Automated detection of cortical dysplasia type II in MRI-negative epilepsy

Seok-Jun Hong, MSc
Hosung Kim, PhD
Dewi Schrader, MD
Neda Bernasconi, MD,
PhD
Boris C. Bernhardt, PhD
Andrea Bernasconi, MD

Correspondence to
Dr. Bernasconi:
andrea@bic.mni.mcgill.ca

ABSTRACT

Objective: To detect automatically focal cortical dysplasia (FCD) type II in patients with extratemporal epilepsy initially diagnosed as MRI-negative on routine inspection of 1.5 and 3.0T scans.

Methods: We implemented an automated classifier relying on surface-based features of FCD morphology and intensity, taking advantage of their covariance. The method was tested on 19 patients (15 with histologically confirmed FCD) scanned at 3.0T, and cross-validated using a leave-one-out strategy. We assessed specificity in 24 healthy controls and 11 disease controls with temporal lobe epilepsy. Cross-dataset classification performance was evaluated in 20 healthy controls and 14 patients with histologically verified FCD examined at 1.5T.

Results: Sensitivity was 74%, with 100% specificity (i.e., no lesions detected in healthy or disease controls). In 50% of cases, a single cluster colocalized with the FCD lesion, while in the remaining cases a median of 1 extralesional cluster was found. Applying the classifier (trained on 3.0T data) to the 1.5T dataset yielded comparable performance (sensitivity 71%, specificity 95%).

Conclusion: In patients initially diagnosed as MRI-negative, our fully automated multivariate approach offered a substantial gain in sensitivity over standard radiologic assessment. The proposed method showed generalizability across cohorts, scanners, and field strengths. Machine learning may assist presurgical decision-making by facilitating hypothesis formulation about the epileptogenic zone.

Classification of evidence: This study provides Class II evidence that automated machine learning of MRI patterns accurately identifies FCD among patients with extratemporal epilepsy initially diagnosed as MRI-negative. *Neurology*® 2014;83:48-55

GLOSSARY

FCD = focal cortical dysplasia; **GM** = gray matter; **LDA** = linear discriminant analysis; **MNI** = Montreal Neurological Institute; **RI** = relative intensity; **SEEG** = stereotactic implanted depth electrodes; **TE** = echo time; **TLE** = temporal lobe epilepsy; **TR** = repetition time; **WM** = white matter.

Focal cortical dysplasia (FCD) type II, an epileptogenic developmental malformation,¹ is characterized by cortical dyslamination, hypertrophic and dysmorphic neurons, and balloon cells²; it is the most common histopathology in surgical series of extratemporal lobe epilepsy.³ Reliable detection of this lesion is critical for successful surgery.⁴

On MRI, FCD type II is characterized by cortical thickening, blurring of the gray–white matter junction, and hyperintense signal.⁵ Many lesions, however, elude best-practice neuroimaging protocols. To enhance visibility, previous studies have modeled its main features using voxel-based methods, such as texture and morphometric analysis.⁶ The evaluation of multiple maps generated through these quantitative techniques is done visually, so that the yield and diagnostic confidence depend on the reader's familiarity with the algorithm. Limited generalizability also stems from the fact that these approaches have been validated mainly with lesions recognized on routine radiologic evaluation.^{7–11}

We address the pressing issue of lesion detection in MRI-negative FCD. We combined machine learning with surface-based analysis in patients with FCD type II initially diagnosed

Supplemental data
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From the NeuroImaging of Epilepsy Laboratory, Department of Neurology and McConnell Brain Imaging Center, McGill University, Montreal Neurological Institute and Hospital, Canada.

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Table 1 Demographics and results of automatic classification in MRI-negative patients examined at 3.0T

N	Age, y/sex	Duration, y	EEG interictal/ictal	PET (FDG)	Automatic detection lesion/ extralesional clusters	FCD histology	Engel, mo
1	26/F	24	R FCT/none	—	Yes/1	—	—
2	33/F	25	Bilateral F/none	—	—	IIa	Ia (33)
3	21/M	21	L CP/L FC	Normal	Yes/3	IIa	Ia (15)
4	25/M	4	L FC/none	—	Yes/0	—	—
5	24/F	20	Bilateral FC/bilateral F	R F	Yes/0	IIb	II (32)
6	26/F	18	L FCT/L FCT	—	Yes/1	IIb	Ia (26)
7	22/F	5	Bilateral F/none	L FT	Yes/0	IIa	II (26)
8	29/F	27	L F/L FC	Normal	Yes/0	IIb	Ia (24)
9	24/M	24	None/L FCT	Normal	Yes/1	IIb	II (24)
10	48/M	18	None/bilateral F	R FP	—	IIa	Ia (25)
11	37/M	18	R F/R F	R F	—	IIb	Ia (31)
12	31/F	15	L T/L TP	LT	Yes/0	—	—
13	34/M	18	Bilateral FC/R FC	R T	Yes/1	IIa	Ia (12)
14	25/F	13	R FCT/R F	R FT	Yes/2	—	—
15	19/F	7	CzPz/CzPz	Normal	Yes/0	IIa	Ia (10)
16	30/M	13	Bilateral FT/R F	L T	Yes/0	IIb	Ia (19)
17	34/M	27	Bilateral F/bilateral F	L F	—	IIa	Ia (12)
18	28/M	25	Bilateral CP/bilateral CP	—	—	IIb	III (18)
19	22/F	4	Bilateral FT/L FCT	Normal	Yes/3	IIb	III (10)

Abbreviations: CP = centroparietal; F = frontal; FC = frontocentral; FCD = focal cortical dysplasia; FCT = frontocentrotemporal; FT = frontotemporal; L = left; R = right; T = temporal; TP = temporoparietal.

as MRI-negative on routine radiologic inspection. Compared to voxel-based techniques, a surface-based approach preserves cortical topology and quantifies sulco-gyral anomalies, at times the only sign of dysgenesis.¹²

METHODS We present an automated algorithm trained on MRI-negative patients with histologically confirmed FCD. We ruled out sources of spectrum bias¹³ by evaluating the specificity of our algorithm against healthy individuals and clinically well-characterized disease controls. To minimize incorporation bias, our classifier trained on 3.0T data was tested on an independent cohort of patients and controls examined at 1.5T. Our method provides Class II evidence for diagnostic accuracy.¹⁴

Subjects. From a database of 45 consecutive patients with FCD admitted to the Montreal Neurological Institute (MNI) between 2009 and 2012 for the treatment of drug-resistant extratemporal lobe epilepsy, we selected 19 subjects (9 male; mean $\pm$ SD age 29 ± 8 years) in whom the initial routine radiologic assessment was unremarkable at both 1.5 and 3T, and thus diagnosed as MRI-negative. The dysplastic lesion was subsequently recognized through expert evaluation (A.B.) of texture maps.^{15,16} In the majority of patients (14/19 [74%]), the lesion had been overlooked likely because of its small size (mean $\pm$ SD volume 877 ± 832 mm³; range 45–2,679 mm³). In the remaining 5, although the lesion was relatively large ($6,333 \pm 2,164$ mm³), it was not seen because of the mild degree of morphologic and signal anomalies blending into the

adjacent cortex. Lesions were located in the frontal (14), cingulate (2), parietal (2), and insular (1) cortices.

The presurgical workup included seizure history, neurologic examination, neuroimaging, and video-EEG telemetry. Interictal spikes had lateralizing value in 8 patients (42%); ictal discharges were localized in 10 (53%). The 15 patients (79%) who had surgery underwent invasive monitoring using stereotactic implanted depth electrodes (SEEG), with positioning of the leads guided by the putative lesion seen on texture maps. In all, SEEG demonstrated a very active interictal activity and focal changes at seizure onset in the electrodes targeted at the lesion. According to the histopathologic grading,² 7 had FCD type IIa and 8 FCD type IIb. Mean postoperative follow-up was 21.1 ± 8.0 months. Ten patients (67%) became seizure-free (Engel class Ia),¹⁷ 3 had rare disabling seizures (class II), and 2 with lesions encroaching eloquent areas had worthwhile improvement (class III) as lesionectomy was incomplete. Three patients await surgery and one postponed it. Demographic and clinical data of patients are detailed in table 1; the flow diagram (figure 1) outlines the study design and results.

To assess the specificity of our algorithm, we examined 24 healthy controls (13 male; mean $\pm$ SD age 27 ± 4 years) and disease controls consisting of 11 patients with temporal lobe epilepsy (TLE) and hippocampal sclerosis (6 male; mean $\pm$ SD age 35 ± 11 years) who had undergone a selective amygdalo-hippocampectomy and were seizure-free (i.e., Engel Ia, mean $\pm$ SD follow up of 45 ± 8.4 months). Age and sex did not differ among groups ($t < 1.5$, $p > 0.1$).

Standard protocol approvals, registrations, and patient consent. The ethics committee of the MNI approved the study and written informed consent was obtained from all participants.

Figure 1 Flow diagram of study design and results

*Classifier trained on 3.0T MRI of patients with histologically proven focal cortical dysplasia (FCD). Engel Ia = completely seizure-free in Engel classification; FN = false-negatives; FP = false-positives; TLE-HS = temporal lobe epilepsy with histologically proven hippocampal sclerosis; TN = true-negatives; TP = true-positives.

MRI acquisition and image preparation. The 1.5T MRI protocol has been described in detail elsewhere.¹⁸ The 3.0T images were acquired on a Siemens (Munich, Germany) Trio Tim scanner using a 32-channel phased-array head coil. The protocol included a 3D magnetization-prepared rapid-acquisition gradient echo sequence providing isotropic voxels of $1 \times 1 \times 1 \text{ mm}^3$ (repetition time [TR] = 2,300 ms, echo time [TE] = 2.98 ms, flip angle = 7°), axial proton density and T2-weighted images (voxel size = $0.4 \times 0.4 \times 3 \text{ mm}$, TR = 2,300, 11,000 ms, TE = 20, 81 ms), coronal fluid attenuation inversion recovery (fluid-attenuated inversion recovery, voxel size = $1 \times 1 \times 3 \text{ mm}$, TR = 9,000 ms, TE = 80 ms), and coronal T2-weighted images (voxel size = $0.5 \times 0.5 \times 5 \text{ mm}$, TR = 7,000 ms, TE = 79 ms). Preprocessing involved automated correction of all images for intensity nonuniformity and intensity standardization,¹⁹ linear registration into standardized stereotaxic space,²⁰ and automatic classification of T1-weighted images into white matter (WM), gray matter (GM), and CSF.²¹

Cortical surface construction and FCD feature extraction. We applied the Constrained Laplacian Anatomic Segmentation using Proximity algorithm²² on preprocessed T1-weighted images to generate a model of the GM-WM and GM-CSF surfaces with 40,962 vertices per hemisphere. This algorithm iteratively warps a surface mesh to fit the GM-WM boundary in the segmented image. The outer surface is then estimated by expanding the inner surface along a Laplacian map between GM-WM and GM-CSF boundaries. During this step, partial volume information is used to preserve the

morphology of the GM-CSF boundary. The expansion proceeds at a uniform rate proportional to local thickness and is governed by topologic constraints. Extracted surfaces were nonlinearly aligned to the surface template using a 2D registration procedure based on patterns of cortical folding that improves interindividual correspondence.²³ The accuracy of surface extraction was verified by visual inspection prior to further analysis. We calculated at each vertex of the cortical surface the following morphologic and intensity-based features. To avoid data interpolation related to registration, features were computed after surfaces were warped back into each individual's native space.

Morphologic features. Cortical thickness. We measured thickness as the distance between corresponding vertices on the GM-WM and GM-CSF surfaces.²²

Sulcal depth. We have shown that small FCD lesions are often located at the bottom of a deep sulcus.¹⁸ To calculate sulcal depth across the entire cortex, we first overlaid a brain hull model on the cortical manifold to detect vertices on the gyral crowns, which were initialized with a depth of zero. The depth of vertices located within sulci was then computed using the geodesic distance from gyral crown vertices.²⁴

Curvature. By disrupting the mechanical properties of the cortical mantle, FCD lesions may cause local changes in curvature.¹⁸ We obtained the absolute mean curvature by calculating the area-minimizing flow that defines the deviation from the cortical surface to a sphere.

Intensity-based features. Relative intensity. We used a modified version of our previous index of relative intensity (RI)²⁵ as follows: $RI(x) = 100 \times (I(x) - GM_{peak}) / (B - GM_{peak})$, where $I(x)$ is the intensity at voxel x , GM_{peak} the intensity of GM peak obtained from the whole-brain histogram, and B the intensity at the boundary between GM and WM. For surface-based sampling of RI, we constructed 3 equidistant intracortical surfaces by placing uniformly spaced vertices between linked vertices of inner (GM-WM) and outer (GM-CSF) surfaces. The RI was then interpolated at each vertex of these surfaces and averaged.

Gradient. To model blurring at the GM-WM interface, we applied a gradient operator that measured intensity differences 0.5 mm above and below the GM-WM interface along the surface normal vector.

Classifier design. Classification was performed using Fisher linear discriminant analysis (LDA), an algorithm that automatically finds the optimal weights for a linear combination of features to achieve maximal separation between classes.²⁶ Prior to classification, features were smoothed using a 5-mm full-width-at-half-maximum Gaussian surface kernel and normalized with respect to healthy controls' distribution through a z transform. FCD lesions were segmented manually on MRI by an expert (D.S.), projected onto cortical surfaces, and blurred with a kernel of the same size. We trained and cross-validated the classifier using a leave-one-out strategy, by which a patient is classified based on data of all patients other than that patient. This procedure allows an unbiased assessment of lesion detection performance for previously unseen FCD cases.

The classification steps are detailed in figure e-1 on the *Neurology*[®] Web site at Neurology.org. The classifier was trained on patients' multivariate set of features sampled from all lesional and randomly selected nonlesional vertices, balancing their number in both classes. It generated vertex-wise probability maps for each individual to test (i.e., patients and controls). On these maps, a cluster was defined as a collection of vertices that form 6-connected neighbors on the triangulated cortical surface. Within each cluster, we assessed the overall load of anomalies by computing the Mahalanobis distance (a multivariate z transform between each patient's feature vector and the corresponding distribution in controls). For the set of vertices displaying the highest distance, we computed statistical moments (i.e., mean, asymmetry, SD, skewness, and kurtosis representing the shape of the distribution of each feature) and spatial location (as determined by anatomical parcellation²⁷ and 3D coordinates). We fed these values to a second classifier and generated probability maps. For both classification schemes, we set the threshold of probability maps at the highest detection and lowest false-positive rates.

Evaluation of classification accuracy. Performance of the classifier was assessed with regards to manual lesion labels. Sensitivity was defined as the proportion of patients in whom a detected cluster correctly colocalized with the manual lesion label. Specificity was calculated as the proportion of healthy or disease controls in whom no FCD lesion cluster was falsely identified.

Cross-dataset classification. We also evaluated the performance of our classifier trained on 3.0T data on a different dataset acquired at 1.5T including 14 patients (7 male, mean $\pm$ SD age 28 ± 11 years) with histologically proven FCD (4 type IIa and 10 type IIb) and 20 age- and sex-matched healthy controls (8 male, mean $\pm$ SD age 27 ± 5 years). As for the 3.0T dataset, lesions had been overlooked on the initial radiologic assessment and subsequently recognized through expert evaluation of texture maps.

RESULTS For the vertex-wise classification, the threshold of the posterior probability providing the

best tradeoff rate between true-positives and false-positives was 0.90. At this threshold, the classifier detected all but one lesion ($18/19 = 95\%$); nevertheless, there was still a high proportion of false-positives (mean $\pm$ SD clusters: patients 32 ± 17 ; controls 27 ± 16). In the subsequent cluster-wise classification (threshold of 0.90), no lesional clusters were identified in healthy subjects or the disease control TLE group, resulting in 100% specificity. The LDA assigned the highest normalized weights (i.e., more than 10% of total weighting) as follows: vertex-wise classification was mainly driven by perpendicular gradient (42%), followed by cortical thickness (41%), and sulcal depth (14%). Cluster-wise classification was largely based on perpendicular gradient (48%), followed by sulcal depth (13%), and cortical thickness (11%).

In FCD patients, the detected clusters colocalized with the manual lesion in $14/19$, yielding a sensitivity of 74%. In 50% of them ($7/14$), the cluster corresponded to the FCD lesion (figure 2). In the remaining 7 patients, besides the cluster colocalizing with the manual label, a median of one extralesional cluster was found (range 1–3); in all but one patient, the extralesional clusters had the smallest size or the lowest multivariate z score, the most abnormal feature being increased sulcal depth (figure 3). Extralesional clusters were found in frontal or central areas. They were located in the same lobe as the primary lesion in 2 patients; in 3 of the remaining 5, they were in the contralateral hemisphere, bilateral in 2. Among these 7 patients, 5 were operated at the primary lesion site; extralesional clusters were not resected. Three patients (60%) became completely seizure-free (Engel class Ia), one had class II outcome, and incomplete resection of the primary lesion was likely responsible for the unsatisfactory result (Engel class III) in the remaining one.

Repeating the analysis in the 15 patients with histologically proven FCD, the classifier performance was virtually identical as in the overall group of 19, with $10/15$ lesions detected (67% sensitivity, 100% specificity against healthy and disease controls, median of one extralesional cluster; table e-1).

Lesion classification in the 1.5T dataset provided virtually identical results compared to the 3.0T cohort. In the vertex-wise classification, the classifier achieved high sensitivity ($13/14 = 93\%$) with a high proportion of false-positives (mean $\pm$ SD clusters: patients = 38 ± 18 ; controls = 17 ± 17). Subsequent cluster-wise classification eliminated false-positive clusters in both patients and controls, while maintaining a high lesion detection rate, with 71% sensitivity (lesion detected in $10/14$ patients) and 95% specificity (3 false-positive clusters in a single control; table e-2).

Figure 2 Examples of automated focal cortical dysplasia type II detection

The axial T1-weighted MRI sections show the region containing the focal cortical dysplasia (FCD) (dashed square). The magnified panel displays the manually segmented FCD label (dotted green line) and its volume; the label is projected onto the surface template. In these 3 examples, the vertex-wise classification identified several putative lesions (red), whereas the subsequent cluster-wise classification discarded all false-positives except the cluster colocalizing with the manual label (blue). The case number refers to that listed in table 1.

DISCUSSION MRI has transformed the management of drug-resistant epilepsy by allowing the detection of structural lesions associated with the epileptogenic zone. However, despite technical improvements in hardware and sequences, MRI inspection is often unremarkable, as shown by our patients who were considered MRI-negative on both 1.5 and 3.0T scanners. Reassessment guided by texture analysis, nevertheless, identified the lesion in all. Notably, although texture maps model FCD characteristics in a quantitative fashion, they are evaluated visually, making the distinction between lesional areas and false-positives challenging. Moreover, integrating the diverse and complex information embedded in the various maps requires expertise that few centers have developed so far. Another source of difficulty arises from the paucity or lack of localizing clinical semiology and surface EEG findings to direct the search for FCD.

Our previous automatic FCD detection on 1.5T MRI relied on voxel-based texture analysis combined

with a Bayesian classifier.²⁸ The algorithm was validated with mid- to large-sized lesions visible on routine radiologic inspection. Nevertheless, classification failed in up to 20% of cases. Such performance is unsatisfactory given current referral patterns, with an increasing number of patients with extratemporal epilepsy and non-diagnostic MRI, even at 3.0T. In these patients, lesions are subtle, with morphologic characteristics that may differ only slightly from normal tissue. Voxel-based methods do not optimally characterize morphology as they neglect anatomical relationships across the folded cortex; while relatively efficient in detecting obvious lesions, they amplify unwanted partial volume effects, leading to a loss of signal from confined or subtle abnormalities.²⁹ Our current algorithm relies on surface-based multivariate pattern recognition that statistically combines morphology and intensity, taking advantage of their covariance, thus unveiling subthreshold tissue properties not readily identified on a single modality. For automated lesion detection, we chose a linear

Figure 3 Extralesional findings

Results of the automated classification are projected onto the patient's cortical surface (case 1; see table 1 for details). Z scores of sulcal depth, thickness, and gradient for the lesional (blue) and extralesional (red) clusters are indicated. While the lesional cluster colocalizing with the manually segmented focal cortical dysplasia label (dotted green line on axial T1-weighted MRI) exhibits abnormalities evenly distributed across the different features, the extralesional cluster is mainly characterized by increased sulcal depth. Visual MRI inspection in this region (dashed white circle, frontal operculum) does not reveal any obvious anomaly besides altered sulcal arrangement.

discriminant model, a supervised technique that is mathematically robust and simple to interpret.³⁰ The most significant contribution of machine learning to clinical practice is that it provides an automatic and objective way to extend knowledge obtained from training data to unknown (i.e., first seen) cases. Compared to previous work, we explicitly circumvented several sources of bias. First, we cross-validated our findings using a leave-one-out strategy and obtained a sensitivity of 74% after post hoc removal of false-positives, half of patients presenting with a single lesional cluster. Secondly, when applying our classifier trained on 3.0T images to an independent dataset of patients with histologically proven FCD acquired at 1.5T, we maintained high sensitivity. Given that all subjects were initially diagnosed as MRI-negative, this fully automated approach offered a substantial gain in sensitivity over standard radiologic assessment. Cross-dataset classification results support the generalizability of our method to MRI-negative FCD across different cohorts, scanners, and field strengths.

In addition to high sensitivity, another equally important result is that, after removal of false-positives, no lesional vertices were identified in healthy or disease control subjects. Such high specificity indicates that our classifier correctly ignored healthy tissue in normal controls, and disregarded FCD-unrelated pathology in the disease control group. These findings are especially relevant as in 50% of patients the classifier identified 1–3 extralesional clusters (median of 1). Extralesional clusters were not resected; thus no pathology was available. Retrospective analysis revealed that, although these clusters presented with features similar to those of the primary FCD, they were smaller and their contribution to the multivariate distribution was somewhat different. While cortical thickness had the highest *z* score within the primary lesion, sulcal depth typified extralesional clusters. Additionally, there were no EEG anomalies associated with the latter; no clinical or histopathologic characteristics differentiated these patients from those with a single cluster. Yet the absence of false-positives in healthy and disease controls combined with reports of diffuse³¹ or multifocal FCD³² suggests that these clusters may indeed indicate abnormal, not necessarily epileptogenic regions that are otherwise undetectable via conventional means. Sulcal abnormalities in cortical malformations have been described in the proximity of MRI-visible lesions,¹⁸ but also at distance,^{12,33,34} and are thought to result from disturbed neuronal connectivity and WM organization.^{35,36} Alternatively, these regions may present with variations in cyto- and myelo-architecture and decreased neuronal density,³⁷ leading to changes in micromechanical properties,³⁸ resulting in local weakness within the developing neocortex.

The absence of a visible lesion is one of the greatest challenges in epilepsy surgery and has led to an increase in invasive EEG studies. Yet without informed, image-guided implantation, even with widespread coverage, sampling errors may occur in up to 40% of cases; consequently, the target cannot be defined and the outcome of surgery, if considered, is poorer.³⁹ To optimize hypothesis formulation and to improve the patient's safety while minimizing costs of the presurgical diagnostic procedures, future efforts should aim at creating independent noninvasive techniques that take into account all facets of the epileptogenic process.

AUTHOR CONTRIBUTIONS

S.-J. Hong: study concept and design, image processing, statistical analysis, drafting manuscript. Dr. Kim: study design, statistical analysis. Dr. Schrader: lesion segmentation, drafting manuscript. Dr. Bernhardt: statistical analysis, revising manuscript. Dr. Bernasconi: study concept and design, revising manuscript, obtaining funding. Dr. Bernasconi: study concept and design, revising manuscript including medical writing, obtaining funding.

Comment: Has automated detection of cortical dysplasias come of age?

Cortical dysplasias cause pharmacoresistant epilepsy and are amenable to surgical treatment, but their detection relies on expert visual analysis of MRI. Variability in MRI interpretation, false-positives, and false-negatives are problematic. Therefore, validated, accurate, automated algorithms to identify cortical dysplasias would be a great step forward. Hong et al.¹ describe such an algorithm for type II cortical dysplasias.

Key questions about new diagnostic tools include whether they are valid and accurate (find what they are supposed to find), reliable (perform consistently in various settings), and usable in practice. For data-driven tools, we also need to know about model robustness and whether clinical expertise iteratively informed their development—i.e., do they make sense clinically?

The model, patient selection, and analyses are well-described in this study. The sensitivity (~70%) and specificity (95%–100%) achieved are impressive, providing good rationale for validating the algorithm in other settings. However, performance in actual practice may be less impressive for several reasons. First, the technical aspects and expertise must be correctly replicated. Second, the algorithm was developed in patients with known type II cortical dysplasia identified by expert visual analysis of MRI, those with known hippocampal sclerosis (HS), or normal controls. Using preselected patients in tool development inflates sensitivity and specificity. By contrast, clinicians will likely use the algorithm in patients with suspected but unclear cortical dysplasia, not in healthy controls or in those with known HS. Third, the algorithm identified positive clusters that were not studied further: are they false-positive (lower specificity) or real? Finally, the findings apply only to type II cortical dysplasia, which can be more readily identified by visual analysis than the more challenging type I dysplasias.

This study is an excellent example of the development of much-needed data-driven, automated detection algorithms for cortical dysplasia—a great step forward that awaits validation.

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Samuel Wiebe, MD, FCAHS

From the Department of Clinical Neurosciences and Hotchkiss Brain Institute, Calgary, Canada.

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