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Research Article

Regional Atrophy in Temporal Lobe Epilepsy: Correlations with Cognitive Impairment

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Abstract

Purpose: Cognitive impairment is commonly observed in patients with temporal lobe epilepsy (TLE). Recently, volumetric analysis showed widespread cortical and subcortical atrophy in patients with TLE. In this study, we hypothesized that the diffuse atrophy in TLE with and without mesial temporal sclerosis (MTS) was associated with cognitive impairment.

Methods: To investigate atrophy patterns in TLE, we studied 40 patients with TLE and MTS and 34 patients with TLE without MTS determined by gross visual inspection of structural magnetic resonance imaging (MRI). Volumetric analysis was performed using FreeSurfer software. The relationship between volume/cortical thickness and performance on neuropsychological tests was evaluated in 33 patients.

Results: Whole brain volume loss and widespread sub-cortical regional atrophy was noted in both TLE with and without MTS regardless of lateralization of seizure onset. Bilateral hippocampus atrophy was seen in both TLE with and without MTS. However, hippocampal volume loss was asymmetrical with more prominent ipsilateral atrophy in the TLE patients with MTS and symmetrical bilaterally in these without MTS. Widespread neocortical thinning was noted in all TLE patients. In TLE without MTS, the cortical thinning pattern was similar in patients with left and right seizure onset. In TLE with MTS, patients with left MTS had more diffused contralateral cortical involvement compared to these with right MTS. One-to-one structural-functional association was only found in immediate and delayed memory performance in all groups. In addition to left hippocampal volume, the cortical thickness in the inferior frontal gyrus and bilateral amygdala also had additional predictive value to performance in memory tests.

Conclusions: The results of this study confirmed widespread regional atrophy in the TLE patients with and without MTS. It also provided evidence that extra-hippocampal atrophy (i.e., in prefrontal regions and amygdala) contributes to memory impairment in medically intractable TLE.

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- Temporal lobe epilepsy
- MRI
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ABBREVIATIONS

TLE: Temporal Lobe Epilepsy; MTS: Mesial Temporal Sclerosis; NL: Nonlesional

INTRODUCTION

Temporal lobe epilepsy (TLE) is the most common cause of medically intractable epilepsy in adults [1-3]. About 60-70% of TLE is associated with mesial temporal sclerosis (MTS), which is characterized by abnormal signal or hippocampus volume loss on structural MRI. Another 30-40% of TLE is associated with a normal appearing hippocampus on the MRI and only mild or no neuronal loss on the histological examination[2]. Patients with TLE commonly develop neurobehavioral comorbidities including abnormalities in cognition, psychiatric status and social adaptive

behavior [4]. The cognitive complications of epilepsy can be heterogeneous, affecting language, attention, and executive functions. However, the most expected cognitive deficit in TLE is memory impairment.

Different factors contribute to cognitive impairment in patients with chronic TLE. These include underlying etiology, adverse effects of antiepileptic medications, frequency and severity of seizures, complications such as status epilepticus, electroencephalography (EEG) abnormalities, and other factors [5-12]. One possible explanation for the observed broad-based cognitive impairment is that structural abnormalities may also extend beyond the confines of the mesial temporal lobe and that these extratemporal abnormalities could have additional cognitive consequences. Recent advances in neuroimaging support this hypothesis. Measurements of cortical thickness have shown diffuse cortical thinning involving both ipsilateral and contralateral temporal and extratemporal regions in TLE with and without MTS [13-16]. A previous study showed that reduced volumes in the orbito-frontal cortex are related to poor executive functioning and impaired memory in these patients [17]. A functional magnetic resonance imaging (fMRI) study demonstrated that the deficits in the processes involved in transient working memory are related to functional connectivity in the prefrontal brain in TLE patients without MTS [18].

The goal of our study was to determine if extratemporal structural changes in TLE could be correlated to cognitive impairment in patients. Given that cognitive deficits are experienced by TLE patients with or without MTS, we hypothesized that the diffuse extratemporal atrophy observed in TLE was associated with pre-surgical cognitive impairment. We used FreeSurfer software (Version 4.5.0) to measure the regional brain volume in TLE patients with and without MTS and a battery of neuropsycological tests to measure cognitive performance. We also evaluated whether extra-hippocampal cortical thickness, especially in prefrontal regions, could contribute to predicting neuropsychological performance in TLE.

MATERIALS AND METHODS

Research participants

This was a retrospective, cross-sectional, single-site study. The patients were selected over a 5-year period (January 2005 to June 2010) from the Epilepsy Monitoring Unit at Parkland Memorial Hospital, an affiliate of the University of Texas Southwestern Medical Center in Dallas, Texas. Demographic and clinical data were obtained through a prospectively maintained electronic database. Temporal lobe epilepsy diagnosis, and seizure localization and lateralization, were determined by a comprehensive evaluation including detailed history, neurologic examination, review of medical records and video-EEG recordings. The inclusion criteria included: (1) refractory chronic unilateral temporal lobe onset seizure documented by video-EEG recording and (2) at least one 3.0 Tesla (3T) MRI with high resolution three-dimensional (3D) T1 sequence. Exclusion criteria included: (1) patients with focal lesions (such as encephalomalacia, vascular malformations or lesions, brain tumor, neurocysticercosis or brain abscess) and (2) other conditions which may result in abnormal MRI findings and compromise cognitive functions (i.e., multiple sclerosis, encephalitis/meningitis, Alzheimer's disease/mild cognitive impairment, history of mental retardation and psychiatric disease). Twenty-two age- and gender-matched healthy volunteers were recruited as controls. Patients with MTS defined by MRI evidence of abnormal fluid-attenuated inversion recovery (FLAIR) hyperintensity in the hippocampal region or gross hippocampal atrophy were classified as TLE-MTS. Patients with normal MRI were classified as nonlesional (NL)-TLE. All study procedures were reviewed and approved by the University of Texas Southwestern Medical Center Institutional Review Board.

Magnetic resonance imaging acquisition and processing

Structural MRI was performed using a General Electric Signal Excite 3T MR scanner (GE, Milwaukee, WI). Three-dimensional T1-weighted structural images were obtained with a slice thickness of 1 mm. The Digital Imaging and Communications in Medicine (DICOM) files were transferred to a Macintosh workstation for analysis with the FreeSurfer suite (Version 4.5.0; Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA), which has been described in detail in the past [19-22]. Briefly, the FreeSurfer analysis includes averaging of multiple volumetric T1-weighted images, removal of non-brain tissue, conversion to Talairach coordinates, automated segmentation of subcortical white and deep gray matter structures, tessellation of the gray-white matter junction, surface deformation along intensity gradients for optimal placement of gray-white and gray-cerebrospinal fluid borders, and cortical parcellation with sub-millimeter precision into units based on gyral and sulcal structure. These procedures result in high-resolution quantification of thickness, surface area and volume over the entire brain, in addition to delineating the atlas-derived subcortical and cortical brain regions. The volume of subcortical structures is obtained from the segmentation step.

Neuropsychological evaluations

The battery of neuropsychological tests included: Wide Range Achievement Test ¾, a reading subtest for a premorbid estimate of intelligence; Wechsler Adult Intelligence Scale ¾ (WAIS), block design and vocabulary subscales for an estimate of intelligence; WAIS for attention; Trail Making Test A and WAIS, a coding subtest for processing speed; Boston Naming Test (BNT) for letter fluency and animal fluency for language; Rey-Osterreith Complex Figure, a test for visuoconstruction; total California Verbal Learning Test (CVLT-II), Rey-Osterreith Complex Figure – immediate and WAIS- immediate logical memory and visual reproduction for immediate memory; CVLT-II long delay, Rey-Osterreith Complex Figure delay, and WAIS delay logical memory and visual reproduction for delayed memory; Trail Making Test B and Wisconsin card sorting total categories for executive functions; and finger tapping for fine motor speed. The results from the neuropsychological evaluations were transformed into Z scores based on the mean and standard deviation of the age-matched normal population.

Statistical analysis

Differences in cortical thickness between controls and NL-TLE, and between controls and MTS-TLE were tested in a

regionally unbiased way using the statistical tools provided by FreeSurfer. Briefly, the cortical structures were reconstructed and voxel-wise volume changes between groups were computed with a general linear model for groups using a 10-mm full-width half-maxmium Gaussian kernel. A false discovery rate (FDR) of 0.05 was used for all the analyses to correct for multiple comparisons. Z-scores (standardized scores defined by the number of standard deviations away from the mean of the respective control group) were calculated for all the subcortical and neocortical regions in each patient group based on the mean and standard deviation of the controls. Differences in the subcortical structure volumes among patient groups were directly compared using two-tailed *t* tests.

The correlations between regional atrophy and cognitive measurement were calculated using Spearman's correlation coefficients and a screening FDR threshold of 0.05. The differences in neuropsychological performance between the groups were evaluated by one-way ANOVA. Linear regression analysis was used to assess whether the subcortical structure and cortical thickness would contribute to predicting neuropsychological performance. Statistical analysis was performed with SPSS (version 11.5; SPSS Inc, Chicago, Illinois).

Morphometric analyses were conducted by 2 independent raters (K.D. and Y.G.), and inter-rater reliability was determined by having each rater analyze 20 brains to determine the intra-class correlation coefficients using two-way ANOVA with mixed effects.

RESULTS

Demographic characteristics

We identified 34 patients in the NL-TLE group and 40 patients in the MTS-TLE group. In the NL-TLE group, 16 patients had left temporal lobe seizure onset based on EEG (L NL-TLE) and 18 had right temporal lobe seizure onset (R NL-TLE). In the MTS-TLE group, 31 patients had left temporal lobe onset (L MTS-TLE) and 9 had right side seizure onset (R MTS-TLE). There were no statistically significant differences between the groups in terms of gender and age at the time of MRI evaluation. Compared to the NL-TLE group, the MTS-TLE group had a younger age of seizure onset (9 vs. 16 years, $p = 0.006$) and longer epilepsy duration (26 vs. 18 years, $p = 0.01$). Within NL and MTS groups, there were no significant differences in age at seizure onset or epilepsy duration between the right and left sided seizure onsets. Demographic information for the patient and control groups is summarized in Table 1.

Inter-rater reliability

The mean intra-class correlation coefficient for inter-rater reliability was 0.990 (median 0.993; range, 0.953 – 0.999). Six cortical regions (left and right entorhinal, precentral, and frontal pole) had variation greater than 20% in controls, and were excluded from subsequent FreeSurfer analysis.

Global atrophy

Global volumetric measures suggested that there was whole brain volume (WBV) loss in both NL-TLE and MTS-TLE patients (Table 2). Compared to controls, L NL-TLE, R NL-TLE and L MTS-TLE had significant decreases of WBV (Z score range from -0.79 to -1.06) and bilateral cerebral white matter volume (Z score range from -0.32 to -1.44). There was a trend towards decreased WBV and cerebral white matter volume in R TLE-MTS but differences were not statistically significant.

Subcortical atrophy

Atrophy of subcortical structures was demonstrated in the hippocampus, thalamus, cerebellum, and brainstem in all groups (Table 3). Specifically, in the L MTS-TLE group, the hippocampal volume was -2.47 ± 0.76 on the left and -0.76 ± 1.13 on the right. In the R MTS-TLE group, the hippocampal volume was -2.07 ± 0.74 on the right, and -0.38 ± 0.47 on the left. On other hand, in the L NL-TLE group, the hippocampus volume was -1.16 ± 0.96 on the left and - 0.90 ± 1.02 on the right. Similarly in the R NL-TLE group, the hippocampus volume was -0.76 ± 1.5 on the right and -0.63 ± 1.14 on the left. Therefore, bilateral hippocampus atrophy was observed in both MTS-TLE and NL-TLE groups. However, hippocampal volume loss was asymmetrical with more prominent ipsilateral atrophy in the MTS-TLE patients and symmetrical in the NL-TLE patients.

Cortical thinning

We compared the cortical thickness pattern in NL-TLE and MTS-TLE patients using FreeSurfer (Figure 1). The L MTS, R NL-TLE, and L NL-TLE groups had a similar neocortical atrophy pattern involving the following regions (FDR 0.05): bilateral inferior temporal, parahippocampal, fusiform, lingual, pericalcarine, cuneus, paracentral lobule, superior frontal, superior parietal, precentral regions, pars orbitalis, pars triangularis, and cingulate. The R MTS-TLE group had a similar pattern but the distribution of atrophy was much less widespread. The pattern of neocortical thinning was similar in R and L NL-TLE patients, but L MTS-TLE patients had more diffuse contralateral cortical involvement compared to R MTS-TLE patients. In summary, widespread neocortical thinning was observed in all groups.

Regional atrophy and cognitive measurement

We reviewed the neuropsychological measures in 33 patients (8 L NL-TLE, 9 R NL-TLE, 8 L MTS-TLE, 8 R MTS-TLE) (Table 4). There were no significant differences in terms of age, epilepsy duration, and handedness among the groups. Reading speed and estimated IQ were used as estimates of premorbid functioning. All TLE patients had diffuse mild impairment of cognitive function in all the tested domains. Patients in both NL and MTS groups had similar performance in all the tested domains.

Further, we investigated the relationship between the regional volume/cortical thickness and neuropsychological measures. In each patient group, there was significant correlation between regional volume and memory performance only (Supplementary Tables 1-4).

Because NL-TLE and MTS-TLE patients had similar neurocognitive test performance, we combined all groups to investigate the predictive value of brain volume for pre-operative memory performance. We used linear multiple regression models to determine the correlation between brain volume and neuropsychological performance (Table 5). According to our analysis, the observed 21% variance of immediate memory

Table 1: Demographic characteristics.

	N	Gender, %Male	Age at MRI, Y M (SD, Median)	Seizure Onset, Y M (SD, Median)	Seizure Duration, Y M (SD, Median)
L NL-TLE	16	38%	36 (14, 32)	16 (14, 14)*	20 (14, 16)*
R NL-TLE	18	28%	34 (12, 35)	15 (13, 14)*	19 (12, 19)*
L MTS-TLE	31	48%	36 (11, 34)	10 (9, 7)	26 (13, 24)
R MTS-TLE	9	56%	35 (10,31)	7 (10,3)	28 (10,27)
Control	22	41%	33.0 (12.8)	-	-

Abbreviations: TLE: Temporal Lobe Epilepsy; NL: Non-Lesional; MTS: Mesial Temporal Sclerosis; L: Left; R: Right; M: Mean; SD: Standard Deviation; Y: Years. * p< 0.01

Table 2: Global brain atrophy in temporal lobe epilepsy.

Volumes	L-NLTLE Mean (SD)	R-NLTLE Mean (SD)	L-MTS Mean (SD)	R-MTS Mean (SD)
ICV	0.11 (1.13)	0.00 (1.53)	- 0.88 (1.42)	- 0.63 (1.10)
WBV *	- 0.97 (0.82)	- 0.79 (0.75)	- 1.06 (0.94)	- 0.91 (0.68)
L Cerebral Cortex	- 0.33 (1.13)	- 0.19 (1.03)	- 0.34 (1.06)	- 0.44 (0.52)
R Cerebral Cortex	- 0.40 (1.19)	- 0.34 (1.23)	- 0.56 (1.18)	- 0.28 (0.55)
L Cerebral WM*	- 1.00 (0.55)	- 1.06 (0.71)	- 1.17 (0.91)	- 0.90 (0.96)
R Cerebral WM*	- 0.32 (1.13)	- 1.44 (1.76)	- 1.32 (0.88)	- 0.76 (0.77)

Data is presented as Z score normalized to the normal control group. ICV: Intracranial Volume; WBV: Whole Brain Volume; WM: White Matter; NLTLE: Non-Lesional Temporal Lobe Epilepsy; MTS: Mesial Temporal Sclerosis; L: Left; R: Right. *FDR: 0.05 (uncorrected p < 0.025 for NLTLE, < 0.01 for MTS)

Table 3: Widespread subcortical atrophy in temporal lobe epilepsy.

Brain region	L- NLTLE Mean (SD)	R- NLTLE Mean (SD)	L-MTS Mean (SD)	R-MTS Mean (SD)
Brainstem*	- 0.94 (0.61)	- 0.67 (0.70)	- 0.96 (0.83)	- 0.65 (0.84)
R Cerebellum WM*	- 1.13 (0.81)	- 0.28 (0.82)	- 0.97 (1.35)	- 0.08 (0.54)
L Cerebellum WM*	- 0.67 (0.60)	- 0.04 (0.65)	- 0.65 (1.09)	0.08 (0.84)
R Cerebellum Cortex*	- 1.61 (1.01)	- 1.12 (0.72)	- 1.69 (1.18)	- 0.87 (0.54)
L Cerebellum Cortex*	- 1.50 (0.85)	-1.18 (0.61)	- 1.60 (0.99)	- 0.85 (0.36)
CC Posterior	- 0.38 (1.33)	- 1.25 (1.40)	- 0.81 (1.25)	- 0.17 (1.69)
R Hippocampus*	- 0.90 (1.02)	- 0.76 (1.5)	- 0.76 (1.13)	- 2.07 (0.74)
L Hippocampus*	- 1.16 (0.96)	- 0.63 (1.14)	-2.47 (1.24)	- 0.38 (0.47)
R Thalamus*	- 0.98 (0.80)	- 0.79 (0.78)	- 1.10 (0.80)	- 1.14 (0.62)
L Thalamus*	- 1.10 (0.78)	- 0.79 (0.58)	- 1.27 (0.80)	- 0.90 (0.39)

Data presented as Z scores normalized to the normal control group. WM: White Matter, CC: Corpus Collosum; NLTLE: Non-Lesional Temporal Lobe Epilepsy; MTS: Mesial Temporal Sclerosis; R: Right; L: Left. * FDR< 0.05 (uncorrected p < 0.025 for NLTLE and < 0.01 for MTS)

Table 4: Cognitive test performance of temporal lobe epilepsy patients.

Variable tested	L NL-TLE (N=8)	R NL-TLE (N=9)	L MTS-TLE (N=8)	R MTS-TLE (N=8)
Age (yr)	30(12)	36(11)	31(9)	38(10)
Seizure Duration (yr)	15(8)	21(14)	24(12)	30(11)
Male	3	4	3	6
R handedness	6	9	6	5
Reading SS	86.5(15.6)	90.7(20.8)	90.75(6.3)	82.9(12.6)
IQ estimate	83.8(12.8)	85.6(19.7)	86.0(12.1)	85.1(14.1)
Attention	-0.78 (0.82)	-0.21(1.34)	-0.88(1.06)	-1.26(1.09)
Processing Speed	-1.05(0.76)	-1.14(0.95)	-0.76(0.55)	-0.88(0.68)
Language	-1.55(0.82)	-1.57(0.95)	-1.3(1.06)	-1.6(0.86)
Visuoperceptual	-0.26(1.60)	-0.18(1.62)	0.6(1.42)	0.55(1.71)
Immediate Memory	-1.04(0.99)	-0.68(1.18)	-0.96(0.77)	-0.63(1.03)
Delayed Memory	-0.88(0.91)	-0.52(1.19)	-1.18(0.92)	-0.5(1.22)
Executive Function	-1.11(1.00)	-0.73(1.38)	-0.45(0.71)	-1.3(0.79)
Motor Speed	-0.99(0.88)	-0.99(0.88)	-0.85(0.75)	-0.33(0.94)
Global Deficit Score	-0.91(0.67)	-0.74(0.96)	-0.73(0.50)	-0.78(0.68)

Data is presented as the mean (standard deviation) of Z scores normalized to the age- and education- matched normal population. N: Numbers; NLTLE: Non-Lesional Temporal Lobe Epilepsy; MTS: Mesial Temporal Sclerosis; L: Left; R: Right

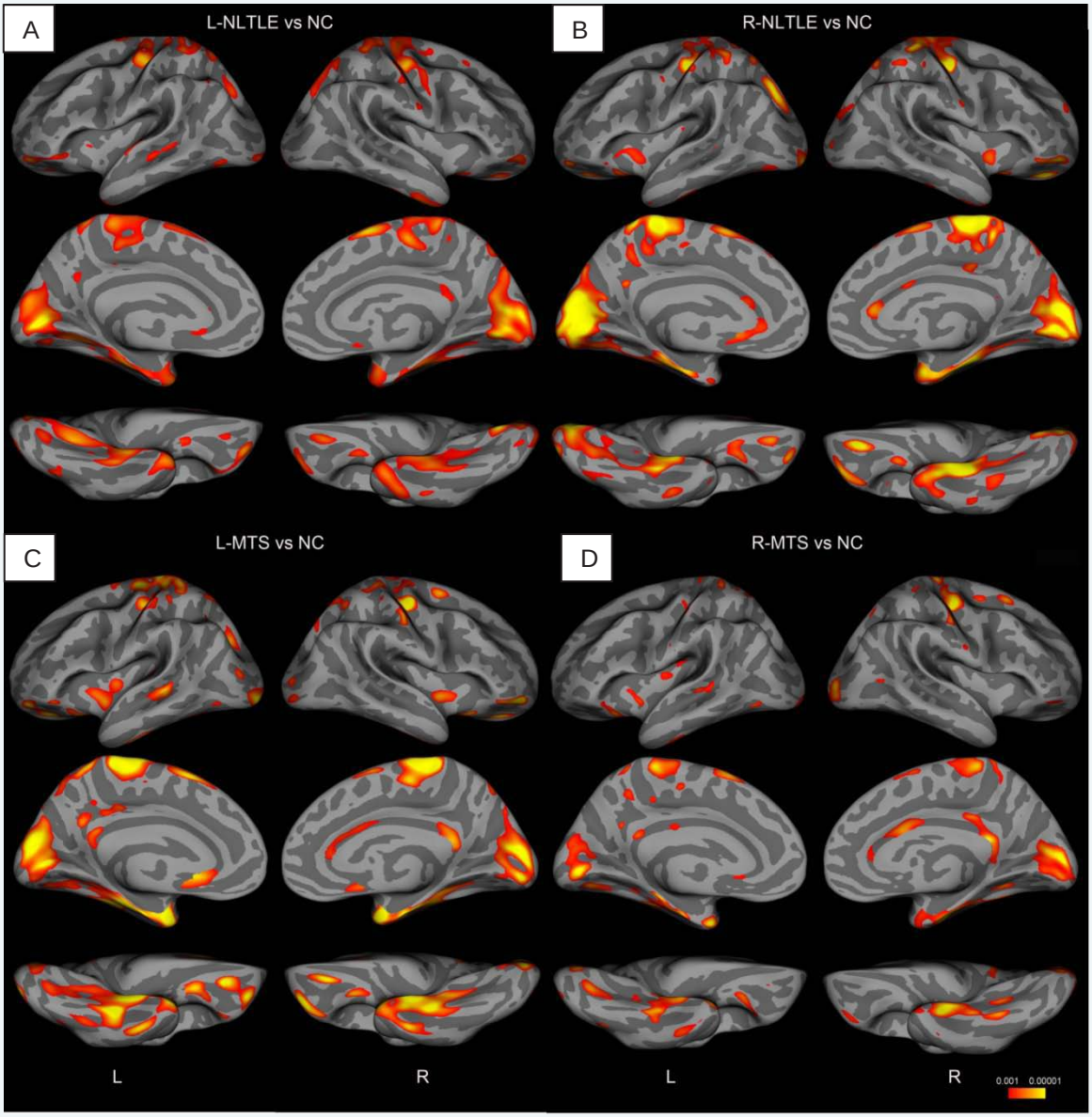

Figure 1 Cortical Atrophy in temporal lobe epilepsy
Saggital view of cortical thickness for TLE groups compared to healthy controls. Maps are presented as inflated reconstructed cortical surface. Red (p= 0.001) and yellow (p = 0.00001) represent regions with significant neocortical thinning in the TLE groups with FDR of 0.1. (A) Regions with significant neocortical thinning in the L-NLTLE group compared to controls. (B) Regions with significant neocortical thinning in the R-NLTLE group compared to controls. (C) Regions with significant neocortical thinning in the L-MTS group compared to controls. (D) Regions with significant neocortical thinning in the R-MTS group compared to controls. NC: normal control, TLE: temporal lobe epilepsy; NLTLE: non-lesional temporal lobe epilepsy; MTS: mesial temporal sclerosis; L: left, R: right.

Table 5: Memory performance is dependent on brain volume in temporal lobe epilepsy.

Test		R^2	Model P-value	Predictor
Immediate memory	Model 1	0.213	0.004	L Hip
	Model 2	0.28	0.012	L Hip + B Amygdala
	Model 3	0.415	0.009	L Hip + B Amygdala + L Pars opercularis+ L Pars triangularis + L Pars orbitalis
Delayed memory	Model 1	0.314	<0.001	L Hip
	Model 2	0.385	0.001	L Hip + B Amygdala
	Model 3	0.468	0.003	L Hip + B Amygdala + L Pars opercularis+ L Pars Triangularis + L Pars orbitalis

Results of the multiple linear regression analyses of brain region volumes and memory performance. Hip: Hippocampus; L: Left; B: Bilateral; R^2: Coefficient of Determination.

and 31% variance of delayed memory was dependent on left hippocampus volume. The additional 7% variance of immediate memory and 7% variance of delayed memory was dependent on bilateral amygdale volume. Finally, the 42% variance of immediate memory and 47% variance of delayed memory was dependent on the combination of the cortical thickness of the left pars opercularis, pars triangularis, and pars orbitalis with the volume of left hippocampus and the volume of the bilateral amygdala. These findings suggest that the left hippocampus, bilateral amygdala, and the thickness of left inferior frontal regions were essential for memory performance in TLE patients.

DISCUSSION

The main results of this study were: (1) Whole brain volume loss and widespread sub-cortical regional atrophy was noted in both TLE with and without MTS, regardless of lateralization of seizure onset; (2) Bilateral hippocampus atrophy was seen in both MTS-TLE and NL-TLE groups. However, hippocampal volume loss was asymmetrical with more prominent ipsilateral atrophy in MTS-TLE patients and symmetrical bilaterally in NL-TLE patients; (3) Widespread neocortical thinning was noted in all TLE patients. The cortical thinning pattern was similar in right and left NL-TLE patients, while L MTS-TLE patients had more diffuse contralateral cortical involvement compared to R MTS-TLE patients; (4) One-to-one structural-functional association was only found in memory performance in all groups. Combined left hippocampal volume, the cortical thickness in inferior frontal gyrus and bilateral amygdale volume also had additional predictive value for performance in memory tests. Taken together, these data support our hypothesis that the diffuse extratemporal atrophy observed in TLE is associated with pre-surgical cognitive impairment.

Recent MRI volumetric studies have demonstrated widespread bilateral regional atrophy in TLE patients [13,14,23,24]. A diffusion tensor imaging study in TLE has also shown extensive bilateral white matter abnormalities [25]. These studies investigating the structural volumes of TLE brain are also consistent with functional MRI findings. Using EEG and resting state fMRI data, Pittau et. al. demonstrated that in patients with unilateral mesial TLE, the bilateral amygdala and hippocampus had decreased connectivity with the dompaminergic mesolimbic and default mode network[26]. These observations suggest that TLE has diffuse structural and functional abnormalities involving widespread ipisilateral and contralateral networks. Our results are consistent with these observations. We found widespread volume loss in neocortical and subcortical regions in TLE patients with and without MTS. These patients displayed significant volume loss in cerebral white matter, bilateral hippocampus, bilateral amygdala, and reduced cortical thickness in bilateral parahippocampal, fusiform, temporal, frontal and parietal regions.

Interestingly, the NL-TLE patients in our study with either left or right side seizure onset had symmetrical cortical thinning in both hemispheres. On the other hand, MTS-TLE patients with left side seizure onset had cortical thinning bilaterally in a symmetrical manner while the MTS-TLE patients with right side seizure onset had more restricted contralateral neocortical thinning. This difference could be explained by the small sample size in the right MTS group, but this finding is also consistent with previous observations [27-29]. It was proposed that there are inherent differences between L MTS-TLE and R MTS-TLE in the extrahippocampal brain structure, with L MTS-TLE resulting in a more bilateral extensive pattern of atrophy [30]. This difference can also explain why L MTS-TLE patients often suffer more profound cognitive impairment. Our results support this hypothesis and suggest that left MTS is more likely to associate with bilateral neocortical atrophy in contrast to R MTS-TLE.

Our study demonstrates that the combined volume of the left hippocampus, bilateral amygdala, and cortical thickness of left pars opercularis, pars triangularis, and pars orbitalis were significant predictors of memory test performance in TLE patients. Our findings were consistent with previously demonstrated changes in hippocampus, prefrontal, and amygdala networks related to memory dysfunction. A quantitative MRI study has shown that the volume of the left hippocampus and the degree of asymmetry of perirhinal cortex volume were significant and independent predictors of performance on general memory, verbal memory, and verbal fluency tests in mesial TLE patients [31]. A memory functional MRI study showed that the most prominent activation in the verbal memory paradigm was found in the left inferior frontal gyrus [32]. Furthermore, reduced functional connectivity in the prefrontal network of the TLE patients was associated with poorer working memory performance [18]. On the other hand, the amygdala provides an emotional "tag" to memory traces with direct, as well as indirect, connections to the hippocampus. The amygdala also has connections to the orbitofrontal and temporal cortices, and appears to be necessary for learning the reward and emotional valence of sensory stimuli [33]. Our findings indicate that the memory impairment in TLE patients is caused by the network dysfunction beyond the affected hippocampus.

This study has several limitations. First, this is retrospective study with a moderate sample size. The findings in the current study need to be validated in prospective study with larger patient population. Second, the memory performance scores presented were composite scores. We were not able to dissect the verbal from non-verbal component because of limited access to original neuropsychological assessment.

CONCLUSION

In conclusion, the results of this study confirmed widespread regional atrophy in TLE with and without MTS and provided evidence that extra-temporal atrophy (i.e., in prefrontal regions and amygdala) contributes to memory impairment in medically intractable TLE.

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