Received: 13 January 2023 | Accepted: 15 March 2023

DOI: 10.1002/epd2.20050

Epileptic Disorders

ORIGINAL ARTICLE

Impact of an optimized epilepsy surgery imaging protocol for focal epilepsy: A monocentric prospective study

Anna Elisabetta Vaudano[1,2] | Alice Ballerini[1] | Francesca Zucchini[3] | Elisa Micalizzi[4,5] | Simona Scolastico[1] | Francesca Talami[1] | Giada Giovannini[2,5] | Matteo Pugnaghi[2] | Niccolò Orlandi[1] | Niccolò Biagioli[1] | Maria Cristina Cioclu[1,2] | Stefano Vallone[3] | Maurilio Genovese[3] | Alessandra Todeschini[3] | Francesca Cavalleri[3] | Marcella Malagoli[3] | Stefano Meletti[1,2]

[1]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

[2]Neurology Unit, OCB Hospital, AOU Modena, Modena, Italy

[3]Neuroradiology Unit, OCB Hospital, AOU Modena, Modena, Italy

[4]Neurophysiology Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy

[5]Clinical and Experimental Medicine PhD Program, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

Correspondence
Stefano Meletti, Department of Biomedical, Metabolic, and Neural Sciences, Center for Neurosciences and Neurotechnology, University of Modena and Reggio Emilia, Modena, Italy; Neurology Unit, OCB Hospital, AOU Modena, Via Giardini, 1355 – Ospedale Civile Baggiovara, 41126 Modena, Italy.
Email: stefano.meletti@unimore.it

Funding information
Ministero dell'Istruzione, dell'Università e della Ricerca; Regione Emilia-Romagna

Abstract

Objective: To evaluate in a real clinical scenario the impact of the ILAE-recommended "Harmonized neuroimaging of epilepsy structural sequences"-HARNESS protocol in patients affected by focal epilepsy.

Methods: We prospectively enrolled focal epilepsy patients who underwent a structural brain MRI between 2020 and 2021 at Modena University Hospital. For all patients, MRIs were: (a) acquired according to the HARNESS-MRI protocol (H-MRI); (b) reviewed by the same neuroradiology team. MRI outcomes measures were: the number of positive (diagnostic) and negative MRI; the type of radiological diagnosis classified in: (1) Hippocampal Sclerosis; (2) Malformations of cortical development (MCD); (3) Vascular malformations; (4) Glial scars; (5) Low-grade epilepsy-associated tumors; (6) Dual pathology. For each patient we verified for previous MRI (without HARNESS protocol, noH-MRI) and the presence of clinical information in the MRI request form. Then the measured outcomes were reviewed and compared as appropriate.

Results: A total of 131 patients with H-MRI were included in the study. 100 patients out from this cohort had at least one previous noH-MRI scan. Of those, 92/100 were acquired at the same Hospital than H-MRI and 71/92 on a 3T scanner. The HARNESS protocol revealed 81 (62%) positive and 50 (38%) negative MRI, and MCD was the most common diagnosis (60%). Among the entire pool of 100 noH-MRI, 36 resulted positive with a significant difference ($p < .001$) compared to H-MRI. Similar findings were observed when accounting for the expert radiologists (H-MRI = 57 positive; noH-MRI = 33, $p < .001$) and the scanner field strength (H-MRI 43 = positive, noH-MRI = 23, $p < .001$), while clinical information were more present in H-MRI ($p < .002$).

Significance: The adoption of a standardized and optimized MRI acquisition protocol together with adequate clinical information contribute to identify a higher number of potentially epileptogenic lesions (especially FCD) thus impacting concretely on the clinical management of patients with focal epilepsy.

KEYWORDS

drug-resistant epilepsy, focal cortical dysplasia, focal epilepsy, HARNESS-MRI, magnetic resonance imaging, structural imaging

1 | INTRODUCTION

Brain MRI is essential in the management of patients with epilepsy being one cornerstone in the diagnostic work-up together with seizure's semiology, ictal/interictal EEG, and advanced imaging (e.g., Fluorodeoxyglucose-positron emission tomography [FDG-PET]).[1,2] It is especially crucial to detect the presence of epileptogenic lesions in patients with focal epilepsy as the identification of a clear-cut lesion on structural MRI is associated with favorable seizure outcomes after surgery.[3,4] Around 18%–43% of patients with focal epilepsy evaluated presurgically have an MRI scan not showing structural abnormalities potentially causative of epilepsy (referred to hereafter as MRI negative).[5,6] Focal epilepsies with a negative MRI are not necessarily nonlesional.[5] Previous studies showed that 30%–46% of examinations at first considered MRI negative were instead positive (i.e., with a lesion linked to the patient's epilepsy) after improved MRI acquisition (field strength and sequence selection) and/or experienced evaluation.[7,8] Furthermore, lesions might not be visible on MRI but can have histopathological correlates.[9]

In 2019, the International League Against Epilepsy (ILAE) published the official recommendation of structural MRI for focal epilepsy.[10] In that, the following sequences were recommended as the minimum required protocol: 3D millimetric T1-weighted images (T1WI) and fluid-attenuated inversion recovery (FLAIR) images, and 2D sub millimetric coronal T2-weighted images (T2WI) acquired perpendicular to the long axis of the hippocampus. The "Harmonized neuroimaging of epilepsy structural sequences" (HARNESS) protocol has been developed with the idea to standardize the best-practice neuroimaging of epilepsy in outpatient clinics and specialized surgery centers. Technical differences in MRI acquisition protocol (e.g., slice thickness, interslice gaps) could indeed potentially impact lesion detection.[11–13] So far, the diagnostic yield of the HARNESS protocol has been verified throughout single case descriptions[14–16] while prospective studies on larger cohort of patients are missed. Such type of study would be of importance in resource-poor communities where the access to MRI is limited.

Key points

- The adoption of an optimized imaging protocol together with adequate clinical information improve the detection of potentially epileptogenic lesions.
- A dedicated and optimized MRI protocol might be particularly helpful for detection of FCD in focal epilepsies.
- An optimized imaging protocol might improve access to the MRI services even in poor-resource countries.

In this study, we aimed to assess the clinical utility of the HARNESS protocol in a prospective cohort of patients with focal epilepsy who underwent a structural MRI for diagnostic purposes in the last 18 months. Our purpose was to investigate whether the adoption of this standardized and optimized protocol, together with relevant clinical information, would impact the detection of epileptogenic lesions thus improving the clinical management of patients with focal epilepsy.

2 | MATERIALS AND METHODS

We prospectively and consecutively enrolled all the patients (older than 14 years of age) who fulfilled the following inclusion criteria: (a) a diagnosis of focal epilepsy according to electroclinical data collected at outpatients' clinics and (b) access to the epilepsy program at the Neurology Unit, Modena University Hospital (Modena, Italy). We excluded patients with intracranial tumors (i.e., high-grade gliomas; meningiomas), postischemic neonatal damages, stroke, and suspected neurodegenerative diseases (i.e., Alzheimer Disease).

The HARNESS-MRI protocol was performed for all patients using a 3.0 Tesla GE Healthcare MRI scanner (Chicago, United States). All the MRI datasets were acquired in a dedicated session occurring once or twice every

month. The protocol follows the ILAE-recommended HARNESS-MRI[10] and included as minimum sequences a 3D 1 mm-isotropic voxels T1-weighted sequence, a fluid-attenuated inversion recovery (FLAIR), and a bidimensional coronal T2-weighted image acquired perpendicular to the long axis of the hippocampus. Additional sequences were a bidimensional axial Diffusion Weighted Imaging (DWI) and Gradient Echo (GRE) sequence (Table 1).

All the HARNESS-MRI scans were reviewed by the same team of neuroradiologists (MM, MG, FC, and AT) with expertise in epilepsy. Images were reviewed using PACS workstation that contains the patient's clinical history. The images were inspected at their original thickness (1 mm for 3D and 2 mm for T2) without any reformatting process. MM, FC, and AT had more than 15 years of practice in reading MRI images, MG had 10 years of practice. Clinical information was made available to the neuroradiologists in the motivation for the MRI scan (usually one-to-two sentences) and in clinical letters attached to the request.

For each recruited patient, we checked for previous MRI scans performed in the same hospital or outside. For all MRI datasets with (H-MRI) or without (noH-MRI) HARNESS, we collected the following information by inspecting the radiological reports and when available the MRI images: strength of the MRI scanner; type of MRI sequences; presence/absence of clinical information in the MR request form. Clinical information was considered "present" if it includes at least one of these data: (a) epilepsy side/lobe of the suspected epileptic focus; (b) seizure semiology; (c) EEG (electroencephalogram) findings. Otherwise, clinical information was labeled as "absent" (e.g., if the information was simply "focal epilepsy" it was considered absent). If a patient had more than one previous noH-MRI scan, the more recent to the H-MRI was considered for evaluation and comparison. Review process of H-MRI and noH-MRI was performed independently and at different times. The team of experts was the same for H-MRI and noH-MRI only for those MRI scans acquired at Modena University Hospital. For these datasets, each H-MRI and noH-MRI examination (not necessarily of the same patient) was reviewed by one of the four expert readers. In case of unclear radiological diagnosis, the related images were discussed within the expert team until a consensus was achieved and summarized in the report.

For both H-MRI and noH-MRI, the number of diagnostic positive (i.e., "abnormal") and nondiagnostic, negative (i.e., "normal") MRI was calculated. Further, the distribution of the MRI-positive scans was estimated according to the type of radiological diagnosis, classified into the following: (1) Hippocampal Sclerosis (HS); (2) Malformations of cortical development [Focal Cortical Dysplasia (FCD), polymicrogyria, tuberous sclerosis, lissencephaly, subcortical band heterotopia, gray matter heterotopia, hemimegalencephaly, schizencephaly, and hypothalamic amartoma]; (3) Vascular malformations; (4) Glial scars; (5) Low-grade epilepsy-associated tumors (LEATs) (e.g., Dysembryoplastic neuroepithelial tumor, gangliocytoma, ganglioglioma); (6) Dual pathology (e.g., HS + FCD).

For each positive MRI scan, after inspecting the MRI reports, the clinicians (AEV, EM, GG, MP, and SM) reviewed the clinical information including EEG (ictal and interictal), seizure semiology, and other imaging modalities (e.g., FDG-PET, EEG coregistered to fMRI) and compared the presumed epileptogenic zone with the MRI abnormality location and type. The lesion/s was/were considered "contributory" to the clinical assessment if concordant with the electroclinical hypothesis, "not contributory" otherwise. At the end of recruitment, we verified whether any of the included patient had epilepsy surgery, and in this case, the histological reports were collected.

2.1 | Statistical analysis

Firstly, a descriptive statistical analysis was performed to assess mean age, gender distribution of the recruited patients, the rate of positive and negative MRIs and of each radiological diagnosis.

Secondly, we compared the rate of positive and negative MRI and the type of radiological diagnosis in those

TABLE 1 Details of the MRI sequences of the HARNESS protocol.

MRI sequence	Slices thickness (mm)/gap (mm)	FOV	Matrix	TR/TE (ms)	Slice (*n*)	Acquisition time (min:s)
sag 3D MPRAGE	1/−0.5	25.6	256×256	2230/3	352	5:16
sag 3D FLAIR-SPACE	1.2/−0.6	25.6	256×256	6000/117	304	5:51
cor 2D T2-TSE	2/0	20	416×416	9600/120	60	7:03
ax 2D DWI-SE EPI	3.6/0.4	25	128×160	9140/70	36	2:46
ax 2D T2 GRE	3/0.3	25	224×320	1070/13	44	3:49

Note: The gray color identifies the mandatory sequences of the HARNESS protocol, the white color the additional sequences.

Abbreviations: ms, milliseconds; *n*, number; TE, echo time; TR, repetition time.

patients who had at least two MRI scans, one with (H-MRI) and one without (noH-MRI) HARNESS protocol. Comparative results were obtained using a nonparametric McNemar's test. Initially, the statistical analysis was performed considering every patient regardless the field strength of the scanner (i.e., 1.5 or 3 Tesla) and team of neuroradiologists who reviewed the noH-MRI scans. To account for the same neuroradiologists, we repeated the same analyses considering only subjects who underwent the previous noH-MRI at our Hospital. Finally, to account for the strength of the scanner, we selected only patients who underwent the previous noH-MRI at our Hospital and on a 3T scanner.

All statistical analyses were performed using SPSS software 27 (IBM). Statistical significance for all tests was set at $p < .05$.

The study was approved by the local Ethical Committee of Area Vasta Emilia Nord (322/15, NET-2013-02355313-3). Patients gave written informed consent for the use of their clinical records in this study. The study was conducted in accordance with the World Medical Association Declaration of Helsinki.

3 | RESULTS

Between January 2020 and June 2021, a total of 131 patients with H-MRI datasets were prospectively included in the study (44 females; mean age of 36.69 + 15.60 years, range 15–74 years). At present 10/131 patients underwent surgery and the histological reports documented 3 HS, 5 FCD (3 FCD Ia, 2 FCD IIb), 1 gliosis, and one LEAT (MNVT: Multinodular and vacuolating neuronal tumor). The histopathological reports agreed with the H-MRI diagnoses in all cases. The clinical follow-up (time after surgery between 8 and 14 months) was Engel Class Ia for all patients except one FCD Ia who reported, at 12 months, persisting rare disabling seizures after surgery (Engel Class IIb).[17] Table 2 summarizes the clinical and demographic variables of the patients' population.

Eighty-one H-MRI (62%) were diagnostic (positive), and 50 (38%) were negative. In 76 patients (94%) the MRI finding was contributory, while for 5 patients (6%), the reported lesion was not contributory to the clinical assessment. As far as the single diagnostic categories the following diagnoses were reported (Figure 1): 48 out of 81 datasets (60%, $p < .001$) were malformations of cortical development, 17 (21%) hippocampal sclerosis, 6 (7%) vascular malformations, 5 (6%) dual pathology, 3 (4%) LEAT, and 2 (2%) glial scars. Out of 48 patients with cortical malformations, 31 had a radiological diagnosis of FCD (64%). Clinical information was present for the neuroradiologists in most of the patients (109/131, 77%).

From the original pool of 131 patients, 100 had a previous noH-MRI scan. In these patients, the average number of previous MRI/per patients was 1.5. Three patients (3%) underwent one noH-MRI, while the majority (97/100) had at least 2 MRI before the H-MRI, with the extreme situation of one patient who underwent 5 previous MRI examinations. Ninety-two noH-MRI out of the 100 patients were acquired at the same Hospital as the H-MRI (and reviewed by the same team of neuroradiologists) and 71 by using a 3T magnet. As far as the sequences' details, this information was available only for the 92 datasets previously acquired at our hospital. The noH-MRI protocol included a $1\,mm^3$ 3D T1 image in 56 patients (61%), a $1\,mm^3$ 3D FLAIR image in 54 (59%), both sequences in 41 (44%) while a 2D $0.4 \times 0.4 \times 2$ mm coronal T2 was never acquired. Beside these core sequences, the noH-MRI included: an axial DWI sequence in all cases, and depending on the clinical question, an axial T2, an axial T2*, and for suspected tumors as an axial or 3D T1 with gadolinium.

Out of the 100 noH-MRI examinations evaluated, 64 were nondiagnostic (negative), and 36 were diagnostic (positive) (Table S1). The mean distance in months between H-MRI and noH-MRI was 48 ± 216 (range 1–1381). Five reports out of the 36 positive noH-MRI (13%) were classified as not contributory to the clinical assessment.

When comparing the results of the H-MRI with noH-MRI, a significant increase in the number of MRI-positive examinations was observed (Figure 2A and Table S1): the H-MRI demonstrated lesions in the 62% of patients compared to 36% of noH-MRI ($p < .001$).

As far as the single diagnostic categories, no significant differences were observed between H-MRI and noH-MRI for HS and dual pathology, glial scars, LEATs, and vascular malformations. On the contrary, the detection of malformations of cortical development was significantly higher in H-MRI compared to noH-MRI (40 vs. 21, $p < .001$), and within this group, FCDs were the most common unrecognized entity (Figure 2A and Table S1).

To account for the same group of neuroradiologists, we selected only patients who underwent the previous noH-MRI at our Hospital (92/100). Of these, 59 were reported negative and 33 positives. On the contrary, in this group of patients, the H-MRI demonstrated 35 normal MRI scans and 57 with lesion/s ($p < .001$), with 24 scans previously regarded as negative turning out to be positive when adopting the H-MRI protocol. Malformation of cortical development, particularly FCD, confirmed to be the most common unrecognized pathology. The noH-MRI examinations disclosed 20 malformations of cortical development that increased to 38 by the H-MRI protocol ($p < .001$). Specifically, the number of FCD raised from 12 to 24 after the H-MRI ($p = .002$) (Figure 2B and Table S1).

TABLE 2 Clinical details of the H-MRI population.

	H-MRI ($N=131$)
Age, years (range)	37.64 ± 15.74 (Range 14–74)
Gender (F/M)	61/70
Age at onset, years	24.91 ± 16.92
Epilepsy duration, years	13.37 ± 13.03
Side of epileptic focus (Left/Right/Bilat)	56/59/16
Number of ASM at MRI	1.6 ± 1
Seizure frequency	
>1 per year	83
≥1 per month	21
≥1 per week	21
Daily	6
Epilepsy Syndrome	
TLE	88
FLE	35
OLE	5
PLE	3
Epilepsy surgery ($N=10$)	
FCD	3 FCD Ia 2 FCD IIb
HS	3
Gliosis	1
LEAT	1 (MVNT)

Note: Thirty-one patients out from the original H-MRI pool underwent only one brain MRI as new epilepsy diagnoses; the remaining 100 patients had one or more brain MRI performed without the HARNESS Protocol (noH-MRI).

Abbreviations: ASM, antiseizure medications; Bilat, bilateral; F, female; FLE, frontal lobe epilepsy; H-MRI, MRI performed with HARNESS Protocol; M, male; MVNT, multinodular and vacuolating neuronal tumors; OLE, occipital lobe epilepsy; PLE, parietal lobe epilepsy; TLE, temporal lobe epilepsy.

Finally, to account for the scanner field strength, we selected only the patients who underwent the previous MRI at our Hospital, with the same team of neuroradiologists, and on a 3T scanner (71 patients). The noH-MRI reported 26 positive and 45 negative MRI, while the H-MRI protocol on the same pool of patients was positive in 43 and negative in 28 cases ($p<.001$) (Figure 2C and Table S1). Specifically, 18 MRIs previously reported as negative, became positive, and malformations of cortical development were confirmed as the most unrecognized entity ($p<.001$), particularly FCD ($p=.006$). The Sankey diagram in Figure 3 displays graphically the percentage and distribution of radiological diagnoses that changed when adopting the H-MRI. To note, except for one single patient whose MRI diagnosis changed from positive (with noH-MRI) to negative with H-MRI, H-MRI contributed to detect lesions on MRI previously reported negative and FCD was the most frequent report (up to 50% of all changed diagnoses).

Finally, in the subgroup of 18 patients in whom despite the same scanner field strength and the same team of radiologists, the MR diagnosis was changed, we checked whether other variables might have impacted the clinical radiological outcome. Table S2 details the clinical and EEG information of these subjects. The median interscan intervals was 6.44 months (range between 1–13 months). In five out of 18 patients (28%) the clinical information was accessible for both MRIs (noH-MRI and H-MRI), while for the other 72% (13/18) it was available only for the H-MRI scan ($p=.002$). Only in one patient (pt#16), clinical information were not present in both examinations. The H-MRI radiological diagnoses were considered contributory to the clinical assessment in all the patients except one (pt#18). In patient #18, indeed, while the presumed Seizure Onset Zone (SOZ) was supposed to be left frontal, the H-MRI reported a bilateral frontal development venous anomaly, thus not fully concordant with the clinical hypothesis. Three out of these 18 patients underwent surgery (pt#5, pt#9, and pt#11): the histopathological reports were in agreement with the H-MRI diagnoses in all cases. All the patients are seizure-free after surgery (Engel Class Ia) with a follow-up between 8 to 14 months. Figure 4 shows two representative examples of patients in whom the radiological diagnosis changed from noH-MRI to H-MRI.

4 | DISCUSSION

To the best of our knowledge, this is the first study that evaluates prospectively the clinical impact of an optimized epilepsy surgery imaging protocol including the HARNESS recommendations (H-MRI) in consecutive focal epilepsy patients. By comparing the radiological outcome of the H-MRI protocol versus the noH-MRI in the same patients (a within-subjects comparison), we show a significant increase in FCD diagnosis, but not of HS, LEAT, and vascular malformations, when the H-MRI was adopted. Our results while supporting previous observations that a dedicated MRI protocol significantly improves the diagnosis of focal epilepsy,[8] expand the available knowledge and show that it might be particularly helpful for the search of FCD. The increase in FCD detection seems independent of the neuroradiologists' expertise and the scanner's field strength, while the presence of adequate clinical information contributes to the detection rate. Considering the feasibility and short time of imaging acquisition of the core sequences of the HARNESS protocol, the findings of the present study are important for patients being assessed for

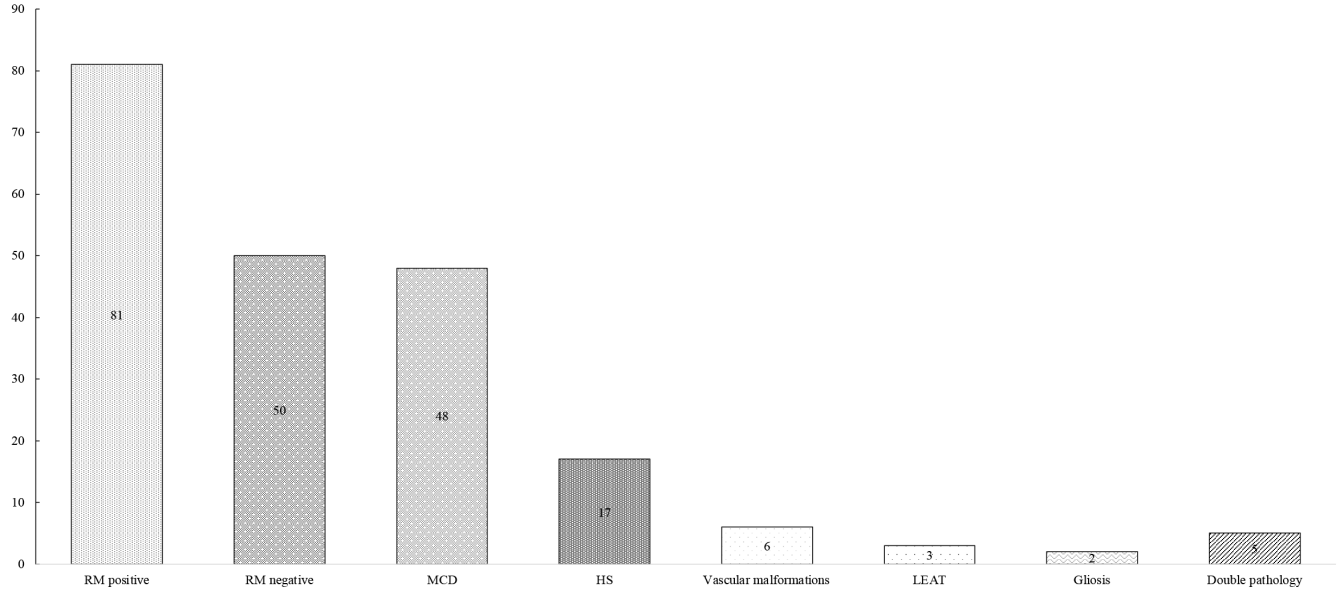

FIGURE 1 Histograms showing the radiological findings of the H-MRI protocol in 131 prospective patients. FCD, focal cortical dysplasia; HS, hippocampal sclerosis; LEAT, low-grade epilepsy-associated tumors; MCD, malformation of cortical development.

epilepsy surgery even in resource-poor locations where access to MRI scanners is limited.

4.1 | The clinical yield of the HARNESS protocol

The importance of a dedicated epilepsy imaging protocol applied to focal epilepsy patients has been recognized for more than two decades. In 2002, von Oertzen and colleagues[11] pointed that the application of an epilepsy-tailored MRI protocol plus an expert neuroradiologist reading resulted in a failure rate significantly lower than a "standard" MRI and nonexperts reports (9% in the former situation versus 61% in the latter). Similar conclusions were reported later[8,9,18] and different time-effective epilepsy-MRI protocol for drug-resistant epilepsy have been published so far.[11–13,18,19] A recent systematic review and meta-analysis demonstrated that a dedicated MRI protocol benefits the detection rate in epilepsy surgery candidates, particularly for FCD.[8] Nevertheless, the same study (which did not include studies adopting the HARNESS protocol) highlighted a wide heterogeneity regarding the MRI type of sequences and parameters and stated that only 25% of the epilepsy center in Europe adhere to the applicable guidelines on MRI imaging standards.[20]

The HARNESS proposal[10] represents a generalizable and feasible protocol, applicable worldwide regardless of the clinical setting and country, and identifies a set of sequences, with three-dimensional acquisitions at its core, that maximize lesion detection. However, since its publication in 2019 only single case reports[14–16] verified the improved diagnostic yield compared to pre-HARNESS-MRI. In this scenario, the present work might contribute to sensitize the epilepsy community about the need of reducing the clinical and technical MRI variability throughout a wider application of the HARNESS-MRI protocol in focal epileptic patients. Additionally, even in resource-limited settings, the demonstration of its clinical impact, might persuade the local health organizations to improve access to the MRI services.

After reviewing the reports of focal epilepsy patients who underwent MRI with HARNESS protocol at our hospital, we observed a rate of positive MRI >60% (81/131) (Figure 1). Of those, the majority (nearly 94%) were concordant with the electroclinical hypothesis, thus impacting on the patient's management (i.e., accelerating the decision-making process to surgery or not).

Despite different studies[19,21,22] and a recent review[23] reporting the hippocampal sclerosis as the most common pathology, in our population the most frequent MRI-observed lesions were the malformations of cortical development (60%) and of those 64% were FCDs (Figure 1). Our epilepsy center has developed an epilepsy surgery program recently and represents one of two hubs dedicated to the surgical treatment of epilepsy in the Emilia-Romagna region, northern Italy (about 4 500 000 population). Therefore, it is possible that we recruited more complicated cases from a radiological perspective.

One hundred out of the original pool of H-MRI datasets had previous MRI scans performed with another MRI protocol (noH-MRI), not including or including partly the core sequences of the H-MRI. Interestingly, on average each patient had more than one noH-MRI (with a

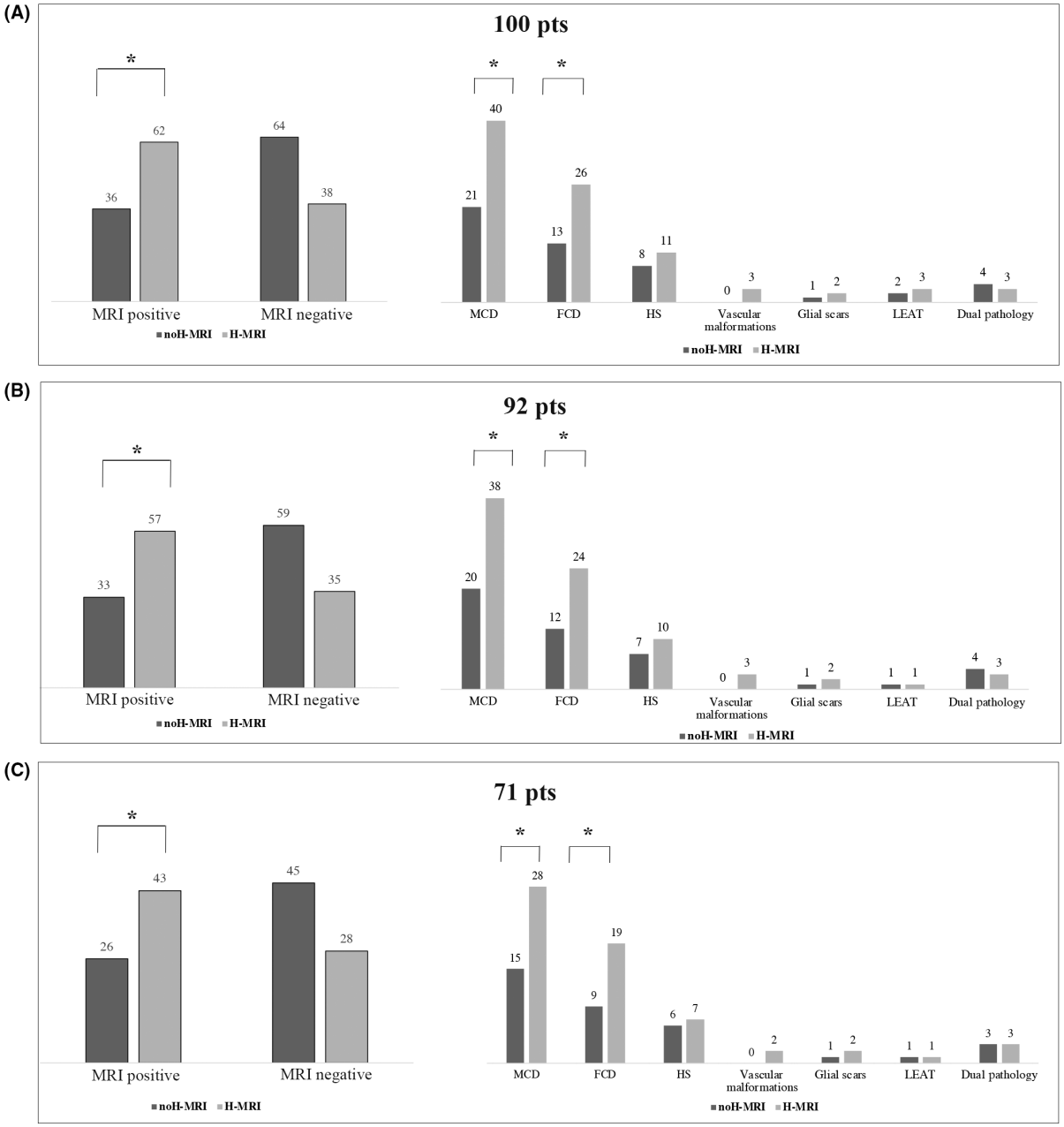

FIGURE 2 Comparison between H-MRI and noH-MRI diagnostic performances. (Panel A) Histograms showing the radiological findings of H-MRI and noH-MRI in 100 patients. (Panel B) Histograms showing the radiological findings of H-MRI and noH-MRI in 92 patients (patients with a previous noH-MRI reviewed by the same neuroradiologists team). (Panel C) Histograms showing the radiological findings of H-MRI and noH-MRI in 71 patients (patients with a previous noH-MRI reviewed by the same neuroradiologists team and on a 3T magnet). *Statistically significant, $p < .001$. FCD, focal cortical dysplasia; HS, hippocampal sclerosis; LEAT, low-grade epilepsy-associated tumors; MCD, malformation of cortical development.

maximum of 5 scans in one case). This finding is important and confirms that an adequate standardization of MRI acquisition parameters and sequences might potentially avoid unnecessary examinations and thus contributes saving time and resources for patients first and national health system afterward.

The comparisons of the absolute number of positive and negative MRI between H-MRI and noH-MRI showed a significant increased detection of FCDs (Figure 2, Panel A). FCD is the epileptogenic lesion most often missed, particularly FCD type I. In a recent paper aiming to verify the detection rate of epileptogenic lesions by expert and less expert readers on more 1000 MRI scans, FCDs were the diagnosis less recognized.[18] On the other side, the identification of a FCD is crucial, because of an excellent surgical outcome.[24] Accordingly, different computational

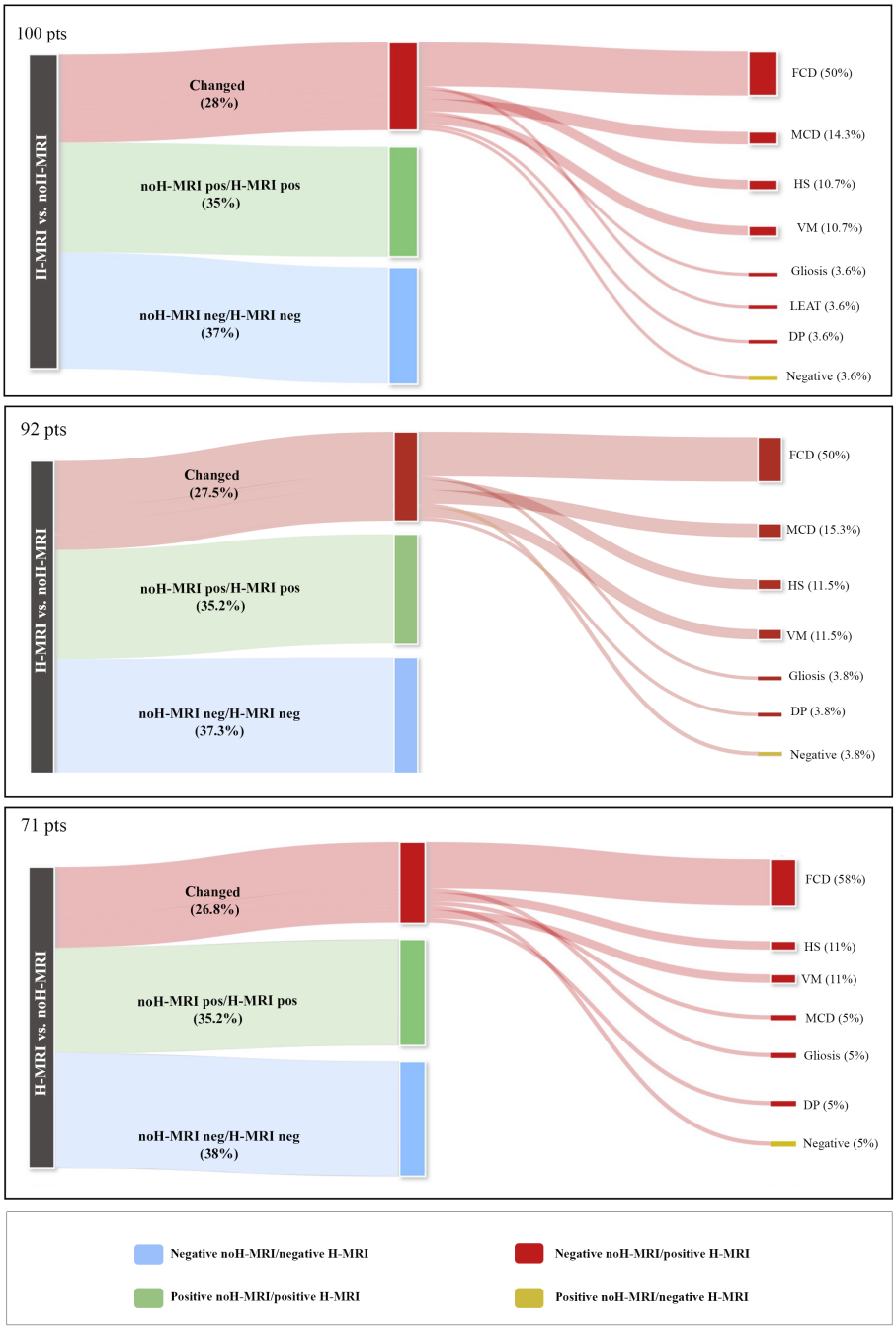

FIGURE 3 Sankey Chart showing the percentage and distribution of radiological diagnoses that changed when adopting the H-MRI versus noH-MRI. DP, dual pathology; FCD, focal cortical dysplasia; HS, hippocampal sclerosis; LEAT, low-grade epilepsy-associated tumors; MCD, malformation of cortical development; pts, patients; VM, vascular malformations.

strategies have been developed (and many are ongoing) to facilitate the FCD recognition on an apparent negative MRI.[25–28]

Detection rate of epileptogenic lesions on MRI might be influenced by several factors beyond the MRI protocol itself. Some of these aspects might be difficult to control. In the present study, we attempted to verify the performances of the H-MRI by controlling all the variables we are aware of. The expertise of neuroradiologists is one of them according to different evidence.[7,18] This expertise arises from specialized training, repeated evaluations of images, and constant communication with the clinicians. At our hospital, the neuroradiologists dedicated to epilepsy, established for more than 6 years, have these skills and there is an active and constant exchange with the epileptology team, even before the HARNESS protocol application. We thus extracted for the 100 noH-MRI scans, only those reviewed by our neuroradiologists ($n = 92$). The

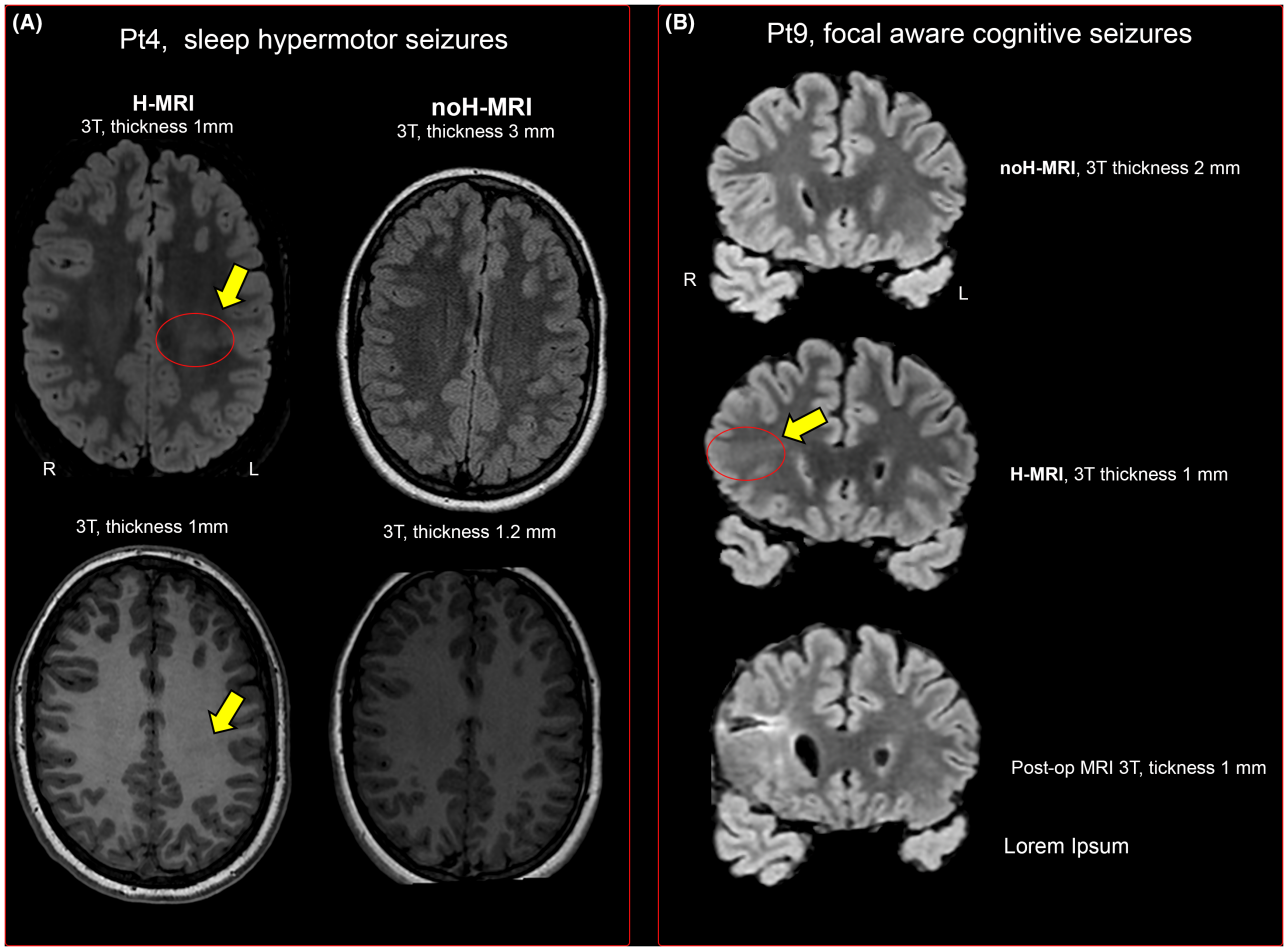

FIGURE 4 Representative examples of patients in whom the radiological diagnosis changed from noH-MRI to H-MRI. (Panel A) Patient #4 of Table S1. The patient presented daily drug-resistant sleep hypermotor seizures from the age of 10 years old. Interictal scalp EEG showed left frontal epileptiform abnormalities. The noH-MRI (performed at the time of diagnosis) was reported as normal (negative). The H-MRI (performed 30 months later than noH-MRI) demonstrated a radiological labeled FCD at the left postcentral gyrus (yellow arrow) with a clear transmantle sign (red ellipse). The patient refused invasive further investigations. FLAIR axial images in the upper row, T1 axial images in the lower row. (Panel B) Patient #9 of Table S1. The patient presented daily drug-resistant focal aware seizures and rarer focal to bilateral tonic–clonic seizures. A subjective premonitory feeling of forced thought and/or confusion was described. Interictal EEG showed right frontal epileptiform abnormalities and ictal EEG a right frontal onset (F8). The patient underwent two previous noH-MRI (the latest 3 years before the H-MRI) reported both as negative. The H-MRI showed on FLAIR sequences a blurring of gray matter-white matter boundary at the right frontal operculum (red ellipse and yellow arrow). Patient underwent surgery and he is seizure-free at 10 months (Engel Ia). Histology reported a Focal Cortical Dysplasia, Type Ia. L, Left; R, Right.

statistical comparisons between noH-MRI and H-MRI showed a greater number of potentially epileptogenic lesions with H-MRI, and FCD was again the diagnosis less recognized by noH-MRI (Figure 2, Panel B). This observation, while does not deny the importance of a high level of expertise of the neuroradiologists, suggests that the characteristics of the MRI protocol might contribute to the lesion detection process. We cannot exclude, however, that other factors could also influence these results as changes in the level of confidence of the radiologists due to their continuous training or their subjective tendency to rate abnormalities in the cortical anatomy. Nevertheless, these aspects are difficult to be measured. Further studies are warranted to confirm our observations, ideally by involving an external pool of expert radiologists to reevaluate blindly the H-MRI and noH-MRI datasets.

In our H-MRI patients, the expert radiologists had sufficient clinical information available in most of the cases (77%). Several arguments stressed the importance of clinical information in facilitating the radiological reading, not only in the epilepsy field.[29–31] A recent paper showed that the only factor that can affect the MRI lesion detection in focal epilepsy patients is the presence of focal EEG abnormalities regardless of field strength, the qualitative tissue contrasts, or artifact score on images.[7] Interestingly, in the 18 patients who shown

a change from a negative noH-MRI to a positive H-MRI, despite identical readers and scanner field strength, a significant difference in the availability of clinical information was observed. Thus, the present findings highlight the importance to provide adequate clinical details to the radiologists being a contributing factor toward an improvement in lesion detection using a dedicated MRI protocol.

All H-MRI scans were performed on a 3.0 Tesla scanner. Several studies support the idea that 3T MRI scanners offer a better lesion detection than 1.5T.[19,21,32] However, recent manuscripts and a metanalysis were concordant to show the lack of a significant increased diagnostic yield when adopting a 3T compared to a 1.5T in patients with focal epilepsy.[7,8,18] Our data support these suggestions. In our population, among the 92 patients with noH-MRI and H-MRI, 71 had the examinations on a 3T scanner for both MRIs. Even in this situation, the performances of the H-MRI protocol were better (a higher number of positive MRI and FCD) than noH-MRI (Figure 2, Panel C) suggesting that a dedicated protocol might be superior to the strength of the MRI-field per se.

Despite the adoption of the H-MRI protocol, the high-level expertise of the radiologists, and the high-field strength scanner, we showed a persistent percentage of negative MRI close to 40% (see Figure 2). This rate is in line with previous data.[6,10,33] Many patients have subtle lesions that might be undetected on routine MRI but have an histopathological correlation.[9,33] The crucial need to detect surgically amenable lesions in patients with focal epilepsy has motivated the development of sophisticated detection methods.[27,34–36] Our findings by confirming a relatively consistent rate of MRI negative even adopting an optimized protocol, highlights the intrinsic limits of the visual MRI inspection and support, in specific situations, the efforts of computer-aided methods to contribute revealing the structural lesion. Similar observation has been endorsed by the HARNESS original paper.[10] Importantly, the HARNESS protocol accounts for two 3D images, which represent (particularly the 3D-T1) the common basis to the postprocessing pipelines.[34,36]

4.2 | Limitations

We recognize that the study has some limitations. The first is the lack of the histopathological proofs of the radiological diagnoses in most of the patients. By counterpart, we verified the HARNESS outcomes versus the clinical and electrophysiological hypothesis. The aim of the present study was to investigate the diagnostic performances of the HARNESS protocol in a real clinical scenario when an MRI scan might be performed at the beginning of the presurgical assessment. Being a prospective study, more histological data will be available in the next future and will be used in a further study to validate the HARNESS findings based on visual inspection. Another potential limitation is the time interval between scans (noH-MRI and H-MRI) during which some lesions like tumors or vascular malformations could evolve or other events (like trauma, seizures) can occur, thus affecting the advanced diagnostic yield of the H-MRI. However, patients with rapidly growing lesions, like gliomas were excluded. More importantly, our data suggest that H-MRI is particularly helpful to reveal FCD, the presence of which is normally not influenced by the time between the MRI and the epilepsy diagnosis. Finally, we did not discuss the potential role of HARNESS optional sequences (like gadolinium-enhanced MRI and Susceptibility weighted image)[23] in the detection of the epileptogenic lesions. This is motivated by the primary aim of this manuscript, which was specifically to evaluate the clinical impact of the HARNESS protocol, focusing on the mandatory core sequences.

AUTHOR CONTRIBUTIONS

A.E.V., A.B. made substantial contributions to the design and conceptualization of the study, acquired and collected the data, analyzed and interpreted the data, and drafted the work; F.Z., N.B., N.O., S.S., F.T., and E.M., made substantial contributions to data collection and analysis; F.C., A.T., M.G., M.M., F.Z., and S.V., made substantial contributions to the data acquisition; G.G., G.T., M.C.C, M.P., and S.M. made substantial contributions to the conception of the study and revised the final manuscript.

FUNDING INFORMATION

The present work was supported by "Dipartimento di eccellenza 2018–2022", MIUR (Ministero dell'Istruzione, dell'Università e della Ricerca), Italy, to the Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia; Emilia-Romagna regional funding to the Azienda Ospedaliera-Universitaria di Modena "Centro hub per la chirurgia dell'epilessia" (DGR 1172/18).

CONFLICT OF INTEREST STATEMENT

S. Meletti received research grant support from the Ministry of Health (MOH), the nonprofit organization Foundation "Fondazione Cassa di Risparmio di Modena - FCRM"; he has received personal compensation as scientific advisory board member for UCB, GW, Jazz pharmaceuticals and EISAI. A.E. Vaudano received personal compensation as scientific advisory board member for Angelini Pharma. The other authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Anna Elisabetta Vaudano https://orcid.org/0000-0002-6280-7526
Alice Ballerini https://orcid.org/0000-0002-0544-1599
Elisa Micalizzi https://orcid.org/0000-0003-3991-3918
Simona Scolastico https://orcid.org/0000-0003-3202-3429
Giada Giovannini https://orcid.org/0000-0002-3585-5872
Matteo Pugnaghi https://orcid.org/0000-0002-3090-6247
Niccolò Orlandi https://orcid.org/0000-0002-5717-7363
Stefano Meletti https://orcid.org/0000-0003-0334-539X

REFERENCES

1. Duncan JS, Winston GP, Koepp MJ, Ourselin S. Brain imaging in the assessment for epilepsy surgery. Lancet Neurol. 2016;15(4):420–33.
2. Bernasconi N, Wang I. Emerging trends in neuroimaging of epilepsy. Epilepsy Curr. 2021;21(2):79–82.
3. Ho K, Lawn N, Bynevelt M, Lee J, Dunne J. Neuroimaging of first-ever seizure. Neurol Clin Pract. 2013;3:398–403.
4. Téllez-Zenteno JF, Hernández Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. Epilepsy Res. 2010;89(2–3):310–8.
5. Bien CG, Szinay M, Wagner J, Clusmann H, Becker AJ, Urbach H. Characteristics and surgical outcomes of patients with refractory magnetic resonance imaging-negative epilepsies. Arch Neurol. 2009;66(12):1491–9.
6. Nguyen DK, Mbacfou MT, Nguyen DB, Lassonde M. Prevalence of nonlesional focal epilepsy in an adult epilepsy clinic. Can J Neurol Sci J Can Sci Neurol. 2013;40(2):198–202.
7. Zhu H, Scott J, Hurley A, Gaxiola-Valdez I, Peedicail JS, Federico P. 1.5 versus 3 Tesla structural MRI in patients with focal epilepsy. Epileptic Disord. 2022;24(2):13.
8. Rados M, Mouthaan B, Barsi P, Carmichael D, Heckemann RA, Kelemen A, et al. Diagnostic value of MRI in the presurgical evaluation of patients with epilepsy: influence of field strength and sequence selection: a systematic review and meta-analysis from the E-PILEPSY Consortium. Epileptic Disord. 2022;24(2):323–42.
9. Bernasconi A, Bernasconi N. The role of MRI in the treatment of drug-resistant focal epilepsy. Eur Neurol. 2022;85(5):333–41.
10. Bernasconi A, Cendes F, Theodore WH, Gill RS, Koepp MJ, Hogan RE, et al. Recommendations for the use of structural magnetic resonance imaging in the care of patients with epilepsy: a consensus report from the International League Against Epilepsy Neuroimaging Task Force. Epilepsia. 2019;60:2143–4.
11. von Oertzen J. Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy. J Neurol Neurosurg Psychiatry. 2002;73(6):643–7.
12. Wellmer J, Quesada CM, Rothe L, Elger CE, Bien CG, Urbach H. Proposal for a magnetic resonance imaging protocol for the detection of epileptogenic lesions at early outpatient stages. Epilepsia. 2013;54(11):1977–87.
13. Friedman E. Epilepsy imaging in adults: getting it right. AJR Am J Roentgenol. 2014;203(5):1093–103.
14. Larivière S, Federico P, Chinvarun Y, Jackson G, Morgan V, Rampp S, et al. ILAE Neuroimaging Task Force Highlight: harnessing optimized imaging protocols for drug-resistant childhood epilepsy. Epileptic Disord. 2021;23(5):675–81.
15. Clavijo Prado CA, Federico P, Bernasconi A, Bernhardt B, Caciagli L, Concha L, et al. Imaging characteristics of temporopolar blurring in the context of hippocampal sclerosis. Epileptic Disord. 2022;24(1):1–8.
16. Federico P, Ng DW, Bernasconi A, Bernhardt B, Blumenfeld H, Cendes F, et al. ILAE neuroimaging task force highlight: review MRI scans with semiology in mind. Epileptic Disord Int Epilepsy J Videotape. 2020;22(5):683–7.
17. Engel J, editor. Surgical treatment of the epilepsies. 2nd ed. New York: Raven Press; 1993; 786 p.
18. Wehner T, Weckesser P, Schulz S, Kowoll A, Fischer S, Bosch J, et al. Factors influencing the detection of treatable epileptogenic lesions on MRI. A randomized prospective study. Neurol Res Pract. 2021;3(1):41.
19. Knake S, Triantafyllou C, Wald LL, Wiggins G, Kirk GP, Larsson PG, et al. 3T phased array MRI improves the presurgical evaluation in focal epilepsies: a prospective study. Neurology. 2005;65(7):1026–31.
20. Mouthaan BE, Rados M, Barsi P, Boon P, Carmichael DW, Carrette E, et al. Current use of imaging and electromagnetic source localization procedures in epilepsy surgery centers across Europe. Epilepsia. 2016;57(5):770–6.
21. Ladino LD, Balaguera P, Rascovsky S, Delgado J, Llano J, Hernández-Ronquillo L, et al. Clinical benefit of 3 Tesla magnetic resonance imaging rescanning in patients with focal epilepsy and negative 1.5 Tesla magnetic resonance imaging. Rev Investig Clin Organo Hosp Enfermedades Nutr. 2016;68(3):112–8.
22. Blumcke I, Spreafico R, Haaker G, Coras R, Kobow K, Bien CG, et al. Histopathological findings in brain tissue obtained during epilepsy surgery. N Engl J Med. 2017;377(17):1648–56.
23. Wang I, Bernasconi A, Bernhardt B, Blumenfeld H, Cendes F, Chinvarun Y, et al. MRI essentials in epileptology: a review from the ILAE Imaging Taskforce. Epileptic Disord. 2020;22(4):421–37.
24. Willard A, Antonic-Baker A, Chen Z, O'Brien TJ, Kwan P, Perucca P. Seizure outcome after surgery for MRI-diagnosed focal cortical dysplasia: a systematic review and meta-analysis. Neurology. 2022;98(3):e236–48.
25. Wagstyl K, Whitaker K, Raznahan A, Seidlitz J, Vértes PE, Foldes S, et al. Atlas of lesion locations and postsurgical seizure freedom in focal cortical dysplasia: a MELD study. Epilepsia. 2022;63(1):61–74.
26. Spitzer H, Ripart M, Whitaker K, D'Arco F, Mankad K, Chen AA, et al. Interpretable surface-based detection of focal cortical dysplasias: a Multi-centre Epilepsy Lesion Detection study. Brain J Neurol. 2022;145:3859–71.
27. Gill RS, Lee HM, Caldairou B, Hong SJ, Barba C, Deleo F, et al. Multicenter validation of a deep learning detection algorithm for focal cortical dysplasia. Neurology. 2021;97(16):e1571–82.

28. Lee HM, Gill RS, Fadaie F, Cho KH, Guiot MC, Hong SJ, et al. Unsupervised machine learning reveals lesional variability in focal cortical dysplasia at mesoscopic scale. NeuroImage Clin. 2020;28:102438.
29. Loy CT, Irwig L. Accuracy of diagnostic tests read with and without clinical information: a systematic review. JAMA. 2004;292(13):1602–9.
30. Berbaum KS, Franken EAJ, el-Khoury GY. Impact of clinical history on radiographic detection of fractures: a comparison of radiologists and orthopedists. AJR Am J Roentgenol. 1989;153(6):1221–4.
31. Leslie A, Jones AJ, Goddard PR. The influence of clinical information on the reporting of CT by radiologists. Br J Radiol. 2000;73(874):1052–5.
32. Zijlmans M, de Kort GAP, Witkamp TD, Huiskamp GM, Seppenwoolde JH, van Huffelen AC, et al. 3T versus 1.5T phased-array MRI in the presurgical work-up of patients with partial epilepsy of uncertain focus. J Magn Reson Imaging. 2009;30(2):256–62.
33. Muhlhofer W, Tan Y, Mueller SG, Knowlton R. MRI -negative temporal lobe epilepsy—what do we know? Epilepsia. 2017;58(5):727–42.
34. Wagner J, Weber B, Urbach H, Elger CE, Huppertz HJ. Morphometric MRI analysis improves detection of focal cortical dysplasia type II. Brain. 2011;134(10):2844–54.
35. Wang ZI, Jones SE, Jaisani Z, Najm IM, Prayson RA, Burgess RC, et al. Voxel-based morphometric magnetic resonance imaging (MRI) postprocessing in MRI-negative epilepsies: MAP in nonlesional epilepsies. Ann Neurol. 2015;77(6):1060–75.
36. Huppertz HJ, Wagner J, Weber B, House P, Urbach H. Automated quantitative FLAIR analysis in hippocampal sclerosis. Epilepsy Res. 2011;97(1–2):146–56.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Vaudano AE, Ballerini A, Zucchini F, Micalizzi E, Scolastico S, Talami F, et al. Impact of an optimized epilepsy surgery imaging protocol for focal epilepsy: A monocentric prospective study. Epileptic Disorders. 2023;25:45–56. https://doi.org/10.1002/epd2.20050

Test yourself

1. Which are the core mandatory MRI sequence(s) according to the HARNESS protocol?
   A. Susceptibility weighted imaging (T2*)
   B. 3D-T1, 3D FLAIR and sub millimetric coronal T2
   C. 3D-T1 without and with gadolinium
   D. Axial spin echo/T2
2. Focal epilepsies with MRI negative (not diagnostic)
   A. Are necessarily not-lesional and the patients with negative MRI must be excluded from surgery
   B. Do not exist, as a lesion can always be found using sophisticated postprocessing methods on MRI sequences
   C. Can be not-lesional but efforts should be made to check for quality and completeness of the MRI imaging protocol, as well as evaluation by expert neuroradiologists
   D. Do not have an histopathological correlate
3. Which are the factors that might improve the detection of potentially epileptogenic lesions with MRI?
   A. The duration of the imaging epilepsy protocol
   B. The presence of adequate clinical information in the MR request form
   C. An optimized imaging protocol
   D. B + C

Answers may be found in the supporting information.