Temporal Lobe Epilepsy: Differential Pattern of Damage in Temporopolar Cortex and White Matter

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Abstract: Our purpose was to quantify structural changes of the temporopolar cortex (TPC) and its white matter (TPWM) in temporal lobe epilepsy (TLE) using MRI volumetry and texture analysis. We studied 23 patients with hippocampal atrophy, and 20 healthy controls. Gradient magnitude and entropy were calculated to model signal intensity blurring on T1-MRI. Two observers assessed signal changes and atrophy visually. Compared to controls, TLE patients had a decrease in TPC and TPWM volume ipsilateral to the seizure focus. The gradient magnitude and entropy were decreased ipsilateral to the focus only in TPWM, indicating blurring of this compartment. Eighty-seven percent of TLE patients had at least one volumetric or textural abnormality. Although sensitivity of visual and quantitative assessment of TPC atrophy was comparable (43 and 39%), specificity was higher for volumetry (54% vs. 95%). Compared to visual analysis of signal changes in TPWM on T1-MRI, texture metrics had higher sensitivity (65% vs. 17%) and specificity (100% vs. 69%). The proportion of patients with blurring of TPWM as determined by texture analysis was higher than that seen on visual inspection of T2 images (78% vs. 43%). We found no clear association between volumetric or textural changes of TPC and TPWM and outcome after surgery. Structural changes of the anatomically distinct TPC and TPWM are found ipsilateral to the seizure focus in the majority of TLE patients with hippocampal sclerosis. MRI post-processing allows dissociating different pathological tissue characteristics and shows that atrophy involves gray and white matter, whereas blurring is confined to white matter. *Hum Brain Mapp* 29:931–944, 2008. © 2007 Wiley-Liss, Inc.

Key words: temporal lobe epilepsy; temporopolar cortex; volumetric MRI; texture analysis

INTRODUCTION

Contract grant sponsor: Canadian Institutes of Health Research (CIHR); Contract grant number: 203707.

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Received for publication 8 August 2006; Revised 17 April 2007; Accepted 15 May 2007

DOI: 10.1002/hbm.20437

Published online 17 July 2007 in Wiley InterScience (www.interscience.wiley.com).

Temporal lobe epilepsy (TLE) is the most common medically intractable partial epilepsy in adults. Hippocampal sclerosis is found in about 70% of TLE patients [Babb and Brown, 1987; Wolf et al., 1993] and its presence is predictive of a favorable seizure outcome after surgery [Arruda et al., 1996; Jutila et al., 2002; Salanova et al., 1998]. Mesial TLE is typically associated with predominantly unilateral anterior and infero-medial temporal epileptic abnormalities on scalp EEG and hippocampal

atrophy on MRI [Engel et al., 1997; Jackson et al., 2005; Wieser et al., 1993].

In earlier studies, most attention has been dedicated to the hippocampus, which plays a pivotal role in the genesis of epileptic phenomena. However, recent observations in animal models of TLE indicate that the epileptogenic zone is broad and suggest that the substrate for seizure generation is distributed over several limbic structures [Benini et al., 2003; Bertram, 1997; D'Antuono et al., 2002; de Guzman et al., 2004; Kobayashi et al., 2003]. MRI studies have confirmed that pathology in TLE extends to extra-hippocampal mesial limbic structures such as the entorhinal cortex [Bernasconi et al., 1999, 2001b, 2003, 2004; Jutila et al., 2001] as well as extra-temporal areas [Bernasconi et al., 2004; Lee et al., 1998; McMillan et al., 2004; Natsume et al., 2003; Seidenberg et al., 2005]. MRI morphometry has also shown evidence for reduction in the temporal neocortical gray matter (GM) and white matter (WM) volumes [Coste et al., 2002; Jutila et al., 2001; Lee et al., 1998; Moran et al., 2001]. These findings suggest that the evaluation of the hippocampus in isolation may be insufficient to understand the epileptogenic process in TLE.

Several studies have clearly highlighted the occurrence of histological [Bothwell et al., 2001; Choi et al., 1999; Meiners et al., 1999; Mitchell et al., 1999], morphological [Jutila et al., 2001; Moran et al., 2001], and metabolic [Rubin et al., 1995; Ryvlin et al., 1998; Semah et al., 1995] changes in the anterior part of the temporal lobe in TLE. Electrophysiological [Chabardes et al., 2005] and perfusion studies using single photon emission computed tomography [Weder et al., 2006] have demonstrated the early involvement of the temporal pole in the genesis of seizures. There have been also observations of MRI signal changes, most notably an increase in T2-weighted signal intensity in the WM of the anterior temporal lobe, which is sometimes associated with hypointense signal on T1-weighted images [Mitchell et al., 1999]. These abnormalities have been referred to as WM blurring and loss of the GM-WM demarcation, respectively [Meiners et al., 1994, 1999; Mitchell et al., 1999; Ryvlin et al., 1991].

The terms "temporal pole" and "anterior temporal region" have been used interchangeably in the literature. This convention is imprecise because the temporal pole, a paralimbic area, is actually a distinct anatomical region of the temporal lobe [Chabardes et al., 2002]. Covering the rostral tip of the temporal lobe like a cap, the temporal pole is extensively interconnected to major limbic and paralimbic areas, including the amygdala, the hippocampus, the temporal neocortex, the entorhinal cortex, the orbitofrontal region, the insula, and the thalamus [Gloor, 1997; Moran et al., 1987]. The GM of the anatomic temporal pole, known as the temporopolar cortex (TPC), roughly corresponds to Brodmann's area 38 [Brodmann, 1925] or to the area TG of Von Bonin and Bailey [Von Bonin and Bailey, 1947]. This cortex is made up of dysgranular, para-limbic association cortex (mesocortex), which

serves as a cytoarchitectonic transition between agranular olfactory allocortex and granular isocortex [Braak, 1978]. Temporopolar abnormalities reported in the majority of MRI studies in TLE usually describe signal changes observed in the anterior part of the temporal lobe, rather than changes corresponding to the precise anatomical temporal pole. This may be related to the inherent complexity of the convolutional pattern of the temporal pole and its small volume relative to the rest of the brain, making signal abnormalities in this region more difficult to identify visually.

Quantitative MR image-analysis techniques provide metrics for the assessment of structural integrity of the human brain. Manual segmentation, the gold standard for the MR-based assessment of brain atrophy, has demonstrated evidence for volume losses in the mesial temporal lobe structures of patients with TLE [Bernasconi et al., 2003; Cascino et al., 1991; Cook et al., 1992; Jack et al., 1990b]. The overall purpose of novel, automated post-acquisition processing methods is to generate data that are rater-independent and to improve detection of abnormal brain tissue, including changes that may not be readily recognizable by visual analysis alone. Among them, computer-based texture analysis of digital images provides quantitative information about spatial grey level intensities distributions in pixel neighborhoods resulting in numerical feature descriptors [Haralick et al., 1973; Lerski et al., 1993; Mathias et al., 1999; Schad et al., 1993]. First-order texture methods measure intensity-based properties of an image, such as mean intensity, variance, or gradient. These types of properties can generally be appreciated through visual analysis. Second-order texture methods analyze the spatial distribution of intensity patterns that are not easily perceived through visual inspection by means of a gray-level co-occurrence method [Haralick et al., 1973]. In medical imaging, texture analysis has been shown to increase the level of diagnostic information extracted from many modalities such as MRI and ultrasound [Garra et al., 1993; Lerski et al., 1993]. The usefulness of applying texture analysis to brain MRI arises from an intuitive parallel between changes in spatial distributions of gray level intensity patterns and abnormal tissue organization [Lerski et al., 1993; Schad et al., 1993]. Indeed, this technique has been proven to be efficient in identifying subtle brain pathology in Alzheimer's disease [Freeborough and Fox, 1998] and multiple sclerosis [Mathias et al., 1999]. We previously developed image-processing operators based on texture analysis and demonstrated that these computational models surpass visual inspection in identifying subtle abnormalities of cortical development [Antel et al., 2002, 2003; Bernasconi et al., 2001a; Colliot et al., 2006a,b,c].

The purpose of this study was to quantitatively characterize, in vivo, structural changes of the TPC and its underlying white matter (TPWM) in patients with intractable TLE by using MRI volumetry and MRI texture analysis.

METHODS

Subjects

We studied 23 consecutive patients (11 males; mean age 31 ± 11 years) referred to our hospital for the investigation of medically intractable TLE over a period of 6 months and 20 healthy subjects (7 males; mean age 27 ± 7 years). All patients had unilateral hippocampal atrophy as measured on volumetric MRI [Bernasconi et al., 2003]. Demographic and clinical data were obtained through interviews and hospital chart reviews. The Ethics Board 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, neurological examination, video-EEG telemetry, and neuropsychological evaluation in all patients. Based on these criteria, patients were divided into those with a left-sided (LTLE, $n = 11$) or a right-sided (RTLE, $n = 12$) seizure focus.

Twenty patients were operated by two neurosurgeons. The two distinct surgical approaches, i.e. selective amygdalo-hippocampectomy (SAH) and amygdalo-hippocampectomy with temporal cortical resection (CAH), depended uniquely on the surgeon's preference and not on differences on clinical characteristics. The mean post-surgical follow-up was 3.4 years (range: 1–8 years). Sixteen patients underwent a SAH: 9 had an outcome of Engel class I [Engel et al., 1993], 5 had a class II outcome, and 2 a class III outcome. Qualitative pathologic examination [Meencke and Veith, 1991] of the resected tissue revealed hippocampal sclerosis in 13 patients and specimens were not sufficient for review in the other three. Four patients had an amygdalo-hippocampectomy with temporal cortical resection (CAH) and became seizure free (Engel class I). Qualitative histopathology showed hippocampal sclerosis in three, which was associated with architectural abnormalities with cortical dyslamination and columnar disorganization of the temporal lobe GM in one, and GM gliosis in another. Due to subpial aspiration, specimens were unsuitable for histopathology of the hippocampus in one patient and of the temporal neocortex in two patients.

MRI Acquisition

In all subjects, MR volumetric images were acquired on a 1.5 T Gyroscan (Philips Medical System, Best, The Netherlands) using a T1-fast field echo sequence (TR = 18, TE = 10, 1 acquisition average pulse sequence, flip angle = 30° , matrix size = 256×256 , FOV = 256, thickness = 1 mm). This high-resolution T1-weighted 3D gradient-echo sequence provides exquisite anatomic details with an isotropic voxel size of $1 \times 1 \times 1 \text{ mm}^3$ and features high signal-to-noise and contrast-to-noise [Antel et al., 2002].

As part of our clinical protocol, coronal and axial proton-density and T2-weighted images (thickness 3.0–5.0 mm, gap 0.3 mm, TR 2100 ms, TE 20, 78 ms), coronal fluid attenuation inversion recovery images (FLAIR, slice thickness 3.0 mm, inter-slice gap 0.3 mm, TR 6,000 ms, TE 150 ms, TI 1,900 ms, FOV 230 mm) were obtained in all patients.

Image Analysis

MRI volumetry

T1-weighted MRIs were registered into a standardized stereotaxic coordinate space based on the Talairach atlas [Talairach and Tournoux, 1988] to adjust for differences in total brain volume and brain orientation and to facilitate the identification of boundaries by minimizing variability in slice orientation [Collins et al., 1994]. This procedure uses an automatic, multiscale feature-matching algorithm [Collins et al., 1994] that performs a nine-parameter linear transformation to match each brain to a template brain. The reference image used for the linear registration was the ICBM 152 T1-weighted target, a voxel-by-voxel average of the 152 normal subjects previously registered in the Talairach-like stereotaxic space [Mazziotta et al., 1995]. The resampling procedure was performed using a trilinear interpolation. Each image underwent automated correction for intensity nonuniformity and intensity standardization [Sled et al., 1998]. This correction produces consistent relative GM, WM, and cerebrospinal fluid intensities. Volumetric analysis was performed using an interactive software package *Display* developed at the Brain Imaging Center of the Montreal Neurological Institute. This program allows simultaneous viewing of MR images in coronal, sagittal, and horizontal orientations. It is to note that the ICBM 152 brain template is 30–35% bigger in volume than an average brain. Therefore, normalized average volumes in the ICBM 152 are ~30–35% larger than the native absolute values.

Volumetric analysis of the TPC and TPW was performed manually based on the anatomical boundaries published by Insausti et al. [1998] with minor modifications. The rostral border of the TPC (Fig. 1A) was the rostralmost coronal section in which the cortex of the temporal lobe became visible (i.e., the temporal tip). The entire rostral extent of the temporal lobe neocortex anterior to the first appearance of the superior temporal sulcus (STS) on the ventrolateral surface of the temporal lobe was assigned to the TPC. In some cases, the inferior temporal sulcus (ITS) appeared more anteriorly than the STS; in these cases the entire temporal lobe cortex rostral to the ITS belonged to the TPC. In agreement with Insausti et al. [1998] in virtually all cases we found that the STS or ITS appeared between six and eight slices from the temporal tip. The rostralmost 6–8 mm of the temporal lobe was therefore almost invariably comprised of cortex belonging only to the TPC. Owing to the variability in the location of the STS

Figure 1.

Anatomical boundaries of the temporopolar cortex (TPC) on coronal MRI in a healthy control subject. **A:** The rostral boundary of the TPC is the rostralmost coronal section in which the cortex of the temporal lobe becomes visible. **B:** The dorsolateral border is the lateral bank of the temporopolar sulcus (TPS), whereas the ventrolateral border is a line drawn perpendicularly downward from the medial tip of the temporopolar white mat-

ter (block arrow). **C:** MRI coronal slice at the same level than panel B showing the temporopolar white matter (TPWM) that occupies the white matter of the temporal lobe underlying the TPC. **D:** The caudal border of the TPC is considered to be the coronal slice immediately anterior to the slice where the collateral sulcus (CS) first appears. On panels B and C, ITS = inferior temporal sulcus.

and ITS along the ventral aspect of the temporal lobe, we chose to define the ventrolateral border of the TPC by a vertical line drawn from the medial tip of the temporal lobe WM to the inferior edge of the temporal cortex (Fig. 1B). Establishing the exact position of the STS or ITS was not crucial in our protocol. Instead, knowing the first coronal slice on which either the STS or ITS appear was the only key consideration. Admittedly, this meant that in each case we may have neglected a very small portion of the ventrolateral temporal lobe, which probably belongs to the TPC. The dorsolateral border of the TPC was considered to be the lateral bank of the most lateral temporopolar sulcus, once it appeared on coronal section (Fig. 1B). If the temporopolar sulcus was not present, then the dorsolateral border was the dorsal midpoint between the medial and lateral edges of the temporal lobe. The caudal border of the TPC was considered to be the coronal slice immediately anterior to the slice where the collateral sulcus first appeared (Fig. 1D).

The TPWM was defined on each coronal slice as the WM located medial to a line drawn diagonally from the superolateral edge of the TPC to the apex of STS or ITS, whichever indented the ventrolateral surface of the temporal lobe (Fig. 1C). On those coronal slices where all the temporal GM belonged to the TPC, all accompanying WM

was assigned to the TPWM. Axial, sagittal, and 3D views of the segmented TPWM confirmed that our protocol appropriately excluded WM, which clearly belonged to either the superior temporal gyrus or other convolutions of the temporal lobe. Furthermore, to ensure that individual voxels were included in either the TPC or the TPWM, but not both structures, the TPC was segmented first in each case and its boundaries were displayed on-screen when the TPWM was being segmented.

A 3D rendering of the T1-weighted MRI with superimposed label of the TPC in a healthy subject is presented in Figure 2.

MRI texture

In TLE, temporopolar signal abnormalities are characterized visually by an increase in T2 and decrease in T1-weighted signal, giving a “dirty” and blurred aspect to this region. Based on our previous experience, we used features that are intuitively the closest to a biological meaningful representation of blurring, thus facilitating the interpretation of the results.

We calculated two texture features on high-resolution 3D T1-weighted MRI: gradient magnitude, a first-order texture feature measuring the rate of change in gray level inten-

Figure 2.

Three-dimensional rendering of the T1-weighted MRI with superimposed label of the temporopolar cortex (TPC, in red) in a healthy subject. A mesio-basal (left) and a fronto-lateral (right) view are presented. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

sities, and entropy, a second-order texture feature measuring their randomness [Haralick et al., 1973]. We previously demonstrated that these two features are efficient in modeling blurring in focal cortical dysplasia [Antel et al., 2003; Bernasconi et al., 2001a; Colliot et al., 2006a]. These measures were performed in the volumetric labels of left and right TPC and TPWM obtained through the manual segmentation. The gradient magnitude was calculated at each voxel over a Gaussian kernel (FWHM = 3 mm). The mean gradient magnitude was then calculated over the entire label. Entropy was calculated over the label as the sum of $-g(x) \times \log(g(x))$ for each voxel x within the label, where $g(x)$ is the gray level intensity at voxel x . A blurred region would be expected to exhibit a decrease in gradient, as blurring tends to decrease the intensity difference between neighboring voxels. This trend of intensity homogenization also results in a less random intensity pattern, and thus a decrease in entropy.

MRI visual analysis

Raw T1- and T2-weighted images were numerically coded and presented in random order on a console independently to two trained observers unaware of the clinical information. To avoid a bias due to the presence of hippocampal atrophy, images were cropped so that only the temporal lobes anterior to the amygdalae were available for the visual inspection.

Analysis of signal changes. TPWM abnormalities were defined as an increase in signal intensity within the

TPWM on T2-weighted MRI and a decrease in signal intensity on T1-weighted MRI. In such case, the signal intensity approaches that of the neocortex resulting in poor demarcation between GM and WM [Ryvlin et al., 2002]. Signal intensity abnormalities were evaluated on coronal sections by comparing relative differences between the two temporal lobes. The rostralmost 6–8 mm of the temporal lobe comprises the cortex belonging only to the TPC and underlying TPWM. To be consistent in the evaluation of the T2-weighted abnormalities within TPWM, an abnormal signal was considered to be present if seen at least on two consecutive anteriormost T2-weighted coronal slices (3 mm thickness) and on six consecutive anteriormost T1-weighted coronal slices (1 mm thickness). In patients with TLE, signal changes were evaluated on both T1 and T2-weighted images. In instances when the two observers disagreed, a final consensus was obtained. Sensitivity and specificity were assessed in a separate analysis comprising all TLE patients and 13 randomly selected healthy controls by evaluating signal changes on T1-weighted MRI only, since T2-weighted images were not available in controls.

Analysis of atrophy. The presence of atrophy was assessed on spatially normalized T1-weighted MRI in controls and TLE patients by comparing relative size differences between the two temporal poles. TP atrophy was defined on coronal sections as an obvious standing back of at least 3 mm between the right and left temporal poles [Coste et al., 2002], a distance corresponding to the thickness of three consecutive coronal slices on T1-weighted MRI, or a persistent asymmetry.

Statistical analysis

To assess the performance of qualitative visual assessment of signal and atrophy, and quantitative volumetric and texture parameters, we calculated: sensitivity (the percentage of positives correctly identified = true positives/[true positives + false negatives]) and specificity (the percentage of negatives correctly identified = true negatives/[true negatives + false positives]).

For the visual evaluation of the TPWM abnormalities and TPC atrophy, inter-observer agreement was assessed using Cohen's kappa coefficient.

The assumption for normal distribution of the data was assessed using the Shapiro-Wilks test. A series of one-way analysis of variance (ANOVA) were used to examine the effect of seizure focus lateralization and hemisphere on the mean volumes of the TPC and TPWM, as well as texture features. All ANOVA tests were followed by Bonferroni planned comparisons. The degree of left-right asymmetry in volumes and texture values in patients with TLE was assessed by calculating an asymmetry ratio: asymmetry ratio (%) = $[100 \times (L - R)] / [(L + R)/2]$, where R is the volume or texture value of the right TPC or TPWM, and L represents the volume or texture value of the left TPC or TPWM. Asymmetry ratios were compared between groups using one-way ANOVA, followed by Bonferroni planned comparisons.

The volumes of the TPC and TPWM were obtained from segmentation performed by a single observer (T.S.) unaware of the identity of each subject. To assess intra-rater reliability, the same observer (T.S.) segmented the TPC and TPWM in seven individuals, 6 months apart. Inter-rater reliability was assessed by segmentation of five individuals by two observers (N.B. and T.S.) blinded to each other's segmentation. Intra-rater and inter-rater variability were calculated using the absolute value of the difference between two measures divided by the first expressed as a percentage ($100 \times |x - y|/x$). Intra- and inter-rater agreements were also assessed using a similarity index S as proposed by Dice [1945], which was shown to be a special case of the kappa statistic [Zijdenbos and Dawant, 1994]. It is calculated as twice the intersection of two volumes ($M1$ and $M2$), divided by their sum:

$$S = 2|M1 \cap M2| / (|M1| + |M2|). \quad (1)$$

Kappa ranges from 0 to 1, where 0 indicates agreement equal to pure chance, and 1 indicates perfect agreement. In general, a kappa value of 0.7 or higher is considered excellent agreement [Bartko, 1991].

Each individual's measurements (volume and texture) were standardized relative to the value of healthy controls using a z-score transformation. For any individual, a z-score of -1.0 on any measure indicates a raw value that is one SD below the mean of healthy controls on that measure. For analysis of individual patients, we considered as

abnormal values that were 2 SD below the mean of healthy controls.

Association between type of surgery, surgical outcome, and MR data was evaluated using Fisher's exact test.

RESULTS

Reliability Tests

Intra-rater variability for the TPC volume was $3.9\% \pm 2.9\%$ and $6.4\% \pm 4.6\%$ for the TPWM volume. The mean similarity index for TPC volume was 0.91 ± 0.05 and 0.87 ± 0.07 for TPWM volume. Inter-rater variability for the TPC volume was $5.0\% \pm 3.2\%$ and $7.7\% \pm 7.5\%$ for the TPWM volume. The mean similarity index for TPC volume was 0.89 ± 0.07 and 0.89 ± 0.08 for TPWM volume.

Group Analysis

Volumetric MRI

The mean volumes $\pm$ SD, and asymmetry ratios of the TPC and TPWM in healthy controls and patients are given below and summarized in Table I. In controls, the mean volume of the right TPC was larger than that of the left ($3,585 \pm 493 \text{ mm}^3$ vs. $3,223 \pm 452 \text{ mm}^3$, $P < 0.003$). There was no difference in volume between the left and right TPWM ($1,176 \pm 264 \text{ mm}^3$ vs. $1,278 \pm 281 \text{ mm}^3$).

Compared to controls, in patients with right TLE, TPC and TPWM volumes were decreased ipsilateral to the seizure focus ($P < 0.004$; 16% difference for TPC and 28% for TPWM). In patients with left TLE there was a significant

TABLE I. Mean $\pm$ standard deviation (in mm^3) and asymmetry ratios (in %) of the temporopolar cortex (TPC) and temporopolar white matter (TPWM) normalized volumes in patients with temporal lobe epilepsy (TLE) and healthy controls

Volume	Healthy controls	Left TLE	Right TLE
TPC			
Left	$3,223 \pm 452$ (2,237–3,831)	$2,776 \pm 597^*$ (2,138–3,728)	$2,956 \pm 442$ (2,444–3,727)
Right	$3,585 \pm 493$ (2,858–4,739)	$3,458 \pm 307$ (2,978–3,887)	$2,996 \pm 567^{**}$ (2,217–3,959)
Asymmetry ratio	-10.7 ± 13.5	$-23.3 \pm 19.1^*$	-0.7 ± 18.7
TPWM			
Left	$1,176 \pm 264$ (698–1,671)	978 ± 254 (651–1,455)	$1,348 \pm 223$ (664–1,523)
Right	$1,278 \pm 281$ (2,237–3,831)	$1,057 \pm 292$ (1,049–1,682)	$918 \pm 271^{**}$ (587–1,444)
Asymmetry ratio	-8.7 ± 20	$-33.0 \pm 27.4^{**}$	$13.9 \pm 27^*$

The normalized average volumes in the ICBM 152 are ~ 30 – 35% larger than the native absolute values. The asymmetry ratios, however, are unaffected by these volume changes.

* $P < 0.05$ (uncorrected).

** $P < 0.004$ (corrected for multiple comparisons).

TABLE II. Mean gradient magnitude and entropy values (in arbitrary units $\pm$ standard deviation), the range (in brackets), and asymmetry ratios (in %) of the temporopolar cortex (TPC) and temporopolar white matter (TPWM) in patients with temporal lobe epilepsy (TLE) and healthy controls

Texture feature	Healthy controls	Left TLE	Right TLE
<i>Gradient</i>			
TPC			
Left	147.07 $\pm$ 19.72 (114.34–182.89)	149.37 $\pm$ 25.40 (112.26–188.56)	149.92 $\pm$ 21.09 (117.63–193.60)
Right	160.61 $\pm$ 21.24 (131.60–194.77)	152.30 $\pm$ 17.10 (115.12–171.88)	153.79 $\pm$ 27.02 (110.24–200.24)
Asymmetry	–11.2 $\pm$ 13.4	–2.6 $\pm$ 16.5	–6.1 $\pm$ 8.9
TPWM			
Left	88.41 $\pm$ 6.91 (80.50–98.57)	78.03 $\pm$ 10.24* (65.35–97.08)	84.67 $\pm$ 7.03 (72.47–100.00)
Right	90.01 $\pm$ 5.70 (80.52–97.55)	83.57 $\pm$ 10.61 (70.89–106.47)	71.67 $\pm$ 10.48** (54.09–85.86)
Asymmetry	–2.1 $\pm$ 4.6	–6.9 $\pm$ 13.9	17.9 $\pm$ 14.3**
<i>Entropy</i>			
TPC			
Left	9.08 $\pm$ 0.24 (8.57–9.43)	8.89 $\pm$ 0.36 (8.17–9.26)	8.97 $\pm$ 0.18 (8.68–9.32)
Right	9.12 $\pm$ 0.21 (8.76–9.52)	9.13 $\pm$ 0.23 (7.27–9.53)	9.04 $\pm$ 0.17 (8.74–9.37)
Asymmetry	–0.5 $\pm$ 2.3	–0.6 $\pm$ 4.6	–0.8 $\pm$ 1.1
TPWM			
Left	8.90 $\pm$ 0.20 (8.53–9.28)	8.56 $\pm$ 0.48 (7.44–9.06)	8.83 $\pm$ 0.21 (8.51–9.11)
Right	9.02 $\pm$ 0.18 (8.77–9.43)	9.02 $\pm$ 0.21 (7.81–9.30)	8.63 $\pm$ 0.25** (8.34–9.06)
Asymmetry	–1.2 $\pm$ 1.3	–3.9 $\pm$ 2.9**	2.3 $\pm$ 2.8**

* $P \leq 0.03$ (uncorrected).** $P \leq 0.006$ (corrected for multiple comparisons).

asymmetry in TPWM volume (left TPWM smaller than right TPWM, $P < 0.004$).

MRI texture analysis

The mean values and asymmetry ratios of gradient magnitude and intensity entropy of the TPC and TPWM in healthy controls and TLE patients are summarized in Table II. Compared to controls, in patients with right TLE, TPWM gradient ($P < 0.0001$; 20% difference) and entropy ($P < 0.0004$; 5% difference) were decreased ipsilateral to the seizure focus ($P < 0.006$; 20 and 5% difference, respectively) and there was a significant asymmetry ($P < 0.006$). In patients with left TLE, there was a significant asymmetry in TPWM entropy ($P < 0.006$).

No textural abnormalities were detected in the TPC. We calculated the effect size in order to define the sample size needed for a power of 0.8. The effect size was 0.4 for the TPC entropy and 0.2 for the TPC gradient. Given these small effect sizes and a power of 0.8, we would have required ~60 subjects in each group (controls and patients) to detect a significant difference in TPC entropy and 500 subjects for the TPC gradient.

TABLE III. Frequencies of MR changes related to surgical outcome

	Outcome			Outcome	
	I	II and III		I	II and III
SAH + vol	8/10	2/10	SAH + txt	9/13	4/13
SAH – vol	2/6	4/6	SAH – txt	0/3	3/3
CAH + vol	1/1	0/1	CAH + txt	3/3	0/3
CAH – vol	3/3	0/3	CAH – txt	1/1	0/1

CAH: amygdalo-hippocampectomy with temporal cortical resection; SAH: selective amygdalo-hippocampectomy; +/– vol: presence/absence of atrophy of the temporopolar cortex or white matter; +/– txt: presence/absence of textural abnormalities in the temporopolar white matter.

Relation of MR data to surgical outcome

Because there was no difference in the preoperative clinical characteristics, we combined the two surgical groups. We found no significant association between volumetric and textural changes, and seizure outcome (Table III). We also performed the analysis separately and found in patients with SAH a trend ($P < 0.06$) towards a favorable outcome in patients with textural abnormalities.

Individual Analysis

Sensitivity and specificity of visual and quantitative evaluation of the TPC and TPWM on T1-weighted MRI in healthy controls and TLE are given in Table IV.

Quantitative analysis

At least one volumetric or textural abnormality was found in 20/23 (87%) TLE patients. In all patients volumetric abnormalities were found ipsilateral to the seizure

TABLE IV. Sensitivity and specificity of visual and quantitative assessment of the temporopolar cortex (TPC) and temporopolar white matter (TPWM) on T1-weighted MRI

	Sensitivity (%)	Specificity (%)
Visual		
TPC atrophy	43	54
TPWM signal decrease	17	69
Volumetric MRI		
TPC atrophy	39	95
TPWM atrophy	43	90
Texture MRI		
Entropy-decrease		
TPC	13	90
TPWM	65	100
Gradient-decrease		
TPC	0	0
TPWM	61	100

focus. In nine patients (9/23 = 39%) there was a reduction in TPC volume and in 10/23 (43%) a reduction of the TPWM volume.

In 14/23 (61%) patients there was a reduction of the TPWM gradient: in 11 of them the reduction was ipsilateral to the focus, in two bilateral asymmetric (lower on the focus side), and in one bilateral symmetric. TPWM entropy was decreased in 15/23 (65%) patients: in 14 of them the decrease was ipsilateral to the seizure focus and in one bilateral asymmetric (lower on the focus side). Three patients (3/23 = 13%) had a reduction of the TPC entropy ipsilateral to the seizure focus.

Qualitative analysis

For visual analysis of signal abnormalities within the TPWM in TLE patients, inter-observer agreement was 0.83, indicating almost perfect agreement [Landis and Koch, 1977]. Ten patients (10/23 = 43%) had increased ipsilateral T2 signal in the TPWM, four of whom (4/23 = 17%) had concomitant decrease in T1-weighted signal.

All 10 patients with visual T2 signal increase in the TPWM had a decrease in entropy or gradient. The proportion of patients with textural abnormalities (either low entropy or low gradient) in the TPWM on T1-weighted MRI was higher than that of patients with T2 signal increase (18/23 = 78% vs. 10/23 = 43%, $P < 0.05$).

For visual analysis of TPC atrophy, we obtained a sensitivity of 43% and a specificity of 54% with a false positives rate of 46% (Table IV). Inter-rater agreement was 0.83, indicating almost perfect agreement between the two observers [Landis and Koch, 1977].

For visual analysis of TPWM T1-signal decrease, we obtained a sensitivity of 17% and a specificity of 69% with a false positives rate of 31% (Table IV). Inter-rater agreement was 0.22, indicating fair agreement between the two observers [Landis and Koch, 1977].

Figure 3 shows coronal T2-weighted MR images in a TLE patient demonstrating a clear increase in signal intensity in the TPWM. No obvious signal intensity changes or atrophy can be seen on T1-weighted images. However, texture analysis indicates the presence of blurring of the TPWM (TPWM entropy: -3.7 ; and TPWM gradient: -6.3 ; values are in z-scores) and volumetry TPC and TPWM atrophy ipsilateral to the seizure focus (TPC volume: -2.1 and TPWM: -2.3).

DISCUSSION

Our purpose was to evaluate quantitatively the structural integrity of the TPC, an anatomically and functionally distinct paralimbic area within the human temporal lobe, and its underlying WM in patients with pharmacologically intractable TLE. Volumetric MRI showed that both the TPC and TPWM were atrophic ipsilateral to the seizure focus. MRI texture analysis demonstrated a decrease in the

gradient magnitude and entropy of the TPWM ipsilateral to the seizure focus. Our results also showed that texture analysis of T1-weighted MRI was more sensitive than visual inspection of T2-weighted images in detecting blurring of the TPWM.

Temporopolar Cortex and White Matter Can Be Reliably Segmented on MRI

In healthy controls, the volume of the right TPC was significantly larger than that of the left. This finding supports the notion that there is a physiologic asymmetry between the right and left temporal lobes in healthy controls and is in agreement with previous studies reporting larger right anterior temporal region [Jack et al., 1989; Lee et al., 1998], hippocampus [Bernasconi et al., 2003; Cascino et al., 1991; Jack et al., 1990a; Pruessner et al., 2000], amygdala [Bernasconi et al., 2003; Filipek et al., 1994; Watson et al., 1992], entorhinal cortex [Bernasconi et al., 1999; Insausti et al., 1998], and perirhinal cortex [Bernasconi et al., 2003].

Our tests of overlap and reliability proved our measurements to be highly reproducible, with lower intra-rater variability than that reported previously by Insausti et al. [1998] (3.9% vs. 7.3%). However, a direct comparison is not possible because the authors did not report the formula used to calculate reliability and did not perform inter-rater variability assessment. Nevertheless, our good results are most probably due to the use of higher resolution isotropic MR images with a voxel size of 1 mm^3 allowing for accurate segmentation of relatively small structures [Bernasconi et al., 2003]. This can also explain the higher proportion of TLE patients with ipsilateral TPC atrophy in our study compared to those reported by the same group (39% vs. 22%) [Jutila et al., 2001]. Diversity in image processing methods, such as manual correction for total intracranial volume, may introduce variability among volumetric measurements obtained with different protocols. We registered automatically the MR images in a standard stereotaxic space before conducting volumetric analysis. This automatic procedure adjusts for differences in total brain volume and brain orientation, and facilitates the identification of boundaries by minimizing variability in slice orientation. Furthermore, it has been shown that the automatic stereotaxic transformation is as accurate as the manual procedure, but shows higher stability [Collins, 1994]. Moreover, using only a linear transformation, there is no modification of the relationship between different brain structures, and the ratio of volumes between brain structures remains the same.

Texture Analysis is More Sensitive Than Conventional MRI in Detecting Blurring of the TPWM

On MRI, temporopolar signal abnormalities in TLE are characterized visually by signal changes giving a "dirty"

Figure 3.

Coronal MR images across the temporal lobe in a TLE patient. Cranial to caudal slices are shown from left to right. **A:** T2-weighted images showing increase in signal intensity in the temporopolar white matter (TPWM) and its extent (arrows). **B:** T1-weighted images reformatted to be at the same level and orientation than T2-weighted images do not show obvious signal intensity changes. **C:** TPC (red) and TPWM (yellow) manual labels in the most ante-

rior slice are presented. Texture analysis of T1-weighted MR images indicated the presence of ipsilateral blurring of the TPWM and showed z-score values of -3.7 for the TPWM entropy and -6.3 for the TPWM gradient. Volumetry showed both TPC and TPWM atrophy ipsilateral to the seizure focus (TPC volume: -2.1 and TPWM TPWM: -2.3). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

and blurred aspect to the cortex and white matter. Similarly to our previous work aiming at modeling *in vivo* MRI blurring of focal cortical dysplasia [Antel et al., 2002; Bernasconi et al., 2001a; Colliot et al., 2006a], in the present study we chose texture features that were considered to be effective in modeling blurring (i.e., smooth variations of gray levels). Gradient, a first-order texture feature measuring the rate of change in gray-level intensities, was expected to quantify visually discernable information. On the other hand, entropy, a second-order texture feature that calculates gray-level intensities randomness by quantifying the spatial relationships of intensity pairs [Haralick et al., 1973], was used to assess subtle blurring not readily accessible by visual analysis.

Signal intensity abnormalities of the TPC and TPWM have not been quantitatively assessed previously. Based on

visual assessment of MRI, other groups have shown an increase in T2-weighted signal intensity in the anterior temporal lobe WM in 32–65% of TLE patients [Choi et al., 1999; Coste et al., 2002; Meiners et al., 1999; Mitchell et al., 1999]. Subjective factors, variations in the region of interest within the temporal lobe, and differences between TLE populations may account for the wide range of variability in these incidences. Our visual analysis revealed similar results to those reported by Ryvlin et al. [1991], with 43% of our TLE patients showing increased ipsilateral T2 signal in the TPWM, four of whom (17%) with concomitant decrease in T1-weighted signal. The aforementioned observations of T2-weighted signal blurring have been performed on sequences with a thickness of 3–5 mm making an accurate evaluation of small areas such as the TPC and TPWM difficult.

The proportion of patients with blurring of TPWM on T1-weighted MRI, as determined by texture analysis, was higher than that seen on visual inspection of T2-weighted images (78% vs. 43%) and higher than by visual inspection of T1-weighted images (65% vs. 17%). Interestingly, all patients who had visible T1- or T2-signal changes in the TPWM had a decrease in entropy or gradient. An advantage of texture analysis is that it operates in 3D. This allows the simultaneous consideration of information from consecutive slices of the brain, whereas a human observer performing standard visual analysis examines the brain volume a slice at a time, and therefore must synthesize information from consecutive slices.

Interpretation of Textural Abnormalities

Temporal lobe WM abnormalities in TLE have been known since early pathological studies examining surgical specimens [Falconer et al., 1964; Margerison and Corsellis, 1966]. Falconer et al. [1964] suggested that the sclerotic process affecting the mesial structures involves the temporal lobe widely, leading to a generalized atrophy and gliosis of both the cortex and the WM. However, recent studies have failed to show a consistent abnormality in the WM of the temporal lobe and have suggested a range of changes, including gliosis [Mitchell et al., 1999; Swartz et al., 1992], microdysgenesis [Hardiman et al., 1988; Kasper et al., 1999; Thom et al., 2001], demyelination [Meiners et al., 1999; Mitchell et al., 1999, 2003], and neuronal ectopia [Bothwell et al., 2001; Choi et al., 1999]. The origin of the anterior temporal WM signal changes seen on MRI remains also unclear. In general, however, histological and MRI studies are difficult to compare because of variations of the temporal lobe regions analyzed and the use of different techniques. This applies to both, comparisons between and across modalities. To the best of our knowledge, only one quantitative histopathological study examining specifically the TPC and the TPWM suggested an increased number and density of ectopic neurons in the TPWM [Bothwell et al., 2001]. Positron emission tomography (PET) studies with ^{18}F -fluorodeoxyglucose indicate that T2 signal changes in the temporal pole are associated with glucose hypometabolism in the neighboring neocortex [Chassoux, 2003; Choi et al., 1999; Ryvlin et al., 2002; Semah, 2002]. Partial volume effect-corrected PET with carbon-11-labeled-flumazenil (FMZ-PET), a marker for the functional integrity of the GABAergic inhibitory neurotransmitter system, is uniquely suited to the study of microdysgenesis in the WM due to its highly specific binding to neurons and the resulting high contrast-to-noise ratio. This elegant technique has shown that in the WM, ^{11}C -flumazenil binding is strongly related to the number of heterotopic neurons measured semiquantitatively *ex vivo* in resected specimens of patients who underwent anterior temporal lobe resection [Hammers

et al., 2001, 2002]. Therefore, it is conceivable that our models of blurring mirror increased neuronal heterotopia in this compartment.

Our results demonstrated that TPWM exhibit a decreased mean gradient, as blurring tends to decrease the intensity difference between neighboring voxels, and that this homogenization also results in a less complex intensity pattern [Haralick et al., 1973; Lerski et al., 1993], and thus a decrease in entropy. We previously reported decreased gradient and entropy within lesions of cortical dysplasia in relation to a smooth and homogeneous GM-WM transition, reflective of abnormal neuronal accumulation in this area. Histopathological and mathematical findings indicate that the pattern in texture feature values seen in malformative lesions and in TLE may reflect similar changes in image complexity suggestive of a breakdown of structural integrity due to the disease process. Likely pathological processes include gliosis and demyelination. Data from other studies suggest in fact that textural changes may be observed within the sclerotic hippocampus in TLE [Yu et al., 2001, 2002] and demyelinating processes [Gasperini et al., 1996; Mathias et al., 1999]. Alternatively, in light of the histopathological findings described earlier [Hammers et al., 2001, 2002], it is possible that the “simplified” TPWM texture as defined by entropy may point to alterations in the course of corticogenesis and is reflective of heterotopia, a developmental malformation leading to abnormal neuronal collection and positioning.

As for the pathological correlate for TPC and TPWM atrophy in TLE, using design-based stereology, Bothwell et al. [2001] found a reduction in neocortical width and challenged the common belief by showing that atrophy is not associated to loss of neurons, but rather to a decrease in the volume of neuropil and its associated elements. Moreover, neurons were significantly larger in TLE compared to controls. The fact that we found textural abnormalities in a minority of patients (13%) in the TPC could be due to the relative lack of sensitivity of our features to such histopathological changes or to a lower degree of neocortical blurring. Indeed, power analysis showed that the negative group results were not due to insufficient number of subjects, but rather due to the small magnitude of the differences in TLE patients, as shown by the low effect size.

Histology of the temporal lobe neocortex was available only in 2/4 CAH patients. One had architectural abnormalities with cortical dyslamination and columnar disorganization of the temporal lobe GM. The MRI volumetry and texture were normal in this subject. The second patient had GM gliosis. This subject had a reduction of both GM and WM volumes and a reduction in WM gradient and entropy in the temporal lobe ipsilateral to the focus. A direct comparison between our measurements and histopathology in these subjects is not possible because the GM tissue samples were taken in the temporal neocortex posteriorly to the borders of the TPC.

Can TPC and TPWM Abnormalities Predict Surgical Outcome in TLE?

The significance of the temporopolar abnormalities in relation to surgical outcome remains a controversial issue [Choi et al., 1999; Coste et al., 2002; Mitchell et al., 1999; Townsend et al., 2004]. Only one study found an association between improved outcome and the presence of an increased T2-weighted signal change in the anterior temporal WM [Choi et al., 1999]. Using T2-relaxometry [Townsend et al., 2004], we previously showed that the majority of patients with hippocampal atrophy became seizure free after surgery, whereas those with normal hippocampal volume did not achieve a favorable outcome regardless of the pattern of T2 changes, i.e. bilateral symmetric or ipsilateral. Indeed, the presence of unilateral hippocampal atrophy was the best indicator of favorable surgical outcome.

Given that the standard anterior temporal resection involves the removal of the temporal pole, while SAH does not, it is conceivable that failure to ablate the TPC may at least in part explain suboptimal results obtained in some patients undergoing the selective procedure. A recent stereo encephalography study performed in TLE patients who underwent tailored anterior temporal resections showed a weak association between a favorable surgical outcome and the presence of TP involvement at the onset of seizures as opposed to a seizure onset in the hippocampus [Chabardes et al., 2005]. The authors concluded that the frequent TP involvement at the onset of seizures could be an explanation for some failures of SAH procedures. A direct comparison with our study is not possible for the following reasons: we studied a homogeneous population of TLE patients with mesial temporal sclerosis and documented hippocampal atrophy on MRI, whereas in the aforementioned study 25% of the patients had foreign tissue lesions (mostly benign tumors) in the temporal lobe. Moreover, no patients included in that study underwent a SAH and 35% of those with TP involvement at the onset of seizures had lesions known to be associated with favorable surgical outcome. In our study, the proportion of volumetric and textural changes in patients with favorable outcome was higher (82 and 75%, respectively) than that of those with negative findings (56 and 25%, respectively), suggesting some predictive value for a good seizure outcome. However, when considering all groups in a contingency table we did not find a significant association. Nevertheless, when performing the analysis only in patients with SAH, we found a trend towards a favorable outcome in patients with textural abnormalities. Establishing a definite prognostic value of MRI temporopolar changes in TLE surgery would require prospective studies involving a larger population with balanced number of patients with respect to surgical outcome groups.

In conclusion, we found structural changes in the TPC and TPWM ipsilateral to the seizure focus in the majority of TLE patients with hippocampal sclerosis. Post-process-

ing analysis of T1-weighted MRI alone was more powerful than visual assessment of signal changes in T2 images and evaluation of atrophy on T1-weighted MRI. In particular, visual appraisal of atrophy lacked specificity. Widespread availability of powerful computing facilities and sophisticated algorithms, combined with improved spatial resolution and tissue contrast provided by high-field MRI, is continuing to expand the power of image processing. As a consequence, as suggested by initial evidence [Briellmann et al., 2001; Han et al., 2006; Jovicich et al., 2006], quantitation becomes more accurate at higher field strength, thus improving the measurement's reliability. This will allow refining further the *in vivo* patterns of brain pathology within anatomically and functionally distinct areas, and may provide the basis for more accurate correlates of histopathological findings.

ACKNOWLEDGMENTS

The authors thank Dr. A. Evans and L. Collins for their insightful comments.

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