Shape Analysis of Hippocampal Surface Structure in Patients With Unilateral Mesial Temporal Sclerosis

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Structural hippocampal magnetic resonance (MR) imaging-based analysis is helpful in the diagnosis and treatment of mesial temporal epileptic seizures. Computational anatomic techniques provide a framework for objective assessment of three-dimensional hippocampal structure. We applied a previously validated technique of deformation-based hippocampal segmentations in 20 subjects with documented unilateral mesial temporal sclerosis (MTS) and temporal lobe epilepsy. Using composite images, we then measured shape differences between the epileptogenic, smaller hippocampus, and contralateral hippocampus. Final shape differences were projected on the contralateral "normal" side. We calculated results for the left MTS group (10 patients) and right MTS group (10 patients) separately. Both groups showed similar regions of maximal inward deformation in the affected hippocampus, which were the medial and lateral aspect of the head, and posterior aspect of the tail. These results suggest that there are specific three-dimensional patterns of volume loss in patients with mesial temporal epilepsy.

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MAGNETIC RESONANCE (MR) imaging-based hippocampal volumetric measurements are useful in the diagnosis of patients with mesial temporal lobe epilepsy. In the clinical setting of an epileptic seizure history compatible with mesial temporal lobe epilepsy, a significant hippocampal volume asymmetry is predictive of mesial temporal sclerosis (MTS),^{1,2} and a favorable outcome after epilepsy surgery.³⁻⁷ Past studies have used manual segmentation of the hippocampus on MR images to determine hippocampal volumes.⁸ The difficulty in manual segmentations lies in the subjective interpretations of anatomical variations. The emerging field of computational anatomy founded on general pattern theory^{9,10} provides tools and a framework for accommodating and studying this variability.¹¹⁻¹³ In this framework, an electronic atlas of the hippocampus is used as a deformable template, which is matched to an individual MR to extract and study the individual hippocampal areas. Use of computational anatomy allows for the objective analysis of the three-dimensional shape of neuroanatomic structures.^{10,14}

We have previously validated our technique of deformation-based hippocampal segmentations in

a group of patients with mesial temporal lobe epilepsy, and pathologically verified MTS.¹⁵

In this study, 20 subjects with documented unilateral MTS (10 right-sided MTS, 10 left-sided MTS) underwent MR imaging examination. The images were analyzed to automatically generate a three-dimensional surface representation of both hippocampi. Shape analysis was performed on the surfaces by calculating their statistical deviation from a composite image, and comparing the abnormal and "normal" (contralateral) hippocampal images. The results of the analysis were displayed on contour maps in a color gradient to demonstrate surface deviation of the diseased hippocampi from the "normal" surface.

METHODS

MR imaging scanning was performed with a 1.5-tesla Signa scanner (General Electric scanner, Milwaukee, WI). Whole-brain acquisitions were obtained in the coronal plane with a fast spoiled grass technique (FSPGR), TR = 14, TE = 3, flip angle = 30°. Voxel dimensions were 0.859 mm × 0.859 mm × 1.5 mm. Field of view was 22 cm × 22 cm. Matrix size was 256 × 256.

For deformation-based segmentations, MR data sets underwent preprocessing in preparation for the mapping algorithm. This consisted of two steps: global landmarking and hippocampus-specific landmarking. The preprocessing was manually done using Java-based software and took approximately 10 to 15 minutes per scan.

Landmarking provided an initial condition for the intensity-matching algorithm by roughly aligning the patient and atlas scans. The first step in landmarking was identifying global landmarks that scale and align the atlas brain to the patient brain using standard landmarks based on the Talairach coordinate system, as previously described.¹⁶ The second step was individually landmarking each hippocampus. This was done by first identifying the head and tail of the hippocampus, which specifies the long axis of the hippocampus. Then, four landmarks were identified on five cross sections equally spaced along this axis. The landmarks were placed on the medial,

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lateral, superior, and inferior boarder of the hippocampus on each cross section.

Images and landmarking data were then integrated into a Unix-based software program (proprietary software, Broomfield, CO). Within this program, the mapping algorithm employed a coarse-to-fine procedure for generating a transformation field from an atlas reference MR to patient MR. The atlas reference MR was segmented as previously described.¹⁴ The “coarse” aspect of the procedure relied on the landmark information provided by expert segmenters to provide an initial low-dimensional coregistration of atlas and patient images.¹⁷ The landmark information was provided in the form of the global and hippocampus-specific landmarks described in the previous section, which was used to derive a coarse manifold transformation¹⁸ from the reference to the patient images.

Having completed the coarse first step in the transformation, the volumes were roughly aligned and attention focused on the fine-featured substructures. The “fine” procedure involved the next two steps. The second step was to solve the registration problem using a linear elastic basis formulation and the full volume data, as previously described.^{12,19} This was fully automatic and only driven by the volume data itself. The three-dimensional whole-brain maps corresponded to the maximizer, whose variation solution corresponded to a solution of a nonlinear partial differential equation (PDE), consisting of between 10^7 and 10^8 parameters. The third and final step of the algorithm was to solve the nonlinear PDE corresponding to the Bayesian maximizer associated with the fluid formulation at each voxel of the full volume.^{11,20,21}

To quantitate the variation in shape of the above-described hippocampal deformations, we defined the “average” hippocampus in the right and left MTS groups by generating a mean transformation (from the atlas segmentation) for the 10 deformation images in each group. This mean transformation was then applied to the atlas itself to generate the average hippocampi. Figure 1 shows the average hippocampi of the subjects with left MTS. The composite left hippocampus with MTS is noticeably

smaller. To further quantify the difference between the right and left hippocampi, we calculated a minimum mean squared error (MMSE) estimation by flipping and rotating the right hippocampal transformation (for right MTS cases) to coregister it to the left hippocampal transformation. By calculating differences in right and left hippocampal transformation coregistration using the MMSE, we made a direct comparison between the shape of the left and the right hippocampus. An identical procedure, for left MTS cases, was performed using the opposite sides for each step outlined above. Final results were projected on the “normal” side, which was contralateral to the MTS. Therefore, results of shape changes showed areas of inward deformation, due to the smaller size of the hippocampus with MTS.

RESULTS

Left hippocampal abnormalities showed accentuated inward deformation in the lateral and inferomedial head, lateral body, and posterolateral tail regions. Right hippocampal abnormalities were accentuated in the superomedial head, inferolateral head, and lateral tail regions. For the left MTS group, deformation maximum amplitude (amp) = 1.51 mm, minimum amp = -3.57 mm, surface area = 1,602 mm². Surface areas with deformation amp greater than 1.0 mm, 2.0 mm, and 3.0 mm were 593 mm², 130 mm², and 15.8 mm², respectively. The average displacement was -0.78 mm. For the right MTS group, deformation maximum amp = 1.77 mm, minimum amp = -2.81 mm, surface area = 1,482 mm². Surface areas with deformation amp greater than 1.0 mm, 2.0 mm, and 3.0 mm were 379 mm², 13.2 mm², and 0 mm²,

Fig 1. Composite transformation hippocampal deformation images of the 10 subjects with left MTS. The composite left hippocampus with MTS is noticeably smaller.

respectively. The average displacement was -0.52 mm.

DISCUSSION

There are many clinical applications for MR-based hippocampal volumetric studies. Many studies continue to explore applications in the areas of epilepsy, Alzheimer's disease,^{22,23} amnesic syndromes,²⁴ and schizophrenia.^{25,26} Deformation-based segmentation has the ability to examine three-dimensional aspects of hippocampal shape, and therefore may improve the sensitivity and specificity of structural MR-based hippocampal analysis for these disease states.

In schizophrenia, analysis of changes in hippocampal shape as compared with controls showed significant changes, while hippocampal volume changes alone were not significantly different between the two groups.^{17,25,27} Csernansky et al²⁵ showed that regional hippocampal shape changes were most pronounced in the lateral hippocampal head and subiculum in patients with schizophrenia. Our results, like the results in patients with schizophrenia, show regional shape changes in the hippocampus in patients with MTS.

In mesial temporal lobe epilepsy, there are well-documented changes in regional hippocampal anatomy, such as volume loss localized only to the

hippocampal head,^{28,29} and loss of digitations of the hippocampal head.³⁰ Loss of digitations of the hippocampal head showed a sensitivity of 92% and specificity of 100% for MR diagnosis of MTS. However, hippocampal sclerosis may be present without associated total hippocampal volume asymmetries.³¹ Our results show that there are specific regions of volume loss within the hippocampus in patients with epilepsy and MTS, with the most prominent changes isolated to the hippocampal head and tail regions. Overall, regions of involvement were similar between the right and left MTS groups. Slight differences may be related to variance of degree of MTS between groups, normal shape differences between right and left hippocampi, or some degree of abnormal shape of the contralateral hippocampi. Past studies have shown involvement of the contralateral hippocampus in up to 30% of patients with mesial temporal lobe epilepsy.⁸

Application of deformation shape analysis enables better localization of hippocampal neuroanatomical abnormalities in patients with mesial temporal lobe epilepsy. This may add important correlative information to the localization of structural hippocampal abnormalities in patients with temporal lobe epilepsy and otherwise normal standard hippocampal imaging studies.

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