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Amygdala enlargement: temporal lobe epilepsy subtype or nonspecific finding?

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Abstract

Objective—Amygdala enlargement (AE) is observed in patients with temporal lobe epilepsy (TLE), which has led to the suggestion that it represents a distinct TLE subtype; however, it is unclear whether AE is found at similar rates in other epilepsy syndromes or in healthy controls, which would limit its value as a marker for focal epileptogenicity.

Methods—We compared rates of AE, defined quantitatively from high-resolution T1-weighted MRI, in a large multi-site sample of 136 patients with nonlesional localization related epilepsy (LRE), including TLE and extratemporal (exTLE) focal epilepsy, 34 patients with idiopathic generalized epilepsy (IGE), and 233 healthy controls (HCs).

Results—AE was found in all groups including HCs; however, the rate of AE was higher in LRE (18.4%) than in IGE (5.9%) and HCs (6.4%). Patients with unilateral LRE were further evaluated to compare rates of concordant ipsilateral AE in TLE and exTLE, with the hypothesis that rates of ipsilateral AE would be higher in TLE. Although ipsilateral AE was higher in TLE (19.4%) than

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exTLE (10.5%), this difference was not significant. Furthermore, among the 25 patients with unilateral LRE and AE, 13 (52%) had either bilateral AE or AE contralateral to seizure onset.

Conclusion—Results suggest that AE, as defined with MRI volumetry, may represent an associated feature of nonlesional localization related epilepsy with limited seizure onset localization value.

Keywords

MRI; morphometry; temporal lobe epilepsy; nonlesional epilepsy

1.1 INTRODUCTION

Amygdala enlargement (AE) is reported on MRI in patients with nonlesional temporal lobe epilepsy (TLE) at rates that range from 12% to 63% (Bower et al., 2003; Coan et al., 2013; Minami et al., 2015). This has led to the hypothesis that AE represents a distinct subtype of TLE (Lv et al., 2014). However, it remains unclear whether AE is more common in nonlesional TLE than in other nonlesional epilepsy syndromes. Prior comparison groups have included TLE with hippocampal sclerosis and healthy controls (Bower et al., 2003; Mitsueda-Ono et al., 2011; Takaya et al., 2014); however, none have examined rates of AE in nonlesional extratemporal lobe epilepsy (exTLE) or idiopathic generalized epilepsy (IGE). This leaves it unclear whether AE is a marker for focal epileptogenicity in TLE or a nonspecific finding that is common across many epilepsy syndromes.

Evidence for focal epileptogenicity in the enlarged amygdala would support AE as a pathogenic structural anomaly that gives rise to a distinct TLE subtype. However, AE is observed at high rates in the amygdala contralateral to seizure onset (Coan et al., 2013) and epileptogenic activity appears to arise from the hippocampus, not the enlarged amygdala (Minami et al., 2015). Prior AE studies included only TLE patients that had concordant EEG findings (Kim et al., 2012; Kimura et al., 2015; Sone et al., 2015; Takaya et al., 2014) or did not specify whether they applied this selection criterion (Coan et al., 2013; Lv et al, 2014; Mitsueda-Ono et al., 2011). To address this unresolved issue, we compare rates of AE, defined quantitatively, across a large sample of individuals with normal MRI and either localization related epilepsy (LRE), IGE, or no epilepsy [i.e., healthy controls (HC)]. We test the hypothesis that AE is found at higher rates in LRE relative to the IGE and HC groups, as well as at higher rates in TLE relative to extratemporal lobe epilepsy (exTLE).

1.2 METHODS

1.2.1 Subjects

Data were collected from three different sites, New York University (NYU), University of California, San Diego (UCSD), and The Florey Institute of Neuroscience and Mental Health, University of Melbourne (The Florey). Local Institutional Review Boards (IRB) approved procedures for data acquisition in all sites and informed consent was obtained from all subjects.

Localization-Related Epilepsy Group (LRE): LRE patients were ascertained through referral from each site's comprehensive epilepsy surgery evaluation program. Patients met criteria for the LRE group if they were between 15 and 65 years of age, had no abnormality on clinical MRI reviewed by board-certified radiologists, and a diagnosis of medically refractory epilepsy as determined by board-certified neurologists with expertise in epileptology and in accordance with criteria defined by the International League Against Epilepsy (Kwan et al., 2010). Primary seizure onset localization was established by board-certified neurologists/epileptologists based on review of clinical history, results from neurologic exam, continuous video EEG monitoring, and neuroimaging evaluation. Although not available in all cases, information from neuropsychological evaluation, intracranial EEG monitoring, and/or nuclear medicine studies (FDG-PET and/or Ictal-Interictal SPECT) was used to support localization. Age of seizure onset and epilepsy duration were abstracted from medical records.

Idiopathic Generalized Epilepsy (IGE): Patients with IGE were recruited at the NYU Comprehensive Epilepsy Center. To meet criteria for inclusion, patients needed to have been between the ages of 18 to 65, have MRIs read as normal on radiological exam, and show typical generalized epileptiform spikes on electrophysiological evaluation.

Healthy Controls (HCs): HCs were included if they were between 18 and 65 years of age and had no history of self-reported neurologic or psychiatric disease. HCs were excluded if they had incidental findings on research MRI scans or excessive head motion.

1.2.2 MRI acquisition

NYU—MRI data were collected using a 3T Siemens Allegra head-only MRI scanner. Image acquisition included a conventional 3-plane localizer, a T1-weighted volume (TE=3.25 ms, TR= 2530 ms, TI= 1.100 ms, flip angle = 7°, field of view = 256 mm, voxel size= 1×1×1.33mm). Scanner and sequence parameters were identical for patients and HCs.

UCSD—MRI data were collected on a General Electric Discovery MR750 3T scanner with an 8-channel phased-array head coil. Image acquisition included a conventional three-plane localizer, GE calibration scan, and a T1-weighted 3D structural scan (TE = 3.16 ms, TR = 8.08 ms, TI = 600 ms, flip angle = 8°, FOV = 256 mm, matrix = 256 × 192, voxel size = 1×1×1.3mm). Scanner and sequence parameters were identical for all patients and HCs.

The Florey—MRI data were collected on a 3T Siemens Trio Tim scanner using a 12-channel head coil. Image acquisition included a T1-weighted MPRAGE sequence (TE = 2.6 ms, TR =1900 ms, TI = 900ms, flip angle = 9°, matrix = 256 × 256, 192 sagittal slices, voxel size 0.9mm isotropic). Scanner and sequence parameters were identical for all patients and HCs.

1.2.3 Amygdala segmentation

Across all sites, T1-weighted images were processed with the FreeSurfer (v5.1 at NYU and UCSD, v5.3 at The Florey) software package (http://surfer.nmr.mgh.harvard.edu) for semi-automated segmentation and labeling of the amygdala, which has been validated against

manual tracing of the amygdala (Fischl et al., 2002; Grimm et al., 2015 Morey et al., 2009). Visual inspection of amygdala segmentation accuracy was performed by trained, blinded technicians at each site.

1.2.4 Standard score calculations

In order to combine data across the three sites and avoid scanner-related or sequence-related differences, site-specific HCs were used to generate z-scores [$z = x - \mu/\sigma$; z-score = (individual amygdala volume – HC group amygdala volume mean)/HC group amygdala volume standard deviation]. Left and right amygdala volumes were divided by total intracranial volume to control for individual differences in brain size, resulting in a ratio score. The mean and standard deviation of the HCs' left and right ratio scores were calculated. Individual z-scores for each patient were generated based on site-specific HCs' mean and standard deviation. Similar procedures were performed for each HC with the exception of removing that HC from the mean and standard deviation of the HC group before generating the amygdala volume z-score. We used the Kruskal-Wallis Test to confirm that there were no site differences in the distribution of amygdala z-scores in HCs (left: $p = 0.99$; right: $p = 0.98$) or patients (left: $p = 0.27$; right: $p = 0.80$). For patients with unilateral LRE, left and right amygdala z-scores were designated ipsilateral or contralateral depending on lateralization of the seizure focus for each patient. Patients with bilateral seizure onset were excluded from group comparison of ipsilateral AE rates between the TLE and exTLE group. Amygdala enlargement (AE) was defined as a z-score more than two standard deviations above the site-specific HC mean.

1.2.5 Statistical analyses

We compared sex and age distributions across groups using chi-square analysis and ANOVA, respectively. We used chi-square and Fisher's exact test to compare AE rates in LRE with AE rates in IGE and HCs, as well as to compare ipsilateral AE rates in TLE with exTLE. Given high base rates of TLE in most surgical series, we used a Bayesian approach to calculate the positive and negative predictive value of AE as a diagnostic marker for TLE, which took into account the base rate of TLE in our LRE sample. We used ANOVA to compare mean amygdala z-scores across groups (LRE, IGE, and HCs) with posthoc *t*-test contrasts. Independent samples *t*-tests were used to compare mean amygdala z-scores between TLE and exTLE. These analyses were repeated in a subset of the sample that had resective surgery and an Engel classification score ≤ 2, which provided the highest level of confidence in accurate localization of seizure onset. Two-tailed pairwise *t*-tests were used for within-subject ipsilateral and contralateral z-score comparisons. A Mann-Whitney U-test was used to compare ipsilateral AE scores between the TLE and exTLE groups due to the smaller sample size of the exTLE AE group. Finally, we used independent samples t-tests and Mann-Whitney U-tests to determine whether there were group differences in epilepsy features (e.g., age of seizure onset, epilepsy duration) between patients with and without AE, including those with bilateral and contralateral AE.

1.3 RESULTS

1.3.1 Participant Characteristics

One hundred and thirty-six patients met criteria for inclusion as nonlesional LRE across all three sites (NYU: N=76; UCSD: N=28; The Florey: N=32). Of these, ninety-four were clinically diagnosed as TLE (41 males, age range 15–65 years, mean age 35.93 years) and forty-two as extratemporal LRE (16 males, age range 18–52 years, mean age 30.56 years). Localization was supported by intracranial EEG in 45% of the LRE group (41 TLE and 19 exTLE) and by continuous video EEG monitoring in the remaining 55% (51 TLE and 23 exTLE). Forty-four patients had resective surgery with either a seizure-free (Engel 1) outcome (TLE = 25; exTLE = 7) or only rare post-surgical seizures (Engel 2;TLE = 10; exTLE = 2). Thirty-four patients met criteria for IGE from NYU (18 males, age range 20–50 years, mean age 32.59 years). Two-hundred and thirty-five healthy individuals met criteria for inclusion as HCs across all three sites [NYU: N=84; UCSD: N=37; The Florey: N=112 (121 males, age range 18–65 years, mean age 35.3 years)]. There were no differences in gender distribution [χ^2= 3.73, p =0.155] or mean age across the LRE, IGE, and HC groups [F (2,400) = 1.01, p=0.365] (see Table 1).

1.3.2 Do rates of amygdala enlargement differ between LRE, IGE, and HCs?

Table 2 shows rates of AE in each group, which differed across the LRE, IGE, and HC groups (p = 0.001). Rates of AE were higher in the LRE group than in the HC group (p = 0.0004) but equivalent between the LRE and IGE group (p =0.113). AE rates were equivalent between the IGE and HC group (p = 1). Group comparisons revealed differences in left [F (2,399) = 7.936; p < 0.001] and right [F (2,399) = 6.464; p = 0.002] amygdala volume z-scores between the LRE, IGE, and HC groups, with posthoc contrasts showing the largest difference between LRE and HCs (left: p <0.001; right p = 0.001) but no difference between LRE and IGE (left: p = 0.396; right p = 0.434) or IGE and HCs (left: p = 0.606; right p = 0.688) (See Fig. 1).

1.3.3 Does the presence of amygdala enlargement offer localization or lateralization value in LRE?

There was no difference in the proportion of patients with ipsilateral AE between the TLE and exTLE group (p =0.305). When considering ipsilateral AE as a “test-positive” finding, sensitivity for accurately diagnosing TLE was 19.4% and specificity was 89%. Using formulas to determine predictive values derived from Bayes theorem (Labarge et al., 2003), which take into account the high base rate of TLE (71%) in our unilateral LRE sample, the positive predictive value of AE for a TLE diagnosis was 99% and the negative predictive value was 31%. Thus, the likelihood that an individual with a normal MRI, unilateral EEG findings, and concordant AE has TLE is high (due to high base rates of TLE) but the likelihood that an absence of AE scores correctly predicts the absence of TLE is low. Repeating the analysis in patients with Engel ≤ 2 outcomes revealed similar findings with no difference in the proportion of patients with ipsilateral (p = 0.66) or contralateral (p = 0.57) AE between TLE and exTLE. Taken together, these results indicate that AE is a poor diagnostic marker for seizure onset in the temporal lobe.

There was no difference in ipsilateral amygdala z-scores between the TLE and exTLE groups [$t(129) = 0.627$; $p = 0.532$] (see Fig. 2). Within subject pairwise t-tests revealed that ipsilateral amygdala z-scores were higher than contralateral amygdala z-scores in the TLE group [$t(92) = 2.71$; $p = 0.008$, Ipsi: mean = 0.69 ± 1.59, Contra: mean = 0.28, ±1.3] and in the combined TLE and exTLE group [$t(130) = 2.84$; $p = 0.005$, Ipsi: mean = 0.64 ± 1.51, Contra: mean = 0.32, ±1.3], but not the in the exTLE group alone [$t(37) = 0.884$; $p = 0.382$, Ipsi: mean = 0.51 ± 1.32, Contra: mean = 0.42, ±1.19]. These differences were likely driven by the TLE group with AE as comparison between ipsilateral and contralateral amygdala z-scores of only those patients with TLE and AE revealed marginally higher z-scores in the ipsilateral enlarged amygdala [$t(19) = 1.926$, p = 0.069, Ipsi: mean = 2.98 ± 1.11, Contra: mean = 1.54, ±1.49]. However, there were no differences in the magnitude of ipsilateral AE between the TLE and exTLE groups, when comparing z-scores between these two groups (see Table 2).

Of the 20 patients with unilateral TLE and AE, 11 had unilateral AE that was ipsilateral to the epileptic focus, two had contralateral AE, and seven had bilateral AE. Of the five patients with unilateral extratemporal lobe epilepsy and AE, one had unilateral AE ipsilateral to the seizure focus, one had unilateral AE contralateral to the seizure focus, and three had bilateral AE. Thus, among the 25 patients with unilateral LRE and AE, 13 (52%) had either bilateral AE or AE that was contralateral to seizure onset (see Table 3).

1.3.4 Are there differences in epilepsy features between patients with and without AE?

There were no differences in age of epilepsy onset and duration of epilepsy between LRE patients with and without AE [age of seizure onset: $t(117) = -0.655$; $p = 0.514$; AE mean: 17.84 ± 12.34, no AE mean: 19.77 ± 13.25; epilepsy duration: $t(117) = -0.272$; $p = 0.786$; AE mean: 14.65 ± 11.36, no AE mean: 15.37 ± 11.84]. In addition, there were no differences in age of epilepsy onset and duration of epilepsy between TLE patients with and without AE [age of seizure onset: $t(86) = -0.941$, $p = 0.35$; AE mean: 19.7 ± 12.8, no AE mean: 22.97 ±13.9; epilepsy duration: $t(86) = 0.19$, $p = 0.85$; AE mean: 14.32 ± 12.06, no AE mean: 13.74 ± 11.9], or between exTLE patients with and without AE [age of seizure onset: U = 55.5, $p = 0.609$; AE mean:10.4 ± 6.98, no AE mean: 11.38 ± 5.83; epilepsy duration: U = 53.5, $p = 0.536$; AE mean: 15.98 ± 8.94, no AE mean: 19.63 ± 10.56]. In sum, there was no evidence for group differences in epilepsy features between individuals with and without AE.

1.5 DISCUSSION

Prior observations of AE in a subset of patients with TLE have led to the proposal that AE represents a subtype of TLE (Lv et al., 2014). However, small sample sizes and variable methods for defining AE in prior studies make it difficult to evaluate whether AE is specific to TLE (Beh et al., 2016). Although the rate of AE has been shown to be higher in nonlesional TLE than in TLE with MTS (Coan et al., 2013; Mitsueda-Ono et al., 2011; Takaya et al., 2014), no prior studies have examined AE rates in nonlesional exTLE or IGE, leaving it unclear whether AE is found across multiple epilepsy syndromes. We examined AE rates in a large multi-site sample of nonlesional patients, by generating individual

amygdala volume z-scores for each case from site-specific HCs, thereby controlling for site differences in MRI scanner, sequences, and FreeSurfer software version. AE was observed in 18.4% of patients with LRE, which was higher than rates observed in IGE (5.9%) and in HCs (6.4%). AE rates in the IGE and HC groups are consistent with what would be expected in the normal population distribution (~5%) and are thus attributable to this statistical property rather than a pathological finding. These results confirm that AE is found at elevated rates in LRE, which supports AE as an associated feature of “nonlesional” focal epilepsy.

In order to determine whether AE represents a focal structural anomaly that gives rise to a distinct TLE subtype, concordance between AE and the primary seizure onset zone must be demonstrated. Most of the prior investigations of AE in TLE were not optimally designed to investigate concordance due to selection biases (i.e., selecting patients based on concordance between AE and EEG findings (Kim et al., 2012; Kimura et al., 2015; Sone et al., 2015; Takaya et al., 2014), exclusion of non-TLE patients (Bower et al., 2003; Coan et al., 2013; Lv et al., 2014) or group comparisons of mean amygdala volumes and asymmetries, rather than individual volumetric analysis (Mitsueda-Ono et al., 2011). In the single study that examined individual AE rates in a large sample of nonlesional TLE patients (N=66), AE was found contralateral to the side of seizure onset in 43% of patients (Coan et al., 2013). Similarly, we found that 45% of the patients in our unilateral TLE sample had AE on the contralateral side (2 unilateral and 7 bilateral). This suggests that discordant EEG findings are common in AE, at least in samples that are predominantly comprised of individuals being with treatment resistant focal epilepsy who are being evaluated for epilepsy surgery. It is in this population where the presence of AE as a localizing sign would be of high clinical value. However, we found that rates of ipsilateral AE were not statistically different across the TLE and exTLE groups, further indicating that AE is a poor diagnostic marker for localization in treatment resistant nonlesional LRE. Finally, we did not observe any differences in clinical features of epilepsy such as age of seizure onset or epilepsy duration between patients with and without AE, which challenges the proposal that AE is a distinct subtype of TLE.

In terms of the magnitude of AE, ipsilateral amygdala z-scores were marginally higher than contralateral amygdala z-scores in the TLE group with AE. Larger ipsilateral than contralateral amygdalae are a common finding among previous AE studies (Kimura et al., 2015; Lv et al., 2014; Mitsueda-Ono et al., 2011; Sone et al., 2015), which has contributed to the argument that TLE with AE represents a subtype of TLE. However, ipsilateral amygdala z-scores were not different between the TLE and exTLE groups, even when considering only the z-scores from those that met criteria for ipsilateral AE. This leaves it unclear whether more severe AE offers additional localizing value. It may suggest a concordant focus in the context of normal contralateral amygdala volumes and additional clinical signs of TLE but may not offer additional clinical value if clinical signs for TLE and exTLE are equivocal.

Imaging, clinical, and histopathological characteristics of TLE with AE are heterogeneous (Beh et al., 2016), which also challenges the hypothesis of AE as a distinct TLE subtype. An enlarged amygdala has been found to contain focal cortical dysplasia (Kimura et al., 2015;

Mitsueda-Ono et al., 2011; Takaya et al., 2014), long-term epilepsy associated tumors (Kim et al., 2012), or the results of neuroinflammatory processes (Minami et al., 2015). Most studies report a higher age of seizure onset for patients with AE than patients with hippocampal sclerosis or TLE without AE; however, this is highly variable, which may be due to small sample sizes and inconsistent ascertainment methods (Beh et al., 2016). Patients with AE also vary in their response to antiepileptic medication; although some studies report a good response (Kimura et al., 2015; Mitsueda-Ono et al., 2011), treatment resistance is also observed (Sone et al., 2015).

We found high rates of bilateral AE in our LRE sample; seven TLE (35%) and three exTLE patients (60%) had bilateral AE. These findings are in agreement with previous studies that observed bilateral AE in unilateral TLE (Coan et al., 2013; Lv et al., 2014; Mitsueda-Ono et al., 2011). Bilateral abnormal amygdala T_2 relaxometry is found in approximately 50% of patients with intractable TLE with normal routine MRI (Van Paesschen et al., 1996). Bilateral AE has been linked to psychiatric comorbidities in TLE (Lv et al., 2014; Van Elst et al., 1999; Van Elst et al., 2002), however, it remains unclear whether this association extends to exTLE. Our finding of comparable rates of AE in exTLE suggests that future studies should investigate clinical phenotypes associated with AE, particularly bilateral AE, in the broader LRE population.

Our study is limited by a lack of intracranial EEG depth recordings from the enlarged amygdala, multimodal imaging, and histopathological analyses of resected tissue. Although many of the patients in the LRE sample proceeded to surgery, the amygdala is not typically studied with intracranial depth electrodes or included in pathological evaluations of epilepsy surgery tissue at the institutions participating in this study. Therefore, it is possible that discordant AE contained abnormal tissue features or epileptogenic discharges, even though the primary seizure focus was determined to be elsewhere. Furthermore, T2 and FLAIR images were not systematically collected across sites, which could have facilitated differentiation of pathological from non-pathological amygdala enlargement. In order to determine whether the enlarged amygdala contains pathological features or epileptiform activity, even when the primary seizure focus may be elsewhere, future studies should prospectively evaluate a surgical series for AE with multi-modal imaging, amygdala depth electrodes, and neuropathological evaluation of resected amygdala tissue. Finally, it is important to note that the TLE and exTLE groups were comprised of individuals with treatment resistant epilepsy that were being evaluated for epilepsy surgery. Prior investigations of AE included patients with treatment responsive epilepsy and some found that AE is associated with better treatment response (Kimura et al., 2015; Mitsueda-Ono et al., 2011). Thus, our finding of no difference in AE rates between patients with TLE and exTLE should be considered generalizable to patients with treatment resistant epilepsy only. With that said, the finding that volumetrically-defined AE has limited localization value is most relevant to this clinical population.

1.6 Conclusion

Individual quantitative evaluation of AE reveals higher rates in LRE than in IGE and HCs, which suggests that further study of clinical phenotypes associated with AE is needed.

However, an enlarged amygdala can be found outside of the primary seizure focus and even in the opposite hemisphere of people with LRE. This suggests that AE is a nonspecific feature of LRE with limited seizure onset localization value in patients with treatment resistant epilepsy. Future studies should examine whether features such as abnormal shape, function, or connectivity can distinguish pathogenic from non-pathogenic AE.

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References

Beh SJ, Cook MJ, D'Souza WJ. Isolated amygdala enlargement in temporal lobe epilepsy: A systematic review. Epilepsy & Behavior. 2016; 60:33–41. [PubMed: 27176882]

Bower SPC, Vogrin SJ, Morris K, Cox I, Murphy M, Kilpatrick CJ, Cook MJ. Amygdala volumetry in "imaging-negative" temporal lobe epilepsy. Journal of Neurology, Neurosurgery & Psychiatry. 2003; 74(9):1245–1249.

Coan AC, Morita ME, Campos BM, Yasuda CL, Cendes F. Amygdala enlargement in patients with mesial temporal lobe epilepsy without hippocampal sclerosis. Frontiers in neurology. 2013; 4:166. [PubMed: 24298266]

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, Van Der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002; 33(3):341–355. [PubMed: 11832223]

Grimm O, Pohlack S, Cacciaglia R, Winkelmann T, Plichta MM, Demirakca T, Flor H. Amygdalar and hippocampal volume: A comparison between manual segmentation, Freesurfer and VBM. Journal of neuroscience methods. 2015; 253:254–261. [PubMed: 26057114]

Kim DW, Lee SK, Chung CK, Koh YC, Choe G, Lim SD. Clinical features and pathological characteristics of amygdala enlargement in mesial temporal lobe epilepsy. Journal of Clinical Neuroscience. 2012; 19(4):509–512. [PubMed: 22321366]

Kimura Y, Sato N, Saito Y, Ito K, Kamiya K, Nakata Y, Watanabe M, Maikusa N, Matsuda H, Sugimoto H. Temporal lobe epilepsy with unilateral amygdala enlargement: morphometric MR analysis with clinical and pathological study. Journal of Neuroimaging. 2015; 25(2):175–183. [PubMed: 24593820]

Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010; 51(6):1069–1077. [PubMed: 19889013]

Labarge AS, McCaffrey RJ, Brown TA. Neuropsychologists' abilities to determine the predictive value of diagnostic tests. Archives of Clinical Neuropsychology. 2003; 18(2):165–175. [PubMed: 14591468]

Lv RJ, Sun ZR, Cui T, Guan HZ, Ren HT, Shao XQ. Temporal lobe epilepsy with amygdala enlargement: a subtype of temporal lobe epilepsy. BMC neurology. 2014; 14(1):1. [PubMed: 24383721]

Minami N, Morino M, Uda T, Komori T, Nakata Y, Arai N, Kohmura E, Nakano I. Surgery for amygdala enlargement with mesial temporal lobe epilepsy: pathological findings and seizure outcome. Journal of Neurology, Neurosurgery & Psychiatry. 2015; 86(8):887–894.

Mitsueda-Ono T, Ikeda A, Inouchi M, Takaya S, Matsumoto R, Hanakawa T, Sawamoto N, Mikuni N, Fukuyama H, Takahashi R. Amygdalar enlargement in patients with temporal lobe epilepsy. Journal of Neurology, Neurosurgery & Psychiatry. 2011; 82(6):652–657.

Morey RA, Petty CM, Xu Y, Hayes JP, Wagner HR, Lewis DV, LaBar KS, Styner M, McCarthy G. A comparison of automated segmentation and manual tracing for quantifying hippocampal and amygdala volumes. Neuroimage. 2009; 45(3):855–866. [PubMed: 19162198]

Sone D, Ito K, Taniguchi G, Murata Y, Nakata Y, Watanabe Y, Okazaki M, Sato N, Matsuda H, Watanabe M. Evaluation of amygdala pathology using 11 C-methionine positron emission tomography/computed tomography in patients with temporal lobe epilepsy and amygdala enlargement. Epilepsy Research. 2015; 112:114–121. [PubMed: 25847346]

Takaya S, Ikeda A, Mitsueda-Ono T, Matsumoto R, Inouchi M, Namiki C, Oishi N, Mikuni N, Ishizu K, Takahashi R, Fukuyama H. Temporal lobe epilepsy with amygdala enlargement: a morphologic and functional study. Journal of Neuroimaging. 2014; 24(1):54–62. [PubMed: 22304227]

Van Elst LT, Woermann FG, Lemieux L, Trimble MR. Amygdala enlargement in dysthymia—a volumetric study of patients with temporal lobe epilepsy. Biological Psychiatry. 1999; 46(12): 1614–1623. [PubMed: 10624542]

Van Elst LT, Baeumer D, Lemieux L, Woermann FG, Koepp M, Krishnamoorthy S, Thompson PJ, Ebert D, Trimble MR. Amygdala pathology in psychosis of epilepsy. Brain. 2002; 125(1):140–149. [PubMed: 11834599]

Van Paesschen W, Connelly A, Johnson CL, Duncan JS. The amygdala and intractable temporal lobe epilepsy: A quantitative magnetic resonance imaging study. Neurology. 1996; 47(4):1021–1031. [PubMed: 8857739]

Highlights

- Higher rates of AE were found in the localization related epilepsy group relative to idiopathic generalized epilepsy and healthy controls.
- Similar rates of AE were found in temporal and extratemporal lobe epilepsy.
- Bilateral and contralateral amygdala enlargement was a common finding.

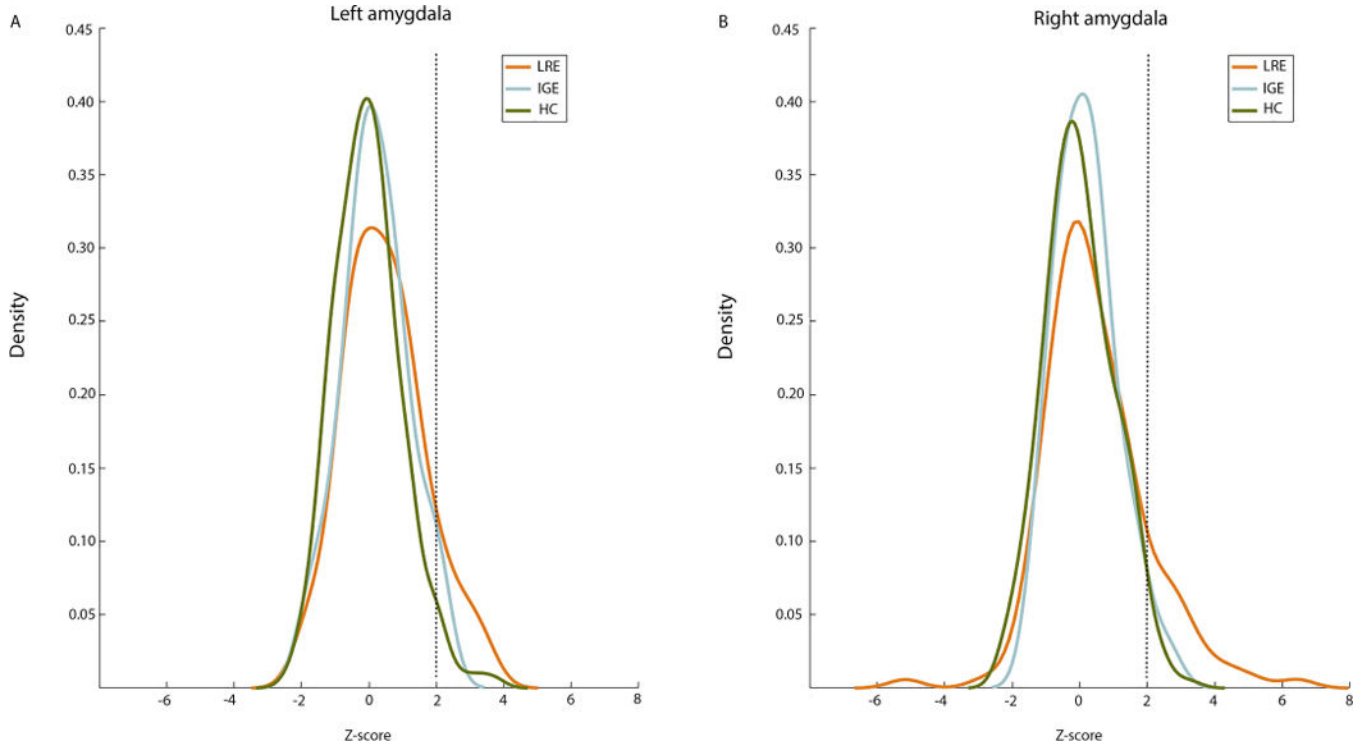

Figure 1.

Kernel density plots for amygdala volume z-scores in the LRE, IGE, and HC groups. The estimate of the probability density function is plotted against (A) left and (B) right amygdala volume z-scores. The dotted line represents the z-score cutoff for amygdala enlargement ($z > 2$). (A) The left amygdala distribution across groups shows a larger percentage of individuals with amygdala enlargement in the LRE group (12%) relative to the IGE (6%) and HC (4%) groups. (B) Similarly, there were a greater percentage of individuals with right amygdala enlargement in the LRE group (14%) relative to the IGE (3%) and HC group (3%). LRE=Localization Related Epilepsy; IGE=Idiopathic Generalized Epilepsy; HC=Healthy Controls.

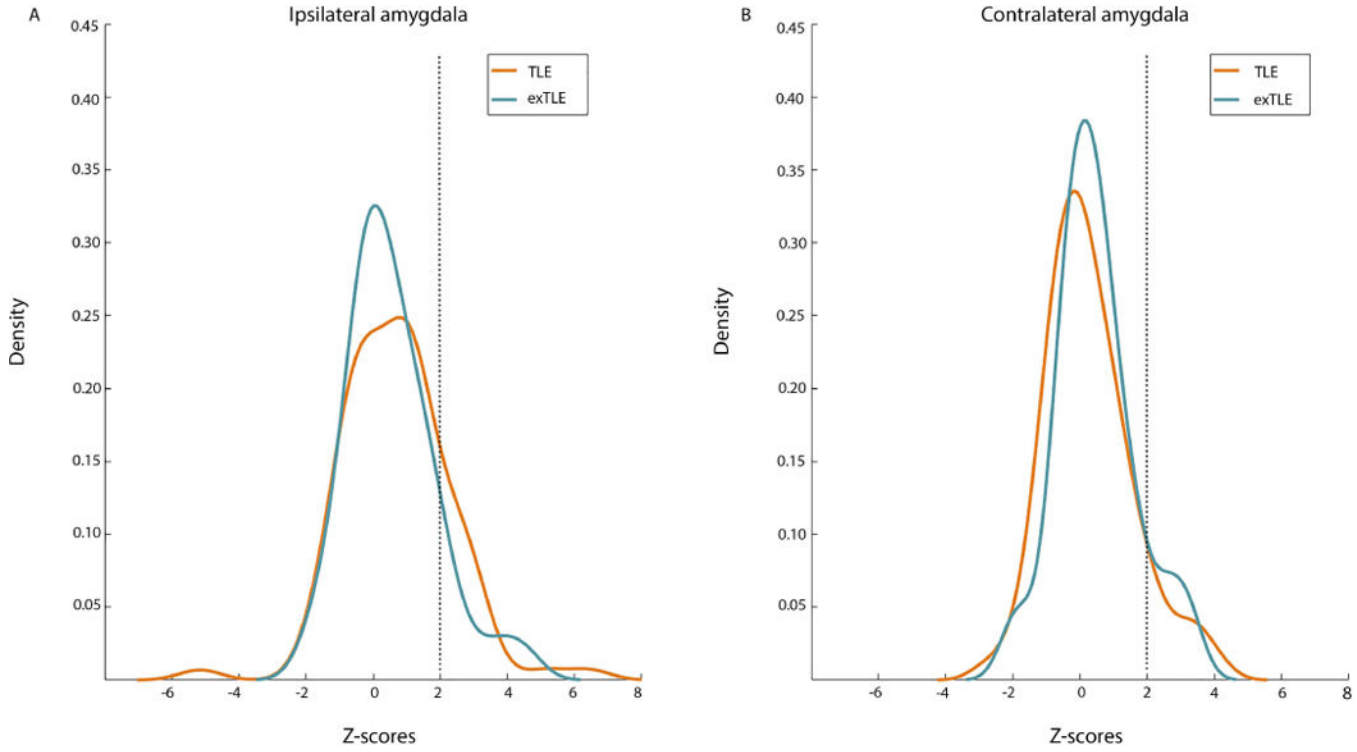

Figure 2.

Kernel density plots for amygdala volume z-scores in the TLE and exTLE groups. The estimate of the probability density function is plotted against (A) ipsilateral and (B) contralateral amygdala volume z-scores. The dotted line represents z-score cutoff for amygdala enlargement. (A) The ipsilateral amygdala distribution across groups shows a higher percentage of individuals with amygdala enlargement in the TLE group (19%) relative to the exTLE (11%) group, although this difference was not significant. (B) There was no difference in the percentage of individuals with contralateral amygdala enlargement between the TLE group (10%) and exTLE (11%) groups. TLE=Temporal Lobe Epilepsy; exTLE= Extratemporal Lobe Epilepsy.

Table 1

Clinical features of patients and demographics of healthy controls by site

	NYU			UCSD		The Florey	
	LRE (N=76)	**IGE (N=34)**	**HC (N=84)**	**LRE (N=28)**	**HC (N=37)**	**LRE (N=32)**	**HC (N=112)**
Sex (males/females)	30/46	18/16	40/44	12/16	18/19	15/17	63/49
Side of onset (L/R/B)	38/34/3			14/14/0		18/14/0	
		Mean (SD)			Mean (SD)		Mean (SD)
Age	33.1 (10.85)	32.6 (9.37)	36.34 (12.67)	37.89 (13.68)	34.70 (13.74)	33.97 (9.40)	34.73 (10.61)
Epilepsy duration *	17.76 (12.2)	21.57 (10.89)		12.75 (13.32)		12.45 (8.13)	
Age of seizure onset *	15.6 (11.42)	13.39 (7.27)		25.14 (17.06)		21.32 (9.44)	
Left amygdala	1581.66 (254.18)	1605.78 (241.5)	1516.5 (243.19)	1665.96 (324.52)	1556.87 (269.64)	1778.68 (212.09)	1718.74 (206.36)
Right amygdala	1705.53 (407.32)	1715.44 (264.53)	1626.46 (262.72)	1766.93 (341.10)	1706.15 (244.54)	1791.21 (232.48)	1736.61 (226.42)

* When available; NYU = New York University; UCSD = University of California SanDiego; LRE = localization-related epilepsy; IGE = idiopathic generalized epilepsy; HC = healthy control; L = left; R = right; B = Bilateral; SD = standard deviation; TLE = temporal lobe epilepsy; exTLE = extratemporal epilepsy

Table 2

Proportion of amygdala enlargement (AE) across different types of nonlesional epilepsy

	LRE	IGE	HC	FE value	*p*-value
Left AE	16/136 (11.8%)	2/34 (5.9%)	10/233 (4.3%)	7.05	0.003
Right AE	19/136 (14.0%)	1/34 (2.9%)	7/233(3.0%)	15.53	0.00038
Total AE	25/136 (18.4%)	2/34 (5.9%)	15/233 (6.4%)	12.72	0.001

	Unilateral Temporal	Unilateral Extratemporal	χ^2	FE *p*-value
Ipsilateral AE*	18/93 (19.4%)	4/38 (10.5 %)	1.51	0.305
Contralateral AE*	9/93 (9.7%)	4/38 (10.5%)	0.02	1.00

	Temporal z-scores		Extratemporal z-scores		Mann-Whitney U	
	Range	Mean (SD)	Range	Mean (SD)	U	*p*-value
Ipsilateral AE	2.09 – 6.44	2.97 (1.11)	2 – 4.47	3.19 (1.09)	33	0.798
Contralateral AE	2.12 – 4.15	3.02 (0.7)	2.47 – 3.26	2.83 (0.41)		

*Ipsilateral and contralateral AE counts include cases with bilateral AE; therefore, single cases may be represented in both the ipsilateral and contralateral rows.

AE = amygdala enlargement, LRE = localization-related epilepsy, IGE = idiopathic generalized epilepsy, HC = healthy control, FE= Fisher's Exact

Table 3

Volumetry and clinical characteristics of patients with amygdala enlargement (AE)

Patient	Epilepsy subtype	Onset side	Amygdala vol. (mm^3)		Z-score		Age of Onset
			Left	Right	Ipsi	Contra	
1	Temporal	Left	1854	1813	2.09	1.5	4
2	Temporal	Left	2183	2009	2.18	1.16	35
3	Temporal	Right	1844	2112	2.36	1.76	12
4	Extratemporal	Left	1595	1438	2.63	1.41	9
5	Temporal	Left	1748	1680	3.06	2.28	6
6	Temporal	Right	1297	854	−0.7	2.33	31
7	Temporal	Right	1318	2854	2.66	−1.51	16
8	Temporal	Right	1318	2854	5.1	−0.35	2
9	Temporal	Right	1993	2218	2.27	1.88	19
10	Extratemporal	Left	1446	1629	2	2.5	22
11	Temporal	Right	1751	1719	2.87	3.49	17
12	Temporal	Right	1593	2157	3.31	0.75	42
13	Temporal	Left	2181	2304	2.80	3.25	23
14	Temporal	Right	1459	2074	3.22	0.34	11
15	Temporal	Right	2802	2770	2.81	3.09	17
16	Temporal	Left	1409	2210	0.17	4.13	5
17	Temporal	Right	1468	1512	2.85	2.72	42
18	Temporal	Right	1673	2052	6.44	3.64	2
19	Temporal	Right	1836.5	2028.7	2.75	1.79	29
20	Temporal	Right	1717.6	2095.4	2.09	0.16	35
21	Temporal	Right	1818.6	1900.3	2.43	2.12	24
22	Temporal	Left	2107.9	1630	2.27	−0.48	21
23	Extratemporal	Right	2252.5	2368.5	3.65	3.26	11
24	Extratemporal	Right	1650	1585	1.72	2.47	5
25	Extratemporal	Right	1627	1981	4.47	3.11	5

Z-scores were calculated based on amygdala volume corrected for intracranial volume (amygdala volume/intracranial volume); Mean age of onset for the temporal group was 19.7 (SD: 12.80) and mean age of onset for the extratemporal group was 10.4 (SD: 6.99); SD = standard deviation.