Basal temporal sulcal morphology in healthy controls and patients with temporal lobe epilepsy

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ABSTRACT

Background: We previously demonstrated that shape variants of the hippocampal formation are more prevalent in patients with temporal lobe epilepsy (TLE) than in healthy individuals.

Objective: To categorize sulcal patterns of the basal temporal lobe in TLE compared to healthy controls.

Methods: We studied 51 healthy controls and 69 patients with TLE (37 left, 32 right TLE). Brain sulci were identified and labeled automatically on MRI using an algorithm based on a congregation of neural networks that allows mapping three-dimensional sulcal models on the cortical surface. We used four sulcal patterns classes to categorize the sulcal arrangement in the inferior surface of the temporal lobe in each subject: Type 1, i.e., single-branch, unbroken collateral sulcus (CS) connected with the rhinal sulcus (RS) anteriorly; Type 2, i.e., CS connected with the occipitotemporal sulcus (OTS), but separated from the RS; Type 3, i.e., CS separated from the OTS and RS, which are connected; and Type 4, i.e., CS, OTS and RS separated.

Results: In healthy controls, Type 1 and Type 2 were the patterns seen most frequently. Overall, 82% (42/51) of subjects had the same sulcal pattern in both temporal lobes. Inter-rater reliability for 35 randomly selected subjects indicated excellent agreement (Cohen's Kappa: 0.84). Compared to controls, we found an increased frequency of Type 1 CS in patients with TLE, both in the left (77% vs 47%, $p = 0.004$) and the right hemispheres (72% vs 41%, $p = 0.002$). On the other hand, we found a decreased frequency of Type 2 CS in patients with TLE, both in the left (4% vs 31%, $p = 0.00002$) and the right hemisphere (4% vs 35%, $p < 0.00001$).

Conclusions: A single-branch, unbroken collateral sulcus is the predominant sulcal pattern found in temporal lobe epilepsy. This "simplified" arrangement may be an indicator of neurodevelopmental deviance associated with this condition. *Neurology*® 2008;70:2159–2165

GLOSSARY

CS = collateral sulcus; **OTS** = occipitotemporal sulcus; **RS** = rhinal sulcus; **TLE** = temporal lobe epilepsy.

Temporal lobe epilepsy (TLE) is the most common medically intractable partial epilepsy in adults. Although hippocampal atrophy on MRI is a hallmark of the disorder in the majority of cases, several studies have confirmed that pathology in TLE extends to extrahippocampal mesial limbic structures such as the entorhinal cortex.[1-4]

The vast majority of MRI studies in TLE have been focused on assessing changes in gray and white matter volumes. Other aspects of cortical morphology such as sulcal shape, positioning, and patterning may give additional insights on structural brain changes associated with TLE. There is growing evidence that developmental hippocampal abnormalities increase susceptibility to seizures and neuronal loss, and may facilitate subsequent hippocampal sclerosis in patients with TLE.[5] We previously demonstrated that shape and positioning variants of the hippocampal formation are more prevalent in patients with epilepsy than in healthy individuals, and are found in a similar proportion

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in those with malformations of cortical development and TLE.[6] In addition, atypical morphologies of the collateral sulcus (CS) have been described in relation to anomalous hippocampal shape and positioning.[6,7]

Morphologic MRI studies of sulcal patterns using cortical surface rendering techniques have provided evidence for neurodevelopmental deviance in several neurologic disorders, including schizophrenia[8] and Williams syndrome.[9] In TLE, one previous study[10] categorized the CS into three types according to its relationship to the rhinal sulcus. In that 2D MRI study, which did not include healthy control subjects, no predominant sulcal pattern was found.

Although MRI offers an opportunity to complement labor-intensive postmortem studies of cortical anatomy, the complexity of the brain's convolution makes the visual identification of sulcal-gyral abnormalities difficult on orthogonal planes obtained in conventional MRI. To bypass this disadvantage, precise and robust computer-based sulcal identification techniques have been developed to allow sulcal pattern analysis and automatic labeling on the brain surface.[11]

In the present study, we sought to investigate the morphologic sulcal patterns of the medio-basal temporal lobe on MRI using an automated sulcal extraction method. We chose to study the collateral sulcus and the occipito-temporal sulci, which are the major landmarks separating the lateral and mesial temporal lobe. The collateral sulcus borders the entorhinal and perirhinal cortices,[12] which have a strong functional connection with the hippocampus[13] and are involved in the epileptogenic network in TLE.

METHODS

Subjects. We randomly selected 69 patients with unilateral medically intractable TLE (33 men; mean age = 32 ± 9 years, range = 16–49) and no mass lesion (obvious malformations of cortical development, tumor, or vascular malformations) on MRI from our database. The control group consisted of 51 healthy subjects (25 men; mean age = 32 ± 11 years, range = 20–56). Demographic and clinical data were obtained through interviews and hospital chart reviews. The Ethics Committee of the Montreal Neurological Institute and Hospital approved the study and written informed consent was obtained from all participants.

TLE diagnosis and lateralization of the seizure focus were determined by comprehensive evaluation, including detailed seizure history and semiology, neurologic examination, video-EEG telemetry, and neuropsychological evaluation in all patients. Based on these criteria, patients were divided into those with a left-sided (LTLE, n = 37) or a right-sided (RTLE, n = 32) seizure focus.

Forty-four patients were operated (44/69 = 64%). The mean postsurgical follow-up was 3.4 years (range: 1 to 6 years). Twenty-five patients underwent a selective amygdalo-hippocampectomy: 20 had an outcome of Engel class I,[14] 4 had a class II, and 1 a class III outcome. Qualitative pathologic examination of the resected tissue revealed hippocampal sclerosis in 19 patients and specimens were not sufficient for review in the other six. Nineteen patients had an amygdalo-hippocampectomy with temporal cortical resection: 13 became seizure free (Engel class I), 1 had class II, and 5 class III outcome. Qualitative histopathology showed hippocampal sclerosis in 12 patients, which was associated with neocortical dyslamination and columnar disorganization in 2, and gray matter gliosis in 2 others. Gliosis of the cortical gray matter was seen in 2 patients and heterotopic neurons in the temporal lobe white matter in another. Due to subpial aspiration, specimens were unsuitable for histopathology in 4 patients.

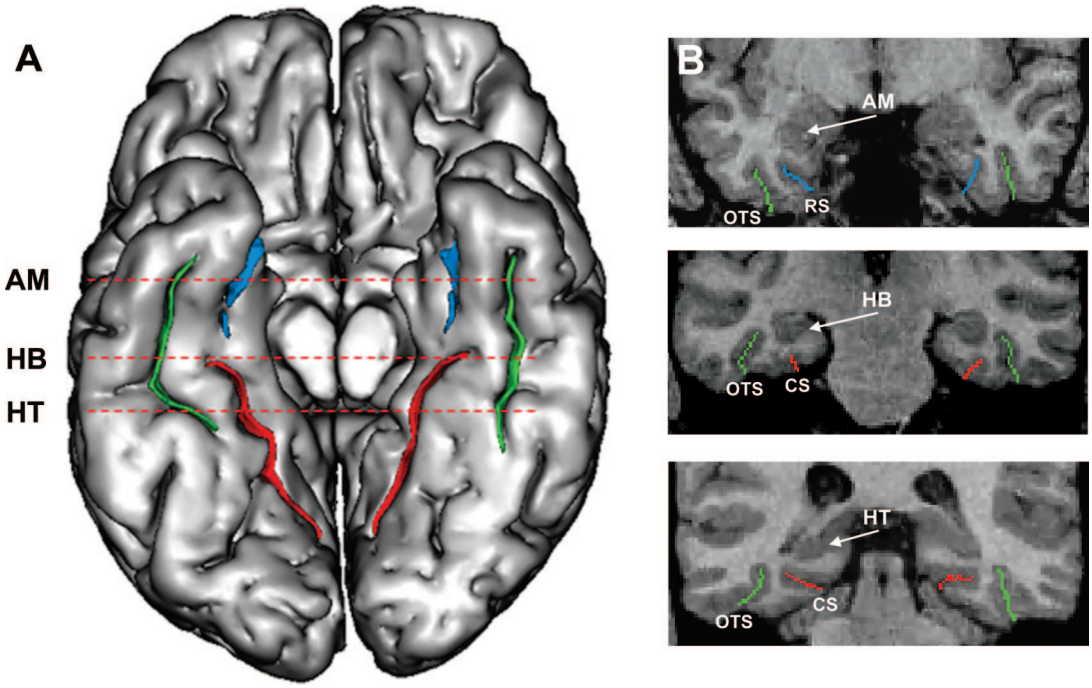
MRI acquisition and image preprocessing. In all subjects, images were acquired on a 1.5 T Gyroscan (Philips Medical System, Eindhoven, Netherlands) using a three-dimensional T1-fast field echo sequence (repetition time = 18, echo time = 10, 1 acquisition average pulse sequence, flip angle = 30°, matrix size = 256 × 256, field of view = 256, slice thickness = 1 mm). This high-resolution T1-weighted three-dimensional gradient-echo sequence provides exquisite anatomic details with an isotropic voxel size of 1 × 1 × 1 mm and features high signal-to-noise and contrast-to-noise.[15]

Each image underwent automated correction for intensity non-uniformity and intensity standardization. Images were then registered into a standardized stereotaxic coordinate space based on the Talairach atlas[16] to adjust for differences in total brain volume and brain orientation and to facilitate the identification of boundaries by minimizing variability in slice orientation.[17] This procedure uses an automatic, multiscale feature-matching algorithm[17] that performs a 9-parameter linear transformation to match each brain to a template brain.

Automatic sulcal extraction and labeling. ***Generation of brain surfaces and sulcal models.*** For sulcal extraction, images were processed using BrainVISA, a brain image analysis software that allows the user to reconstruct the surfaces corresponding to GM-WM and GM-CSF interfaces and to extract the brain sulci.[11] To compute accurate cortical surfaces and brain sulcal folds, image processing includes the following steps: 1) brain segmentation; 2) classification of WM, GM, and CSF generating separate maps in each hemisphere; 3) reconstruction of the surfaces corresponding to the GM-WM and GM-CSF interface using the above classification maps; 4) extraction of the sulcal folds by segmenting the skeletonized GM/CSF interface into simple surfaces.

Sulcal labeling. After extraction, sulci are automatically labeled using a congregation of neural networks trained on a manually identified database of sulci.[11] Recognition of structures is achieved by maximizing similarity of sulci features and sulci relations.

Figure 1 Three-dimensional surface rendering (A) and coronal MRI slices of the basal temporal lobe (B) showing the collateral sulcus (CS, red), rhinal sulcus (RS, blue), and occipitotemporal sulcus (OTS, green)



AM = amygdala; HH = hippocampal head; HB = hippocampal body; HT = hippocampal tail.

Categorization of sulcal patterns of the basal temporal lobe. The ventral and medial surfaces of the temporal lobe are organized into strips by two prominent rostrocaudally oriented sulci. The more lateral of the two is the occipitotemporal sulcus (OTS), which is often broken forming small, transverse gyri. The more medial is the collateral sulcus (CS) and marks the border between the parahippocampal gyrus and the occipitotemporal (i.e., fusiform) gyrus. The CS may be continuous rostrally with the rhinal sulcus (RS).[18] Figure 1shows the various sulci on orthogonal MRI slices and a three-dimensional MRI surface rendering.

The normal sulcal anatomy of the inferior surface of the temporal lobe includes four main patterns based on the relationship between the CS and neighboring sulci, i.e., the RS and OTS.[19] We used these four pattern classes to describe the sulcal arrangement in each subject as shown in figure 2:

- Type 1: single-branch, unbroken CS connected with the RS anteriorly
- Type 2: CS connected with the OTS, but separated from the RS
- Type 3: CS separated from the OTS and RS, which are connected
- Type 4: CS, OTS, and RS separated

MR images were numerically coded and presented in random order on a console independently to the observers unaware of the clinical information. The left and right hemispheres were analyzed separately.

MRI volumetry. Volumetric analysis of the hippocampus was performed manually according to our previously published protocol.[1] Based on a 2 SD cutoff from the mean of healthy controls, 36/69 (52%) patients with TLE had hippocampal atrophy and 33/69 (48%) normal hippocampal volumes.

Statistical analysis. We evaluated associations between CS branch types in each hemispheres and groups (healthy controls and patients with TLE), gender, side of seizure focus, and history of febrile seizures using χ^2 test for categorical data analysis. Associations between CS branching types and hippocampal volume were also analyzed in the same way.

Two raters (H.K. and B.B.) analyzed 35 randomly selected subjects (i.e., 70 hemispheres), including patients of all categories and healthy controls. We assessed the chance-corrected inter-rater agreement between the two observers by computing Cohen's Kappa.

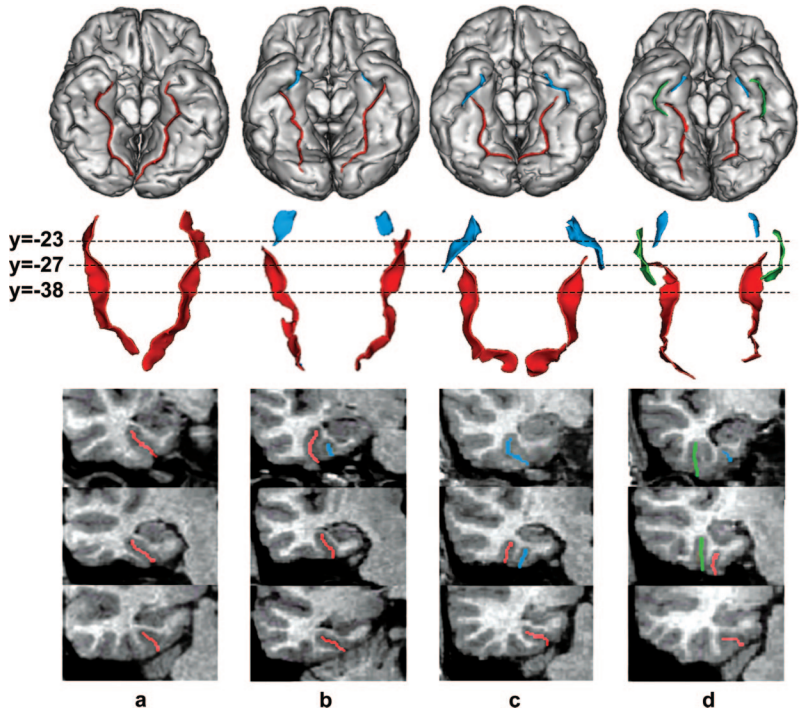
Table Frequencies of sulcal pattern types in the basal temporal lobe in healthy controls and patients with temporal lobe epilepsy (TLE)

	Healthy controls (n = 51)		Patients with TLE (n = 69)	
Sulcal pattern	Left	Right	Left	Right
Type 1: CS connected with the RS	47% (24/51)	41% (21/51)	77%* (53/69)	72%* (50/69)
Type 2: CS connected with the OTS, but separated from the RS	31% (16/51)	35% (18/51)	4%† (3/69)	4%† (3/69)
Type 3: CS separated from the OTS and RS, which are connected	6% (3/51)	4% (2/51)	9% (6/69)	12% (8/69)
Type 4: CS, OTS, and RS separated	16% (8/51)	20% (10/51)	10% (7/69)	12% (8/69)

*$p < 0.005$; †$p < 0.00005$.
CS = collateral sulcus; OTS = occipitotemporal sulcus; RS = rhinal sulcus.

RESULTS The two raters differed only in 3 of the 70 possible ratings. We obtained a chance-

Figure 2 Sulcal pattern classes



Upper panels: basal view of the three-dimensional MRI rendering with sulci mapped on the cortical surface. Middle panels: extracted sulci, i.e., collateral sulcus (CS, red), rhinal sulcus (RS, blue), and occipitotemporal sulcus (OTS, green). Lower panels: three coronal MRI slices with sulci marked at the level of hippocampal head, body, and tail at the level indicated by the Talairach coordinates in coronal plane (y) on the middle panels (dashed line). Sulcal pattern classes: (A) Type 1: one-branch CS connected with RS; (B) Type 2: two-branch CS connected with OTS in its posterior portion; (C) Type 3: two-branch CS having connection between RS and OTS in its anterior portion; (D) Type 4: three-branch CS with no connection between the sulci.

corrected Cohen's $\kappa = 0.84$, which represents excellent agreement.

Frequencies of the various sulcal pattern types in controls and patients with TLE are presented in the table. In healthy controls, Type 1 and Type 2 were the patterns seen most frequently. Overall, 82% (42/51) of subjects had the same sulcal pattern in both temporal lobes. There was no association between any sulcal pattern type and gender.

Compared to controls, in patients with TLE we found the following: 1) an increased frequency in pattern Type 1 (single-branch, unbroken CS connected with the RS) in the left (77% vs 47%; $\chi^2 = 8.2$, $df = 1$, $p = 0.004$) and right hemisphere (72% vs 41%; $\chi^2 = 9.2$, $df = 1$, $p = 0.002$); 2) a decreased frequency of sulcal pattern Type 2 (CS connected with the OTS, but separated from the RS) in the left (4% vs 31%; $\chi^2 = 17.0$, $df = 1$, $p = 0.00002$) and the right hemisphere (4% vs 35%; $\chi^2 = 19.1$, $df = 1$, $p < 0.00001$). There was no group difference in the frequency of Type 3 and 4 sulcal patterns. A total of 77% (53/69) of patients had the same sulcal pattern in both temporal lobes. In relation to gender, sulcal pattern Type 1 was more frequently associated with men than women (58/66 = 88% vs 45/72 = 63%, $p = 0.001$) and Type 4 with women than men (14/72 = 19% vs 4/66 = 6%, $p = 0.03$). There was no relationship between sulcal patterns and seizure focus lateralization, or any associations between CS sulcal patterns and hippocampal volume. Likewise, we found no association between sulcal patterns and history of febrile seizures.

DISCUSSION Studying the morphologic patterns of the inferior surface of the temporal lobe in healthy controls and patients with TLE, we found that more than 70% of patients with TLE exhibit a single-branch, unbroken CS connected with the RS. On the other hand, more than half of the controls presented with patterns displaying a lack of continuity between these two sulci. In particular, a Type 2 CS connected with the OTS, but separated from the RS, was more common in healthy controls than in patients. Cortical complexity can be described by the spatial frequency of fissuration.[20] When this criterion is applied to compare sulcal patterns among our subjects, Type 1 CS appears as "simplified," since its relationship with the surrounding sulci produces a low degree of complex arrangement (figure 1).

During the initial phase of brain development, the surface of the hemispheres is smooth. Most sulci and gyri develop during the third trimester, and the primary and secondary fissures are visible at birth.[19,21] Typically, the major sulci continue to develop after birth[22] and during early childhood the degree of gyrification stabilizes.[23] Sulcal patterns are an effect of the expansion of cortical gray matter and the development of interconnecting circuits. Mechanisms leading to cortical folding involve mechanical forces resulting from different tension of growth between early cortical strata,[24] tension along axons between interactive cortical areas,[25] and changes in subcortical connectivity patterns.[26] A variety of non-genetic factors, including intrauterine environment,[27,28] modulate hemispheric sulcal morphology, while data from morphologic analysis of individual sulci suggest genetic encoding.[29] The CS is among the deep sulci that appear early during human gestation, around the 23rd week of gestation.[21]

In non-diseased brains, postmortem studies have reported variable folding patterns in the inferior surface of the temporal lobe. A study of 25 brains[19] described CS categories based on its connection patterns to the neighboring sulci and found that the CS was connected with the RS in 26% of the specimens. In another observation,[30]

only one out of the five brains examined presented with an unbroken long collateral sulcus extending into the uncal region. The limited number of brain specimens included in these studies could explain the relatively low percentages compared to our results. To our knowledge, CS has been previously studied in healthy subjects only once using in vivo high-resolution MRI.[31] Our findings are in agreement with this study that used a similar number of subjects and showed an unbroken single-branch CS connected with the RS in about 45% of individuals. This study also reported comparable proportions of Type 2 and Type 3 CS in about 35%, and Type 4 in 20% of subjects.

Type 1 single-branch, unbroken long CS connected with the RS was present in more than 70% of our patients with TLE, while Type 2 (i.e., CS connected with the OTS, but separated from the RS) was found in only 4% of them. Sulcal anatomy of the basal temporal lobe in TLE has been assessed only in one previous study[10] in which a CS Type 1 was seen in 33% of the patients. This low incidence is most likely explained by the use of coronal, low-resolution MRI, potentially leading to incorrect determination of sulcal depth, connective patterns, and interruptions. Our high-resolution MRI protocol with 1 mm isotropic voxels and no interslice gap allowed for an improved in vivo identification of sulcal patterns. Furthermore, the combination with advanced image processing enabled us not only to inspect brain surfaces in a similar way as in postmortem studies, but also to evaluate the morphology by means of three-dimensional sulcal models. Importantly, the comparison with healthy controls allowed us to establish that Type 1 CS is the predominant sulcal pattern in TLE. In our patients, we did not find any association with sulcal patterns and the side of the seizure focus, indicating that the location of the epileptogenic focus and morphologic changes may not necessarily overlap.

Other brain pathologies unrelated to epilepsy have been associated with particular constellations of sulcal morphology. Atypical configurations of the diagonal sulcus, a secondary sulcus bifurcating the pars opercularis of Broca area in two segments, have been seen more often in adults with persistent developmental stuttering than in healthy controls, suggesting that this sulcal morphology may be adequate to support the development of language, but may put individuals at risk for developmental stuttering.[32] Sylvian fissure variants have been found more frequently in the right hemisphere of patients with Williams syndrome than in controls.[33] Reduced frequency of the paracingulate sulcus has been reported in schizophrenia.[34] Generally, sulcal variants in these conditions have been considered to be indicators of neurodevelopmental deviance.

Perturbation in connections may alter the mechanical tension that has been hypothesized as required for normal development of cortical folding.[25] Experimental data indicate that early disruption in connectivity can lead to the emergence of anomalous sulcal patterns.[26] Altered sulcal patterns in epilepsy are usually found in patients with malformations of cortical development. In the absence of an obvious malformation, unusual sulcal patterns are thought to be a marker of subtle cortical dysgenesis.[35] Some patients with refractory TLE and hippocampal sclerosis also have radiologically detected dysplastic abnormalities[36] and are regarded as examples of dual pathology. However, even when MRI reveals no evidence of an evident malformation, histopathology may show microscopic dysplasia in the neocortical tissue of about 40% of patients with TLE with hippocampal sclerosis.[37] These mild structural abnormalities reflect a spectrum of developmental changes, typically involving the architectonic cortical organization, such as laminar disarray, abnormal neuronal aggregates, dysmorphic neurons, and neuronal glial clustering, and are not related to febrile seizures.[38] Therefore, our findings give rise to the question as to whether in TLE the "simplified" Type 1 CS may be the marker of a subtle developmental structural abnormality of the temporal lobe.[5,7]

Although a given sulco-gyral pattern may be more prevalent in patients than in healthy individuals, its impact in epilepsy is not yet determined. In TLE, several authors have suggested that a pre-existing abnormality constitutes a susceptibility factor predisposing the temporal lobe to insults, thereby triggering the epileptogenic process. Developmental dysplastic lesions have been proposed as candidates, because these malformations are clearly present before the onset of epilepsy.[39] We previously demonstrated that shape variants of the hippocampal formation are found more frequently in patients with obvious cortical malformations and in TLE with hippocampal sclerosis than in healthy controls. We postulated that in TLE these changes may be indicators of a disorder of brain development and may promote epileptogenesis. Similarly, a single-branch, unbroken CS may leave the temporal lobe of some patients with TLE more vulnerable to

precipitating injuries occurring as early as the third trimester of gestation. An early nature of these events in our patients is supported by our results showing the lack of relationship between sulcal morphology and history of febrile seizures.

The predominant "simplified" Type 1 CS found in TLE may be the result of various overlapping mechanisms including incomplete maturation and variations in the underlying, possibly disturbed neuronal connectivity in areas adjacent to the CS known to be involved in the epileptogenic network in TLE, namely the entorhinal and perirhinal cortices.[1,40] Future studies are needed to determine the relationship between MRI and histologic findings in order to clarify the spectrum of developmental abnormalities and their significance in the genesis of seizures in TLE.

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