External validation of automated focal cortical dysplasia detection using morphometric analysis

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Abstract
Objective: Focal cortical dysplasias (FCDs) are a common cause of drug-resistant focal epilepsy but frequently remain undetected by conventional magnetic resonance imaging (MRI) assessment. The visual detection can be facilitated by morphometric analysis of T1-weighted images, for example, using the Morphometric Analysis Program (v2018; MAP18), which was introduced in 2005, independently validated for its clinical benefits, and successfully integrated in standard presurgical workflows of numerous epilepsy centers worldwide. Here we aimed to develop an artificial neural network (ANN) classifier for robust automated detection
Focal cortical dysplasias (FCDs) are congenital disruptions of neuronal proliferation and organization during early brain development. As such, these lesions are among the three most common pathologies for drug-resistant focal epilepsy in adults and the most common cause of medically intractable focal epilepsy in children. Patients presenting with FCD lesions usually undergo presurgical evaluation at specialized tertiary epilepsy centers. Here, postsurgical outcome significantly depends on detecting dysplastic regions by conventional, neuroradiological assessment of magnetic resonance (MR) images. However, the proportions of patients with subtle FCD lesions undetected by conventional visual assessment range from 20% to 80%, thereby necessitating further computationally aided MR analyses.

In recent years, significant effort has been put into the development of advanced postprocessing routines to enhance visualization as well as fully automated approaches to detect dysplastic regions. However, many of these approaches neither have been validated on an independent data set nor systematically tested for their benefits compared to conventional visual assessment. The Morphometric Analysis Program (v2018; MAP18) was first introduced in 2005 and independently validated for its clinical benefits against expert neuroradiological assessments and successfully integrated into standard presurgical workflows of over 60 epilepsy centers in 22 different countries. The clinical reach of MAP18 can further be attributed to the fact that the processing pipeline only requires an isotropic T1-weighted volume, which is part of the recommended epilepsy imaging protocol.

**Methods:** In this retrospective study, we created a feed-forward ANN for FCD detection based on the morphometric output maps of MAP18. The ANN was trained and cross-validated on 113 patients (62 female, mean age ± SD = 29.5 ± 13.6 years) with manually segmented FCDs and 362 healthy controls (161 female, mean age ± SD = 30.2 ± 9.6 years) acquired on 13 different scanners. In addition, we validated the performance of the trained ANN on an independent, unseen data set of 60 FCD patients (28 female, mean age ± SD = 30 ± 15.26 years) and 70 healthy controls (42 females, mean age ± SD = 40.0 ± 12.54 years).

**Results:** In the cross-validation, the ANN achieved a sensitivity of 87.4% at a specificity of 85.4% on the training data set. On the independent validation data set, our method still reached a sensitivity of 81.0% at a comparably high specificity of 84.3%.

**Significance:** Our method shows a robust automated detection of FCDs and performance generalizability, largely independent of scanning site or MR-sequence parameters. Taken together with the minimal input requirements of a standard T1 image, our approach constitutes a clinically viable and useful tool in the presurgical diagnostic routine for drug-resistant focal epilepsy.

**Keywords**
- artificial neural network
- epilepsy
- lesion localization
- MAP
- MRI
- validation
MAP18 is based on the freely available Statistical Parametric Mapping toolbox (SPM12, Wellcome Trust Centre). By a combination of tissue segmentations, kernel convolutions, and statistical comparisons to a healthy control group, it produces morphometric maps specifically enhancing the visualization of abnormal blurring of the gray-white matter junction, abnormal extension of gray matter into deep white matter, as well as an increased cortical thickness. Although proven to have a clinical benefit in the detection of FCDs in highly specialized epilepsy centers,20–22 these so-called “junction,” “extension,” and “thickness” maps still require neuroradiological expertise and training to read and interpret correctly. Here we aim to integrate the information of the three resulting morphometric maps together with the results of the tissue segmentations in an artificial neural network (ANN) classifier producing an automatized classification tool for subtle FCD lesions. To ensure the generalizability of our approach, we validate the performance of our ANN furthermore on an independent data set of radiologically and histologically proven FCDs.

2 MATERIAL AND METHODS

2.1 Morphometric MRI analysis

Morphometric MR imaging (MRI) analysis was carried out on three-dimensional (3D) T1-weighted structural MR images using the fully automated MAP18 running in MATLAB version R2019a (MathWorks). The method has been described in detail in previous publications.19, 26–28 See Supplementary Material for a brief analysis description. Based on this analysis, 3D morphometric maps, called “extension image,” “junction image,” and “thickness image” were created. (See Figure 1 for the full processing pipeline.)

2.2 Artificial neural network

The Deep Learning Toolbox in MATLAB R2019a (MathWorks) was used to create a two-layer supervised (feedforward) pattern-recognition network with five sigmoid neurons in the hidden layer and two SoftMax output neurons (Figure 2). Intended for classification on voxel level, this ANN was trained to classify each voxel of a T1 input image independently into two classes, that is, dysplastic and non-dysplastic voxels.

For the classification of a specific voxel, the values from the following 15 maps were read at the corresponding voxel location and used as input for the ANN (Figure 2):

- intensity normalized T1 input image: the voxel intensities of the spatially normalized and bias corrected T1 image were linearly rescaled so that the mean brain intensity, determined as the mean value of separately averaged gray matter (GM) and white matter (WM) intensities, equated an arbitrarily chosen value of 100.
- morphometric maps: extension, junction, and thickness image resulting from morphometric analysis
- smoothed morphometric maps: after smoothing by a fixed Gaussian kernel of 6 mm full width at half maximum
- tissue maps: GM, WM, and cerebrospinal fluid (CSF) maps resulting from segmentation
- smoothed tissue maps: after smoothing by a fixed Gaussian kernel of 6 mm full width half maximum (FWHM)
- brain map: the sum of GM and WM tissue maps
- GM/WM border map: resulting from multiplication of GM map, WM map, and a mask of all cerebral gyri, composed with the LONI Probabilistic Brain Atlas (LPBA40)29

The relative importance of these input feature maps was ascertained for the fully trained ANN employing Garson’s algorithm as implemented by Goh.30 For more information about the architecture and input of the ANN, as well as Garson’s algorithm, please see Supplementary Material.

2.3 Training of the ANN

The ANN was trained at the Swiss Epilepsy Clinic (Zurich, Switzerland) using high-resolution (1 mm voxel size) 3D T1-weighted MRI data sets of 113 patients (62 female, mean age ± SD = 29.5 ± 13.6 years, age range of 1.2–66.4 years) and 362 healthy controls (161 female, mean age ± SD = 30.2 ± 9.6 years, age range of 18.0–67.6 years). Patients were chosen for training if the typical radiological criteria of FCD such as gyration anomalies, focal thickening of the cortex, blurring of the GM-WM junction, abnormal cortical and subcortical signal intensity, or transmantle sign were clearly identifiable in visual analysis of clinical standard high-resolution MRI (cf. Table S1 for a clinical description of the training data set).9 Each dysplastic lesion was manually labeled in the 3D T1 image by two raters (J. K. and H.-J. H.). Manual labels served as target parameters for the training of the ANN classifier. Finally, the ANN was trained voxelwise with the values of the 15 input maps of all patients and controls using scaled conjugate gradient backpropagation for gradient computation and cross-entropy as loss function. (For more information about the training procedure please see Supplementary Material.)
2.4 | Cross-validation

As a basis for later comparison with the validation data, the performance of the ANN on the training data was determined using a 10-fold cross-validation scheme. This analysis was repeated 10 times by randomly shuffling the data set to obtain average performance values. During testing (both in cross- and independent validation), all voxels of the respective test cases were presented in a real world setting to the pretrained classifier, that is, explicitly without applying any prior decimation or modulation factor. Please note that for subsequent independent validation on
an unseen data set, the ANN was trained on the complete training data set.

### 2.5 Independent validation

To better approximate the real estimation error of our method, we validated its performance on an unseen data set. We retrospectively ascertained T1 data sets of 60 patients (28 female, mean age ± SD = 30 ± 15.26 years, age range of 5–70) with histologically and/or radiologically described FCDs who underwent presurgical evaluation at the University Hospital Bonn Department of Epileptology and met the following inclusion criteria: (a) suspicion of FCD after conventional visual assessment by expert neuroradiologists at the University Hospital Bonn and (b) availability of an isotropic T1-weighted and fluid-attenuated inversion recovery (FLAIR) volume. In addition, we retrospectively ascertained 76 age- and sex-matched healthy controls (42 female, mean age ± SD = 40.0 ± 12.54 years, age range of 20–62) to assess an out-of-sample specificity score. Two FCD patients and six healthy controls had to be excluded because of excessive image artifacts. In patients, ground-truth lesion masks of the dysplastic cortical regions were collaboratively demarcated by two experienced raters (F. S. and T. R.). Both patients and healthy participants underwent the same processing pipeline as the training data set. Prediction of dysplastic voxels was performed using the pretrained ANN as described above. (For more information about the independent validation please refer to the Supplementary Material.)

### 2.6 Performance measures

Sensitivity, specificity, accuracy, and balanced accuracy were used to assess the classification performance of the trained ANN on case level. The accuracy was defined as the number of correctly classified cases divided by the total number of cases.
Most FCDs were localized in the frontal lobe \((n = 37, 64\%\) followed by the parietal \((n = 3, 5\%\) and temporal lobe \((n = 3, 5\%\) (Table 1; Figure S1). Twenty-one of 47 FCD patients (44\%) receiving a previous neuroradiological assessment in other centers had negative MRI reports. In the clinical setting at our center, the FCD could be identified in 34 of 58 patients (59\%) by help of morphometric analysis (former MAP version without ANN). Invasive EEG recording was performed in 23 patients. Forty-two patients underwent focal resections at a mean age of 27.7 years. Histology confirmed FCD type IIa in 11 patients (26\%) and FCD type IIb in 31 patients (74\%). Twenty-nine of 41 patients (71\%) were completely seizure-free (Engel class IA/International League Against Epilepsy (ILAE) class 1a) at the time of the last follow-up on average 39.2 months after surgery. Thirty-six of 41 patients (88\%) had experienced enhanced seizure control at the time of the last follow-up on average (Engel I-III/ILAE classes 1–4). Only in five of 41 patients (12\%), seizure control was unchanged or worse.

### 3.2 Cross-validation performance on training data set

The performance of the ANN was tested on the training data using 10 iterations of 10-fold cross-validation. On average, the ANN detected 98.8 of 113 FCDs corresponding to a mean sensitivity of 87.4\% (95\% CI 86.9–88.0\%). In addition, our ANN maintained a high specificity of 85.4\% on average (95\% CI 84.8–85.9\%), meaning that on average 309.2 of 362 healthy participants did not show false-positive clusters. This corresponds to an accuracy of 85.9\% (95\% CI 85.5–86.3\%) and a balanced accuracy of 86.4\% (95\% CI 86.1–86.7\%). Comparable results were observed in the subgroup of the 35 patients with histologically confirmed FCD. On average, 30 of 35 FCDs were correctly localized by our method, corresponding to a mean sensitivity of 85.4\% (95\% CI 84.8–86.1\%), a mean accuracy of 85.4\% (95\% CI 84.9–86.0\%), and a mean balanced accuracy of 85.4\% (95\% CI 84.9–86.0\%). Similar results were found for the subgroups of patients with Engel outcome I and II, patients younger and older than or equal to 18 years, patients scanned at 1.5 T and 3 T scanners, as well as separately for FCD type I and type II cases (cf. Table 2 for all results). ROC curve analysis confirmed an optimal threshold of 0.5 for the probability of dysplastic tissue and resulted in an area under the curve (AUC) value of 0.929 (95\% CI 0.896–0.963\%) with a Youden's index of 0.729 (see Figure S2). Figure 3 displays three cases from the training data demonstrating a potentially added diagnostic value of our method, namely the detection of possibly overlooked secondary lesions as well as lesions that seem to extend further than originally thought, but also an example for false-positive findings due to incidental brain alterations.

### 3.1 Clinical characteristics of the validation data set

A total of 58 patients with a radiologically and/or histologically defined FCD and 70 healthy controls were included in our study (Table 1). FCD lesions were evenly spread between the left \((n = 29)\) and right \((n = 29)\) hemispheres. Most FCDs were localized in the frontal lobe \((n = 37, 64\%)\), followed by the parietal \((n = 13, 22\%)\), occipital \((n = 5, 9\%)\), and temporal lobe \((n = 3, 5\%)\) (Table 1; Figure S1). Twenty-one of 47 FCD patients (44\%) receiving a previous neuroradiological assessment in other centers had negative MRI reports. In the clinical setting at our center, the FCD could be identified in 34 of 58 patients (59\%) by help of morphometric analysis (former MAP version without ANN). Invasive EEG recording was performed in 23 patients. Forty-two patients underwent focal resections at a mean age of 27.7 years. Histology confirmed FCD type IIa in 11 patients (26\%) and FCD type IIb in 31 patients (74\%). Twenty-nine of 41 patients (71\%) were completely seizure-free (Engel class IA/International League Against Epilepsy (ILAE) class 1a) at the time of the last follow-up on average 39.2 months after surgery. Thirty-six of 41 patients (88\%) had experienced enhanced seizure control at the time of the last follow-up on average (Engel I-III/ILAE classes 1–4). Only in five of 41 patients (12\%), seizure control was unchanged or worse.

### 2.7 Standard protocol approvals, patient consents, and data availability

Selection and inclusion of patients and controls were in accordance with local institutional review board requirements. The retrospective analysis was approved by the local institutional review board, and all participants provided written informed consent. The data that support the findings of this study are available upon reasonable request from the corresponding author. Data sets are not publicly available as they contain information that could compromise the privacy of patients and research participants.

### 3 RESULTS

### 3.1 Clinical characteristics of the validation data set

A total of 58 patients with a radiologically and/or histologically defined FCD and 70 healthy controls were included in our study (Table 1). FCD lesions were evenly spread between the left \((n = 29)\) and right \((n = 29)\) hemispheres. Most FCDs were localized in the frontal lobe \((n = 37, 64\%)\), followed by the parietal \((n = 13, 22\%)\), occipital \((n = 5, 9\%)\), and temporal lobe \((n = 3, 5\%)\) (Table 1; Figure S1). Twenty-one of 47 FCD patients (44\%) receiving a previous neuroradiological assessment in other centers had negative MRI reports. In the clinical setting at our center, the FCD could be identified in 34 of 58 patients (59\%) by help of morphometric analysis (former MAP version without ANN). Invasive EEG recording was performed in 23 patients. Forty-two patients underwent focal resections at a mean age of 27.7 years. Histology confirmed FCD type IIa in 11 patients (26\%) and FCD type IIb in 31 patients (74\%). Twenty-nine of 41 patients (71\%) were completely seizure-free (Engel class IA/International League Against Epilepsy (ILAE) class 1a) at the time of the last follow-up on average 39.2 months after surgery. Thirty-six of 41 patients (88\%) had experienced enhanced seizure control at the time of the last follow-up on average (Engel I-III/ILAE classes 1–4). Only in five of 41 patients (12\%), seizure control was unchanged or worse.

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The feature importance evaluation of the ANN, trained on the complete training data set, revealed that both tissue
(22.4%) and morphometric maps (63.2%) show a relevant level of feature importance for the distinction of dysplastic and nondysplastic tissue. Especially the three smoothed morphometric maps show high cumulative feature importance (42.7%) (see Figure S3).

### 3.3 Classifier performance on the validation data set

The pretrained ANN achieved comparably high performance scores in our independent validation data set. Our method detected 47 of 58 FCDs, thereby reaching a sensitivity of 81.0% (see Figure 4 for representative cases and Figure S4 for a summary of all cases). Of the 47 true-positive cases, 11 showed one false-positive cluster and two cases presented two false-positive clusters. Of the 11 false-negative cases, one patient showed a single false-positive cluster. In the healthy control group, 11 of 70 participants showed false-positive suprathreshold clusters, corresponding to an out-of-sample specificity of 84.3%. Of the 11 false-positive cases, 10 showed one false-positive cluster and one participant showed two false-positive clusters (see Figure S5 for a summary of all false-positive clusters). This performance corresponds to an overall accuracy of 82.8% and a balanced accuracy of 82.7%. In the subgroup of patients with histologically confirmed FCDs, our classifier reached a sensitivity of 78.6%. For patients with an Engel outcome of II and above, the ANN still reached a sensitivity of 77.8%. See Table 2 for an overview of all performance metrics in both cross-validation and independent validation. For a more fine-grained morphometric characterization of all true- and false-positive clusters, please refer to the respective section in the Supplementary Material.

### 4 DISCUSSION

In this study, we extended the well-established MAP18 program by implementing an ANN classifier that, solely based on a T1-weighted image as input, detects FCDs in a fully automated fashion. Our classifier showed a high sensitivity and specificity during cross-validation on the training data set. Most importantly, however, our method shows a robust generalization by detecting FCDs in a large independent data set with a sensitivity of 81.0% and specificity of 84.3%.

Our approach aims to automatize the detection of FCDs, utilizing only a minimal imaging protocol and, as such, still reaches a comparably high performance on a large independent data set, whereas previous, partly more complex methods report on cross-validation results only.14–18 The pitfalls of reporting k-fold cross-validation results (especially using leave-one-out schemes) on a single data set with a small sample size have recently been subject of debate in neuroimaging methods development.31 Here the development of unbiased estimators can largely be hindered by vastly underestimating the generalization error due to the error correlations across cross-validation folds.32 Ignoring the dependency of cross-validation folds can lead to an overfitting classifier, highly sensitive to implicit biases of the underlying data set.33 Furthermore, minimal methodological variations of the underlying algorithm may lead to large effects in cross-validation results, especially if working with limited sample sizes. These so-called vibration effects can thereby lead to the report of inflated performance estimations.31,33 The outlined problems can reliably be tackled by testing classification approaches on at least one more independent data set, as it is commonly practiced in the computer vision and machine learning literature.34 Approaches to tackle this problem in epilepsy lesion imaging, which is so far mostly limited by small sample sizes, are under development in the form of data-sharing initiatives (see MELD-Project).35 By further training our approach on a heterogeneous training data set from several clinics, we mitigate the bias of our classifier toward specific scan characteristics due to hardware or parameter specifications of the T1-weighted sequences, such as field inhomogeneity, site-specific geometric distortions, or differing head-coil sensitivity.36–38 In addition, we prove the robust generalization performance of our approach by testing it on another independently acquired and labeled data set of FCDs. Despite our efforts toward an unbiased two-step validation procedure and our comparably large sample sizes, we cannot completely rule out an underlying selection bias in our study population, as all our data stem from specialized epilepsy centers.

Apart from the robust generalization performance, another advantage of our method is the simplicity of input requirements. Previous automatized approaches to detect FCDs were based mostly on (and hence limited to) multimodal inputs, namely T1-weighted, FLAIR, and positron emission tomography (PET) scans. Although the overarching benefits of multimodality for epilepsy imaging, especially lesion localization in MR-negative patients, have been proven and discussed multiple times, the overall availability of advanced imaging modalities is already limited in specialized epilepsy centers and even more so in peripheral outpatient clinics.39,40 Ensuring a robust detection of FCDs on the most basic imaging modality, a standard T1-weighted MR scan, while avoiding the need for manual intervention due to error-prone pre-processing steps, as, for example, a cortical surface reconstruction, we aimed to extend the usability of our approach to less-specialized centers.

It is noteworthy that 31 of the FCDs (~66% of 47 patients with externally available information) in the independent validation data set were not found in previous conventional visual assessments in external centers (cf. “unspecfic abnormalities,” unrelated with the underlying FCD lesion, and “no
| ID  | Age at first seizure (years)a   | Previous MRI-diagnosis at other centersb | Age at in-house MRI-SCAN (years) | In-house MRI-diagnosis   | Morphometric analysis per-formedc | Morphometric analysis helpful | Invasive EEG evaluation | Age at epilepsy surgery (years) | Histo-pathology (Palmini/ILAE) |
|-----|--------------------------------|------------------------------------------|---------------------------------|--------------------------|----------------------------------|-------------------------------|----------------------------|-----------------------------|-------------------------------|
| 1   | 6–10                           | No abnormalities                          | 46–50                           | Suspicion of FCD         | Yes                              | Yes                           | Yes                       | 46–50                       | II/IIB                        |
| 2   | 1–5                            | Unspecific abnormalities                  | 51–55                           | FCD II                   | No                               | No                            | No                        | No surgery                  | No surgery                    |
| 3   | 16–20                          | N/A                                       | 21–55                           | FCD II                   | Yes                              | Yes                           | Yes                       | 21–25                       | II/IIB                        |
| 4   | 6–10                           | Suspicion of FCD                          | 16–20                           | Suspicion of FCD         | Yes                              | Yes                           | Yes                       | 16–20                       | II/IIB                        |
| 5   | 6–10                           | N/A                                       | 26–30                           | Suspicion of FCD         | Yes                              | Yes                           | Yes                       | 26–30                       | II/IIB                        |
| 6   | 1–5                            | Suspicion of FCD                          | 21–25                           | FCD II                   | Yes                              | No                            | Yes                       | No surgery                  | No surgery                    |
| 7   | 1–5                            | N/A                                       | 16–20                           | FCD II                   | Yes                              | No                            | Yes                       | 16–20                       | II/IIB                        |
| 8   | 1–5                            | No abnormalities                          | 31–35                           | FCD II                   | Yes                              | Yes                           | Yes                       | 31–35                       | II/IA/IIA                     |
| 9   | 16–20                          | Unspecific abnormalities                  | 56–60                           | FCD II                   | Yes                              | Yes                           | Yes                       | 56–60                       | II/IIB                        |
| 10  | 11–15                          | No abnormalities                          | 36–40                           | Suspicion of FCD         | No                               | No                            | No                        | 36–40                       | II/IIB                        |
| 11  | 11–15                          | No abnormalities                          | 26–30                           | FCD II                   | Yes                              | Yes                           | No                       | No surgery                  | No surgery                    |
| 12  | 1–5                            | No abnormalities                          | 41–45                           | Suspicion of FCD         | Yes                              | Yes                           | Yes                       | 41–45                       | II/IIB                        |
| 13  | 6–10                           | No abnormalities                          | 21–25                           | Suspicion of FCD         | Yes                              | Yes                           | Yes                       | 21–25                       | II/IIB                        |
| 14  | 1–5                            | Suspicion of FCD                          | 21–25                           | FCD II                   | No                               | No                            | No                       | No surgery                  | No surgery                    |
| 15  | 6–10                           | Unspecific abnormalities                  | 26–30                           | Suspicion of FCD         | Yes                              | Yes                           | No                       | No surgery                  | No surgery                    |
| 16  | 6–10                           | N/A                                       | 46–50                           | Suspicion of FCD         | Yes                              | Yes                           | No                       | 46–50                       | II/IIB                        |
| 17  | 16–10                          | Suspicion of FCD                          | 16–20                           | Suspicion of FCD         | No                               | No                            | No                       | No surgery                  | No surgery                    |
| 18  | 1–5                            | Unspecific abnormalities                  | 21–25                           | Suspicion of FCD         | No                               | No                            | No                       | 21–25                       | II/IIB                        |
| 19  | 21–25                          | Suspicion of FCD                          | 26–30                           | Suspicion of FCD         | Yes                              | No                            | No                       | No surgery                  | No surgery                    |
| 20  | 6–10                           | Suspicion of FCD                          | 21–25                           | FCD II                   | No                               | No                            | Yes                       | 21–25                       | II/IIB                        |
| 21  | 1–5                            | Suspicion of FCD                          | 16–20                           | FCD II                   | No                               | No                            | No                       | 16–20                       | II/IIB                        |
| 22  | 6–10                           | No abnormalities                          | 31–35                           | Suspicion of FCD         | No                               | No                            | No                       | No surgery                  | No surgery                    |
| 23  | 6–10                           | No abnormalities                          | 11–15                           | FCD II                   | No                               | No                            | No                       | 11–15                       | II/IIB                        |
| 24  | 1–5                            | Unspecific abnormalities                  | 6–10                            | FCD II                   | No                               | No                            | No                       | 6–10                        | II/IIB                        |
| 25  | 1–5                            | Unspecific abnormalities                  | 51–55                           | FCD II                   | No                               | No                            | No                       | No surgery                  | No surgery                    |
| 26  | 1–5                            | N/A                                       | 1–5                             | Suspicion of FCD         | No                               | No                            | No                       | 1–5                        | II/IIB                        |
| 27  | 6–10                           | Suspicion of FCD                          | 6–10                            | FCD II                   | Yes                              | Yes                           | No                       | 6–10                        | II/IA/IIA                     |
| 28  | 1–5                            | Unspecific abnormalities                  | 31–35                           | FCD II                   | Yes                              | Yes                           | No                       | 31–35                       | II/IIB                        |
| 29  | 1–5                            | N/A                                       | 16–20                           | FCD II                   | Yes                              | No                            | Yes                       | 16–20                       | II/IIB                        |
| 30  | 16–20                          | No abnormalities                          | 21–25                           | Suspicion of FCD         | Yes                              | Yes                           | Yes                       | 21–25                       | II/IA/IIA                     |
| 31  | 6–10                           | Suspicion of FCD                          | 21–25                           | FCD II                   | Yes                              | Yes                           | No                       | 21–25                       | II/IIB                        |
| 32  | 11–15                          | No abnormalities                          | 26–30                           | FCD II                   | Yes                              | Yes                           | No                       | No surgery                  | No surgery                    |
| 33  | 1–5                            | No abnormalities                          | 26–30                           | Suspicion of FCD         | Yes                              | Yes                           | No                       | 26–30                       | II/IIB                        |
| 34  | 6–10                           | No abnormalities                          | 61–65                           | FCD II                   | No                               | No                            | No                       | No surgery                  | No surgery                    |
| 35  | 6–10                           | No abnormalities                          | 41–45                           | FCD II                   | No                               | No                            | No                       | 41–45                       | II/IIB                        |
| Outcome: one year after surgery (Engel / ILAE class) | Last follow-up after surgery (months) | Outcome: last follow-up (Engel / ILAE class) | Lesion size (mL) | Location of lesion | Abnormal gyration | Blurred gray-white matter junction | Thickened cortex | Transmantle sign |
|---------------------------------------------------|--------------------------------------|---------------------------------------------|-----------------|-------------------|-----------------|-----------------------------------|----------------|-----------------|
| IA/1a                                             | 24                                   | IA/1a                                       | 1.06            | Right FL          | No              | Yes                              | No             | No              |
| No surgery                                        | No surgery                           | No surgery                                 | 9.28            | Right PL          | No              | No                               | Yes            | Yes             |
| IA/1a                                             | 29                                   | IA/1a                                       | 2.48            | Right FL          | No              | No                               | Yes            | No              |
| IA/1a                                             | 15                                   | IA/1a                                       | 8.69            | Right PL          | No              | Yes                              | Yes            | No              |
| II/3                                              | 45                                   | IVC/6                                       | 2.99            | Right FL          | No              | No                               | Yes            | Yes             |
| No surgery                                        | No surgery                           | No surgery                                 | 0.84            | Left FL           | No              | No                               | Yes            | Yes             |
| N/A                                               | 11                                   | IA/1a                                       | 1.21            | Left FL           | No              | Yes                              | No             | No              |
| IVB/5                                             | 19                                   | IVB/5                                       | 5.66            | Left PL           | No              | Yes                              | No             | No              |
| IA/1a                                             | 17                                   | IA/1a                                       | 0.45            | Left FL           | No              | Yes                              | Yes            | Yes             |
| IA/1a                                             | 46                                   | IA/1a                                       | 1.16            | Right FL          | No              | No                               | No             | Yes             |
| No surgery                                        | No surgery                           | No surgery                                 | 2.11            | Left FL           | No              | No                               | Yes            | Yes             |
| N/A                                               | 11                                   | IA/1a                                       | 2.75            | Right PL          | No              | Yes                              | Yes            | Yes             |
| IA/1a                                             | 23                                   | IA/1a                                       | 2.32            | Right FL          | No              | No                               | Yes            | Yes             |
| No surgery                                        | No surgery                           | No surgery                                 | 1.70            | Left FL & PL      | Yes              | Yes                              | Yes            | Yes             |
| No surgery                                        | No surgery                           | No surgery                                 | 0.56            | Left FL           | Yes              | Yes                              | Yes            | Yes             |
| IA/1a                                             | 12                                   | IA/1a                                       | 4.57            | Left PL           | No              | No                               | Yes            | Yes             |
| No surgery                                        | No surgery                           | No surgery                                 | 5.32            | left FL           | No              | Yes                              | No             | No              |
| N/A                                               | 7                                    | IVC/6                                       | 4.30            | Right PL          | Yes              | Yes                              | Yes            | No              |
| No surgery                                        | No surgery                           | No surgery                                 | 1.17            | Right PL          | Yes              | No                               | Yes            | Yes             |
| N/A                                               | N/A                                  | N/A                                         | 0.66            | Right FL          | Yes              | No                               | Yes            | Yes             |
| IA/1a                                             | 24                                   | IA/1a                                       | 19.96           | Left FL           | No              | No                               | Yes            | Yes             |
| No surgery                                        | No surgery                           | No surgery                                 | 12.32           | Left PL           | No              | Yes                              | Yes            | No              |
| IA/1a                                             | 83                                   | IA/1a                                       | 5.41            | Right FL          | No              | Yes                              | Yes            | Yes             |
| IA/1a                                             | 62                                   | IA/1a                                       | 9.59            | Left PL           | Yes              | Yes                              | Yes            | Yes             |
| No surgery                                        | No surgery                           | No surgery                                 | 4.27            | left FL           | No              | Yes                              | Yes            | No              |
| IA/1a                                             | 13                                   | IA/1a                                       | 2.77            | Right FL          | No              | Yes                              | Yes            | No              |
| IA/1a                                             | 106                                  | II/3                                        | 1.15            | Right FL          | No              | Yes                              | Yes            | No              |
| IVB/5                                             | 30                                   | II/3                                        | 4.45            | Right TL          | Yes              | Yes                              | Yes            | Yes             |
| IA/1a                                             | 135                                  | IA/1a                                       | 5.00            | Right TL & PL     | No              | No                               | Yes            | No              |
| IA/1a                                             | 119                                  | II/3                                        | 3.97            | Left FL           | No              | Yes                              | Yes            | No              |
| IA/1a                                             | 38                                   | IA/1a                                       | 10.24           | Left PL           | No              | Yes                              | No             | Yes             |
| No surgery                                        | No surgery                           | No surgery                                 | 1.07            | Left OL           | No              | Yes                              | Yes            | No              |
| IA/1a                                             | 70                                   | IA/1a                                       | 9.50            | Right OL          | Yes              | Yes                              | Yes            | No              |
| No surgery                                        | No surgery                           | No surgery                                 | 3.73            | Right FL          | No              | No                               | Yes            | Yes             |
| IA/1a                                             | 24                                   | IA/1a                                       | 1.34            | Right FL          | No              | No                               | Yes            | Yes             |

(Continues)
| ID  | Age at first seizure (years) | Previous MRI-diagnosis at other centers | Age at in-house MRI-SCAN (years) | In-house MRI diagnosis | Morphometric analysis performed | Morphometric analysis helpful | Invasive EEG evaluation | Age at epilepsy surgery (years) | Histo-pathology (Palmini/ILAE) |
|-----|----------------------------|-----------------------------------------|---------------------------------|------------------------|-----------------------------|-----------------------------|---------------------------|-------------------------------|--------------------------------|
| 36  | 16–10                      | No abnormalities                        | 26–30                           | Suspicion of FCD       | Yes                         | Yes                         | No                        | No surgery                    | No surgery                     |
| 37  | 41–45                      | No abnormalities                        | 51–55                           | Suspicion of FCD       | Yes                         | Yes                         | Yes                       | 56–60                         | IIA/IIA                        |
| 38  | 16–20                      | Suspicion of FCD                        | 21–25                           | FCD II                 | No                          | No                          | No                        | 21–25                         | II/B/IIB                       |
| 39  | 6–10                       | No abnormalities                        | 16–20                           | FCD II                 | No                          | No                          | No                        | 16–20                         | IIA/IIA                        |
| 40  | 11–15                      | Unspecific abnormalities                 | 21–25                           | Suspicion of FCD       | No                          | No                          | Yes                       | 21–25                         | II/B/IIB                       |
| 41  | 6–10                       | No abnormalities                        | 16–20                           | Suspicion of FCD       | Yes                         | Yes                         | No                        | 16–20                         | IIA/IIA                        |
| 42  | 6–10                       | Suspicion of FCD                        | 51–55                           | FCD II                 | Yes                         | Yes                         | Yes                       | 51–55                         | II/B/IIB                       |
| 43  | 1–5                        | Suspicion of FCD                        | 41–45                           | FCD II                 | No                          | No                          | No                        | 41–45                         | II/B/IIB                       |
| 44  | 6–10                       | No abnormalities                        | 26–30                           | FCD II                 | Yes                         | Yes                         | Yes                       | 26–30                         | II/B/IIB                       |
| 45  | 16–20                      | N/A                                      | 36–40                           | Suspicion of FCD       | Yes                         | Yes                         | Yes                       | 36–40                         | II/B/IIB                       |
| 46  | 6–10                       | N/A                                      | 6–10                            | FCD II                 | Yes                         | Yes                         | Yes                       | 6–10                          | IIA/IIA                        |
| 47  | 1–5                        | Suspicion of FCD                        | 6–10                            | Suspicion of FCD       | No                          | No                          | No                        | 6–10                          | II/B/IIB                       |
| 48  | 1–5                        | Suspicion of FCD                        | 36–40                           | Suspicion of FCD       | Yes                         | Yes                         | No                        | No surgery                    | No surgery                     |
| 49  | 6–10                       | No abnormalities                        | 16–20                           | Suspicion of FCD       | Yes                         | Yes                         | Yes                       | 16–20                         | IIA/IIA                        |
| 50  | 1–5                        | No abnormalities                        | 11–15                           | FCD II                 | YES                        | No                          | Yes                       | 11–15                         | IIA/IIA                        |
| 51  | 16–20                      | No abnormalities                        | 36–40                           | FCD II                 | Yes                         | Yes                         | Yes                       | 36–40                         | II/B/IIB                       |
| 52  | 6–10                       | Suspicion of FCD                        | 66–70                           | FCD II                 | Yes                         | Yes                         | No                        | 66–70                         | II/B/IIB                       |
| 53  | 1–5                        | Unspecific abnormalities                 | 16–20                           | FCD II                 | Yes                         | Yes                         | Yes                       | 16–20                         | IIA/IIA                        |
| 54  | 1–5                        | N/A                                      | 11–15                           | Suspicion of FCD       | Yes                         | Yes                         | Yes                       | 11–15                         | IIA/IIA                        |
| 55  | 6–10                       | N/A                                      | 51–55                           | FCD II                 | No                          | No                          | Yes                       | No surgery                    | No surgery                     |
| 56  | 1–5                        | Unspecific abnormalities                 | 21–25                           | FCD II                 | Yes                         | Yes                         | No                        | 21–25                         | IIA/IIA                        |
| 57  | 1–5                        | Suspicion of FCD                        | 21–25                           | FCD II                 | No                          | No                          | No                        | No surgery                    | No surgery                     |
| 58  | 6–10                       | N/A                                      | 36–40                           | Suspicion of FCD       | Yes                         | Yes                         | No                        | No surgery                    | No surgery                     |

**Summary**

| Age at first seizure (years) | Previous MRI-diagnosis at other centers | Age at in-house MRI-SCAN (years) | In-house MRI diagnosis | Morphometric analysis performed | Morphometric analysis helpful | Invasive EEG evaluation | Age at epilepsy surgery (years) |
|-----------------------------|-----------------------------------------|---------------------------------|------------------------|-----------------------------|-----------------------------|---------------------------|-------------------------------|
| Mean/total                  | 8.40                                    | 29.52                           | 37                     | 34                          | 23                          | 27.67                     |                                |
| suspension of FCD           | 16                                       | 25                              |                        |                            |                            |                          |                                |
| FCD IIA                     | 33                                       |                                 |                        |                            |                            |                          |                                |
| unspecific abnormalities    | 10                                       |                                 |                        |                            |                            |                          |                                |
| no abnormalities            | 21                                       |                                 |                        |                            |                            |                          |                                |
| N/A                         | 11                                       |                                 |                        |                            |                            |                          |                                |
| no surgery                  | 16                                       |                                 |                        |                            |                            |                          |                                |
| Engel I A                   |                                          |                                 |                        |                            |                            |                          |                                |
| Engel I B                   |                                          |                                 |                        |                            |                            |                          |                                |
| Engel I C                   |                                          |                                 |                        |                            |                            |                          |                                |
| Engel II A                  |                                          |                                 |                        |                            |                            |                          |                                |
| Engel II B                  |                                          |                                 |                        |                            |                            |                          |                                |
| Age at first seizure (years) | Previous MRI-diagnosis at other centers | Age at in-house MRI-SCAN (years) | In-house MRI-diagnosis | Morphometric analysis performed | Morphometric analysis helpful | Invasive EEG evaluation | Age at epilepsy surgery (years) | Histo-pathology | Outcome: one year after surgery (Engel / ILAE class) | Last follow-up after surgery (months) | Outcome: last follow-up (Engel / ILAE class) | Lesion size (mL) | Location of lesion | Abnormal gyration | Blurred gray-white matter junction | Thickened cortex | Trans-mantle sign |
|-----------------------------|-----------------------------------------|---------------------------------|------------------------|-------------------------------|-------------------------------|---------------------------|-----------------------------|------------------------------|-----------------------------------|---------------------|---------------------|------------------|-------------------|------------------|------------------|
| 36                          | 16–10                                   | No abnormalities                | 26–30                  | Suspicion of FCD              | Yes                             | No                        | No                          | Surgery                        | No surgery                        | No surgery              | No surgery              | 4.09             | Left FL           | No               | Yes               | No               | No               |
| 37                          | 41–45                                   | No abnormalities                | 51–55                  | Suspicion of FCD              | Yes                             | Yes                      | Yes                        | Surgery                        | 46–50                             | IIA/IIA              | IVB/5                | 3.38             | Left TL           | No               | Yes               | Yes             | No               |
| 38                          | 16–20                                   | Suspicion of FCD                | 21–25                  | FCD II                        | No                             | No                       | No                         | Surgery                        | No surgery                        | No surgery              | IIB/IIB              | 0.94             | Right PL          | Yes               | Yes               | No             | No               |
| 39                          | 6–10                                    | No abnormalities                | 16–20                  | FCD II                        | No                             | No                       | No                         | Surgery                        | No surgery                        | No surgery              | IIA/IIA              | 1.84             | Left FL           | No               | Yes               | No             | No               |
| 40                          | 11–15                                   | Unspecific abnormalities        | 21–25                  | Suspicion of FCD              | No                             | Yes                      | Yes                        | Surgery                        | 44–48                             | IIB/IIB              | N/A                  | 2.65             | Right FL&TL        | Yes              | Yes               | No             | No               |
| 41                          | 6–10                                    | No abnormalities                | 16–20                  | Suspicion of FCD              | Yes                             | Yes                      | No                         | Surgery                        | No surgery                        | No surgery              | IIA/IIA              | 2.81             | Left FL           | Yes               | Yes               | No             | No               |
| 42                          | 6–10                                    | Suspicion of FCD                | 51–55                  | FCD II                        | Yes                             | Yes                      | Yes                        | Surgery                        | 47–51                             | IIB/IIB              | N/A                  | 4.05             | Right FL          | Yes               | Yes               | No             | No               |
| 43                          | 1–5                                     | Suspicion of FCD                | 41–45                  | FCD II                        | No                             | No                       | No                         | Surgery                        | No surgery                        | No surgery              | N/A                  | 1.25             | Right TL          | No               | Yes               | No             | No               |
| 44                          | 6–10                                    | No abnormalities                | 26–30                  | FCD II                        | Yes                             | Yes                      | Yes                        | Surgery                        | No surgery                        | No surgery              | IIB/IIB              | 1.13             | Left FL           | Yes               | Yes               | No             | No               |
| 45                          | 16–20                                   | N/A                             | 36–40                  | Suspicion of FCD              | Yes                             | Yes                      | Yes                        | Surgery                        | 42–46                             | IIB/IIB              | IA/1a                | 2.42             | Left PL           | No               | Yes               | Yes             | No               |
| 46                          | 6–10                                    | N/A                             | 6–10                   | FCD II                        | Yes                             | Yes                      | No                         | Surgery                        | No surgery                        | No surgery              | N/A                  | 2.61             | Left FL           | Yes               | Yes               | No             | No               |
| 47                          | 1–5                                     | Suspicion of FCD                | 6–10                   | Suspicion of FCD              | No                             | No                       | No                         | Surgery                        | No surgery                        | No surgery              | N/A                  | 9.03             | Left FL           | Yes               | Yes               | No             | No               |
| 48                          | 1–5                                     | Suspicion of FCD                | 36–40                  | Suspicion of FCD              | Yes                             | Yes                      | No                         | Surgery                        | No surgery                        | No surgery              | N/A                  | 1.72             | Right PL&OL        | Yes              | Yes               | No             | No               |
| 49                          | 6–10                                    | No abnormalities                | 16–20                  | Suspicion of FCD              | Yes                             | Yes                      | Yes                        | Surgery                        | No surgery                        | No surgery              | IIA/IIA              | 15.36            | Right PL          | Yes               | Yes               | No             | No               |
| 50                          | 1–5                                     | No abnormalities                | 11–15                  | FCD II                        | Yes                             | Yes                      | No                         | Surgery                        | No surgery                        | No surgery              | IA/1a                | 0.85             | Left FL           | Yes               | Yes               | No             | No               |
| 51                          | 16–20                                   | N/A                             | 36–40                  | FCD II                        | Yes                             | Yes                      | Yes                        | Surgery                        | No surgery                        | No surgery              | N/A                  | 3.82             | Right PL          | Yes               | Yes               | Yes             | No               |
| 52                          | 6–10                                    | Suspicion of FCD                | 66–70                  | FCD II                        | Yes                             | Yes                      | No                         | Surgery                        | No surgery                        | No surgery              | IA/1a                | 3.66             | Right FL          | No               | Yes               | Yes             | No               |
| 53                          | 1–5                                     | Unspecific abnormalities        | 16–20                  | FCD II                        | Yes                             | Yes                      | No                         | Surgery                        | No surgery                        | No surgery              | IA/1a                | 1.43             | Right FL          | No               | Yes               | No             | No               |
| 54                          | 1–5                                     | N/A                             | 21–25                  | FCD II                        | Yes                             | Yes                      | No                         | Surgery                        | No surgery                        | No surgery              | IA/1a                | 1.25             | Right TL          | No               | Yes               | No             | No               |
| 55                          | 6–10                                    | N/A                             | 51–55                  | FCD II                        | No                             | No                       | Yes                        | Surgery                        | No surgery                        | No surgery              | N/A                  | 0.81             | Left FL           | No               | Yes               | No             | No               |
| 56                          | 1–5                                     | Unspecific abnormalities        | 21–25                  | FCD II                        | Yes                             | Yes                      | No                         | Surgery                        | No surgery                        | No surgery              | IA/1a                | 1.25             | Right TL          | Yes               | Yes               | No             | No               |
| 57                          | 1–5                                     | Suspicion of FCD                | 21–25                  | FCD II                        | No                             | No                       | No                         | Surgery                        | No surgery                        | No surgery              | N/A                  | 8.78             | Left PL           | Yes               | Yes               | Yes             | Yes               |
| 58                          | 6–10                                    | N/A                             | 36–40                  | Suspicion of FCD              | Yes                             | Yes                      | No                         | Surgery                        | No surgery                        | No surgery              | N/A                  | 0.60             | Left FL           | No               | No               | No             | Yes               |

**Summary**

| Lesion size (mL) | Location of lesion | Abnormal gyration | Blurred gray-white matter junction | Thickened cortex | Trans-mantle sign |
|------------------|--------------------|-------------------|-----------------------------------|------------------|------------------|
| 39.17            | 3.97               | Right:29          | 8                                 | 39               | 47               | 30               |

**Histopathology**

- Engel I A: 29
- Engel I B: 1
- Engel I C: 0
- Engel II A: 1
- Engel II B: 1
- N/A: 1
- FL: 37
- TL: 5
- PL: 17
- OL: 3

(Continues)
abnormalities” in column 3 of Table 1). Of these, 23 were automatically localized by our algorithm. Moreover, in 18 cases, the definite diagnosis of FCD could still not be established, despite an elaborate in-house MRI evaluation including morphometric postprocessing (cf. “suspicion of FCD” in column 5 of Table 1) but was only confirmed by postoperative histology. Of these 18 cases, 14 were confirmed by our ANN. Furthermore, as shown in Figure 3, the output of our ANN hinted at a second region presenting with FCD-typical characteristics and seemingly demarcated the extent of another FCD beyond what has been visible to the naked eye at first sight. However, 11 healthy individuals in our validation data set showed false-positive clusters that did not correspond to a real FCD. Although there is generally a trade-off between sensitivity and specificity when defining a static classification-threshold, false-positive clusters were mostly localized in the occipital or frontobasal cortex in this data set (see Figure S5) and smaller in size (Cohen’s $d = 0.64$, see Figure S6). As this holds true for both patients and healthy controls, we assume that these findings can be traced back to a decreased GM-WM contrast due to $B_0$ inhomogeneities. The poor tissue contrast in turn can lead to an inaccurate automated segmentation (mirrored in the morphometric maps) that is falsely identified as dysplastic tissue by our ANN. This might also in part explain the higher specificity for 1.5 T data in our subgroup analyses, as the signal inhomogeneities are less severe in these cases. However, the increased specificity at 1.5 T also mirrors a selection bias because lesions visible in 1.5 T are most likely less subtle and, therefore, easier to detect. Nevertheless, our method might benefit from a locally adaptive thresholding procedure as recently described by Sundaresan and colleagues for lesion probability maps.\(^{41}\) This might, furthermore, account for the non-uniform distribution of FCDs across different lobes. Apart from that, the ANN that we currently use is a simple, shallow network. This has the advantage of requiring less training data than state-of-the-art deep learning methods would. However, our shallow ANN shows shortcomings in excluding morphometrically similar false-positive clusters but misses smaller FCD lesions despite similar morphometric profiles (see Figure S6). Taking this into account, a hint toward the benefit of deeper convolutional neural networks in the detection of FCDs can additionally be deduced from the relative feature importance displayed in Figure S3. Specifically, the smoothed morphometric maps show a high relative feature importance in our classifier. The smoothing of these maps with a three-dimensional Gaussian kernel crudely approximates the basic principle of convolutional neural networks but avoids learning a large number of parameters for internal convolutions. If one increases the sample size significantly, however, the use of, for example, a 3D, patch-based convolutional neural network, which mathematically integrates the local and global neighborhood of each voxel, might very well improve the overall classification performance.\(^{42}\)

As mentioned earlier, we tackled the problem of automated FCD detection by classifying into dysplastic and healthy tissue on the level of single voxels. Therefore, we considered a single voxel, overlapping with the manual ground-truth mask, as detection of the FCD and, with the same rigorousness, a single voxel in healthy tissue of a control participant as false-positive finding on case level (cf. Figure S5). We chose this convention because the minimum size of FCDs is unknown and any other detection threshold of positive voxels would have restricted the sensitivity of our algorithm to an arbitrarily chosen minimal lesion size. It is important to note that despite our strict heuristic the classifier reached a sufficiently high specificity and provided a decent balance of the sensitivity-specificity trade-off on case level.

Another limitation of our approach is that the morphometric maps, and thereby our overall classifier, are largely...
dependent on the statistical comparison with a population of healthy individuals. This processing step might introduce unobserved biases in the generation of our z-statistic feature maps. Although our healthy control population has been sampled from several different clinics, scanners, and MR protocols, it is conceivable that our approach might fail when used on undersampled FCD cohorts, as, for example, pediatric patients or FCD type I cases. However, in a subgroup analysis of patients younger than 18-years-old (ie, younger than the youngest subject in our control group) and in a highly limited subgroup analysis of FCD type I cases, our classifier still showed robustly high performance metrics. In comparison, other approaches have been specifically and successfully designed to accommodate pediatric FCD patients.16 Although our approach can possibly be tuned toward different age groups using a matching control

| TABLE 2 | ANN performance in 10-fold cross-validation and independent validation |
|----------|-------------------------------------------------------------------|
| Data set | Patients | Healthy controls | TP | TN | FP | FN | Sensitivity | Specificity | Accuracy | Balanced accuracy |
| Training | 113      | 362               | 98.8 | 309.2 | 52.8 | 14.2 | 87.4% | 85.4% | 85.9% | 86.4% |
| Training (available histopathology) | 35 | 362 | 29.9 | 309.2 | 52.8 | 5.1 | 85.4% | 85.4% | 85.4% | 85.4% |
| Training (FCD Type I) | 4 | 362 | 3.9 | 309.2 | 52.8 | 0.1 | 97.5% | 85.4% | 85.5% | 91.5% |
| Training (FCD Type II) | 31 | 362 | 26.0 | 309.2 | 52.8 | 5.0 | 83.9% | 85.4% | 85.3% | 84.6% |
| Training (patients <18 y) | 26 | 362 | 23.2 | 309.2 | 52.8 | 2.8 | 89.2% | 85.4% | 85.7% | 87.3% |
| Training (patients ≥18 y) | 87 | 362 | 75.6 | 309.2 | 52.8 | 11.4 | 86.9% | 85.4% | 85.7% | 86.2% |
| Training (scanned at 1.5 T) | 46 | 89 | 40.3 | 86.2 | 2.8 | 5.7 | 87.6% | 96.9% | 93.7% | 92.2% |
| Training (scanned at 3 T) | 67 | 273 | 58.5 | 223.0 | 50.0 | 8.5 | 87.3% | 81.7% | 82.8% | 84.5% |
| Training (Engel outcome 1 + 2) | 32 | 362 | 26.9 | 309.2 | 52.8 | 5.1 | 84.1% | 85.4% | 85.3% | 84.7% |
| Validation | 58 | 70 | 47 | 59 | 11 | 11 | 81.0% | 84.3% | 82.8% | 82.7% |
| Validation (available histo-pathology) | 42 | 70 | 33 | 59 | 11 | 9 | 78.6% | 84.3% | 82.1% | 81.4% |
| Validation (patients <18 y) | 17 | 70 | 14 | 59 | 11 | 3 | 82.4% | 84.3% | 83.9% | 83.4% |
| Validation (patients ≥18 y) | 41 | 70 | 33 | 59 | 11 | 8 | 80.5% | 84.3% | 82.9% | 82.4% |
| Validation (Engel outcome 1 + 2) | 36 | 70 | 28 | 59 | 11 | 8 | 77.8% | 84.3% | 82.1% | 81.0% |

Note: Values for the training data set indicate the average performance over 10 random repetitions of the 10-fold cross-validation procedure. Bold values indicate the main results for the data set.
Abbreviations: FN, false negative; FP, false positive; TN, true negative; TP, true positive.
population, future approaches might instead benefit from the power of current deep generative methods, such as, for example, Generative Adversarial Networks or (Variational) Autoencoders, to generate synthetic images that can serve as a patient-specific control modality and thereby render an external healthy control group as obsolete. Similar approaches have already been described for tumor segmentation. Furthermore, the possible broadening of these
A comparison of the ANN output and the ground-truth labels shows that the overlap between both only covers a fraction of the manually labeled lesion extent in the validation data (Figure S4). Apparently, our method is not capable of clearly visualizing the boundaries of dysplastic lesions. In some cases, the FCD probability map may indicate that the lesion extends farther than visually recognizable (as shown in example B of Figure 3), but in general the ANN, as it is currently designed, only facilitates the detection of FCDs but does not reliably reflect the boundaries of the lesion. Considering the serious imbalance in the prevalence of dysplastic vs nondysplastic voxels in patients with FCD (on average 2.4 mL lesion volume in this study vs about 1400 mL mean volume of adult brains), any slight improvement in dysplasia detection on voxel level would

**FIGURE 4**  Eight representative classification results from the independent validation data set. Results shown in radiological display convention. Red patient numbers indicate false-negative cases. Asterisks indicate cases presenting with extralesional false-positive clusters. The ANN output (i.e., the FCD probability map) is thresholded at 0.5 as described in the article. Intensity windows of the morphometric maps have been individually adjusted to best visualize the lesion. Coronal slices were chosen manually according to the maximum extent of the lesion. For a complete overview of all classification results please see Figure S4. For a complete overview of all false-positive clusters please see Figure S5.
result in a significant increase in false-positive findings in the rest of the brain. This limits possible network optimizations for lesion segmentation (compared to lesion detection) by favoring dysplastic vs nondysplastic voxels. Given our clinical experiences with highly discrete FCDs, their widespread occurrence (cf. Figure S1), and the fact that there is no lower bound to the size of dysplastic lesions (in our study the smallest segmented FCD had a volume of only 0.1 ml), it seems unlikely that a method will be developed in the future that allows complete separation of dysplastic and nondysplastic voxels.

Taken together, the robustness to localize FCDs proven in an independent data set and the minimal imaging requirements render our approach as a viable tool, developed for the clinical routine. The automatized localization minimizes the expertise that users of the MAP18 program require to analyze and interpret the results, which in turn facilitates the use of our approach in medical centers even without specialized epilepsy unit. As such, we hope that the integration of the ANN in the current version of MAP18 will reduce the number of MR-negative cases and thereby significantly contribute to the presurgical diagnostics in patients with epilepsy around the world.

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CONFLICT OF INTEREST
Dr. Kröll-Seger received fees from Nutricia and Desitin. Dr. Wagner received fees from Eisai, Bial and UCB. Dr. Wellmer received fees from Eisai, Desitin, Bial, UCB and Medtronic. Dr. Urbach received fees from Bayer AG, Bracco, Eisai, Stryker, UCB Pharma, and is shareholder of the Veobrain GmbH. Dr. Elger received fees from UCB, Desitin, BIAL. Dr. Surges received fees from Bial, Desitin, Eisai, LivaNova, Novartis and UCB Pharma. Dr. Huppertz is the author of MAP18. The program is available for other epilepsy centers on request. In this case, the Swiss Epilepsy Clinic, Dr. Huppertz’s employer, charges a fee for creating a scanner-specific normal database. The remaining authors have no conflicts of interest.

[Correction added on April 3, 2021 after first online publication: The Conflict of Interest section has been updated.]

ETHICAL PUBLICATION STATEMENT
We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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