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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 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.

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).

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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).

1.1. Methods

1.1.1. 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.

1.1.2. 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 × 1.33 mm). 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 × 1.3 mm). 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 = 900 ms, flip angle = 9°, matrix = 256 × 256, 192 sagittal slices, voxel size 0.9 mm isotropic). Scanner and sequence parameters were identical for all patients and HCs.

1.1.3. 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.

1.1.4. 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.

1.1.5. 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.

1.2. Results

1.2.1. 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