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Advanced Imaging Techniques in the Diagnosis of Nonlesional Epilepsy: MRI, MRS, PET, and SPECT

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Once patients have a diagnosis of localization related epilepsy (LRE), it is critical to further classify those patients into lesional or nonlesional for treatment and prognostic reasons. An individual with LRE may be classified as nonlesional for two reasons: 1) a lesion may not exist; that is, the structural abnormality that gives rise to seizures may be at the channel level or be spatially distributed in such a way that it would not be accurately termed a lesion, or 2) a lesion exists but is so subtle that standard clinical imaging is not sensitive enough to discriminate between the lesion and surrounding healthy brain tissue. As with any technology and disease process, this definition is dynamic, as we know that future imaging techniques will be developed and new disease mechanisms will be discovered, making detection of the *epileptogenic underlying abnormality* an ever-changing target.

For the purposes of this review, we define nonlesional epilepsy as any epilepsy in which a *lesion or a dysfunctional defined area* is not observable using visual inspection of standard clinical neuroimaging. Thus, any new techniques discussed here aim at identifying or improving the certainty of detection of an area of abnormality corresponding to the epileptogenic lesion.

It is critical to mention that although there is no standardized epilepsy imaging protocol in place among different institutions and hospitals, the primary clinical neuroimaging modality is MRI, with the acquisition of a whole brain T1 acquisition for imaging anatomy, and various T2-based acquisitions for detecting tissue pathology, such as fast low angle inversion recovery (FLAIR) and gradient recalled echo (GRE). Apart from this basic study, every center has different imaging protocols that vary a great deal in quality, specifications, and sensitivity.

There are a number of imaging-based research avenues aimed at characterizing and diagnosing nonlesional epilepsy. A review of recent developments for the detection and mapping of brain abnormalities in nonlesional epilepsy follows.

Computational Post-Processing of Structural MRI

Computational post-processing techniques may be used to quantify brain morphological features and allow the use of statistical inference (rather than visual inspection) to identify abnormalities, based on comparison with healthy controls. There are a number of epilepsy-relevant features that may be measured using a whole brain T1- or T2-weighted MRI scan: local gray matter volume, measured using voxel-based morphometry (1); cortical thickness (2); blurring of the boundary between gray and white matter in the cortex (3, 4); sulcal depth (5); and more exotic measures that quantify local spatial properties of tissue, such as cortical gyrification (6) and texture analysis (7, 8). The most sensitive methods for identifying relevant epilepsy -related brain regions in nonlesional epilepsies will likely involve a combination of these features (9). A review by Bernasconi et al. discusses morphometric approaches for the detection of cryptogenic epileptogenic tissue in more detail (10).

Another less widely explored avenue is the application of post-processing methods to alternative imaging sequences, such as FLAIR or T2-weighted imaging. The application of voxel-based methods to FLAIR imaging identified structural changes in 11.4% of lesion-negative focal epilepsy cases in a study published in 2009 (11). These acquisitions have not been explored as much as whole brain T1-weighted MRI because hardware limitations in the past have made it difficult to acquire scans with full brain coverage in a reasonable acquisition time. However, the availability of multi-channel coils from all major MR manufacturers now means that T2-weighted images may be acquired with the same spatial resolution as older T1-weighted MRI acquisitions (~1 mm isotropic).

These methods have been applied to either confirmed cases of focal dysplasia (FCD) or non-visible FCD. The latter is more important, as these techniques can have the potential of identifying 30% more patients who currently have no identifiable focal abnormality (4).

The task of determining the optimal combination of quantitative features—whether these are multiple morphometric parameters derived from a single acquisition, or features obtained from multiple image acquisitions (T1- and T2-weighted imaging in combination)—is not simple and relies upon

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sophisticated multivariate statistical methods. There are a wide variety of machine learning techniques currently available; the primary challenge in applying these methods to neuroimaging data are low numbers of subjects relative to the large number of candidate morphometric features.

Functional MRI

Functional MRI methods allow us to map temporal changes in oxygenated blood flow (blood-oxygenation-level-dependent [BOLD] contrast imaging and related methods). Of particular relevance to epilepsy is simultaneous EEG-fMRI, in which EEG is acquired during fMRI acquisition, and the timing from EEG events is used to map BOLD changes in response to electrographic discharges. A recent paper reported that BOLD response in EEG-fMRI was useful for identifying epileptogenic regions in 55% of nonlesional epilepsy cases, which the authors interpreted as useful for identification of subtle lesions or for guiding implantation of electrodes for further localization (12). A related study with a modest sample size ($n = 9$) in lesion-negative frontal epilepsy also found that EEG-fMRI assisted in delineating the epileptogenic zone (13). Another fMRI method that holds great promise for imaging networks in lesion-negative epilepsy is resting state fMRI, in which subjects at rest are imaged using standard BOLD fMRI, and brain regions with correlated BOLD fluctuations are interpreted as networks. Resting state fMRI has been used to demonstrate differences in functional connectivity in individuals with childhood absence epilepsy (14). The primary challenges in resting state fMRI studies are 1) the detection and removal of non-neural correlations, for example due to motion, cardiac and respiration (15), and 2) identification of relevant epilepsy-related networks for further analysis. Elimination of non-neural signals may be aided by the acquisition of physiological data synchronized with the fMRI acquisition, as well as post-processing noise removal techniques. Individual networks may be identified using statistical methods, such as independent components analysis (16). There is extensive literature on the use of fMRI in epilepsy; for a recent review of ictal fMRI, we refer interested readers to the 2013 study from Chaudry et al. (17). Preoperative fMRI is of use clinically for language and memory function but has a limited role in distinguishing lesional versus nonlesional epilepsy and, thus, is not discussed further.

Diffusion-Weighted Imaging (DWI)

Water diffusion in white matter is anisotropic, and the most common approach to modeling water diffusion is with diffusion tensor imaging (DTI). DTI allows generation of maps of quantitative diffusion measures, such as fractional anisotropy, mean diffusivity, and apparent diffusion coefficient. Although there is clear evidence that these measures are affected in MRI-visible cases (18), there is less evidence that DWI and related image processing methods can identify epilepsy-related white matter changes, although some findings have been reported (19). The most consistent finding is that DWI changes are particularly pronounced following seizures (20–22). The lack of evidence for DWI-based changes in nonlesional epilepsy may be due to methodological issues with DTI, in particular, the inability of the tensor to resolve white matter pathways in voxels containing multiple fibers, which have been estimated to be present in 63 to 90 percent of white matter voxels (23). More recent developments, such as the use of high angular resolution diffusion imaging (HARDI) in combination with more sophisticated modeling techniques, such as constrained spherical deconvolution, may overcome these limitations (24). A recent approach called Apparent Fiber Density allows diffusion differences to be detected in individual white fiber tracts within voxels that contain multiple fibers (25); this method was used to provide preliminary evidence that lesion-negative temporal lobe epilepsy has a pattern of bilateral white matter changes that is distinct from lesional TLE (26).

Improved Structural MRI Acquisition

Development of better hardware increases spatial resolution, signal, or sensitivity to tissue pathology. The most standard method for increased spatial resolution is the use of higher field MRI scanners, such as 7T MRI. To date, there is limited evidence that the use of 7T imaging is useful for imaging nonlesional epilepsy cases, which is likely due to the limited availability of high-field scanners, appropriate acquisition sequences, and lack of systematic studies. Some promising results have been reported for the use of high-field MRI to detect small lesions in vivo in other neurological disorders, such as multiple sclerosis, which may be directly applicable to epilepsy (27). Another hardware development that is increasingly available is multichannel head coils. Although these coils generate better images in terms of signal-to-noise ratio (SNR) and may also be used to reduce scan time, improved diagnostic yield has not been well demonstrated (28). Newer acquisitions include double inversion recovery MRI and MP2RAGE, a variant on the well-known MPRAGE (magnetization-prepared rapid gradient echo) acquisition. Double inversion recovery reduces the signal from CSF and white matter, allowing for improved contrast in the cortex and detection of subtle lesions. The method has been shown to identify structural abnormalities in lesion-negative epilepsy cases (29). MP2RAGE is a more recent method that combines images acquired with two inversion times to generate a single image that has high T1 weighting and is very "flat" (low bias field) (30). Images acquired using this method have excellent contrast and will be well suited to the quantitative methods discussed in the first section.

MRS

MRS has the benefit of identifying areas of metabolic dysfunction in focal epilepsy akin to FDG-PET. Proton spectroscopy is sensitive to neuronal dysfunction by showing reduced NAA (n-acetylaspartate) levels in focal epileptogenic areas irrespective of pathology reflecting mitochondrial dysfunction. Multiple studies have shown MRS abnormalities in epileptogenic temporal lobe regions with asymmetries reported in 70 to 80 percent of TLE patients with LRE. In clinical studies, MRS has also shown predictive value after epilepsy surgery when structural MRI is normal. Technical challenges, in particular, limited whole brain coverage, and cortical lipid contamination limit the use of MRS in extratemporal lobe epilepsy. However, recent improvements in whole brain metabolite measurements and analysis can overcome many of these problems (31).

MRS studies have shown also network metabolic dysfunction (32). A recent study showed a close metabolic relationship between hippocampal and thalamic regions, probably representing the relationships that occur in the context of seizure propagation. These findings may play a role in identifying network distribution patterns in LRE and may allow for identification of potential targets for surgery.

PET

In patients with LRE defined by ictal or interictal EEG, the main indication for FDG PET is to identify a single focal abnormality when an MRI is normal. FDG PET can also be of some value when there is possibly more than one focal ictal zone or when clinical data are discordant with EEG findings. FDG PET yield can be improved by using statistical analysis methods, such as statistical parametric mapping (SPM) as well as by PET/MRI co-registration on a clinical level which improves sensitivity (33).

So far, receptor PET studies have been limited to research laboratories. In some patients, α-methyl-l-tryptophan (AMT) PET can improve detection of epileptogenic tubers (34). Studies have reported that PET imaging using the $GABA_A$/benzodiazepine-specific radiotracers, such as ^{11}C-flumazenil or ^{18}F-radiolabeled flumazenil can identify more restricted regions of abnormalities in the epileptogenic zone and have higher sensitivity in extratemporal localization. Similarly, other PET receptor tracers have been tested, such as serotonin markers (5-HT1A, MPPF (4-(2′-methoxyphenyl)-1-[2′-[N-(2″-pyridinyl)-p-fluorobenzamido]ethyl]-piperazine), dopamine system receptors (18F]-fluoro-L-Dopa, 88F]-Fallypride), glutamate/NMDA receptors (11C]-S-ketamine, 11C]-CNS 5161) and opiate receptors (11C-carfentanil) (35, 36). However, practical limitations of using any of these radiotracers include the lack of commercially available radiotracers, short half-life that necessitates an onsite cyclotron, moderate signal-to-noise ratio, and the need for arterial blood sampling to model tracer-binding features. In addition, to date, none has demonstrated a clear clinical role in nonlesional epilepsy.

SPECT

Perictal SPECT has proven very valuable in studying localization-related epilepsy patients (37). SPECT is primarily used in patients with nonlesional TLE but more commonly in patients with nonlesional extra-TLE or in those with poorly localized seizures when other data suggest a likely focal onset. The yield of ictal SPECT in patients with an abnormal MRI is of limited value. The wide availability of SPECT and stable radiotracers balances the limitations imposed by the need for perictal injections.

SPECT sensitivity and specificity have improved using SISCOM (subtraction ictal SPECT co-registered to MRI) analysis. Several studies have shown enhanced sensitivity and specificity versus ictal studies alone (38). Furthermore, SPECT studies using statistical analysis based on normalized brain blood flow models have demonstrated superior sensitivity to SISCOM. Recent studies have shown that statistical based techniques models identified a hyperperfusion focus in 84% of patients versus SISCOM in 66% ($p > 0.05$). Moreover, the probability of seizure-free outcome improves when statistical models correctly localize a focal area compared to indeterminate localization (81% vs 53%; $p > 0.03$).

Summary

New technical developments and improved statistical imaging analysis methods are increasing the yield for detecting abnormalities in LRE. Determination and classification of LRE is likely to increase in the future as techniques become more sensitive and imaging epilepsy networks becomes a reality.

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