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Predictive value of hippocampal internal architecture asymmetry in temporal lobe epilepsy

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Abstract

Background—Asymmetry of hippocampal internal architecture (HIA) clarity has been suggested to be a sign of hippocampal sclerosis (HS) and is frequently associated with other MRI findings of HS. The goal of this work is to use a previously developed HIA visual scoring system (Ver Hoef et al., under review) to quantify HIA asymmetry in a retrospective series of consecutive temporal lobe epilepsy (TLE) patients and evaluate its value in predicting laterality of seizure onset both in patients with other signs of HS (HS+) and those without (HS−).

Methods—The HIA scoring system was used to rate hippocampal asymmetry and to assess the agreement between HIA and seizure lateralization. The median values of the average HIA scores for each hippocampus were compared for HS+ epileptogenic hippocampi, HS− epileptogenic hippocampi, and non-epileptogenic hippocampi with a Kruskal-Wallis one-way analysis of variance by ranks. Pairwise differences between groups were evaluated with the two-tailed Mann-Whitney U test. A logistic regression model examined the utility of average HIA asymmetry score in predicting the true laterality of seizure onset as determined by video-EEG. Sensitivity and specificity are calculated using various asymmetry thresholds in each patient group.

Results—Fifty-five patients were identified who met inclusion criteria. Thirteen patients (24%) were found to have hippocampal atrophy and/or signal abnormality indicative of HS (HS+) and 42 did not (HS−). Significant differences were observed in the distribution of individual and average

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HIA scores between each of the groups of hippocampi, with HS+ hippocampi having the lowest HIA scores and non-epileptogenic hippocampi having the highest. Logistic regression analysis showed that the average HIA asymmetry score was a strong predictor of the laterality of seizure onset (β=3.93508, $p<0.001$). HIA asymmetry remained significant even after adjustment for HS +/HS− status (β =3.8854, $p<0.001$). Among HS− patients, when the average HIA asymmetry score was equal to or exceeded a threshold value of 0.5, the specificity for correctly predicting the side of seizure onset was between 95% and 100% with a sensitivity of 40% to 45%. Among HS+ patients, a threshold of 0.3 yielded a sensitivity of 85% and specificity of 100%.

Conclusions—In this report we show for the first time that HIA asymmetry is a significant predictor of the laterality of seizure onset in TLE patients with otherwise normal MRI findings, and that the proposed HIA scoring system has high specificity and moderate sensitivity for lateralizing seizure onset in patients with TLE.

1. Introduction

The hippocampus is the most frequently epileptogenic area of the human brain. As such, identification of a structural abnormality of the hippocampus on MRI is an important finding in the epilepsy patient, particularly if that patient is being evaluated for epilepsy surgery. The most frequently encountered hippocampal abnormality in epilepsy patients is hippocampal sclerosis (HS) [1]. The classic hallmarks of HS on MRI are atrophy and signal hyperintensity on T2-weighted or FLAIR images [2]. The presence of either of these findings is a strong indicator of hippocampal pathology and portends an excellent prognosis for a seizure-free outcome after surgical resection of the hippocampus [3]. Loss of hippocampal internal architecture clarity has been suggested as a third hallmark of HS [2, 4]. Hippocampal internal architecture (HIA) as it is used here refers to the laminar structure of the body of the hippocampus that has a spiral appearance in the coronal plane due to the apposing layers of gray and white matter that define Ammon's horn [5]. Loss of HIA has been reported to be present in a large majority of patients with other findings of HS [4, 6]. However, previous studies of HIA asymmetry have been almost entirely in patients with other MRI evidence of HS, and therefore the value of HIA asymmetry as an independent biomarker of the epileptogenic hippocampus in the absence of atrophy or signal abnormality has not been shown heretofore. The purpose of this work is to determine if asymmetric loss of HIA has value in predicting the laterality of seizure onset in TLE patients. We have developed a simple scoring system for rating HIA clarity [5] to allow for statistical analysis of HIA clarity and its asymmetries. In this report we describe the HIA clarity scores of both the epileptogenic (ipsilateral to the side of seizure onset) and non-epileptogenic (contralateral to the side of seizure onset) hippocampi of a series of TLE patients and assess the sensitivity and specificity of this rating scheme for predicting the laterality of seizure onset based on the results of video-EEG monitoring.

2. Methods

After IRB approval was obtained, our epilepsy and MRI databases were reviewed to retrospectively find consecutive patients who had an MRI scan done according to our temporal lobe protocol on a Philips Achieva 3T scanner (Eindhoven, Netherlands) from

2004 through 2008 who also had a positive video-EEG study with ictal evidence of unilateral temporal lobe epilepsy. Patients with only inter-ictal abnormalities suggestive of TLE were not included to ensure that the diagnosis of unilateral TLE was as certain as possible. The images used for analysis were from a high-resolution T2-weighted TSE sequence with slices oriented in the oblique coronal plane orthogonal to the long axis of the body of the hippocampus to optimally view the hippocampal body in cross-section. This sequence used the following imaging parameters: TR 3000/ TE 110/ flip angle 90/NEX 2/FOV 240 mm/acquisition matrix 912x912/reconstruction matrix 1024x1024/slice 3 mm/gap 1 mm. Patients with MRI scans with significant movement artifact were excluded. Both patients with and without hippocampal atrophy or signal abnormality were included. The presence or absence of atrophy or signal abnormality was determined based on visual inspection by a board-certified neurologist (LV) with additional fellowship training and certification in neuroimaging (American Society of Neuroimaging and United Council of Neurologic Subspecialties) with over 7 years of experience interpreting clinical MRI scans as the physician of record. Quantitative hippocampal volumetry was not performed. Images were anonymized so the reviewer was blinded to patient identity and laterality of seizure onset.

For each patient, each slice through the hippocampal body was scored on each side according to our HIA rating scale starting with the first slice posterior to the hippocampal head and continuing until the upward turn of the tail produced noticeable through-plane volume averaging effects. A single rater (LV) scored the scans of all patients. Our HIA rating scale is described in detail in our companion paper and has been reported to have good inter-rater reliability among experienced reviewers [5]. In brief, this rating system is based on visual assessment of HIA clarity and allows the reviewer to assign a score from “1” to “4” to a single hippocampal image with a “4” indicating excellent internal architecture differentiation and a “1” indicating no perceptible internal architecture. All scores were generated by a single reviewer. These individual scores for each side in each slice will be referred to simply as “HIA scores”. For each hippocampus in each patient, the HIA scores on a given side were averaged across all the slices to produce an “average HIA score” for each hippocampus. Then, an average HIA asymmetry score was calculated for each individual by subtracting the left average HIA score from the right such that a *positive* HIA asymmetry score indicates a relative loss of HIA clarity on the *left* and a *negative* HIA asymmetry score indicates a relative loss of HIA clarity on the *right*. Therefore three sets of values were generated for analysis: an HIA score for each side in each slice, an average HIA score for each hippocampus, and an average HIA asymmetry score for each patient. Figure 1 illustrates this process. The number of individual slices within which an asymmetry in HIA scores was seen was also recorded along with the magnitude of the difference between HIA scores within the slice.

The distribution of HIA scores across the four levels of the scoring system was tabulated for each of the following categories: HIA scores from non-epileptogenic hippocampi (contralateral to the side of seizure onset); HIA scores from all the epileptogenic hippocampi (ipsilateral to the side of seizure onset); HIA scores from only epileptogenic hippocampi with other evidence of HS (HS+); HIA scores from only epileptogenic hippocampi without

other evidence of HS (HS−). These were compared using a chi-square test and pertinent differences and similarities are reported.

Histograms of the average HIA scores from each hippocampus were generated for the HS+ hippocampi, the HS− hippocampi, and the non-epileptogenic hippocampi. The median values of the average HIA scores were compared for all three groups with a Kruskal-Wallis one-way analysis of variance by ranks. Pairwise differences between groups were evaluated with the two-tailed Mann-Whitney U test.

A logistic regression model was used to examine the utility of average HIA asymmetry score in predicting the true laterality as determined by video EEG. This included unadjusted models, as well as adjusted models incorporating presence or absence of typical HS features on MRI to determine the added predictive value of HIA asymmetry scores.

To use HIA asymmetry as a discriminant test of TLE laterality, a threshold value must be chosen such that when the absolute value of the asymmetry score is greater than or equal to the threshold the result is considered to be conclusively lateralizing (LEFT if positive, or RIGHT if negative), and considered diagnostically negative (non-lateralizing) when below the threshold. This threshold could be set anywhere from zero to the most extreme value observed, but it makes the most sense to choose a small non-zero value to allow for a slight degree of asymmetry that may be insignificant. We conducted a sensitively analysis at various threshold values. Because the outcome of the test has 3 possible values (lateralizing-LEFT, lateralizing-RIGHT, and non-lateralizing), sensitivity and specificity, which can only be applied to a *binary* classifier, cannot be calculated directly for the whole group. Alternatively, when considered only as a test for right TLE using the left TLE patients as controls, and then separately considered as a test for left TLE using the right TLE patients as controls, the outcome becomes binary and sensitivity and specificity can be calculated separately for each test of laterality. Sensitivity and specificity were calculated in this fashion for each side using various asymmetry score threshold values from 0.25 to 1. These values were calculated for both the HS+ and HS− subgroups.

3. Results

Fifty-five patients were identified who met inclusion criteria. Demographics and descriptive features of the cohort are shown in Table 1. Thirty-five patients were female (63%). Twenty-eight patients had right TLE (61% female), and 27 had left TLE (66% female). Thirteen patients (24%) were found to have hippocampal atrophy and/or signal hyperintensity indicative of hippocampal sclerosis (HS+) and 42 did not (HS−).

Figure 2 shows the distributions of HIA scores from each slice for four groups: the non-epileptogenic hippocampi, all epileptogenic hippocampi, and the HS+ and HS− subgroups of epileptogenic hippocampi. As expected, the HS+ hippocampal images showed the most severe loss of HIA clarity of any of the subgroups with almost 60% of images showing no discernible HIA (HIA score = 1). However, even among the non-epileptogenic hippocampi over half of the hippocampal images scored as either a 1 or 2, and only 39% of the images had good or excellent HIA clarity. The proportion of images receiving a score of 2 in HS−

epileptogenic hippocampi was similar to that of the nonepileptogenic images (42% vs. 48% respectively), $X^2(1, N=366) = 1.333$, $p=0.25$, but the HS− group had a significantly higher proportion of low scores (HIA Score = 1) than the non-epileptogenic group (31% vs. 12%), $X^2(1, N=366) = 19.689$, $p<0.001$, and a lower proportion of scores of 3 (20% vs. 30%), $X^2(1, N=366) = 4.458$, $p=0.035$.

When HIA scores from both sides of individual slices are compared, an asymmetry of HIA was observed within a given slice in 52% (107 of 205 slices) across the entire cohort. Among those slices within which an asymmetry of HIA scores was observed, the right and left HIA scores differed by one point in 85%, two points in 12%, and 3 points in 3%.

Histograms demonstrating the distribution of the average HIA scores of the HS+ hippocampi, HShippocami, and non-epileptogenic hippocami are shown in Figure 3. The results of a Kruskal–Wallis test were significant (H=15.7, 2 d.f., p=0.0004); the mean ranks of average HIA scores are significantly different among the three groups of hippocampi. Medians of the average HIA scores in HS+ hippocampi, HS− hippocampi, and non-epileptogenic hippocampi were 1.5, 2.0, and 2.33 respectively; the distribution of scores in all three groups differed significantly from each other (HS+ vs. HS−: $U = 379$, $n_1 = 13$, $n_2 = 42$, $p=0.036$; HS+ vs. non-epileptogenic $U = 578$, $n_1 = 13$, $n_2 = 55$, $p=0.0006$; HS− vs. non-epileptogenic: $U = 1513$, $n_1 = 42$, $n_2 = 55$, $p=0.009$).

When an average of the HIA scores across the slices that make up each hippocampus was calculated for each individual and the left and right sides were compared, some degree of asymmetry of the average HIA score was seen in 85% (11 of 13) of the HS+ group and 77% (31 of 42) of the HSgroup, however in some cases the asymmetry of the average HIA score was slight. Logistic regression analysis showed that the HIA asymmetry score was a strong predictor of the laterality of seizure onset (β=3.93508, SE β=1.16873, Z=3.367, p=0.00076). HIA asymmetry remained significant even after adjustment for HS+ / HS− status (β =3.8854, SE β=1.1587, Z=3.353, p=0.000798), indicating that HIA asymmetry has utility in predicting laterality beyond that offered by assessment of relative hippocampal atrophy and/or T2 signal hyperintensity.

Plots of sensitivity and specificity as a function of threshold value among HS− patients are shown in Figure 4. Using a threshold value of 0.5, the specificity is 95% to 100% with a sensitivity of 40% to 45% among HS− patients. To give a practical example of what this threshold value represents, an asymmetry score of 0.5 corresponds to a one-point asymmetry in half of the slices through the hippocampal body in an individual patient’s scan. Among HS+ patients, a threshold of 0.3 produced 85% sensitivity and 100% specificity, or if a threshold of 0.5 is used the sensitivity is 62% and specificity remains 100%.

4. Discussion

The main goal of this study was to apply a previously developed HIA scoring system [5] to the evaluation patients with TLE and assess the sensitivity and specificity of this rating system for predicting the laterality of seizure onset, particularly in patients with otherwise normal hippocampal MR imaging. Our findings indicate that an asymmetric loss of

hippocampal internal architecture clarity on MRI is a common finding in TLE patients – even in those without other MRI evidence of HS. It has long been accepted that loss of HIA can be seen with atrophy and T2 signal hyperintensity in patients with HS [2]. This is not surprising since atrophy will decrease the size of structures that are already on the margin of what can be clearly resolved with common MRI techniques, and T2 signal hyperintensity could easily obliterate the T2 contrast between the apposing gray and white matter structures. However, HIA asymmetry has not been studied previously in a large number of TLE patients with otherwise “normal” hippocampal MR imaging. Our results show that with high resolution scans HIA asymmetry is a common finding in so-called *MRI-negative* TLE, and when present, it is highly predictive of the side of seizure onset. If asymmetric loss of HIA with concordant ictal EEG findings can be shown prospectively to be an independent marker of HS or otherwise a predictor of excellent surgical outcome, it could dramatically impact the evaluation of many TLE patients. The identification of signs of HS or other hippocampal abnormalities on MRI is a crucial branching point in the evaluation of refractory epilepsy patients in that it indicates a high likelihood of seizure-freedom after anterior-medial temporal lobectomy [3]. Furthermore, it could abbreviate the non-invasive surgical work by reducing or eliminating the need for additional imaging such as PET, SPECT and MEG, but, even more importantly, it could reduce the need for intracranial monitoring and the attendant risk and cost.

A particular strength of these results is the high specificity seen even when using a low threshold of asymmetry values. An HIA score asymmetry of one point, as shown in “Slice 1” of Figure 1, is a relatively subtle difference, but when an asymmetry of this magnitude was seen in half or more of the slices through the hippocampal body in a given subject, the specificity for predicting side of seizure onset was greater than 95%, and when it was seen in three out of four slices the specificity was 100% in this study sample. Many novel imaging findings described in the literature show statistically significant correlations with a disease state only on a group level (i.e. *not* on an individual level). While they may give insight to pathogenic processes in the study of disease, group level associations are not of much use in clinical decision making unless they are also highly predictive on an individual level, as this measure is.

In the HS+ group, an HIA asymmetry was seen in 85% of patients and in each case it was correctly lateralizing. This is similar to previous reports in patients with other MRI findings of HS [2]. If a common threshold of 0.5 is used, the sensitivity in the HS+ group drops to 62%, but these specificity and sensitivity values should be interpreted with caution due to the number of HS+ patients in this cohort (N=13). In the HS− group, sensitivity was 40–45% when a threshold asymmetry score of 0.5 was used to maximize specificity. While ideally a test would have both extremely high sensitivity and specificity in all patient groups, it is important to point out that the 40–45% sensitivity in the HS− group is in a group of patients who were already considered MRI-negative by conventional clinical MRI methodology. For comparison, a recent study comparing automated hippocampal volumetry to visual inspection by experienced neuroradiologists in patients with video-EEG proven TLE showed that quantitative volumetry correctly lateralized the side of seizure onset in 30 of 34 patients (88%) [7]. However, in the same study using a common T1-weighted 3D

gradient echo sequence on a 1.5T scanner visual inspection detected atrophy in 29 of 34 patients (85%), therefore among the five patients who were “MRI-negative” by visual inspection, quantitative volumetry correctly lateralized only one additional TLE patient in that cohort, versus >40% of the MRI-negative patients in our cohort that were correctly lateralized using HIA asymmetry. Therefore the apparently higher sensitivity of automated volumetry in that study is most likely related to the much higher rate of clear hippocampal atrophy in their cohort as compared to ours (88% vs. 24%).

A limitation of our study is that hippocampal volumes were not measured quantitatively, which precludes assessing a linear correlation between volume loss and HIA clarity. However, as mentioned above, visual detection of hippocampal atrophy by an experienced clinical neuroimaging expert has been shown to have excellent sensitivity compared to automated quantitative volumetry in TLE patients [7], therefore we feel visual assessment of features of HS is acceptable to categorize patients for clinical purposes as intended in the present study.

A surprising finding of this study is that even in patients with clear evidence of HS, 15% of the scored slices showed good to excellent HIA differentiation (HIA score of 3 or 4), an example of which is shown in Figure 5. The fact that some HS+ hippocampi had good HIA clarity further supports the notion that loss of HIA clarity is a distinct finding from atrophy and signal change, though it tends to be highly correlated [2]. This raises the possibility that alterations in the appearance of HIA might be the result of a particular microscopic pathological phenomenon that is part of the constellation of findings in HS, much like atrophy is correlated with the severity of neuronal loss [8, 9] and T2 signal hyperintensity is associated with the degree of gliosis [10], both of which are seen to varying degrees in HS. However, it is more likely that loss of HIA clarity represents a variant on the spectrum of histopathologic findings associated with HS, and certainly some degree of hippocampal neuronal loss is commonly seen in MRI-negative TLE patients [8, 9]. A precise clinico-pathologic correlation of in vivo imaging findings and ex vivo pathologic findings among TLE patients with and without loss of HIA clarity is a worthwhile endeavor but is beyond the scope of this work.

In our approach to quantifying an asymmetry of HIA clarity we calculated an asymmetry score by averaging the HIA scores through all of the slices on each side and subtracting one side from the other. This requires that an asymmetry be present and consistent across multiple slices or be very obvious in a single slice. As such, an asymmetry in a given slice affects the overall interpretation only in light of the adjacent slices. This reflects the general practice of radiologists and neurologists of being suspicious of a subtle finding seen in single slice that is not confirmed on adjacent slices. However, generally speaking if a subtle finding is seen consistently across multiple slices, its significance is given greater weight. In this study 85% of the asymmetries observed in individual slices had only a 1-point difference in score, and a clear asymmetry in the average HIA score was more often the result of a subtle asymmetry consistent across multiple slices than a dramatic difference in a single slice. Our data does not suggest that an HIA score of 1 or 2 in a single slice is necessarily pathologically abnormal, or even that a low average HIA score for a given hippocampus is necessarily abnormal. Figure 3 shows an obvious difference in the

distribution of average HIA scores between HS+, HS−, and non-epileptogenic hippocampi, yet even some clearly sclerotic hippocampi have an average HIA score of >3.0, and some non-epileptogenic hippocampi have an average HIA score between 1.0 and 2.0. By using an asymmetry score instead of an absolute score as the marker of abnormality, the contralateral hippocampus serves as an internal reference and allows for the fact that some individuals may have greater or lesser baseline HIA clarity perhaps due to individual variability in microcopic or gross anatomy and limitations of image quality.

One limitation of this study is that the reliance on asymmetry is not helpful in detecting cases of bilateral TLE. Our finding that an asymmetric loss of HIA is predictive of the side of seizure onset is not incompatible with the hypothesis that *bilateral* loss of HIA seen in most or all slices may be a sign of bilateral TLE. Patients with bilateral TLE were specifically excluded from this study therefore the significance of a bilateral loss of HIA clarity in this patient population is unknown. Many patients with bilateral TLE have one side from which the majority of their seizures arise, and conceivably may have an HIA asymmetry associated with this, therefore the reader is cautioned against assuming that the presence of an HIA asymmetry rules out the possibility of bilateral TLE. This is an area for future study.

Several groups have attempted volumetric measurements of hippocampal subfields based on landmarks of HIA in normal individuals as well as TLE patients [11–16]. Each of these volumetric studies is based on manual segmentation, which is somewhat subjective in nature, particularly in the hippocampus where boundaries of subfields are not always clearly visible. Different groups of investigators have used various approaches to estimating the area of CA1, CA2, CA3 and CA4/dentate gyrus. One group approximated the border between CA1 and CA2 by dividing the line along the longest diameter of the hippocampus by two and drawing a line perpendicular to this line, and approximated the area of CA2 as a square whose sides were determined by the thickness of CA1 at the CA1/CA2 border [14, 15]. This approach considered CA3 and CA4/dentate gyrus to be a single area. In contrast, another group segmented CA1-3 as a single area and CA4/dentate gyrus as a separate area [13]. Others considered CA2, CA3, and CA4/dentate gyrus as a single area and defined the border of CA1 and CA2 as a line drawn from the end of the hippocampal fissure to the lateral ventricle at a 45-degree angle [11, 12, 16]. Each of these studies relied on anatomical atlases and landmarks to some degree to aid in boundary drawing where it was ambiguous. While *intra*-rater reproducibility of subfield volumes was reported to be high (ICC=0.89–0.96) in two studies [12, 13], *inter*-rater reliability was only reported in one other study (ICC=0.68–0.93) [14] and was comparable to the scoring system developed by our group (ICC=0.76–0.85) [5].

None of the above mentioned studies reported consistent and clear visualization of all of the subfields of Ammon’s horn [11–16]. In contrast to the above approaches, our method evaluates how clearly or poorly defined the hippocampal subfields are visualized as a whole. An advantage of our approach is the relative ease with which the assessment of HIA clarity and asymmetry can be made. Once a reviewer is familiar with the HIA scoring system an evaluation of the HIA scores and calculation of the asymmetry score adds less than a minute to the routine review of an epilepsy patient’s MRI. In a related study we have shown that our

HIA scoring system has good inter-rater reliability amongst neurologists and radiologists experienced in neuroimaging, and it can be quickly learned by nonexpert reviewers [5]. We have made a reference set of 48 consensus-scored hippocampal images available that individuals could use as a scoring guide [5]. Though this is a subjective measure, any similar *objective* measure would require additional time and processing resources, which would limit the practical utility and potential for widespread adoption of such an approach, particularly in the clinical arena. Manual segmentation of hippocampal subfields is very time-intensive, and though quantitative, volumetry based on manual segmentation is also not a true objective measure.

Only one other report examining clarity of HIA visualization specifically has been published [17]. The approach, however, differed in several ways. The measure of HIA clarity was based on whether or not at least two-thirds of the hypointense band that defines the internal structure of the hippocampus could be clearly delineated in at least two slices. The results were consistent with ours in that a loss of clarity of the internal structure of the hippocampus was frequently seen in TLE, however their measure had a specificity of only 80% versus ours which was 95% or greater. The higher false positive rate with their approach is most likely related to the fact that a binary measure of HIA clarity was used, while we used a 4-point scale that allows for more specific classification of subtle differences. Furthermore, their approach assesses each hippocampus on its own without comparing it to the contralateral side. Our data showed that even in the non-epileptogenic hippocampi of TLE patients 12% of the slices had no discernable HIA (HIA score = 1) and almost half of the slices had minimal HIA (HIA score = 2) on our scale, indicating that only a portion of the hypointense white matter band is visible. Many of these images would likely fail to meet their criterion of having two-thirds of the length visible and would be classified as abnormal despite originating from the nonepileptogenic side.

The goal of this work was to further efforts to identify new MRI abnormalities in TLE patients with otherwise “normal” MRIs. This is the first publication we are aware of that specifically examines features of hippocampal structure and demonstrates significant findings in a large number of TLE patients without other MRI evidence of HS. Of the studies referenced above, only one [14] examined TLE patients with otherwise normal appearing hippocampi separately from patients with other signs of HS (atrophy, T2 signal hyperintensity), and that approach showed no significant difference in subfield volumes compared to controls. Another study [17] included normal-MRI TLE patients in their analysis along with patients with classic MRI signs of HS but the analysis did not differentiate between the two subgroups of TLE patients.

Why there is such a variation from individual to individual in the baseline HIA clarity is not obvious, but the fact that over half of the non-epileptogenic hippocampal images were scored as “1” or “2” even when there is little doubt that the actual structure of Ammon’s horn is present indicates that current MRI techniques may be lacking in regard to demonstrating HIA. The layers of Ammon’s horn we are trying to visualize are on the order of 1 mm or less in thickness and are therefore on the margin of what can be clearly visualized with common MR images, making study of HIA asymmetries in epilepsy patients challenging without ultra high-field imaging or special techniques. As imaging techniques

improve we may be able to more consistently image HIA and be more able to detect a disturbance thereof. Already there have been several reports of HIA being clearly depicted using 7T scanners [18, 19]. One study compared the clarity of HIA imaging at 7T vs 1.5T using T2, T2* and FLAIR sequences in three healthy volunteers, and showed that HIA is much more clearly seen at 7T than 1.5T due to improved SNR and resolution [19]. Example images show that individual delineation of CA1, 2, 3, and 4 is feasible. Another study using similar sequences at 7T examined six patients with HS and found that differences in patterns of atrophy of specific subfields was detectable [18]. However, the results of these reports were qualitative in nature, and how consistently HIA was seen across slices was not a focus. Imaging at 7T may be a useful research tool for studying HIA, but the complexities of imaging at ultra-high field strengths, the lack of FDA approval for the use in clinical populations, and the very low number of centers with 7T scanners limits its widespread availability for the near future.

5. Conclusions

Our results show that with high resolution scans acquired at 3T HIA asymmetry is a common finding in patients with TLE with MRI scans otherwise interpreted as normal and, when present, it is highly predictive of the side of seizure onset. While current MRI methods may show HIA with good or excellent clarity in some slices, over half of the slices through non-epileptogenic hippocampi showed minimal or no HIA differentiation. This indicates that current MRI techniques frequently show HIA and asymmetries thereof, but do not show HIA clearly and consistently even in non-epileptogenic hippocampi. HIA asymmetry should be studied prospectively to precisely determine its value in predicting side of seizure onset and surgical outcome in patients who undergo anterior temporal lobectomy. Most asymmetries of HIA in TLE patient are subtle. Improvements in MRI techniques through advances in coil design, image acquisition, reconstruction techniques, and/or field strength may improve HIA definition and allow more confident differentiation of mild asymmetries and more sensitive detection of very subtle asymmetries.

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Abbreviations

HIA	hippocampal internal architecture
HS	hippocampal sclerosis
TLE	temporal lobe epilepsy
HS+	hippocampal sclerosis positive
HS−	hippocampal sclerosis negative

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Highlights

- Hippocampal internal architecture (HIA) asymmetry is a common finding in temporal lobe epilepsy
- This study employs a previously developed HIA scoring system to evaluate HIA asymmetry in TLE
- A significant HIA asymmetry is seen in in at least 40% of TLE patients with otherwise normal MRI scans
- An HIA asymmetry score of ≥0.5 has a specificity of >95% for predicting the side of seizure onset

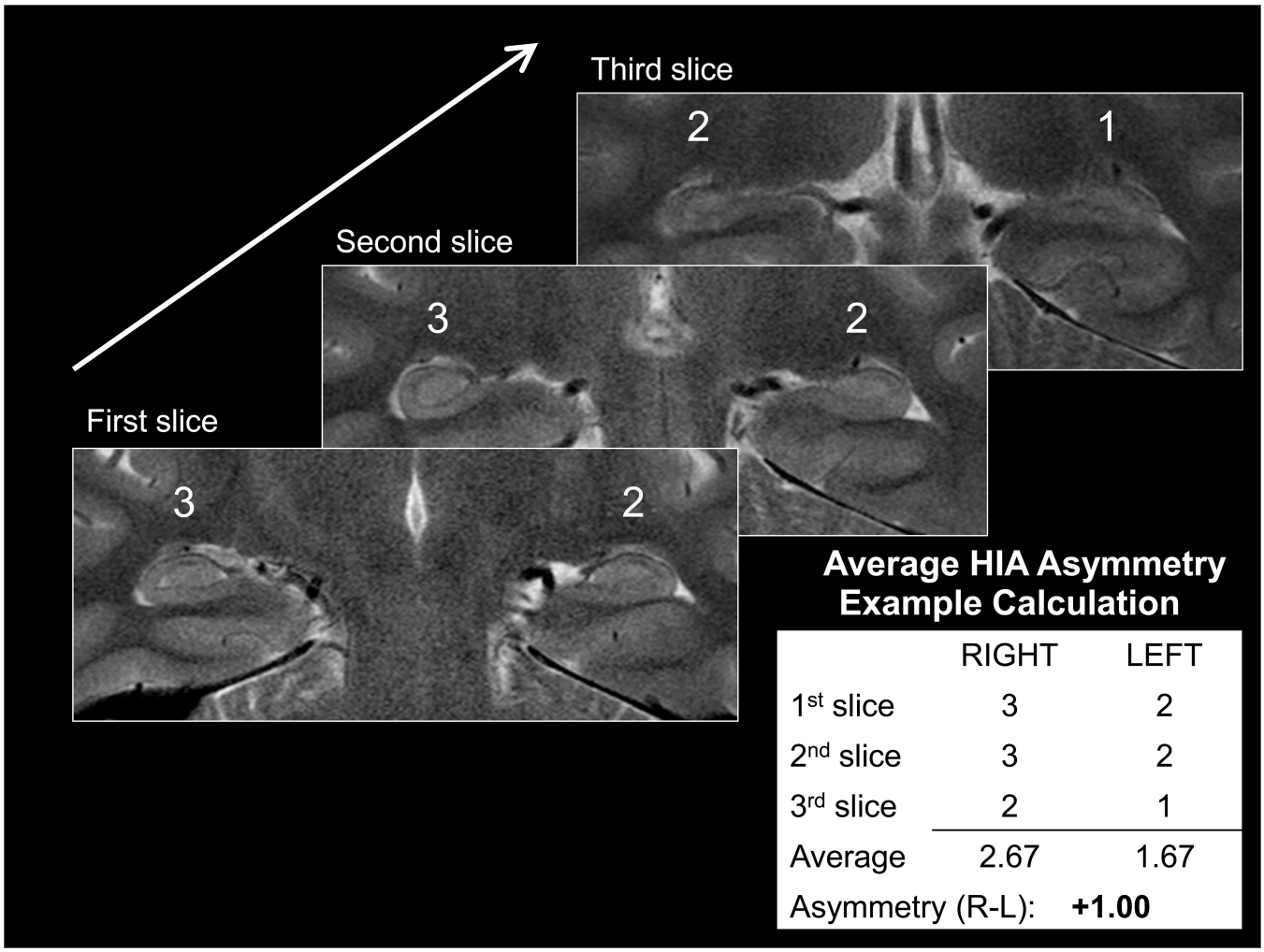


Figure 1.

Illustration of how the HIA asymmetry score is calculated. Three sequential slices from a single individual are shown. Each side is given an HIA score in each image (shown in white), and the scores for each side are averaged to produce an average HIA score for each hippocampus, and then left average HIA score is subtracted from right to produce an average HIA asymmetry score. Images are presented in radiological convention with left on the image corresponding to right brain.

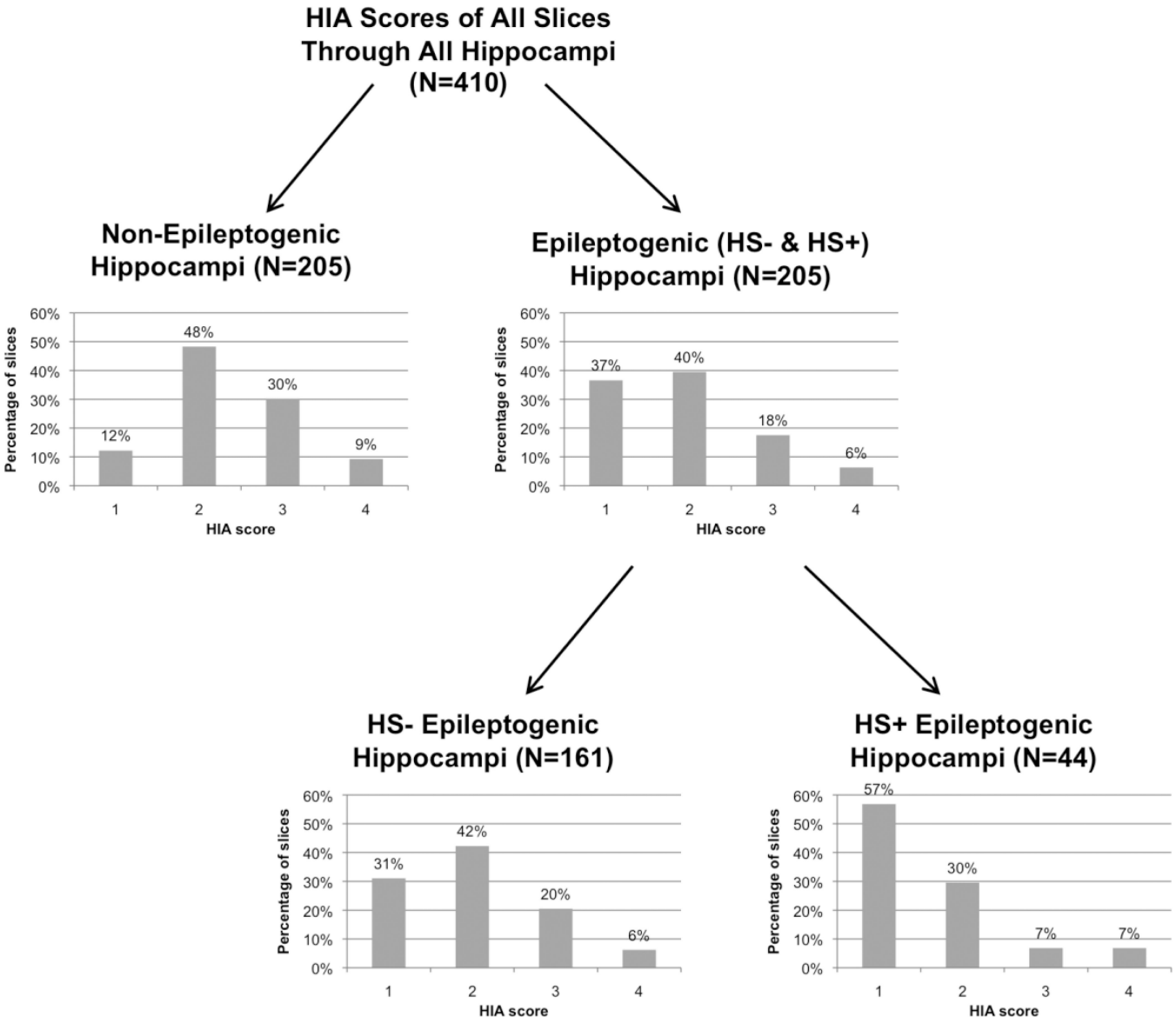


Figure 2.

Distributions of HIA scores rendered from each side of each slice. Each patient has multiple slices through the hippocampi, and each slice has a right and a left score, so the total number of scores is greater than the total number of patients.

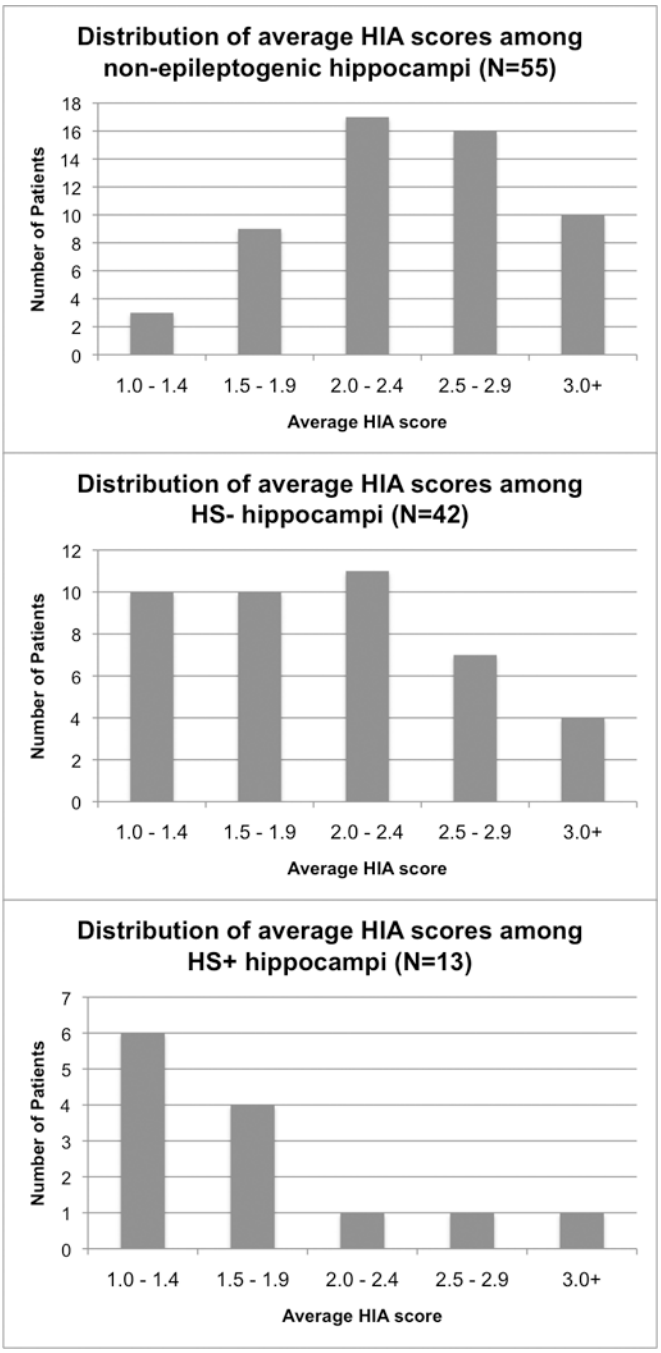
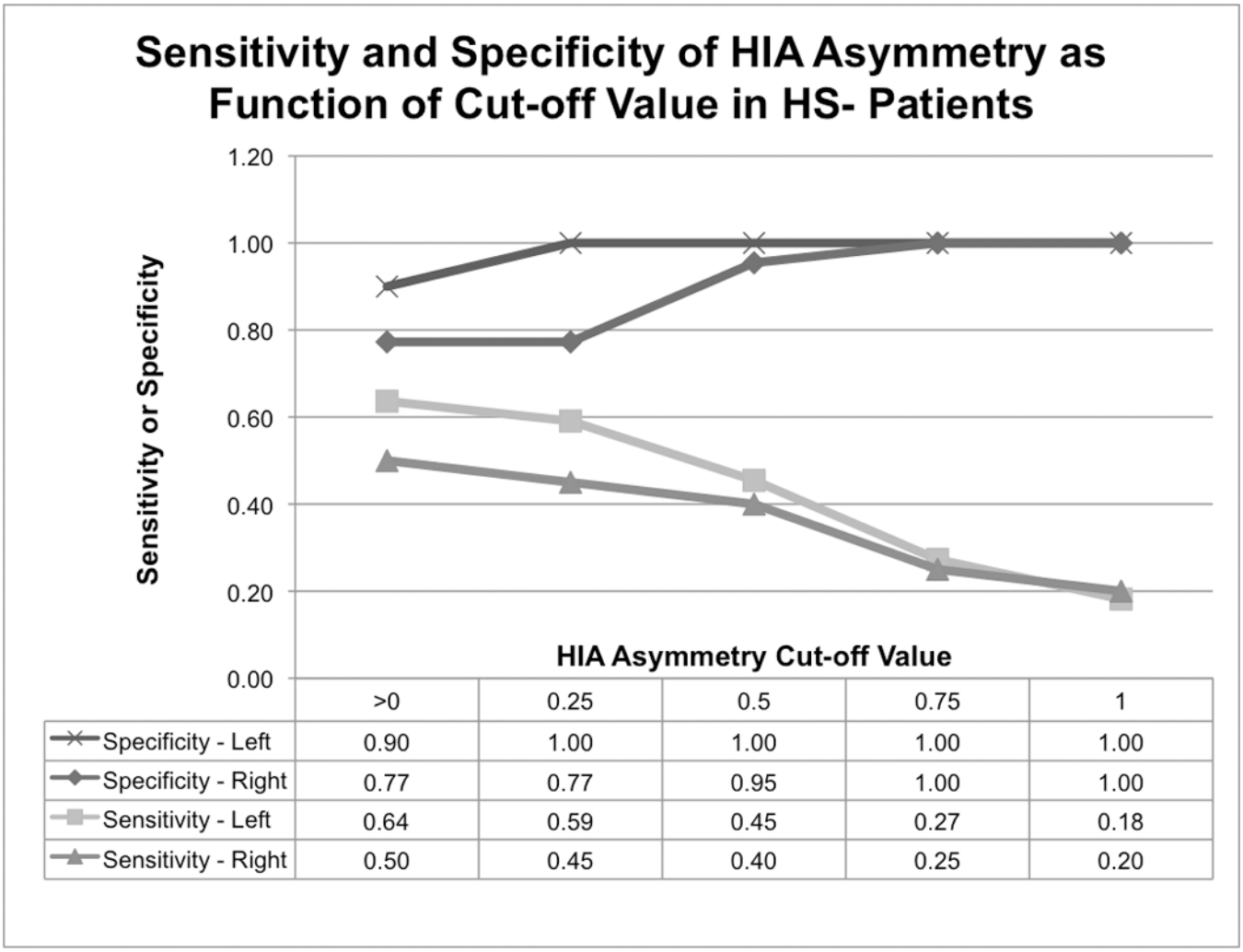


Figure 3.

Frequency histograms showing distributions of average HIA scores for each group of hippocampi. An average HIA score is calculated for each hippocampus in each patient. A bin width of 0.5 HIA score units is used for the first 4 bins and the last bin includes all hippocampi with an average HIA score of 3.0 or higher.



	>0	0.25	0.5	0.75	1
Specificity - Left	0.90	1.00	1.00	1.00	1.00
Specificity - Right	0.77	0.77	0.95	1.00	1.00
Sensitivity - Left	0.64	0.59	0.45	0.27	0.18
Sensitivity - Right	0.50	0.45	0.40	0.25	0.20

Figure 4.

The plot and table above shows how HIA rating scheme sensitivity and specificity change with various cut-off values used to predict the side of seizure onset in HS− patients. When the absolute value of the average HIA asymmetry score is less than the cut-off, the test is considered indeterminate. Sensitivity and specificity were calculated separately for tests of left-sided onset and right-sided onset and both are shown on the same plot. Using a cut-off of 0.5 the estimates of accuracy vary by no more than 5% between left and right.

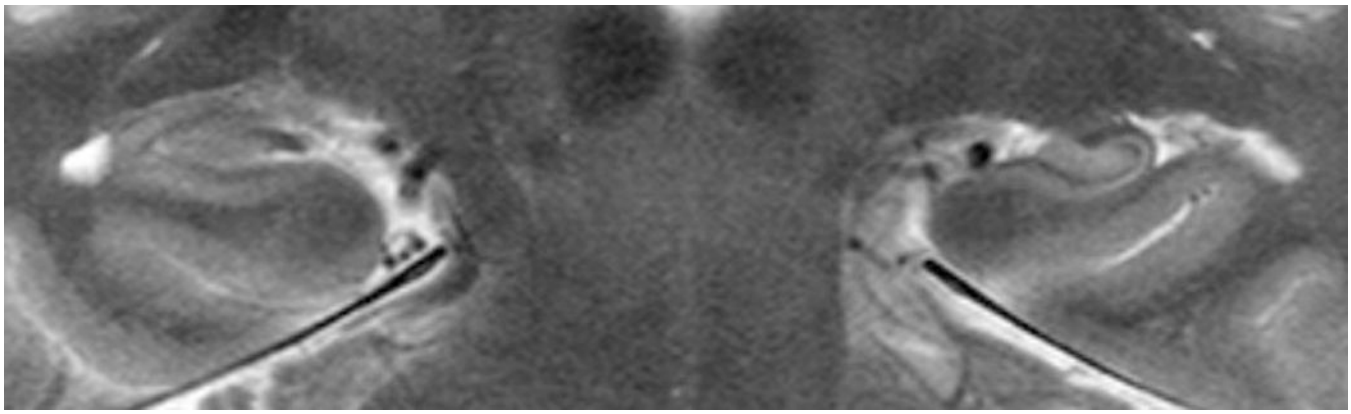


Figure 5.

The left hippocampus shows unexpectedly well-preserved HIA clarity despite marked atrophy and moderate T2 signal hyperintensity, thus demonstrating that HIA is not universally lost even in patients with obvious HS, though this is atypical. The left hippocampus has a cross-sectional area roughly half that of the right hippocampus in this slice. Radiologic convention is used with the left side of the brain on the right side of the image.

Table 1

Demographics and descriptive features of cohort

Characteristic	n (%)	Mean	SD
Age (years)		39	12.7
Female	35 (63.6%)		
Race			
African-american	19 (35%)		
White	36 (65%)		
Right-handed	50 (91%)		
Right TLE	28 (51%)		
Left TLE	27 (49%)		
age of onset (years)		26	16.2
duration of epilepsy (years)		13	13.9
Number of current AEDs		1.8	0.8
Number of lifetime AEDs		4.3	2.2

Abbreviations: TLE = temporal lobe epilepsy; AED = Anti-epileptic drug