Radiology

Temporal Lobe Epilepsy: Quantitative MR Volumetry in Detection of Hippocampal Atrophy[1]

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Purpose: To determine the ability of fully automated volumetric magnetic resonance (MR) imaging to depict hippocampal atrophy (HA) and to help correctly lateralize the seizure focus in patients with temporal lobe epilepsy (TLE).

Materials and Methods: This study was conducted with institutional review board approval and in compliance with HIPAA regulations. Volumetric MR imaging data were analyzed for 34 patients with TLE and 116 control subjects. Structural volumes were calculated by using U.S. Food and Drug Administration–cleared software for automated quantitative MR imaging analysis (NeuroQuant). Results of quantitative MR imaging were compared with visual detection of atrophy, and, when available, with histologic specimens. Receiver operating characteristic analyses were performed to determine the optimal sensitivity and specificity of quantitative MR imaging for detecting HA and asymmetry. A linear classifier with cross validation was used to estimate the ability of quantitative MR imaging to help lateralize the seizure focus.

Results: Quantitative MR imaging–derived hippocampal asymmetries discriminated patients with TLE from control subjects with high sensitivity (86.7%–89.5%) and specificity (92.2%–94.1%). When a linear classifier was used to discriminate left versus right TLE, hippocampal asymmetry achieved 94% classification accuracy. Volumetric asymmetries of other subcortical structures did not improve classification. Compared with invasive video electroencephalographic recordings, lateralization accuracy was 88% with quantitative MR imaging and 85% with visual inspection of volumetric MR imaging studies but only 76% with visual inspection of clinical MR imaging studies.

Conclusion: Quantitative MR imaging can depict the presence and laterality of HA in TLE with accuracy rates that may exceed those achieved with visual inspection of clinical MR imaging studies. Thus, quantitative MR imaging may enhance standard visual analysis, providing a useful and viable means for translating volumetric analysis into clinical practice.

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For patients with temporal lobe epilepsy (TLE) that is refractory to medical therapy, the best option for achieving freedom from seizures is surgical resection, especially when hippocampal atrophy (HA) is present at magnetic resonance (MR) imaging (1). Although most clinical MR imaging studies are sufficient for the detection of gross HA, subtle HA that may characterize early disease is often missed (2). This is particularly true when MR imaging studies are interpreted by radiologists outside epilepsy centers who may lack sufficient experience with this diagnosis (3). To facilitate clinical interpretations, quantitative volumetric methods have been developed, and these methods correlate well with manual tracings (4–7) and histologically confirmed hippocampal cell loss (4). Thus, hippocampal volumetry is a strong surrogate marker for the presence and severity of HA.

Despite its established utility, hippocampal volumetry has been difficult to integrate into clinical practice because of the time demands and technical skills needed. However, recent advances in technology have led to the development of automated software for generic quantitative morphometrics that has been cleared by the U.S. Food and Drug Administration for clinical use. These tools have been successfully used to detect HA in Alzheimer disease (AD) (6,8), have been validated against manual tracings (9), and are the standard of care in many AD clinics.

The goal of this study was to determine the ability of fully automated volumetric MR imaging to depict HA and help correctly lateralize the seizure focus in patients with TLE.

Advances in Knowledge

- Hippocampal asymmetry is a stronger classifier of seizure lateralization (area under the receiver operating characteristic curve [AUC], 0.939 for left temporal lobe epilepsy [TLE] and 0.915 for right TLE) than hippocampal asymmetry adjusted for size of the inferior lateral ventricle (AUC, 0.750 for left TLE and 0.671 for right TLE).
- Hippocampal asymmetry alone was a robust classifier (94%) of seizure lateralization, whereas asymmetries of other subcortical structures did not contribute to classification accuracy.
- Quantitative MR imaging can depict the presence and laterality of hippocampal atrophy in TLE, with accuracy rates for seizure lateralization of 88% versus the 76% achieved with visual inspection of clinical MR imaging studies.

Materials and Methods

The research protocol was approved by the local institutional review board and was in compliance with Health Insurance Portability and Accountability Act regulations. Written informed consent was obtained from each participant prospectively enrolled in the study from January 2007 through April 2011. Two of the coauthors (M.E.S. and S.W.M) are employees of CorTechs, the company that owns the device used for quantitative MR imaging analysis in this study (NeuroQuant). S.W.M. is the director of science and engineering and M.E.S. is the chief executive officer of CorTechs Laboratories. However, this study was not industry sponsored, and the first and senior authors (who are not employees of or affiliated with CorTechs) had complete control of the data and all information that might present a conflict of interest for those employed by CorTechs throughout the duration of the study.

Participants

Participants included a group of healthy control subjects (total, 116; mean age, 28.7 years ± 11.0 [standard deviation]; range, 18–64 years; 52 men [mean age, 28.1 years ± 10.5; range, 19–64 years], 64 women [mean age, 29.3 years ± 11.4; range, 18–57 years]) and a group of patients with medically refractory TLE (total, 37; mean age, 36.7 years ± 10.8; range, 19–63 years; 15 men [mean age, 37.8 years ± 13.5; range, 19–63 years], 22 women [mean age, 36.8 years ± 10.0; range, 22–52 years]). There was a statistically significant difference in mean age between the two groups ($F = 13.787$, $P < .001$).

All patients underwent video electroencephalographic (EEG) monitoring at the University of California San Diego Epilepsy Center performed by using scalp and foramen ovale electrodes to diagnose their seizure disorder. Patients were included in the study if they were between 18 and 65 years of age, had disease that was refractory to

Implication for Patient Care

- The quantitative MR imaging device described provides a means for translating volumetric data into an easy-to-read format with age- and sex-appropriate norms that can facilitate radiologic interpretation in clinical practice.

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Abbreviations:
AD = Alzheimer disease
ANOVA = analysis of variance
AUC = area under the ROC curve
CI = confidence interval
EEG = electroencephalography
FLAIR = fluid-attenuated inversion recovery
HA = hippocampal atrophy
HOC = hippocampal occupancy
ICV = intracranial volume
ILV = inferior lateral ventricle
MTS = mesial temporal sclerosis
ROC = receiver operating characteristic
TLE = temporal lobe epilepsy

Author contributions:
Guarantor of integrity of entire study, C.R.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, H.M.G., W.Y.L., C.R.M.; clinical studies, W.Y.L., R.R.L.; statistical analysis, N.K., S.W.M., C.R.M.; and manuscript editing, N.F., H.M.G., N.K., S.W.M., R.R.L., C.R.M.

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medical therapy, and had evidence of unilateral temporal lobe epileptiform activity during inpatient video EEG, as diagnosed by a board-certified neurologist with more than 30 years of experience in epileptology. Patients were excluded if they showed evidence of extrahippocampal disease at clinical MR imaging (n = 3; see below) or electrographic seizure onset bilaterally (n = 0). Patients were classified as having left TLE (n = 19) or right TLE (n = 18) on the basis of invasive video EEG recordings and seizure semiology. Together, these variables were used as the reference standard for seizure lateralization.

Clinical MR imaging examinations for all patients utilized a specialized epilepsy imaging protocol that included a coronal oblique T2-weighted fast spin-echo sequence (repetition time msec/echo time msec, 2983/120; number of sections, 26; section thickness, 2.5 mm; field of view, 22 cm; matrix, 512 × 384; number of signals acquired, two; echo train length, 24; and voxel resolution, 0.4 × 0.6 × 2.5 mm) and a coronal oblique T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence (9002/127; inversion time, 2300 msec; number of sections, 26; section thickness, 2.5 mm; field of view, 22 cm; matrix, 384 × 320; number of signals acquired, one; and voxel resolution, 0.6 × 0.7 × 2.5 mm).

All clinical MR imaging studies were visually inspected by one of several board-certified academic neuroradiologists with 19 or more years of experience (including R.R.L., with 19 years of experience) for detection of mesial temporal sclerosis (MTS) and the exclusion of dual disease. Three patients with right TLE were excluded from the study because of the presence of extrahippocampal disease (two low-grade gliomas and one unknown temporal lobe mass). In a subset of patients (n = 17 [50%]), the side of electrographic onset was further confirmed by surgical outcome (Engel class I or II), and the presence or absence of MTS was confirmed by findings in histologic specimens (n = 12 [35%]) that were reviewed by a board-certified neuropathologist with 28 years of experience. Histologic findings for these 12 patients were in 100% agreement with the classification based on invasive video EEG monitoring. Histologic findings were missing or inconclusive in five patients (approximately 15%). The remaining 17 patients (50%) elected not to undergo surgery or are awaiting further evaluation (ie, the intracarotid amobarbital procedure).

Volumetry

Volumetric MR imaging studies were performed with a 1.5-T MR imaging unit (EXCITE HD; GE Healthcare, Milwaukee, Wis) with an eight-channel phased-array head coil. The image acquisition included a conventional three-plane localizer sequence, a GE calibration sequence, and a three-dimensional volumetric T1-weighted gradient-echo sequence (10.7/4.9; inversion time, 1 second; flip angle, 8°; bandwidth, 31.25 Hz/pixel; number of sections, 176; section thickness, 1.0 mm; field of view, 25.6 cm; matrix, 256 × 192; and voxel resolution, 1.0 × 1.3 × 1.0 mm). Images were processed by using fully automated volumetric segmentation with a quantitative MR imaging software package (NeuroQuant; CorTechs Laboratories, La Jolla, Calif), as previously described (6,8,9).

Images were corrected for gradient nonlinearity and B_1 field inhomogeneity, followed by automated segmentation and labeling of structures by using a probabilistic brain atlas. Volumes obtained by using NeuroQuant have been validated against manual segmentations, and this software has received U.S. Food and Drug Administration clearance for clinical use (6,9). A representative hippocampal segmentation is shown in Figure E1 (online), along with a description of the segmentation procedure.

Previous results indicate highly significant correlations between quantitative MR imaging and manual segmentations for medial temporal regions of interest (intraclass correlation coefficient, 0.92 for inferior lateral ventricle [ILV] and 0.93 for hippocampus; $P <$ .001) (6). The quantitative MR imaging process can be performed on a desktop computer and does not require any user input, aside from selecting a T1-weighted volumetric study to be segmented. Output of the software includes numeric volumes and images that have been annotated with graphic color overlays, with each color representing a specific segmented structure. However, a visual quality review and clinical interpretation by an imaging expert remains important. Therefore, the outcome includes a file that allows the clinician to scroll through the segmented MR images in all three planes to confirm the accuracy of the segmentation and to perform a clinical interpretation. In this study, all images were processed and inspected for quality assurance by the same two image analysis experts (H.M.G., with 4 years of experience, and C.R.M., with 6 years of experience). Full agreement was achieved between experts (κ = 1.0), and no studies were rejected because of poor anatomic segmentation.

The NeuroQuant quantitative MR imaging output compares an individual patient's regional brain volumes with those of a normative database, correcting for sex, head size, and age (ie, raw volumes are expressed as percentages of intracranial volume [ICV], along with age-specific normative ranges). Existing norms were developed for use with an AD population (ie, healthy individuals aged 50–100 years). However, because brain structures may vary by age and sex and hippocampal asymmetries naturally occur in healthy individuals (10), determination of atrophy and asymmetry should be based on comparison with matched control subjects. Therefore, we derived new age- and sex-appropriate norms from our healthy control subjects (aged 18–65 years) for use with a surgical epilepsy population and added these to the normative database. Figure 1 displays an age- and sex-normalized example for a patient with left TLE. This epilepsy-specific report includes norms for each hippocampal volume and hippocampal asymmetry, as well as morphometric values, including total volumes, ICV-adjusted volumes, and volumetric asymmetries for the numerous subcortical structures. The Table presents the group means of

the subcortical volumes and asymmetry values based on the output obtained from these reports.

After segmentation, quantitative MR imaging estimates of HA were compared with ratings based on visual inspection. Clinical MR imaging studies were interpreted by one of several board-certified neuroradiologists and were based on the studies routinely obtained per the epilepsy protocol but without volumetric MR imaging. This method was selected to best reflect day-to-day practice in most community settings, where the interpreting radiologist may or may not be an epilepsy specialist. Conversely, all volumetric MR imaging studies were interpreted by two board-certified academic neuroradiologists (N.F., with 2 years of experience, and W.Y.L., with 4 years of experience) with expertise in epilepsy who were able to re-section the three-dimensional acquisition into any orientation but who did not have access to the clinical MR imaging studies and were blinded to the clinical interpretation and patient information. This method allowed us to compare quantitative MR imaging with visual inspection of both standard clinical MR imaging and volumetric MR imaging studies.

Statistical Analysis

Hippocampal volumes and asymmetries were first evaluated in control subjects to quantify any naturally occurring asymmetry as a function of age or sex. This was accomplished by using repeated-measures analyses of variance (ANOVAs) on ICV-adjusted hippocampal volumes and hippocampal occupancy (HOC) volumes, with sex as a between-subject factor and side of the hippocampus as a within-subject factor. Next, to test the sensitivity and specificity of quantitative MR imaging for detecting HA in patients, a receiver operating characteristic (ROC) analysis was performed between each patient group and control subjects with four hippocampal values: ICV-adjusted hippocampal volume, hippocampal asymmetry, HOC volume, and HOC asymmetry. Whereas the ICV-adjusted hippocampal volume adjusts for overall head size, the HOC volume is the ratio of hippocampal volume to the sum of the hippocampal and ILV volumes and provides an estimate of ex vacuo dilatation, indicating expansion of the ILV as a function of brain tissue loss. This measure was developed to differentiate individuals with congenitally small hippocampi from those with small hippocampi due to a degenerative disorder and has been shown to be a better predictor of conversion to AD than the more typically used ICV-adjusted volume (11). Asymmetry scores were calculated for each individual as {(left – right)/[(left + right)/2]} · 100. All variables were converted into *z* scores, based on the mean and the standard deviation of the values in the control subjects. This conversion was performed to *(a)* account for any naturally occurring hippocampal asymmetry in control subjects and *(b)* make the comparison across different hippocampal measures easier to interpret.

Because there is evidence that a combination of subcortical asymmetries may enhance seizure lateralization when hippocampal asymmetries are minimal or absent (12,13), a discriminant function analysis with cross

Figure 1

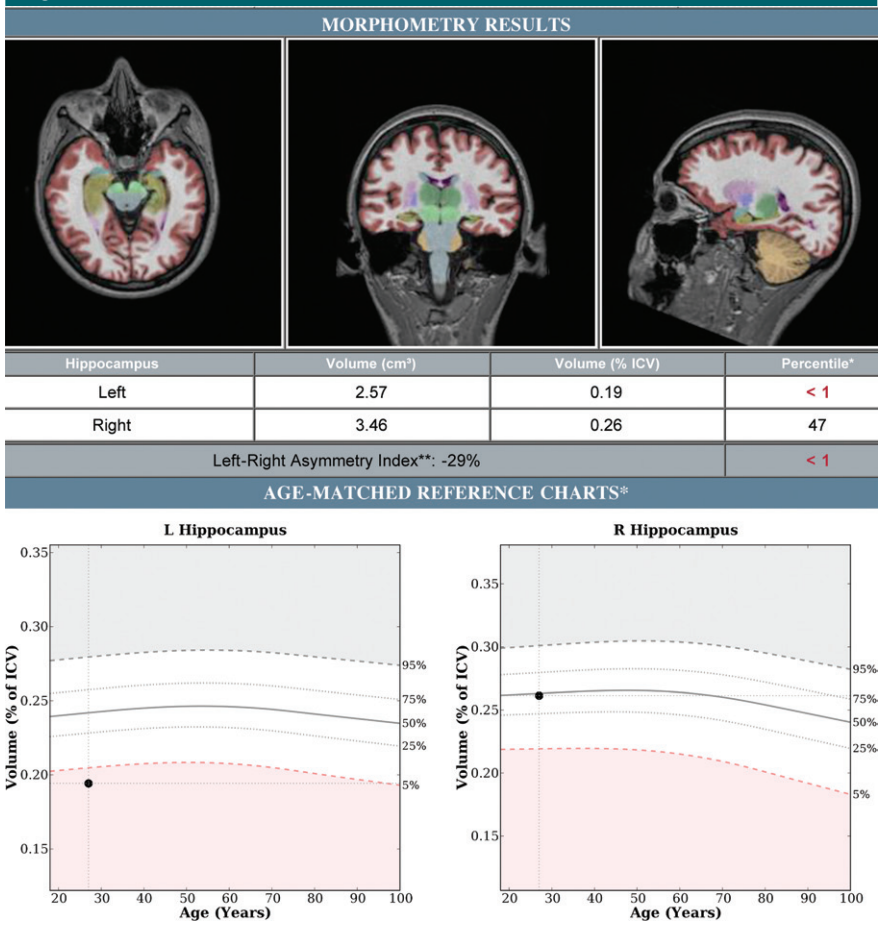

Figure 1: Hippocampal volume asymmetries for a patient with left TLE. Graphs show left and right hippocampal volumes for this patient, plotted against a large sample of age-matched control subjects. This visual depiction of both volumes enables the determination of unilateral HA (one volume falls below the 95% confidence interval [CI]) versus bilateral HA (both volumes fall below the 95% CI) relative to age-matched control subjects. The right and left hippocampal volumes are also provided, as well as their percentage asymmetry and age- and sex-corrected percentiles.

Mean Volumes, ICV–adjusted Volumes, and Asymmetry Indexes for Selected Subcortical Structures at Quantitative MR Imaging

	Control Subjects (n = 116)		Patients with Left TLE (n = 19)		Patients with Right TLE (n = 15)	
Brain Structure	Mean Volume (cm^3)/ICV-adjusted Volume (%)	Asymmetry Index	Mean Volume (cm^3)/ICV-adjusted Volume (%)	Asymmetry Index	Mean Volume (cm^3)/ICV-adjusted Volume (%)	Asymmetry Index
Hippocampus						
Left	3.82/0.24	−4.46*†	3.15/0.21	−27.98†‡	3.83/0.26	19.21*‡
Right	4.00/0.25		4.13/0.28		3.20/0.22	
Amygdala						
Left	1.71/0.11	−2.01*†	1.57/0.11	−15.94†‡	1.80/0.12	8.52*‡
Right	1.74/0.11		1.83/0.12		1.66/0.11	
Caudate nucleus						
Left	3.52/0.22	−5.20	3.26/0.22	−4.41	3.24/0.22	−3.98
Right	3.70/0.24		3.42/0.23		3.38/0.23	
Putamen						
Left	5.71/0.36	5.37	5.16/0.35	2.45†	5.18/0.35	8.90*
Right	5.41/0.34		5.02/0.34		4.74/0.32	
Pallidus						
Left	1.18/0.08	−3.31*	1.05/0.07	−11.80‡	1.10/0.07	−2.12
Right	1.22/0.08		1.16/0.08		1.12/0.08	
Thalamus						
Left	8.04/0.51	−6.38	7.53/0.50	−6.01	7.54/0.51	−0.16
Right	8.57/0.55		7.95/0.53		7.56/0.60	

Note.—The asymmetry index is the difference between left and right volumes divided by their mean (as a percentage).

* Mean asymmetry value is significantly different ($P < .05$) from that in patients with left TLE.

† Mean asymmetry value is significantly different ($P < .05$) from that in patients with right TLE.

‡ Mean asymmetry value is significantly different ($P < .05$) from that in control subjects.

validation was performed, first using hippocampal asymmetry only, and then using six subcortical asymmetries (hippocampus, amygdala, thalamus, caudate nucleus, globus pallidus, and putamen). All analyses were performed by using statistical software (SPSS, version 17.0; SPSS, Chicago, Ill).

Hippocampal asymmetry detected at quantitative MR imaging (using optimal cutoffs established in the ROC analysis) was compared with detection based on visual inspection of *(a)* clinical MR imaging studies and *(b)* volumetric MR imaging studies. κ Coefficients were calculated to evaluate the interrater agreement between the two neuroradiologists as to the presence or absence of HA. The ability of each method to help correctly classify patients as having right TLE or left TLE as determined by video EEG results was evaluated. $P <$ .05 was considered to indicate a significant difference.

Results

Figure 2 displays the mean hippocampal volume and asymmetry values and the Table presents the mean volume and asymmetry values for subcortical structures for patients and control subjects. The homogeneity of covariance assumption for repeated-measures ANOVA was met for the volume analysis (Box's M = 6.77, P = .08) and for the HOC analysis (Box's M = 1.225, P = .75). A repeated-measures ANOVA on ICV-adjusted hippocampal volumes in control subjects, with sex as a between-subject factor and side of the hippocampus as a within-subject factor, revealed a main effect of side, with the right hippocampus being larger than the left (F = 37.033, $P <$ .001). In addition, the main effect of sex was significant (F = 10.571, $P <$ .01), with women showing larger hippocampi than men when values were corrected for ICV. A repeated-measures ANOVA on HOC scores in control subjects revealed significant main effects of sex (F = 5.151, $P <$ .05), with women showing larger HOC volumes than men, and side (F = 16.983, $P <$ .001), with right HOC being larger than left. Despite the significant effect of sex on the hippocampal volume and HOC scores, when asymmetry scores were calculated, neither hippocampal asymmetry nor HOC asymmetry correlated with sex or age. The rightward asymmetry of the ICV-adjusted hippocampal and HOC scores was consistent across the age range in healthy men and women. Therefore, z scores were used to correct for this asymmetry in the patient analyses. In

addition, sex effects were regressed out of the ICV-adjusted and HOC scores in the subsequent analyses.

Diagnostic Accuracy, Sensitivity, and Specificity of Quantitative MR Imaging

The ROC analysis indicated that the hippocampal asymmetry *z* score (area under the ROC curve [AUC] for left TLE, 0.939 [95% CI: 0.865, 1.00]; AUC for right TLE, 0.915 [95% CI: 0.730, 1.00]) outperformed the *z* scores of sex-adjusted HOC (AUC for left TLE, 0.598 [95% CI: 0.445, 0.751]; AUC for right TLE, 0.612 [95% CI: 0.448, 0.777]), HOC asymmetry (AUC for left TLE, 0.750 [95% CI: 0.632, 0.868]; AUC for right TLE, 0.671 [95% CI: 0.503, 0.838]), and sex-adjusted ipsilateral hippocampal volumes (AUC for left TLE, 0.796 [95% CI: 0.666, 0.925]; AUC for right TLE, 0.786 [95% CI: 0.625, 0.946]) in distinguishing patients with left TLE and those with right TLE from control subjects (Fig 3). By using a hippocampal asymmetry z-score of −1.45, a sensitivity of 89.5% and a specificity of 92.2% was achieved for detecting left TLE. By using a hippocampal asymmetry *z* score of −1.58, a sensitivity of 86.7% and a specificity of 94.1% were achieved for detecting right TLE.

Discriminant function analysis with hippocampal asymmetry correctly classified all but two patients (32 of 34; 94% correct classification) with cross validation ($\chi^2[1] = 45.05$, $P < .001$). Although amygdala asymmetry was also significantly different among the groups (Table), neither amygdala asymmetry nor other subcortical asymmetries improved classification accuracy when hippocampal asymmetry was included in the model ($\chi^2[2] = 44.37$, $P < .001$). This reflects the strong classifying power of hippocampal asymmetry and the likely redundancy between hippocampal and amygdala asymmetry measures in a given patient.

Concordance of Quantitative MR Imaging Findings with Visual Ratings and Histologic Findings

Visual inspection of the volumetric MR imaging studies by the two board-certified neuroradiologists resulted in 85% agreement (29 of 34, κ = 0.75, $P < .001$). Using the optimal cutoff points derived from the ROC analysis for detecting hippocampal volume asymmetry, agreement between quantitative MR imaging asymmetry and visual inspection of the volumetric MR imaging studies was 91% for one rater (31 of 34) and 97% for the other rater (33 of 34). In three cases of HA, hippocampal asymmetry was missed by at least one of the raters of the volumetric MR imaging studies but was detected at quantitative MR imaging. In each case, the asymmetry detected with quantitative MR imaging was consistent with invasive video EEG, which was considered the standard of reference for correct lateralization (12).

Agreement between quantitative MR imaging asymmetry and visual inspection of the clinical MR imaging studies was 85% (29 of 34). In four cases, hippocampal asymmetry was missed on visual inspection but was detected at quantitative MR imaging. In one case, clinical MR imaging depicted a slight hippocampal asymmetry in the right hippocampus (in the absence of signal change) that was missed at quantitative MR imaging and volumetric MR imaging visual inspection. When each method was compared with invasive video EEG recordings and surgical outcome, classification accuracy was 88% with quantitative MR imaging (30 of 34), 85% with visual inspection of volumetric MR imaging studies (29 of 34 for both interpretations), and 76% with

Figure 2

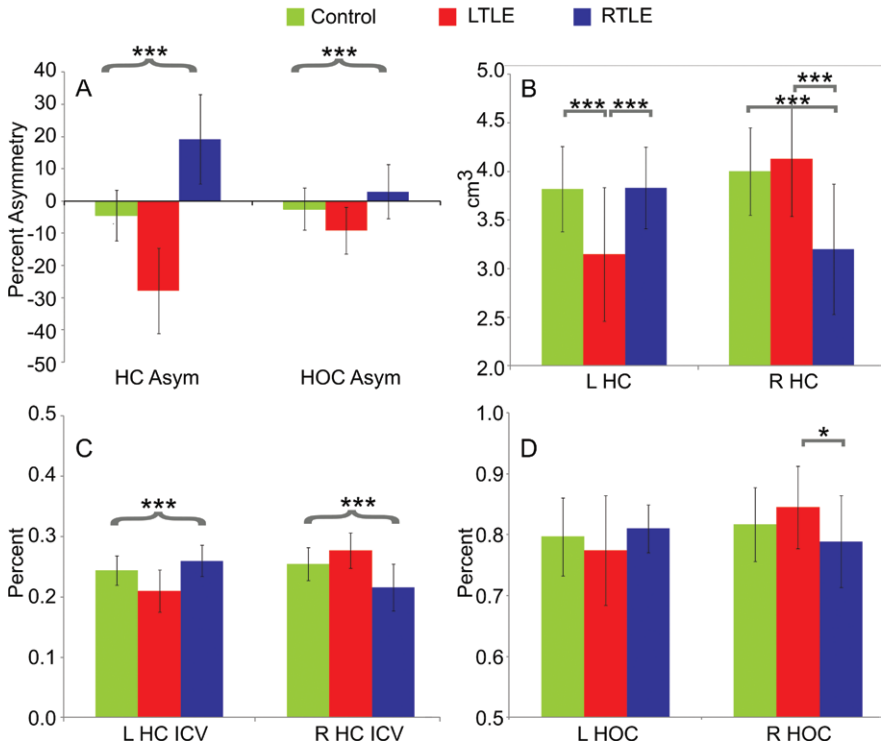

Figure 2: Bar graphs show mean quantitative MR imaging–derived, *A,* hippocampal *(HC)* and HOC asymmetry *(Asym)*, *B,* raw hippocampal volumes in cubic centimeters, and, *C, D,* hippocampal volumes as a percentage of, *C,* ICV and, *D,* HOC. Positive values on the asymmetry graphs indicate that left is greater than right volume, whereas negative values indicate that right is greater than left volume. Error bars = standard deviations. *L* = left, *LTLE* = left TLE, *R* = right, *RTLE* = right TLE. ***$P < .001$, *$P < .05$. Curly brackets = all pairwise comparisons were significant, straight brackets = specific pairwise comparisons.

Figure 3

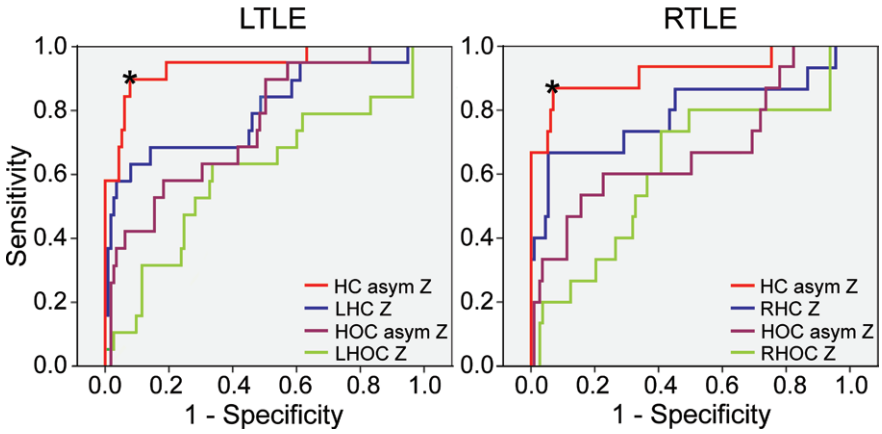

Figure 3: ROC curves show sensitivity and specificity of quantitative MR imaging for depicting HA in patients with (left) left TLE *(LTLE)* and (right) right LTE *(RTLE)*. * = Optimal cutoff point along each curve for discriminating each patient group from control subjects. This corresponds to $z = -1.45$ for left TLE and $z = 1.58$ for right TLE. *asym* = Asymmetry, *HC* = hippocampal, *LHC* = left hippocampal, *LHOC* = left HOC, *RHC* = right hippocampal, *RHOC* = right HOC.

visual inspection of clinical MR imaging studies (26 of 34).

Neuropathologic reports were available for 12 patients (approximately 35%) who underwent surgical resection. In 83% of the histologically confirmed cases (10 of 12), HA was identified by both visual inspection and quantitative MR imaging. In 17% of cases (two of 12), HA was missed at visual inspection but was captured with quantitative MR imaging. There were no cases of histologically confirmed HA in which atrophy was detected at visual inspection but was missed at quantitative MR imaging.

Discussion

We demonstrate the ability of a fully automated Food and Drug Administration–cleared clinical device to depict HA and asymmetry in patients with TLE, classifying patients at rates that may exceed those based on visual inspection of clinical studies obtained with a specialized epilepsy MR imaging protocol. Our results demonstrate that quantitative MR imaging estimates of hippocampal asymmetry yield high sensitivity and specificity for discriminating patients from control subjects, outperforming ICV-adjusted hippocampal volumes, HOC volume, and HOC asymmetry. In this study, quantitative MR imaging asymmetry scores achieved the highest accuracy rate for lateralization of the seizure focus, followed by volumetric MR imaging interpretation and then by clinical interpretation without volumetry. This pattern of results is similar to that reported in previous studies (2,13–17) in which automated or manual segmentation was compared with visual inspection, indicating that hippocampal volumetry provides unique information that can enhance visual detection of HA in complex cases of TLE.

It is well appreciated that moderate to severe HA can be visually detected by most neuroradiologists when a specialized epilepsy MR imaging protocol is performed (18,19). However, recent studies have shown that MR imaging hippocampal volumetry can aid expert visual inspection in at least four situations—when volume loss is subtle (ie, when volume ratios exceed 0.70) (2); when bilateral volume loss is present, resulting in little or no asymmetry; when the head is tilted in the MR imaging unit, preventing a clear visualization of asymmetry (20); and when centers lack an expert in epilepsy imaging (5). The last situation is of particular concern, given that patients who lack an MR imaging–visible lesion are less likely to be given a diagnosis and to be referred to surgical epilepsy centers (18), and many MR imaging studies initially interpreted as normal in community settings are later determined to reveal HA at a tertiary epilepsy program (3). Therefore, missed HA could delay referrals to epilepsy surgical centers, resulting in suboptimal care for potential surgical candidates. It is noteworthy that there was strong concordance between hippocampal asymmetry, as quantified by means of quantitative MR imaging, and visual inspection of the volumetric MR imaging studies by two neuroradiologists trained to detect HA (91%–97%). This highlights the utility of volumetric MR imaging and indicates that quantitative MR imaging can serve as an expert "eye" in centers that lack such expertise. However, we believe that the most important comparison is between quantitative MR imaging and visual inspection of the clinical MR imaging study, because the latter is what is most frequently available in standard clinical practice. Our results revealed that quantitative MR imaging depicted HA in patients at rates that may exceed those based on visual inspection of the clinical MR imaging study (88% vs 76%). Furthermore, even epilepsy specialists are more reluctant to offer surgery in the absence of MTS that correlates with the electrographic onset, because of evidence that success rates drop from over 80% in patients with TLE and MTS to approximately 60% in those with normal-appearing MR imaging studies (21). Therefore, clinically available methods that improve the detection and certainty of HA could enhance clinical care at community and tertiary epilepsy centers.

In our analysis, hippocampal asymmetry alone was a robust classifier, whereas other structural asymmetries did not contribute to classification accuracy. This was unexpected, because two-thirds of patients with TLE demonstrate amygdala asymmetries concordant with the seizure focus (12). However, in the current patient series,

there was little room for improvement in the model. Other structural asymmetries may be valuable predictors of seizure lateralization in a series of patients with no quantifiable HA (22). In addition, although HOC volumes have demonstrated superior ability to reveal conversion to AD when compared with ICV-adjusted volumes (11), neither the HOC volume nor its asymmetry was a strong classifier in patients with TLE. This may reflect the fact that the expansion of the ILV associated with AD reflects tissue loss that is predominantly secondary to neurodegeneration, whereas the HA associated with TLE is the product of both neurodevelopmental and neurodegenerative factors (23–26). Therefore, adjusting for overall head size rather than ILV size better captures the hippocampal pathology associated with TLE.

A number of limitations should be addressed. First, surgical outcomes and histologic confirmation of HA were not available for all patients. Thus, the diagnosis of left TLE versus right TLE was based on results from invasive video EEG monitoring. Second, it is important to note that HA is only one component of MTS. Abnormal signal on T2-weighted FLAIR images and loss of internal architecture are also key elements of this diagnosis (27). However, there are recent data suggesting that HA is specific to TLE, whereas signal change on T2-weighted FLAIR images is observed in control subjects and patients with TLE at a similar rate (28). Therefore, HA may be a stronger biomarker for seizure lateralization. Third, although comparison of the standard nonvolumetric epilepsy-specific MR imaging protocol with quantitative MR imaging for detection of HA may seem somewhat artificial, this comparison was deemed necessary because the standard MR imaging protocol represents what is available in the majority of clinical settings. Furthermore, the comparison of visual inspection of the volumetric study with quantitative MR imaging was also included to create a more equal comparison of qualitative and quantitative analysis. Last, both the clinical and volumetric MR imaging interpretations were biased by the fact that the neuroradiologist interpreting the study was aware that the patient had a clinical diagnosis of TLE. In other words, only the quantitative MR imaging interpretation was truly blinded to patients versus control subjects, further demonstrating the ability of quantitative MR imaging findings to accurately predict the presence and laterality of HA.

Integrating MR imaging volumetry into the clinical workflow requires that the output of the processing be clinically useful, time efficient, and easy to interpret by a range of clinicians. The quantitative MR imaging device described here provides a means for translating volumetric data into an easy-to-read format that can facilitate radiologic interpretation in a variety of clinical settings. These data could also be used to derive quantitative values for use in large clinical trials that require high-throughput MR imaging analysis.

We describe the ability of quantitative MR imaging findings to predict the presence and laterality of HA at rates that may exceed those achieved by neuroradiologists performing standard clinical interpretations. Quantitative MR imaging can enhance standard visual analysis, providing a viable means for translating volumetric analysis into clinical practice and increasing the detection of HA in TLE in both community and tertiary care settings.

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