Clinical study

MRI morphology of the hippocampus in drug-resistant temporal lobe epilepsy: Shape inflation of left hippocampus and correlation of right-sided hippocampal volume and shape with visuospatial function in patients with right-sided TLE

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ARTICLE INFO

Article history:

Received 12 April 2019

Accepted 10 June 2019

Keywords:

Epilepsy
Temporal lobe
Hippocampus
MRI
Morphology
Morphometry

ABSTRACT

We sought to quantify the morphology in vivo of hippocampi in patients with drug resistant temporal lobe epilepsy (TLE) via magnetic resonance imaging (MRI), prior to temporal lobe resection, and the correlation of surface-based shape analysis of morphology and clinical cognitive function.

Thirty patients with drug-resistant TLE and twenty healthy controls underwent clinical neuropsychological testing, and brain MRI at Lund University Hospital prior to hippocampal resection. A neuroradiologist categorised radiological findings into normal hippocampus, subtle changes or definite hippocampal sclerosis. We manually segmented MRI of the hippocampus of participants using ANALYZE 11.0 software; and analysed hippocampal shape using SPHARM-PDM software.

For radiologist visual-ratings of definite left hippocampal sclerosis in those with left-sided TLE, hippocampal volumes were significantly smaller compared to normal controls. In right-sided TLE we found contralateral shape inflation of the left hippocampus, partially confirming previous shape analytic studies of the hippocampus in TLE. We found significant correlation of volume and surface deflation of the right hippocampus in right-sided TLE with reduced performance on the two right-lateralised visuospatial memory tests, the Rey Complex Figure Test (Immediate and Delayed recall) and the Recognition Memory Test for faces. Decreased hippocampal volume was correlated with poorer performance on these tasks.

The morphology of the hippocampus can be quantified via neuroimaging shape analysis in TLE. Contralateral shape inflation of the left hippocampus in right-sided TLE is intriguing, and may result from functional compensation and/or abnormal tissue. In right-sided TLE, hippocampal structural integrity, quantified as hippocampal shape, is correlated with lateralised visuospatial function.

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1. Introduction

Temporal lobe epilepsy (TLE) is the most common form of drug-resistant epilepsy in surgical series [1]. Alterations of the mesiotemporal network, traversing the hippocampus, have recently been demonstrated in TLE [1]. Hippocampal resection is a common treatment for drug-resistant TLE and the most common

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histopathological finding in resected tissue is hippocampal sclerosis [HS] [2], which occurs in approximately 65% of patients [3]. HS prevalence is approximately 0.1% of the general population [4]. HS is clinically characterised by gliosis, loss of synaptic organisation, and alteration of cellular structures within various regions of the hippocampus [5]. The underlying mechanism responsible for the hippocampal pathology is unclear but is likely to be attributable to environmental and polygenetic factors that have not been identified to date [3].

For certain TLE patients, resection of the sclerotic region of the hippocampus can clinically result in a significant decrease in frequency of seizures [6]. However, up to one third of patients who have undergone hippocampal resection are unchanged regarding the frequency of seizures, and the reason for this is yet undiscovered.

MRI is currently used to assess the morphology of the hippocampus prior to surgical resection via expert neuroradiologist visual diagnosis. Pre-surgical ipsilateral hippocampal integrity is an important predictor of post-surgical outcome in relation to seizures and memory performance [7]. Accordingly, we consider that quantifying the hippocampal volume via manual segmentation on MRI [8] and through advanced morphometric (shape and volume) analysis [9] may potentially aid in understanding pathophysiology, diagnosis, pre-surgical work up and prognosis of post-operative outcomes amongst patients with TLE [3,7].

We aimed to quantitatively characterise MRI pre-surgery surface morphology of the hippocampus and its relationship to: pre-operative radiologist ratings of hippocampal sclerosis, pre-surgical assessment of cognitive function (as assessed by neuropsychological memory tests), and post-operative reduction in seizure frequency (Engel Class).

2. Materials and methods

2.1. Participants and protocol

Thirty patients with therapy resistant TLE, eligible for surgical resection, attending Lund University Hospital Department of Neurology in Skåne, Sweden were selected, excluding other neurological disorders (stroke, multiple sclerosis, movement disorders, dementia, and neurodegenerative disease), between January 2005 and December 2011. A surgical decision was made by a team discussion based on video-EEG recordings, semiological analysis, structural and functional imaging.

MRI scans were performed in accordance with the surgical protocol for TLE using a 3.0T Philips MR scanner, equipped with an eight-channel head coil (Philips Achieva®, Philips Medical Systems, Best, The Netherlands). High resolution anatomical images were acquired using a T1-weighted turbo field echo pulse sequence with parameters set as follows: TR 8 ms; TE 4 ms; TI 650 ms; FA 10°; NEX 2; SENSE-factor 2.5; matrix 240 × 240; FOV 240; resulting voxel size 1 × 1 × 1 mm³. In total 175 contiguous coronal slices were obtained. T1-weighted MRI images obtained were visually inspected and analysed by a qualified neuroradiologist (DVW), who allocated the 30 patients with TLE into three diagnostic groups of hippocampal sclerosis, subtle hippocampal changes, or no evidence of hippocampal changes. Visual assessment was performed without prior knowledge of the histology, and comprised evaluation of the size and signal intensity of the hippocampus, temporal lobe, temporal horn, collateral white matter, fornix, mammillary bodies as well as the number of indentations [10].

There were three groups in this study: right-sided TLE patients (n = 19), left-sided TLE patients (n = 11), and age-matched healthy controls (n = 20). Controls were all recruited during the same time period and had undergone MRI-scanning using the same scanner

and protocol as the TLE patients for comparison. Neuropsychological assessments included: for verbal memory, the Claeson-Dahl Test for Verbal Learning and Memory (CDT) [11] including variables *Total Learning and Delayed Recall*; and for visuospatial memory, the Recognition Memory Test for faces (RMT) [12] test variable *Number of recalled faces*, and the Rey Complex Figure Test (RCFT) [13], including variables *Immediate recall* and *Delayed recall*. These tests were drawn from a larger standardised protocol for evaluating pre-surgical memory in epilepsy surgery and were performed by a clinical neuropsychologist. Only TLE patients underwent the neuropsychological assessment, and not the controls.

Histopathologic analysis of the surgically resected hippocampal specimen was performed for validation of the radiological diagnosis, but was not further investigated in this study.

Seizures two years post-resection of the hippocampus were assessed in accordance with the modified Engel Classification of post-operative seizure outcome in the Swedish National Epilepsy Surgery Registry [14] by an specialist neurologist-epileptologist (KK)[Class I: free of disabling seizures; II: rare disabling seizures; III: worthwhile improvement; IV: no improvement].

2.2. MRI shape analysis

A single trained researcher (JY) manually segmented the hippocampus on MRI scans of subjects using a validated protocol (intra-rater intra-class correlation co-efficient ranging 0.959–0.972) and ANALYZE 11.0 (Mayo Foundation, Rochester, MI, USA) software as defined by the anatomical criteria as well as estimating intracranial brain volumes as per Velakoulis et al [8].

3-D Binaries from the traced structures were processed using the SPHARM-PDM analysis software (<http://www.ia.unc.edu/dev/download/shapeanalysis>) [9]. Binaries were smoothed with a 1 mm Gaussian kernel and spherical harmonics were used to generate 1002 corresponding surface vertices [9,15]. Shapes were aligned using Procrustes method to a group mean for the entire sample. Statistical group comparisons were performed using a MANCOVA test, with the vertex coordinates as dependent variables, TLE or control group as independent variables, with intracranial volume and age as covariates. Across each structure a false discovery rate correction (FDR) was applied, set at $p < 0.05$. Pearson's correlation analyses were performed with the independent variable calculated as the magnitude of displacement between surface normals at each vertex from the mean shape. Covariates and correction for multiple comparisons were performed as for the group comparisons.

2.3. Demographic and MRI volumetric analysis

Volumetric statistical analysis in this study was completed using the IBM® SPSS® (version 21.0.0.0, IBM, New York, NY, USA). Differences in demographic factors between the four groups within the study population were compared and tested with the Kruskal-Wallis test (for age and intracranial volume) and the Chi-square test for independence (for gender). Analysis of co-variance (ANCOVA) and pairwise comparisons of hippocampal volumes between various diagnostic groups (or multiple diagnostic groups combined) were conducted to test for statistical significance with age and intracranial volumes incorporated as co-variables [8].

2.4. Ethics

All participants involved in this study were informed and consented to data collection. Ethical permission for retrospective analysis of the data was applied for but waived by the Lund University Hospital Regional Ethics Committee, since the analysis would not influence the current diagnosis or treatment of the participants.

Ethical approval was also obtained from the Australian National University Human Research Ethics Committee.

3. Results

3.1. Demographics

Table 1

3.2. Between-group comparisons

3.2.1. Volumetric analysis of hippocampus in patients with TLE

We conducted a planned analysis comparing manually segmented hippocampal volumes of persons with TLE with healthy controls but found no significant differences in right or left hippocampal volumes with right or left TLE. Similarly, we also conducted a planned analysis of hippocampal volume between different post-operative seizure outcomes of Engel classes for those with right or left TLE, and in comparison to controls but found no significant differences, including analyses of stratified Engel Class groupings (I-II vs. III-IV and I vs. II-IV).

For radiologist ratings of hippocampal sclerosis (three ratings: normal hippocampus, subtle hippocampal changes or definite hippocampal sclerosis), we found a statistically significant difference in left hippocampal volume between normal controls ($M = 2583 \text{ mm}^3$, $SD = 333 \text{ mm}^3$, $n = 20$) and the group with definite hippocampal sclerosis ($M = 2169 \text{ mm}^3$, $SD = 426 \text{ mm}^3$; $p = 0.004$, $n = 6$ of 11 with left-sided TLE); but not between healthy controls and subtle hippocampal sclerosis ($M = 2476$, $SD = 495 \text{ mm}^3$, $n = 5$ of 11 with left-sided TLE); and not between normal controls and subtle ($n = 4$ of 19) or definite hippocampal sclerosis changes in ($n = 8$ of 19) with right-sided TLE. These results may be influenced by the small numbers of hippocampal sclerosis ratings of subtle ($n = 5$) and definite ($n = 6$) hippocampal sclerosis in left-sided TLE compared to normal ($n = 7$), subtle ($n = 4$) and definite ($n = 8$) in right-sided TLE.

3.2.2. Analysis of hippocampal shape in patients with TLE

We conducted a planned analysis and found there was a significant difference, after false discovery rate correction, between the average-shape of the left hippocampus in persons with right sided TLE compared to healthy controls (See Fig. 1). There were no

significant differences in the shape of the right hippocampus between the controls and persons with left TLE.

3.3. Within-group analyses

3.3.1. Within-group regression analyses

We conducted planned regression analyses of the z-scores of neuropsychological test scores with hippocampal volumes. Larger right hippocampal volumes were significantly associated with higher RCFT *Immediate recall* scores in both patients with right TLE ($\text{Beta} = 0.694$, $p = 0.010$) and either right or left TLE ($\text{Beta} = 0.651$, $p = 0.007$). Furthermore, larger right hippocampal volumes were also associated with higher RCFT *Delayed recall* in patients with either right or left TLE ($\text{Beta} = 0.562$, $p = 0.013$). No significant correlations were observed for left TLE or left hippocampal measures with verbal memory on the CDT.

3.3.2. Within-group shape analyses

For the right hippocampus in patients with right TLE, there was a significant association of regional expansion with higher scores on RCFT *Immediate recall*, RCFT *Delayed recall*, and RMT *Number of recalled faces* (Fig. 2). No significant correlations were observed for left TLE or left hippocampal measures with verbal memory on the CDT.

4. Discussion

In this study we demonstrated that hippocampal volumes in those with left-sided TLE were significantly smaller in the neuroradiologist-rated definite hippocampal sclerosis group, compared with normal controls. We also found contralateral shape inflation of the left hippocampus in right-sided TLE. Finally, we demonstrated significant correlation of volume loss and surface deflation of the right hippocampus in right sided TLE with performance on the right-lateralised visuospatial memory tests, the Rey Complex Figure Test (*Immediate and Delayed recall*), as well as the Recognition Memory Test for faces.

4.1. Between group findings

4.1.1. Radiologist visual-ratings of hippocampal sclerosis

We found that hippocampal volumes in those with left-sided TLE were significantly smaller in the neuroradiologist-rated

Table 1
Demographic factors between patients with TLE and controls.

Variable	TLE	Controls
N	30	20
Male: Female	15:15	9:11
Age (SD)	38.43 (10.84)	45.20 (11.40)
Years of Education	10.90 (2.024)	
TLE side (R:L)	19:11	
Radiological grouping	7	
Normal		
Radiological grouping	9	
Subtle		
Radiological grouping	14	
Hippocampal Sclerosis		
Engel Class I – free of disabling seizures	16	
Engel Class II – rare disabling seizures	6	
Engel Class III – worthwhile improvement	3	
Engel Class IV – no worthwhile improvement	4	
Left Hippocampus Volume (SD)	2358 (454)	2475 (345)
Right Hippocampus Volume (SD)	2378 (628)	2554 (366)
Bilateral Hippocampus Volume (SD)	4736 (956)	5029 (701)
RCFT <i>Immediate recall</i> Normal Distribution –z-score (SD)	–1.357 (1.319)	
RCFT <i>Delayed recall</i> Normal Distribution –z-score (SD)	–1.393 (1.176)	
RMT <i>Number of recalled faces</i> Normal Distribution – z-score (SD)	–1.078 (2.006)

Fig. 1. Shape of left hippocampus in patients with right sided TLE vs shape of left hippocampus in controls (contralateral comparison): Left hippocampus, inferior surface at top, superior surface at base of image. Displacement map on the left; False Discovery-Rate (FDR) corrected p-values of significant shape change on the right; Scale on left, millimetres of surface displacement – cooler colours indicate surface deflation, while warmer colours indicate surface inflation; Scale on right indicates FDR corrected p-values of significant shape change – cooler colours indicate lesser significance, and warmer colours significant change.

“definite hippocampal sclerosis” group compared with normal controls. However, the relatively small numbers of the individual neuroradiologist-rated subgroupings for right- and left-sided TLE respectively prompt caution in interpretation. Tentatively, these findings confirm the clinical utility of specialist radiologist visual ratings of hippocampal sclerosis.

A previous shape analysis study comparing those persons with TLE a radiologist-rated as having hippocampal sclerosis (HS), to those rated as not, found those with HS had ipsilateral smaller cornu ammonis (CA) regions CA1, CA2, CA3 and dentate gyrus [4]. This is concordant with another recent shape analysis study using clinical radiologist ratings to stratify by hippocampal sclerosis found ipsilateral hippocampal atrophy was more pronounced in those rated as MRI-positive with hippocampal sclerosis, but atrophy was also evident in those rated as MRI-negative with hippocampal sclerosis [16].

4.1.2. Hippocampal morphometric measures

We found a significant difference in the shape of the left hippocampus of persons with right-sided TLE compared to the left hippocampus of controls. As volumetric measures of themselves do not differentiate normal from abnormal tissue, we have used morphometrics (shape analysis) to determine if there are regional

hippocampal differences in morphology, indicative of disease. In context, we acknowledge the burgeoning field of hippocampal sub-field analysis may yield more detail in future [17]; and in contrast to our findings, a number of studies over the last two decades have found that there are significant volumetric and shape differences between those with TLE and healthy controls [17–19].

The significant difference in the shape of the left hippocampus of persons with right-sided TLE compared to the left hippocampus of controls is robust after correction for Type I and Type II errors used in the SPHARM shape analysis. These intriguing findings are consistent with a number of shape analysis studies cited below, demonstrating spatial distribution of shape change in primarily surface hippocampal regions corresponding to CA1, with atrophy in the inferior surface of the head of the left hippocampus, and additional apparent hypertrophy in the head in CA1 in those with right TLE.

Hogan first demonstrated, in 10 persons with left TLE and right TLE respectively, inward deformation, representing atrophy, affecting the medio-lateral head and posterior tail of the hippocampus [18]. These findings were confirmed in follow-up studies by the same group, using deformation-based [20] and subsequently, large-deformation high-dimensional mapping [21]. Another study, comparing persons with TLE to persons with Alzheimer's disease

Fig. 2. Significant shape changes in the right hippocampus for patients with right sided TLE correlated with z-scores of neuropsychological tests: Figures show areas of significant (FDR < 0.05) expansion (in mm) in association with higher neuropsychological test scores. Warmer colours indicate greater expansion. RCFT: Rey Complex Figure Test; Imm: immediate recall; Del: delayed recall; RMFT: Recognition Memory Test for faces.

(AD) found that those with TLE-related hippocampal sclerosis demonstrated more hippocampal atrophy and shape deformation than in AD [22].

More recently, studies using advanced morphometric techniques for analysis in TLE have found ipsilateral surface-based atrophy of the cornu ammonis 1 (CA1) hippocampal region [23]; CA1 and subiculum in radiologist rated positive and hippocampal sclerosis [16]; and in those stratified on hippocampal volume as high atrophy patients [24]. In contrast, those stratified on hippocampal volume as low atrophy patients were found to have medial atrophy corresponding to the CA2–4 regions [24]. Another recent shape analysis study found localised atrophy of the hippocampus contralateral to the side of TLE (i.e. contralateral to the side resected), as we found, although this was in patients with persistent postoperative seizures [25].

Recent automated image shape analysis studies focusing on hippocampal subfield pathology in TLE have found: ipsilateral CA1, CA4 and dentate gyrus atrophy those rated as showing hippocampal sclerosis [26]; and ipsilateral CA1, CA2–3, CA4–dentate gyrus atrophy in persons with unilateral TLE, with regional inward shape deformation in ipsilateral CA1 in right and left TLE [27]. A recent meta-analysis of MRI findings in 371 persons with hippocampal sclerosis compared to 121 controls also found greater neuronal loss in CA1 compared to CA2, 3 and 4 [28].

In terms of correspondence to histopathological subtyping, our pre-resection hippocampal morphology findings most closely

resemble the International League Against Epilepsy (ILAE) Type II hippocampal sclerosis [29]. In a histopathological study, those persons classified as demonstrating hippocampal sclerosis using neuropathological criteria were found to have smaller hippocampal volumes than those without hippocampal sclerosis; and these abnormal hippocampal volumes were correlated with histopathological neuronal density in CA1, CA2 and CA4 [2].

Thus, broadly speaking, our findings of shape inflation of the surface corresponding to CA1, contralateral to the epileptogenic temporal lobe, are consistent with findings of atrophy in the corresponding region in the ipsilateral temporal lobe. Our findings differ in demonstrating regions of shape inflation, possibly signifying relative hypertrophy, in primarily CA1. Potentially, such hypertrophy of the contralateral hippocampus in those with right sided TLE represents a functional compensation, or alternatively could represent abnormal tissue. Unfortunately, our small sample size precludes further subgroup analyses of seizure outcome and side of TLE, but we acknowledge this would be interesting to explore.

4.2. Within group findings

4.2.1. Hippocampal volumetric measures and correlations

We found that lateralised cognitive function (controlling for Age, ICV and years of education), i.e. visuospatial memory, as assessed via the Rey Complex Figure Test (RCFT), *Immediate recall*, is significantly correlated in hierarchical regression with the vol-

ume of the right hippocampus in right or left sided TLE, explaining 9.7% of the variance. The majority of the significance in the regression is explained by the volume of the right hippocampus in right sided TLE, explaining 50.5% of the variance of the model. Similarly, larger right hippocampal volumes were also associated with higher RCFT *Delayed recall* in patients with either right or left TLE.

4.2.2. Hippocampal morphometric measures and correlations

The volumetric finding for volume of the right hippocampus in right sided TLE regressing with RCFT, *Immediate recall* and *Delayed Recall* is further supported by the shape analysis correlation of RCFT, *Immediate recall* and *Delayed Recall* z-score and FDR-corrected surface inflation of the right hippocampus broadly across the superior and inferior surface of the hippocampus, primarily corresponding to surface areas CA1. This indicates that structural integrity of the ipsilateral hippocampus in TLE is directly related to performance on immediate visuospatial memory.

We found no significant correlations were observed for left TLE or left hippocampal measures of volume or shape with Claeson-Dahl Test for Verbal Learning and Memory, neither for list-learning nor for recall [11]. In contrast, a previous study investigating the relationship between hippocampal volumes and neuropsychological testing in TLE that found verbal memory impairment on similar, but not identical, verbal memory measures (*auditory immediate and delayed memory recall* from the Wechsler Memory Scale III) significantly regressed with hippocampal subfield volumes CA1, CA3 and dentate gyrus, among other regions [30]. However, that study did not appear to assess non-verbal visuospatial memory, such as with the RCFT.

We also found that the FDR corrected expansion of the shape of the right hippocampus in right sided TLE was correlated with memory for faces (RMT) [12]. This indicates that larger volume, as quantified by shape, was correlated with performance on the RMT, i.e. larger volumes were associated with better performance. This is in accordance with previous evidence that patients with right TLE were more impaired than those with left TLE in memory for faces test and that that resection of the right medial temporal lobe results in affected memory for faces on the RMT [31,32]. While previous research did not map correlations to the surface of the hippocampus, we found correlations primarily in the CA1, CA2-3 regions and more widespread correlations in the subiculum.

4.3. Limitations

This study has a relatively small sample size, and the group size for some of the clinical rating subgroups, e.g. Engel class and neuroradiologic HS ratings, may be underpowered to detect differences. We were not able to perform neuropsychological testing in the control group for comparisons of correlational analyses.

Manual segmentation is one of the most sensitive forms of volumetric methods to assess the hippocampus [33] and is considered the gold standard for volumetric measurements of the hippocampus [34]. The alternatives available include using automated or semi-automated voxel based morphometry techniques that are less labour intensive but have reduced sensitivity to change [33].

The shape analysis methods we used, SPHARM-PDM, rely upon comparison of vertices on the shape meshes and other authors have observed that such methods may be relatively more sensitive to detecting changes in outer hippocampal subfields (CA1, subiculum) rather than in medial subfields (CA3-4, dentate gyrus) [4,27].

Against these limitations, the strengths of the study must be balanced: a well characterised clinical sample and partial confirmation of findings of previous studies of the volumetric and shape analysis of the hippocampus.

5. Conclusion

Our study demonstrates that the morphology of the hippocampus can be quantified via neuroimaging shape analysis in TLE, and has face validity with neuroradiologist visual ratings.

We found that hippocampal volumes in those with left-sided TLE were significantly smaller in the neuroradiologist-rated definite hippocampal sclerosis group, compared with normal controls. The finding of contralateral shape inflation of the left hippocampus in right-sided TLE is intriguing, and speculatively may result from functional compensation, abnormal tissue or a combination of both. We found significant correlation of volume loss and surface deflation of the right hippocampus in right sided TLE with performance on the right-lateralised visuospatial memory tests, the Rey Complex Figure Test (*Immediate and Delayed recall*), as well as the Recognition Memory Test for faces. These findings indicated that preserved volume is correlated with better performance on these tasks. In relation to the pathophysiology of right-sided TLE, putatively hippocampal structural integrity, quantified as hippocampal shape, is correlated with lateralised visuospatial memory function.

Further studies, with larger sample sizes and possibly automated hippocampal subfield analysis are needed to see if our exploratory findings hold true.

Acknowledgments

This study was an initiative of the Australian United States Scandinavian-Spanish Imaging Exchange (AUSSIE), coordinated at the Australian National University Medical School, Canberra, Australia by JCLL, who self-funded travel and infrastructure costs to coordinate the research. KK's research time was funded by: a Stig and Ragna Gorthons research grant; and a Region Skånes project grant.

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