Advanced Magnetic Resonance Imaging in Epilepsy

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Abstract

Magnetic resonance imaging (MRI) is the most commonly used noninvasive imaging modality for epilepsy diagnosis, etiologic classification, and management. The availability of 3T scanners and multiple channel coils mean isotropic T2-weighted MRI can also be readily obtained with a similar spatial resolution to T1w MRI. These acquisitions in combination with quantitative morphometric techniques can be used to detect subtle cortical and subcortical brain abnormalities associated with epilepsy. Functional MRI (fMRI) methods including electroencephalography (EEG)-fMRI and resting state imaging have been used to study network activity, such as language and memory in surgical candidates. Diffusion MRI can be used to map white matter pathways and provide an alternative structural view of connections between brain regions. These techniques will increase the yield of abnormalities in epilepsy patients previously considered nonlesional.

Keywords

MRI, epilepsy, neuroimaging, surgery, MR spectroscopy

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Magnetic resonance imaging (MRI) is the most commonly used noninvasive imaging modality for epilepsy diagnosis, etiologic classification, and management. MRI is mandatory for all patients with new onset epilepsy, particularly for those who do not respond to medication. The primary aim of MRI scanning in an individual with epilepsy is to uncover abnormal brain regions that are associated with seizures. Modern MRI-based methods may be used to reveal discrete structural and functional brain abnormalities or distributed network changes. In this article we review recent developments in MRI for individuals with epilepsy.

The most effective intervention for medically intractable epilepsy is surgical resection, although alternative interventions, such as the ketogenic diet and neurostimulation approaches, may also be used. Surgical outcomes have improved over the last 30 years and this is likely partly due to improvements in MRI technology and availability.[1] A predictor of a good surgical outcome is the identification of a lesion on MRI.[2] A focus of current research is to improve lesion detection using improved structural image acquisition protocols and postprocessing methods. As well as identifying a part of the brain to remove, it is also important to identify brain regions that are functionally critical. Functional MRI (fMRI) techniques, comprising task-related or resting state blood oxygenation level dependent (BOLD) imaging, can be used to estimate language networks and lateralization and memory networks, and may therefore inform the presurgical planning process. Similarly, diffusion MRI (dMRI) is becoming widely used in research settings to image white matter pathways. Although this is still a nascent technology, an example of a useful application of diffusion MRI is to image the optic radiations and therefore assist the surgeon in avoiding the Meyer loop and preventing visual field deficits following anterior temporal lobectomy.[3]

Structural Magnetic Resonance Imaging

Most modern epilepsy imaging protocols include a whole brain T1-weighted MRI scan. Voxel resolution is of the order of 1 mm. Current acquisitions are typically isotropic, and most modern MRI viewing software packages allow these images to be resliced to any preferred plane. These acquisitions provide a detailed anatomical image that can be used to identify epilepsy-related brain abnormalities. Examples of these abnormalities include focal cortical dysplasia, which may be associated with thickened cortex and blurred boundary between the neocortical gray matter layer and underlying white matter; reduced hippocampal volume in association with hippocampal sclerosis in temporal lobe epilepsy (TLE); heterotopic gray matter in periventricular nodular heterotopia or subcortical band heterotopia; and a variety of cortical folding abnormalities in association with other malformations of cortical development, such as lissencephaly/agyria and polymicrogyria.[4]

Two of the most relevant improvements in MRI hardware are the routine use of 3T MRI scanners and the availability of multiple channel receive coils. 3T MRI provides higher signal than 1.5T imaging, which may be used to reduce

scan time or increase spatial resolution of the acquisition. Susceptibility effects also increase at higher fields, which, depending on the application, may be an improvement or a disadvantage. Increased susceptibility effects lead to increased signal difference between oxygenated and deoxygenated blood, which improves fMRI. Conversely susceptibility artifacts, for example at the bone/tissue interface, are worse at 3T relative to 1.5T; however, there are methods for mitigating these artifacts, such as increasing bandwidth or decreasing echo time and slice thickness.

A useful current development for structural imaging of epilepsy is the availability of multiple channel receive coils on modern MRI scanners. Multiple channel coils are available from all major commercial MRI manufacturers, and although these coils may be a tight fit for people with large heads, the latest generation of multichannel head coils use an improved design to address this matter. Each coil detects signals from nearby tissue, and reconstruction algorithms are used to combine these signals to generate a whole brain image. The use of multichannel head coils allows for either a shorter acquisition time, which can minimize motion artifact, or increased spatial resolution for the same acquisition time as an equivalent single channel coil acquisition. Higher spatial resolution is desirable because it allows the reader to identify subtle brain abnormalities. The use of multiple receive coils is referred to as parallel imaging and can be used for both T1- and T2-weighted imaging.

The use of parallel imaging in combination with a turbo spin-echo 3D acquisition allows for the acquisition of 3D T2-weighted and fluid-attenuated inversion recovery (FLAIR) images in a clinically feasible acquisition time (e.g. 7 minutes). Like T1-weighted 3D acquisitions, these images can be resliced to any desired viewing plane (see *Figure 1*). T2-weighted and T2-FLAIR acquisitions are sensitive to pathologic damage in tissue and in particular are useful for detecting abnormalities in focal epilepsy cases, such as hippocampal sclerosis and some types of focal cortical dysplasia.

More specialist acquisitions are available such as double inversion recovery MRI and MP2RAGE, which is a variant of the well-known MPRAGE acquisition. Double inversion recovery MRI isolates the signal from gray matter by nulling both white matter and cerebrospinal fluid (CSF) signals using carefully timed application of two inversion pulses. The resulting image primarily comprises gray matter and has been found to be useful for identifying candidate neocortical brain abnormalities in individuals with cryptogenic focal epilepsy,[5] and may be useful for further surgical planning procedures, such as intracranial electrode implantations.[6] MP2RAGE is a more recent method that is used to generate images with two inversion times, which are then combined arithmetically to generate a single image that is free from bias field and transmit field homogeneity.[7] These images have good gray–white matter contrast and are very 'flat,' which means they will be useful for quantitative image analyses. Findings at 7T suggest that the high contrast associated with MP2RAGE images can be used to identify individual thalamic nuclei and hippocampal substructures.[8] The thalamus and hippocampus are often implicated in epilepsy disorders, so it is likely that this new acquisition will be useful for future epilepsy imaging applications.

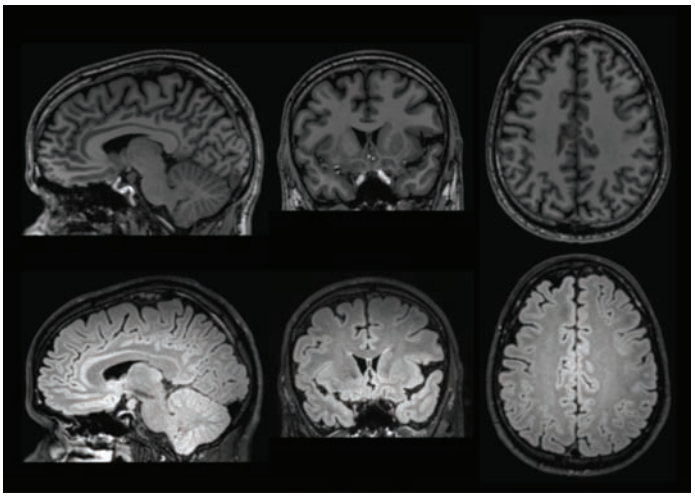
Quantitative Analysis of Structural Magnetic Resonance Imaging

Structural MRI data may be postprocessed in order to allow a statistical comparison of morphometric features in groups of patients or individual patients with a control group. This approach allows for objective detection of brain changes associated with epilepsy. These approaches vary according to the morphometric feature that is measured and compared between groups. Voxel-based morphometry (VBM) uses T1-weighted whole brain MRI to model regional tissue content relative to a template brain. The technique consists of four fundamental image processing steps: segmentation of gray and white matter, nonrigid coregistration of scans to a common template, smoothing, and statistical analysis. The output of a VBM image is a statistical map of brain regions that are different between groups or correlated with a variable of interest.

VBM has been widely used in epilepsy imaging research. Examples of epilepsy-related brain changes include hippocampal and anterior temporal lobe white matter atrophy in TLE,[9] thalamic atrophy in a number of epilepsy subtypes including TLE, childhood absence epilepsy, and juvenile myoclonic epilepsy,[10–12] and focal cortical dysplasia.[13] Some groups have extended the voxel-based approach to provide quantitative features that index blurring of the gray–white interface at the cortex or local image texture. These methods have been used to improve identification of focal cortical dysplasia, as well as identifying abnormal tissue in other brain regions such as the thalamus.[14–16]

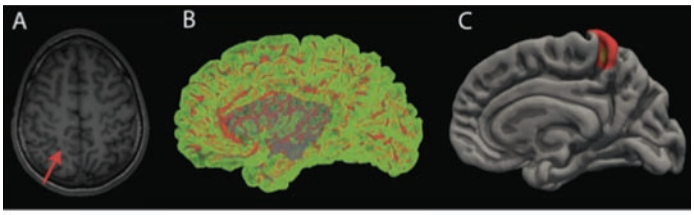
Cortical surface modeling allows for the measurement of more precisely defined morphometric features than conventional VBM; however, it is a more computationally demanding technique that also requires higher-quality (resolution and contrast) scanning. All modern scanners are easily capable of acquiring whole brain T1-weighted MRI suitable for cortical surface modeling. The method is a software-based approach that takes a whole brain T1-weighted MRI scan and generates a geometric model of the boundary between the white matter and overlying neocortical gray matter. These surface models can then be used to measure various

Figure 1: Routine Epilepsy Structural Image Acquisition



Whole brain 1 mm isotropic T1-weighted (top row: MPRAGE acquisition, echo time (TE) 2.96 ms, repetition time (TR) 2,500 ms, inversion time (TI) 900 ms, flip angle 8°, acceleration factor 2, acquisition time 5:42 min:sec) and fluid-attenuated inversion recovery (FLAIR) imaging (bottom row: T2 FLAIR SPACE, TE 388 ms, TR 5,400 ms, TI 1,800 ms, acceleration factor 2, acquisition time 6:57 min:sec) in an individual with new onset epilepsy, acquired using a Siemens 3T TIM Trio MRI scanner. These two acquisitions have been obtained with the same spatial resolution and so are already coregistered without any postprocessing. Images may be resliced to any viewing plane, maintaining high spatial resolution.

Figure 2: Detection of Focal Cortical Dysplasia Using Cortical Thickness Mapping



A. Axial slice of individual with focal cortical dysplasia, indicated with the arrow. B. A geometric model of the cortical surface is constructed using software; the Freesurfer program was used in this example. C. Comparison of cortical thickness in the individual with epilepsy with healthy controls allows us to map the focal cortical dysplasia on the cortical surface.

properties of the cortex, such as cortical thickness, contrast between gray and white matter, and higher order morphometric parameters such as local gyrification and surface complexity. The cortical surfaces are coregistered to a template to allow statistical comparison of these morphometric features across groups or between an individual epilepsy patient and controls. These image-processing methods have been applied to a number of epilepsy subtypes and pathologies, including TLE,[17] childhood epilepsy syndromes, such as rolandic epilepsy and juvenile myoclonic epilepsy,[18,19] and focal cortical dysplasia.[20]

Voxel- and surface-based approaches have also been applied to T2-weighted and FLAIR imaging, but to a lesser extent than T1-weighted MRI, presumably because high-quality 3D T2-weighted MRI has only recently been available.[21,22] These techniques work on a similar principle as described above, but may be used to detect pathology-related signal intensity increases (as opposed to morphologic changes, which are typically assessed using T1-weighted MRI) in hippocampal sclerosis or focal cortical dysplasia.[23] In the case of surface-based methods, the T1-weighted MRI scan is used to model the cortical surface and the local signal in the T2-weighted or FLAIR MRI is mapped onto the cortical surface. Recent work has been carried out to combine T1- and T2-weighted imaging modalities to obtain surfaces that putatively map myelin content.[24] Combined T1 and T2 voxel-based approaches have been used to objectively map T2 relaxation time and volume changes in TLE over the brain.[25]

Additional methods exist that target specific brain structures. The hippocampus is often a potential surgical target in TLE. Hippocampal segmentation from T1-weighted MRI is used to measure hippocampal volume, which can be used to identify hippocampal sclerosis and lateralize TLE. T2 relaxometry of the hippocampus provides a quantitative measure of hippocampal integrity, which is sensitive to hippocampal sclerosis and seizure-related changes. It is possible that hippocampal volume and T2 relaxometry may be useful for discriminating between developmental brain abnormalities that predispose an individual to epilepsy, and brain changes that occur following seizures.

Recent studies investigating hippocampal volume and T2 relaxometry in asymptomatic relatives of individuals with TLE have identified abnormalities in both hippocampal volume and T2 relaxation time, which suggest there may be genetic factors involved in the development of TLE.[26,27] Results are not entirely consistent across studies; for example, Tsai et al. did not identify similar hippocampal T2 changes reported in the Suemitsu et al. paper. Further research will clarify the matter. Additional morphological properties of the hippocampus and temporal lobe have been investigated, such as hippocampal shape, positioning, and volumes of subregions of the hippocampus.[28,29]

There are a variety of postprocessing methods available to assist the clinician by providing quantitative, objective support for identification of brain abnormalities in epilepsy patients. The methods described in this paper are unlikely to replace detailed visual inspection of MRI in the near future; however, they serve a complementary role by identifying candidate brain regions for detailed scrutiny and further investigations. Additionally they can be used to statistically map subtle, consistent brain changes in groups of patients that may not be appreciated by visual inspection of individual scans.

Functional Magnetic Resonance Imaging

One of the primary applications of fMRI is to identify eloquent cortex and map language and memory networks prior to surgery. There are a number of studies that use task-based fMRI to investigate how memory is affected by temporal lobe resection for epilepsy treatment.[30–33] Resting state fMRI paradigms may be used to lateralize language function.[34,35] It is a topic of current debate whether fMRI-based methods may be used to replace the Wada test for language lateralization.

A typical fMRI acquisition consists of echo-planar imaging acquisitions of whole brain images every couple of seconds for approximately 6 minutes or more. These images are typically T2*-weighted and have slightly different signals if the voxel contains oxygenated or deoxygenated blood. Statistical comparison of images is used to identify regions in which there are signal differences due to blood oxygenation; there is strong evidence that BOLD contrast corresponds to some aspects of local neural activity.[36]

fMRI methodologies may be broadly categorized into (i) task- or event-based analyses or (ii) functional connectivity analyses. Task-based methods involve the performance of a task in the scanner while BOLD MRI is being acquired. Statistical modeling of voxel-wise signal changes over time is used to identify voxels in which BOLD contrast is significantly changed during task performance. In this way brain regions that are active during a specific task may be identified. Electroencephalography (EEG) acquired in-scanner with a simultaneous BOLD acquisition can be modeled using event-related fMRI analysis. This is a sophisticated approach that leverages the high temporal resolution of EEG with the spatial resolution of MRI in order to image cortical regions that are associated with epileptogenic brain activity.[37,38] One of the challenges with this technique is to minimize noise caused by the use of electrodes in the scanner.[39]

It has long been known that epilepsy-related electrical activity occurs between spatially separate brain regions, such as the thalamus and neocortex.[40] There is considerable interest in using fMRI methods to probe correlated activity *in vivo*. Functional connectivity analysis uses BOLD imaging to infer functional connections between brain regions by examining voxel to voxel correlations of signal intensity. These analyses may be undertaken while the participant is carrying out a task in the scanner, or while at rest; the latter is known as resting state fMRI. Resting state functional connectivity approaches are attractive to clinical researchers because they overcome the requirement of task performance in the scanner, and have the potential to provide information

regarding multiple brain networks. Specific spatial patterns of correlated brain regions have been consistently identified across studies. The most frequently investigated is the default mode network, which is a collection of brain regions that exhibit correlated BOLD signals when an individual is at rest.[41] The consistent observation of the default mode network across subjects has led to extensive investigation of the properties of this network in epilepsy and other diseases. An example of recent research is the identification of development-related changes in default mode and salience networks in children with localization-related epilepsy.[42] We refer the interested reader to the following review papers for further information about resting state fMRI analysis.[43,44]

Diffusion Imaging

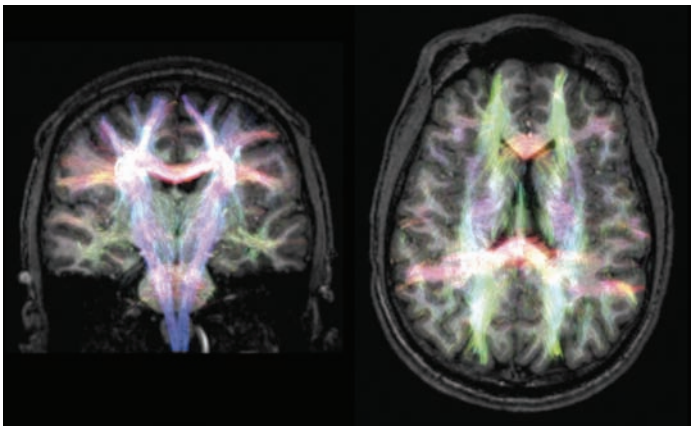
White matter pathways may be examined using diffusion weighted imaging (DWI), and therefore allows for the investigation of structural connections between cortical and subcortical brain regions. The method uses diffusion weighting gradients applied along a number of directions in the scanner, which provides an image with a signal that is dependent on local diffusion of water protons in tissue. In white matter, diffusion is restricted across axons and is relatively higher along the length of axons. DWI is then processed using software-based methods in order to reconstruct white matter pathways noninvasively, particularly in voxels in which the majority of axon bundles are aligned.[45] Tractography refers to modeling techniques that are used to infer the 3D structure of white matter pathways from DWI data (see *Figure 3*). A particularly challenging factor in DWI research is how to model diffusion in voxels in which axons are oriented in more than one direction; this is known as the crossing fiber problem and has been estimated to affect up to 63–90 % of white matter voxels in the brain.[46] The widely used diffusion tensor model has been shown to be inadequate for modeling fiber orientation in the presence of crossing fibers, and newer high angular resolution acquisitions (HARDI) and modeling techniques, such as constrained spherical deconvolution, have been developed to address this matter.[45,47,48] The development of methods for objective, whole-brain analysis of metrics derived from diffusion imaging data is an active field of research. A challenge for these methods is to accurately coregister white matter pathways across subjects. Example methods for whole brain analysis of metrics derived from diffusion MRI include tract-based spatial statistics (TBSS) and apparent fiber density analysis.[49,50]

Because diffusion MRI is able to map white matter pathways that connect brain regions, there are numerous studies that apply diffusion imaging to epilepsy, in particular to TLE. As mentioned previously, it may be used to identify optic radiations and therefore used to plan anterior temporal lobe resections. Beyond this application, the clinical utility of diffusion imaging methods over conventional structural MRI is still unclear; for example, a study from 2007 did not find any evidence for improved lateralization of TLE patients who were unable to be lateralized using structural MRI.[51] However given the demonstrated sensitivity of diffusion imaging-based methods to brain changes in TLE, it is likely that recent developments in diffusion acquisition and analysis will increased the utility of this method for epilepsy.

Magnetic Resonance Spectroscopy

The properties of magnetic resonance spectroscopy (MRS) allow many cerebral compounds associated with brain metabolism to be evaluated.

Figure 3: Whole Brain Diffusion Tractography Image



Diffusion weighted imaging and image postprocessing can be used to generate whole-brain diffusion streamline tractography images. Diffusion imaging allows us to visualize white matter pathways that cannot be seen using conventional magnetic resonance imaging (MRI); for example, the cortico-spinal tract and corpus callosum can be clearly observed on the coronal slice on the left. Tracks are color-coded, with anterior–posterior tracks colored green, left–right colored red, and inferior–superior tracks colored blue. Diffusion images were acquired on a 3T Siemens Achieva MRI scanner, 2.5 mm isotropic voxel size, 60 diffusion directions, b = 3,000 s/mm, TE 99 ms, TR 7,900 ms. The fiber orientation distribution was modeled using the constrained spherical deconvolution method implemented in the software package mrtrix (https://github.com/jdtournier/mrtrix3/wiki).

MRS has been applied to study both clinical and research aspects of epilepsy. The use of MRS in epilepsy began 2 decades ago using proton magnetic resonance spectroscopy (1H-MRS) as a marker for neuronal cell loss in TLE, but expanded to other modalities and types of epilepsies.

Studies performed in the early 1990s established the ability of 1H-MRS to lateralize the seizure focus in temporal lobes and to test the validity of MRSI to already established methods of localization, using video-EEG as gold standard as well as MRI-volumetry (MRIV), 2-[18F]Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), and single photon emission computed tomography (SPECT). Hugg et al.[52] initially demonstrated a significant asymmetry of N-acetyl aspartate (NAA) left/right metabolite ratios and further studies have demonstrated comparable results. These studies demonstrate a decrease in NAA in the affected temporal lobe of TLE patients. Kuzniecky et al.[53] investigated the validity of 1H-MRS in lateralizing the pathologic area in 30 consecutive preoperative TLE patients with mesial temporal lobe sclerosis on MRI showing that 1H-MRS had a concordance rate of 97 %. Similar results were described by others in patients with intractable mesial TLE (MTLE). These results and others support the fact that 1H-MRS is a valid method even in bilateral cases presenting a high concordance to the degree of bilateral EEG findings in patients with TLE. Recent data have also demonstrated that the decrements in NAA are not just localized to the ipsilateral hippocampus, but consistent with existing PET finding a network of involved limbic and subcortical nuclei. Apart from 1H-MRS, laboratories have tested 31P-magnetic resonance spectroscopy (31P-MRS) to study metabolic function showing a lower but sensitive method for lateralization in TLE.

It has also been known that mild to moderate oxidative stress can also cause major abnormalities in gamma-aminobutyric acid (GABA) and glutamate. Studies show that GABA neurotransmission and metabolic function might be correlated, certainly in the ictal regions. Recent work

suggests that GABA measurements using MRS at high field can identify abnormal levels in regions close to the epilepsy focus in TLE and also at a distance reflecting abnormal pathways or metabolic dysfunction.

MRS work in patients with structurally identified cortical malformations has revealed that NAA changes are specific to the epileptogenic zone, and are 'normal' in patients whose seizures are well controlled. Furthermore, in patients with ongoing seizures, the regions that are anatomically abnormal but nonepileptogenic also display normal NAA levels.[54]

Epilepsy surgery outcome is another test for MRS and in the clearer clinical group of MTLE, several groups[55,56] have demonstrated that bilateral metabolic alterations in TLE patients with hippocampal sclerosis have a predictive value for postoperative outcome. Patients demonstrating severe bilateral or even metabolic changes contralateral to planned removal had a poorer postoperative seizure outcome than patients demonstrating unilateral metabolite alterations ipsilateral to the hemisphere in which surgery was performed. The results indicate that contralateral changes in 1H-MRS are a good predictor for poor seizure outcome.

Following these early studies, MRS has not been widely adopted for clinical use, due to relatively high technical requirements for successful implementation. The requirement of high magnetic field homogeneity has been noted as a concern for the clinical use of MRS in epilepsy and limits brain coverage in the temporal lobes, which is an important target for individuals undergoing presurgical assessment. Technical improvements have overcome these limitations and the recent development of spectroscopic imaging methods has been shown to be useful for identifying metabolite differences in both temporal lobe and neocortical epilepsies at both 3T and higher field strengths.[57–59]

Conclusions

Advances in MR hardware, computational power, and analysis techniques and the use of multi-image coregistration are improving the detection rate of abnormalities in patients with epilepsy. It is likely that with higher magnetic field strength, such as 7T and higher, multichannel receiver coils, faster imaging sequences, and large database analytical techniques we will be able to detect a higher rate of abnormalities in many patients that presently are considered idiopathic or cryptogenic in etiology. ■

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