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Recommendations for the use of structural MRI in the care of patients with epilepsy: A consensus report from the ILAE Neuroimaging Task Force

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SUMMARY

Structural magnetic resonance imaging (MRI) is of fundamental importance to the diagnosis and treatment of epilepsy, particularly when surgery is being considered. Despite previous recommendations and guidelines, practices on the use of MRI, however, are variable world-wide and may not harness the full potential of recent technological advances for the benefit of people with epilepsy. The International League Against Epilepsy (ILAE) Diagnostic Methods Commission has thus charged the 2013-2017 Neuroimaging Task Force to develop a set of recommendations addressing the following questions: (1) Who should have an MRI? (2) What are the minimum requirements for an MRI epilepsy protocol? (3) How should MR images be evaluated? (4) How to optimize lesion detection? These recommendations target clinicians in established epilepsy centers and neurologists in general/district hospitals. They endorse routine structural MRI imaging in new-onset generalized and focal epilepsy alike and describe the range of situations when detailed assessment is indicated. The Neuroimaging Task Force identified a set of sequences, with 3D acquisitions at its core (the harmonized neuroimaging of epilepsy structural sequences – HARNESS-MRI protocol). As these sequences are available on most MR scanner, the HARNESS-MRI protocol is generalizable, regardless of the clinical setting and country. The Task Force also endorses the use of computer-aided image post-processing methods to provide an objective account of an individual's brain anatomy and pathology. By discussing the breadth and depth of scope of MRI, this report emphasizes the unique role of this non-invasive investigation in the care of people with epilepsy.

KEY POINTS

- Practices on the use of structural MRI are variable worldwide and may not harness the full potential of technological advances for the benefit of people with epilepsy.

- The Task Force recommends the use the *Harmonized Neuroimaging of Epilepsy Structural Sequences* (HARNESS-MRI) protocol with isotropic, millimetric 3D T1 and FLAIR images, and high-resolution 2D sub-millimetric T2 images.
- The use of the HARNESS-MRI protocol standardizes best-practice neuroimaging of epilepsy in out-patient clinics and specialized surgery centers alike.

INTRODUCTION

Since its inception in the early 80s, steady advances in magnetic resonance imaging (MRI) technology have led to dramatic improvements in the ability to obtain high-quality detailed information about the brain, thereby providing insights into disease processes. Computational approaches and novel quantitative MRI acquisition and post-processing techniques have emerged to study neuronatomy, yielding increasingly sophisticated markers of tissue microstructural integrity. In epileptology, MRI has revolutionized our ability to detect lesions, shifting the field from prevailing electro-clinical correlations to a multidisciplinary approach. In particular, this technique has become fundamental in the management of drug-resistant epilepsy, as the identification of a clear-cut lesion on structural MRI is associated with favorable seizure outcome after surgery [1].

The rapid pace of technical advances and developments in neuroimaging has not systematically translated into clinical care. This is due to a number of reasons, including variability in economic resources and technical infrastructures, difficulty to perform prospective randomized controlled trials to assess level of evidence and added value of a given test, as well as lack of standardized image acquisition protocols and post-processing methods. Collectively, these factors may slow down or impede timely validation of imaging markers and assessment of generalizability, thus creating a sense of disconnect between research and clinical practice. Over the years, the International League Against Epilepsy (ILAE) has thus produced consensus several recommendations on the use of MRI in the diagnosis and management of people with epilepsy. The first was published in 1997 [2], followed by guidelines focused on patients with drug-resistant epilepsy [3] and functional neuroimaging [4] published in the 1998 and 2000, respectively. In 2009, the subcommittee for pediatric neuroimaging recommended structural MRI as the exam of choice in recent-onset epilepsy [5]. In 2015, the Task Force Report for the

ILAE Commission of Pediatrics recommended neuroimaging at all levels of care for infants presenting with epilepsy, with level A recommendation for structural MRI as standard investigation [6].

Despite previous ILAE recommendations and guidelines, 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. The International League Against Epilepsy (ILAE) Diagnostic Methods Commission has thus charged the 2013-2017 Neuroimaging Task Force to formulate a new consensus recommendation for the use of MRI in epilepsy answering the following key questions: (1) Who should have an MRI? (2) What are the minimum requirements for an MRI epilepsy protocol? (3) How should MR images be evaluated? (4) How to optimize lesion detection? As the ultimate purpose of this recommendations is to standardize epilepsy diagnostic imaging in out-patient clinics and specialized surgery centers alike, the categorization of these questions is intentionally broad and independent from the clinical definition of drug-resistance and non-lesional MRI. Indeed, despite American Academy of Neurology guidelines recommending referral for surgical evaluation to specialized centers and ILAE recommendations defining refractory epilepsy (*e.g.*, failure to respond to two adequately tried medications) [7; 8] often these criteria are not applied by the treating physicians and, on average, adult patients who do get surgery have had intractable epilepsy for 20 years or more [9-11]. Moreover, the terminology "non-lesional MRI" is currently ill-defined and depends on multiple factors, including the type of imaging, the reader's expertise and the use of post-processing [12; 13].

METHODS

The current recommendations derive from the following considerations, with the aim of providing a consensus view on the role of structural MRI in epilepsy. Firstly, they build upon previous ILAE neuroimaging reports. Secondly, they derive from clinical protocols conducted in the institutions of the members of the Task Force with basic sequences available on most MR scanners and thus generalizable to many centers, regardless of the clinical setting and country. Thirdly, they consider review papers, evidence-based guidelines and reports on the role of structural MRI in the diagnosis and management of seizure disorders [14-25], with particular attention to studies that meet at least some standards for evidence classification. These sources of information were complemented by a literature review based on a Ovid MEDLINE query

between 2002 and 2018. The search strategy and list of 67 identified publications are detailed in the **Supplementary Material 1**. Our recommendations, which take into account clinical indications, new developments in MRI hardware and sequences, as well as research findings, are intended to be primarily applicable to adult patients; the overall principles, however, are generalizable to children. Also, they are intentionally broad to assist clinicians in established epilepsy surgery centers and general neurology clinics alike. Implementation of such recommendations necessarily will vary depending on available resources and organization of care. Ideally, in the developed world, only centers meeting appropriate standards should image patients with epilepsy. In resource-limited settings where technical infrastructure and specialist training may not be available, epilepsy care must still be provided; these recommendations are thus an essential resource to persuade local health organizations to provide or improve both training and access to MRI services.

In the following paragraphs, Task Force recommendations on the use of MRI pertain to the proposed *Harmonized Neuroimaging of Epilepsy Structural Sequences* (HARNESS-MRI) protocol (as described in Section 2).

1) WHO SHOULD HAVE AN MRI?

Once the first seizure occurs, recurrence will depend on numerous factors. Compared to patients in whom the cause is unknown, the rate of seizure recurrence increases two-fold in those with a lesion on MRI, from 10 to 26% at 1 year and from 29 to 48% at 5 years [23]. Numerous studies have related the presence and types of MRI abnormalities to clinical outcomes. In a cohort of 764 patients undergoing MRI at the time or soon after a first seizure, 23% had a potentially epileptogenic lesion, including stroke, trauma, a developmental abnormality, or a tumor [26]. Another showed that patients with focal epilepsy and unremarkable MRI have a 42% chance to have their seizures controlled with antiepileptic drugs, while this is true in 54% of cases with post-stroke epilepsy; conversely, seizure control with medication was achieved in <10% of patients with hippocampal sclerosis on MRI [27].

First-seizure

Data from the WHO show that CT is widely available in hospitals worldwide [28]. Evidence-based guidelines of the therapeutics and technology assessment subcommittee of the American

Academy of Neurology [29] recommend immediate non-contrast CT in emergency patients presenting with a first seizure to guide appropriate acute management, especially in those with abnormal neurological examination, predisposing history, or focal seizure onset. Indeed, in these situations there is great potential for pathology that may require immediate management, such as a hemorrhage or large mass. Notably, non-contrast CT can detect some tumors, large arteriovenous malformations, stroke, and calcified lesions. CT with contrast is indicated in cases with suspicion for infection or small neoplasms (including metastases) [30], if MRI is unavailable.

In accordance with a recent ILAE publication [31], the Task Force advises that the HARNESS-MRI protocol should be done soon after the first seizure, if resources allow; this will help establishing a syndromic definition and guiding management. Indeed, MRI has high sensitivity and specificity [23] for developmental cortical malformations, including focal cortical dysplasias, and mesiotemporal sclerosis, a group of prevalent structural lesions associated with increased risk of drug-resistance [32-34]. Notably, an early MRI is particularly important in young children as ongoing myelination may mask the appearance of cortical dysplasias on later scans; in these cases, conclusions may be misleading with respect to diagnosis and appropriateness of surgical treatment [35].

Newly-diagnosed epilepsy

The identification of a structural lesion in recent-onset epilepsy is a strong indicator of drug-resistance and should be an incentive to strictly adhere to the ILAE criteria for drug-resistance [8]. In other words, once a lesion is discovered on MRI, a patient should be referred to a specialized epilepsy surgery center to evaluate surgical candidacy [36]. While, a non-progressive brain lesion may be associated with response to anti-epileptic drugs, a recent prospective longitudinal cohort study showed that patients with mild mesial temporal lobe epilepsy (TLE) and hippocampal sclerosis seen on MRI early in the course of the disease have three times higher likelihood of becoming refractory than those without such lesion [37]. A meta-analysis showed that odds of becoming seizure free after surgery were 2.5 times higher in patients with MRI-defined lesions [38]. Moreover, > 60% of patients with drug-resistant frontal lobe epilepsy achieve post-surgical seizure freedom if operated within 5 years of disease onset compared to only 30% when surgery is delayed [39]. This body of evidence should become knowledge for every practicing neurologist

since epilepsy surgery remains largely underutilized, with only a fraction of patients being evaluated in specialized tertiary centers [9; 11; 40; 41]. Moreover, drug-resistant epilepsy is associated with increased risk of injury and mortality, affective disturbances, and cognitive decline [42]. Deferring surgery may thus cost the patient chances of seizure-freedom, cognitive benefits, and years of life expectancy.

There is currently insufficient evidence to recommend the systematic use of MRI in patients with genetic generalized syndromes, such as juvenile myoclonic epilepsy, and self-limited drug-responsive syndromes, such as childhood epilepsy with centro-temporal spikes. While neuroimaging studies demonstrate structural and functional anomalies in these epilepsies [5; 43], their prognostic value remains to be determined. Notably, focal epilepsy may mimic generalized syndromes; in these cases, the HARNESS-MRI protocol is recommended in the presence of atypical features such as abnormal neurologic development, cognitive decline, difficult-to-treat seizures, or focal interictal epileptic spikes [31].

The Task Force acknowledges that in resource-limited areas MRI may not be readily obtainable [28]; in this scenario, a CT scan would be the exam of choice awaiting future availabilities.

The importance of repeating the MRI

The MRI should be repeated using the HARNESS-MRI protocol if images of a previous exam are not available or the type and quality of previous acquisitions were suboptimal. Relying on a written radiological report may be insufficient as putative anomalies may have been overlooked due to poor image quality or lack of the reader's expertise in neuroimaging of epilepsy [24]. Importantly, images should be evaluated in light of the evolving electro-clinical picture, particularly an unexplained increase in seizure frequency (*i.e.*, not related to toxic-metabolic factors, medication compliance, etc.), rapid cognitive decline, or appearance/worsening of neuropsychiatric symptoms. Given the evidence for progressive brain atrophy developing over 1-3 years in both patients with refractory and well-controlled seizures [37; 44-46], repeated MRI may have prognostic value. In drug-resistant TLE, indeed, progressive atrophy of the neocortex and mesiotemporal lobe structures are associated with poor outcome after surgery [44; 47]. Finally, the diagnostic yield depends heavily upon logistics, including image resolution, magnetic field

strength, number of phased-array head coils, and expertise of the reader [12]. It is thus utterly important to repeat the examination with an optimized protocol [48], particularly in patients with drug-resistant epilepsy and previous "normal" MRI, as this may reveal a lesion in 30-65% of cases [49-51]; when MRI is combined with image post-processing, sensitivity may be as high as 70% [52], thereby significantly improving clinical decision-making. Notably, imaging in the first year of life may be helpful in identifying FCD associated with very subtle signal changes on later images of the post-myelinated, matured brain and should be retained for comparison [35].

2) WHAT ARE THE MINIMUM REQUIREMENTS FOR AN EPILEPSY PROTOCOL?

It is the consensus of the Task Force that neuroimaging workup of patients with epilepsy requires a minimum set of MRI basic sequences that are available on most MR scanners, and thus generalizable, regardless of the clinical setting and country. Beyond this Task Force, previous independent expert opinion has underlined the importance of high spatial resolution and image contrast with complete brain coverage to optimally appraise brain anatomy, the interface between grey matter and white matter, as well as signal anomalies. In particular, three-dimensional (3D) sequences with isotropic voxels (*i.e.*, cube-shaped voxels of identical length on each side or image plane) of 1 mm or less dramatically reduce partial volume effects, a phenomenon resulting from the presence of multiple tissue types within a given voxel. Notably, partial volume is detrimental when looking for subtle cortical dysplasias as it mimics tissue blurring, a cardinal feature of these lesions.

Previous MRI protocols: Summary and limitations

The original guidelines established two decades ago by the ILAE proposed T1- and T2-weighted MRI with the minimum slice thickness possible, acquired in two orthogonal planes (axial and coronal), and a 3D volumetric T1-weighted acquisition. To obtain 2D images with whole-brain coverage in a clinically acceptable time, it was necessary to apply inter-slice gaps of 3-5 mm. Moreover, epilepsy protocols were divided according to clinical syndromes into temporal and extra-temporal with a series of coronal, axial and sometimes sagittal cuts, a strategy still in practice in many institutions. Initial volumetric 3D sequences, obtained on 1.5 Tesla scanners, were only possible for T1-weighted sequences, with slice thickness varying between 1 and 3 mm, rarely acquired with isotropic voxels, either because of time or hardware constraints.

Notably, while in 3D acquisitions with isotropic voxels, thickness and resolution are interchangeable quantities, for 2D images the in-plane voxel dimension (not slice thickness) defines image resolution. To achieve finer in-plane resolutions (≤1 mm), one had to reduce the size of the field of view or introduce inter-slice gaps, thus sacrificing whole-brain coverage, with the risk of missing lesions.

Harmonized neuroimaging of epilepsy structural sequences (HARNESS-MRI)

The advent of high-field magnets at 3 Tesla, combined with the use of multiple phased arrays instead of conventional quadrature coils, has resulted in accelerated image acquisition, improved signal-to-noise ratio and increased image contrast. Importantly, 3D MR images with isotropic voxel resolution and no inter-slice gap eliminate the need for syndrome-specific protocols, as images can be reformatted and inspected in any plane with equal resolution. Additional considerations for optimal imaging include comfortable padding of the head with foam cushions to minimize motion artifacts and centering the head in the coil prior to starting the acquisition. Head positioning can be verified on the scout image (or "localizer") done at the beginning of the session. Any tilt or rotation should be corrected for planning of the subsequent sequences and later side-by-side analysis of brain structures; this is particularly important when acquiring 2D coronal T2-weighted images, as specified below. Sedation-related recommendations have been discussed in a special report published by the ILAE subcommittee for pediatric neuroimaging in 2009.

The Task Force proposes the *Harmonized Neuroimaging of Epilepsy Structural Sequences* (HARNESS-MRI), a core structural MRI protocol comprising three acquisitions. The HARNESS-MRI protocol and is applicable to adults and children alike. It is time-effective as each sequence lasts 7-10 minutes, for a total time not exceeding 30 minutes when using multiple phased-array coils (8-, 12- or 32-channels) with accelerated parallel imaging (*e.g.*, GRAPPA, ASSET, SENSE). **Table 1** present key points regarding the protocol. The HARNESS-MRI protocol is optimized for 3 Tesla scanners, if available. Notably, while it is possible to obtain this protocol on new generations of 1.5 Tesla systems, the overall image quality may be inferior.

Suggested acquisition parameters for the HARNESS-MRI protocol on a 3 Tesla scanner are shown **in Supplementary Material 2**. The Task Force recommends all patients in whom

previous investigations were unremarkable to undergo a repeated scan using the HARNESS-MRI protocol. Even in patients in whom seizures are associated with other conditions, such as head trauma, neurodegenerative disorders, multiple sclerosis or alcoholism, the HARNESS-MRI protocol can be used as it contains basic sequences that are available on most MR scanners.

1) *High-resolution 3D T1-weighted MRI* (**Figure 1**). The magnetization-prepared rapid gradient-echo (MP-RAGE) sequence, as well as the equivalent spoiled gradient echo (3D SPGR) and turbo field echo (3D TFE) protocols with isotropic millimetric voxel resolution (*i.e.*, 1x1x1 mm^3, no inter-slice gap) are the most popular 3D T1-weighted gradient echo (GRE) sequences. They allow for optimal evaluation of brain anatomy and morphology.

2) *High-resolution 3D fluid attenuation inversion recovery (FLAIR)* (**Figure 1**). This 3D-FLAIR sequence (named CUBE, VISTA or SPACE, depending on the MR vendor) is best suited for assessing signal anomalies, in particular hyperintensities related to gliosis and increased extra-cellular space. Compared to conventional T2-weighted contrasts, the nulling of CSF signal enhances the visibility of hyperintense cortical lesions. This acquisition should also be acquired with isotropic millimetric voxel resolution (*i.e.*, 1x1x1 mm^3) and no inter-slice gap. Because limbic structures are inherently hyperintense [53], FLAIR may not be sensitive to detect very subtle hippocampal sclerosis. Moreover, FLAIR images are not sensitive to epilepsy-associated pathology in neonates and infants before 24 months, as myelination is not yet complete.

3) *High in-plane resolution 2D coronal T2-weighted MRI* (**Figure 2**). This turbo spin echo (TSE) sequence is the exam of choice for assessing the hippocampal internal structure, given that images are acquired perpendicular to the long axis of the hippocampus and using sub-millimetric voxel resolution (for example 0.4mmx0.4mmx2mm, no inter-slice gap). Notably, the densely myelinated molecular layer appearing as a dark ribbon inside the hippocampus allows discriminating CA subfields from the dentate gyrus.

When a tumor, vascular malformation or infectious process is suspected, the HARNESS-MRI protocol should be complemented by T1-MRI with gadolinium to look for contrast enhancement and susceptibility weighted imaging (SWI) and T2* contrasts sensitive to venous blood, hemorrhage, iron deposits and calcifications.

3) HOW SHOULD MR IMAGES BE EVALUATED?

To embrace the multidisciplinary facets of disease diagnostics, epileptologists should be given the opportunity to train and receive continued medical education in neuroimaging [54]. Indeed, even with an appropriate MRI protocol, the interpretation strongly depends on the reader's expertise in imaging of epilepsy [24]. Notably, in-depth inspection, particularly when dealing with small cortical dysplasias or subtle hippocampal sclerosis, requires significant time investment. Importantly, optimal sensitivity for lesion detection is achieved when the reader has access to a detailed description of the electro-clinical findings, including the suspected hemisphere and lobe, an information oftentimes missing in the radiology requisition [24]. In some cases, particularly at disease onset, it may be difficult to establish the exact syndromic classification. In light of new electro-clinical data or information derived from any other test, the epileptologist may be best positioned to evaluate previous scans or decide to repeat them, if necessary.

Because of the large number of MRI cuts, instead of inspecting the original native high-resolution format, some radiologists may decide to inspect images that have been reconstructed into thicker slices. For instance, 1 mm^3 isotropic resolution T1 or FLAIR may be reformatted at 3 mm thickness, at times with inter-slice gaps that further reduce the number of slices to inspect, from approximately 170 to less than 50. This process is detrimental and counteracts the purpose of 3D MRI, as it generates lower resolution images and accentuates partial volume effects, potentially masking subtle lesions (**Figure 3**). Visualization techniques, such as the widely-used clinical picture archiving and communication systems (PACS) as well as several freely-available imaging platforms, have greatly facilitated the inspection of 3D MRI by allowing time-effective simultaneous inspection of images in all three orthogonal planes (coronal, axial and sagittal). These platforms also allow to view different MRI contrasts side-by-side and evaluate both morphology and signal, as co-occurring anomalies increase diagnostic confidence.

The following paragraphs give a short overview on the main criteria for the visual inspection of prevalent epileptogenic lesions associated with drug-resistant epilepsy.

Visual MRI analysis in temporal lobe epilepsy

In temporal lobe epilepsy (TLE), the most frequent histopathological finding is mesiotemporal sclerosis (MTS) characterized by cell loss and astrocytic gliosis [55]. These features are not limited to the hippocampus, but are often found in the amygdala, entorhinal cortex, temporopolar cortex, and the temporal lobe [56]. On MRI, typical MTS is characterized by anomalies more easily

appreciated in the hippocampus proper, including atrophy, loss of internal structure, decreased T1 and increased T2 signal intensity. Additional features may include atrophy of the ipsilateral fornix, mammillary body and the temporal lobe, particularly the pole. Inspection of coronal sections allows for side-by-side comparison of asymmetry in volume, shape and signal, while sagittal images provide a complete antero-posterior view, facilitating appraisal of patterns of signal distribution within the hippocampus and parahippocampus. Field strengths at 3 Tesla (and above), allow visual evaluation of the internal architecture of the hippocampus [57] and thus better appreciation of subtle volume loss within individual subfields, particularly CA1, and CA4-dentate. In addition, the molecular layer, a band of white matter running through the CA regions and dentate gyrus, may become thin and blurred, a characteristic seen on T2-weighted images (**Figure 4A**). Besides atrophy and signal changes, about 40% of patients with TLE present with malrotation characterized by an abnormally round and vertically orientated hippocampus, and a deep collateral sulcus [58]. This neurodevelopmental shape variant occurs more frequently in the left hemisphere and may be misinterpreted as hippocampal atrophy. While more prevalent in patients than in healthy controls, its relation to epileptogenicity remains unclear [59].

Encephaloceles of the temporal pole [60-62] and parahippocampal dysplasia [63] may be under-diagnosed, treatable causes of refractory TLE. Encephaloceles present as a herniation of brain tissue trough a defect in the skull base, often the greater wing of the sphenoid bone. Their detection is facilitated by high-resolution 3D sequences and signal hyperintensity on T2 and FLAIR; high-resolution CT confirms the bony defects in the inner table of the skull. Parahippocampal dysplasia is characterized by prevailing white matter signal anomalies, without apparent increased in cortical thickness. Because of the presence of nearby blood vessels, this lesion may be mislabeled as flow or partial volume artifacts, if the MRI cuts are thick. An in-depth inspection of the temporal lobe should also include the periventricular zone, in search of nodular heterotopia, a cortical malformation often associated with drug-resistant TLE [64].

Visual MRI analysis of focal cortical dysplasia

Focal cortical dysplasias (FCD) are a prevalent cause of medically-intractable epilepsy and among the most frequent histological findings in patients undergoing epilepsy surgery [34]. The

last decades have witnessed numerous attempts to provide a histological grading system. Currently, FCDs are classified into three types (I-III) and several subtypes (*e.g.*, Type IIA and IIB) based on a combination of architectural alterations of cortical layers either alone (Type-I, Type-III) or together with cell overgrowth and morphological aberrations, including giant dysmorphic neurons (Type-IIA) and balloon cells (Type-IIB) [65]. Gliosis and demyelination are also seen in the lesion and underlying white matter. The MRI signature of FCD Type-I remains unclear. Conversely, FCD Type-II is mainly characterized by increased cortical thickness and blurring of the gray-white matter interface on T1-weighted MRI in 50–90% of cases. Analysis of T2-weighted MRI, particularly FLAIR, reveals gray matter hyperintensity in up to 100% of patients. In many patients, however, FCD Type-II features may be very subtle and the MRI, consequently, reported as unremarkable [12] (**Figure 4B**). In these cases, the inspection of axial slices allows for side-by-side comparisons in search for asymmetries in sulco-gyral patterns. This is particularly important, as small FCD lesions may be preferentially located at the bottom of deep sulci [66]. The transmantle sign, a funnel shaped signal extending from the ventricular wall to the neocortex harboring the lesion, may be the first feature to attract the observer's attention towards a small FCD lesion, underlying the importance of systematical inspection of the white matter.

4) How to optimize lesion detection with MRI post-processing?

Despite technical advances, routine visual MRI inspection does not permit a diagnosis with sufficient degree of confidence in 30-50% of cases, or is simply unremarkable, even though a lesion is found on histology [13]. This clinical conundrum, currently one of the main barriers to effective epilepsy surgery, has motivated the development of computer-aided methods aimed at quantitatively analyzing morphology and signal of 3D MR images [12; 67-69]. However, there are a number of basic steps in data preparation, namely correction for image intensity non-uniformities, registration, and tissue segmentation that need to be carefully evaluated by the user, as their quality greatly influences final results. For instance, subject motion negatively impacts tissue segmentation and leads to artifacts that mimic lesions, including atrophy. Another important point is performance evaluation. Ideally, metrics derived from MRI post-processing should be sensitive and specific (*i.e.*, identify correctly affected and unaffected subjects, respectively), and reproducible (*i.e.*, consistent between repeated measures). Such rigorous

standards are essential to guarantee clinical validity of these advanced image analyses techniques [52; 70].

The following paragraphs give a short overview of image analysis methods for the detection of MTS and FCD. Except for volumetry, the Task Force did not include image processing in the minimal requirements. However, the use of these algorithms is encouraged as there is mounting evidence for their ability to reveal subtle lesions that previously eluded visual inspection, particularly when applied to 3D millimetric or sub-millimetric isotropic multicontrast images [52; 71-74].

Volumetry and shape modeling of mesiotemporal lobe structures. Manual volumetry performed on T1-weighted anatomical MRI has shown increased sensitivity of detecting hippocampal atrophy compared to visual MRI, particularly when values are corrected for head size and normalized with respect to the distribution in healthy controls. Volumetry of the entorhinal cortex, amygdala and temporopolar region, as well as the thalamus, may lateralize the seizure focus, particularly in patients with normal hippocampal volume [69]. Importantly, the degree of MRI volume loss has been shown to correlate with the degree of cell loss on surgical specimens [75]. Thus, hippocampal volumetry is part of the minimal requirement when considering epilepsy surgery in order to lateralize the focus and establish whether the contralateral structures are normal. Indeed, bilateral mesial temporal lobe atrophy raises concerns of markedly reduced chance of seizure freedom after surgery [76] and an increased risk of memory impairment [14]. Over the years, steady technical advances have propelled the design of automated algorithms yielding segmentation of the whole hippocampus (for example [77-79]), and more recently hippocampal subfields [80], thereby creating a solid basis for broad translation (**Figure 5**). Several FDA-approved commercial software packages are currently available for routine use in clinical practice and provide an automated report that details the volume and percentile of each parcellated cortical region compared to a normative database. They have been used to lateralize hippocampal atrophy in TLE patients with accuracy rates that exceed visual inspection [81]. Notably, hippocampal labels may be used to examine structural alterations trough statistical parametric surface shape modeling [82; 83], further increasing sensitivity.

Hippocampal T2-relaxometry. Compared to visual analysis of T2-weighted MRI, T2 relaxometry [84; 85], a sequence providing quantitative estimates of the T2-weighted signal, yields increased

sensitivity for detecting mesiotemporal gliosis [86]. Importantly, it correctly lateralizes the focus in up to 80% of patients with normal hippocampal volume [87]. Measurement of T2-relaxation times can be done by placing a manual or automatically-generated region-of-interest within the hippocampus [88], carefully avoiding the adjacent CSF.

Texture analysis. Voxel-based modeling of grey-white matter blurring and grey matter intensity, derived from 3D T1-MRI, assists visual inspection and increases sensitivity for the detection of FCD Type-II up to 40% relative to conventional MRI [71] (**Figure 6**). Analysis of these maps can be done either by normalizing (z-scoring) data within the same brain [71] or by comparing features to a group of healthy controls [73]. Surface-based methods improve inter-subjects anatomical correspondence and allow for multivariate analysis of MRI contrasts and features to unveil latent tissue properties not readily identified on a single modality [89].

Fully automated lesion detection techniques. Over the last 15 years, a number of algorithms have been developed for automated FCD detection. These methods were initially based on morphology and signal derived from 3D T1-weighted MRI. More recent tools have incorporated 3D FLAIR [90; 91]. A recent publication showed Class II evidence that machine learning of MRI patterns accurately identifies FCD type II in >70% of patients in whom the lesion had been overlooked by routine clinical visual inspection [52].

CONCLUSION

Magnetic resonance imaging provides a unique, versatile and non-invasive tool for brain-wide evaluation of patients with epilepsy. Notwithstanding the relentless progress in hardware and acquisition techniques, as well as methods for computational analysis, any guideline is difficult to implement when resources are scarce, and where technical infrastructure and specialist training may not be available. The Task Force believes, nevertheless, that the proposed recommendations set a tangible basis for a consistent use of structural MRI in epilepsy. By revealing lesions unseen by conventional neuroradiology, the HARNESS-MRI protocol combined with post-processing has the potential to transform MRI-negative into MRI-positive, thereby offering the life-changing benefits of epilepsy surgery to more patients.

Because of the transforming role of MRI in modern epileptology, the forthcoming competency-based ILAE educational curriculum requires neurologists and epileptologists to train in neuroimaging [92]. With the goal to optimally meet the needs of people with epilepsy, the learning objectives will include acquiring a range of skills, from basic MRI visual evaluation to advanced training in image post-processing. Notably, such training may also provide a unique opportunity to optimize skills in neuroimaging of epilepsy for neuroradiologists. Achieving this goal will require a combined effort from ILAE and its regional chapters, medical societies and academies, universities, and centers that offer epilepsy fellowship training. Tangible steps towards this objective are the ILAE-endorsed courses on neuroimaging of epilepsy currently offered around the globe and online educational platforms.

DISCLOSURE

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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FIGURE LEGEND

FIGURE 1. HARNESS-MRI 3D protocol at 3 Tesla. T1-weighted and FLAIR images, with representative axial, coronal, sagittal cuts with millimetric resolution.

FIGURE 2. HARNESS-MRI 2D protocol at 3 Tesla. Coronal T2-weighted images at submillimetric in-plane resolution cover the entire extent of the temporal lobes and hippocampi. Representative cuts at the level of the hippocampal head (Ant), body (Mid), and tail (Post) are shown. Slices are acquired perpendicular to the long axis of the hippocampus as shown in the sagittal view to optimize the evaluation of the hippocampal internal structure. In the magnified panel one can appreciate the densely myelinated molecular layer of the CA and dentate gyrus fused across the hippocampal sulcus appearing as a dark ribbon, which allows discriminating these compartments.

FIGURE 3. Image resampling vs. original resolution. Axial 3 Tesla 3D FLAIR images of a patient with histologically-proven focal cortical dysplasia ILAE Type II. Upper panels. The radiological evaluation was initially done on images reconstructed from the original 3D high-resolution 1 mm acquisition into thick 3mm slabs. This exam was reported as unremarkable. Lower panels. The repeated inspection of the original (native) 3D high-resolution 1mm isotropic images revealed the initially overlooked subtle dysplasia characterized by blurring of the lesional boundaries (seen on all the slices, as indicated by the arrows) and a minute transmantle sign (arrow head).

FIGURE 4. The MRI spectrum of epileptogenic lesions. A) Coronal T1- and T2-weighted 3T MRI in two cases with drug-resistant temporal lobe epilepsy (TLE) and histologically confirmed hippocampal sclerosis. In the MRI positive case, the right hippocampus is clearly atrophic and shows T1 hypo- and T2 hyperintensity (arrows). In the case initially reported as "MRI-negative", careful examination of the T2 weighted MRI shows a subtle T2 signal hyperintensity across the left CA1-3 regions. Moreover, compared to the contralateral side, the dark ribbon representing the molecular layer is blurred, making the distinction between the CA subfields and the dentate gyrus difficult to appreciate (see magnified panel). B) Axial T1- and T2-weighted 3T MRI in two cases with drug-resistant left frontal lobe epilepsy (FLE) and histologically confirmed focal cortical dysplasia type II. In the MRI positive case, there is cortical thickening and blurring of the gray-white matter transition in the left superior frontal gyrus (arrows). In the case initially reported as "MRI-negative", re-examination of the FLAIR images shows a subtle blurring at the bottom of a sulcus (arrowhead), which is hard to appreciate on T1-weighted images.

FIGURE 5. Hippocampal subfield volumetry in temporal lobe epilepsy. Coronal T1- and T2-weighted MRI at the level of hippocampal body and 4 μm thick paraffin-embedded histology sections with NeuN immunohistochemistry at comparable level in two patients with right temporal focus. In A), volumes of subiculum (green), CA1-3 (red) and CA4-DG (blue) are >-3SD below mean of healthy controls and pathology shows severe pan-hippocampal neuronal loss. In B), volumetry detected subtle CA1-3 atrophy (-2.2 SD) and histology shows CA1 minimal neuronal loss. In this "MRI-negative" patient, whole conventional whole-hippocampal volumetry was unremarkable. Scale bar = 2 mm.

FIGURE 6. Texture analysis of "MRI-negative" focal cortical dysplasia. 3D T1 and FLAIR axial, sagittal and coronal views in a patient with right frontal lobe epilepsy initially reported as "MRI-negative". The last row shows cuts of the 3D gradient map obtained from the T1-weighted MRI, which calculates the rate of change of intensities across the volume, thereby modeling blurring at the interface between the gray (GM) and white matter (WM). In regions of normal transition, the gradient is expected to be steep, thus appearing hyperintense. In regions of blurring, the gradient is expected to be less steep, thus appearing hypointense. In this case, there

is a clear breakdown in the gradient, with a hypointense region within the right orbitofrontal region (outlined by the dashed rectangle). The re-inspection of the T1- and T2-weighted images, informed by the texture map, reveals an extensive blurring in the same area initially overlooked by conventional radiological examination.

Table 1. Key points summarizing the main advantages of the HARNESS-MRI protocol.

High-contrast, 3D sequences with isotropic voxels (i.e., identical dimensions across planes)

Can be obtained on 1.5T and 3T scanners

Applicable to adults and children

Provide complete brain coverage

No need for operator-dependent slice angulations

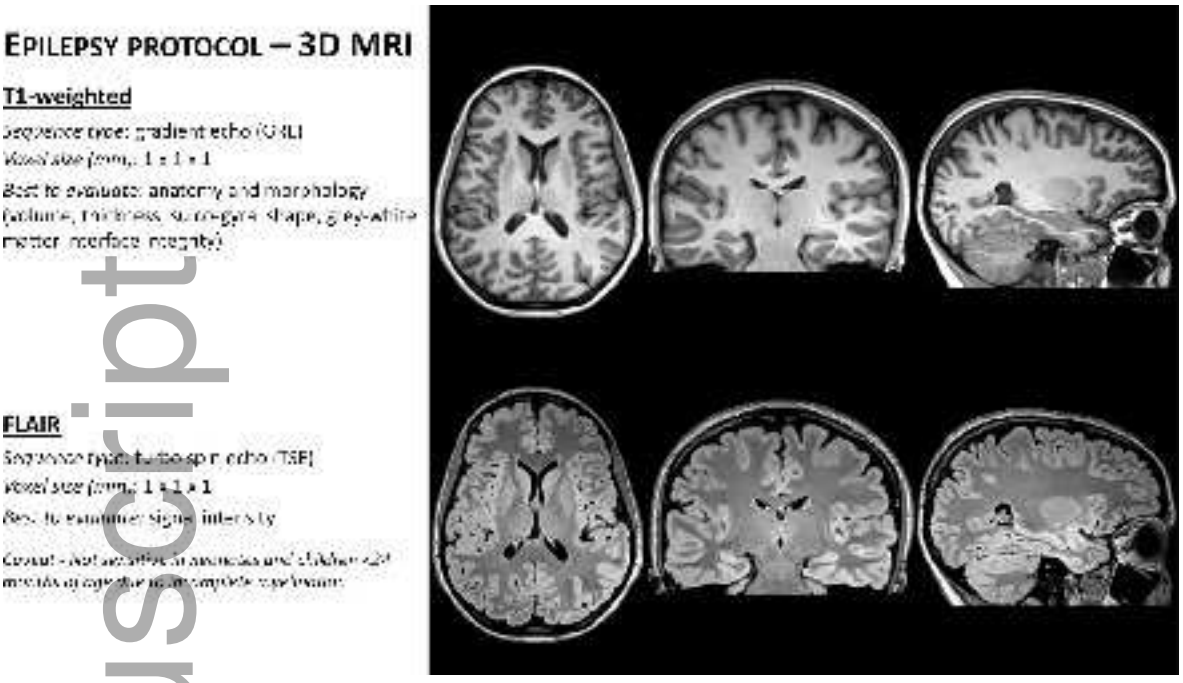
Images may be reformatted in any plane without loss of resolution

Greatly reduce partial volume effect (i.e., multiple tissue types present within a given voxel)

Multiple phased-arrays head coils

Provide improved signal-to-noise ratio and tissue contrast

Allow for accelerated image acquisition (GRAPPA, ASSET, SENSE)



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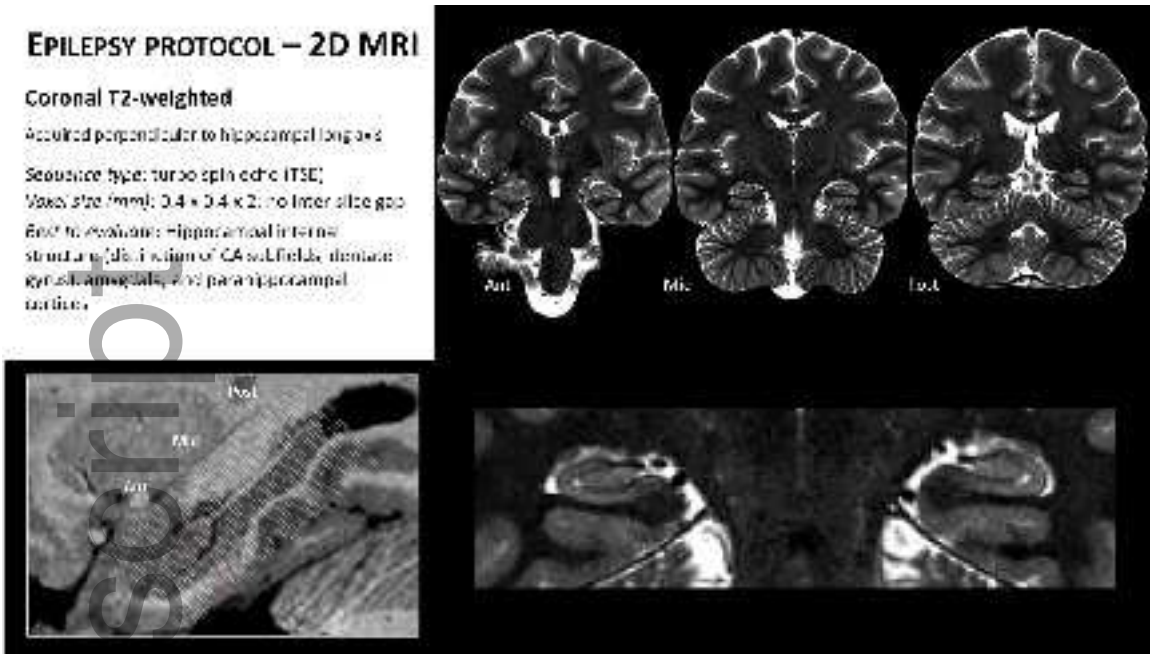

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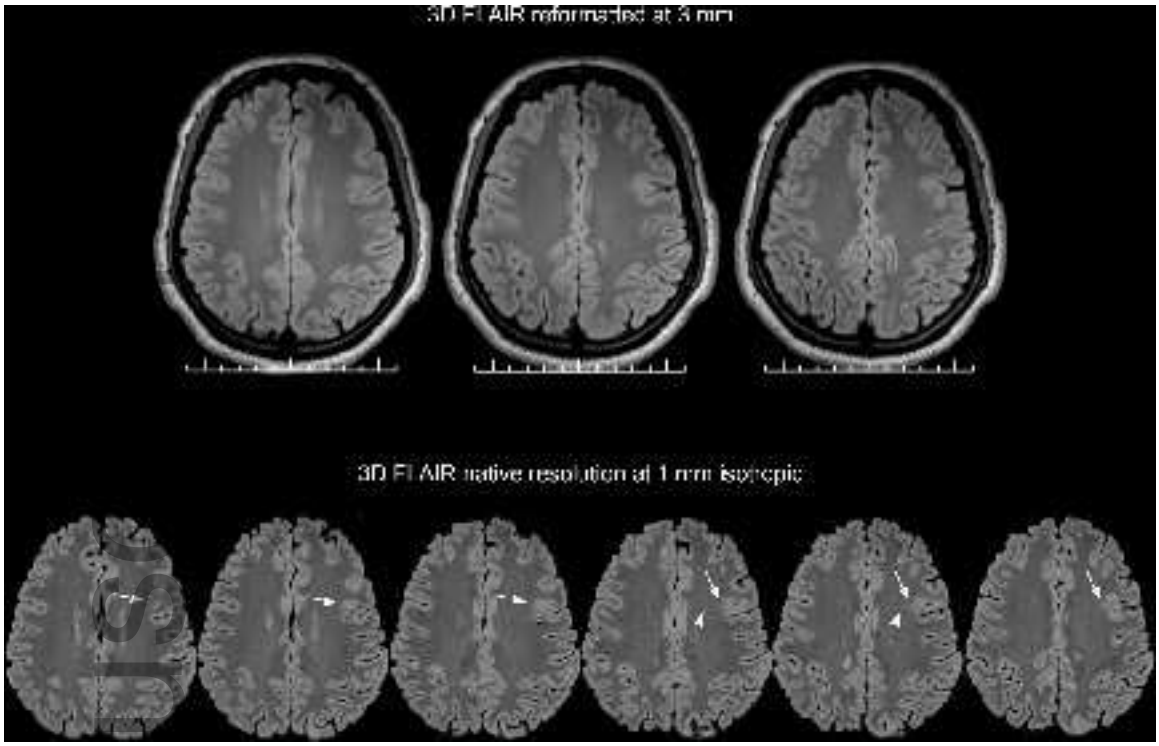

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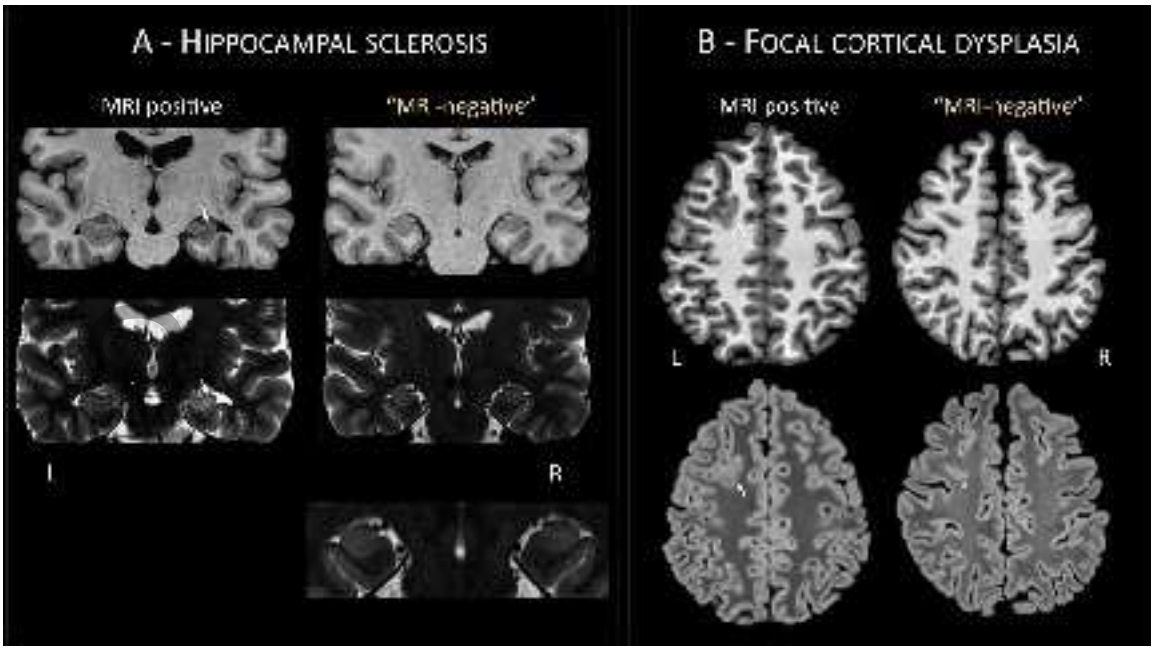

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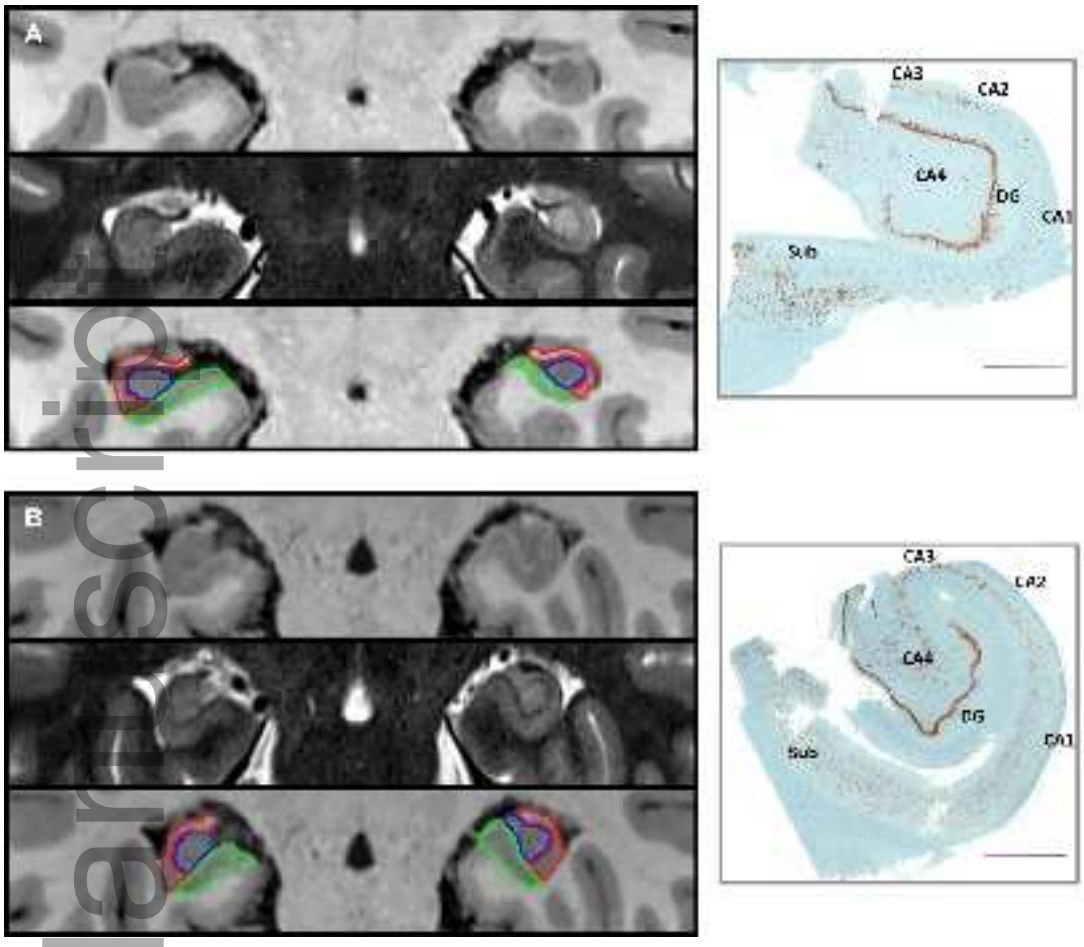

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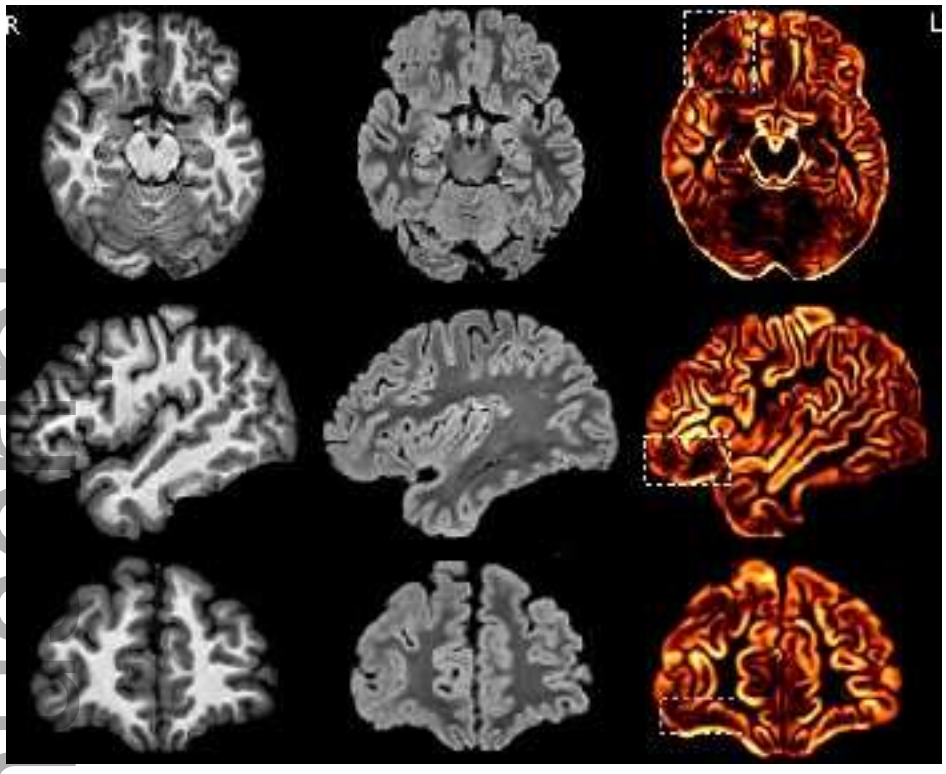

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