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Automated subfield volumetric analysis of amygdala, hippocampus, and thalamic nuclei in mesial temporal lobe epilepsy

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ABSTRACT

Purpose: Identifying relationships between clinical features and quantitative characteristics of the amygdala-hippocampal and thalamic subregions in mesial temporal lobe epilepsy (mTLE) may offer insights into pathophysiology and the basis for imaging prognostic markers of treatment outcome. Our aim was to ascertain different patterns of atrophy or hypertrophy in mesial temporal sclerosis (MTS) patients and their associations with post-surgical seizure outcomes. To assess this aim, this study is designed in 2 folds: (1) hemispheric changes within MTS group and (2) association with postsurgical seizure outcomes.

Methods and materials: 27 mTLE subjects with mesial temporal sclerosis (MTS) were scanned for conventional 3D T1w MPRAGE images and T2w scans. With respect to 12 months post-surgical seizure outcomes, 15 subjects reported being seizure free (SF) and 12 reported continued seizures. Quantitative automated segmentation and cortical parcellation were performed using Freesurfer. Automatic labeling and volume estimation of hippocampal subfields, amygdala, and thalamic subnuclei were also performed. The volume ratio (VR) for each label was computed and compared between (1) between contralateral and ipsilateral MTS using Wilcoxon rank-sum test and (2) SF and not seizure free (NSF) groups using linear regression analysis. False Discovery rate (FDR) with significant level of 0.05 were used in both analyses to correct for multiple comparisons.

Results: Amygdala: The medial nucleus of the amygdala was the most significantly reduced in patients with continued seizures when compared to patients who remained seizure free. *Hippocampus:* Comparison of ipsilateral and contralateral volumes with seizure outcomes showed volume loss was most evident in the mesial hippocampal regions such as CA4 and hippocampal fissure. Volume loss was also most explicit in the presubiculum body in patients with continued seizures at the time of their follow-up. Ipsilateral MTS compared to contralateral MTS analysis showed the heads of the ipsilateral subiculum, presubiculum, parasubiculum, dentate gyrus, CA4, and CA3 were more significantly affected than their respective bodies. Volume loss was most noted in mesial hippocampal regions. *Thalamus:* VPL and PuL were the most significantly reduced thalamic nuclei in NSF patients. In all statistically significant areas, volume reduction was observed in the NSF group. No significant volume reductions were noted in the thalamus and amygdala when comparing ipsilateral to contralateral sides in mTLE subjects.

Conclusions: Varying degrees of volume loss were demonstrated in the hippocampus, thalamus, and amygdala subregions of MTS, especially between patients who remained seizure-free and those who did not. The results obtained can be used to further understand mTLE pathophysiology.

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Clinical relevance/application: In the future, we hope these results can be used to deepen the understanding of mTLE pathophysiology, leading to improved patient outcomes and treatments.

1. Introduction

Temporal Lobe Epilepsy (TLE) is the most frequent focal epilepsy and the most common cause of drug-resistant seizures in adults.[1,2] Volumetric Magnetic resonance imaging (MRI) studies have demonstrated the association of TLE with hippocampal sclerosis (HS), identified in approximately 65% of patients amygdala-hippocampal atrophy, and volumetric changes in thalamic nuclei.[1–8] These anatomic changes have been previously correlated with various clinical features of epileptic seizure, including the age of onset of intractable seizures, duration of epilepsy, presence of secondary generalized seizure, and postoperative seizure outcome.[4,9] Quantitative structural-based analyses such as volumetric and surface-based morphometry have been developed and associated with histological changes in TLE patients.[10] Approaches to identify volumetric changes in different neurological pathologies included semi-quantitative visual rating scales, quantitative manual tracing, and, more recently, fully automated volumetric MRI.[11] The anatomical volume diminution in TLE patients occurs mainly in gray matter structures strongly connected to the hippocampal formation, such as the amygdala and thalamus.[12,13]

Disseminated gray matter atrophy has been demonstrated in patients with TLE when compared to normal controls (NC).[3,4,14,15] Other studies support the existence of direct or reciprocal connections between neuronal structures and the mesial temporal lobe, accounting for the temporal lobe and thalamic structural alterations.[7,16] A theory to be contemplated for the extensive morphologic changes may be the recurrent seizures or the underlying symptomatic proconvulsant etiology. Thalamic volume loss is a common observation among patients with temporal lobe epilepsy. Additionally, clinical and animal studies have implicated the amygdala in the pathogenesis and symptomatology of the mTLE.[17] Several previous studies have focused on whole region volumetric analysis, with some having done subfield hippocampal analysis. Establishing subregion volume changes would facilitate quantifying the effects of the seizure network on these subregions, thereby further enhancing our understanding of the pathophysiology of mTLE. Our first aim was to ascertain hemispheric patterns of atrophy or hypertrophy within mesial temporal sclerosis (MTS) patients. Our second aim was to examine post-surgical seizure outcomes and their associations with patterns of volume change in these patients.

Our study analyzed subnuclei volumes in addition to whole region volumes, thereby seeking to ascertain local volume change distributions within these structures. We hypothesize that the subfields and nuclei volumes of the amygdala, hippocampus, and the thalamus on the epileptogenic side will be smaller than the contralateral side. Additionally, we hypothesize that the volumes of these regions will be significantly reduced in patients who report continued seizures following laser interstitial thermal therapy (LITT).

2. Methods

2.1. Participants

This retrospective study was approved by the institutional review board (IRB). Informed consent was obtained from all individual participants included in this study. 35 subjects who had a history of mTLE with unilateral MTS based on standard clinical criteria (International League Against Epilepsy (ILAE) classification, semiology, MRI, video EEG, PET scans, and neurocognitive examinations) were selected for this study. Demographic data for the included patients can be seen in Table 1. The inclusion criteria for subjects comprised of:

Table 1

Demographics and clinical characteristics of TLE subjects with MTS included in the study.

Variables	Seizure free at 12 months	Persistent seizures at 12 months
Sample size, n	15	12
Sex: Male/Female	6/9	3/9
Age at MRI	<30 = 1	<30 = 2
	30-50 = 5	30-50 = 2
	50+ = 9	50+ = 8
Age at Epilepsy Onset	<30 = 8	<30 = 7
	>30 = 7	>30 = 5
Side of MTS, Left/Right	10/5	10/2
Seizure type	SP = 15	TC = 7
		CP = 2
		CP w/secondary = 3

MTS = Mesial Temporal Sclerosis; R = Right-sided lesion, L = Left-sided lesion, SP= Simple partial seizures, TC = Tonic-clonic seizures, CP- Complex Partial.

1. Unilateral MTS on MRI as interpreted by a board-certified neuroradiologist
2. Drug-resistant mTLE
3. Scanned in 3 T MRI scanner with high-resolution T1 weighted scan (spatial resolution less than 1 mm) as well as T2 weighted scans
4. No obvious diffuse or focal neurologic pathologies in MRI other than MTS
5. Adult patients only (>18 years of age)
6. No history of other neurologic disorders
7. LITT of mesial temporal structures including amygdala and hippocampus;
8. Follow up of at least 12 months.

Patients were excluded if they required repeat procedures, had seizure etiology other than MTS, or lacked a preoperative high resolution anatomical scans. Outcomes were obtained from medical records and the patients were clustered as seizure-free (SF) group (n = 15) containing patients who had no seizures or had only auras, and not seizure-free (NSF) group (n = 12) containing patients with any type of seizure postoperatively.

Subjects underwent MRI-guided LITT surgery. In this surgical procedure, subjects were placed in a stereotactic frame and trajectories were planned using the NeuroSight Arc Trajectory Planning Software (Integra Neurosciences, Plainsboro, NJ, U.S.A.). The laser system used included a cooling catheter and 980-nm diode laser fiber (Visualase Inc, Houston, TX, U.S.A.) Once the initial MRI scan confirmed adequate laser probe location, a series of ablations were performed along the long axis of the amygdalohippocampal complex using MRI thermometry. Post ablation MRI with gadolinium images were obtained to assess ablation volumes.[18]

2.2. MRI acquisition and data analysis

All subjects were scanned in a 3 T Philips scanner with an eight-channel head coil preoperatively. They were scanned for conventional 3D T1w MPRAGE and T2 weighted MR images. The T1-weighted imaging parameters used were: FOV = 24.0 cm, voxel size = $1.0 \times 1.0 \times 1.0$mm3, matrix size = 512×512, TR = 12 ms, TE = 6 ms and slice thickness = 1 mm. The T2 image parameters were FOV = 24.0 cm, voxel size = 1x1x1mm3, matrix size = 320x247, TR = 3000, TE = 105.

The FreeSurfer software version 7 was used to evaluate the volumes

of the hippocampus, amygdala, and thalamic sub-regions.[19] We performed quantitative automated segmentation and cortical parcellation of T1w data using FreeSurfer. FreeSurfer segmentation of the amygdala-hippocampus subregion in a representative normal subject can be seen in Figs. 1 and 2. Automatic labeling and volume estimation of hippocampal subfields (21 ROIs), amygdala (9 ROIs), and thalamic (25 ROIs) nuclei were guided by the segmentation of the whole hippocampus, amygdala, and thalamus and performed using the adaptive segmentation technique.[19] All segmentations were visually inspected by a trained neurosurgeon to avoid segmentation errors and to confirm accuracy through a pass/fail system. Figs. 1 and 2 show the anatomical locations of the hippocampal subfields, amygdala nuclei as well as thalamic nuclei on T1 images in a normal control. The protocol co-registered T1 and T2 data and used these images simultaneously to generate labels and volumes for the whole hippocampal subfields as well as amygdala and thalamic nuclei.

2.3. Statistical analysis

Volume ratio (VR) was calculated by dividing individual subnuclei by the whole amygdala, hippocampus, or thalamus. For aim 1, the comparison was done between ipsilateral and contralateral mTLE subjects using the Wilcoxon rank-sum test and FDR correction with a significant level of 0.05. For aim 2 of this study VR of each label was compared between seizure SF and NSF groups using linear regression model with FDR correction set at the level of <0.05. In this model, age, sex, existence of tonic-clonic, age of seizure onset, and seizure class were used as confounding variables. Additionally, total intracranial volumes (TIV), total gray matter volume (TGV), total cortical gray matter volume (TCGV) and total subcortical gray matter volume (TSGV) were calculated, and a two tailed *t*-test was performed for the differences with respect to post-surgical seizure outcomes.

3. Results

Eight subjects were excluded due to motion-degraded images. A total of 27 epilepsy subjects (10 male and 17 female) aged 19–69 were included in our final analysis. Table 1 represents the demographic and clinical characteristics of epilepsy patients. There were no statistically significant differences in TIV (t = 0.63, p-value = 0.53), TGV (t = 0.44, p-value = 0.67), TCGV (t = 0.24, p-value = 0.81) and TSGV (t = 1.60, p-value = 0.12) with respect to post-surgical seizure outcomes.

3.1. Hemispheric (ipsilateral vs. contralateral) based analysis

We compared nuclei of the amygdala, thalamus, and hippocampus between the contralateral and ipsilateral sides relative to the MTS lesion.

a. **Volumetric analysis of amygdala nuclei:** No significant changes were found between the ipsilateral and contralateral amygdala in MTS.
b. **Volumetric analysis of hippocampal subfields:** Comparing the ipsilateral MTS subfields with contralateral MTS subfields yielded several significant subfields all of which were smaller than the contralateral side, as shown in Fig. 3 and Appendix Table 1. The heads of the ipsilateral subiculum, presubiculum, parasubiculum, dentate gyrus, CA4, and CA3 were more significantly affected than their respective bodies when compared with contralateral MTS regions.
c. **Volumetric analysis of thalamic nuclei:** No significant changes were found between the ipsilateral and contralateral thalamus in MTS.
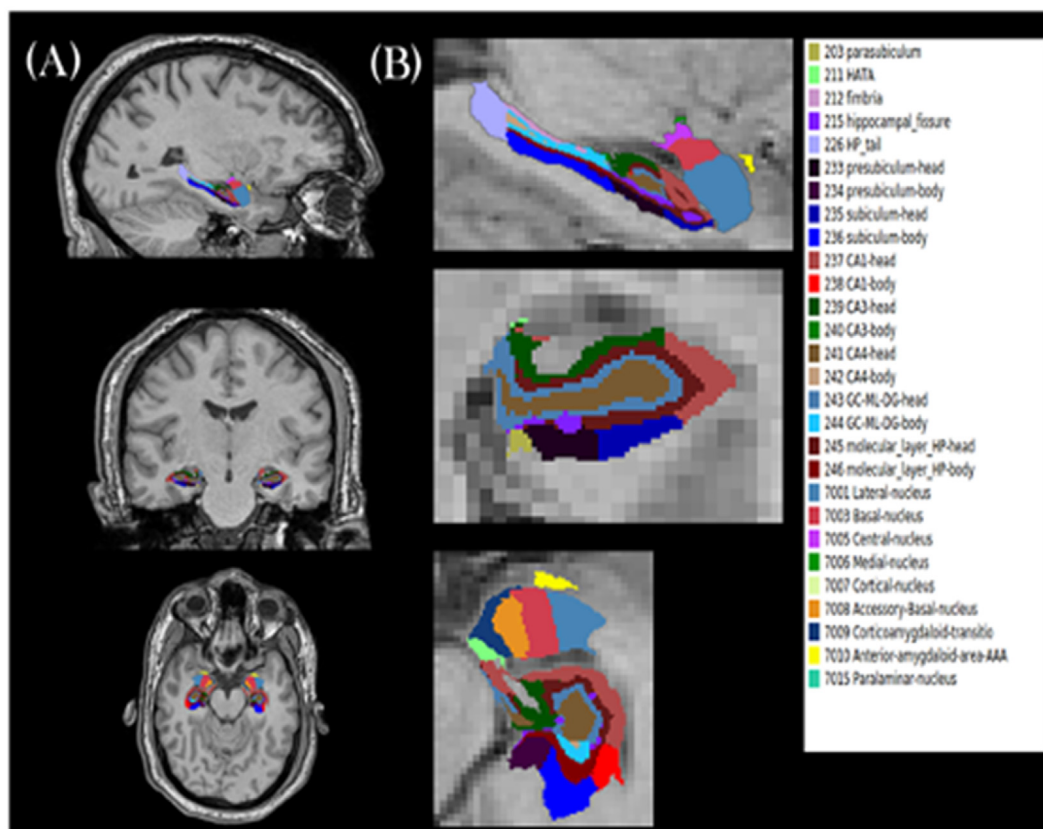

Fig. 1. Amygdala-Hippocampus subregion segmentation with labels in a representative normal subject; A) T1w images of subfields and nuclei in sagittal, coronal, and axial views; B) magnified segmentation view with ROI Labels.
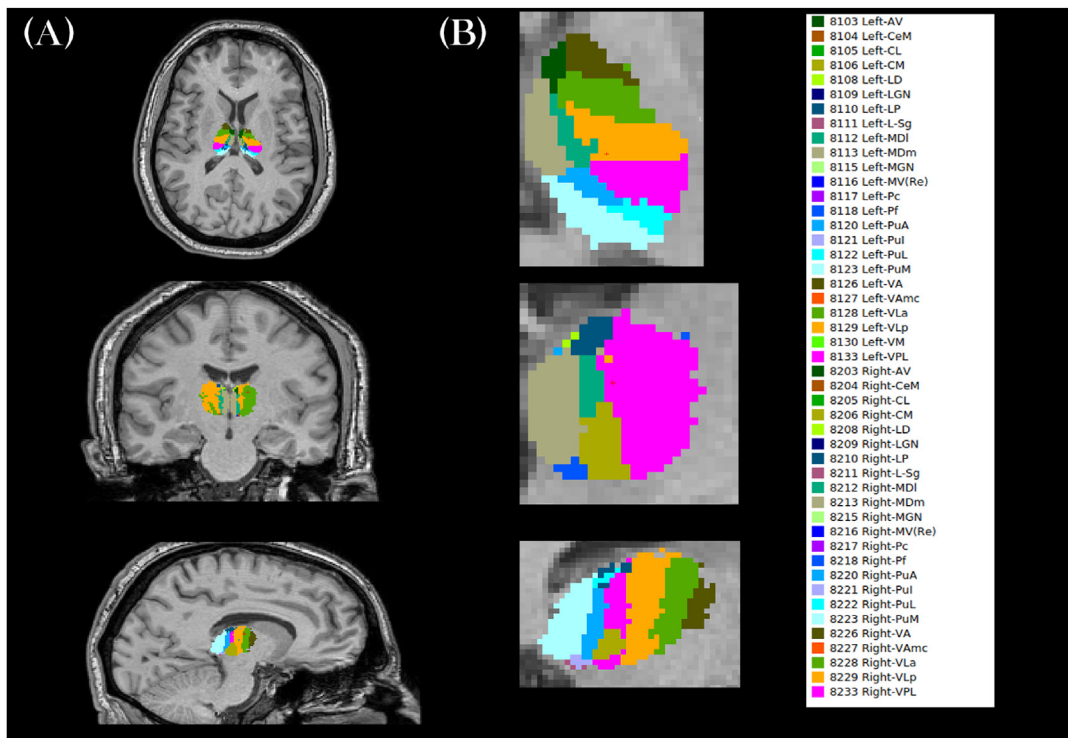
Fig. 2. Thalamic nuclei segmentation with labels; A) T1w images of nuclei in sagittal, coronal and axial views; B) Magnified segmentation view.
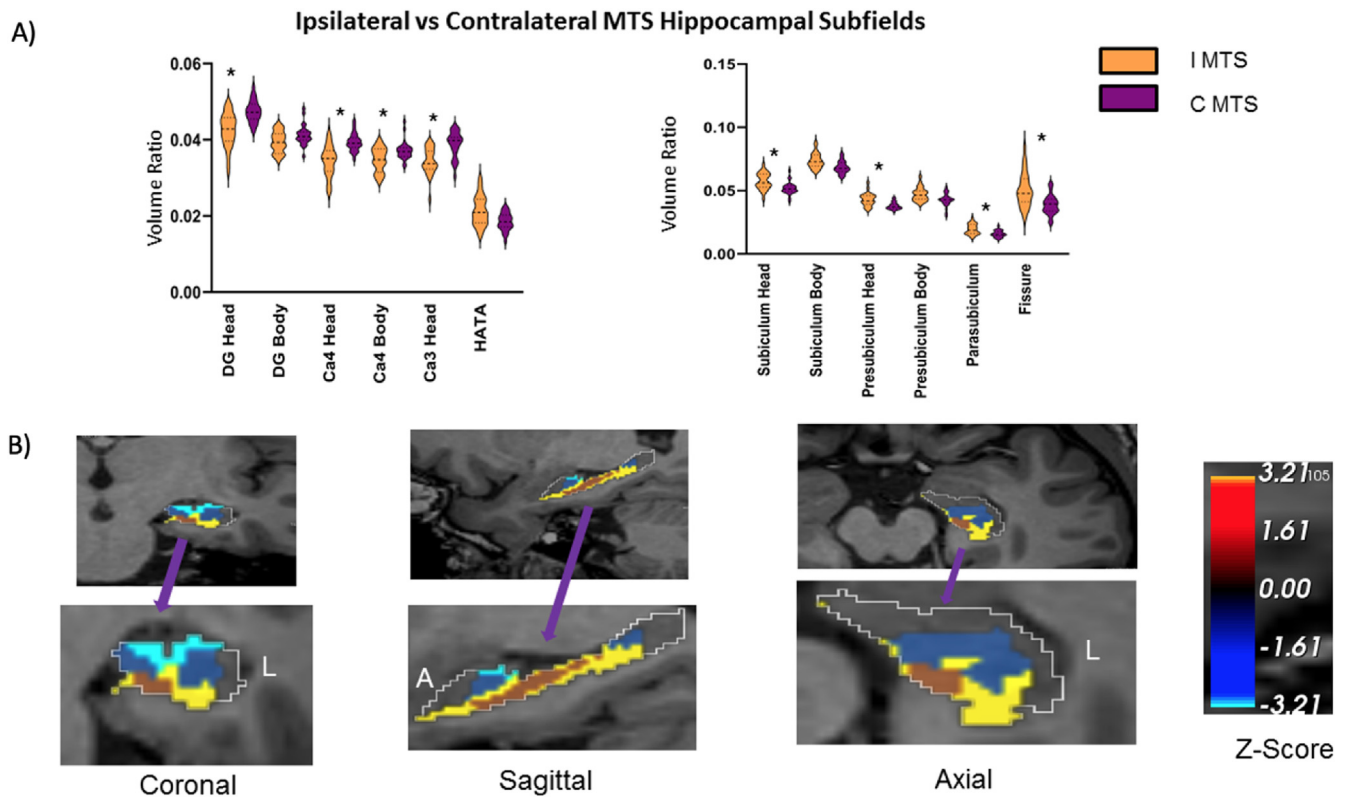
Fig. 3. A: ipsilateral and contralateral hippocampal subfield volume ratios in MTS subjects, B Heat map of changes of ipsilateral vs contralateral hippocampal MTS subfields in three anatomic planes of the ipsilateral hippocampus, increased volume ratio (yellow) noted based on Z-scores. CA: Cornu ammonis; I: Ipsilateral; C: Contralateral; A: Anterior; L: Lateral; * indicates FDR p-value <0.001. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Association of post-surgical seizure outcomes with preoperative volumes

We also compared subfields of the amygdala, hippocampus, and thalamus in patients with respect to post-surgical seizure outcomes after LITT surgery. Our comparison was made between two groups: patients with continued seizures following surgical intervention and those who were seizure-free. Fig. 4 and Table 2 outline the significant regions discussed in this comparison.

d. **Volumetric analysis of amygdala nuclei:** With respect to the amygdala nuclei, three regions were significantly altered when comparing post-surgical seizure outcomes. In the group with continued seizures, the ipsilateral medial nucleus was the most significantly reduced (T value = 2.78, p value = 0.012) when compared to the seizure-free group. Additionally, the ipsilateral AAA (T value = 2.13, p = 0.046) and contralateral medial nucleus (T value = 2.37, p = 0.028) were also significantly reduced when comparing the aforementioned groups.

e. **Volumetric analysis of hippocampal subfields:** In the hippocampus, three ipsilateral regions and one contralateral region had reduced volumes in the non-seizure-free group compared to the seizure-free patients. Overall, the ipsilateral presubiculum body (T value = 2.40, p = 0.026) was the most significantly reduced subfield. Also ipsilaterally, the hippocampal fissure (T value = 2.23, p = 0.038) and CA4 head (T value = 2.05, p = 0.05) were significantly reduced in the aforementioned groups. Contralaterally, the hippocampal fissure (T value = 2.36, p = 0.029) was significantly reduced in the group with persistent seizures when compared to the seizure-free group.

f. **Volumetric analysis of thalamic nuclei:** The thalamus demonstrated eight total regions whose volumes were significantly reduced in the NSF group when compared to the SF group. VPL, PuL and VM showed bilateral volume reduction in the NSF group. Also, ipsilaterally, the volume of the LGN (T value = 2.48, p = 0.022) and contralaterally, volume of the LD (T value = 2.42, p = 0.037) were significantly decreased in the NSF group.

4. Discussion

Our results provide insight into the pathological variations within each subfield of the amygdala, hippocampus, and thalamus in mTLE patients with MTS. We have attempted to stratify volumetric differences and associate them with epilepsy pathogenesis.

Table 2

Statistically significant ($p < 0.05$) amygdala and thalamic nuclei as well as hippocampal subfields with respect to 12 months post-surgical seizure outcomes after LiTT surgery.

Volumetric analysis of amygdala nuclei				
Name of nucleus	Standard error (SE)	R^2	T value	*P* value
SF versus NSF (ipsilateral side)				
AAA	0.42	0.85	2.13	0.046
Medial nucleus	0.38	0.86	2.78	0.012
SF versus NSF (contralateral side)				
Medial nucleus	0.31	0.84	2.37	0.028
Volumetric analysis of hippocampal subfields				
Name of subfield	Standard error (SE)	R^2	T value	*P* value
SF versus NSF (ipsilateral side)				
Hippocampal fissure	0.27	0.84	2.23	0.038
Presubiculum body	0.43	0.85	2.40	0.026
CA4 head	0.43	0.85	2.05	0.05
SF versus NSF (contralateral side)				
Hippocampal fissure	0.28	0.84	2.36	0.029
Volumetric analysis of thalamic nuclei				
Name of nucleus	Standard error (SE)	R^2	T value	*P* value
SF versus NSF (ipsilateral side)				
LGN	0.34	0.85	2.48	0.022
PuL	0.38	0.84	2.12	0.047
VPL	0.52	0.87	3.20	0.005
VM	0.44	0.86	2.72	0.013
SF versus NSF (contralateral side)				
PuL	0.31	0.86	2.84	0.01
VPL	0.50	0.85	2.29	0.033
VM	0.40	0.84	2.11	0.048
LD	0.23	0.84	2.42	0.037

AAA: anterior-amygdaloid-area; CA: cornu ammonis; LGN: Lateral geniculate nucleus; PuL: Pulvinar nucleus; VPL: Ventral posterior lateral nucleus; VM: Ventromedial; LD: Laterodorsal.

4.1. Amygdala in mesial temporal lobe epilepsy

The ipsilateral lateral nucleus was demonstrated to be the most severely affected region of the amygdala in pathology studies by Betram 2009 in mTLE.[20] The lateral nucleus acts as the main receiver of projections in the amygdala. It receives projections from the thalamus and hippocampus and projects to central, basal, accessory basal, and paralaminar nuclei.[21] Graebenitz et al 2011 hypothesized that the presence of abnormal synaptic and receptor densities in the lateral nucleus might contribute to spontaneous seizure activity.[22] Our results identified that the volume of the bilateral medial nuclei is significantly reduced in patients who have persistent seizures following LiTT surgery. The medial
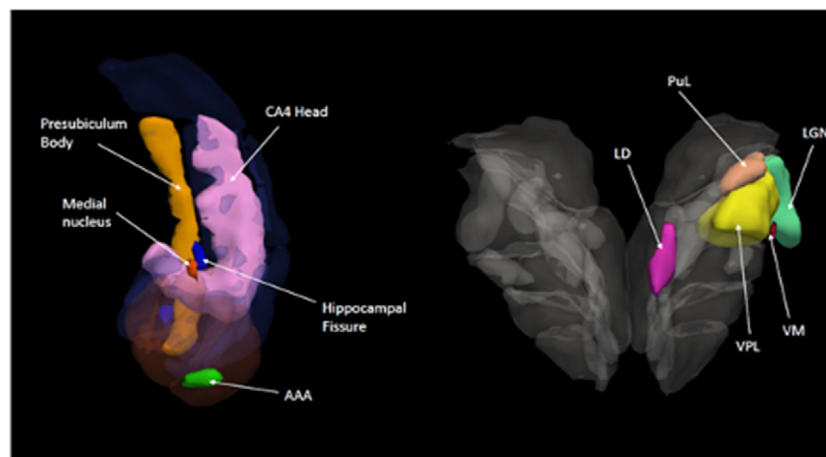

Fig. 4. Significant amygdala-hippocampus subregion segmentation (left) and thalamus nuclei segmentation (right) with labels in a representative normal subject.

nucleus projects to the subiculum of the hippocampus as output projections. The medial and cortical nuclei both receive projections from the Medial Geniculate Nucleus (MGN) and pulvinar nucleus of the thalamus as well as from the hippocampus.

When comparing the ipsilateral volume of whole amygdala to the contralateral volume of whole amygdala, McDonald et al found the ipsilateral volume of whole amygdala was significantly smaller.[23] Ballerini et al (2022) noted whole amygdala volumes on the ipsilateral side to be smaller than in controls in their subfield analysis[24] Our findings showed a similar pattern with ipsilateral whole amygdala volumes relative to the contralateral side but were not significantly different after FDR correction. The classical pathologic features of MTS consist of hippocampal sclerosis, neuronal loss, and astrogliosis, however, these features have been found to extend beyond the hippocampus into the amygdala and entorhinal cortex. The amygdala is involved in the seizure circuitry of mTLE and could potentially act independently or assist in the excitability of nearby structures to generate seizures.[25,20] The amygdala is structurally and functionally connected to the hippocampal formation but undergoes far less sclerosis than the hippocampus. Bernasconi et al 2003 and McDonald et al 2008 hypothesized that amygdala atrophy in mTLE could be due to repeated seizure activity or an effect of disease progression.[23,26] Whether this pattern of volume loss in these nuclei is due to their specific projections or association with the epileptiform network remains to be investigated. The presence of volumetric changes that are not confined to the ipsilateral side suggests that the disease process may not be restricted to one hemisphere alone.

4.2. Hippocampus in mesial temporal epilepsy

Luby et al 1995 demonstrated that hippocampal volumetric analysis corresponded to hippocampal neuronal loss.[27] Hippocampal sclerosis is classified pathologically into 3 types according to neuronal cell loss patterns in the subfields by ILAE.[28] These are neuronal loss and gliosis predominantly in CA4 and CA1 (type 1), CA1 predominant (type 2), and CA4 predominant (type 3). Our results demonstrated smaller mean volumes in ipsilateral CA3 and CA4 heads, and in the CA4 body relative to the contralateral MTS side. Blumcke et al (2009) demonstrated that the dentate gyrus was affected in all three types of MTS subjects through histopathological analysis of granule cells.[28] Our volumetric analysis exhibited volume reductions in regions corresponding to the granule cell and molecular layer of the ipsilateral dentate gyrus head and body compared to the contralateral MTS side, agreeing with previous pathology study results.

A review of voxel-based morphometry (VBM) studies in mTLE by Keller and Roberts 2008 showed that the ipsilateral hippocampus has the most asymmetric distribution of volume loss among medial temporal lobe structures.[29] Due to the hippocampus being the primary site of sclerosis in MTS, the ipsilateral subfields are more prone to volume loss and neuronal loss. All significant volume changes in ipsilateral subfields were smaller relative to contralateral subfields. The ipsilateral presubiculum body was the most affected region in the NSF group, additionally it was smaller in the ipsilateral side vs the contralateral. Kim (2005) found that this region was smaller compared to healthy controls.[30] The presubiculum lies between the subiculum and the parasubiculum and has been implicated in driving epileptiform discharges to the entorhinal cortex, which it projects into[31–34].

4.3. Thalamus in mesial temporal epilepsy

Several animal studies have revealed the importance of an intact thalamocortical circuit in mTLE seizure propagation.[20] Evidence of asymmetric bilateral volume loss in the thalamus is a consistent finding in previous studies of mTLE.[23,35,36] Bertram et al 2008 have described the thalamus as a physiological synchronizer of seizures.[20] Previous studies showed that volume reductions were found to be more common in thalamic regions that are preferentially connected to the hippocampus,

including the anterior group, mediodorsal region, and the pulvinar nucleus.[26,37] Keller et al (2008) proposed the existence of a tightly connected epileptiform network involving the thalamus, which correlates with the pattern of volume loss seen in mTLE.[29] Prior studies showed that the anterior nuclei, dorsomedial nucleus, and pulvinar nucleus are preferentially functionally and structurally connected to the temporal lobe.[38] These pathological correlates also correspond to electrophysiological studies which have shown the involvement of the posterior pulvinar nucleus in seizure onset in mTLE. The pulvinar nucleus is an association nucleus, receiving afferents from the association cortex and the superior colliculus.[39] It projects to the association areas in the parietotemporal cortex and to the secondary visual areas.[40] The PuL in both the ipsilateral and contralateral sides of our NSF group was significantly smaller than the SF group.

The VPL is a somatosensory relay nucleus with strong connections to both motor and sensory cortices. mTLE has been known to be associated with somatosensory clinical features such as automatisms. Previous studies on functional connectivity have shown that the VPL may be a part of the epileptogenic networks involved in seizure semiology in mTLE. The VPL was the most significantly affected nucleus in the ipsilateral NSF group relative to the SF group.[41] Dreiffus et al (2001) demonstrated that changes in thalamic nuclei volume were consistent irrespective of the duration of seizures.[36] This implies that the volumetric changes shown may not be caused by prolonged duration of seizures. Neuromodulation of particular thalamic nuclei has been shown to affect seizure control which may indicate the importance of the thalamic network for seizure propagation.[42,43] Lee et al (2020) performed quantitative thalamic subfield analysis in epilepsy patients with hippocampal sclerosis and found nuclear volumes varying with the type of sclerosis further emphasizing the importance of the hippocampal-thalamic network.[44] Prior evidence emphasizes the importance of the thalamus and its role in mTLE seizure propagation, thereby validating the potential use of thalamic subfield volumetrics in disease monitoring and treatment planning. To the best of our knowledge, this paper is the first to show that volumetric changes in nuclear regions of the bilateral thalami corresponding to known physiological pathways in mesial temporal lobe epilepsy with postsurgical outcomes.

5. Limitations

It is important to consider the limitations of our study while interpreting the results. Firstly, we used an automated segmentation method that used normal controls (NCs) for reference. Although visual inspection of the segmentations was done, using NCs as a reference may overestimate or underestimate the subfield volumes in subjects. Secondly, newer advanced imaging such as neurite orientation dispersion and density imaging (NODDI) could have provided more details for further comprehension of microstructure. Supplementing imaging with diffusion weighted imaging (DWI) and fiber tractography could help to overcome this limitation in future studies. Apart from the three regions we have focused on, other regions such as the parahippocampal gyrus have been implicated in the seizure network of mTLE which can be analyzed in future studies. We used the non-lesional hemisphere as the control group to compare the lesion side subfields to study microstructure changes in the individual subjects. Additional comparison of both hemispheres with age-matched healthy controls and larger sample size in future studies could further elaborate on the pathophysiologic effects of mTLE.Finally, only MRI-positive MTS cases were included. There may be different volumetric patterns associated with MRI negative, PET/sEEG positive MTS subjects. Future studies should take these limitations into account while exploring subfield volume analyses.

6. Conclusion

Almost all the significant volumetric change between SF and NSF groups revealed smaller volumes in the NSF group. We hypothesize that a

significant amount of sclerosis and volume loss must have occurred in this group that translated to their prognosis post-operatively. This study demonstrates the volumetric differences between the epileptogenic focus side and the contralateral side and between SF and NSF groups in three important regions involved in seizure pathology in mTLE subjects. Our results, along with a growing body of evidence, emphasize the importance of analyzing individual subfields volumetrically to better understand mTLE neuropathology.

CRediT authorship contribution statement

Arichena Manmatharayan: Conceptualization, Data curation, Writing – original draft. **Michael Kogan:** Conceptualization, Formal analysis, Supervision, Validation. **Caio Matias:** Conceptualization, Data curation, Methodology. **Mashaal Syed:** Conceptualization, Methodology. **India Shelley:** Data curation, Visualization. **Amar Chinni:** Data curation, Visualization. **Kichang Kang:** Software, Visualization. **Kiran Talekar:** Conceptualization, Writing – review & editing. **Scott H. Faro:** Conceptualization, Writing – review & editing. **Feroze B. Mohamed:** Conceptualization, Writing – review & editing. **Ashwini Sharan:** Conceptualization, Resources, Writing – review & editing. **Chengyuan Wu:** Conceptualization, Resources, Writing – review & editing. **Mahdi Alizadeh:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

Arichena R Manmatharayan, MBBS, MD: No disclosure. Michael Kogan, MD, PhD: No disclosure Caio Matias, MD, PhD: No disclosure India Shelley, BA: No disclosure Amar Chinni, BA: No disclosure Kichang Kang, BA: No disclosure Kiran Talekar, MD: No disclosure Scott Faro, MD: No disclosure Feroze B. Mohamed, Ph. D: No disclosure Ashwini Sharan, MD: No disclosure Chengyuan Wu, MD, MSBmE: No disclosure Mahdi Alizadeh, PhD: No disclosure.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.wnsx.2023.100212.

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