Cortical Changes in Epilepsy Patients With Focal Cortical Dysplasia: New Insights With T_2 Mapping

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Background: In epilepsy patients with focal cortical dysplasia (FCD) as the epileptogenic focus, global cortical signal changes are generally not visible on conventional MRI. However, epileptic seizures or antiepileptic medication might affect normal-appearing cerebral cortex and lead to subtle damage.
Purpose: To investigate cortical properties outside FCD regions with T_2-relaxometry.
Study Type: Prospective study.
Subjects: Sixteen patients with epilepsy and FCD and 16 age-/sex-matched healthy controls.
Field Strength/Sequence: 3T, fast spin-echo T_2-mapping, fluid-attenuated inversion recovery (FLAIR), and synthetic T_1-weighted magnetization-prepared rapid acquisition of gradient-echoes (MP-RAGE) datasets derived from T_1-maps.
Assessment: Reconstruction of the white matter and cortical surfaces based on MP-RAGE structural images was performed to extract cortical T_2 values, excluding lesion areas. Three independent raters confirmed that morphological cortical/juxtacortical changes in the conventional FLAIR datasets outside the FCD areas were definitely absent for all patients. Averaged global cortical T_2 values were compared between groups. Furthermore, group comparisons of regional cortical T_2 values were performed using a surface-based approach. Tests for correlations with clinical parameters were carried out.
Statistical Tests: General linear model analysis, permutation simulations, paired and unpaired *t*-tests, and Pearson correlations.
Results: Cortical T_2 values were increased outside FCD regions in patients (83.4 ± 2.1 msec, control group 81.4 ± 2.1 msec, $P = 0.01$). T_2 increases were widespread, affecting mainly frontal, but also parietal and temporal regions of both hemispheres. Significant correlations were not observed ($P \geq 0.55$) between cortical T_2 values in the patient group and the number of seizures in the last 3 months or the number of anticonvulsive drugs in the medical history.
Data Conclusion: Widespread increases in cortical T_2 in FCD-associated epilepsy patients were found, suggesting that structural epilepsy in patients with FCD is not only a symptom of a focal cerebral lesion, but also leads to global cortical damage not visible on conventional MRI.
Evidence Level: 21
Technical efficacy Stage: 3

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FOCAL CORTICAL DYSPLASIA (FCD) is a malformation with a high epileptogenic potential[1] caused by abnormalities of cortical development. FCD is characterized by cortical disorganization and the occurrence of dysmorphic cells. Histopathological[2] and immunohistochemical studies[3] have not observed abnormalities outside lesions in FCD

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patients, suggesting that patients with FCD exhibit focal rather than global pathological changes.

However, volumetric magnetic resonance imaging (MRI) studies have indicated global structural abnormalities in epilepsy patients, demonstrating multifocal gray matter (GM) volume changes in patients with malformations of cortical development other than FCD[4] and generalized volume loss in 41% of the patients with chronic epilepsy.[5] Apart from the adverse effects of antiepileptic medication such as neurotoxic side effects,[6,7] long-standing epileptic activity might affect the cortex,[8,9] leading to microstructural damage. Such cortical changes might, in addition to incomplete resections, at least in part, explain why approximately half of patients are not seizure-free after FCD resection.[10]

Previous volumetric studies in epilepsy[4,5,11] employed conventional MRI techniques that allow for quantification of volume changes such as atrophy but do not assess the underlying microstructural abnormalities. In contrast, quantitative MRI (qMRI) techniques measure actual tissue parameters, such as the T_2 relaxation time, reducing effects of the scanner hard- and software.[12] T_2 relaxometry allows for the assessment of diffuse or inconspicuous changes in tissue architecture, such as abnormalities in relative myelin, iron, or free water content.[12,13] Bernasconi et al observed hippocampal T_2 changes in temporal lobe epilepsy (TLE), even in patients showing no signs of atrophy.[14] In addition, qMRI data can help to distinguish between patients with TLE and healthy subjects.[15,16] Furthermore, hippocampal profiling using volumetry and T_2 values aids to spatially localize hippocampal MRI abnormalities.[17] Reeves et al.[18] described T_1 and T_2* differences between the FCD region of interest in white matter (WM) and normal-appearing WM and magnetization transfer ratio changes in cortical GM inside FCDs, indicating microstructural abnormalities; however, the normal-appearing cortex was not investigated for abnormalities.

The main purpose of our study was to investigate T_2 values in normal-appearing cortical tissue in patients with FCD, hypothesizing that pathologic tissue changes exceed FCD areas in epilepsy patients.

Materials and Methods

Participants

This study was approved by the local Ethics Committee, and participants gave written informed consent before participation. The study was conducted according to the principles expressed in the Declaration of Helsinki.

Inclusion criteria of the study were: patients with epilepsy and neuroradiologically diagnosed FCD and age- and sex-matched healthy subjects. Exclusion criteria were: other neurological or psychiatric disorders, MRI contraindications, uncontrolled arterial hypertension, or diabetes mellitus.

Sixteen patients (13 male, age: mean ± SD: 27.6 ± 10.3 years) and 16 matched healthy subjects (13 male, age: mean ± SD: 27.3 ± 9.4 years) were investigated. Recruitment was performed in 2018 and 2019 at Goethe University Hospital. The presence or absence of the typical transmantle sign was evaluated based on conventional fluid-attenuated inversion recovery (FLAIR) data (acquisition parameters as detailed below in the section "MRI acquisition and T_2 mapping") for each subject by an experienced neurologist (10 years of experience) and by a senior neuroradiologist specialized in epilepsy imaging (15 years of experience), making decisions by consensus. The number of seizures during a period of 3 months before data acquisition and the number of anticonvulsive drugs in the medical history were obtained anamnestically. In case patients underwent resection, pathology reports were reviewed. In addition, the report of the last electroencephalography (EEG) recording before MRI data acquisition was taken into account for each patient in order to correlate EEG findings with FCD locations. The study presented here is part of a larger prospective scientific project addressing different research questions. Accordingly, the group of patients and healthy control subjects and the acquired data overlap in part with those of previous studies with different aims, presenting novel methods for FCD detection or creating improved synthetic T_1-weighted datasets.[19–21]

MRI Acquisition and T_2 Mapping

Data acquisition was performed using a 3T MR scanner (Magnetom Trio, Siemens Healthineers, Erlangen, Germany). The system utilizes a body coil for radiofrequency (RF) transmission and an 8-channel phased-array head coil for signal reception.

Custom-built programs were used for data analysis, employing functions included in MatLab (MathWorks, Natick, MA), FreeSurfer (Athinoula A. Martinos Center for Biomedical Imaging, Boston, MA),[22] and the FMRIB Software Library (FSL, Oxford, UK).[23]

For voxelwise measurement of the T_2 relaxation time, four fast spin echo datasets with different echo times (TEs) were acquired using the following acquisition parameters: matrix size = 256 × 176, number of axial slices = 69, slice thickness = 2 mm, no interslice gap, slice coverage of 138 mm (whole brain), spatial resolution = 1 × 1 × 2 mm^3, resulting field of view = 256 × 176 mm^2, TE = 13, 67, 93, and 106 msec, repetition time (TR) = 10 seconds, bandwidth = 176 Hz/pixel, refocusing angle = 160°, turbo factor = 13, parallel imaging with a reduction factor of 2, and acquisition time for each dataset = 1 minute 32 seconds. Each of the datasets was acquired twice for averaging, resulting in a total acquisition time of 12 minutes 16 seconds.

To correct for subject motion, all datasets were first coregistered to a common target. For each TE, the two respective datasets were then averaged. Exponential fitting of the dependence between TE and the signal intensities in the averaged datasets yielded apparent T_2 values (T_2app). It has been shown that T_2app can deviate considerably from the true T_2 value if the actual refocusing angle deviates from the ideal value of 180°, yielding stimulated or secondary echoes.[24] This can be due to B_1 inhomogeneities, deviations of the slice profile from a perfectly rectangular shape or deliberate choice of a reduced refocusing angle to reduce the RF power, as in this study. Thus, a B_1-dependent correction was performed, converting T_2app into actual T_2 values as described previously.[25] To allow for whole-brain coverage at a feasible imaging time, only four TE values were chosen. However, a previous study

showed that a similar protocol yielded accurate T_2 mapping with a scan–rescan deviation of about only 1.5%.[26]

For FCD definition, conventional FLAIR datasets were obtained with the following acquisition parameters: matrix size = 256 × 220 × 160, isotropic resolution = 1 mm, field of view = 256 × 220 × 160 mm^3, TE = 353 msec, TR = 5000 msec, inversion time (TI) = 1800 msec, bandwidth = 930 Hz/pixel, duration = 7 minutes 12 seconds.

For tissue segmentation, synthetic T_1-weighted magnetization-prepared rapid acquisition of gradient echoes (MP-RAGE) datasets were derived from quantitative T_1 maps using the same MR protocols (total duration = 16 minutes 43 seconds) and postprocessing algorithms as described previously[19] and assuming the following virtual acquisition parameters: matrix size = 256 × 224 × 160, isotropic resolution = 1 mm^3, field of view = 256 × 224 × 160 mm^3, TR = 1900 msec, TI = 900 msec, flip angle (α) = 9°, echo spacing = 8.1 msec.

Segmentation and Data Analysis

The cerebral cortex and the cortical and WM surfaces were identified, and the cortical thickness was determined vertex-wise by applying the "recon-all" stream implemented in the Freesurfer toolbox to the synthetic MP-RAGE datasets. Boundary-based coregistration of the T_2 and FLAIR datasets to the synthetic MP-RAGE datasets was performed with BBRegister.[27]

Based on the FLAIR datasets, masks of FCD areas were manually defined for each subject. Voxels were selected that appeared abnormal in conventional FLAIR datasets and which were part of or associated with a neuroradiologically diagnosed FCD. A systematic standardized assessment of FLAIR data was performed by three independent raters to exclude subtle morphologic cortical and juxtacortical changes outside the FCD areas. This analysis was performed by an experienced neurologist (10 years of experience) and by two senior neuroradiologists specialized in epilepsy imaging (15 years and 18 years of experience). A confidence score was obtained from each rater for each dataset. The raters stated whether morphologic cortical / juxtacortical changes outside the FCD areas were definitely or probably present or absent (1, definitely absent; 2, probably absent; 3, equivocal; 4, probably present; or 5, definitely present).[28] The FCD voxels were removed from the T_2 maps to exclude FCD-associated changes from the analysis. To reduce partial volume effects with cerebrospinal fluid (CSF) and WM, T_2 values were sampled in the central 20% of the cortex[29] and saved in surface datasets.

Statistical Analysis

Mean cortical T_2 values were determined across all non-zero vertices for each subject, as discussed in a previous study,[30] and compared between groups with an unpaired *t*-test. The Pearson correlation coefficients between these values and clinical parameters (number of seizures in the previous 3 months and number of anticonvulsive drugs in the medical history, including current treatment) were calculated. Additionally, T_2 values were averaged separately for each hemisphere and compared via paired *t*-tests between the hemisphere where the FCD was located and the contralateral side across the patient cohort. Compensation for multiple comparisons was performed via the Benjamini–Hochberg / False Discovery Rate (FDR) method for the respective statistical tests (comparing average cortical T_2 values between all patients and healthy subjects, estimating the correlation of T_2 and clinical parameters, and comparing T_2 between the hemispheres). A secondary comparison of mean cortical T_2 values was performed between the subgroup with a low seizure rate (≤12 seizures in the 3 months before data acquisition) and the control group to eliminate the effects of patients with aggressive disease.

Surface-based group analysis was performed for cortical T_2 values and for the cortical thickness. The T_2 surface data and cortical thickness maps were normalized and smoothed with a Gaussian kernel (full-width at half-maximum of 1 cm). A General Linear Model (GLM) analysis was performed for group comparisons. For a given region, only the data from patients without a local FCD in this region were included in the GLM calculation. Permutation simulations were performed for vertices with significant *P* values (<0.05) to detect clusters indicating group differences and to correct for multiple comparisons (5000 simulations, clusterwise threshold = 0.05).

An FDR of 0.05 was chosen for the Benjamini–Hochberg procedure. Corrected *P* values below 0.05 were considered significant for the surface-based analysis.

Results

The number of seizures of the 16 FCD patients during a period of 3 months before the investigation was 130 ± 293 (mean ± standard deviation, SD). However, 11 of the patients had equal to or less than 12 seizures during this time. The number of anticonvulsive drugs in medical history including current treatment was 4.1 ± 2.2 (range 1–7). Ten of the 16 patients had an FCD with a positive transmantle sign. Figure S1 in the Supplemental Material shows the FCDs in FLAIR and MP-RAGE datasets for three representative patients. The three independent raters found that morphological cortical and juxtacortical changes outside the FCD areas were definitely absent for all patients. For three patients, the FCD type was histopathologically confirmed after data acquisition and resection (1x type IIa and 2x type IIb). EEG recordings revealed abnormalities at the FCD locations in 12 patients (findings indicating structural abnormalities in seven patients, epileptiform activity in one patient, both in four patients).

A normalized map of cortical T_2 values for a single representative subject is shown in Figure 1. Mean cortical T_2 values were significantly increased (P = 0.01) in the patient group (group mean ± SD: 83.4 ± 2.1 msec) compared to the control group (81.4 ± 2.1 msec). The cortical T_2 values in the patient group were neither correlated with the number of seizures in 3 months (r = 0.16, P = 0.55), nor the number of anticonvulsive drugs in medical history (r = 0.09, P = 0.74). Cortical T_2 values were also increased in the subgroup with 11 patients with a low seizure rate (82.9 ± 1.3 msec, P = 0.026).

Figure 2 presents regions with cortical T_2 differences between groups. The spatial distribution of the clusters in Fig. 2 after correction for multiple comparisons demonstrates

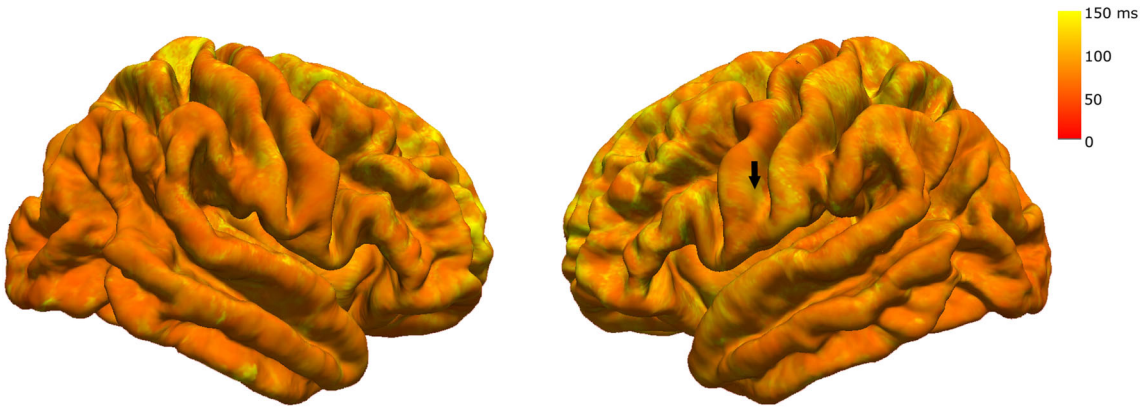

FIGURE 1: A normalized map of cortical T_2 values for a single representative subject. A normalized map of cortical T_2 values extracted from the central 20% of the cerebral cortex and projected on the cortical surface is shown for the right (first column) and left (second column) hemispheres. It should be noted that the T_2 values in the focal cortical dysplasia (FCD) region (black arrow) were included in this figure for demonstration purposes only, but excluded from the quantitative analysis.

that, for the investigated cohort of FCD patients, cortical T_2 increases were mainly observed for the frontal and parietal lobes. However, the uncorrected maps suggest that a T_2 increase might also be present in some temporal regions. Surface-based analysis of the cortical thickness after correction for multiple comparisons revealed no clusters of a significant increase or decrease in cortical thickness. Mean unilateral cortical T_2 values in the patient group did not differ between the hemisphere where the FCD was located (83.5 $\pm$ 2.6 msec) and the contralateral hemisphere (83.2 $\pm$ 1.9 msec, P= 0.67). Figure 3 demonstrates surface maps of the FCD locations of all patients, the red/yellow color indicating the presence of an FCD in one/two patients at the respective locations.

Discussion

Our study used T_2 relaxometry and surface-based analysis techniques to investigate normal-appearing cortical tissue in epilepsy patients with FCD. Widespread cortical T_2 increases in frontal, parietal, and some temporal regions were observed in the patient group, suggesting effects of the disease in cortical regions beyond FCD areas.

The underlying microstructural changes for the T_2 differences we observed are not known. However, a previous investigation reported that gliosis correlated with a hippocampal T_2 increase in temporal lobe epilepsy.[31] These results indicate that gliosis might either cause an increase of the tissue parameter T_2 or affect the T_2 measurement. Although pathological immunoreactivity outside the FCD was not observed in an immunohistochemical study by Rossini et al.,[3] gliosis on a microstructural level is a candidate for a remodeling process which might explain the observed T_2 increases. Importantly, clusters indicating atrophy were not observed in the investigated cohort, which is in line with a previous study demonstrating hippocampal T_2 changes in temporal lobe epilepsy, even in patients showing no signs of atrophy.[14] Furthermore, it has been reported that hippocampal gliosis may occur without atrophy.[32] Since T_2 depends on the free water content in tissue,[12,13] cortical reconstruction characterized by tissue damage and replacement of cells in nervous tissue by water on a microstructural level could potentially be another mechanism leading to increased cortical T_2 values in epilepsy patients with FCD.

However, factors driving these tissue changes in epilepsy are not yet fully understood. Cortical T_2 changes in epilepsy patients with FCD might be caused by seizure activity. It should be noted that, to the best of our knowledge, none of the investigated patients had experienced a status epilepticus at the time of this study. Since seizures might contribute to hippocampal gliosis in temporal lobe epilepsy,[9] the pathogenesis of the observed tissue changes might also be related to seizure activity. However, both in our study and in a previous investigation by Liu et al,[5] which evaluated atrophy in patients with epilepsy longitudinally, no significant relationship between structural parameters and seizure recurrence was observed. Furthermore, in the present study T_2 changes were also observed in the subgroup with a lower seizure rate. Additionally, multiple antiepileptic drug exposure might be another risk factor for neocortical damage in epilepsy.[5] However, a significant correlation of cortical T_2 values in the patient group and the number of anticonvulsive drugs in the medical history was not observed in our study. As it is likely that multiple factors contribute to the widespread T_2 increases, more extensive relaxometry studies might better characterize and separate the different effects.

It should be noted that, although cerebellar atrophy is a common finding in patients with long-standing epilepsies, particularly under treatment with anticonvulsive drugs,[7] the cerebral cortex was deemed a better target for qMRI analysis in epilepsy patients with FCD for the following reason: The cerebellar cortical layer is relatively thin and tightly folded.

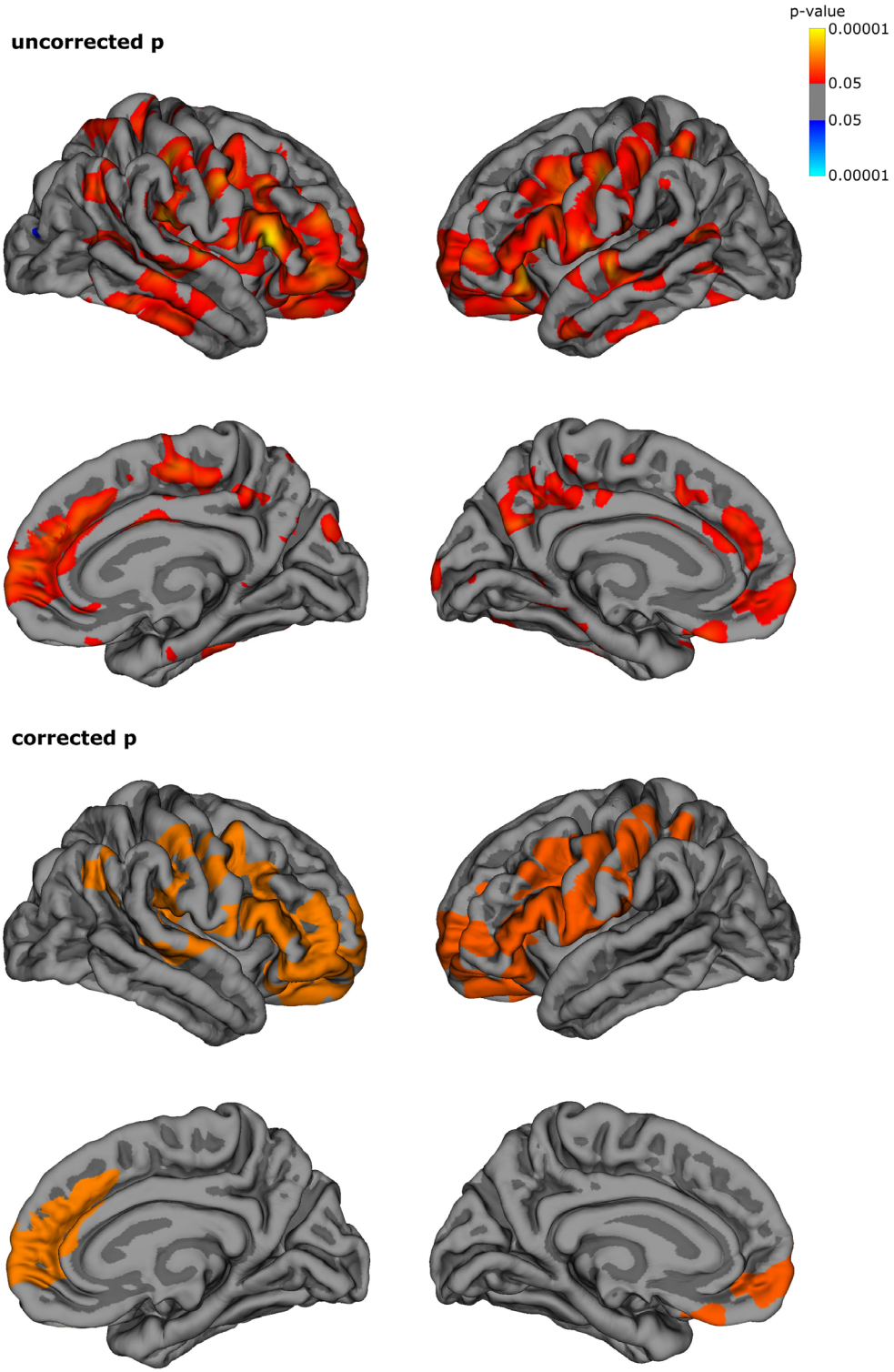

FIGURE 2: Cortical areas with T_2 differences between groups, hot colors indicating a T_2 increase for patients. The top two rows demonstrate uncorrected *P* values and the bottom two rows clusters after correction for multiple comparisons. The right/left hemisphere is presented in the first/second column, respectively. The lateral view is shown in the first and third row and the medial view in the second and last row.

Therefore, analysis of cerebellar T_2 values would result in strong partial volume effects, and thus increase the variability of average T_2 values in cerebellar WM and GM across the groups, rendering group comparisons difficult. For the analysis of the cerebral cortex, T_2 values were read in the central 20% of the cortical layer to reduce partial volume effects. This approach would not be feasible for the thin cerebellar cortex, considering the given resolution.

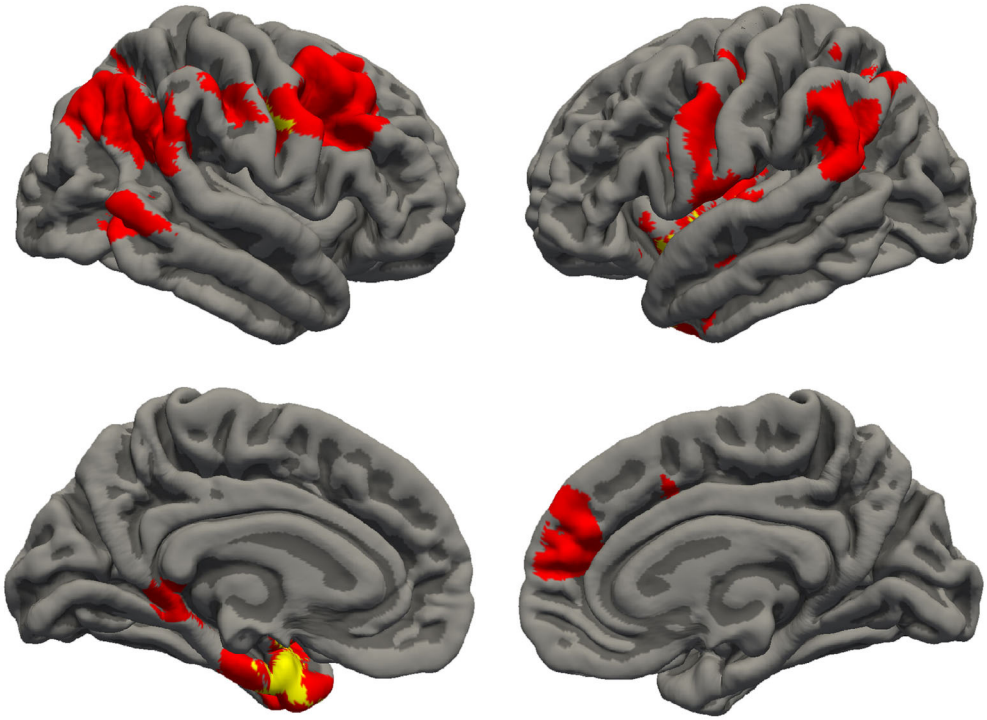

FIGURE 3: Surface maps of the focal cortical dysplasia (FCD) locations of all patients. The red color indicates the presence of one and the yellow color of two FCDs at the respective locations. Lateral (first row) and medial (second row) views are presented for both hemispheres.

Several volumetric studies have demonstrated cortical changes,[4,5,11] suggesting that epilepsy might systemically affect the brain beyond underlying focal lesions. Observations included multifocal abnormalities in GM volume in patients with malformations of cortical development,[4] focal neocortical volume loss in 14% and generalized volume loss in 41% of patients with chronic epilepsy,[5] and extratemporal cortical atrophy in temporal lobe epilepsy.[11] In our study, cortical atrophy was not observed, indicating that T_2 relaxometry might be more sensitive for the assessment of cortical tissue changes in epilepsy, particularly in smaller cohorts. Additionally, a diffusion tensor imaging study by Rugg-Gunn et al. reported abnormal anisotropy and diffusivity in areas that appeared to be normal on conventional images in patients with epilepsy and cerebral lesions.[33] In our study, cortical T_2 values in the patient group did not differ between the hemisphere where the FCD is located and the contralateral side, also supporting a global character of tissue changes. It is unclear so far whether tissue abnormalities outside focal lesions exhibit an epileptogenic potential. However, in a previous study regions with increased diffusivity matched areas of epileptiform EEG activity in some patients with normal conventional MRI findings.[33]

Limitations

A limitation of the study is the potential risk of underestimating cortical T_2 increases in patients in the surface-based analysis. When analyzing data obtained from patients with a cerebral lesion, the question arises how to exclude the lesion and how to handle this region in the further steps of the analysis. A potential procedure would be to fill the lesion with average values taken from the surrounding cortex ("lesion filling"). However, since T_2 values are increased in normal-appearing cortex in patients, this approach may yield a focal overestimation of the T_2 increase in the epilepsy group. Here, a more conservative approach was followed, by calculating the GLM analysis for each vertex only for the patients for whom cortical T_2 values outside the FCD were available, ie, excluding patients who showed an FCD in the respective region. Further limitations are the small sample size and the relatively long MRI acquisition time.

Conclusion

The observed widespread cortical T_2 increases suggest cortical remodeling on a global level in normal-appearing cortex in epilepsy patients with FCD. However, the etiology of these cortical changes is not fully understood, and it is likely that a combination of multiple factors contributes to cortical abnormalities in the tissue composition in patients with epilepsy and FCD.

Conflicts of Interest

The authors report no conflicts of interest relevant to this study. Dr. E. Hattingen has received speaker's honoraria from

BRACCO. Dr. F. Rosenow has received honoraria for presentations and consultations from EISAI, UCB Pharma, Desitin Arzneimittel, Hexal, Novartis, Medtronic, GW-Pharma, Shire, Sandoz, and Cerbomed, as well as research grants from UCB, European Union, Deutsche Forschungsgemeinschaft, European Science Foundation and the Hessonian Ministries of Science and Arts and of Social Affairs and Integration. Dr. H. Steinmetz has received speaker's honoraria from Bayer, Sanofi, and Boehringer Ingelheim. The remaining authors have no conflicts of interest.

Data Accessibility Statement

Data and code are not available publicly or upon direct request because data sharing does not comply with the institutional ethics approval.

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