



Emerging Trends in Neuroimaging of Epilepsy

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Abstract

Neuroimaging techniques, particularly magnetic resonance imaging, yield increasingly sophisticated markers of brain structure and function. Combined with ongoing developments in machine learning, these methods refine our abilities to detect subtle epileptogenic lesions and develop reliable prognostics.

Keywords

MRI, imaging techniques, epilepsy surgery, drug-resistant epilepsy, image processing

Hardware and Acquisition Techniques

The reliability of any imaging diagnostic technique depends on the type and quality of the input. This is particularly relevant for drug-resistant epilepsy, as the identification of a structural lesion on magnetic resonance imaging (MRI) is associated with favorable seizure outcome after surgery. Consequently, the most recent recommendations of the International League Against Epilepsy endorse the use of the Harmonized Neuroimaging of Epilepsy Structural Sequences protocol, with high-resolution 3-dimensional (3D) T1-weighted MRI, 3D fluid-attenuated inversion recovery, and 2-dimensional coronal T2-weighted MRI at its core.¹ These sequences yield best image quality at 3 T, particularly when combined with multiple phased arrays allowing parallel imaging, which shortens scanning time in addition to increasing signal- and contrast-to-noise ratios. Reduced acquisition time allows adding quantitative contrasts to the epilepsy protocol for a more in-depth analysis of tissue microstructural properties and function.

Diffusion-weighted MRI and its analytical extension diffusion tensor imaging (DTI) are widely used to image the white matter.² One of the main limitations of DTI, however, resides in its inability to resolve distinct populations of crossing fibers;

moreover, DTI-derived metrics lack specificity as they may be affected by multiple features.³ The potential, however, continues to grow with advanced techniques based on multicompartiment compartmental models describing diffusion within distinct microstructural constituents. Thus, besides helping the interpretation of conventional diffusion metrics, such models offer more sensitive markers of the microstructural environment of epileptogenic lesions,⁴ which may ultimately refine their detection. Among them, high angular resolution diffusion imaging⁵ based on sampling of a large number of diffusion sensitization directions is arguably the most efficient sequence to resolve crossing fibers. Techniques such as diffusion kurtosis imaging have gained popularity for their ability to quantify intravoxel tissue properties.⁶ In temporal lobe epilepsy (TLE), in addition to revealing altered diffusion profiles along white matter fibers ipsilateral to the seizure focus,⁷⁻⁹ these techniques have shown abnormalities in both the gray and white matter extending to regions not detected by conventional DTI.⁸ Similar findings were obtained with fixel-based analysis, a reconstruction technique which combines measurements of fiber cross-sectional area and density, thereby providing a sensitive marker of intra-axonal volume.^{10,11} Neurite orientation dispersion and density imaging, commonly referred to as NODDI, is



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another reconstruction technique based on a multishell acquisition protocol that estimates intra- and extracellular volume fractions of neurites (ie, dendrites and axons), both in the gray and white matter.^{12,13}

Unlike conventional “weighted” contrasts that combine multiple tissue parameters, quantitative contrasts reflect actual quantities biophysically linked to tissue microstructure. Among them, T_1 mapping has been suggested to reflect myelin.¹⁴ In TLE, T_1 mapping along the cortical mantle and hippocampal subfield surfaces revealed altered myelin content in ipsilateral temporal and frontal limbic regions. Anomalies remained consistent after correcting for cortical thickness and cortical interface gradient supporting a role for T_1 mapping to assess intracortical structural integrity independently from morphology and intensity.¹⁵ Multiparametric MRI fingerprinting (MRF) is a relatively new technique that quantifies several contrasts (eg, T_1 , T_2 , and proton density)¹⁶ in a single acquisition, thus providing a comprehensive description of multiple tissue properties. In particular, fast 3D MRF delivers high-resolution (1.2 mm isotropic) whole-brain quantitative maps in a clinically plausible acquisition time.¹⁷ Preliminary evidence suggests increased sensitivity of MRF compared to visual evaluation.^{17,18} In particular, partial volume estimation can be applied to separately examine the gray and white matter,¹⁷ which may be beneficial to assess anomalies at their interface, such as those in the temporal pole in TLE or malformations of cortical development affecting other neocortical regions. Notably, the flexible nature of the MRF allows incorporating additional contrasts, such as diffusion, perfusion, and susceptibility. Multiparametric imaging combining anatomical, functional, and metabolic data can also be obtained using hybrid Positron emission tomography-MRI systems, which may be informative when conventional radiology is negative.^{19,20} Notwithstanding the practical advantages of multiparametric imaging, considering the high-level technical competences required, the added clinical value compared to traditional coregistration remains to be established.

Gains in signal- and contrast-to-noise ratio provided by the shift from 1.5 T to 3 T scanners have significantly improved our ability to appraise epileptogenic lesions.²¹ The potential of 7 T to resolve the cortical laminar structure will likely push detection capabilities a step further.²² The best example so far has been the improved visualization of hippocampal subfields²³ and cortical dysplasias,²⁴ particularly when combined with postprocessing.²⁵ However, so far it has been infrequent to see cortical dysplasia at 7 T that is completely invisible at 3 T.^{26,27} Better visualization of lesional boundaries, nevertheless, may help refine the surgical resection and improve outcome.²⁸⁻³⁰ Perhaps even more relevant is the possibility to perform molecular imaging of neurotransmitters that are difficult to evaluate at 3 T, such as γ -aminobutyric acid and glutamate.³¹ In relation to functional MRI (fMRI), improvements in signal-to-noise ratio and connectivity coefficients are likely to reveal previously unresolved microscopic features, including laminar functional organization.³² Disadvantages of ultra-high field imaging include far greater signal inhomogeneities and

higher energy deposition in tissue, particularly in the anteroinferior temporal and frontal lobes.²² As strategies such as adiabatic pulses and parallel transmission emerge to address these challenges, the case for clinical adoption of this technology becomes more straightforward.²²

Lesion Detection and Disease Biotyping Techniques

The pivotal role of the lesion in the surgical management of drug-resistant epilepsy has motivated the development of increasingly sophisticated detection methods. In TLE, medial surface models sampling multiparametric features of hippocampal sclerosis along the central path of subfields lateralize the focus and predict pathological grading.^{33,34} Surface-based Laplacian *in vivo* models of the neocortex and subcortical white matter profiling focal cortical dysplasia (FCD) improve the identification of subtle lesions that escape conventional radiological analysis. Notwithstanding these advances, detection algorithms have relied on limited set of features designed by human experts, which may not capture the full complexity of pathology. Alternatively, deep learning, a data-driven method incorporating feature engineering into the learning step, alleviates the challenge of handcrafting pathological features. Initial evidence suggests high sensitivity in detecting MRI-negative FCD. Generalizability across cohorts with variable age, hardware and sequence parameters promise potential for broad clinical translation.³⁵

Data-driven, unsupervised machine learning also offers novel perspectives on the understanding of disease neurobiology. In TLE, MRI morphometry combined with clustering identified subgroups of patients with distinct patterns of mesiotemporal atrophy that did not spatially overlap.³⁶ Leveraging individual variability, these techniques may further refine clinical predictors, such as cognitive profiles^{37,38} and postsurgical seizure outcome.³⁶ In FCD type II, recent data identified tissue classes with distinct structural, functional, and histopathological profiles within lesions and across patients.³⁹ Addressing the full spectrum of developmental cortical malformations may play a key role in establishing genotype–phenotype associations, opening opportunities to inform novel personalized treatments so far hindered by the lack of phenotypes linked to somatic variants.

Network science is expanding and offers unprecedented opportunities to appraise system-level features of epilepsy. In parallel to a large body of descriptive studies, initial evidence suggests that combining connectivity metrics with machine learning may identify salient features from high-dimensional imaging data sets. In TLE, a series of reports demonstrated the utility of the structural connectome as well as measures of intrinsic brain function to predict seizure outcome.⁴⁰⁻⁴² In FCD, lesion-based functional connectivity models (ie, connectivity from dysplastic tissue to the rest of the cortex) have demonstrated that network dysfunction can dissociate patients with favorable from those with suboptimal postsurgical seizure outcomes.⁴³ Network pathology is also relevant

for the understanding of multidomain cognitive dysfunction; for example, structural connectome metrics outperform hippocampal volumetry and tractography of large association fibers to predict memory and language impairment in TLE.^{44,45} Other recent work has shown the ability of preoperative resting state fMRI and white matter connectome markers to predict postoperative cognition, particularly in relation to language.⁴⁶

Conclusion

The integration of increasingly complex imaging techniques into routine clinical practice remains a challenge. Success is contingent to continued efforts in education and training of epileptologists, ultimately fostering close collaborations with research scientists. In this context, Open Science⁴⁷ collaborative efforts are expected to catalyze translation of advanced analytic methods. A leading example is the ENIGMA-Epilepsy consortium,⁴⁸ which has used meta- and mega-analyses to assess group-level morphology,⁴⁹ microstructure, and network models⁵⁰ of structural compromise across thousands of patients. Knowledge derived from these large-scale studies is expected to set the basis of novel, clinically applicable individualized disease biomarkers.

Declaration of Conflicting Interests

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