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The Role of Magnetic Resonance Imaging (MRI) in the Diagnosis of Epilepsy: A Review

Sultan Alamri

Radiological Sciences Department, College of Applied Medical Sciences, Taif University**, Saudi Arabia**

***Correspondence:** s.alamri@tu.edu.sa **Received 26-09-2020, Revised: 30-11-2020, Accepted: 01-12-2020 e-Published: 02-12-2020**

Magnetic resonance imaging (MRI) plays an essential role in the diagnosis, management, and treatment of epilepsy. Recent advances in MRI have allowed both structural and functional abnormalities to be visualized. Epilepsy is a common neurological disorder that benefits greatly from MRI. Abnormal MRI findings indicate a greater chance of having recurrent seizures and also indicate that seizures can be controlled by antiepileptic drugs (AEDs). Additionally, MRI can assist in the pre-surgical evaluation and planning of patients with epilepsy. In this review, different MRI techniques and their applications in both diagnosis and treatment of epilepsy are discussed.

Keywords: Epilepsy, MRI, neuroimaging

INTRODUCTION

Epilepsy is a disorder of the central nervous system that is characterized by recurrent unprovoked seizures. It is one of the most serious neurological diseases and requires long-term healthcare as drugs can only control the seizures. It is more common in developing countries, as 80% of the 65 million people with epilepsy worldwide live in such countries (Alamri, 2016). In the United States of America (USA), epilepsy is more common than other neurological disorders, including Parkinson's, autism, cerebral palsy, amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS) combined (French and Meador, 2015).

Imaging techniques, including computed tomography (CT), structural and functional MRI (fMRI), MR spectroscopy (MRS), electroencephalography (EEG) and EEG combined with fMRI, positron emission tomography (PET), single photon emission computerized tomography (SPECT), and magnetoencephalography (MEG), are essential in the diagnosis and treatment planning of epilepsy. In addition to the fact that the presence of epileptogenic abnormalities increases the chance of having recurrent seizures (Krumholz et al., 2015), the presence of abnormal findings also results in greater effort to control the seizures by using antiepileptic drugs (AEDs) (Shah and Mittal, 2014). Moreover, imaging can assess the effectiveness of the AED used and thus improve the clinical decision making in epilepsy (Beltramini et al., 2015; Caciagli et al., 2017; Shah and Mittal, 2014). In cases where the AED is not effective, epilepsy surgery is necessary. Using imaging to evaluate the feasibility of surgeries as well as to ensure that resection of the ictal onset does not cause any brain deficit is crucial. It has been shown that 65% of patients with temporal lobe epilepsy undergoing epilepsy surgeries become seizure-free compared with only 50% of patients with extra temporal lobe epilepsy (Téllez-Zenteno et al., 2010). Because the presence of abnormal MRI findings greatly affects the outcomes, it is important that a patient with epilepsy undergo a thorough evaluation in order to advise them about the current state of their epilepsy and treatment options.

The main purpose of this review is to provide

an overview of the recent developments in the role of MRI techniques to diagnose and/or plan treatment.

Structural imaging:

Anyone could argue that MRI is the modality of choice because of its high sensitivity and specificity (Krumholz et al., 2015); however, because of the high availability and rapidity of CT, CT is commonly preferred in the acute setting to rule out emergent cases, such as infarction. Patients with negative CT findings should be further evaluated by MRI. Evidence has shown than approximately 12% of patients with a negative CT are likely to have a positive MRI (Krumholz et al., 2015).

Additionally, high magnetic field strengths (>1.5 tesla [T]) provide a better visualization in a shorter time compared with 1.5 T (Ladino et al., 2016). This is particularly important in patients undergoing surgical assessment. It is also important to closely inspect the hippocampus when assessing for causes of seizures. Three tesla and above can clearly show the hippocampal internal architecture and thus better detect any volume loss within the hippocampal subfields, especially Cornu Amonis (CA) 1 and 4, and the dentate gyrus (Costa et al., 2019; Peixoto-Santos et al., 2018; Santyr et al., 2017). Even though the qualitative assessment of the hippocampus is essential in the diagnosis, with the improved methods of hippocampal segmentation, quantitative assessment allows more sensitive and specific assessment of early damage (Carmo et al., 2020; Kreilkamp et al., 2018; Moghaddam et al., 2020; Peixoto-Santos et al., 2018).

Since the approval of clinical 7 T MRI by the U.S. Food and Drug Administration (FDA), there has been an increase in studies showing the advantages and disadvantages of using such a high field in epilepsy assessment (Guye et al., 2019; Rutland et al., 2018; Santyr et al., 2017; Veersema et al., 2017, 2016). About 30% of patients with focal epilepsy have negative MRI. These patients are most likely to have reduced surgical success as they do not have identifiable lesions that can be completely removed (Feldman et al., 2019). Because the signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR), and spatial resolution are higher in 7 T compared with 3 T and 1.5 T, the lesion detection rate is increased (Ciantis et al., 2016; Feldman et al., 2019), and consequently, successful surgical outcomes are increased as well. Another advantage of 7 T scanners is related to the post-processing of fMRI. Seven tesla can provide a much better characterization of the region of interest (ROI) due to the improved functional contrast and less partial volume artifacts (T Vu et al., 2017). Although the use of 7 T scanners is increasing due to benefits from the advantages they offer, safety concerns (including increased force on metallic implants and induced tissue heating) should be considered.

In order to image the morphologically complicated structures as well as make use of new developments in the MRI hardware and sequences, consensus recommendations on the use of structural MRI in patients with epilepsy were established by the International League Against Epilepsy (ILAE) Neuroimaging Task Force (Bernasconi et al., 2019). This optimal epilepsy protocol (known as the HARNESS-MRI protocol, short for harmonized neuroimaging of epilepsy structural sequences) can be generalized because the recommended sequences are basic and available on most MR scanners. As shown in Table 1, the HARNESS-MRI protocol consists of three basic sequences. First is the high-resolution 3D T1 weighted imaging that allows optimal visualization of both anatomy and morphology. This can be achieved by the magnetization-prepared rapid gradient echo (MP-RAGE) sequence in Siemens scanners, the 3D spoiled gradient echo sequence (SPGR) in GE scanners, or the 3D turbo field echo (TFE) sequence in Philips scanners. The voxel sizes should be 1 x 1 x 1 mm^3 with no gap between slices. Second is the high-resolution 3D fluid attenuated inversion recovery (FLAIR). This can be achieved by SPACE sequence in Siemens scanners, CUBE in GE scanners, or VISTA sequence in Philips scanners. The voxel sizes should be 1 x 1 x 1 mm^3 with no gap between slices. Because the cerebral spinal fluid (CSF) is nulled in this sequence, the visualization of epileptic pathologies such as hippocampal sclerosis and glial scars is increased. Just like the previous sequence, the voxel sizes should be 1 x 1 x 1 mm^3 with no gap between slices. Third is the high-resolution 2D coronal T2 weighted imaging. This is the sequence of choice for the visualization of hippocampal internal structures. The voxel sizes are recommended to be 0.4 x 0.4 x 2 mm^3 with no gap between slices. In addition to HARNESS-MRI protocol, T1-post gadolinium and susceptibility weighted imaging are necessary when looking for tumors and hemorrhage, respectively (Bernasconi et al., 2019).

Due to the recent developments in the MRI sequences, additional sequences can also be added to the epilepsy protocol, for example, MP2-RAGE to increase contrast distinction between

tissues (Kotikalapudi et al., 2019) and double inversion recovery to null the signal from white matter, leading to a maximized lesion detection rate (Wychowski et al., 2016).

Table 1: HARNESS-MRI Protocol by Bernasconi and his colleagues (2019).

	HARNESS-MRI Protocol
1	High-resolution 3D T1 weighted imaging (MP-RAGE, SPGR, or TFE)
2	High-resolution 3D fluid attenuated inversion recovery (SPACE, CUBE, or VISTA)
3	High-resolution 2D coronal T2 weighted imaging

Epilepsy patients can also benefit from advances in MRI processing software, including FSL (Minkin et al., 2019, p.), SPM (Popescu et al., 2016), BrainSuite (Akrami et al., 2020, p.), Brain Voyager (Gould et al., 2020; Koç et al., 2020), and FreeSurfer (Allebone et al., 2020). These software help to investigate morphological changes (Farokhian et al., 2017, p. 12), brain connectivity (Courtiol et al., 2020; González et al., 2020), and volume measurement (Fujiwara et al., 2020; Perani et al., 2018).

Diffusion imaging:

Diffusion-weighted imaging (DWI) is a technique that can determine the mobility of molecular water. This technique provides important information in the peri-ictal stage, showing a low apparent diffusion coefficient (ADC) and hyperintensity on the DWI (Yokoi et al., 2019). Diffusion tensor imaging (DTI) is an emerging technique that uses anisotropic diffusion to show the characteristics and direction of white matter tracts (Gross, 2011). Several studies have shown abnormalities in the white matter tracts in patients with epilepsy (Eriksson et al., 2001; Focke et al., 2008; Leyden et al., 2015). In addition, tractography is another technique that uses data from DTI to reconstruct 3D images for a better visualization of white matter tracts. A number of studies have found alterations of the DTI tracts in patients with epilepsy and that they have important clinical applications in neurosurgery (Hamandi et al., 2008; Kreilkamp et al., 2017; Lilja and Nilsson, 2015). Moreover, diffusion kurtosis imaging (DKI) is a new technique that differs from DTI in that it uses at least 3 b values (as compared with only 2 for DTI) and at least 30 diffusion gradient directions (as compared with 6 for DTI). Previous studies suggested that DKI is more sensitive than DTI in both focal and generalized epilepsies (Liu et al., 2019; Winston, 2015). Both DTI and DKI have some limitations, including the false assumption of DTI that diffusion in the brain is homogenous and the difficult interpretation of the DKI parameter changes (Kamagata et al., 2016). To overcome these challenges, neurite orientation dispersion and density imaging (NODDI) was introduced. This technique has proven useful for detecting microstructural changes in patients with epilepsy (Rostampour et al., 2018; Sone et al., 2018).

fMRI:

fMRI is an MRI technique that utilizes the changes in blood oxygenation during neural activities. The rationale behind this technique is that when an area of the brain is activated, the blood flow will increase in this area to compensate for the oxygen demand. This is why the fMRI signal is also called blood-oxygenation-level-dependent (BOLD). fMRI is of paramount significance in pre-surgical planning for specifically removing the area of the brain that causes seizures without affecting the surrounding areas (Benjamin et al., 2018; Stippich, 2007; Vakamudi et al., 2020). These areas typically involve functions such as speech (Gould et al., 2020; Gupta, 2014), voluntary and involuntary movement (Kobayashi et al., 2020; Prudente et al., 2016), and vision (Zhou et al., 2020). The idea is to predict any deficit that might occur to a particular function from foci resection. Even though the Wada test is still the technique of choice for pre-surgical localization of language and memory (Pearson et al., 2019), the more non-invasive fMRI is offering promising results (Binder, 2011; ISHIKAWA et al., 2017; Massot-Tarrús et al., 2019) and can be used as a complementary technique to increase the prediction of neuropsychological risks before surgeries.

fMRI has a good spatial resolution of around 2-3 mm at 3 T and below a millimeter at 7 T (Moerel et al., 2020). However, one of the disadvantages of fMRI is the inherent low temporal resolution of the BOLD signal. It takes approximately 6 seconds

from the onset of the neural activity to reach the peak of the signal. This can be overcome by combining EEG, which has an excellent temporal resolution of milliseconds, with fMRI. Studies have shown that this can help in the localization of the onset zone of the seizure (Shaikh et al., 2019). Additionally, several studies utilizing the EEG/fMRI technique have allowed for a better understanding of the mechanism of epilepsy. For example, it has been demonstrated that changes related to the epileptiform discharges (EDs) on the EEG are not limited to the seizure area but also seen in other cortical and subcortical regions, which suggests involvement of the epileptic network in spike generation (Middlebrooks et al., 2017). Furthermore, the EEG/fMRI technique can be used for pre-surgical evaluation. In one study, the results of EEG/fMRI modified the initial surgical plan in 77% of the patients (Buyukturkoglu et al., 2019).

Combined PET/MRI:

PET is a nuclear medicine technique that utilizes radioactive tracers to visualize changes in the metabolic processes. 2-deoxy-2 (18F)-fluoro-d-glucose (FDG) is the most common tracer in neuroimaging. PET/MRI is a relatively new technique that allows the functional data from the PET scan to be registered on the high soft tissue contrast of MR images. PET/MRI has the potential to decrease the number of required examinations and consequently lower radiation exposure and sedations. Several studies have demonstrated the usefulness of PET/MRI in the diagnosis of epilepsy. For example, a study by Oldan et al. (2018) showed that PET/MRI can identify more focal epileptic lesions than MRI or PET alone (Oldan et al., 2018). In addition, it was found that PET/MRI can precisely locate the seizure onset and optimize the stereo-electroencephalography (SEEG) electrode placement (Liu et al., 2020; Zhang et al., 2020).

MRS:

MRS is a noninvasive technique that provides metabolic information about certain tissue. Since metabolic abnormalities are often seen before structural changes, MRS can detect abnormalities that are not seen in structural MRI (Aun et al., 2016). Just like MRI, for its high abundance and concentration, hydrogen protons have the greatest sensitivity in MRS. Detectable metabolites in MRS typically include N-acetylaspartate (NAA), creatine, choline, lactate, glutamate, and gamma aminobutyric acid (GABA). NAA, which resonates at 2.0 ppm, has been found to be a marker for neuronal function (Pan and Takahashi, 2005), whereas creatine, which resonates at 3.0 ppm, is important for energy supply and neuroprotection (Avgerinos et al., 2018).Creatine maintains a constant level over different tissue types and thus can be a normalization factor (Aun et al., 2016). Because the highest concentration of creatine is found in astrocytes, the ratio of NAA/Cr is commonly used as a normalized parameter. Several studies have shown a reduced NAA/Cr ratio in patients with epilepsy (Cendes et al., 1997; Fan et al., 2017; Kuzniecky et al., 1998). One study by El-Bayoumy et al. (2020) found that the sensitivity and specificity of NAA/Cr ratio in children with epilepsy was 96.7 and 93.3, respectively (HASSAN et al., 2020). In addition, choline, which resonates at 3.2 ppm, is another compound that is investigated by MRS. It is known as a marker of cellular membrane turnover (Aun et al., 2016). Studies have shown a reduction in the NAA/Cho+Cr ratio in patients with epilepsy (Todua et al., 2017). Finally, although GABA (the main inhibitory neurotransmitter) and glutamate (the main excitatory neurotransmitter) can be detected by MRS (Egerton, 2019), they exist in a very complex chemical structure, which leads to inaccurate conclusions.

CONCLUSION

MRI can provide information that assists in the understanding of epilepsy mechanisms, as well as the diagnosis and treatment of patients with epilepsy. Although some of the above techniques are still not routinely used in clinical settings, research is published on a daily basis to bring these techniques to the surface. With the help of the technological advancement of these imaging devices, it is expected that some of these research techniques will become more common in the near future.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

SA designed, performed and also wrote and reviewded the manuscript.

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