Advances in Image Processing for Epileptogenic Zone Detection with MRI

Radiology

REVIEWS AND COMMENTARY • REVIEW

Advances in Image Processing for Epileptogenic Zone Detection with MRI

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Supported by the Dutch Epilepsy Foundation (Epilepsiefonds) (WAR project number 2020-09).

Conflicts of interest are listed at the end of this article.

Radiology 2023; 307(5):e220927 • https://doi.org/10.1148/radiol.220927 • Content codes: NR MR

Focal epilepsy is a common and severe neurologic disorder. Neuroimaging aims to identify the epileptogenic zone (EZ), preferably as a macroscopic structural lesion. For approximately a third of patients with chronic drug-resistant focal epilepsy, the EZ cannot be precisely identified using standard 3.0-T MRI. This may be due to either the EZ being undetectable at imaging or the seizure activity being caused by a physiologic abnormality rather than a structural lesion. Computational image processing has recently been shown to aid radiologic assessments and increase the success rate of uncovering suspicious regions by enhancing their visual conspicuity. While structural image analysis is at the forefront of EZ detection, physiologic image analysis has also been shown to provide valuable information about EZ location. This narrative review summarizes and explains the current state-of-the-art computational approaches for image analysis and presents their potential for EZ detection. Current limitations of the methods and possible future directions to augment EZ detection are discussed.

Focal epilepsy is characterized by unprovoked recurrent seizures and represents one of the most common chronic neurologic disorders globally (1,2). Seizures can be classified as primarily generalized, focal, or with an unknown onset. Seizures are often accompanied by motor or nonmotor symptoms in combination with either impaired or retained awareness (3). Focal seizures originate from a specific onset epileptogenic zone (EZ) on one side of the brain, whereas generalized seizures affect both hemispheres, but may still have a focal onset. Epileptic seizures can be controlled with antiseizure medication in 70% of patients, while 30% of patients have drug-resistant epilepsy(4). When medication does not result in seizure freedom and an epileptogenic lesion is localized, surgery becomes a curative treatment option (5–8). Along with electroencephalography and seizure semiology assessment, medical imaging is a crucial cornerstone for presurgical work-up (9).

In most centers, MRI is the reference standard for structural assessment of the brain in patients with epilepsy (10). MRI allows not only for the identification of subtle structural and functional abnormalities but also for the assessment of the overall brain anatomy (11). The EZ is not visible on MRI scans in approximately 30% of patients with drug-resistant epilepsy (12); these patients are commonly referred to as MRI-negative patients. MRI-positive patients have an approximately 2.5 times higher chance of becoming seizure-free after surgical intervention (13). Lesion identification is therefore a major predictive factor for a good postoperative outcome (13).

The aim of image processing in this context is to provide additional input for radiologists to detect subtle abnormalities by improving visual conspicuity. In particular, small cortical lesions can often be difficult to recognize. Although structural MRI is the most commonly used approach, more evidence is emerging that physiologic MRI can also provide valuable information about the EZ (14).

The purpose of this narrative review is to *(a)* outline the principles behind the image processing methods along with relevant findings and *(b)* provide an overview of recent neuroimaging research in the field of EZ detection.

Structural Image Analysis

Structural imaging is an important basis for diagnostic decision-making during presurgical work-up for patients with epilepsy.

Morphometric Analysis

Comparison of structural images between patients with epilepsy and individuals without epilepsy can reveal previously undetected focal structural differences. This can result in a morphometric map that highlights those voxels that statistically differ compared with the control data set.

Voxel-based morphometry (VBM) compares images voxel-by-voxel, and VBM of T1-weighted images has been studied substantially over the past decades. VBM findings may serve as a guide for the radiologist to focally re-examine the structural images and provide input for invasive diagnostic procedures such as stereoelectroencephalography. A commonly used implementation of VBM is the Morphometric Analysis Program (hereafter, MAP; *https://www.*

Abbreviations

ALFF = amplitude of low-frequency fluctuations, ASL = arterial spin labeling, EZ = epileptogenic zone, FA = fractional anisotropy, FCD = focal cortical dysplasia, FLAIR = fluid-attenuated inversion recovery, Grad-CAM = gradient-weighted class activation mapping, TBSS = tract-based spatial statistics, TLE = temporal lobe epilepsy, UHF = ultrahigh field strength, VBM = voxel-based morphometry

Summary

Dedicated MRI processing techniques can provide valuable information about the epileptogenic zone (EZ) location and improve the EZ detection rate.

Essentials

- Image processing of structural, diffusion-weighted, and functional MRI should be considered in the presurgical work-up for epilepsy to increase the epileptogenic zone (EZ) detection rate.
- In vivo validation of the image processing outputs remains challenging, and more research is necessary to reduce false-positive findings.
- Ultrahigh-field-strength MRI and artificial intelligence may provide an additional performance boost to the computational methods and may further increase the EZ detection rate.

translationalneuroimaging.de/map18) (15). The MAP software uses T1-weighted input images to calculate three separate morphometric maps: *(a)* a junction map, which is sensitive to blurry gray-white matter transitions; *(b)* an extension map, which is sensitive to the abnormal presence of gray matter in white matter; and *(c)* a cortical thickness map, which highlights unusual cortical thickening (Fig 1). The specific process of computing these separate images has been extensively described elsewhere (16). Although MAP was primarily conceived as a tool for detection of focal cortical dysplasia (FCD), heterotopia and polymicrogyria were also successfully detected (16). Multiple studies in patients with epilepsy have shown the diagnostic yield of MAP in MRI-negative patients (17–19). MAP has also been demonstrated to help guide stereotactic implantation of depth electrodes and limit the number of implanted electrodes (20).

In addition to T1-weighted imaging, T2-weighted and/or fluid-attenuated inversion recovery (FLAIR) sequences have also been used for VBM analysis in both adult (21,22) and pediatric (23) patients with epilepsy. A recent study using multiple contrasts as inputs for the analysis (so-called multispectral VBM) showed that the input combination of T1-weighted and T2-weighted and/or FLAIR images yielded the best results in highlighting the potential EZ in MRI-negative patients (24).

Region-based morphometry is a method that quantifies properties of specific anatomic (sub)cortical regions (eg, volume or cortical thickness) and compares those values against those of a control cohort. To estimate these quantities, the brain images must be segmented (manually, semiautomatically, or fully automatically) by delineating the borders of anatomic structures (25). Volumetric differences may not directly delineate the potential EZ but rather help by depicting atrophic or hypertrophic brain regions, which may indicate the location of the EZ (26). Moreover, volumetric asymmetry indexes have been used to determine interhemispheric differences, especially for the hippocampus and its subfields in temporal lobe epilepsy (TLE) and

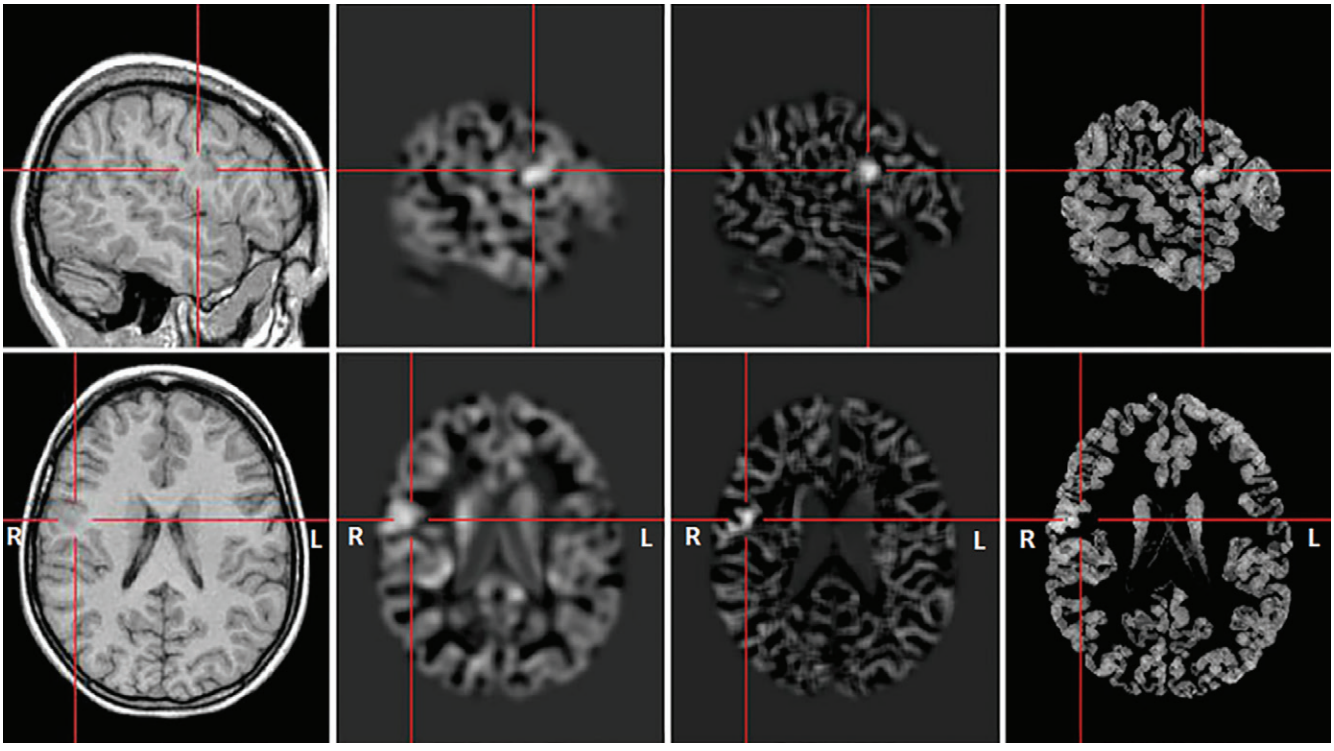

Figure 1: From left to right, T1-weighted MRI scans with calculated extension, junction, and thickness morphometric maps in focal cortical dysplasia IIb (age and sex unknown). The morphometric maps show the signs of a dysplastic lesion (ie, abnormal gyration, blurring of the gray-white matter junction, and abnormal cortical thickness). The red lines are crosshairs, and the center point of the red lines indicate the location of the presumed epileptogenic zone. (Reprinted, with permission, from reference 16.)

frontal lobe epilepsy (27,28). Volumetric analyses have also indicated that FCDs tend to be localized more commonly within atrophic regions (26).

Morphometric approaches are highly dependent on the quality of either image coregistration (ie, structural alignment) or segmentation. Imprecise alignment of the patient and control images can lead to false-positive findings (29). To maximize the potential yield of morphometric analyses, identical sequence protocols from the same MRI system should be used for all individuals. Differences in tissue contrast, signal-to-noise ratio, and scanner-specific properties may hinder the comparison outcome.

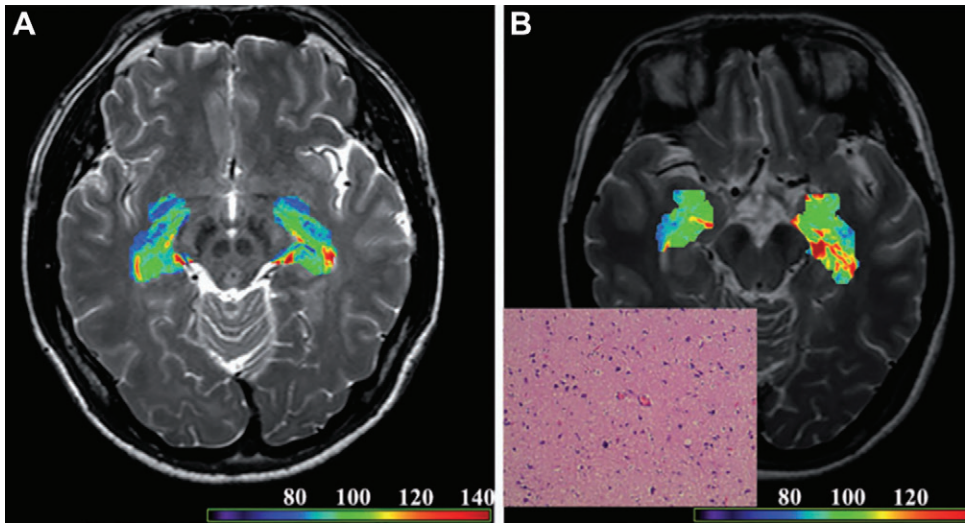

Figure 2: Color-coded T2 relaxometry maps in **(A)** a healthy participant (33-year-old woman) and **(B)** a patient with left-sided mesial temporal lobe epilepsy (41-year-old woman). The temporal lobe is contoured and pixels with elevated T2 values (in milliseconds) are shown in red. Neuronal degeneration and atrophy of hippocampal neurons can be observed on the photomicrograph (hematoxylin-eosin stain) of the resection specimen (inset in **B**). (Reprinted, with permission, from reference 35.)

Quantitative T1 and T2 relaxation time mapping are techniques to obtain the real T1 and T2 values for each scanned voxel. For T1 mapping, the recently introduced magnetization-prepared 2 rapid gradient echo, or MP2RAGE, sequence provides a simplified approach. MP2RAGE acquires two single-inversion-time images, which enables a quick calculation of the quantitative T1 map and a T1-weighted image with improved gray-white matter contrast and reduced B1 inhomogeneity artifacts (30). Higher T1 values were observed in limbic cortices ipsilateral to the EZ in patients with TLE (31). Quantitative T1 has also been shown to be negatively correlated with neuronal density in the hippocampal subfield cornu ammonis 4 and the dentate gyrus in patients with TLE and was reported to be a potential accurate biomarker for hippocampal pathology (32).

Quantitative T2 assessment has been found to have potential for lateralizing TLE as it is sensitive to neuronal loss (33) and abnormal brain regions (34) often demonstrate higher T2 values within the area of the EZ (35) (Fig 2). The use of quantitative T2 mapping was found to depict hippocampal sclerosis with 100% accuracy, compared with 60% accuracy achieved from analyzing normalized FLAIR images (36). The main limitation of T2 relaxometry is the long T2 signal in cerebrospinal fluid, which can introduce unwanted partial volume effects. This is especially relevant for the detection of FCDs and the evaluation of the cortex because it is in very close proximity to the cerebrospinal fluid (22).

Diffusion Image Analysis

Diffusion-weighted imaging helps quantify the mobility of water molecules within tissue. With acquisition of diffusion-weighted images from at least six different directions (so-called diffusion-sensitized gradients), three-dimensional reconstruction of the main white matter tracts is possible with image processing, providing an estimate of structural connectivity. Acquiring diffusion properties from multiple directions, however, increases the scanning time substantially.

Mean diffusivity (MD) is the average water diffusivity within a voxel and can be calculated from merely three orthogonal gradient directions. Abnormal MD values have been reported both ipsilateral and contralateral to the suspected EZs in pediatric patients with epilepsy (37). MD abnormalities have also been found to be widespread and bilaterally distributed in patients with unilateral TLE with higher MD in thalamic regions (38). The diffusion-weighted imaging and MD contrast can be dependent on the time between the MRI examination and the last seizure; however, the exact effect of the seizure-to–scan time delay remains uncertain and may vary per individual (39).

Fractional anisotropy (FA) provides a single value that represents the diffusion anisotropy and that can be calculated from the tensor values in each voxel (Figs 3, 4). FA describes how strong a preferred direction of water diffusion exists within the given voxel and therefore can reflect the integrity of the white matter tracts (40). It has been reported in multiple studies that FA tends to be reduced mainly on the side of the lesion in patients with epilepsy (41,42). Furthermore, FA values were found to be positively correlated with the volume of ipsilateral hippocampal regions in patients with TLE (43). The degree of atrophy of subcortical structures in patients with TLE may correlate with FA values. Lower FA values were found to be correlated with the duration of epilepsy, indicating that FA might be a potential marker of progressive tissue degeneration due to the recurring seizures (44).

Tract-based spatial statistics (TBSS) is a method that may use FA maps to highlight tissue abnormalities between patients with epilepsy and controls. TBSS attempts to improve the sometimes-problematic spatial coregistration of

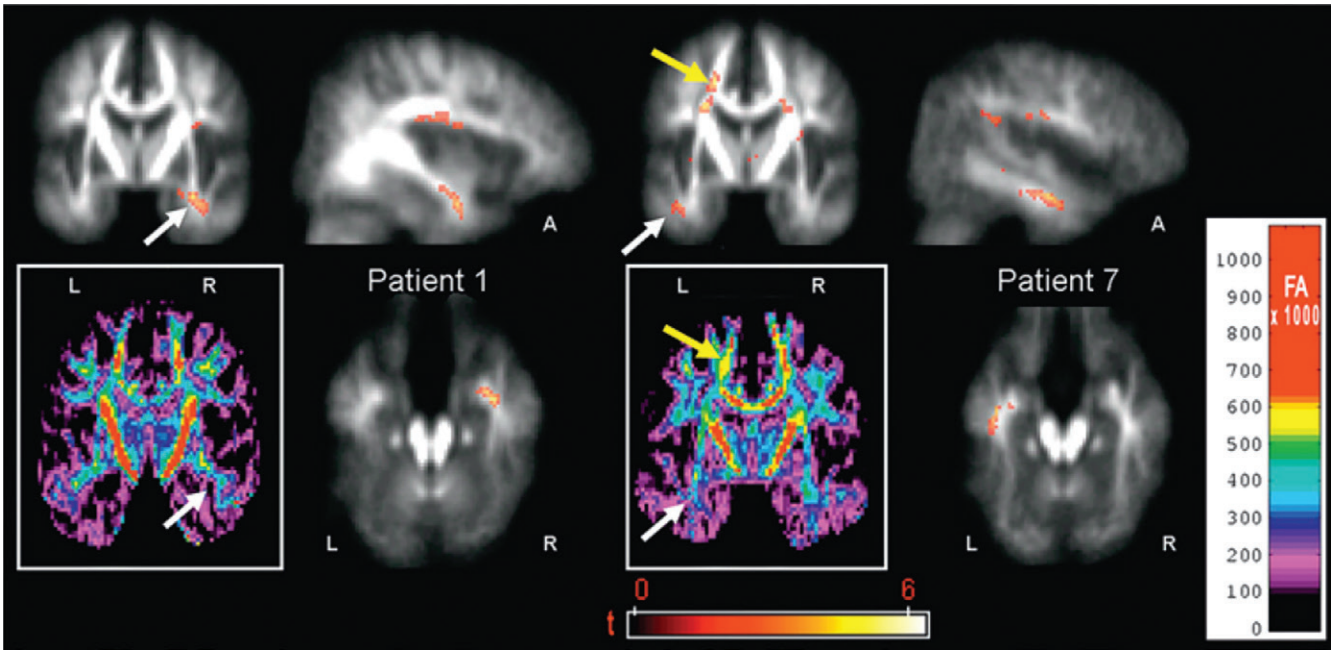

Figure 3: Fractional anisotropy (FA) abnormalities observed in two patients with MRI-negative focal epilepsy. The suspected epileptogenic zone of patient 1 (27-year-old man) and patient 7 (34-year-old woman) was localized in the right and left hemispheres, respectively. The indicated temporal (white arrows) and extratemporal (yellow arrows) FA reductions were also clearly visible in corresponding color-coded FA maps (outlined figures). Notably, false-positive findings can be observed in the FA maps of both patients. (Reprinted, with permission, from reference 42.)

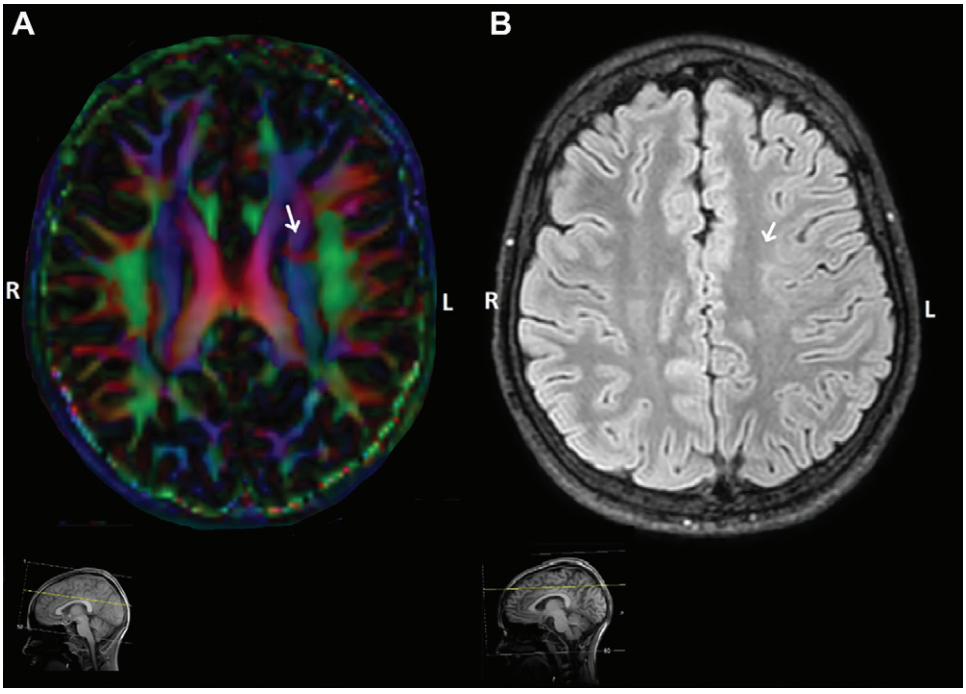

Figure 4: Fractional anisotropy (FA) abnormality in a pediatric patient (14-year-old boy) diagnosed with drug-resistant focal epilepsy. Postresection histopathologic examination classified the lesion as focal cortical dysplasia type IIa. Arrow indicates the location of the abnormal fiber crossing. **(A)** FA map colored according to the directionality of the diffusion. **(B)** Fluid-attenuated inversion recovery MRI scan shows no visible abnormality. (Images courtesy of the Department of Radiology & Nuclear Medicine at Maastricht University Medical Center+, Maastricht, the Netherlands.)

low-resolution images by projecting individual FA maps onto a representative tract map derived as a mean FA map from all control individuals and then applying the morphometric comparison (45). Owing to the projection, TBSS does not require precise coregistration (45,46). Although TBSS based on FA maps uses lower spatial resolution, it has been shown to provide superior output compared with VBM analysis of T1-weighted images (37). Abnormalities detected with TBSS have been found to correlate with myelination and neurodegenerative changes (47). TLE may be associated with widespread white matter alterations (48,49). In patients with unilateral hippocampal sclerosis, differentiation between left- and right-sided mesial TLE was shown to be feasible using TBSS (50). Although TBSS has been demonstrated to help detect mostly ipsilateral microstructural changes in patients with TLE, its diagnostic value for direct EZ localization must be further investigated.

Conventional diffusion-tensor imaging is part of standard MRI protocols for patients with epilepsy and can be used for presurgical planning, for example to visualize the Meyer loop to reduce the risk of optic radiation damage after temporal lobe resection (51,52).

Physiologic Image Analysis

Physiologic MRI aims to provide information about the functional state of brain regions. Epilepsy is being increasingly viewed as a network disorder and as such the information about the brain's functionality may be crucial (53). The EZ can display altered metabolic demands, and physiologic MRI can aid in localizing and delineating the EZ (54,55).

The acquisition of physiologic images generally includes a times series of multiple, often low-spatial-resolution, three-dimensional images to capture hemodynamic or neurovascular coupling features of the pathophysiology. As a result, image processing techniques are required to convert the data into formats that help visualize the dynamic tissue changes.

Blood Oxygen Level–Dependent Functional MRI

Blood oxygen level–dependent, or BOLD, functional MRI relies on the oxygen demand of activated brain regions and as such indirectly reflects neuronal activity. Apart from evoked brain activation, resting-state functional MRI can measure spontaneous fluctuations of ongoing neuronal activity. Resting-state functional MRI has the potential to help determine specific epileptogenic networks and functional interictal abnormalities (55).

Regional homogeneity (ReHo) is a measure of the temporal similarity of a given voxel to its surrounding voxels within a predefined region (55). As such, ReHo may reflect the small-scale abnormal synchronization of the blood oxygen level–dependent response and therefore could be indicative of the spread of epileptic seizure activity (56). Studies suggest that ReHo may have similar sensitivity and specificity for localizing regions with abnormal metabolic demands in patients with epilepsy compared with fluorine 18 (^{18}F) fluorodeoxyglucose PET (Fig 4) (14,57). Previous contralateral asymmetry analyses of ReHo maps suggested further improvement in the detection of EZ (58). In a study focusing on the effect of vagal nerve stimulation on resting-state brain activity in patients with drug-resistant epilepsy, ReHo in the right middle or superior temporal gyrus was found to be indicative of the postoperative seizure outcome (59). However, the functional MRI acquisition introduces intrinsic correlations between adjacent voxels that are not necessarily related to brain activity. These correlations propagate into the ReHo maps and may hinder the results. Furthermore, smoothing the images before ReHo calculations may provide changes in the final output because smoothing distributes the information across neighboring voxels.

Amplitude of low-frequency fluctuations (ALFF) can serve as a marker of a local demand for oxygenated blood supply (60) and is calculated as a mean power of a specific frequency band in a functional MRI voxel. To account for the effects of physiologic noise and signal fluctuations from large nearby blood vessels, fractional ALFF can be calculated by dividing the ALFF value by the mean power of the entire frequency bandwidth (61). Concordance between ALFF and stereoelectroencephalographic abnormalities was reported in individuals with either FCD or undiagnosed focal epilepsy (62). In addition, contralateral asymmetry analysis of the fractional ALFF was shown to indicate lesion lateralization (27) and the presence of abnormal tissue in the temporal lobes (60). Recently, increased ALFF metrics were found bilaterally in subcortical structures in patients with mesial TLE and alterations in ALFF could be traced along white matter tracts, indicating its ability to reflect the epileptic spread through functional networks (63). Both ALFF and functional ALFF are used in research (61).

Functional connectivity (FC) measures the functional relationship between separate brain areas and/or voxels and can be obtained in either a voxel-wise or region-wise manner. FC is calculated using the linear correlation between all pairs of regions or voxels, resulting in an FC matrix. Subsequently, the FC data can be included into a degree centrality map, in which each voxel contains the number of strong functional connections to others. Comparison of FC between patients with epilepsy and healthy controls can reveal alterations in the connectivity and aid with EZ localization. FC abnormalities ipsilateral to the lesional area in TLE have been reported in multiple studies, along with deviations in the default mode network (64,65). FC changes in patients with TLE were found to be present in the hippocampus and amygdala (65), and additional changes were observed in the thalamus of pediatric patients with epilepsy (66). FC was found to be a potentially valuable indicator of epileptogenic circuits and foci locations (67,68).

Arterial Spin Labeling

Perfusion imaging can help measure cerebral blood flow and potential alterations in and around the EZ. Arterial spin labeling (ASL) traces molecules magnetically instead of the radioactive tracer used in PET (69,70). Similar to PET, the tracer has a temporal decay time, which for ASL is equal to the T1 relaxation time of blood (approximately 1.6 seconds at 3 T) (71).

Cerebral blood flow can be quantified from the ASL acquisition as the mean difference between a set of control images (magnetically unlabeled water molecules) and magnetically labeled images. Multiple studies have reported a concordance between ASL and ^{18}F fluorodeoxyglucose PET images (72,73), which may indicate the presence of abnormal metabolic demands associated with the EZ. Cerebral blood flow maps were reported to have high potential for uncovering and delineating the EZ (69,74), and the asymmetry index of the cerebral blood flow maps was reported to be useful for EZ localization (75). However, the time span between the last observed seizure and the time of image acquisition can influence the diagnostic value of ASL for EZ detection as perfusion alterations can be temporary (69). A study that used a subtraction of the interictal acquisition (24 hours after the last seizure) from the postictal acquisition (90 minutes after habitual seizure) reported that the postictal hypoperfusions overlapped with the suspected onset zone in 80% of subjects with significant hypoperfusion and favorably compared with ictal SPECT and interictal PET (76).

Machine Learning and Artificial Intelligence

The implementation of artificial intelligence has been of great interest to epilepsy researchers, especially when combined with multimodal approaches (77). Multiple studies have successfully applied machine learning algorithms for EZ detection, and the advances in this field were recently reviewed (78,79). Manually

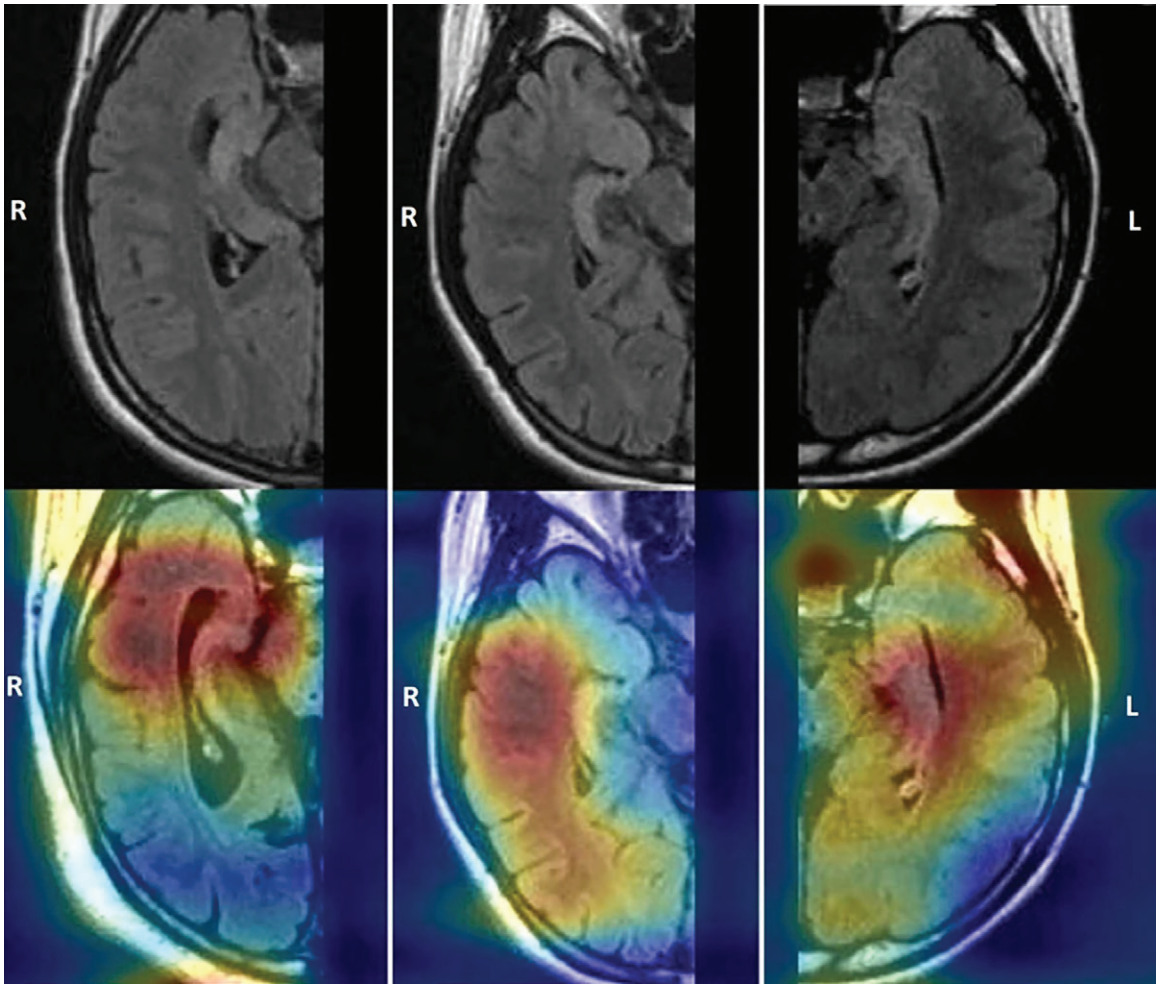

Figure 5: Neural network gradient-weighted class activation mapping (Grad-CAM) in three imaging data sets from patients correctly diagnosed with mesial temporal lobe epilepsy with hippocampal sclerosis by a clinical expert with the help of artificial intelligence. Fluid-attenuated inversion recovery (FLAIR) MRI scans at 3 T in the three patients (age and sex unknown) (top). Grad-CAM heat maps overlayed over the structural images (bottom). A neural network was trained to classify FLAIR images either as mesial temporal lobe epilepsy–hippocampal sclerosis or healthy. Grad-CAM methodology was used to trace back the decision-making process. Hot colors indicate regions that strongly influenced the network's classification. Cold colors indicate regions that weakly influenced the network's classification. (Reprinted, with permission, from reference 81.)

labeled EZ areas are often required for the model to learn the underlying features. For EZ localization purposes, deep learning methods using structural images combined with gradient-weighted class activation mapping (Grad-CAM) recently kindled particular interest (Fig 5). Grad-CAM can provide a heat map where the intensity of a voxel directly corresponds to how much this particular voxel influenced the network's final decision as to whether an individual has epilepsy or not. This approach was demonstrated to be capable of localizing malformations of cortical development (which are often associated with drug-resistant epilepsy) in pediatric patients (80). Recently, deep learning with a Grad-CAM approach was shown to correctly localize mesial TLE with hippocampal sclerosis based on FLAIR images with 91.1% mean sensitivity (81). The main downfall of machine learning approaches is the need for large data sets to facilitate sufficiently accurate and generalizable outcomes. This prompts the need for harmonization and standardization of MRI acquisition protocols across many sites and interinstitutional data sharing.

Ultrahigh-Field-Strength MRI

Ultrahigh-field-strength (UHF) MRI refers to magnet strengths of 7 T and higher. UHF MRI has been shown to lead to higher EZ detection rates, better characterization of specific lesions, and better detection of subtle hippocampal subfield abnormalities compared with 3-T MRI (82). The main benefits of UHF MRI include higher signal-to-noise ratio, improved spatial resolution, and stronger susceptibility contrast. On the other hand, the stronger magnet requires shorter radiofrequency wavelengths for the signal transmission, which can result in increased B0 and B1 inhomogeneities. Previous studies have emphasized recommendations for the use of UHF MRI in clinical practice and demonstrated the benefits in the surgical work-up for patients with epilepsy (Fig 6) (4,83). A recent systematic review reported the average diagnostic gain of UHF MRI to be 31% compared with clinical 3-T MRI (11). The individual gain, however, will largely depend on the selected patient and specific inclusion and exclusion criteria. Over the past years, UHF MRI has been used to study the EZ lesion detection rate. Most studies comparing 3-T versus 7-T MRI for

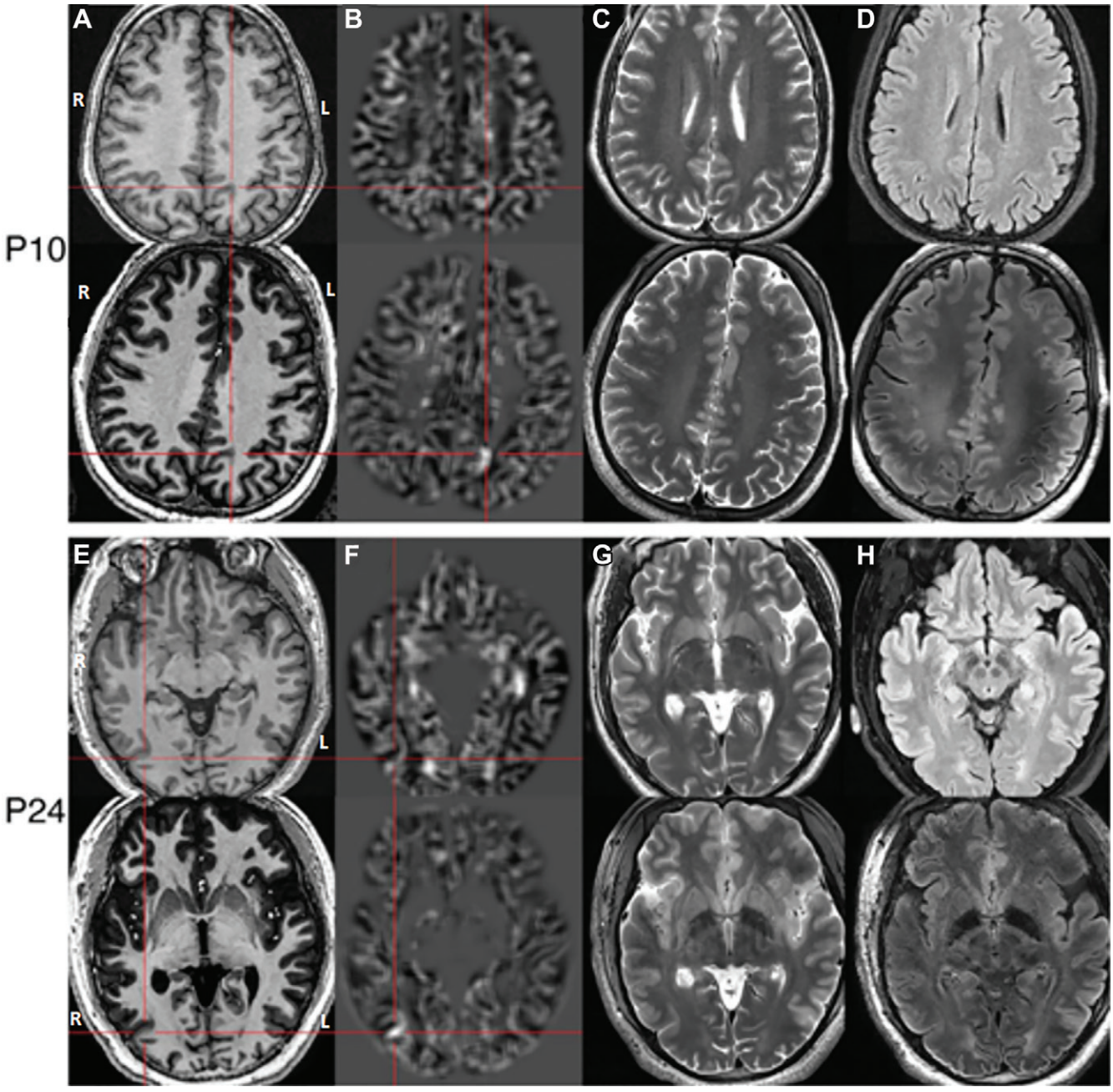

Figure 6: Two focal cortical dysplasia type IIa lesions newly identified at 7-T MRI. For each patient (patient 10 [P10], a 32-year-old man, and patient 24 [P24], a 28-year-old man), the **(A)** T1-weighted, **(B)** morphometric analysis program (MAP) junction map, **(C)** T2-weighted, and **(D)** fluid-attenuated inversion recovery (FLAIR) images from 3-T (upper rows) and 7-T (lower rows) imaging are shown. Images obtained with 3-T MRI and MAP postprocessing (**A, B**; upper row) failed to provide clear localizing clues for these two lesions. In contrast, images obtained with 7-T MRI and MAP postprocessing (**A, B**; lower row) show obvious abnormalities. These two subtle lesions are difficult to identify on T2-weighted or FLAIR images at 3 T and 7 T **(C, D)**. Red lines are crosshairs, and the center point of the red lines indicates the location of the epileptogenic zone. (Adapted, with permission, from reference 84.)

EZ detection used either a visual or VBM approach (4,84–89). Some studies implemented physiologic MRI measures as well (27). Most established image processing methods for 3 T and lower field strengths can be directly used for UHF images with little or no adjustment.

Discussion

In this review, we summarized image processing techniques for structural, diffusion-weighted, and physiologic MRI. These methods are used to assist in the detection of abnormalities in the structure or function of the brain for EZ localization (Table 1). A list of studies focusing on MRI-negative patients, methodology used, and reported detection rate is given in Table 2.

Epilepsy is a complex disorder with many subtypes. Epilepsy can be classified into focal and generalized epilepsy (electrophysiologic classification) and into lesional (FCDs and further cortical malformations) and nonlesional (neuropathologic

Table 1: Summary of the Image Processing Methods Discussed in This Review and Their Value for EZ Localization

MRI Acquisition Type and Processing Method and/or Measure	Utility for EZ Localization	Strengths	Weaknesses
Structural			
VBM (eg, MAP)	Sensitive to structural malformations, FCDs, heterotopia, and polymicrogyria	High spatial resolution, well-established	Significantly dependent on the quality of image coregistration and/or normalization
Volumetric analysis	Volumetric abnormalities indicative of abnormal regions such as HS	Readily available pipelines through open-source software packages (eg, Freesurfer)	Significantly dependent on the quality of image segmentation and/or parcellation
Analysis of quantitative T1 and T2	Provides quantitative measurement of alterations in the cortical microstructure	Quantitative values about the brain's microstructure, less prone to image inhomogeneities	Usually prolonged acquisition time due to specific multiple acquisition settings
Diffusion (MD, FA, TBSS)	Outline white matter tract integrity disruptions Visualize structural connectivity abnormalities	Quantitative assessment of the diffusion of water	Spatial resolution is highly dependent on the acquisition time For quality DTI reconstruction, a longer acquisition time is necessary Can detect edema shortly after a seizure Signal abnormality may be only temporary after a seizure
Functional BOLD (ReHo, fractional ALFF, FC)	Indicative of changes in local or global functional connectivity Shows regional alterations in neuronal synchrony and metabolic demands	Provides an indirect measurement of neuronal activity Can be integrated into simultaneous EEG and functional MRI	Usually low spatial resolution Can be very difficult to acquire due to subject motion or the susceptibility to SAR issues Imaging abnormality may be only temporary
ASL (CBF)	Visualize blood hypo- and/or hyperperfusion	Has been shown to be concordant with FDG PET findings	Usually low spatial resolution Susceptible to variable blood vessel anatomy, in particular arterial transit times Imaging abnormality may be only temporary

Note.—ALFF = amplitude of low frequency fluctuations, ASL = arterial spin labeling, BOLD = blood oxygen level–dependent, CBF = cerebral blood flow, DTI = diffusion-tensor imaging, EEG = electroencephalography, EZ = epileptogenic zone, FA = fractional anisotropy, FC = functional connectivity, FCD = focal cortical dysplasia, FDG = fluorodeoxyglucose, HS = hippocampal sclerosis, MAP = Morphometric Analysis Program, MD = mean diffusivity, ReHo = regional homogeneity, SAR = specific absorption rate, TBSS = tract-based spatial statistics, VBM = voxel-based morphometry.

histologic or genetic classification) epilepsy. No image processing method can enable detection and/or differentiation of all epileptogenic abnormalities. Voxel-based morphometry has been shown to be most sensitive for the detection of FCDs and also performs well in the detection of heterotopia and polymicrogyria. Volumetric abnormalities in hippocampal areas were shown to indicate hippocampal sclerosis, which is the most common cause of TLE. Image processing may be particularly helpful when no structural abnormalities are found or when findings are discordant between diagnostic modalities. While structural changes tend to be permanent (except for edema formation), diffusion or physiologic changes may be only temporary, particularly in the peri-ictal setting. The effect of the time period between the last observed seizure and the MRI examination on the sensitivity and specificity of EZ detection has been discussed for ASL (69) and diffusion-weighted MRI (39).

The main challenge for image processing methods is the validation of the technique. This must be based on correlating the imaging abnormality to *(a)* other noninvasive examinations, *(b)* the histopathologic diagnosis, and *(c)* the postoperative seizure outcome. As most studies do not provide these correlations, reported findings often remain unvalidated.

No image processing methods are exclusively sensitive to epileptogenic abnormalities. Some findings may be clinically relevant, but not epileptogenic. To become epileptogenic, a zone of the brain must have a critical mass of synchronous firing neurons with sufficient connectivity. Such zones can be small dysfunctional areas with a normal-appearing anatomy at MRI. From an imaging standpoint, the detectable size of structural abnormalities associated with an EZ is mainly limited by the acquisition voxel size, which should be a few times smaller than the EZ to be able to recognize subtle morphologic abnormalities. In clinical practice, a voxel size of 1 mm is often used and, as such, an EZ

Table 2: List of Studies Focusing on MRI-negative Individuals, Methodology Used, and Reported Detection Rate

Study	Method Used	Field Strength	Epilepsy Type	No. of Patients and Controls	Detection or Lateralization Rate*	Comparison or Validation
El Tahry et al, 2020 (17)	T1-weighted MAP	3 T	MRI-negative TLE and/or extra-TLE	21 patients, controls unknown	6/21 (28)	Reassessed structural imaging
Sun et al, 2021 (18)	T1-weighted MAP	3 T	MRI-negative focal epilepsy	35 patients, controls unknown	22/35 (63)	Histopathologic examination and seizure outcome
Wang et al, 2020 (19)	T1-weighted MAP	3 T	MRI-negative focal epilepsy	11 patients, controls unknown	3/11 (27)	MEG plus 12-month seizure outcome
Delev et al, 2018 (20)	T1-weighted MAP	3 T	MRI-negative focal epilepsy	14 patients, controls unknown	8/14 (57)	Seizure outcome
Chen et al, 2021 (84)	T1-weighted MAP	7 T	MRI-negative focal epilepsy	24 patients, 30 controls	4/24 (17)	Histopathologic examination
Focke et al, 2009 (21)	T2-weighted FLAIR VBM	3 T	MRI-negative focal epilepsy	70 patients, 25 controls	8/70 (11)	Not specified
Bernasconi et al, 2000 (33)	T2-weighted relaxometry	1.5 T	MRI-negative TLE	11 patients, 14 controls	5/11 (45)	Histopathologic examination
Chen et al, 2016 (35)	T2-weighted relaxometry	3 T	MRI-negative MTLE	17 patients, 14 controls	16/17 (94)	Seizure outcome plus histopathologic examination
Widjaja et al, 2011 (37)	DTI FA	3 T	MRI-negative epilepsy	16 patients, 26 controls	11/16 (69)	MEG
Concha et al, 2012 (39)	DTI MD	1.5 T/3 T	MRI-negative TLE	30 patients, 21 controls	26/30 (87)	Seizure outcome
Tang et al, 2021 (62)	rs-fMRI ALFF	3 T	MRI-negative and/or FCD and/or heterotopia	19 patients, 39 controls	14/19 (74)	SEEG plus histopathologic examination
Weaver et al, 2013 (58)	rs-fMRI ReHo	3 T	MR-negative TLE	4 patients, 16 controls	3/4 (75)	ECoG plus resection zone
Reyes et al, 2016 (60)	rs-fMRI fractional ALFF	3 T	MRI-negative TLE	34 patient, 34 controls	26/34 (76)	Histopathologic examination
Stufflebeam et al, 2011 (67)	rs-fMRI FC	3 T	MRI-negative TLE or unknown	6 patients, 300 controls	5/6 (83)	SEEG
Gajdos et al, 2021 (75)	ASL CBF	3 T	MRI-negative DRE	22 patients, controls unknown	16/22 (73)	Histopathologic examination

Note.—ALFF = amplitude of low frequency fluctuations, ASL = arterial spin labeling, CBF = cerebral blood flow, DRE = drug-resistant epilepsy, DTI = diffusion-tensor imaging, ECoG = electrocorticography, FA = fractional anisotropy, FC = functional connectivity, FCD = focal cortical dysplasia, FLAIR = fluid-attenuated inversion recovery, MAP = Morphometric Analysis Program, MD = mean diffusivity, MEG = magnetoelectroencephalography, MTLE = mesial temporal lobe epilepsy, ReHo = regional homogeneity, rs-fMRI = resting-state functional MRI, SEEG = stereoelectroencephalography, TLE = temporal lobe epilepsy, VBM = voxel-based morphometry.

* Numbers are numbers of patients, with percentages in parentheses.

smaller than 1 or 2 mm will most likely remain undetected. The idea of image processing is to leverage the algorithmic principles to visualize the subtle tissue or connectivity changes that may be relevant to epilepsy. Whether the found abnormalities are truly epileptogenic or not can be further validated via invasive methods (eg, intracranial electroencephalography or histopathologic evaluation). Newer MRI techniques, such as multinuclear imaging, developments in sequence design, contrast-enhanced imaging, innovative image processing methods, use of UHF, and cross-center sequence unification, can further help minimize false-positive findings.

The MRI sequences presented in this review are the ones most commonly used. One of the main benefits of the discussed postprocessing methods is that they can be easily used with available clinical MRI methods and implemented into standard epilepsy MRI protocols. Further MRI acquisition methods are available, however. For instance, there are multiple subtypes of diffusion imaging that can be used for EZ localization, such as diffusion kurtosis imaging, diffusion spectrum imaging, and neurite dispersion and density imaging, all of which have been shown to be either comparably good or superior to the classic diffusion-tensor imaging approach (90,91). MR spectroscopy of neurometabolites γ-aminobutyric acid or glutamate has also provided substantial insights into the study of epilepsy (92), and spectroscopic abnormalities ipsilateral to the EZ are thought to indicate a good surgical outcome (93). These advanced MRI methods currently

have either limited spatial resolution or long acquisition times, which makes them less suitable for standard clinical practice.

In clinical practice, a decision on the localization of a potentially resectable EZ is based on multimodal investigations, convergence of findings, and multidisciplinary consensus. For instance, simultaneous electroencephalography and functional MRI has been part of the epilepsy presurgical work-up for many years in patients with sufficient interictal discharges (94). Multiple studies have shown that fusing data from multiple noninvasive modalities may significantly improve EZ localization (12,77). Noninvasive imaging examinations such as PET, magnetoencephalography, SPECT, and UHF MRI may require further invasive examination by implanting intracerebral depth electrodes to provide evidence for the epileptogenicity. The ultimate goal is an accurate EZ delineation that ensures a seizure-free surgery outcome combined with minimal risk for neurologic complications. Therefore, studying multimodal fusion and relationships between various modalities is not only crucial for understanding the underlying epileptogenic mechanisms but can be implemented into the intraoperative neuronavigation to optimize the surgical workflow.

The transition toward higher magnetic field strengths is a promising next step as an adjunct in the field of EZ localization. In general, UHF MRI may be beneficial for some of the currently used imaging techniques due to the higher spatial resolution and stronger magnetic susceptibility contrast. In addition, ASL may benefit from the stronger magnetic field strengths not only because of the higher signal-to-noise ratio but also because of the longer T1 relaxation time and therefore longer label decay (70). On the other hand, the increased field inhomogeneities due to shorter radiofrequency wavelengths can cause significant image intensity voids and image inhomogeneities, especially in the anterior-inferior temporal lobe and fronto-orbital regions on T2- or T2*-weighted images (89). It remains to be shown whether 7-T imaging provides sufficient confidence to the radiologist without prior 3-T image information. Furthermore, the spatial distortions tend to be more pronounced in UHF MRI and therefore the geometrical accuracy may require more rigorous corrections. More research on UHF MRI with larger sample sizes is needed to fully establish the benefits and downfalls of stronger magnetic fields for EZ localization.

MRI processing holds promise for EZ localization, especially when no macroscopic structural lesion can be found. Furthermore, the underlying pathophysiologic mechanisms that contribute to epilepsy, its onset, and its cognitive comorbidities can be studied more in depth. Ideally, reliable toolsets are developed that provide guidance to radiologists.

Conclusion

Herein, we summarized frequently used image processing approaches for detecting and delineating structural, diffusion, or physiologic alterations in patients with focal drug-resistant epilepsy. Determining a specific brain area that is responsible for seizure onset in MRI-negative patients with drug-resistant epilepsy remains a challenging task. Image processing can be of value in detecting the epileptogenic zone (EZ). Establishing uniform scanning protocols and multi-institutional data pooling would provide more data for training, optimizing, and testing image processing techniques and, as a result, could further improve the sensitivity and specificity of these methods. Further advancements such as stronger magnetic fields in combination with optimized image processing and machine learning may provide additional benefit and increase the detection rate of the EZ, with the goal of maximizing the chances of a postsurgical seizure-free outcome for the patient.

Acknowledgment: We sincerely thank cardiovascular radiologist Suzanne C. Gerretsen, MD, PhD, for critically reviewing the manuscript and providing valuable feedback.

Disclosures of conflicts of interest: D.U. No relevant relationships. **G.S.D.** No relevant relationships. **O.F.M.G.S.** Grant from the Dutch Epilepsy Foundation; chair section functional neurosurgery, European Association of Neurosurgical Societies (EANS). **A.J.C.** Funding of salary costs of the involved PhD from EpilepsyNL. **P.A.M.H.** No relevant relationships. **R.H.G.J.v.L.** No relevant relationships. **C.M.H.** No relevant relationships. **J.F.A.J.** No relevant relationships. **W.H.B.** No relevant relationships.

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