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Study protocol: value of 7-T MRI with prospective motion correction and postprocessing for patients with nonlesional epilepsy

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Abstract

The diagnostic yield of magnetic resonance imaging (MRI) postprocessing using 7-T data for patients with nonlesional epilepsy has been rarely evaluated, but has shown acceptable diagnostic outcomes. However, to date there have been no prospective clinical studies comparing MP2RAGE sequences in 3-T and 7-T MRI in parallel using the same protocol for morphometric analysis. We present a study protocol developed to address the hypothesis that application of 7-T structural MRI increases the rate of detection of structural lesions with morphometric analysis when compared with parallel coherent study protocols in 3-T MRI. The 7-T MRI study protocol is designed to supply data showing the clinical practicability and proof of principle for increasing the detection rate of subtle epileptogenic lesions.

Keywords
Magnetic resonance imaging · Diagnostic imaging · Structural MRI · MRI postprocessing · Prognostic factor

Introduction

A well-defined lesion on magnetic resonance imaging (MRI) that corresponds with electrographic findings is a good prognostic factor for postsurgical seizure outcome [9, 30]. Nonlesional (also known as MRI-negative) epilepsies often require invasive intracranial electroencephalography (EEG) and have poorer seizure outcomes after epilepsy surgery [9, 18, 31]. Thus, the absence of a structural lesion on MRI represents a challenge for surgical management of epilepsy [32].

Improved lesion visualization and detailed characterization of the lesion have been the main aims of any structural MRI study of patients with focal epilepsy [46]. It was shown that identification of epileptogenic lesions is 2.5 times more likely with 3-T MRI than with 1.5-T MRI [26]. The ictal semiology, interictal and ictal scalp EEG, and additional investigations such as magnetoencephalography (MEG), positron emission tomography (PET), or single-photon emission computed tomography (SPECT) support the presence of undetected lesions in conventional 3-T MRI.

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Table 1	7-T MRI sequences used in clinical studies of nonlesional focal epilepsy		
Sequence	Isotropic voxel size (mm, in-plane spatial resolution median range)	Diagnostic advantages	Studies
3D T1w			
MPRAGE	0.60–0.90	Visual diagnosis of FCD and polymicrogyria	[5]
MP2RAGE	0.60–0.80	Visualization of the internal architecture disruption in HS Small isotropic voxel size, which enables better morphometric analysis	[40] [41] [10] [44]
T2/FLAIR			
3D FLAIR	0.70–1.00	Visualization of tuberous sclerosis complex	[1] [27] [37]
FLAIR TSE	0.50–0.80	Visualization of long-term epilepsy-associated tumors (gangliogliomas, DNET)	[1] [27] [37]
T2*w			
2D GRE/3D SWAN/ SWI/QSM	0.25–0.80	Leptomeningeal venous abnormalities Intracortical "black line signs," which is associated with FCD Small cavernous cortical hemangioma Vascular hippocampal abnormalities	[6] [40] [2] [11]
Others			
DWI/DTI 3D DIR	–	Increased connectivity of certain ipsilateral subfields in left temporal lobe epilepsy	[28]

DNET dysembryoplastic neuroepithelial tumors, *FCD* focal cortical dysplasia, *HS* hippocampal sclerosis

The improved signal-to-noise ratio (SNR) in 7-T MRI can potentially lead to better depiction of the cortex and therefore increase the sensitivity for detection of malformations of cortical development and other potentially epileptogenic pathologies. A task force consensus on the use of 7-T MRI [23] in clinical management of patients with drug-resistant focal epilepsy revealed four main indications for 7-T MRI referral: (1) 3-T MRI-negative patients; (2) patients with known or suspected lesion in conventional 3-T MRI; (3) improved visualization of potential epileptogenic lesions for planning of intracranial electrode positioning; (4) mapping of the eloquent areas using stimulation 7-T fMRI [14, 42].

The diagnostic yield of MRI postprocessing using 7-T data for patients with nonlesional epilepsy (nlE) has been evaluated only in a few studies [10, 34, 44, 45]. It was shown that patients with nlE had an acceptable MRI-positive diagnostic outcome in 7-T imaging. These patients are therefore candidates for a better postsurgical seizure outcome. In addition, 7-T MRI has been useful in identifying hippocampal architecture and sclerosis, cortical dysplasia, and vascular malformations as well as improved visualization of the amygdalohippocampal border as well as polymicrogyria (PMG; [10, 20, 34]).

According to a meta-analysis [25], which included 160 patients from nine studies with 7-T MRI investigations and 152 patients from eight studies with 3-T investigations, the overall detection rate of 7-T MRI was 65% while that of 3-T MRI was 22%. The 7-T-positive and 3-T-negative epileptogenic lesions include bilateral PMG, focal cortical dysplasia (FCD), and hippocampal abnormalities (for details, see ◘ Table 1). Additionally, T2*-weighted sequences such as susceptibility weighted imaging (SWI) demonstrated leptomeningeal venous abnormalities or the "intracortical black line sign" both associated with overlying FCD [2, 11].

Ultra-high-field (UHF) MRI provides a significant increase in SNR and gains in contrast weighting in several functional and structural acquisitions. It was shown that an increase in field strength also induces nonuniformities in the transmit field (B1+) that can compromise image contrast nonuniformly. T1-weighted (T1w) image acquisitions for structural imaging provide excellent contrast between gray and white matter and are widely used for brain segmentation. At 7 T, the signal nonuniformities tend to complicate this and, therefore, the self-bias-field corrected MP2RAGE is often used there. In the MP2RAGE sequence even very low local B1+ can cause a loss of SNR and contrast, usually in the cerebellum and temporal lobes [21]. If not adequately addressed, these nonuniformities can compromise the image quality, or even provide incorrect segmentation, inappropriate diagnostic information, or poor co-registration [21].

7 T in potentially epileptogenic lesions

Focal cortical dysplasia

Detection of FCDs type 1 and 2 is generally more difficult than other types of epileptogenic lesions. The advantage of 7 T for the detection of FCDs can mainly be explained by improved gray–white delineation for the cortical convexity in 3D T1-weighted images. Colon et al. reported a comparison between 7-T and 3-T MRI for eight patients with suspected FCD, showing that 7-T MRI scored significantly better for lesion conspicuity and demarcation. To differentiate between types of FCD, typical radiological characteristics of FCD were rated separately in this study. Significant characteristics were features such as gray–white matter blurring, abnormal internal structure, and transition to normal cortex [4].

In SWI sequences, visualization of intracortical signal changes ("black line sign") can improve subtyping of FCD type 2 [2]. Three-dimensional T1-weighted (MPRAGE and MP2RAGE) sequences were shown to be most helpful for the detection of FCD when used with quantitative morphological analysis due to high image contrast at 7 T [7, 39, 44].

Table 2 Potential imaging biomarkers for focal epilepsies on 7-T MRI	
Imaging biomarker	**Studies**
Selectively greater ipsilateral hippocampus atrophy	[15]
CA1 and CA4+dentate gyrus atrophy	[29]
Lower u-fiber counts ipsilateral to the electrophysiological focus	[22]
Increased connectivity of certain ipsilateral subfields in left temporal lobe epilepsy	[28]
Asymmetric distribution of perivascular spaces with maximum asymmetry in the region of the suspected seizure-onset zone	[12]
Change in *N*-acetyl aspartate/creatinine ration and glutamate in MR spectroscopy in patients with malformations of cortical development and epilepsy	[24]

Polymicrogyria

A study of ten patients with polymicrogyria previously diagnosed with 3-T MRI demonstrated improved visualization with 7-T MRI [6]. Special diagnostic landmarks were dilated superficial veins associated with the polymicrogyria revealed in SWI angiography. Furthermore, 3D T1-weighted sequences (MP2RAGE or MPRAGE) are important because they enable clear delineation of the lesion extent, which can guide surgical resection. Three-dimensional T1-weighted sequences can be used to screen the whole brain for polymicrogyria. In addition, 3D T2*-weighted images enable visualization of small pial vessels, seen as thin hypointense lines in the malformed cortex and sulci with an arboriform distribution as an additional identifying feature; the cortex itself appears extra hyperintense in these sequences.

Tuberous sclerosis complex

It was shown that better SNR in 7-T MRI and increased spatial resolution in T1-weigted (MPRAGE and MP2RAGE) and T2*-weighted sequences improve detection of cerebral lesions in tuberous sclerosis complex such as cortical and subependymal tubers. Moreover, a new finding first identified at 7 T is the presence of tortuous veins associated with subependymal tubers, frequently encountered but clearly visible in SWI sequences [27, 37].

Long-term epilepsy-associated tumors

Gangliogliomas and dysembryoplastic neuroepithelial tumors consist of a composition of mature neuronal cells and glial cells [35]. Radiological characteristics include a solid and/or cystic component and perifocal edema. With 7-T MRI, 3D T1-weighted (MP2RAGE or MPRAGE) images better delineate the solid component because of increased image contrast. In addition, 7-T 3D T2-weighted sequences meliorate the depiction of the walls between and around the solid/cystic components, and the extent of any associated edema is more precisely delineated. Both factors are important when planning the resection margin for surgical intervention.

Hippocampal sclerosis

Classic MRI features of hippocampal sclerosis are hippocampal atrophy, increased T2-weighted/FLAIR signal intensity, and loss of normal morphology. 7-T MRI data show hippocampal morphology, including internal structure and surface features. Two-dimensional coronal TSE T2-weighted and 3D T1-weighted/FLAIR sequences are particularly suitable for this [33, 48]. Hippocampal subfields can be more precisely delineated with training based on landmarks and surface features at 7-T MRI, including automated segmentation methods. On coronal 3-T images, prominent infolding can cause the dark band to appear obscured because of partial volume effects, and high-resolution images at 7 T help to avoid this pitfall. The absence of digitations along the hippocampal head is another sensitive and specific finding for hippocampal sclerosis that is considerably more apparent on 7-T images.

Furthermore, 7-T MRI and automated subfield volumetry have enabled detection of hippocampal pathology also in subfield volumes of the CA1, CA2/3, CA4/DG, and the subiculum [11]. Specifically, among patients with unilateral mesial temporal lobe epilepsy (mTLE) with longer disease durations, volume loss was observed in the ipsilateral CA1 and CA2/3 subfields and contralateral CA1. There were no differences in subfield volumes in patients with neocortical epilepsy compared to controls [11].

Pros and cons of different sequences in 7-T imaging

In the task force consensus recommendations on the use of 7-T MRI in clinical practice for epilepsy, the eight8 most useful sequences were identified in a survey from 19 7-T MRI centers experienced in examining patients with epilepsy for research and/or diagnostic purposes. Nevertheless, there is no uniform acquisition protocol among clinical centers, especially concerning those studies focused on morphometric analysis [23].

A number of other indirect signs for epilepsy-associated changes were described in several 7-T MRI pilot studies with different postprocessing methods (◘ Table 2).

There are only few studies with relative homogeneous patient groups and concordant parallel analysis of 3-T and 7-T MRI data [38, 41, 44]. In the study by Wang et al. [44], the morphometric analysis of 3-T MPRAGE sequences was compared with the same analysis on the 7-T MP2RAGE sequence. The general diagnostic yield of 7-T MRI with morphometric analysis was 43% (29 of 67 patients). The study was designed to best utilize 7-T sequences for subtle lesion detection in a clinical setting, rather than to compare the two sequences at different field strengths. However, MP2RAGE sequences are of special importance in the visualization of MCD not only in 7-T images but also in 3-T images. In MP2RAGE sequences, the inhomogeneity effect can be largely canceled out by combining image data from the first and second readouts; T2* and B1 inhomogeneity effects can be largely canceled out, resulting in a strongly T1-weighted image with superior gray matter to white matter contrast than available with MPRAGE sequences. As noted by Demerath et al. [8], the study used only MP2RAGE imaging in their 7-T MRI, so that the high detection rate was possibly due to this sequence and not due to the higher field strength.
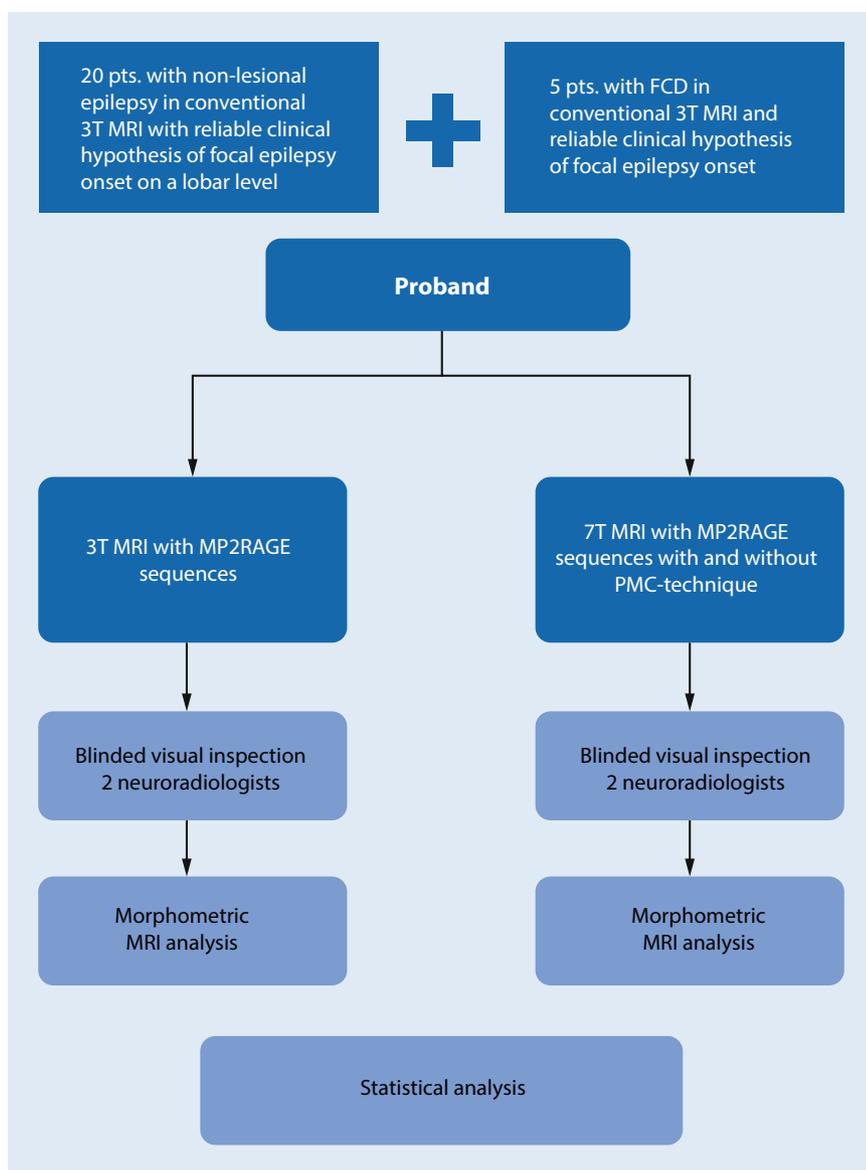
Fig. 1 ▲ Flow diagram of the study selection process. *FCD* focal cortical dysplasia, *PMC* prospective motion correction, *pts.* patients

To date, there have been no prospective clinical studies comparing MP2RAGE sequences in 3-T and 7-T MRI in parallel with the same acquisition protocol for morphometric analysis.

Motion correction technique

The main technical challenges for data acquisition under UHF in 7-T MRI are to produce a strong, homogeneous transverse field and high-quality images. Different approaches are used to minimize the influence of nonuniformities caused by interferences at UHFs and to accelerate and increase the yield regarding the time spent for acquisition and the quality of the image achieved. Motion artifacts represent a substantial limiting factor for very high-resolution imaging, since they reduce the resolution and isotropy of voxel-based imaging and therefore influence the results of analyses and calculations, such as segmentation or gray matter volume and thickness estimates [13]. Motion correction techniques can be used to correct for motion either in real time (prospectively) or offline after the data have been collected (retrospectively). Spin history effects caused by through-plane motion are not corrected by retrospective correction. In contrast to retrospective techniques, prospective motion correction (PMC) ensures that the k-space sampling density stays approximately homogeneous [13].

One of the PMC techniques with an external tracking device was suggested in 2015 by Stucht and colleagues [36]. This technology allows for high-precision tracking of out-of-plane rotations, by deriving pose information from changes in a moiré pattern visible on a 15-mm marker. Moreover, through an external optical tracking system and image processing, the image resolution in 7-T MRI can be substantially increased and therefore is suitable for visualization of very fine structures such as cortical layers [13, 19].

Prospective study protocol

We present a study protocol developed in the Department of Neurology of the University Hospital Magdeburg in collaboration with the Epilepsy Centre Freiburg, Epileptologicum Hamburg, Epilepsy Centre Hessen, University Marburg/Giessen, and Epilepsy Centre Bielefeld-Bethel to address the hypothesis that 7-T structural MRI increases the rate of detection of structural lesions with the application of morphometric analysis when compared with a parallel coherent study protocol in 3-T MRI. The clinical feasibility of performing this study was presented in 2020 at the German Branch of the ILAE meeting in Freiburg. The study will be supported by the Otfrid Förster grant of the German Society for Epileptology e.V.

The aim of the study is to investigate the clinical value of 7-T MRI with postprocessing and PMC for patients with nlE (in 3-T MRI with epilepsy conventional protocol and MP2RAGE sequences).

Primary outcomes will be the rate of detected epileptogenic lesions in standardized UHF in 7-T MRI compared to presurgical 3-T MRI according to a standardized presurgical evaluation with comparable acquisition sequences for both 3-T and 7-T MRI examinations (◻ Fig. 1):
– Via blinded visual inspection
– Via inspection of postprocessing data resulting from analysis with the Morphometric Analysis Program v2018 (MAP18)

Table 3 Imaging protocol for 3-T and 7-T MRI measurements

3 T		7 T	
Sagittal 3D MPRAGE	$1.0 \times 1.0 \times 1.0$ mm	Sagittal 3D MPRAGE	$0.7 \times 0.7 \times 0.7$ mm
Sagittal 3D MP2RAGE	$1.0 \times 1.0 \times 1.0$ mm	Sagittal 3D MP2RAGE	$0.7 \times 0.7 \times 0.7$ mm
Sagittal 3D FLAIR	$1.0 \times 1.0 \times 1.0$ mm	Sagittal 3D FLAIR	$0.7 \times 0.7 \times 0.7$ mm
Axial 2D T2 TSE	$0.4 \times 0.4 \times 3.0$ mm	R2T2*	$0.7 \times 0.7 \times 0.7$ mm
Coronal 2D T2 STIR	$0.4 \times 0.4 \times 2.0$ mm	3D SWI (QSM)	$0.7 \times 0.7 \times 0.7$ mm
DWI EPI	$0.6 \times 0.6 \times 5.0$ mm	T2TSE	$0.4 \times 0.4 \times 2$ mm
Time of acquisition ca. 40 min		Time of acquisition ca. 60 min	

Study design

Prospective, multi-center study of presurgically assessed patients with previous 3-T MRI and a diagnosis of focal epilepsy regarded as nonlesional and with a clear seizure-onset hypothesis that meets the following two criteria:

1. Clinical and semiological hypothesis concerning lateralization and affected lobe
2. Ictal EEG is in line with criterion 1

Or:

3. Magnetic source imaging or electric source imaging is in line with criterion 1.

Patients with temporal and extratemporal drug-resistant epilepsy will be included. According to electroclinical and semiological analysis, a selection of patients will be made oriented toward a search for "expected" malformations of cortical development.

The 3-T MRI for the identification of the nonlesional patients should match basic standards of the use of structural MRI in the care of patients with epilepsy [3, 47].

Exclusion criteria

The exclusion criteria for investigation of patients in a 7-T MRI scanner are according to the 7-T MRI information sheet (supplemental information), i.e., metal objects in their body, patients with claustrophobia or other psychiatric conditions, those who cannot stay in an appropriate position/keep still during the investigation, patients under the age of 14 years, and obese patients with body weight over 140 kg.

MRI data

All patients will be examined in a 3-T MRI scanner (Siemens Magnetom Prisma, Siemens Medical Solutions, Erlangen, Germany) and in a 7-T MRI scanner (Siemens Magnetom Terra). The acquisition protocol for 3-T MRI measurements (◻ **Table 3**) will be designed according to Demerah et al. [7] and the 7-T MRI acquisition will be as close as practicable to the 3-T acquisition protocol.

For systematic reasons, implementing artifact reduction in 7-T image acquisition asks for a direct comparison of this technique with the 3-T imaging. However, the current literature supports the impact of movement artifacts on SNR during examination in 3-T MRI to be insignificant. Additionally, its correction burdens the examination technically [43], and thus we decided for practical reasons to omit this point; especially since studies of 7-T MRI at the same time have shown that it often plays a key role in the quality of the images obtained. The PMC techniques for the 7-T study will be used according to Stucht and colleagues [36] and the morphometric analysis according to Huppertz [16, 17]. A dataset of a control group from the same 7-T MRI scanner and with the same investigation will be used as a normal database for the morphometric analysis. The control group data for comparison of MP2RAGE measurements of 3-T MR images were obtained with an MRI scanner of the same model (Siemens Magnetom Prisma) with an identical measurement protocol that will be used in the clinical group of probands. In each case, results will be reviewed via expert visual inspection by two neuroradiologist/epileptologists, with expertise in epilepsy imaging, who are blinded to the seizure-onset zone . The control dataset will be integrated and used for the SPM12-based MAP18 Toolbox analysis. For MAP analysis, z-scores and probability maps will be used according to the well-known method of Huppertz et al. [17].

Our study protocol is designed to make a larger study after the current small pilot study possible. It places emphasis on the feasibility of the use of 7-T imaging in a clinical study. Since all patients will undergo either subsequent invasive presurgical evaluation or a surgical intervention, if indicated, we will ask for pathology results and outcomes as they are of exceptional clinical importance. A retrospective analysis of the current small study with these patients and outcome parameters is planned.

Discussion and conclusion

Epilepsy, in particular, stands to benefit from the sensitivity gains in the detection of subtle imaging features. The greater sensitivity and resolution provided by UHF imaging have translated into promising results concerning the detection rate of potentially epileptogenic lesions, resulting in direct clinical benefit. However, UHF imaging still faces challenges, particularly those related to reliable image quality such as B1 field inhomogeneity. Therefore, standardization and clinical comparison of current 7-T MRI sequences sensitive to the visualization of main epileptogenic lesion types are of high clinical importance. A cohort study with prospective design and comparable sequences is mandatory.

The suggested prospective study protocol involves conducting a consequent comparison of 3-T and 7-T imaging data and morphometric analysis of patients with nlE. In the future we hope to supply data that will show the clinical practicability and proof of principle of a 7-T MRI protocol for increasing the detection rate of subtle epileptogenic lesions.

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Declarations

Conflict of interest. The scholarship holder is O. Kukhlenko. R. Kukhlenko, C. Tempelmann, O. Speck, H. Hinrichs, H.-J. Heinze, M. Heers, P.M. House, F.G. Woermann, S. Knake, H. Urbach, H.-J. Huppertz, A. Haghikia and F.C. Schmitt declare that they have no competing interests.

All procedures performed in studies involving human participants or on human tissue were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Studienprotokoll: Wert der 7-T-MRT mit prospektiver Bewegungskorrektur und Nachbearbeitung bei Patienten mit nichtläsionaler Epilepsie

Die diagnostische Ausbeute der Magnetresonanztomographie(MRT)-Nachbearbeitung unter Verwendung von 7-T-Daten bei Patienten mit nichtläsionaler Epilepsie wurde nur selten evaluiert und zeigte erste klinisch verwertbare Ergebnisse. Bisher gab es jedoch keine prospektiven klinischen Studien, in denen MP2RAGE-Sequenzen („magnetization-prepared 2 rapid acquisition gradient echo") in 3-T- und 7-T-MRT parallel mit demselben Protokoll zur morphometrischen Analyse verglichen wurden. Die Autoren stellen ein Studienprotokoll vor, das entwickelt wurde, um die Hypothese zu untersuchen, dass die Anwendung der strukturellen 7-T-MRT die Erkennungsrate von strukturellen Läsionen mit der morphometrischen Analyse im Vergleich zu einem parallelen kohärenten Studienprotokoll in der 3-T-MRT erhöht. Dieses 7-T-Protokoll dient dazu Daten zu liefern, die die klinische Praktikabilität und den Grundsatzbeweis für die Erhöhung der Erkennungsrate von subtilen epileptogenen Läsionen darlegen.

Schlüsselwörter
Magnetresonanztomographie · Diagnostische Bildgebung · Strukturelle MRT-Bildgebung · MRT-Nachbearbeitung · Prognosefaktor

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