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Temporal Cortex Morphology in Mesial Temporal Lobe Epilepsy Patients and Their Asymptomatic Siblings

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Abstract

Temporal cortex abnormalities are common in patients with mesial temporal lobe epilepsy due to hippocampal sclerosis (MTLE+HS) and believed to be relevant to the underlying mechanisms. In the present study, we set out to determine the familiarity of temporal cortex morphologic alterations in a cohort of MTLE+HS patients and their asymptomatic siblings. A surface-based morphometry (SBM) method was applied to process MRI data acquired from 140 individuals (50 patients with unilateral MTLE+HS, 50 asymptomatic siblings of patients, and 40 healthy controls). Using a region-of-interest approach, alterations in temporal cortex morphology were determined in patients and their asymptomatic siblings by comparing with the controls. Alterations in temporal cortex morphology were identified in MTLE+HS patients ipsilaterally within the anterior-medial regions, including the entorhinal cortex, parahippocampal gyrus, and temporal pole. Subtle but similar pattern of morphology changes with a medium effect size were also noted in the asymptomatic siblings. These localized alterations were related to volume loss that appeared driven by shared contractions in cerebral cortex surface area. These findings indicate that temporal cortex morphologic alterations are common to patients and their asymptomatic siblings and suggest that such localized traits are possibly heritable.

Key words: asymptomatic siblings, heritability, hippocampal sclerosis, temporal lobe epilepsy

Introduction

There is convergent evidence that hippocampal sclerosis (HS) in mesial temporal lobe epilepsy (MTLE) is accompanied by widespread structural atrophy that extends beyond the epileptogenic zones (Miller 2011). Regional atrophy has been identified in several subcortical gray matter structures, including the amygdala and thalamus (Bernasconi et al. 2003; McDonald et al. 2008), the ipsilateral temporal cortex (Moran et al. 2001; Doherty et al. 2003; Bernasconi et al. 2005), and a number of fronto-limbic cortical regions (Duzel et al. 2006; Voets et al. 2011). Such widespread brain atrophy explains the array of cognitive deficits exhibited by

patients (Bell et al. 2011) and may underpin failure in achieving seizure freedom in some refractory patients who undergo selective surgical treatment (Bonilha et al. 2012). Therefore, the relevance of this extra-hippocampal atrophy has been increasingly recognized; however, its relationship to the underlying mechanisms remains poorly understood. As regional atrophy in MTLE+HS appears progressive over the course of the illness, the majority of this structural change has been attributed to injury induced by poorly controlled seizures (Bernhardt et al. 2009). This explanation is debatable, however, as similar pattern of extra-hippocampal atrophy has been described in patients with benign course of epilepsy (Labate et al. 2010, 2011; Miller 2011).

A number of family-based studies have explored the heritability of HS in MTLE patients and close relatives (Fernandez et al. 1998; Kobayashi et al. 2002; Alhusaini et al. 2013; Tsai et al. 2013). Subtle hippocampal anomalies have been described in asymptomatic relatives of patients with a strong family history of epilepsy, suggesting a role for genetic factors in the contribution to hippocampal abnormalities (Fernandez et al. 1998; Kobayashi et al. 2002; Tsai et al. 2013). In many patients, however, the epileptogenic zones extend to neighboring ipsilateral temporal structures, including the antero-medial regions of the temporal cortex (e.g., entorhinal cortex and parahippocampal gyrus) (Chabardes et al. 2005; Bartolomei et al. 2005). These temporal regions are anatomically connected to the hippocampus, and often they display a similar atrophy pattern to that identified within the hippocampus (Moran et al. 2001; Coste et al. 2002; Sankar et al. 2008). It remains unclear whether this localized regional atrophy reflects seizure-induced injury or some neuroanatomical anomaly that is present prior to seizure onset, predisposing individuals to epileptogenesis.

The goal of the present study was to build on previous investigations of first-degree relatives of MTLE+HS patients by evaluating the familiarity of temporal cortex neuroanatomical changes. Using a well-validated surface-based morphometry (SBM) method, a region-of-interest approach was applied to investigate temporal cortex morphology in patients and their asymptomatic siblings.

Materials and Methods

The research ethics committees of the participating hospitals independently approved this study. Written informed consent was obtained from all participants.

Study Participants

Patients

Patients with MTLE+HS were recruited from Beaumont Hospital and St. James's Hospital in Dublin, Ireland. Both are tertiary referral centers for refractory epilepsy. All patients underwent a comprehensive evaluation that confirmed the clinical diagnosis of

MTLE+HS as defined by the International League Against Epilepsy (Wieser 2004). Seizure lateralization was determined through a comprehensive investigation that included collection of detailed seizure semiology descriptions, inter-ictal/ictal EEG and video-telemetry recordings, and inspection of MR images for evidence of HS. Using a standard manual hippocampal segmentation protocol (Watson et al. 1992), unilateral hippocampal atrophy was confirmed in all patients by detecting volume loss beyond 2 standard deviations of the mean of 40 healthy controls in either the left or right hippocampus, after adjusting for intracranial volume (ICV). Patients with evidence of brain lesions other than HS were excluded. In total, 50 patients were included in this study. All cases were classified as refractory to medical therapy as defined by Kwan et al. (2010). Twenty-eight of the 50 patients (56%) underwent selective surgical treatment. In each of these cases, features of HS were confirmed on histological evaluation. All patients had sporadic MTLE+HS. Patients who reported seizures in first-degree relatives were not included. Initial precipitating insults (IPIs) were reported by 23 patients (46%). The following were considered as IPIs: febrile seizures (FS), central nervous system (CNS) infection, and status epilepticus (see Table 1). Six patients (12%) reported 2 or more IPIs. Patients who had a history of significant head trauma leading to loss of consciousness were excluded.

Asymptomatic Siblings

Fifty same-gender, asymptomatic siblings of patients were also recruited for this study. All siblings underwent a complete evaluation that included screening for history of seizures (including childhood FS), CNS infection, or significant head trauma. Siblings with known neurological or psychiatric illness were excluded. See Table 1 for additional details.

Controls

Our control group consisted of 40 healthy individuals (18 males and 22 females), demographically matched to the patient and siblings groups (see Table 1). Control subjects with known neurological deficits, history of seizures, or positive family history of epilepsy were excluded.

Table 1 Demographics and MRI-based hippocampal volume measures of the study participants

	Healthy controls	Asymptomatic siblings of patients	Left MTLE+HS patients	Right MTLE+HS patients
Number	40	50	27	23
Age: mean (SD)	33.7 (9.9)	36.8 (10.3)	35.6 (10.7)	36.3 (10.5)
Gender: number (%)				
Male	18 (45%)	20 (40%)	10 (37%)	10 (43.5%)
Female	22 (55%)	30 (50%)	17 (63%)	13 (56.5)
Age at seizure onset: mean (SD)	—	—	14.3 (10.1)	12.1 (10.1)
Epilepsy duration: mean (SD)	—	—	21.6 (13.6)	24.2 (12.8)
IPIs: number (%)				
FS	0	0	11 (40.7%)	10 (43.5%)
CNS infection	0	0	1 (3.7%)	2 (8.7%)
Status epilepticus	0	0	2 (7.4%)	3 (13%)
Hippocampal volume: mean (SD)				
Left	4606 (381)	4426 (436)	3598 (757)*	4285 (590)
Right	4601 (343)	4383 (456)	4258 (479)	3252 (691)*

Note: Hippocampal volume measures are reported uncorrected in cubic millimeters. Using ANCOVA (covariates: ICV, age, gender), patients were compared with the healthy controls and their asymptomatic siblings. No significant hippocampal differences were noted between the asymptomatic siblings and controls. Age at seizure onset and epilepsy duration are reported in years. SD, standard deviation; IPIs, initial precipitating insults; FS, febrile seizure; CNS, central nervous system.

* $P < 0.0001$ (survived correction for multiple comparisons).

MR Image Acquisition

High-resolution brain MR images were acquired from all subjects using a single imaging protocol on a 1.5T MRI scanner (Signa) at Beaumont Hospital. A three-dimensional (3D) T₁-weighted spoiled gradient recalled sequence (TR/TE = 10.1/4.2 ms, TI = 450 ms, flip angle = 20°, field of view = 24 × 24 cm², matrix = 256 × 256) with 124 sagittal slices (slice thickness = 1.5 mm) was used to acquire the images.

MR Image Processing

Images were processed using FreeSurfer, a well-validated, fully automated SBM tool (version 4.5.0). A detailed description of FreeSurfer process can be found elsewhere (Dale et al. 1999; Fischl et al. 1999, 2001, 2002). Here, we applied FreeSurfer to reconstruct cerebral cortex surfaces and measure ICV and hippocampal volume as described previously (Alhusaini, Doherty, Scanlon et al. 2012; Alhusaini, Doherty, Palaniyappan et al. 2012). Quality control of image segmentation and cerebral cortex surface reconstructions were performed as recommended by the software developers (Fischl et al. 2001).

MR Image Analysis

Hippocampal Volume

Left and right hippocampal volumes were quantified in patients, their asymptomatic siblings and the control subjects using FreeSurfer's standard segmentation process (Fischl et al. 2002; Alhusaini, Doherty, Scanlon et al. 2012). Group differences in hippocampal volumes were determined using analysis of covariance (ANCOVA). The following covariates were included in the model: ICV, age, and gender.

Analysis of Cerebral Cortex Morphology

In order to assess cerebral cortex morphology, surface reconstructions of the cerebral cortex generated using FreeSurfer were inflated to produce a smooth surface, allowing sulcal and gyral folds to be viewed. Each vertex on the inflated cortical surface was subsequently registered to a sphere. This was followed by mapping the spherical representations to an average surface template (Fischl et al. 1999). The amount of metric distortion required to register cortical surfaces to the template was quantified at each vertex in all subjects. This measure, referred to as metric distortion, is driven by mainly the morphology of the cerebral cortex (Fischl et al. 1999; Wisco et al. 2007). Here, metric distortion was chosen to assess the global morphology of the cerebral cortex due to its high sensitivity in detecting subtle morphometric alterations not usually captured using conventional volume or thickness-based analyses, including surface area and folding pattern (Wisco et al. 2007).

Initially, we used a vertex-based approach to determine global differences in cerebral cortex metric distortion between: 1. MTLE+HS patients and the healthy controls, 2. MTLE+HS patients and their asymptomatic siblings, and 3. asymptomatic siblings of patients and the healthy controls. In order to capture the effect of seizure lateralization, patients with left and right MTLE+HS were analyzed separately. Similarly, the asymptomatic siblings were divided into siblings of left and right MTLE+HS patients. General linear models (GLMs) were employed using FreeSurfer to determine group differences in cerebral cortex metric distortion at each vertex, with ICV, age, and gender included as covariates. All data were smoothed with a 15-mm full-width half-maximum Gaussian kernel. Statistical parametric maps of significant group differences were corrected for multiple comparisons using Monte

Carlo permutation cluster analyses (10 000 permutations) using a cluster inclusion threshold of $P < 0.05$ (Holmes et al. 1996).

Quantification of Ipsilateral Temporal Cortex Morphology Changes in Patients and Their Asymptomatic Siblings using a Region-of-Interest Approach

In order to determine the primary geometric measures driving temporal cortex morphology alteration, localized regions of significant metric distortion differences between patients and controls identified within the ipsilateral temporal cortex in the initial vertex-based analyses were defined as anatomical labels (i.e., regions-of-interest, ROIs). These labels were mapped to each subject (in the native space), including patients, the asymptomatic siblings, and the healthy controls. Surface-based geometric properties (i.e., volume, surface area, and average thickness) were subsequently quantified for each label in all subjects. Group differences in these geometric measures were determined using ANCOVA (covariates: ICV, age, and gender). These analyses were conducted using SPSS statistical analysis package (version 18.0). The Bonferroni correction method was applied to correct for multiple comparisons.

Results

Comparisons of Hippocampal Volume between MTLE+HS Patients, Their Asymptomatic Siblings, and the Healthy Controls

As expected, patients with left and right MTLE+HS displayed significant ipsilateral hippocampal volume loss relative to the healthy controls ($P < 0.0001$; see Table 1). No significant contralateral hippocampal volume loss was identified in patients when compared with controls. Similarly, relative to their asymptomatic siblings, patients displayed significant hippocampal volume loss ipsilaterally ($P < 0.0001$). When compared with controls, the asymptomatic siblings of patients displayed no significant volume loss in either left or right hippocampus. However, a trend of hippocampal volume reduction was noted bilaterally (see Table 1).

Comparisons of Cerebral Cortex Morphology between MTLE+HS Patients, Their Asymptomatic Siblings, and the Healthy Controls

Compared with the healthy controls, patients with left MTLE+HS displayed a significant increase in cerebral cortex metric distortion, indicating altered surface morphology, in several regions of the cerebral cortex, including the ipsilateral precuneus cortex, ipsilateral supramarginal gyrus, and contralateral occipital cortex. An increase in cerebral cortex metric distortion, however, was more pronounced in the ipsilateral antero-medial temporal cortex regions, including the entorhinal cortex, parahippocampal gyrus, temporal pole, and the anterior parts of the superior, middle, and inferior temporal gyri (see Fig. 1a). No significant morphology changes were noted on the contralateral temporal cortex.

Interestingly, none of the above-mentioned ipsilateral temporal cortex morphologic changes were noted when left MTLE+HS patients were compared with their asymptomatic siblings (see Fig. 1b). However, in comparison with their siblings, patients displayed significant increase in cerebral cortex metric distortion in the lateral temporal cortex ipsilaterally, including the superior temporal gyrus.

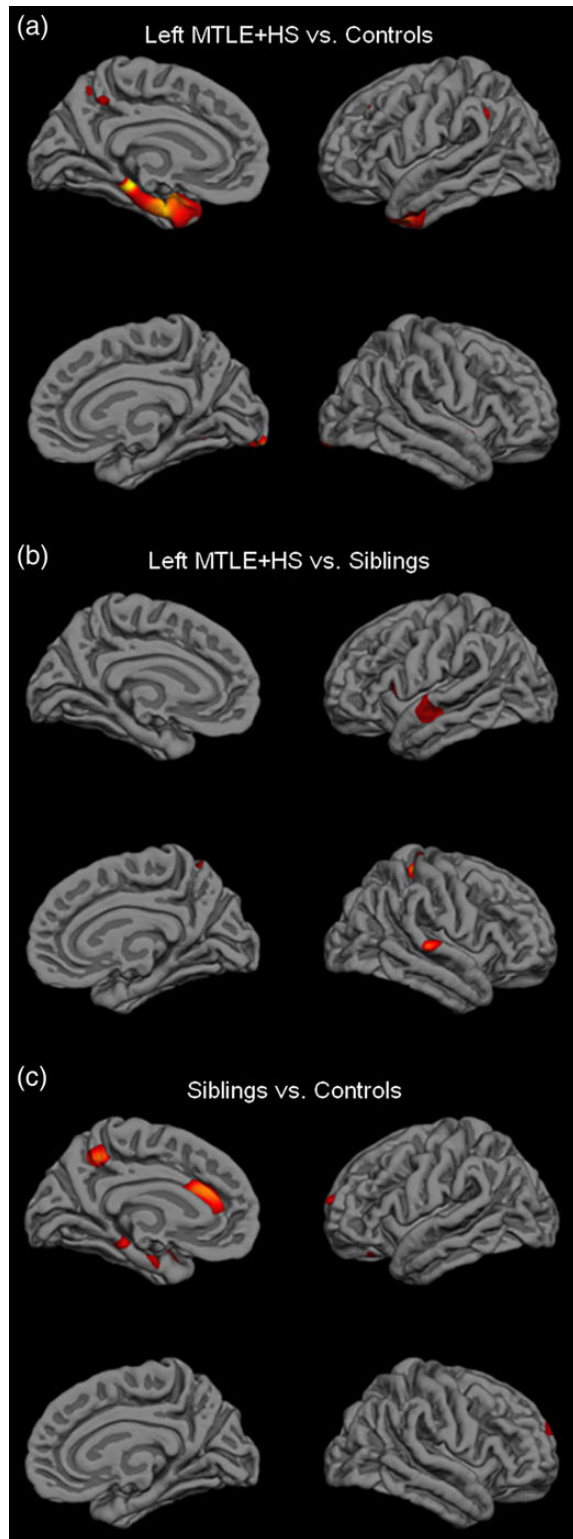


Figure 1. Patterns of altered cerebral cortex morphology in (a) left MTLE+HS patients compared with healthy controls, (b) left MTLE+HS patients compared with their asymptomatic siblings, and (c) siblings of left MTLE+HS patients compared with healthy controls. Areas of increased metric distortion relative to the reference group (i.e., controls or asymptomatic siblings) are shown in red/yellow, whereas areas of reduced metric distortion relative to the reference group are shown in blue/cyan. Maps of metric distortion changes are reported at $P < 0.05$ (all survived correction for multiple comparisons). In each panel, the top row represents the left hemisphere and the bottom row represents the right hemisphere.

In comparison with controls, the asymptomatic siblings of left MTLE+HS patients exhibited significant increase in cerebral cortex metric distortion within localized regions in the left mesial temporal cortex, including the entorhinal cortex and parahippocampal gyrus (see Fig. 1c). It is important to note that these changes were identified in the temporal cortex that is ipsilateral to the seizure focus of their affected siblings (i.e., left MTLE+HS), with no significant morphology changes noted in the contralateral temporal cortex. This pattern of morphology alteration is similar to that displayed by patients, although it was less widespread. Other regions of increased metric distortion displayed by the siblings of left MTLE+HS patients included the left precuneus and anterior cingulate cortices.

In right MTLE+HS patients, the pattern of altered temporal cortex morphology described earlier was largely repeated. Compared with controls, this patient group exhibited significant increase in cerebral cortex metric distortion within the antero-medial regions of the ipsilateral temporal cortex, including the entorhinal cortex, parahippocampal gyrus, temporal pole, and the anterior regions of the superior, middle, and inferior temporal gyri (see Fig. 2a). Similar to left MTLE+HS patients, no significant metric distortion changes were noted within the same temporal cortex regions contralaterally. Other regions of increased metric distortion were noted within the ipsilateral paracentral lobule and medial superior frontal gyrus, and contralateral precuneus cortex and superior temporal gyrus.

In comparison with their asymptomatic siblings, right MTLE+HS patients displayed a significant increase in cerebral cortex metric distortion within the ipsilateral parahippocampal gyrus and lateral temporal cortical regions, including the superior and middle temporal gyri (see Fig. 2b). Further, increased metric distortion was noted in the medial superior frontal gyrus bilaterally, and paracentral lobule and precentral gyrus contralaterally.

When the asymptomatic siblings of right MTLE+HS patients were compared with the control group, a significant increase in cerebral cortex metric distortion was evident within the right entorhinal cortex and temporal pole (see Fig. 2c). These morphology changes also involved the temporal cortex that is ipsilateral to the seizure focus of right MTLE+HS patients, with no morphology changes noted on the contralateral temporal cortex. Other regions of increased metric distortion were noted in left precuneus and right orbitofrontal cortices.

Quantification of Ipsilateral Temporal Cortex Morphology Changes in Patients and Their Asymptomatic Siblings

Next, we defined as anatomical ROIs areas of altered surface morphology (i.e., regions of significant metric distortion differences) detected within the ipsilateral temporal cortex in patients relative to controls. Analyses of cerebral cortex geometric measures within these ROIs revealed volume loss in the patient groups (left MTLE+HS: $P < 0.0001$ [Cohen's $d = 1.8$]; right MTLE+HS: $P < 0.001$ [Cohen's $d = 1.3$]; see Figure 3a,b). This volume loss appeared driven by contractions in cerebral cortex surface area (left and right MTLE+HS: $P < 0.0001$ [Cohen's $d = 1.7$ and 1.3, respectively]), with no significant cortical thinning identified. In the asymptomatic siblings, volume loss was also detected within the same ipsilateral temporal cortex ROIs (siblings of left and right MTLE+HS: $P < 0.001$ [Cohen's $d = 0.89$ and 0.8, respectively]; see Fig. 3a,b). However, this volume loss appeared secondary to a combination of surface area contraction and cortical thinning ($P < 0.01$, these P -values did not survive correction for multiple comparisons [Cohen's d -value ranged from 0.3 to 0.9]).

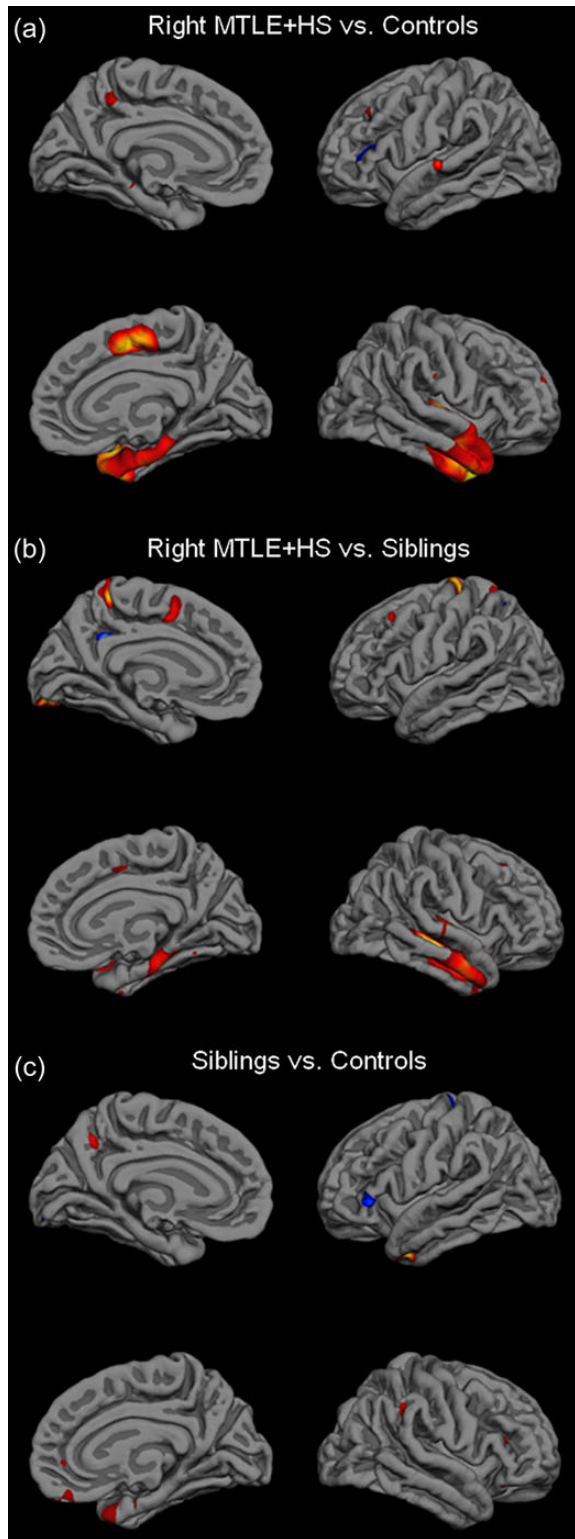


Figure 2. Patterns of altered cerebral cortex morphology in (a) right MTLE+HS patients compared with healthy controls, (b) right MTLE+HS patients compared with their asymptomatic siblings, and (c) siblings of right MTLE+HS patients compared with controls. Areas of increased metric distortion relative to the reference group (i.e., controls or asymptomatic siblings) are shown in red/yellow, whereas areas of reduced metric distortion relative to the reference group are shown in blue/cyan. Maps of metric distortion are reported at $P < 0.05$ (survived correction for multiple comparisons). In each panel, the top row represents the left hemisphere and the bottom row represents the right hemisphere.

Discussion

Using a well-validated SBM method, this study examined the morphology of the temporal cortex in patients with MTLE+HS and their asymptomatic siblings. Altered surface morphology was identified in patients within the antero-medial regions of the ipsilateral temporal cortex. More subtle, but similar, pattern of altered morphology was also evident in their asymptomatic siblings. This localized morphology change appeared to be driven by volume loss that was common to patients and siblings, indicating that such morphometric traits are likely heritable and related to significant underlying mechanisms.

Previous MRI studies of patients with MTLE+HS have identified several neuroanatomical and functional alterations within the temporal cortex (Bernasconi et al. 1999; Coste et al. 2002; Doherty et al. 2003; Sankar et al. 2008). These abnormalities are more pronounced ipsilaterally and considered relevant to the underlying processes (Thom et al. 2009). The epileptogenic zones in many patients extend beyond the hippocampus to adjacent medial temporal cortex (Chabardes et al. 2005; Bartolomei et al. 2005). Indeed, interactions among the hippocampus, entorhinal cortex, and temporal pole seem to play a significant role in the generation and maintenance of some characterizing seizures (Chabardes et al. 2005). Significant structural atrophy has also been described in the antero-medial temporal regions ipsilaterally (Bernasconi et al. 1999; Moran et al. 2001; Coste et al. 2002; Sankar et al. 2008). This localized regional atrophy correlates highly with the structural alteration detected within the hippocampus (Moran et al. 2001; Voets et al. 2011). Such correlations highlight the possibility of a common underlying pathology; however, the exact underpinning mechanism of such structural change remains poorly understood. Several mechanisms have been proposed, implicating genetic, early environmental, and disease-related factors, including seizure-induced injury (Miller 2011; Bernhardt et al. 2013).

MRI studies of first-degree relatives of MTLE+HS patients with strong family history of epilepsy have previously identified subtle hippocampal architectural anomalies in the asymptomatic relatives (Fernandez et al. 1998; Kobayashi et al. 2002; Tsai et al. 2013). These findings support a role for genetic factors in contributing to hippocampal atrophy in familial forms of MTLE+HS and imply that subtle, but relevant, hippocampal alterations may exist prior to the onset of seizures and represent risk factor for disease development (Tsai et al. 2013). In this study, the asymptomatic siblings of patients displayed a trend of hippocampal volume reduction, although this did not reach statistical significance. It is important to note that, compared with previous studies, our sample was compromised of siblings of patients with sporadic MTLE+HS. This may explain our failure to replicate the findings of previous reports, which included first-degree relatives of mostly familial forms of MTLE+HS (Tsai et al. 2013). Another possible explanation could be related to the fact that we quantified hippocampal volume using FreeSurfer segmentation protocol. Although this automated segmentation method has previously been found to correlate highly with manual tracing, it was less sensitive to detect subtle hippocampal atrophy related to HS when compared with manual volumetry (Pardoe et al. 2009). In order to evaluate the familiarity of structural alteration in other relevant brain regions, the current study expanded the investigation to the entire temporal cortex. Subtle morphologic changes were revealed in the asymptomatic siblings of patients within the antero-medial temporal cortex in a pattern similar to that displayed by index cases. The presence of such structural alterations in relevant temporal cortex regions of high-risk individuals (e.g., relatives of

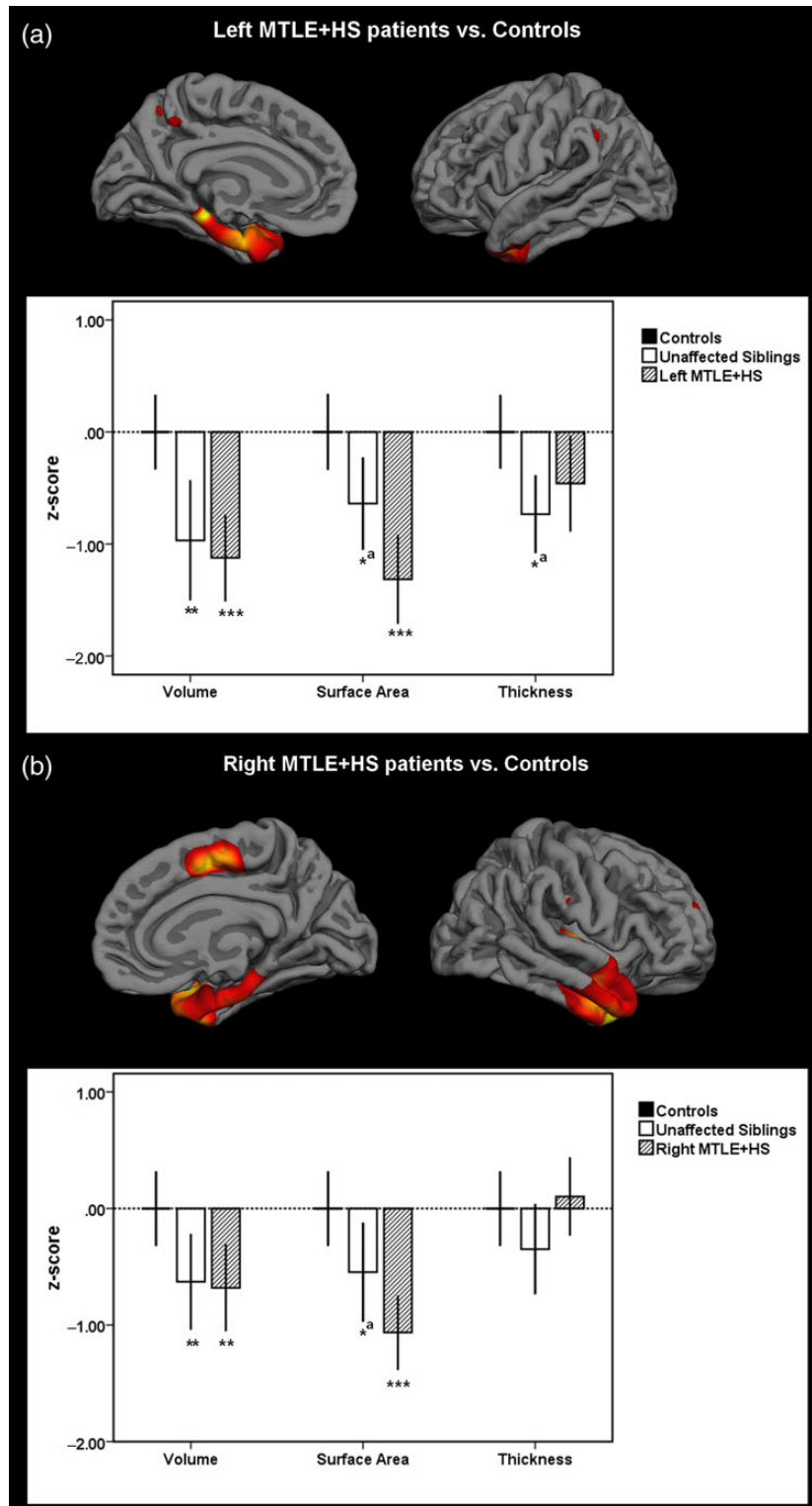


Figure 3. Geometric measures of ipsilateral temporal cortex ROIs, including volume, surface area, and thickness, are displayed for left (a) and right (b) MTL+HS patients, their asymptomatic siblings, and the controls. Data are reported as z-scores (derived from the mean of the control data). Error bands represent 95% confidence intervals. * $P < 0.01$; ** $P < 0.001$; *** $P < 0.0001$; ^a P -values that did not survive correction for multiple comparisons (Bonferroni method was applied).

patients) indicates that these ipsilateral morphologic traits are possibly determined by strong genetic predisposition. “Shared” early environmental factors, however, can also be implicated.

In the current study, it was evident that the degree of cortical metric distortion was more sensitive to changes in cerebral

cortex surface area than thickness. As this measure represents the degree of metric distortion (or stretching) required to align the surface of the cerebral cortex to a common spherical atlas, this finding was, to some extent, expected (Fischl et al. 1999; Wisco et al. 2007). Recently, it has been shown that surface

area and thickness contribute independently to gray matter volume (GMV), and each is believed to reflect on distinct neurobiologic and genetic mechanisms (Panizzon et al. 2009). Previous morphometric studies in other brain-related conditions demonstrated that alterations in cerebral cortex GMV relate to abnormalities in either thickness or surface area, with minimal spatial overlap between thickness and surface area changes (Ecker et al. 2013). In keeping with this, the present study demonstrates that the atrophy in the antero-medial temporal cortex in MTLE+HS is attributed largely to cerebral cortex surface area contractions. Alterations in cerebral cortex surface area are thought to result secondary to interruption of normal cerebral cortex development by variation in the genetic determinants of neuronal migration during brain maturation, or early environmental factors (Armstrong et al. 1995). Our findings of “shared” temporal cortex surface area contractions in patients and their asymptomatic siblings are supportive of a genetic influence. Surface folding patterns of the human cerebral cortex are believed to reflect the state of interregional brain connectivity (Im et al. 2008). Based on this, it is tempting to hypothesize that the identified alterations in temporal cortex surface area in patients and their siblings reflect changes in underlying white matter (WM) tracts, including hippocampal-projecting pathways. Indeed, compromised integrity of several WM tracts, particularly those projecting through the ipsilateral temporal lobe (e.g., uncinate fasciculus), has previously been reported in MTLE+HS patients (Bonilha et al. 2010; Scanlon et al. 2013).

MTLE+HS is a progressive disease with continuous brain regional atrophy observed throughout the course of epilepsy (Briellmann et al. 2002; Fuerst et al. 2003; Bernhardt et al. 2009, 2013). This progressive atrophy was largely attributed to the burden of the disease on brain structure, including repeated seizure activity (Miller 2011). In our initial vertex-based analyses, alterations in cerebral cortex morphology were identified in patients relative to their siblings and the healthy controls in a number of cortical regions beyond the antero-medial temporal cortex. These observations are in line with previous reports of widespread cortical abnormalities in MTLE+HS and are supportive of the view that structural alterations beyond the epileptogenic zones are driven by processes related to the burden of the disease itself (Bernhardt et al. 2009). In this study, the morphologic alterations appeared, to some extent, more extensive in patients with right MTLE+HS. Such widespread alterations could be related to the fact that, relative to left MTLE+HS patients, the patients with right MTLE+HS had longer disease duration. Thus, the chronicity of the disease may have had a more profound impact on their brain structure. Additional work is warranted to replicate these findings in an independent sample.

Conclusion

This study presents evidence of subtle morphology alterations in the antero-medial temporal cortex of asymptomatic siblings of MTLE+HS patients. Such localized morphology changes appeared to be driven by common volume loss in patients and siblings. These findings indicate that localized traits of the temporal cortex in MTLE+HS might be heritable and represent “intermediate” phenotypes reflecting relevant underlying mechanisms.

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Notes

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