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Hippocampal volumetric integrity in mesial temporal lobe epilepsy: A fast novel method for analysis of structural MRI

Mathew Hakimi[a], Babak A. Ardekani[b,c], Christina Pressl[a], Karen Blackmon[a], Thomas Thesen[a], Orrin Devinsky[a], Ruben I. Kuzniecky[a], Heath R. Pardoe[a,*]

[a] Comprehensive Epilepsy Center, Department of Neurology, NYU Langone Health, United States
[b] The Nathan S. Kline Institute for Psychiatric Research, United States
[c] Department of Psychiatry, NYU Langone Health, United States

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ABSTRACT

Objective: We investigate whether a rapid and novel automated MRI processing technique for assessing hippocampal volumetric integrity (HVI) can be used to identify hippocampal sclerosis (HS) in patients with mesial temporal lobe epilepsy (mTLE) and determine its performance relative to hippocampal volumetry (HV) and visual inspection.
Methods: We applied the HVI technique to T1-weighted brain images from healthy control (n = 35), mTLE (n = 29), non-HS temporal lobe epilepsy (TLE, n = 44), and extratemporal focal epilepsy (EXTLE, n = 25) subjects imaged using a standardized epilepsy research imaging protocol and on non-standardized clinically acquired images from mTLE subjects (n = 40) to investigate if the technique is translatable to clinical practice. Performance of HVI, HV, and visual inspection was assessed using receiver operating characteristic (ROC) analysis.
Results: mTLE patients from both research and clinical groups had significantly reduced ipsilateral HVI relative to controls (effect size: -0.053, 5.62%, $p =$ 0.002 using a standardized research imaging protocol). For lateralizing mTLE, HVI had a sensitivity of 88% compared with a HV sensitivity of 92% when using specificity equal to 70%.
Conclusions: The novel HVI approach can effectively detect HS in clinical populations, with an average image processing time of less than a minute. The fast processing speed suggests this technique could have utility as a quantitative tool to assist with imaging-based diagnosis and lateralization of HS in a clinical setting.

1. Introduction

In this study we apply a novel automated magnetic resonance imaging (MRI) analysis technique for assessing hippocampal volumetric integrity (HVI) to mesial temporal lobe epilepsy (mTLE). The method uses standard whole brain T1-weighted MRI to estimate the ratio of cerebrospinal fluid (CSF) to non-CSF brain tissue within a hippocampal region defined using neuroanatomical landmarks, in which a greater proportion of CSF corresponds to a lower HVI and greater hippocampal atrophy (Ardekani, Convit et al. 2015).

Our proposed method is a potential alternative to established MRI-based diagnostic methods for hippocampal sclerosis (HS), such as volume loss identified on T1-weighted MRI and signal intensity changes on T2 weighted imaging (Jackson, Berkovic et al. 1990; Berkovic, Andermann et al. 1991; Kuzniecky, Burgard et al. 1996; Watson, Cendes et al. 1997; Watson, Jack et al. 1997; Woermann, Barker et al. 1998). Advantages of the HVI technique over these methods are (i) the ability to detect proximal hippocampal CSF changes without requiring a specialized acquisition, and (ii) fast processing time, which is on the order of seconds. The fast processing speed of the HVI technique suggests it may be useful as a feature extraction step for artificial intelligence (AI) applications in biomedical imaging.

Our primary hypothesis is that HVI will be reduced in the affected hippocampus of individuals with mTLE. Our secondary hypothesis is that HVI will be able to detect HS using clinical MRI protocols. In addition, we investigated the classification performance of HVI using automated hippocampal volumetry (HV) and visual inspection as references. Analyses were carried out on (i) standardized research MRI acquisitions acquired on a single scanner, and (ii) clinically acquired images using non-standardized imaging (mix of 3 T and 1.5 T, variable

* Corresponding author at: NYU School of Medicine, 145 East 32nd Street, New York, NY 10016, United States.
E-mail address: heath.pardoe@nyulangone.org (H.R. Pardoe).

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image acquisition parameters). We compared HVI between mTLE patients, non-HS temporal lobe epilepsy (TLE) patients, extratemporal focal epilepsy (EXTLE) patients, and healthy controls. The outcome of this study will determine whether this fast, automated, and objective tool for assessing HVI can be used to screen for HS and complement imaging diagnosis of HS in epilepsy patients.

2. Methods

2.1. Participant selection

We included consecutive individuals who received a research whole brain T1-weighted MRI as part of pre-surgical evaluation at the NYU Comprehensive Epilepsy Center between the years 2008 – 2015. In addition, we included individuals with mTLE who did not receive research MRI but received clinical imaging as part of their pre-surgical evaluation. Localization was determined via clinical investigations at the Comprehensive Epilepsy Center, including EEG, neuroimaging, video monitoring, and seizure semiology. Epilepsy patients with research scans were stratified into three groups: (1) mTLE, comprising individuals with unilateral or bilateral hippocampal sclerosis without any detected additional brain abnormalities, and patients with hippocampal sclerosis with extra-hippocampal epileptogenic foci in other brain regions (multi-lobar), (2) non-HS TLE, comprising individuals with epileptogenic foci in the temporal lobe, including those with multi-lobar epileptogenic foci, and (3) EXTLE including those with multi-lobar epileptogenic foci that did not include the temporal lobe. Seizure lateralization was also recorded for each participant (left, right, or bilateral).

Diagnosis of HS was obtained by visual inspection of MRI and histopathological assessment of resected tissue when available. Participants from the Comprehensive Epilepsy Center patient pool were excluded from the study if they had prior temporal lobe resections or if image processing failed. Healthy controls were recruited via community-based advertisement and scanned contemporaneously with the epilepsy patients.

2.2. Standard protocol approvals, registrations, and patient consents

This study was approved by the NYU School of Medicine IRB and ethical standards committee. All participants provided written informed consent.

2.3. MRI acquisition

The HVI technique uses whole brain T1-weighted MRI. Research T1-weighted imaging consisted of an MPRAGE acquisition obtained on a Siemens Allegra scanner, with the following acquisition parameters: TE = 3.25 ms, TR = 2530 ms, TI = 1100, flip angle = 7°, with a spatial resolution of 1.33 × 1.33 × 1 mm^3. Clinical imaging was obtained on a variety of scanners with different image acquisition parameters, including 1.5 T and 3 T scanners; voxel dimensions ranged from 0.86 to 1.5 mm. A table summarizing clinical imaging acquisition parameters is provided as supplemental material (Supplementary material Table 1).

2.4. Hippocampal volumetric integrity assessment

We assessed the HVI of each hippocampus for all subjects using "kaiba," a software tool distributed as part of the "Automated Registration Toolbox" package (https://www.nitrc.org/projects/art). A comprehensive description of the image processing steps are provided in Ardekani et al. (Ardekani, Convit et al. 2015). In brief, the image processing steps are: (1) automated landmark detection is used to define left and right hippocampal regions of interest (ROI; Fig. 1); (2) histogram-based analysis of signal intensity is used to measure the ratio of brain tissue to cerebrospinal fluid (CSF) within these hippocampal

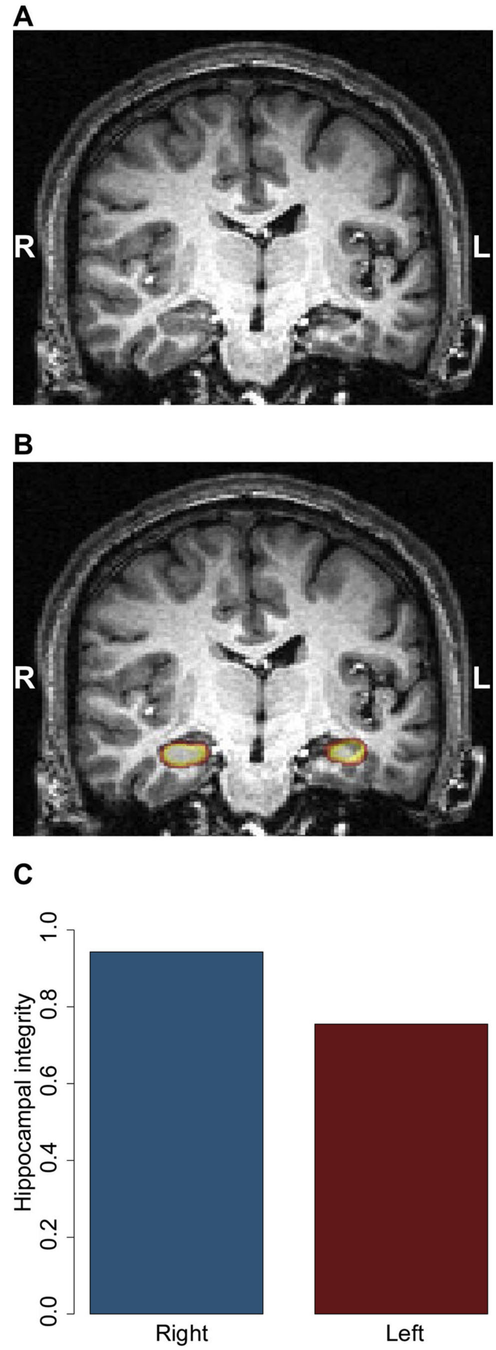

Fig. 1. Hippocampal volumetric integrity is reduced in an individual with left hippocampal sclerosis. (A) T1-weighted whole brain MRI; note left hippocampal atrophy. (B) Right and left hippocampal regions of interest overlaid on the T1-weighted MRI scan. (C) HVI is reduced in the left hippocampus compared to the right (left HVI = 0.76, right HVI = 0.94).

ROIs. Since there is a slight difference in the landmarks used to detect the left and right hippocampus, (3) the technique repeats the analysis for each hippocampus using a left-right flipped image and (4) the final reported values are averages of the original and flipped integrity scores. This ensures that there is no systematic bias between left and right HVI. The computed HVI is the fraction of non-CSF brain tissue in a region delineated to represent a typical healthy hippocampus, where a lower value represents reduced HVI (0 < HVI < 1) and greater atrophy. Processing time for the HVI method was recorded.

Analysis of research scans was done blind to subject classification and lateralization using randomly assigned anonymous identification codes (IDs). Analysis of the clinical scans was done blind to lateralization, however, diagnosis of mTLE was known.

Occasionally the automatic detection of three required initial landmarks (anterior commissure, posterior commissure, and vertex of the superior pontine sulcus) failed (˜ 9% of cases). In these cases, the landmark coordinates were manually entered for the algorithm to accurately detect the hippocampus. A detailed description of the image processing steps is provided in Ardekani et al. (2015) (Ardekani, Convit et al. 2015).

2.5. Hippocampal and brain volumetry

MRI scans were processed using the default image-processing pipeline of FreeSurfer v5.3 (Fischl, Salat et al. 2002). Processing time for the total default Freesurfer processing pipeline was recorded for comparison with the HVI method. Hippocampal and total intracranial volume (ICV) estimates were used for subsequent comparisons with HVI. Hippocampal volume (HV) was corrected using ICV following the covariate method detailed in Free et al. (1995).

2.6. Visual inspection

A clinically trained junior radiologist (CP) and a neuroimaging researcher with extensive manual HV experience (HP) visually assessed each anatomical T1-weighted scan. The raters were blind to both classification and lateralization, and assessed left and right hippocampi as either normal or atrophic. The sensitivity and specificity of visual inspection was then compared to HVI. Visual inspection analysis was limited to research scans.

2.7. Statistical analysis

We investigated if there was a relationship between HVI (dependent variable) and epilepsy subtype (explanatory variable; mTLE, non-HS TLE, EXTLE, or control). HVI of the hippocampus ipsilateral to seizure focus in mTLE patients was compared with control and contralateral hippocampus scores. For the ipsilateral/contralateral analyses, left and right HVI scores for control hippocampi were averaged. Separate left and right, and epilepsy subtype analyses are provided as supplemental material. Mann-Whitney U tests were used for statistical comparisons, since the HVI values are not normally distributed. mTLE patients with clinical imaging were modeled as a separate group. A similar statistical analysis was carried out for HV assessment using ICV-corrected HV as the dependent variable.

Receiver operating characteristic (ROC) analysis was used to assess the classification performance of HVI and HV for detecting HS using the ‘pROC’ package in “R” (Hanley and McNeil, 1982; DeLong et al., 1988; Robin, Turck et al. 2011). Area under the ROC curve (AUC) was used to summarize classification performance. Bilateral mTLE subjects were excluded from ROC analysis due to limited sample size.

HVI in the affected hippocampus of mTLE subjects were compared with (i) HVI in the corresponding hippocampi of healthy controls, (ii) HVI in the corresponding hippocampus of non-HS TLE cases, and (iii) HVI in the contralateral hippocampus of mTLE subjects.

ROC comparisons done for left and right cases separately, including HVI and HV in non-standardized clinical scans, are provided as supplemental material. Analysis (iii) above used difference scores between right and left hippocampi ($HVI_{right} – HVI_{left}$) to determine how well HVI could lateralize HS. If we could demonstrate good classification performance for HVI measured in the clinical scans, this would provide support for the use of HVI in a clinical setting where normative HVI values derived from control MRI scans acquired on the same scanner may not be available. We also compared the sensitivities and specificities of HVI with visual inspection.

3. Results

3.1. Sample description

MRI scans from 174 participants were initially identified for analysis according to our selection criteria. Of the clinical scans, HVI processing failed in one participant due to corpus callosum dysgenesis, therefore lacking in the required landmark structures by the ‘kaiba’ software. HV processing failed in four clinical MRI cases (one bilateral mTLE and three right mTLE) due to poor image quality, thus they were not included in analysis of HV. Therefore, the HVI estimates were obtained from 173 individuals; thirty-five healthy controls (mean age 33.5 ± 11.5 standard deviation (SD) years, 18 female), 98 patients with research scans (32.5 ± 13.4 years, 48 female), and 40 patients with clinical scans (31.8 ± 15.5 years, 19 female). A more detailed description of epilepsy group sample sizes and demographics is provided in the supplemental material (Supplementary material Table 2). Information regarding histopathological assessment of patient brain tissue is provided in Supplementary material Table 3. Average processing time for calculating HVI was 30.4 s (SD = 1.2 s). Average processing time for HV using Freesurfer was 12.3 h (SD = 1.6 h). The Freesurfer morphometric analysis pipeline provides estimates of a number of regional neuroanatomical properties in addition to hippocampal volume.

3.2. Hippocampal volumetric integrity in mesial temporal lobe epilepsy

3.2.1. Hippocampal volumetric integrity changes assessed using standardized research imaging

For ipsilateral vs contralateral comparisons of HVI in epilepsy subjects, we averaged left and right control HVI and confirmed that there were no differences in HVI between left and right hippocampi in healthy controls using a paired *t*-test ($p = 0.637$). Overall, ipsilateral HVI was reduced by 5.62% in mTLE patients relative to controls (effect size = −0.053, $p = 0.002$; Fig. 2). Right mTLE HVI was reduced by 0.048 ($p = 0.012$) and left mTLE HVI was reduced by 0.059 ($p = 0.012$). The single bilateral mTLE patient had bilaterally reduced HVI (0.069 lower right, 0.083 lower left), in line with the findings from the group assessments described above. Right HVI scores were also significantly reduced in left mTLE (0.028 lower, $p = 0.034$) and left EXTLE (0.023 lower, $p = 0.038$) groups. No significant changes in left HVI were observed in the right mTLE ($p = 0.851$) or right EXTLE groups ($p = 0.381$).

3.2.2. Hippocampal volumetric integrity changes assessed using unstandardized clinical imaging

Ipsilateral HVI was reduced by 3.99% in clinical mTLE scans with variable acquisition parameters (effect size = −0.038, $p = 0.020$; Supplementary material Fig. 1). When using unstandardized clinical imaging, right mTLE HVI was reduced by 0.047 ($p = 0.013$) and left mTLE HVI was reduced by 0.028 ($p = 0.142$). The four clinical bilateral mTLE patients had bilaterally reduced HVI (average of 0.015 lower right and 0.035 lower left), in line with the findings from the group assessments described above. HVI distributions per epilepsy group stratified by lateralization are provided in the supplemental material (Supplementary material Fig. 2).

Overall, patients with mTLE had reduced HVI in the hippocampus ipsilateral to seizure focus. The HVI effect size was larger in standardized research MRI than in clinical MRI obtained on a heterogeneous group of scanners. Summary effect sizes and p-values for all epilepsy subtypes are provided in Supplementary material Table 4 (right HVI) and Table 5 (left HVI).

** $p < 0.01$ based on Mann-Whitney U tests.

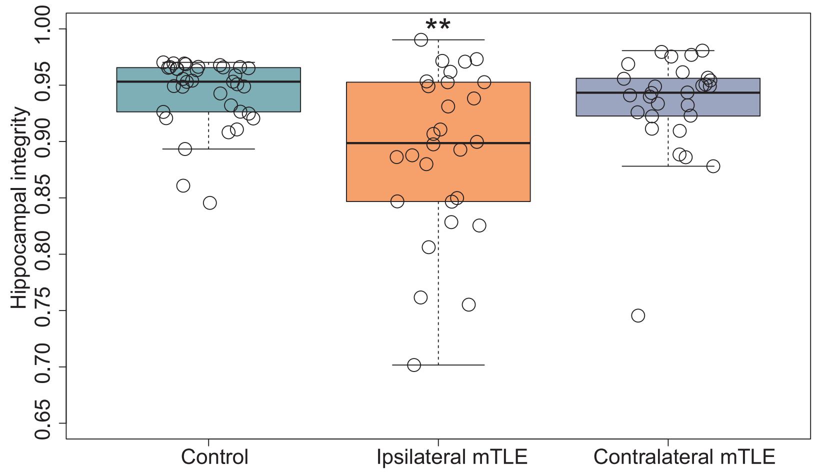

Fig. 2. HVI is reduced in the hippocampus ipsilateral to seizure focus in mTLE. Boxplots show the distribution of HVI in healthy controls, the ipsilateral, and the contralateral hippocampus (ipsilateral effect size = −0.053, 5.62% reduction, $p =$ 0.002). Note that the right and left HVI scores in controls were averaged.

3.3. Hippocampal volumetry assessment in mTLE

The findings for HV were in accordance with the HVI results and previous literature (Coan, Kubota et al. 2014), as confirmed by Mann-Whitney U tests (Supplementary material Fig. 3). HV was reduced by 741 mm^3 (18.98%) on average in mTLE patients relative to controls (683 mm^3 lower in right mTLE, $p = 2 \times 10^{-4}$; 799 mm^3 lower in left mTLE, $p = 2 \times 10^{-4}$). The single bilateral mTLE patient had bilaterally reduced HV (1244 mm^3 lower right; 1428 mm^3 lower left). HV was also reduced in mTLE patients when analyzing subjects imaged using clinical imaging with variable acquisition parameters. HV was reduced by 778 mm^3 (19.83%) on average in clinical mTLE scans relative to controls (924 mm^3 lower in clinical right mTLE, $p = 4 \times 10^{-6}$; 632 mm^3 lower in clinical left mTLE, $p = 6 \times 10^{-5}$). The three clinical bilateral mTLE patients had bilaterally reduced HV (average of 634 mm^3 lower right; 514 mm^3 lower left), in line with the findings from the group assessments described above.

3.4. HVI and HV classification of mTLE using ROC analysis

ROC analysis of HVI demonstrated that it is able to discriminate between mTLE subjects and healthy controls (HVI AUC = 0.72; Fig. 3); between mTLE subjects and non-HS TLE subjects (HVI AUC = 0.685; Supplementary material Fig. 4); and to lateralize mTLE subjects (HVI AUC = 0.91; Fig. 4). Discrimination performance of HVI was lower than HV for discriminating between mTLE subjects and healthy controls (HV AUC = 0.84) and mTLE subjects and non-HS TLE subjects (HV AUC = 0.815), but HVI performance was similar to HV for lateralizing mTLE (HV AUC = 0.93). Lateralization performance in clinical scans is displayed in Supplementary material Fig. 5. Separate ROC assessment of left and right hippocampi comparing mTLE to controls is provided in Supplementary material Fig. 6. ROC AUC values for standardized research scans are provided in Supplementary material Table 6.

3.5. Visual inspection vs. automated methods for detection of hippocampal sclerosis

We compared the sensitivities (true positive rate, ratio of correctly classified individuals with HS to total number of HS cases) and specificities (true negative rate, ratio of correctly classified healthy controls to total number of controls) of the automated techniques with those of our visual inspection raters (HP and CP) averaged. Visual inspection analysis was restricted to the research scans with standardized acquisition parameters. Also note that unlike the ROC analysis, both visual inspection and automated technique calculations included bilateral mTLE cases with left and right scores averaged. Overall we found that the performance of HVI was superior to visual inspection but inferior to HV (Visual inspection sensitivity = 58.6%, HVI sensitivity = 62%, HV sensitivity = 82%; Table 1). Individual rater and clinical sensitivities and specificities are provided in supplemental material (Supplementary

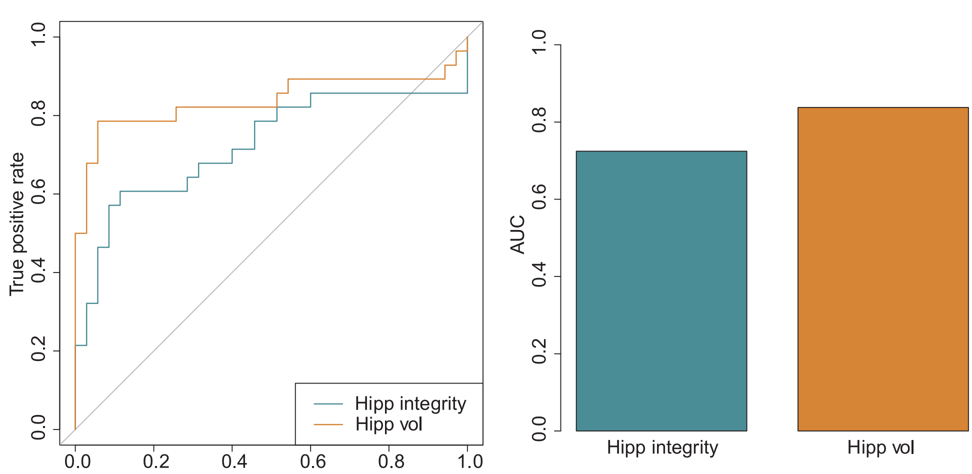

Fig. 3. HVI can be used to discriminate between mTLE patients and healthy controls. ROC curves for diagnosis of mTLE with controls as reference; graphs to the right of curves depict AUC values. ROC analysis indicates that HVI has an ROC AUC = 0.72. Performance is reduced relative to automated HV (AUC = 0.84).

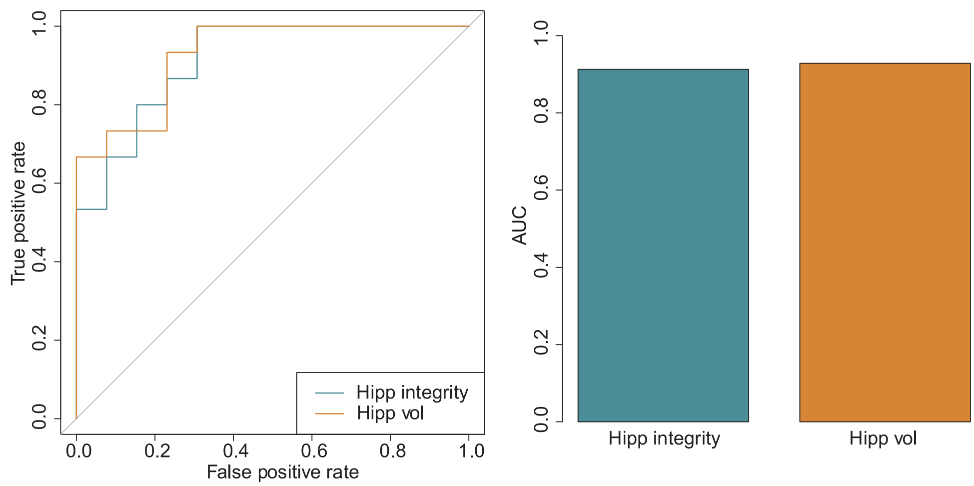

Fig. 4. HVI can lateralize HS in mTLE. ROC curves for lateralization of mTLE using right – left difference score; graphs to the right of curves depicts AUC values. ROC analysis indicates that HVI has an ROC AUC = 0.91 while HV has an ROC AUC = 0.93, suggesting they are comparable in correctly lateralizing HS.

Table 1
Sensitivity and specificity of visual inspection vs. automated methods in research scans.

	Visual analysis	HVI	HV
mTLE	17/29 (58.6%)	18/29 (62%)	23/29 (82%)
Control	25/35 (71.4%)	25/35 (73%)	25/35 (73%)

Abbreviations: mTLE = mesial temporal lobe epilepsy; HVI = hippocampal volumetric integrity; HV = hippocampal volumetry.

material Table 7).

HVI has superior performance to visual inspection in terms of correctly determining whether a subject has HS, while automated HV is superior to both techniques. We determined the sensitivities of the automated techniques based on the averaged value of specificity for the visual inspection raters (73%). Visual inspection analysis was limited to standardized research scans. HVI and HV values were inferred by using the percentages derived from ROC curves to estimate the proportions based on mTLE and control sample sizes.

4. Discussion

In this study we have shown that HVI can detect HS in patients with mTLE and provided preliminary evidence that the HVI technique is suitable for clinical imaging. HVI in mTLE patients with lateralized HS is significantly reduced relative to controls using both standardized and non-standardized image acquisition protocols. Furthermore, we assessed the classification performance of HVI, and demonstrated that HVI can discriminate between mTLE patients and healthy controls, mTLE patients and non-HS TLE patients, and can lateralize mTLE. Although HVI had lower performance for distinguishing mTLE cases from control and non-HS TLE cases when compared to HV, HVI matched HV in lateralizing mTLE patients. We also found that HVI has superior performance to visual inspection by our raters. These preliminary findings provide compelling evidence that this novel imaging metric is capable of detecting and lateralizing HS in most subjects. The primary advantage of the HVI method relative to automated HV is that it is significantly faster than widely used current automated HV methods; processing images and generating HVI scores takes approximately 30 s, whereas processing time for the Freesurfer image analysis pipeline is several hours. Furthermore additional brain measures, such as ICV, do not need to be made when using HVI. In a clinical setting, HVI values could realistically be provided almost immediately following imaging. As an example of a potential clinical application of the HVI technique, the fast processing time would allow for screening for mTLE during subject scanning; a low HVI score could automatically trigger additional acquisitions targeting the temporal lobes, precluding the need for follow-up scanning.

Although HV demonstrated superior performance to HVI, it is important to note that mTLE subjects were diagnosed (and included in our study) based on reduced hippocampal volume on MRI. This may partly explain the superior performance of HV in our sample. Further development of 'kaiba' will likely improve the performance of HVI for detecting hippocampal changes in mTLE.

We also found that the AUC for HVI in clinical scans was consistently lower than the AUC for HVI in research scans. This is likely due to the variability in acquisitions for clinical images, including the use of different scanners. In addition, poor image quality and motion artifact can introduce variability in landmark detection, ROI delineation and HVI calculation. In fact, the proportion of failed automatic landmark detections in clinical scans was twice that in research scans (clinical: 14.6%; research: 7.5%). It is also interesting to note that HVI was less sensitive in distinguishing mTLE cases from non-HS TLE cases. This may be due to underlying pathological changes to the temporal lobes in cases of TLE without clear HS, which skew HVI landmark detection and calculation (Carne et al., 2004; Unnwongse, Alexopoulos et al. 2013).

Previous studies report the sensitivities of their visual inspection raters for detection of HS to be 62% and 85% (Farid, Girard et al. 2012; Coan, Kubota et al. 2014). In our study visual inspection was done for all subjects (controls and all epilepsy sub-groups), and the raters were blinded to clinical diagnosis of epilepsy and lateralization, unlike Coan et al. (2014) and Farid et al. (2012), where raters were only blinded to lateralization (Farid, Girard et al. 2012; Coan, Kubota et al. 2014). Furthermore, our raters did not use any additional information to assist their ratings, such as EEG data or T2 weighted imaging, which were used in Coan et al. (Coan, Kubota et al. 2014). For these reasons our sensitivity estimates are likely to be conservative, since clinical workups will typically utilize these additional sources of information. Integrating our HVI method with additional imaging, histopathological and clinical information will likely improve our ability to detect hippocampal pathology in TLE.

Although the importance of correctly identifying hippocampal sclerosis for surgical intervention is well established, there are a number of unanswered questions relating to this form of epilepsy. In particular there is yet to be an identified common etiology of hippocampal sclerosis. A potentially related question is why fewer hippocampal sclerosis surgical resections have been carried out in a selection of major surgical centers across the USA, Australia and Germany from 1991 to 2011 (Jehi, Friedman et al. 2015). These population-level questions will likely be addressed using multi-center big data approaches, and analysis methods that can be described using the term 'artificial intelligence'. These approaches require the extraction of relevant multi-variate features from imaging data. Our demonstration that HVI is sensitive to brain changes in mTLE suggests that this measure may be a useful feature for these future applications.

5. Conclusion

Automated hippocampal segmentation techniques have become increasingly popular for the quantification of hippocampal volume loss (Pardoe, Pell et al. 2009; Coan, Kubota et al. 2014). This study presents an alternative automated method for MRI-based quantitative assessment of HS that can be used to supplement clinician diagnosis. In summary, we have shown that HVI analysis can be applied to clinical images and can provide a fast and automatic screening tool to complement imaging assessment for identifying hippocampal pathology in epilepsy patients.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.05.014.

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