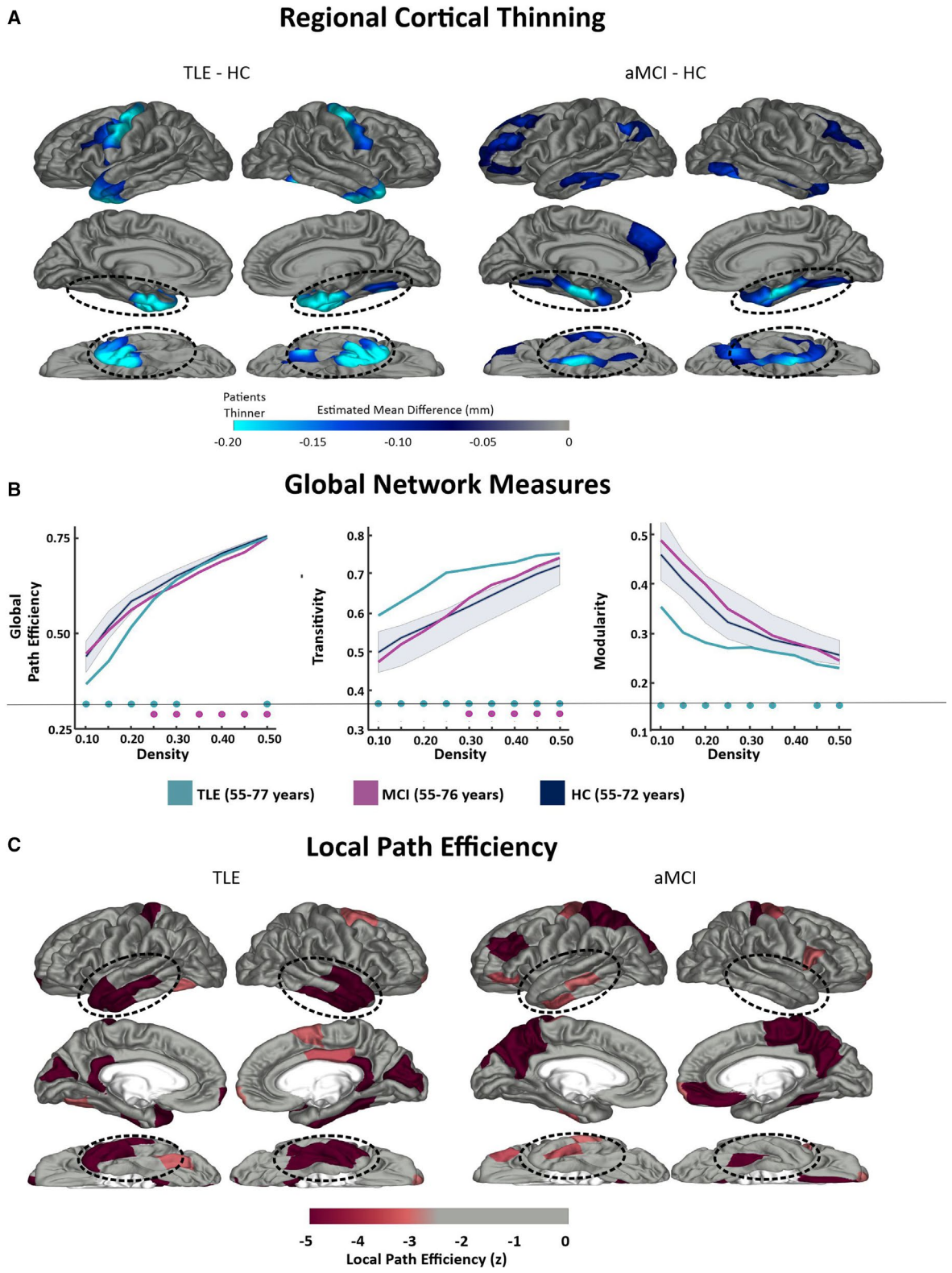

FIGURE 2 Regional and network dysfunction across temporal lobe epilepsy (TLE) and amnestic mild cognitive impairment (aMCI) patients. A, Patterns of cortical thinning for both TLE and aMCI patients relative to healthy controls (HC). Blue denotes cortex significantly thinner than HC for each patient group. Both patient groups showed prominent cortical thinning in bilateral medial temporal lobe regions, highlighted by dashed lines. B, Global graph theory measures for TLE (teal), aMCI (purple), and HC (blue) across densities ranging from 0.10 to 0.50. Colored dots denote significant ($P < .001$) differences in TLE (teal) and aMCI (purple) from the control distribution of values. C, Regions of interest (ROIs) with significantly decreased path efficiency for TLE and aMCI. Values are from the middle density of 0.25, z-scored relative to the HC distribution of values for each ROI. Dashed circles highlight temporal regions displaying marked decreases in local path efficiency for TLE but not aMCI

compared to HC. Laterally, aMCI showed localized atrophy in lateral temporal, left posterior parietal, and dorsolateral prefrontal regions, whereas TLE showed atrophy within anterior temporal and precentral cortex.

3.3 | Structural covariance measures

Globally, TLE subjects had decreased global path efficiency across a range of network densities (0.10-0.30 and 0.50; $P < .001$), as well as increased transitivity (network densities = 0.10-0.50; $P < .001$) and decreased modularity (network densities = 0.10-0.35 and 0.45-0.50; $P < .001$) relative to HC (Figure 2B; Table 1). aMCI showed similar but more muted differences across a smaller range of densities for global path efficiency (0.25-0.50) and transitivity (0.30-0.50), but no differences from HC in modularity. When examining the local path efficiency of individual regions (Figure 2C), TLE patients showed reduced path efficiency clustered in anterior and ventral temporal regions, whereas aMCI patients displayed reduced path efficiency in bilateral frontal and parietal regions. Both groups displayed reduced efficiency in medial temporal-parietal/precuneus cortex.

4 | DISCUSSION

Older patients with TLE demonstrated similar but more pronounced global network alterations relative to aMCI despite both patient groups presenting a similar magnitude of MTL atrophy. Local path efficiency appeared to take a disease-specific regional pattern; in older adults with TLE, reduced path efficiency centered within bilateral anterior and ventral temporal regions, whereas in aMCI patients, reduced path efficiency clustered in frontal-parietal cortex. These results suggest that network disruption at the global and local level is present in both disorders, but global disruption may be a particularly salient feature in older adults with TLE.

TLE is understood to represent a network disorder with alterations in whole-brain network topology.[8] In older patients with TLE, we report disrupted integration (decreased global path efficiency) and segregation (increased transitivity and decreased modularity) of cortical networks. In our group of aMCI patients, we found a similar pattern of decreased integration and increased segregation. However, in aMCI, these abnormalities emerged most strongly only at higher network densities, whereas abnormality in TLE was pronounced across both low and high densities. The most apparent global difference was that in modularity. TLE patients had a decrease across densities, whereas aMCI patients showed much smaller differences from HC. Modularity describes the extent to which networks can be organized into smaller subgroups, a key measure of network efficacy and brain health,[19] which is necessary for the high level of local specialization needed for the demands of different cognitive processes. Therefore, the network in our TLE group was less organized into cohesive subdivisions than in HC and aMCI.

At a regional level, patterns of local path efficiency abnormality differed between TLE and aMCI. In TLE, local path efficiency decreases were mainly localized to bilateral anterior and ventral temporal regions, whereas aMCI showed decreases predominately in bilateral frontal-parietal cortex. In middle-aged patients with TLE, abnormal network connectivity centered in bilateral temporal regions has previously been tied to worse postsurgical seizure outcome.[9] Increasingly impaired cognition in middle-aged TLEs has also been related to decreases in global path efficiency and modularity as well as increases in transitivity. Furthermore, selective deficits in local path efficiency in the superior temporal gyrus were tied to selective language impairment.[10] Although we describe a similar pattern of network changes in much older adults with TLE, the relative magnitude of these abnormalities across age and whether these network changes progress from middle to old age are unknown. In aMCI, patients present intermediate network values between HC and the more disrupted network values in AD in transitivity and modularity.[13] A relationship between worse network disruption in aMCI and worse patient trajectories has been documented in measures of integration and segregation.[12] Therefore, network measures may contain information of clinical importance that may not be reflected in regional measures. Whether the network alterations reported here portend an unfavorable course in older adults with TLE is unclear. Emerging methods interrogate correlates of structural network disruption at the individual patient level. These methods may prove useful in exploring the clinical utility of structural network disruption for understanding the progression of network disruption in aging with epilepsy.[20] Future studies that analyze changes in white matter networks and neuropsychological measures longitudinally will also be useful for determining whether network aberrations can predict cognitive deterioration and disease trajectories for TLE.

With a rapidly aging population, increasing numbers of older patients are presenting with epilepsy. Progressive MTL cortical thinning has been reported in an older TLE cohort,[3] raising concerns that MTL atrophy could suggest a progressive disease course in some patients. Here, the older TLE cohort demonstrated topological network alterations that are as striking as those seen in aMCI, but with unique features. Comparisons across neurological disorders could be helpful for identifying common mechanisms underlying similar clinical presentations that may suggest similar disease

trajectories and/or treatment strategies.[5] With the strong emphasis on early identification and treatment of preclinical neurodegenerative disorders, cross-disease approaches offer the chance to migrate therapies. However, successful translation will be aided by thorough characterizations of the overlaps and divides across diseases. Our study provides evidence that gray matter network disruption is common to both disorders, but with subtle differences. However, the pathological processes contributing to the structural network abnormalities in these patient groups is unknown. Furthermore, as our TLE cohort represented pharmacoresistant patients, it is unknown whether these structural network abnormalities would be present in a more benign cohort. A final limitation is that we combined scans across multiple sites, which may have increased variance in our estimates; this may have attenuated some effects. Given the phenotypic heterogeneity in epilepsy[10] and the range in our cohort's patient characteristics in measures such as age at onset, it is likely that there are multiple underlying disease courses to be disentangled in TLE.[5]

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

ETHICAL PUBLICATION STATEMENT

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

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REFERENCES

1. Sander JW. The epidemiology of epilepsy revisited. Curr Opin Neurol. 2003;16(2):165–70.
2. Witt J-A, Werhahn KJ, Krämer G, Ruckes C, Trinka E, Helmstaedter C. Cognitive-behavioral screening in elderly patients with new-onset epilepsy before treatment. Acta Neurol Scand. 2014;130(3):172–7.
3. Galovic M, van Dooren VQH, Postma TS, Vos SB, Caciagli L, Borzì G, et al. Progressive cortical thinning in patients with focal epilepsy. JAMA Neurol. 2019;76(10):1230.
4. Breteler MMB, Van Duijn CM, Chandra V, Fratiglioni L, Graves AB, Heyman A, et al. Medical history and the risk of Alzheimer's disease: a collaborative re-analysis of case-control studies. Int J Epidemiol. 1991;20(Suppl 2):S36–42.
5. Sen A, Capelli V, Husain M. Cognition and dementia in older patients with epilepsy. Brain. 2018;141(6):1592–608.
6. Tai XY, Koepp M, Duncan JS, Fox N, Thompson P, Baxendale S, et al. Hyperphosphorylated tau in patients with refractory epilepsy correlates with cognitive decline: a study of temporal lobe resections. Brain. 2016;139(9):2441–55.
7. Höller Y, Trinka E. What do temporal lobe epilepsy and progressive mild cognitive impairment have in common? Front Syst Neurosci. 2014;8:58.
8. 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;50:162–70.
9. Bonilha L, Jensen JH, Baker N, Breedlove J, Nesland T, Lin JJ, et al. The brain connectome as a personalized biomarker of seizure outcomes after temporal lobectomy. Neurology. 2015;84(18):1846–53.
10. Reyes A, Kaestner E, Bahrami N, Balachandra A, Hegde M, Paul BM, et al. Cognitive phenotypes in temporal lobe epilepsy are associated with distinct patterns of white matter network abnormalities. Neurology. 2019;92(17):e1957–68.

11. Pievani M, de Haan W, Wu T, Seeley WW, Frisoni GB. Functional network disruption in the degenerative dementias. Lancet Neurol. 2011;10(9):829–43.
12. Dicks E, Tijms BM, ten Kate M, Gouw AA, Benedictus MR, Teunissen CE, et al. Gray matter network measures are associated with cognitive decline in mild cognitive impairment. Neurobiol Aging. 2018;61:198–206.
13. Pereira JB, Mijalkov M, Kakaei E, Mecocci P, Vellas B, Tsolaki M, et al. Disrupted network topology in patients with stable and progressive mild cognitive impairment and Alzheimer's disease. Cereb Cortex. 2016;26(8):3476–93.
14. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):522–30.
15. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006;31(3):968–80.
16. Sanabria-Diaz G, Melie-García L, Iturria-Medina Y, Alemán-Gómez Y, Hernández-González G, Valdés-Urrutia L, et al. Surface area and cortical thickness descriptors reveal different attributes of the structural human brain networks. Neuroimage. 2010;50(4):1497–510.
17. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. Neuroimage. 2010;52(3):1059–69.
18. Worsley KJ, Andermann M, Koulis T, MacDonald D, Evans AC. Detecting changes in nonisotropic images. Hum Brain Mapp. 1999;8(2–3):98–101.
19. van den Heuvel MP, Sporns O. A cross-disorder connectome landscape of brain dysconnectivity. Nat Rev Neurosci. 2019;20(7):435–46.
20. Drenthen GS, Backes WH, Rouhl RPW, et al. Structural covariance networks relate to the severity of epilepsy with focal-onset seizures. Neuroimage Clin. 2018;20:861–7.

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