The Role of MRI in the Treatment of Drug-Resistant Focal Epilepsy

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Abstract
Background: Epilepsy is a prevalent chronic condition affecting about 50 million people worldwide. A third of patients with focal epilepsy suffer from seizures unresponsive to medication. Uncontrolled seizures damage the brain, are associated with cognitive decline, and have negative impact on well-being. For these patients, the surgical resection of the brain region that gives rise to seizures is the most effective treatment. Summary: Magnetic resonance imaging (MRI) plays a central role in detecting epileptogenic brain lesions. In this review, we critically discuss advances in neuroimaging acquisition, analytical post-acquisition techniques, and machine learning methods for the detection of epileptogenic lesions, prediction of clinical outcomes, and identification of disease subtypes. Key Message: MRI is a mandatory investigation for diagnosis and treatment of epilepsy, particularly when surgery is being considered. Continuous progress in imaging techniques, combined with machine learning, will continue to push the boundaries of lesion visibility and provide increasingly precise predictors of clinical outcomes. Current efforts aiming at strengthening the competences of epileptologists in neuroimaging will ultimately reduce the need for invasive diagnostics.

Introduction

Epilepsy is a prevalent chronic condition affecting about 50 million people worldwide. Seizures are generally defined as transient symptoms and signs due to excessive neuronal activity; based on these manifestations, they can be classified as focal or generalized. Various etiologies have been associated with epilepsy, including structural, genetic, infectious, metabolic, and immune. Frequent structural pathologies underlying focal epilepsy include traumatic brain injury, tumors, vascular malformations, stroke, and developmental disorders. In a third of patients with epilepsy, antiseizure medication is ineffective [1]. Uncontrolled seizures damage the brain [2] and are associated with high risks for socioeconomic difficulties, cognitive decline, and mortality [3]. This review addresses drug-resistant focal epilepsy, specifically com-
common syndromes secondary to focal cortical dysplasia (FCD), a malformation of cortical development, and temporal lobe epilepsy (TLE) due to mesiotemporal lobe sclerosis, a histopathological entity that combines neuronal loss and gliosis in the hippocampus and adjacent cortices. To date, the most effective treatment of these pathologies has been resective surgery.

Since the inception of magnetic resonance imaging (MRI) in the 80s, constantly evolving hardware and sequences have provided increasingly detailed appraisal of brain structure and function, making it the main investigative platform in neuroscience of health and disease. While the investigation of epilepsy is multidisciplinary, MRI has been particularly instrumental in the presurgical evaluation as it can reliably detect epileptogenic lesions. Indeed, localizing a structural lesion on MRI strongly predicts a favorable outcome after surgery [4–6]. Yet, challenges remain. Many patients have subtle lesions that are undetected on routine MRI but found on histology. These patients, oftentimes referred to as MRI-negative, represent an utmost clinical challenge. Indeed, notwithstanding long and costly hospitalizations for EEG monitoring with intracerebral electrodes (SEEG), surgery is less likely to be performed [4]; when operated, these patients consistently show worse seizure control compared to those with visible lesions [5]. These shortcomings have motivated the development of advanced analytic techniques for the discovery of diagnostic and prognostic biomarkers. Combined with machine learning, such approaches hold promise to match or exceed the accuracy of the evaluation by human experts [7].

**Hardware and Acquisition Techniques**

Despite its unmatched diagnostic power, practices on the use of MRI are still variable worldwide and do not harness the full potential of technological advances for the benefit of people with epilepsy. To standardize best-practice neuroimaging in outpatient clinics and specialized surgery centers, the most recent guidelines propose the Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNESS) protocol, which includes easy to implement, high-resolution 3D T1-weighted MRI, 3D FLAIR, and 2D coronal T2-weighted MRI [8]. Best quality for these widely available sequences is achieved at 3 Tesla; the use of multiple head coils allows for shorter scanning time in addition to increased signal- and contrast-to-noise ratios. Notably, shorter acquisition times give the option to obtain additional contrasts to interrogate tissue microstructural properties and function. Among them, diffusion-weighted MRI and its analytical extension diffusion tensor imaging (DTI) have been widely used to image the white matter [9]. Advanced models describing diffusion within distinct microstructural constituents, such as high angular resolution diffusion imaging [10], have furthered the ability to resolve crossing fibers [11]. In addition to ease the interpretation of conventional diffusion metrics, such models offer more sensitive markers of the microstructural environment of epileptogenic lesions [12]. Other techniques such as diffusion kurtosis imaging have the ability to quantify intra-voxel tissue properties [13], which may ultimately refine lesion detection. Neurite orientation dispersion and density imaging, commonly referred to as NODDI [14], is a reconstruction technique based on a multi-shell acquisition protocol that estimates intra- and extracellular volume fractions of neurites (i.e., dendrites and axons). In TLE, these techniques have unveiled gray and white matter abnormalities in regions not detected by conventional DTI [15]. Other quantitative contrasts reflect actual quantities biophysically linked to tissue microstructure. T1 mapping along the cortical mantle and hippocampal subfields has revealed altered myelin content in ipsilateral temporal and frontal limbic regions, independent from morphology and intensity [16]. Interestingly, multiparametric imaging combining anatomical, functional, and metabolic data can be obtained using hybrid PET-MRI systems, which may be informative when conventional radiology is negative [17, 18]. Notwithstanding the practical advantages of this technique, the added clinical value compared to traditional single acquisitions with subsequent co-registration remains to be established.

Currently, many epilepsy centers rely on 3T MRI for routine clinical diagnostics. While the move to this platform has significantly improved our ability to detect epileptogenic lesions [19], it is expected that resolving cortical laminar structures at 7T will likely push a step further our capabilities [20]. However, so far, it has been infrequent to see cortical dysplasias at 7T that are completely invisible at 3T [21, 22]. Also, for structural imaging of the neocortex and the immediate subcortical white matter, signal inhomogeneities particularly in the antero-inferior temporal and frontal lobes still pose a challenge for the visualization of subtle lesions [20]. Conversely, the unique possibility to perform molecular imaging of neurotransmitters at 7T, such as GABA and glutamate [23], may open new investigative avenues. Moreover, functional imaging is likely to reveal previously unresolved organizational features at a laminar level [24].
Lesion Detection

The essential role of structural lesions in the surgical management of drug-resistant epilepsy has motivated the development of increasingly sophisticated detection methods. This has been particularly relevant in patients with unremarkable routine MRI. Automated detection is generally performed by supervised classifiers trained to learn imaging features that distinguish lesional from non-lesional. These image analysis techniques provide distinct information through quantitative assessment without the cost of additional scanning time.

In TLE, hippocampal sclerosis (HS) on MRI appears as atrophy [25] and increased signal intensity [26], generally more severe ipsilateral to the seizure focus; accurate identification of these signs is crucial for deciding the side of surgery. Whole-hippocampal volumetry has been one of the first computational analyses applied to TLE [27–31]. Advances in hardware and sequence technology, which enable submillimetric resolution and an improved signal-to-noise ratio, have facilitated accurate visualization of hippocampal subfields or subregions, including the dentate gyrus, subiculum, and the cornu ammonis (CA1–4) regions [32]. Increasing demand to study large patient cohorts has motivated the shift from manual toward automated segmentation, setting the basis for large-scale clinical use [33, 34]. Several methods with fast inference times have been developed for MRI-based subfield segmentation [34–39], providing overlap indices of >80% with manual labels. Among them, the SurfPatch algorithm, operating on T1-weighted MRI, combines multiple templates, parametric surfaces, and patch-based sampling for compact representation of image shape, texture, and intensity, with unparalleled segmentation accuracy [39]. The combination of SurfPatch with 3D surface-based shape models [40, 41] sampling multicontrast features along the central path of hippocampal subfields allows mapping morphological changes at a laminar level that may not be identified visually, thus furthering our knowledge of the HS spectrum [42]. Recently, a linear discriminant classifier trained on T1- and FLAIR-derived laminar features of histologically validated HS accurately lateralized the focus in 93% of TLE patients, with a remarkable 85% sensitivity in MRI-negative cases [43] (Fig. 1). Notably, similar high performance in two independent validation cohorts imaged on different scanners establishes generalizability, setting the basis for broad clinical translation.

Among FCDs, encompassing various epileptogenic developmental malformations, type II lesions are the most common and reliably diagnosed forms [44]. Histopathologically, FCD type II is typified by intracortical dyslamination and dysmorphic neurons, either in isolation (IIA) or together with balloon cells (IIB). Conversely, FCD type I remains elusive on histology and difficult to differentiate from normal cortex [45]. On MRI, while a previous study has shown cortical thinning at a group level, this malformation has been seen only in a handful of pediatric cases [46]. FCD type II presents with an MRI spectrum encompassing variable degrees of gray matter...
and white matter changes that challenges visual identification. Early approaches for computer-assisted visual detection were based on generic voxel-based morphometry, which demonstrated high sensitivity in detecting conspicuous malformations [47–50]; however, they failed to identify two-thirds of subtle FCD lesions overlooked on routine MRI [48, 50]. On the other hand, modeling of gray-white matter blurring and gray matter intensity [51], a simple method applicable to widely available 3D T1-MRI clinical data, has been shown to be a very powerful tool to assist visual inspection. Indeed, this approach increases sensitivity for the detection of FCD type II in at least 40% patients relative to the inspection of conventional images.

Over the last decades, several surface-based algorithms have been developed for fully automated detection of FCD type II [52–60]; the addition of FLAIR has increased sensitivity for the identification of smaller lesions [55]. Importantly, careful preprocessing, including manual corrections of tissue segmentation and surface extraction, have delivered high-fidelity FCD features [61]. Conversely, suboptimal processing of surface-based data may lead to poor performance, even in cases with MRI visible lesions [62]. Admittedly, current benchmark automated detection algorithms fail in 20–40% of patients [55, 56, 59, 63], particularly those with subtle FCD type II, and suffer from relatively high false-positive rates [60]; also, the limited set of features designed by human experts may not capture the full complexity of pathology. Alternatively, in recent years, deep learning has shown high detection performance relative to conventional methods [64, 65]. In epilepsy, a recent study applying deep learning to FCD detection has reached a sensitivity of 93%, while maintaining high specificity both in healthy and disease controls [67]. Importantly, this algorithm detected MRI-negative FCD type II with 85% sensitivity, thus offering a considerable gain over standard radiological assessment. The algorithm relied on T1- and T2-weighted FLAIR MRI of a large cohort of patients with histologically validated lesions collated across multiple tertiary centers. Results were generalizable across cohorts with variable age, hardware, and sequence parameters. A unique feature of this algorithm was the use of Bayesian uncertainty estimation for risk stratification [68, 69], which allowed to stratify predictions according to the confidence to be truly lesion-al. In other words, putative lesional clusters were ranked based on confidence, thus assisting the examiner to gauge the significance of findings (Fig. 2). By pairing predictions with risk stratification, the classifier may assist clini-

Fig. 2. Automated “MRI-negative” FCD using deep learning. Two examples of FCD lesions initially reported as MRI-negative on routine imaging. The left panels show the MRI sections and the probability maps of putative FCD lesions as identified by the convolutional neural network. The bar plots show the probability of the lesion (purple) and FP (blue) clusters sorted by their rank; the superimposed line indicates the degree of confidence for each cluster. The FCD lesion has both the highest probability (close to 1.0) and the highest confidence (rank 1). The right panels show the binary maps of the FCD lesion (1) and FPs. Histopathological analysis of the surgical specimens revealed a subtle FCD type IIA (dysmorphic neurons without balloon cells) in both cases. FP, false-positive.
cians to adjust hypotheses relative to other tests, thereby increasing diagnostic confidence.

**Image-Based Prediction of Clinical Outcomes**

Predicting seizure outcome after surgery has been extensively explored in TLE. While the presence of ipsilateral hippocampal atrophy is a reliable indicator of seizure freedom, alterations beyond the mesial temporal lobe may contribute to seizure relapse [70]. White matter microstructural features derived from DTI achieve high sensitivity but modest specificity [71, 72], similar to functional connectivity measures of the thalamus and whole-brain [73, 74]. While topological features of the structural connectome have shown predictive value for favorable outcome, their specificity for seizure relapse is relatively low [75, 76]. Overall, paucity of large-scale validation and relatively low performance need to be addressed before advocating widespread clinical use of these methods.

Neurological conditions, including epilepsy, are nowadays conceptualized as heterogeneous disorders. This has warranted the development of methods to explicitly model phenotypic variations across subjects, which may be ultimately exploited to predict outcomes [77]. Within biotyping techniques, categorical models provide subtypes of patients with a given phenotype. In TLE, k-means clustering of surface-based morphometry data uncovered classes with distinct patterns of mesiotemporal anomalies that differed with respect to histopathology and postsurgical seizure outcome [42]. In FCD, leveraging hierarchical clustering to model connectivity from the lesion to the rest of the cortex can effectively predict surgical outcome [78]. In addition, a recent work based on consensus clustering applied to multicontrast 3T MRI uncovered FCD tissue classes with distinct profiles of gray and white matter anomalies, variably expressed within and across patients [79]; clinical utility was supported by gain in performance of a lesion detection algorithm trained on class-informed data compared to class-naive paradigm. Analyzing individual variability through unsupervised techniques identified cognitive phenotypes associated with distinct patterns of white matter damage [80] and connectome disorganization [81]. Compared to these categorical models, dimensional approaches allow a more in-depth conceptualization of interindividual heterogeneity by uncovering axes of pathology that are co-expressed, to varying degrees, within and between individual patients. In neurodegenerative disorders, the latent Dirichlet allocation, an unsupervised topic modeling technique, has significantly improved the prediction of outcomes in the expression of disease factors. A recent study in TLE applying this technique to multimodal MRI features of hippocampal and whole-brain gray and white matter pathology uncovered specific dimensions of heterogeneity not expressed in healthy controls and only minimally in patients with frontal lobe epilepsy [82]. Importantly, classifiers trained on the patients’ factor composition predicted response to antiepileptic medications and surgery with an accuracy of 76% and 88%, respectively, as well as memory scores, outperforming learners trained on group-level data (Fig. 3). In translational terms, assessing interindividual variability identifies clinically relevant disease characteristics that would otherwise be missed. Integrating biotyping techniques that exploit intra- and intersubject variability with other biomarkers, such as genomics, will likely offer novel avenues to elucidate disease processes at a molecular level [83].

**A Much-Needed Cultural Change Is Underway**

Currently, many advances in neuroimaging of epilepsy have not fully translated into clinical care. Indeed, practices on the use of imaging is variable worldwide as technical infrastructure and specialized training may not be available or not sufficiently valued. The most dramatic implication of this translational gap relates to lesion identification, with many MRI-positive patients incorrectly labeled as MRI-negative. Paradoxically, while appending MRI-negative status has profound implications in terms of treatment strategies and seizure outcome, this crucial categorization lacks too often objectivity and rigor. This limitation has resulted in a plethora of SEEG, an invasive technique now accessible to many epilepsy centers, with the appealing yet debatable assumption that electro-clinical hypotheses alone may be sufficient to identify the epileptogenic zone. Importantly, SEEG is nonlocalizing in more than 40% of patients, with the consequence that these cases will not undergo epilepsy surgery [84]. The remedy to this therapeutic dead-end is embodied by the ongoing cultural shift fostered by several educational initiatives promoting neuroimaging skills, the availability of standardized MRI acquisition protocols and guidelines, as well as large-scale efforts within the neuroscience community to facilitate access to image analyses techniques. Strengthening and widening the core competences of epileptologists will undoubtedly transform traditional clinical decision-making into a
Fig. 3. Latent disease factors analysis in TLE. Maps show latent disease factors mapped onto neocortical, white matter, and hippocampal surfaces ipsi- and contralateral to the seizure focus. These maps are derived from the application of latent Dirichlet allocation, an unsupervised machine learning technique, to multimodal MRI (T1w, FLAIR, T1w/FLAIR, diffusion-derived FA, and MD) modeling atrophy, gliosis, demyelination, and microstructural damage. The latent Dirichlet allocation uncovers latent relations (disease factors) from these features and quantifies their co-expression. High probability (darker red) signifies greater contribution of a given feature to the factor (or high disease load). Drug response and the seizure outcome after surgery are more accurately predicted when using latent disease factors than when relying on conventional group-level features. Data points indicate mean balanced accuracy for categorical data (drug response, seizure outcome) evaluated based on 100 repetitions of 10-fold cross-validation.
Conclusion

MRI is a mandatory investigation for diagnosis and treatment of epilepsy. The relentless progress in imaging and machine learning techniques will continue to push the boundaries of lesion visibility and to provide increasingly sophisticated predictors of clinical outcomes for the benefit of people with epilepsy.

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