doi:10.1093/brain/awaa397 BRAIN 2020: Page 1 of 15 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Atrophy and cognitive profiles in older adults with temporal lobe epilepsy are similar to mild cognitive impairment

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[‡]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Epilepsy incidence and prevalence peaks in older adults yet systematic studies of brain ageing and cognition in older adults with epilepsy remain limited. Here, we characterize patterns of cortical atrophy and cognitive impairment in 73 older adults with temporal lobe epilepsy (>55 years) and compare these patterns to those observed in 70 healthy controls and 79 patients with amnestic mild cognitive impairment, the prodromal stage of Alzheimer's disease. Patients with temporal lobe epilepsy were recruited from four tertiary epilepsy surgical centres; amnestic mild cognitive impairment and control subjects were obtained from the Alzheimer's Disease Neuroimaging Initiative database. Whole brain and region of interest analyses were conducted between patient groups and controls, as well as between temporal lobe epilepsy patients with early-onset (age of onset <50 years) and late-onset (>50 years) seizures. Older adults with temporal lobe epilepsy demonstrated a similar pattern and magnitude of medial temporal lobe atrophy to amnestic mild cognitive impairment. Region of interest analyses revealed pronounced medial temporal lobe thinning in both patient groups in bilateral entorhinal, temporal pole, and fusiform regions (all $P < 0.05$). Patients with temporal lobe epilepsy demonstrated thinner left entorhinal cortex compared to amnestic mild cognitive impairment ($P = 0.02$). Patients with late-onset temporal lobe epilepsy had a more consistent pattern of cortical thinning than patients with early-onset epilepsy, demonstrating decreased cortical thickness extending into the bilateral fusiform (both $P < 0.01$). Both temporal lobe epilepsy and amnestic mild cognitive impairment groups showed significant memory and language impairment relative to healthy control subjects. However, despite similar performances in language and memory encoding, patients with amnestic mild cognitive impairment demonstrated poorer delayed memory performances relative to both early and late-onset temporal lobe epilepsy. Medial temporal lobe atrophy and cognitive impairment overlap between older adults with temporal lobe epilepsy and amnestic mild cognitive impairment highlights the risks of growing old with epilepsy. Concerns regarding accelerated ageing and Alzheimer's disease co-morbidity in older adults with temporal lobe epilepsy suggests an urgent need for translational research aimed at identifying common mechanisms and/or targeting symptoms shared across a broad neurological disease spectrum.

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Received May 19, 2020. Revised September 2, 2020. Accepted September 21, 2020.

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Keywords: temporal lobe epilepsy; mild cognitive impairment; brain atrophy; dementia; structural MRI

Abbreviations: EO/LO-TLE = early-onset/late-onset temporal lobe epilepsy; MCI = mild cognitive impairment; MTL = medial temporal lobe

Introduction

Given a rapidly ageing global population, the number of older individuals with epilepsy is set to increase substantially. Epilepsy prevalence increases throughout the lifespan with a peak in older adults (Annegers *et al.*, 1998; Joint Epilepsy Council, 2011; Choi *et al.*, 2017; Lezaic *et al.*, 2020), a cohort at increased risk for cognitive impairment (Witt *et al.*, 2014) possibly due to pathological brain ageing (Galovic *et al.*, 2019), including increased risk of progressive neurodegenerative disorders such Alzheimer's disease (Breteler *et al.*, 1991). Therefore, there is a critical need to understand brain changes that occur in older adults with epilepsy to help to guide treatments and/or predict individual patient trajectories.

Pathological brain ageing is of particular concern for patients with temporal lobe epilepsy (TLE), many of whom harbour significant memory deficits that appear similar to those seen in amnestic mild cognitive impairment (MCI), the prodromal phase of Alzheimer's disease (Griffith *et al.*, 2006). However, it is not known if the shared cognitive dysfunction observed in amnestic MCI and older adults with TLE is matched by similar patterns of cortical and hippocampal atrophy. This possibility of shared pathological changes is heightened by increasing evidence of shared mechanisms between TLE and Alzheimer's disease (Lapointe *et al.*, 2016; Sen *et al.*, 2018; Tai *et al.*, 2018), including the presence of tau pathology (Tai *et al.*, 2016) and increased amyloid-β (Sheng *et al.*, 1994) in brain tissue from patients with TLE.

In addition to epilepsy prevalence, incidence also peaks in older age (Annegers *et al.*, 1998; Joint Epilepsy Council, 2011; Choi *et al.*, 2017; Lezaic *et al.*, 2020). Thus, the existence of both chronic TLE patients with early seizure onset who have long disease duration as well as new onset TLE patients with short disease duration complicates interpretations. Patients with early-onset TLE (EO-TLE) are more likely to have mesial temporal sclerosis (MTS). These patients present with elevated health-related risk factors for abnormal cognitive and brain ageing including increased rates of vascular disease risk factors (Hamed *et al.*, 2007), corpora amylacea (Radhakrishnan *et al.*, 2007); altered lifestyle factors (Steinhoff *et al.*, 1996), and long-term treatment with medications now known to adversely affect cholesterol, folate, and glucose metabolism (Hamed and Nabeshima, 2005). Patients with late-onset TLE (LO-TLE) are a less recognized but sizable subgroup with *de novo* development of epilepsy later in life. Aetiologies underlying late-onset epilepsy include occult cerebrovascular disease (Hauser *et al.*, 1991), stroke (De Reuck *et al.*, 2008), head trauma (Annegers *et al.*, 1998), and progressive neurodegenerative disorders (Stefan, 2011), with a large proportion of aetiologies remaining unknown (Morillo, 2012; Sarkis *et al.*, 2019). Given their differing durations and aetiologies, the patterns of brain atrophy and cognitive impairments in older adults with EO-TLE versus LO-TLE may be distinct.

Here we evaluate cortical atrophy patterns and cognitive impairment in a large, multicentre cohort of older patients with TLE in order to directly compare their patterns to those seen in older adults with amnestic MCI and healthy control subjects. In addition, we divide our TLE sample into those with EO-TLE (onset <50 years) and LO-TLE (onset >50 years) to investigate whether these two cohorts show distinct atrophy patterns and cognitive impairment given the likelihood of different aetiologies and clinical course. To our knowledge, this is the first direct comparison of atrophy and cognitive patterns in patients with EO- and LO-TLE to those with amnestic MCI using quantitative imaging and neuropsychological data.

Materials and methods

This study was approved by an ethical standards committee on human subjects at University of California, San Diego (UCSD), Emory University, Cleveland Clinic, and University of Wisconsin-Madison (UWM). 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.

Participant sample

All available TLE subjects from the four epilepsy centres that were older than 55 at the time of scanning were considered for the study. Seventy-three older patients with TLE met inclusion criteria for the study. All patients were between 55 and 80 years of age at the time of MRI and neuropsychological evaluation at a Level 4 epilepsy centre, and were diagnosed with TLE by an epileptologist according to the International League Against Epilepsy criteria (Kwan *et al.*, 2010). All patients were drug-resistant, 78% of the patients were on polytherapy, and had evidence of unilateral or bilateral temporal lobe seizures captured by inpatient video-EEG monitoring. Patients were excluded if they had a lesion that would directly disrupt the cortical mantle precluding image analyses. As a follow-up analysis, patients were split into two groups based on age of seizure onset: EO-TLE with seizure onset before age 50 ($n = 50$), and LO-TLE with seizure onset after 50 ($n = 23$). Age 50 was chosen based on an inflection point in epilepsy incidence around age 50 (Lezaic *et al.*, 2020). Given previous research and our preliminary data indicating bilateral patterns of cortical atrophy even in patients with unilateral TLE (McDonald *et al.*, 2008), patients with right, left, and bilateral TLE were combined in the analyses. For patients with TLE, MRI scans and neuropsychological testing were performed on the same day for 45 of the patients (62%). Overall, there was an average of 3.24 months between the two sessions [standard deviation (SD) = 8.88 months].

Seventy-nine patients with amnestic MCI and 70 older healthy control subjects were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database to match the TLE sample as closely as possible in age and sex. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of amnestic MCI and early Alzheimer's disease. For up-to-date information, see www.adni-info.org.

ADNI's amnestic MCI diagnoses were based on the following: (i) a subjective memory concern; (ii) objective memory loss documented by scoring below education-adjusted norms on delayed free recall on the WMS-R Logical Memory II subtest; (iii) Mini-Mental State Examination (MMSE) score between 24 and 30; (iv) global Clinical Dementia Rating (CDR) score of 0.5; and (v) functional performance sufficiently preserved such that a diagnosis of Alzheimer's disease could not be made. All MRIs and neuropsychological examinations for the amnestic MCI cohort took place within 1 month of study diagnosis and within 1 month of each other.

Healthy control participants in ADNI were classified via the following criteria: (i) no memory complaints, beyond what would be expected for age; (ii) normal memory function documented by education-adjusted scores on delayed free recall on WMS-R Logical Memory II; (iii) MMSE score between 24 and 30; (iv) global CDR of 0; and (v) intact activities of daily living. Patients with amnestic MCI and healthy control subjects were excluded if they had any known neurological disorder, including seizure disorders. ADNI eligibility criteria are described in full at http://adni.loni.usc.edu/methods/documents/. Healthy control MRI and neuropsychological examinations took place within 1 month of one another.

Imaging acquisition

All TLE T_1 MRI data were acquired without gadolinium contrast at each of the four epilepsy centres. The typical scan at UCSD was T_1-weighted 3D customized FSPGR (fast spoiled gradient echo) structural sequence. At 1.5 T the scan parameters were: repetition time = 10.73 ms, echo time = 4.87 ms, inversion time = 1000 ms, flip angle = 8°, field of view = 256 mm, matrix = 256 × 192, slice thickness = 1.0 mm; and at 3 T the scan parameters were: repetition time = 8.08 ms, echo time = 3.16 ms, inversion = 600 ms, flip angle = 8°, field of view = 256 mm, matrix = 256 × 192, slice thickness = 1.0 mm. The typical Cleveland Clinic scan parameters at 3 T were: repetition time = 1860 ms, echo time = 3.4 ms, inversion time = 1.10 ms, flip angle = 10°, matrix = 256 × 256, slice thickness = 0.94 mm; and at 1.5 T the scan parameters were: repetition time = 11 ms, echo time = 4.6 ms, flip angle = 20°, matrix = 256 × 256, slice thickness = 1.25 mm. The typical scan at Emory University at 3 T scan parameters were: repetition time = 2300 ms, echo time = 3 ms, inversion time = 1100 ms, flip angle = 8°, field of view = 256 mm, matrix = 256 × 240, slice thickness = 1 mm. The typical scan at University of Wisconsin-Madison at 1.5 T scan parameters were: repetition time = 24 ms, echo time = 5 ms, flip angle = 40°, field of view = 200 mm, matrix = 256 × 256, slice thickness = 1.5 mm.

All T_1-weighted MRIs from the amnestic MCI patients and healthy control subjects were downloaded from the ADNI database. ADNI data were acquired across a variety of scanners with protocols individualized for each scanner. An example protocol for an MRI system (Magnetom Sonata Syngo; Siemens Medical Solutions), running version MR 2004A software, is the sagittal inversion-prepared 3D T_1-weighted gradient-echo sequence (magnetization-prepared rigid acquisition gradient echo or equivalent), with the following parameters: repetition time = 2400 ms; echo time = 3.5 ms; inversion time = 1000 ms; flip angle 8°; bandwidth 180 Hz/pixel; field of view = 240 mm; matrix 192 192; number of slices 60; slice thickness 1.2 mm.

Cortical and subcortical MRI procedures

All image processing and analyses were performed at the Center for Multimodal Imaging and Genetics Laboratory at UCSD using the same imaging analysis stream. FreeSurfer v5.3 software was used to obtain cortical thickness estimates and hippocampal volume, using validated procedures as described previously (Fischl and Dale, 2000; Desikan *et al.*, 2006). In short, the cortical surface was reconstructed and parcellated using FreeSurfer. A local quality check was performed by visual inspection of all images to identify topological defects, which were subsequently edited using established software guidelines. Quantification of cortical thickness estimates was determined by measurement of the distance between the white matter and the pial surfaces at each vertex. The cortical surface was then parcellated into regions of interest using the Desikan-Killiany atlas (Desikan *et al.*, 2006), and average thickness was calculated within each region of interest. Cortical thickness estimates were computed point-by-point across the cortical mantle, then averaged to create gyral-based regions of interest. To control for differences in brain size, hippocampal volumes were represented as a ratio to total intracranial volume.

Image harmonization

The batch-effect correction tool ComBat was used to harmonize the TLE MRI data, adjusting for between-site variations in cortical thickness and volume across the four epilepsy centres. The ComBat method globally rescales the data (all regions of interest) for each site using a *z*-score transformation map common to all features, as described in Fortin *et al.* (2017). ComBat uses an empirical Bayes framework to improve the variance of the parameter estimates (Johnson *et al.*, 2007), assuming that all regions of interest share the same common distribution. Thus, all regions of interest are used to inform the statistical properties of site effects. Site was used as the batch effect. The ComBat approach has proven effective for harmonizing T_1-weighted MRIs in multinational imaging collectives such as ENIGMA (Radua *et al.*, 2020).

For ADNI, all MRI acquisition, preprocessing, and postprocessing were carefully harmonized across scanner platforms and sites at the outset according to rigorous ADNI protocols, as described in Jack *et al.* (2015). In brief, standardized acquisitions were used across all scanners, protocols were developed that were compatible with a variety of hardware/software configurations, and the ADNI phantom was consistently used for testing. Methodologies were also implemented to improve stability of geometric scaling, image intensity non-uniformity, and geometric warping (Jack *et al.*, 2015), ensuring high quality images that were well-harmonized across sites.

Neuropsychological data

The following neuropsychological measures were available for the TLE patients, amnestic MCI, and healthy controls. Measures of episodic memory included Logical Memory Immediate (LM1) and Delayed (LM2) from the WMS-III (Wechsler, 1997) and the delayed recall and delayed recognition trials from the Rey Auditory Verbal Learning Test [RAVLT-Delayed and RAVLT-Recognition, respectively (Rey, 1964)]. Measures of language included visual confrontation naming with the Boston Naming Test (BNT; Kaplan *et al.*, 2001) and Category Fluency (CF) as measured with animal fluency. Logical Memory scores were corrected for age using the norms provided by the test manual. Language scores were corrected for age, education, sex and race based on normative data from Expanded Halstead-Reitan Battery (Heaton *et al.*, 2004). Scores from the RAVLT were age-corrected using the Mayo Older Americans Normative Study (Ivnik *et al.*, 1992). All scores were converted to T-score and then *z*-scored relative to the control distribution for consistency and ease of interpretability.

Statistical analyses

To ensure cortical atrophy pattern robustness, both vertex-wise and region of interest-based analyses were performed. Vertex-wise analyses reveal patterns of cortical thinning across the whole brain by aligning volumes in an average space, whereas the region of interest analyses provide estimates based on the unsmoothed data in the subject's native space. For the 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 (Fischl *et al.*, 1999). Surface maps were then compared between each patient group (TLE, amnestic MCI, EO-TLE, LO-TLE) and healthy controls using vertex-wise analysis of covariance (ANCOVAs) controlling for age, sex, education, and field strength (1.5 T versus 3 T scans as a Boolean variable). Statistical correction was applied using cluster-based thresholding (Worsley *et al.*, 1999) (cluster-corrected $P < 0.05$). Regions of interest were selected based on regions of known cortical thinning in TLE, including medial and lateral temporal lobe as well as the peri-Rolandic regions (Caciagli *et al.*, 2017; Whelan *et al.*, 2018; Galovic *et al.*, 2019). Region of interest analyses used the same covariates of age, sex, education, and field strength. Multiple comparisons were corrected using Benjamini-Hochberg false discovery rate (Benjamini and Hochberg, 1995) applied to each regional group of regions of interest. When results from the region of interest ANCOVA were significant, group contrasts were assessed using *post hoc* pairwise tests with Bonferroni correction.

For neuropsychological data, ANCOVAs controlling for age, sex, and education were conducted to compare neuropsychological performance across groups. When results from the ANCOVA were significant, group contrasts were assessed using *post hoc* pairwise tests with Bonferroni correction.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Patients demographics

Demographic information and statistical tests for TLE, amnestic MCI, and healthy controls are displayed in Table 1. Sex was balanced across groups; however, age, education, and scanner strength differed. Controls were older relative to TLE ($P < 0.001$) and amnestic MCI ($P < 0.001$) and had greater years of education relative to TLE ($P < 0.001$). The amnestic MCI group was older ($P < 0.001$) and had greater years of education relative to the TLE group ($P < 0.001$). Amnestic MCI (42/37 1.5 T/3 T) had more 1.5 T scans relative to TLE (22/51; $P = 0.006$) and healthy controls (25/45; $P = 0.047$), though the TLE and healthy control groups did not differ ($P = 0.601$). Therefore, age, education, and scanner strength were included as covariates in all ANCOVAs. Demographics, epilepsy characteristics, and risk factors across EO- and LO-TLE are displayed in Table 2. As expected, these groups differed in seizure duration (EO-TLE: 36.42 years, LO-TLE: 6.59 years; $P < 0.001$) as well as a greater proportion of EO-TLE displaying MTS ($P = 0.012$).

Patterns of cortical atrophy in TLE and amnestic MCI

Both TLE and amnestic MCI groups showed prominent cortical thinning in bilateral medial temporal lobe (MTL) regions (Fig. 1A and B) compared to control subjects. Laterally, amnestic MCI showed localized atrophy in lateral

Table 1 Patient and control demographics

	TLE	Amnestic MCI	Healthy controls	Statistic	*P*-value
n	73	79	70		
Age, years	61.15 (4.86) [55–77]	63.67 (3.59) [55–76]	68.10 (4.07) [55–72]	$F = 50.26$	<0.001
Education, years	13.42 (2.5)	16.37 (2.8)	16.27 (2.7)	$F = 27.70$	<0.001
Sex, male/female	30/43	39/40	27/43	Fisher = 1.95	0.381

Data are presented as mean (SD) [range].

Table 2 TLE clinical and demographic characteristics

	Early onset	Late onset	t-value	*P*-value
n	50	23		
Age, years	60.43 (4.49)	62.70 (5.36)	−1.88	0.064
Education, years	13.08 (2.49)	14.13 (2.63)	−1.64	0.106
Age of onset, years	24.02 (15.18)	56.13 (4.29)	**−13.81**[a]	**<0.001**
Duration, years	36.42 (16.56)	6.59 (5.55)	**−11.42**[a]	**<0.001**
Current anti-seizure medications[b], *n*	2.1 (0.76)	2.0 (0.77)	0.75	0.46
Failed anti-seizure medications, *n*	5.60 (2.66)	4.73 (2.12)	1.32	0.190
			Fisher's Exact	***P*-value**
Sex, M/F	20/30	10/13	0.079	0.803
Handedness, L/R/A	2/44/4	5/17/1	5.24	0.066
MTS, Y/N	28/20	6/17	**6.48**	**0.013**
Onset side, L/R/Bilateral	27/14/8	15/6/2	0.855	0.682
Epilepsy risk factors				
Febrile seizures, Y/N	6/42	0/23	3.140	0.167
Family history of epilepsy, Y/N	8/42	3/20	0.108	1.00
Moderate or severe TBI, Y/N	6/44	1/22	1.064	0.421
Vascular risk factors				
History of stroke, Y/N	1/49	0/23		
Diabetes, Y/N	1/49	2/21	1.792	0.232
Hypertension, Y/N	19/31	7/16	0.393	0.606
Hyperlipidaemia, Y/N	13/37	7/16	0.156	0.780
BMI >30, Y/N	10/33	10/11	3.898	0.083

Data are presented as mean (SD). A = ambidextrous; BMI = body mass index; F = females; L = left; M = males; MTS = mesial temporal sclerosis; R = right; TBI = traumatic brain injury. Values in bold represent $P < 0.05$.

[a]Equal variance not assumed.

[b]BMI data were not available for nine patients.

temporal, left posterior parietal, and frontal regions, whereas TLE showed atrophy within the precentral gyrus.

The region of interest ANCOVAs confirmed the robustness of the MTL thinning in both groups compared to healthy controls (Table 3 and Fig. 1C–F; estimated marginal means for all regions of interest are shown in Supplementary Table 1). The ANCOVAs were significant in the bilateral hippocampus, entorhinal, temporal pole, parahippocampal, and fusiform (Table 3). Follow-up tests revealed that TLE patients displayed thinner cortex relative to healthy control subjects across nearly all cortical regions including the bilateral entorhinal [Left (L): $P < 0.001$, Right (R): $P < 0.001$], bilateral temporal pole (L: $P = 0.004$, R: $P < 0.001$), bilateral parahippocampal (L: $P = 0.268$, R: $P = 0.039$), and bilateral fusiform (L: $P = 0.009$, R: $P < 0.001$). In the hippocampus, TLE had lower volume in the right ($P = 0.009$) and a trend toward lower volume in the left hippocampus ($P = 0.077$). When comparing TLE and amnestic MCI, the only difference was in left entorhinal ($P = 0.015$) and left temporal pole ($P = 0.049$), with thinner cortex observed in the TLE group. In the lateral temporal regions of interest, only the bilateral middle temporal gyrus and the right inferior temporal ANCOVAs were significant. This was driven by amnestic MCI demonstrating thinner cortex than healthy controls in the bilateral middle temporal (L: $P = 0.005$; R: $P = 0.030$) and right inferior temporal cortex ($P = 0.045$). In precentral cortex, patients with TLE showed thinner cortex relative to both healthy control subjects (L: $P < 0.001$; R: $P = 0.003$) and amnestic MCI (L: $P = 0.002$; R: $P = 0.002$).

Patterns of cortical atrophy in left, right and bilateral TLE

Cortical atrophy across patients with left, right, and bilateral TLE showed the same regional patterns, including bilateral MTL and lateral precentral thinning (Supplementary Fig. 1).

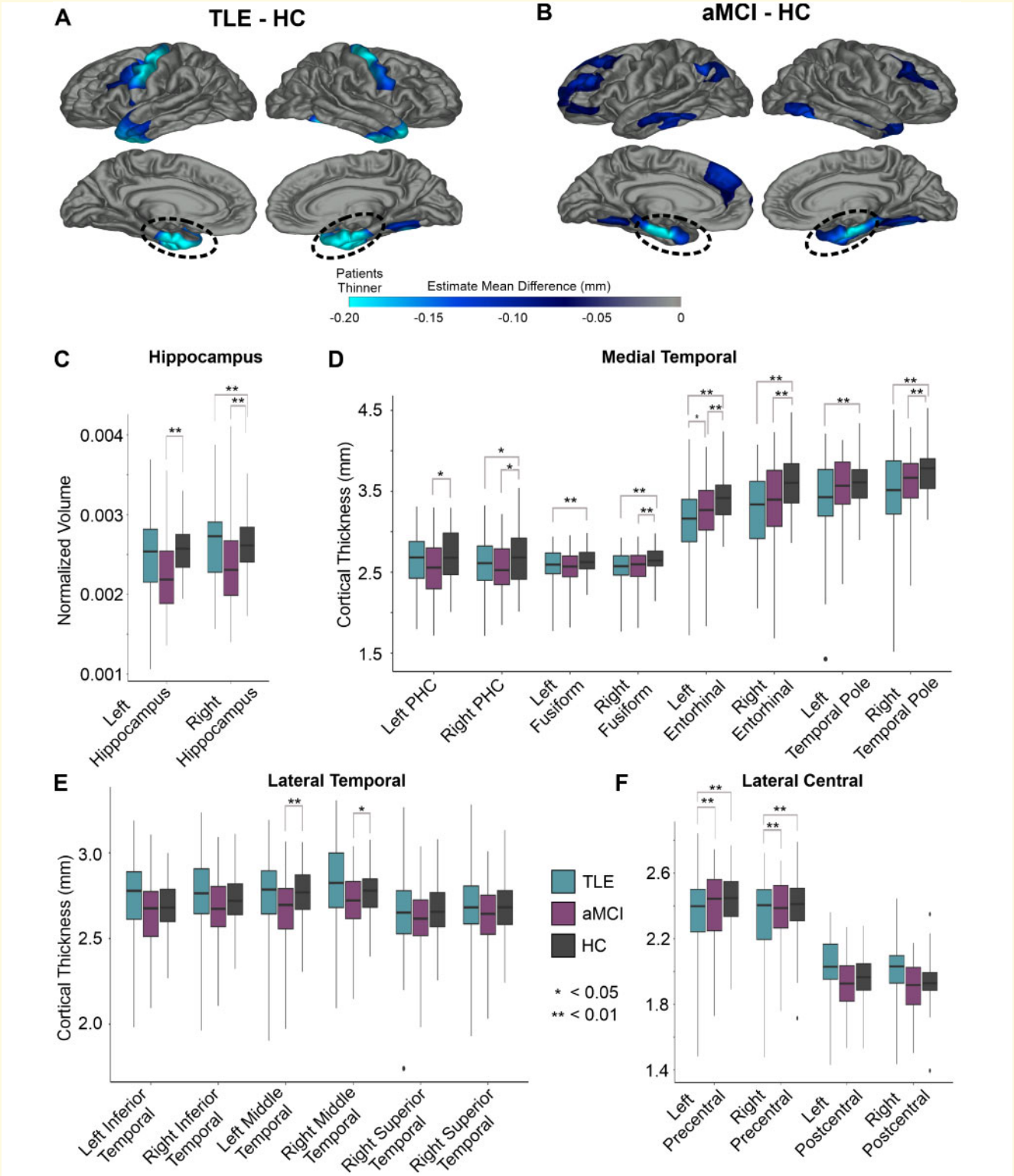

Figure 1 Overlapping patterns of MTL cortical atrophy in TLE and amnestic MCI. (**A** and **B**) Patterns of cortical thinning for both TLE and amnestic MCI (aMCI) relative to healthy control subjects (HC). Blue denotes cortex significantly thinner than healthy controls for each patient group. Both patient groups showed prominent cortical thinning in bilateral medial temporal lobe (MTL) regions highlighted by dashed lines. (**C**–**F**) To confirm the robustness of the surface analyses, region of interest analyses were performed using the Desikan-Killiany parcellation. Similar to the surface analyses, significant thinning was found for patient groups relative to healthy control subjects in MTL regions. Teal = TLE; purple = amnestic MCI; and dark grey = healthy controls. *$P < 0.05$, **$P < 0.01$. PHC = parahippocampal.

Table 3 TLE, amnestic MCI and control group differences in cortical thickness

	ANCOVA	TLE versus HC	Amnestic MCI versus HC	TLE versus amnestic MCI
Medial subcortical				
Left hippocampus	**$F(2,214) = 12.2, P < 0.001$**	$P = 0.077$	**$P < 0.001$**	$P = 0.094$
Right hippocampus	**$F(2,214) = 11.7, P < 0.001$**	**$P = 0.009$**	**$P < 0.001$**	$P = 0.515$
Medial temporal				
Left entorhinal	**$F(2,214) = 13.2, P < 0.001$**	**$P < 0.001$**	**$P = 0.006$**	**$P = 0.007$**
*Right entorhinal	**$F(2,214) = 10.2, P < 0.001$**	**$P < 0.001$**	**$P = 0.005$**	$P = 0.087$
Left temporal pole	**$F(2,214) = 5.34, P = 0.005$**	**$P = 0.004$**	$P = 0.302$	**$P = 0.049$**
Right temporal pole	**$F(2,214) = 7.28, P < 0.001$**	**$P < 0.001$**	**$P = 0.037$**	$P = 0.100$
Left parahippocampal	**$F(2,214) = 3.42, P = 0.035$**	$P = 0.268$	**$P = 0.026$**	$P = 0.785$
Right parahippocampal	**$F(2,214) = 4.19, P = 0.016$**	**$P = 0.039$**	**$P = 0.023$**	$P = 0.935$
Left fusiform	**$F(2,214) = 4.72, P = 0.01$**	**$P = 0.009$**	$P = 0.055$	$P = 0.422$
Right fusiform	**$F(2,214) = 10, P < 0.001$**	**$P < 0.001$**	**$P = 0.003$**	$P = 0.141$
Lateral temporal				
Left inferior temporal	$F(2,214) = 1.68, P = 0.19$	$P = 0.984$	$P = 0.339$	$P = 0.280$
Right inferior temporal	**$F(2,214) = 3.07, P = 0.049$**	$P = 0.659$	**$P = 0.045$**	$P = 0.419$
Left middle temporal	**$F(2,214) = 5.11, P = 0.007$**	$P = 0.175$	**$P = 0.005$**	$P = 0.614$
Right middle temporal	**$F(2,214) = 3.71, P = 0.026$**	$P = 0.776$	**$P = 0.030$**	$P = 0.236$
Left superior temporal	$F(2,214) = 2.56, P = 0.080$	$P = 0.163$	$P = 0.086$	$P = 0.994$
Right superior temporal	$F(2,214) = 2.37, P = 0.096$	$P = 0.206$	$P = 0.096$	$P = 1.00$
Lateral central				
Left precentral	**$F(2,214) = 7.55, P < 0.001$**	**$P = 0.001$**	$P = 0.672$	**$P = 0.002$**
Right precentral	**$F(2,214) = 7, P = 0.001$**	**$P = 0.003$**	$P = 0.923$	**$P = 0.002$**
Left postcentral	$F(2,214) = 1.76, P = 0.17$	$P = 0.809$	$P = 0.509$	$P = 0.183$
Right postcentral	$F(2,214) = 0.765, P = 0.47$	$P = 1.00$	$P = 0.572$	$P = 0.594$

HC = healthy controls. Values in bold represent $P < 0.05$.
Benjamin-Hochberg false discovery rate (FDR) was used to control for multiple comparisons.

Patterns of cortical atrophy in early and late onset TLE

The atrophy patterns within the LO-TLE patients were similar to the overall TLE pattern with prominent thinning in bilateral MTL and precentral regions, but with atrophy more pronounced and extending into prefrontal, lateral temporal, and paracentral regions (Fig. 2A and B). Conversely, the surface patterns for the EO-TLE group were less widespread, with significant thinning apparent in the right MTL and left precentral, but thinning in the left MTL and right precentral regions that was subthreshold in our surface analysis.

ANCOVAs and follow-up comparisons for patients with LO-TLE compared to healthy controls, amnestic MCI, and EO-LTE for hippocampal and MTL regions of interest are shown in Table 4 and Fig. 2C and D. ANCOVAs revealed differences across all MTL regions of interest: bilateral hippocampus [L: $F(3,213) = 10.2$, $P < 0.001$, R: $F(3,213) = 8.9$, $P < 0.001$], entorhinal [L: $F(3,213) = 10.4$, $P < 0.001$, R: $F(3,213) = 7.81$, $P < 0.001$], temporal pole [L: $F(3,213) = 3.58$, $P = 0.015$, R: $F(3,213) = 5.04$, $P = 0.002$], parahippocampal [L: $F(3,213) = 2.96$, $P = 0.033$, R: $F(3,213) = 2.82$, $P = 0.040$], and fusiform [L: $F(3,213) = 5.95$, $P < 0.001$, R: $F(3,213) = 10.30$, $P < 0.001$]. The LO-TLE group showed larger left, but not right hippocampal volume (L: $P = 0.010$; R: $P = 0.203$) compared to the amnestic MCI group, whereas patients with LO-TLE had thinner bilateral entorhinal cortex (L: $P = 0.002$; R: $P = 0.034$) and bilateral fusiform (L: $P = 0.030$; R: $P = 0.003$) compared to patients with amnestic MCI. Patients in the LO-TLE group had significantly thinner cortex in bilateral fusiform (L: $P = 0.025$; R: $P = 0.009$) compared to the EO-TLE group.

Neuropsychological profiles

Supplementary Table 2 shows the ANCOVAs for each neuropsychological test across TLE, amnestic MCI, and healthy control subjects. All ANCOVAs were significant (all $P < 0.001$). Follow-up tests demonstrated that TLE patients had lower test scores relative to healthy controls on LM1, LM2, RAVLT-Delayed, BNT, and CF (all $P < 0.001$). Patients with amnestic MCI had lower scores relative to healthy controls on LM1, LM2, RAVLT-Delayed, RAVLT-Recog, BNT, and CF (all $P < 0.001$). Finally, patients with amnestic MCI displayed lower scores relative to those with TLE on LM2, RAVLT-Delayed, and RAVLT-Recog (all $P < 0.001$).

To determine whether cognitive profiles differed among EO-TLE and LO-TLE, as well as amnestic MCI, ANCOVAs were performed using patient *z*-scores derived from the mean of the healthy control subjects (Fig. 3 and Table 5). Group differences emerged for LM2, RAVLT-Delayed, and RAVLT-Recog (all $P < 0.001$). Follow-up tests revealed no differences between EO-TLE and LO-TLE in LM2

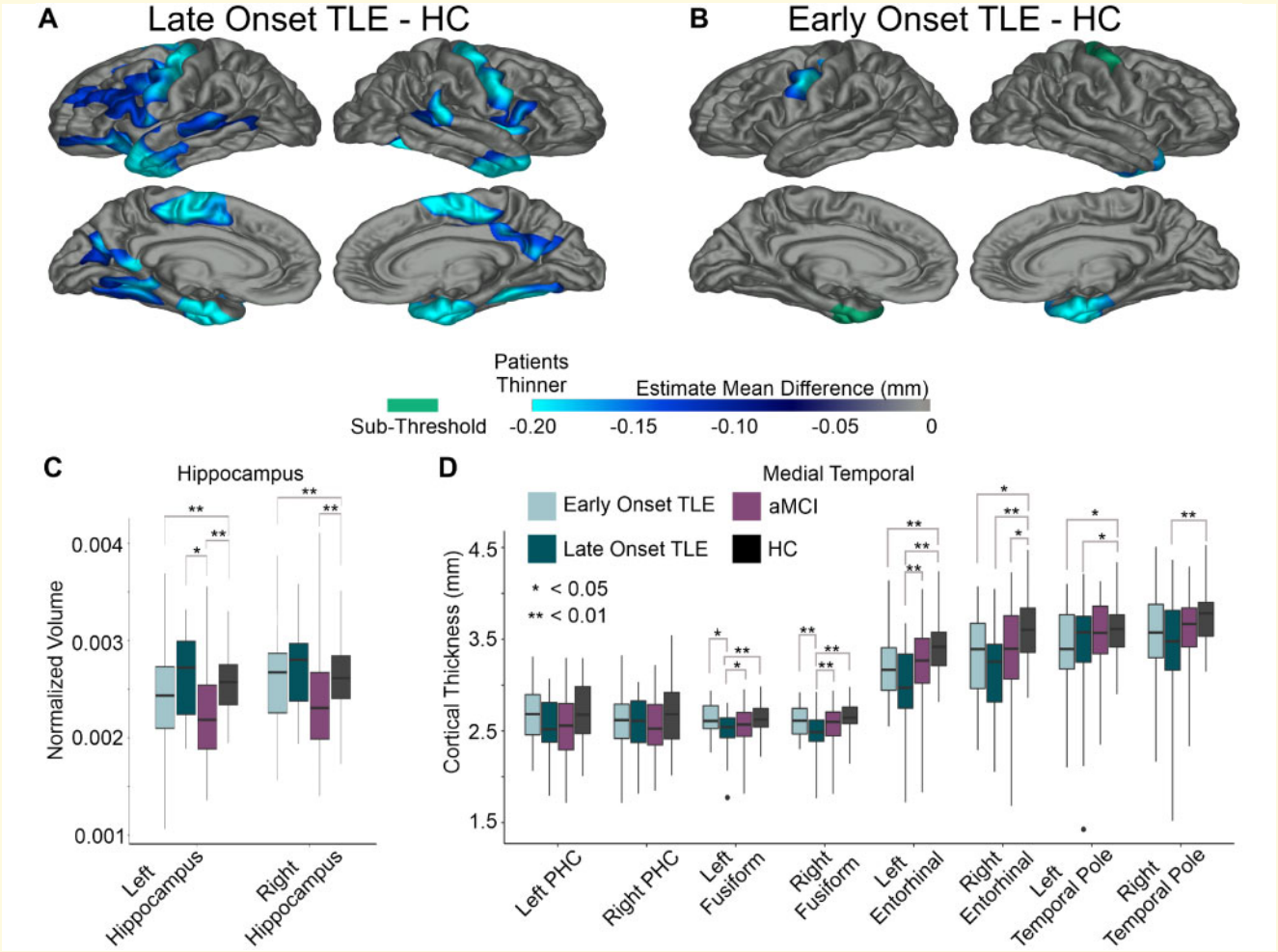

Figure 2 Temporal lobe atrophy is at least as widespread in patients with LO-TLE compared to EO-TLE. (**A** and **B**) Patterns of cortical thinning for both LO-TLE and EO-TLE relative to healthy controls (HC). Blue denotes cortex significantly thinner than healthy controls for each patient group. Teal denotes clusters of thinning that were subthreshold after cluster correction in the EO-TLE group. (**C** and **D**) Region of interest analyses performed using the Desikan parcellation confirm the robustness of the surface patterns. Light teal = EO-TLE; dark teal = LO-TLE; purple = amnestic MCI; dark grey = healthy controls. *$P < 0.05$, **$P < 0.01$. PHC = parahippocampal.

Table 4 LO-TLE group differences in cortical thickness

	ANCOVA	LO-TLE versus HC	LO-TLE versus amnestic MCI	LO-TLE versus EO-TLE
Medial subcortical				
Left hippocampus	**$F(3,213) = 10.2$, $P < 0.001$**	$P = 0.938$	**$P = 0.010$**	$P = 0.084$
Right hippocampus	**$F(3,213) = 8.9$, $P < 0.001$**	$P = 0.396$	$P = 0.203$	$P = 0.292$
Medial temporal				
Left entorhinal	**$F(3,213) = 10.4$, $P < 0.001$**	**$P < 0.001$**	**$P = 0.002$**	$P = 0.165$
*Right entorhinal	**$F(3,213) = 7.81$, $P < 0.001$**	**$P < 0.001$**	**$P = 0.034$**	$P = 0.324$
Left temporal pole	**$F(3,213) = 3.58$, $P = 0.015$**	$P = 0.056$	$P = 0.368$	$P = 0.987$
Right temporal pole	**$F(3,213) = 5.04$, $P = 0.002$**	**$P = 0.002$**	$P = 0.163$	$P = 0.873$
Left parahippocampal	**$F(3,213) = 2.96$, $P = 0.033$**	$P = 0.164$	$P = 0.982$	$P = 0.49$
Right parahippocampal	**$F(3,213) = 2.82$, $P = 0.040$**	$P = 0.112$	$P = 0.962$	$P = 0.986$
Left fusiform	**$F(3,213) = 5.95$, $P < 0.001$**	**$P < 0.001$**	**$P = 0.030$**	**$P = 0.025$**
Right fusiform	**$F(3,213) = 10.3$, $P < 0.001$**	**$P < 0.001$**	**$P = 0.003$**	**$P = 0.009$**

HC = healthy controls. Benjamin-Hochberg false discovery rate (FDR) was used to control for multiple comparisons. Values in bold represent $P < 0.05$.

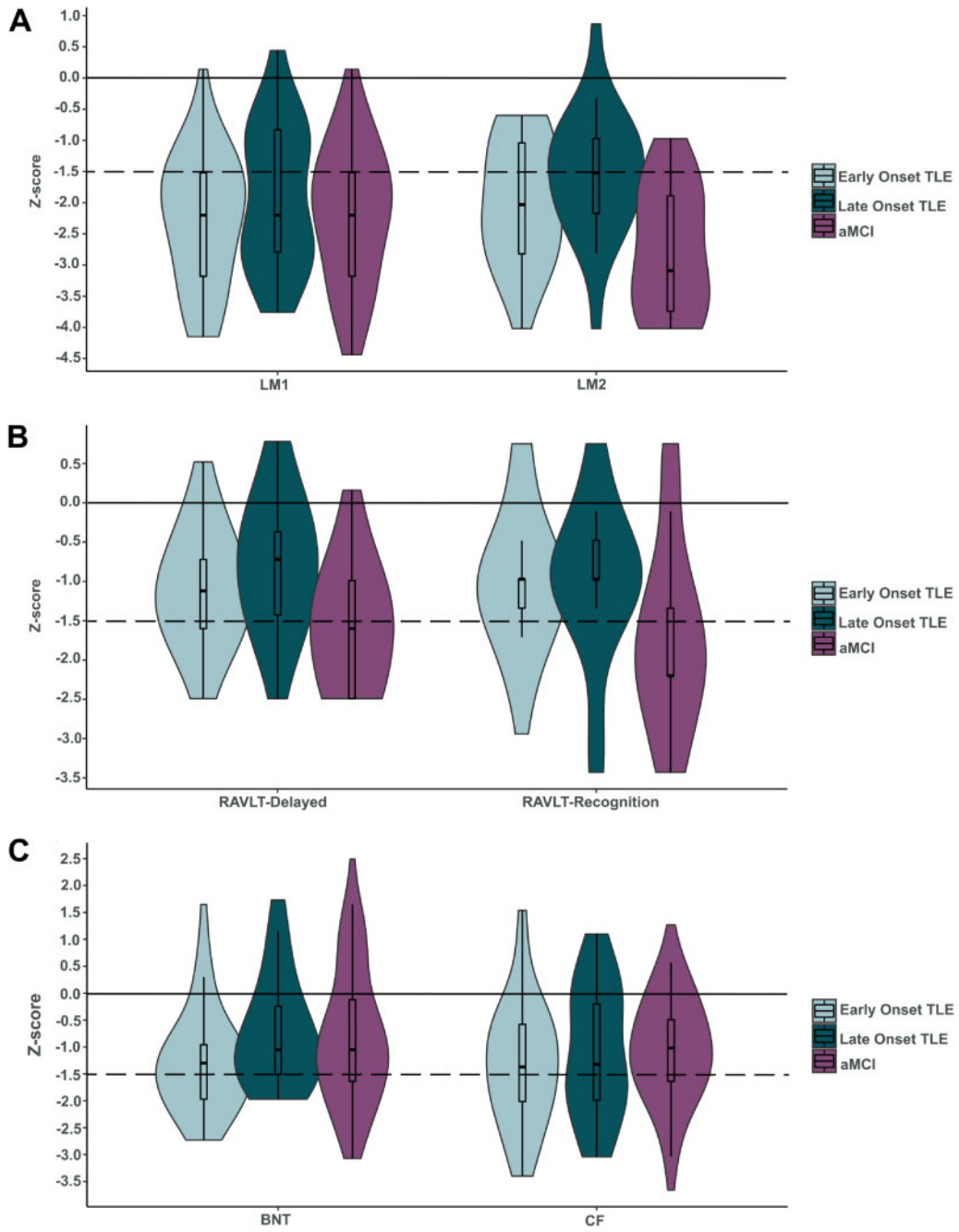

Figure 3 Neuropsychological performance across patient groups. (**A**–**C**) Distribution of z-scores across neuropsychological tests for EO-TLE, LO-TLE, and amnestic MCI (aMCI). Solid line indicates average performance and dotted line indicates impairment at 1.5 SD below the mean of healthy controls (HC). BNT = Boston Naming Test; CF = Category Fluency; RAVLT = Rey Auditory Verbal Learning Test.

($P = 0.52$), RAVLT-Delayed ($P = 0.80$), or RAVLT-Recog ($P = 1.0$). Similar to the omnibus ANCOVA, amnestic MCI had lower scores on LM2 (LO-TLE: $P < 0.001$; EO-TLE: $P < 0.001$), RAVLT-Delayed (LO-TLE: $P < 0.001$; EO-TLE: $P = 0.003$), and RAVLT-Recog (LO-TLE: $P = 0.026$; EO-TLE: $P = 0.003$) compared to TLE patient groups.

As a *post hoc* investigation, we examined the possible influence of number of current medications, number of failed medications, and the presence of leukoaraiosis (as a measure of vascular burden) on neuropsychological performances of the EO-TLE and LO-TLE groups. Stepwise regressions that included age, education, and sex as covariates revealed that none of the clinical variables contributed to any of the cognitive scores in the EO-TLE or LO-TLE groups (all P-values > 0.05).

Table 5 LO-TLE group differences in cognitive performance

	ANCOVA	EO-TLE versus LO-TLE	EO-TLE versus amnestic MCI	LO-TLE versus amnestic MCI
LM1	$F(2,140) = 1.65$, $P = 0.195$	$P = 1.00$	$P = 1.00$	$P = 0.219$
LM2	**$F(2,140) = 19.9$, $P < 0.001$**	$P = 0.517$	**$P < 0.001$**	**$P < 0.001$**
RAVLT-Delayed	**$F(2,126) = 11.54$, $P < 0.001$**	$P = 0.802$	**$P = 0.003$**	**$P < 0.001$**
RAVLT-Recog	**$F(2,119) = 6.97$, $P < 0.001$**	$P = 1.00$	**$P = 0.003$**	**$P = 0.026$**
BNT	$F(2,139) = 2.16$, $P = 0.119$	$P = 0.234$	$P = 0.202$	$P = 1.00$
CF	$F(2,135) = 0.970$, $P = 0.382$	$P = 1.00$	$P = 0.506$	$P = 1.00$

BNT = Boston Naming Test; CF = category fluency; LM1 = logical memory 1; LM2 = logical memory 2; RAVLT-Delayed = Rey Auditory Verbal Learning Test-Delayed; RAVLT-Recog = Rey Auditory Verbal Learning Test-Recognition. Values in bold indicate $P < 0.05$.
Benjamin-Hochberg false discovery rate (FDR) was used to control for multiple comparisons.

Discussion

A quickly growing but understudied population is older patients with epilepsy, a cohort at increased risk for cognitive impairment (Witt *et al.*, 2014), pathological brain ageing (Galovic *et al.*, 2019), and decreased quality of life (Laccheo *et al.*, 2008; McLaughlin *et al.*, 2008). Here, we demonstrate that patients with TLE share a similar pattern and magnitude of MTL cortical thinning to patients with amnestic MCI. Furthermore, this pattern of thinning is not tied directly to duration of seizures, as patients with short-duration LO-TLE demonstrate more consistent atrophy relative to patients with long-duration EO-TLE and indistinguishable cognitive impairment. Similar MTL atrophy patterns and cognitive impairments in TLE and amnestic MCI, combined with recently published data on accelerated cortical atrophy in patients with epilepsy (Galovic *et al.*, 2019), motivates further longitudinal and mechanistic investigations into the effect of TLE, and other epilepsies, on the ageing brain.

Cortical atrophy and cognitive profiles in TLE and amnestic MCI

Shared hippocampal atrophy and memory deficits observed in both older adults with TLE and amnestic MCI have been of keen interest (Lapointe *et al.*, 2016; Sen *et al.*, 2018; Tai *et al.*, 2018). Here we present evidence that these two clinical populations show a similar magnitude and pattern of cortical thinning in bilateral MTL, including the entorhinal, temporal pole, parahippocampal, and fusiform gyri. This shared pattern of MTL atrophy is intriguing in light of emerging clinical and animal studies positing a 'bidirectional relationship' between TLE and amnestic MCI/Alzheimer's disease, suggesting a potential shared pathogenesis. Patients with epilepsy are at increased risk of developing dementia and Alzheimer's disease (Breteler *et al.*, 1991, 1995), and patients with Alzheimer's disease have a 6- to 10-fold higher risk of developing seizures (Imfeld *et al.*, 2013; Cheng *et al.*, 2015). Second, histopathology from patients with TLE has demonstrated the presence of tau pathology (Tai *et al.*, 2016) and amyloid-β precursor protein (Sheng *et al.*, 1994) within resected tissue, which are common pathologies in Alzheimer's disease. Furthermore, in rodent models of TLE, amyloid-β has been tied to epileptiform activity (Minkeviciene *et al.*, 2009; Chin and Scharfman, 2013). Taken together, our findings provide additional evidence of similarities between TLE and prodromal Alzheimer's disease (i.e. amnestic MCI), which could reflect a common pathophysiology in a subset of older patients.

Reports of overlapping histopathology highlights the question of how distinct these patient groups truly are. From a diagnostic perspective, our patient cohorts are presumably distinct. Seizure disorders are an exclusionary criterion for ADNI and none of our patients with TLE had received a formal diagnosis of amnestic MCI at the time of scanning and cognitive testing. However, the diagnosis of seizures in amnestic MCI/Alzheimer's disease is challenging, as is the diagnosis of amnestic MCI/Alzheimer's disease in older patients with epilepsy (Fujimoto *et al.*, 2018; Veluri, 2019; Lezaic *et al.*, 2020). In light of emerging evidence regarding the interrelation of seizures and amnestic MCI/Alzheimer's disease along with evidence of 'silent seizures' in a subset of patients with Alzheimer's disease (Lam *et al.*, 2017; Vossel *et al.*, 2017), future investigations may consider studying potential co-morbidities systematically (i.e. add a routine EEG to large, multisite amnestic MCI/Alzheimer's disease studies) rather than excluding patients suspected of harbouring both conditions. Although not routinely acquired in most clinical settings, the presence of Alzheimer's disease biomarkers could also improve the awareness of amnestic MCI and signal an increased risk for progression in many older adults presenting with TLE.

In this context, it is important to note differences in pathology between groups. The extra-temporal cortical pathology was largely disease-specific in our sample. Bilateral thinning of the precentral gyrus was observed in patients with EO- and LO-TLE but was absent in the amnestic MCI cohort. Precentral/paracentral thinning is frequently observed in patients with TLE and other epilepsy syndromes (McDonald *et al.*, 2008; Whelan *et al.*, 2018) and has been hypothesized to reflect the direct effects of seizures (Bonilha *et al.*, 2006). Thus, this precentral thinning in patients with TLE does not contradict the possibility of shared pathogenesis, but may represent the additional burden of their seizure disorder. Cognitively, despite overlap in memory encoding and language impairment profiles between TLE and

amnestic MCI, patients with amnestic MCI performed more poorly on measures of delayed memory relative to EO-TLE and LO-TLE at the group level. Thus, these patient groups present with nuanced differences in their imaging and cognitive profiles that warrant further investigation.

Late-onset TLE: a unique subtype?

Heterogeneity within older patients with TLE complicates an already complex clinical picture. Aetiologies in LO-TLE often differ from EO-TLE; late-onset is more likely to be the result of occult cerebrovascular disease (Hauser *et al.*, 1991), stroke (De Reuck *et al.*, 2008), head trauma (Annegers *et al.*, 1998), progressive neurodegenerative disorders (Stefan, 2011), or commonly an unknown aetiology (Morillo, 2012; Sarkis *et al.*, 2019). To address this potential heterogeneity, we split patients into onset before and after age 50 to determine whether their patterns of cortical atrophy and cognitive impairment differ. Further, patients with a history of known stroke or tumours were excluded from this study.

Between groups, cortical thinning was at least as widespread if not more so in LO-TLE. In addition, these short-disease duration LO-TLE patients showed similar cognitive impairments on measures of memory and language relative to long disease duration EO-TLE. Highlighting the underlying aetiological differences based on age of onset, in our cohort patients with EO-TLE were significantly more likely to have MTS. Given that TLE patients without MTS may demonstrate more subtle cortical thickness abnormalities (Mueller *et al.*, 2009), we ran a *post hoc* analysis including only MTS-negative patients from the EO-TLE and LO-TLE groups, which showed the same broad pattern of cortical thinning in both cohorts (Supplementary Table 3). The similar pattern of cortical thinning and cognitive impairment across EO-TLE and LO-TLE is particularly noteworthy given the ~30 additional years of average seizure duration in the EO-TLE patients compared to the LO-TLE (who had an average of only 6.7 years of seizures). This is counterintuitive given cross-sectional studies in middle-aged patients with TLE suggesting a relationship between disease duration and greater cortical thinning (Caciagli *et al.*, 2017), which would lead to expectations of greater seizure burden in EO-TLE. One hypothesis is that significant cortical atrophy and cognitive impairments observed in LO-TLE patients preceded the onset of epilepsy, driven by some other insidious pathology (e.g. vascular/Alzheimer's disease), which ultimately led to the development of their temporal lobe seizures (Lapointe *et al.*, 2016). Alternatively, recent longitudinal data suggest that atrophy could be accelerated in older adults with epilepsy due to an already vulnerable brain (Galovic *et al.*, 2019).

Whether cognitive and brain ageing is accelerated due to epilepsy has been a debate in the literature, with some studies suggesting progressive cognitive decline in patients with longstanding TLE (Hermann *et al.*, 2007). However, other studies have shown the presence of cognitive deficits around the time of epilepsy diagnosis (Taylor and Baker, 2010; Baker *et al.*, 2011) which may be particularly pronounced in older patients with late-onset epilepsy who have shown cognitive decline within the first year of diagnosis (Liguori *et al.*, 2019). Education represents another factor. The patients with TLE in our study had lower educational attainment relative to both healthy control subjects and patients with amnestic MCI, which may lead to a lack of cognitive reserve and therefore less capacity to compensate for cognitive decline (Jokeit and Ebner, 1999; Hermann *et al.*, 2002). Of note, education did not differ between EO-TLE and LO-TLE patients despite significant differences (~30 years) in seizure duration. Lower educational attainment in EO-TLE patients is often attributed to the developmental impact of seizures on cognitive and academic development coupled with psychosocial limitations (e.g. inability to drive to class or live alone at college; chronic absenteeism). However, these factors would not explain lower education in the LO-TLE group, raising concerns that other insidious processes may precede the development of seizures by decades in patients with LO-TLE (Osler *et al.*, 2018).

Taking both the cortical thinning and cognitive impairment into account, previous data and our present study suggest that older adults with newly diagnosed TLE may benefit from initial screening for cortical thinning and cognitive deficits at the time of diagnosis, in addition to continued close monitoring to detect early signs of cognitive decline. However, the definition of what age constitutes late-onset epilepsy is debated, with no clearly defined beginning timepoint (Josephson *et al.*, 2016). We chose an age of 50 years as our cut-off because it appears as an inflection point in epilepsy incidence across populations (Banerjee and Hauser, 2008; Beghi *et al.*, 2019; Lezaic *et al.*, 2020). To fully understand LO-TLE and to increase the precision in its characterization will require a large and well-characterized patient sample. However, the multicentre nature of our approach highlights the difficulty of accumulating a large sample of these patients and thus a multinational collaboration, such as ENIGMA-Epilepsy (Whelan *et al.*, 2018) may present a path forward. Disentangling whether the degree of cortical thinning and cognitive impairment in LO-TLE reflects an accelerated disease course after seizure onset or whether it precedes the onset of seizures is of key interest for future studies.

Epilepsy, ageing and risk factors: an evolving picture

Despite increasing interest, there are few empirical studies of brain ageing in older adults with epilepsy. A recent meta-analysis dominated by cross-sectional studies in younger and middle-aged patients with TLE demonstrated low-to-moderate evidence for progressive atrophy in TLE (Caciagli *et al.*, 2017). Additionally, cross-sectional studies using machine learning have supported the concept of accelerated ageing, with the brains of patients with chronic epilepsy appearing

4.5–10.9 years older than age-matched controls (Hwang *et al.*, 2020), though this was not associated with disease duration (Hwang *et al.*, 2020). However, a recent longitudinal study of 190 patients with a variety of focal epilepsies has supported progressive atrophy, especially in older adults. This study reported an annualized rate of global cortical thinning in patients older than 55 years that was twice the rate observed in age-matched controls (Galovic *et al.*, 2019). These changes were most pronounced within the first 5 years after seizure onset and within bilateral MTL in TLE. Other recent cross-sectional studies in patients with late-onset epilepsy have reported lower cortical volumes, especially in the temporal lobes, and an increased white matter hyperintensity volume (Johnson *et al.*, 2018). These late-onset findings may be due to influence of midlife cerebrovascular (e.g. obesity, hypertension) and/or genetic (i.e. *APOE* ε4 allele) risk factors on the likelihood of developing dementia and seizures later in life (Sen *et al.*, 2018). A recent study reported clinically significant cognitive impairment in 59% of their patients with late-onset epilepsy of unknown origin (LOEU; Cesarini *et al.*, 2020). Interestingly, this subset of patients had similar Alzheimer's disease-like CSF profiles to patients with amnestic MCI without seizures. Increased amyloid-β burden has been reported in several studies of patients with LOEU (Costa *et al.*, 2016, 2018, 2019) and has been associated with epileptiform activity (Minkeviciene *et al.*, 2009; Chin and Scharfman, 2013). These findings suggest that amyloid pathology in older adults may lead to both epileptogenesis and cognitive impairment. Currently, a majority of findings remain based on young to middle-aged patients or heterogeneous epilepsy samples. Thus, the likelihood, nature, and rate of progressive brain changes in older adults with TLE remains largely unknown and in great need of additional study.

Strengths and limitations

This study represents the first to characterize cortical atrophy patterns and cognitive impairment in a large cohort of older adults with TLE and directly compare these patterns to those observed in amnestic MCI and healthy control subjects. We accomplish this in a multicentre setting with uniform MRI data processing; this uniformity ensures that similarities and differences in the observed patterns are not due to differences in software, registration, or spatial smoothing. We also investigate atrophy and cognitive impairment patterns in those with EO- versus LO-TLE, demonstrating largely equivalent atrophy and impairment despite divergent epilepsy durations. Given likely aetiological differences between these cohorts, there is a clear need for further research to more fully understand patient trajectories. Our data add to an expanding literature aimed at understanding pathological brain changes in older adults with chronic and new-onset TLE.

The retrospective and cross-sectional nature of our data collection posed limitations to the full characterization of the mechanisms underlying ageing in our epilepsy cohort because additional clinical and neuroimaging data were not available. However, the current limitations of our study serve as potential avenues of further research. Neither clinical nor MRI follow-up data were available to determine whether our TLE patients progressed to Alzheimer's disease or another type of dementia. Similarly, histopathological data are not available on our patients and therefore, we are unable to characterize exact aetiology or co-morbidities. It is possible that incipient Alzheimer's disease, occult cerebrovascular disease, or other disease processes underlie the cortical atrophy and cognitive impairments observed in our LO-TLE patients. As noted, CSF biomarker, amyloid PET, and genetic data relating to neurodegenerative disorders are not routinely collected for patients with TLE. Although 11 TLE patients in our study had a familial history of epilepsy, we did not have information on their specific genetic mutations as genetic testing is not routinely conducted across epilepsy centres. Genetic factors that affect the causation and severity of epilepsy syndromes may be important for understanding long-term prognosis in older adults with TLE. From the available clinical data we cannot systematically determine whether differences in the stability of epilepsy or anti-seizure medication use over time differentially contributed to cortical thinning and cognitive impairment due to pre-existing differences in clinical documentation across centres. The retrospective nature of the data in this study also led to unavoidable age differences between our healthy controls and TLE cohorts. However, because our control subjects were, on average, older than our TLE patients and the cortical mantle thins with age, this age difference would have only minimized our effects and it is possible that we underestimated cortical atrophy in our TLE sample. In our analyses we combined both unilateral and bilateral TLE patients in the same analysis, as subgroups of patients with right, left, and bilateral TLE were too small to study independently; however, our data suggest that cortical atrophy patterns do not differ significantly as a function of side of seizure onset (Supplementary Fig. 1). Finally, our patients with TLE all had pharmacoresistant epilepsy and were referred from epilepsy surgical centres and may not be representative of the older TLE population at large.

To address these shortcomings and to better understand the generalizability of our findings as well as the mechanisms underlying the cortical thinning and cognitive impairment, will require MRI and cognitive data collected prospectively from patients with a wide spectrum of epilepsy severity who are carefully phenotyped over time. Future research into the predictive value of such biomarkers could yield important information regarding risk for progression in TLE and motivate the future collection of these data to help identify patients in the prodromal state of Alzheimer's disease.

Conclusion and clinical implications

With a rapidly ageing population, we will see increasing numbers of older patients suffering from epilepsy. Given the widespread cortical thinning and cognitive impairment

reported here, understanding the intersection between TLE, ageing, cognition, and neurodegenerative processes could facilitate early diagnosis (e.g. Is significant MTL cortical thinning in LO-TLE an early biomarker of Alzheimer's disease?), or guide the development of new treatments (e.g. Are there therapies that could halt or modify disease progression?). Our current study does not directly answer these questions, but provides pieces of the puzzle for understanding similarities between TLE and amnestic MCI/Alzheimer's disease motivating future research. Such comparisons across seemingly distinct neurological disorders highlight shared abnormalities that may be overlooked by focus on single disease states. Indeed, treatment of amnestic MCI/Alzheimer's disease patients with anti-seizure medications has improved cognition (Cumbo and Ligori, 2010; Bakker *et al.*, 2012, 2015), potentially due to silencing interictal discharges (Bakker *et al.*, 2012), illustrating the potential of multisyndrome approaches in treatment decision-making across the neurological disease spectrum.

Funding

We would like to acknowledge funding support from the National Institute of Health (R01 NS065838 to C.R.M., T32 MH018399 to E.K., F31 NS111883-01 to A.R., and R01 NS088748 to D.L.D.). Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. Supported by NIH/NINDS R01 NS065838 (C.R.M.); T32 MH018399 (E.K.); F31 NS111883-01 (A.R.); R01 NS088748 (D.L.D.).

Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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