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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

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ABSTRACT

Objective. MRI is a cornerstone in presurgical evaluation of epilepsy. Despite guidelines, clinical practice varies. In light of the E-PILEPSY pilot reference network, we conducted a systematic review and meta-analysis on the diagnostic value of MRI in the presurgical evaluation of epilepsy patients.

Methods. We included original research articles on diagnostic value of higher MRI field strength and guideline-recommended and additional MRI sequences in detecting an epileptogenic lesion in adult or paediatric epilepsy surgery candidates. Lesion detection rate was used as a metric in meta-analysis.

Results. Eighteen studies were included for MRI field strength and 25 for MRI sequences, none were free from bias. In patients with normal MRI at lower-field strength, 3T improved lesion detection rate by 18% and 7T by 23%. Field strengths higher than 1.5T did not have higher lesion detection rates in patients with hippocampal sclerosis (HS). The lesion detection rate of epilepsy-specific MRI protocols was 83% for temporal lobe epilepsy (TLE) patients. Dedicated MRI protocols and evaluation by an experienced epilepsy neuroradiologist increased lesion detection. For HS, 3DT1, T2, and FLAIR each had a lesion detection rate at around 90%. Apparent diffusion coefficient indices had a lateralizing value of 33% for TLE. DTI fractional anisotropy and mean diffusivity had a localizing value of 8% and 34%.

Significance. A dedicated MRI protocol and expert evaluation benefits lesion detection rate in epilepsy surgery candidates. If patients remain MRI negative, imaging at higher-field strength may reveal lesions. In HS, apparent diffusion coefficient indices may aid lateralization and localization more than increasing field strength. DTI can add further diagnostic information. For other additional sequences, the quality and number of studies is insufficient to draw solid conclusions. Our findings may be used as evidence base for developing new high-quality MRI studies and clinical guidelines.

Key words: magnetic resonance imaging, lesion, diagnostic imaging, refractory epilepsy

Epilepsy surgery is the most effective treatment option for patients with medically refractory focal epilepsy. It necessitates a solid hypothesis on the location and extent of the brain region responsible for seizures in order for this region to be resected [1]. The cornerstone in formulating such hypotheses for individual patients is structural imaging with magnetic resonance imaging (MRI) [2-6].

In a substantial fraction of patients, MRI is considered normal or shows only nonspecific white matter abnormalities or diffuse cerebral atrophy. These so-called MRI-negative results have been shown to be a negative predictor for seizure freedom after surgery in several studies [7, 8].

MRI technology developments, whether by increased field strength, improved coil design, or programming of advanced acquisition sequences, enable richer information to be obtained from the imaged object. This potentially leads to improved detection rate of structural brain lesions in patients with epilepsy [9]. Currently available recommendations and practice guidelines are based on selected studies and expert opinions that reflect the technological state of the art at the time of their formulation [2-6, 10, 11]. The diagnostic value added by higher-field strengths or more recent and non-standard (additional) MRI sequences is disputed, as is evident from the wide variability in the use of MRI in clinical practice found in a recent survey amongst 25 epilepsy surgery centres across Europe [12].

In the context of the European Union-funded E-PILEPSY network (now continuing within the European Reference Network for rare and complex epilepsies [Epi-CARE]), which aims to harmonize epilepsy surgery practice across Europe, several systematic reviews have been published on various diagnostic tests applied in the pre-surgical work-up for epilepsy surgery, including interictal source imaging, long-term video-electroencephalography, and functional tests for memory and language [13-16]. We performed a systematic review to assess the diagnostic value of guideline-recommended (standard) MRI in comparison with MRI at higher-field strengths and with additional MRI sequences in the presurgical evaluation of patients with refractory epilepsy. Our goal was to answer the following questions:

- 1. What is the diagnostic advantage of MRI at a higher-field strength (3T or 7T) in detecting an epileptogenic lesion in epilepsy surgery candidates who were considered MRI-negative on scans at lower-field strength (3T versus 1-1.5T, and 7T versus 1.5-3T)?
- 2. What is the diagnostic value of standard and additional MRI sequences in detecting an epileptogenic lesion in epilepsy surgery candidates?

Methods

This systemic review was conducted according to the PRISMA statement [17].

Preparation: Expert task force

This systematic review was part of the E-PILEPSY project, a European Union-funded pilot reference network consisting of 28 epilepsy surgery centres, with the primary aim of improving awareness and accessibility of epilepsy surgery across Europe. E-PILEPSY is now included in the ERN EpiCARE [16]. By producing systematic reviews, the Consortium sought to provide a firm evidence basis for harmonization and improvement of diagnostic procedures in epilepsy surgery

[13-15]. As a first step, we established an expert panel in the field of MRI from the centres participating in the E-PILEPSY Consortium.

Search strategy

We performed two in-depth searches, one for each research question, in PubMed, Embase, and Cochrane. The last update of the search was on 8th January 2021. The searches were limited to English language articles published from 1 January 1990 onwards. The search strings used are provided in *supplementary table 1*.

Study selection: inclusion criteria

- ***Population***

Original research articles on the diagnostic value of MRI field strength and MRI sequences in detecting an epileptogenic lesion in adult or paediatric epilepsy surgery candidates with medically refractory focal epilepsy were included.

- ***Diagnostic test***

For the first question, we only considered studies that compared the diagnostic value of a higher-field strength (*i.e.* 3T or 7T: index test) to that of a lower-field strength (*i.e.* 1/1.5/3T: comparator test). Inclusion was independent of the MRI protocol applied (*i.e.* conventional imaging or dedicated epilepsy protocol). For the second question, we selected studies that determined the diagnostic value of different MRI sequences, either individually or combined in a protocol. We considered both widely available 'standard' sequences (T1, T2, FLAIR: separately or combined in a protocol) and less commonly used 'additional' sequences (*e.g.* DWI, DTI, T2*). Post-processing techniques (*e.g.* volumetry and voxel-based morphometry) were beyond the scope of this systematic review. Studies on standard sequences were included if they compared the results of these (individually or in a protocol) with the reference standard (see below). Studies on additional sequences were included if they determined the diagnostic advantage of these sequences (index test) as compared to the standard MRI sequences or an epilepsy MRI protocol (comparator test).

- ***Reference standard***

The preferred reference standard was either a histopathologically identified epileptogenic lesion or, as second best, the clinical diagnosis of a presumed epileptogenic zone.

Study selection: exclusion criteria

Studies focusing specifically on technical details of imaging, image quality, or illustrating specific imaging characteristics of a certain pathology were excluded unless the data were presented in such a way that a lesion detection rate could be calculated.

Study selection process

After eliminating duplicates, two authors (BM and MR) independently screened studies on title and abstract (*supplementary table 2*). Discrepancies in judgement were discussed and final agreement was reached in a consensus meeting. Pairs of independent reviewers were formed from the members of the expert taskforce. Included studies were then screened on full text by the reviewer pairs according to the eligibility criteria (*supplementary table 3*). Disagreement was discussed and final agreement was reached before the pairs submitted their full text screening results to the coordinating party (BM and MR). Reference lists of included studies were screened for additional studies matching the inclusion criteria.

Critical appraisal and data extraction

All included articles were appraised on their risk of bias and their directness of evidence independently by two members of the taskforce using predetermined criteria and signalling questions based on the QUADAS-2 methodology (*see supplementary material*) [18]. Quality appraisal and data extraction were simultaneously performed using an online form composed with the NETQ survey programming software (NETQ Healthcare, Utrecht, The Netherlands). Data regarding the study and patient characteristics, MRI details, sample sizes, and lesion detection rates were extracted. The results were analysed by the coordinating party and if any discrepancy within a pair was observed a web meeting or email conversation was initiated to resolve disagreement.

Data analysis and meta-analysis

By including only patients with focal epilepsy who were evaluated for surgery, we assumed the presence of a lesion (either macroscopic or microscopic detectable). The diagnostic value of the index test was therefore defined as the detection rate for relevant (*i.e.* suspected epileptogenic) lesions. Detection rate was calculated as the number of patients with a lesion on MRI, divided by the total number of patients studied. Data provided in the original articles were reviewed and potential epileptogenic lesions as stated by the authors were counted. Patients with generalized epilepsy were excluded. When comparing field strengths or sequences, data had to be available in sufficient detail

that direct comparison within patients was possible for the data to be included in the meta-analysis.
To minimize clinical heterogeneity, studies were categorized into subgroups based on the type of index/comparator test or (presumed) histopathology subgroups or temporal versus extratemporal focal epilepsy. Data on the lesion detection rate were pooled in a meta-analysis when at least two studies were available for a subgroup. Pooling was based on the random-effects model using a conventional two-step method with logit transformation and DerSimonian-Laird algorithm. Meta-analysis and forest plots were constructed using the OpenMetaAnalyst software [19].

Results

MRI field strength

The search yielded 1,348 matches (*supplementary figure 1*). After removal of duplicates, 1,122 articles were screened based on title and abstract, of which 32 met the inclusion criteria and 18 remained after full text screening [20-37].
Ten studies had a prospective and eight a retrospective design (*supplementary table 4*). Sample sizes varied between 10 and 738 patients. Eleven studies included both children and adults, one included only children [20], and six mostly adults [21-26]. One study did not report age [27].
The reference standard in three studies was histopathology [28-30]. Four studies used surgical confirmation in a subset of the patients, and intracranial EEG or non-invasive diagnostics in the others [31-34]. In two articles, both reporting large cohort studies, the reference standard was not clearly specified; instead, the frequency of MRI lesions was given [20, 27]. The remaining studies used the clinical diagnosis as a reference standard.
Eight studies compared 3T MRI with 1/1.5T in patients with focal epilepsy and variable pathology. Seven studies compared 7T MRI with 1.5/3T in patients with focal epilepsy and variable pathology or focal cortical dysplasia (FCD). One study specifically compared 3T with 1.5T in patients with hippocampal sclerosis (HS) [29], two compared 7T with 1.5T in patients with temporal lobe epilepsy (TLE) and variable pathology [23, 25]. Three out of eight 3T versus 1/1.5T studies and one of two 1.5T versus 7T in TLE studies did not show suitable data to calculate lesion detection rates at higher-field strength in those patients in whom the 1/1.5T MRI was reported negative, and could therefore not be included in meta-analysis (*table 1*). In one of these studies, distinct cohorts of patients were scanned at the two field strengths and compared [20].
None of the included studies were free from bias (*supplementary table 5*). A high risk of bias was mostly found for patient selection (16 studies), as inclusion was restricted to *e.g.* MRI-negative patients at lower-field strength, or to patients who underwent resective surgery. Risk of standardization bias was present in six studies due to the use of various field strengths or head coils within the same study. For four studies the risk of a biased reference standard was considered high, as different references within the study were used. Ten studies carried a high risk of bias for patient flow and timing due to suspected information bias (*i.e.* unblinded review of the MRI). Seven studies raised applicability concerns, which were mostly related to the applicability of the index test (five studies) (*supplementary table 5*).

Lesion detection rate

The pooled estimate from the meta-analysis of five studies showed a detection rate of 18% (95% CI: 5-47%) for 3T MRI in MRI-negative patients at 1/1.5T with focal epilepsy and variable suspected pathology (*table 1, figure 1*). In the group of patients with focal epilepsy and variable pathology or FCD, the pooled estimate from seven studies revealed a lesion detection rate for 7T MRI of 23% (95%-CI: 17-30%) in MRI-negative patients at lower-field strengths (*table 1, figure 1*). In four studies, both 1.5T and 3T were compared to 7T [22, 28, 33, 35]. In two of these, all new lesions on 7T were found in those who had previously undergone 3T [28, 33]. In the other two studies, half of the new lesions on 7T were found in those who had previously undergone 3T [22, 35].
MRI at 3T did not reveal new lesions compared to 1.5T MRI in one study including patients with histologically proven HS (*table 1*). For patients with TLE and variable pathology who did not show a lesion on 1.5T MRI, one study showed a lesion detection rate of 67% for 7T MRI (*table 1*) [25].

MRI sequences

Study selection is illustrated in *supplementary figure 2*. After removal of duplicates, the search yielded 1,266 articles, of which 100 were left for full text screening. Based on the eligibility criteria, 25 were finally included [23, 28-30, 38-58].
Eleven studies evaluated standard MRI sequences [28-30, 38-45], five evaluated additional MRI sequences [23, 46-49], and three contained data on both standard and additional sequences [50-52]. Six studies were on DTI [53-58].

▼ **Table 1.** Lesion detection rate according to MRI field strength, with clinical diagnosis or histopathology as reference standard.

Study	Group characteristics	Type of comparison	Lesion detection rate at low-field strength	Lesion detection rate at high-field strength	Lesion detection rate at high-field strength - negative at low-field strength = diagnostic advantage
Focal epilepsy, variable pathology. 3T versus 1/1.5T					
Knake *et al*. 2005 [31]	Candidates for invasive Phase 2 evaluation due to non-conclusive Phase 1 findings	3T versus 1.5T	38% (15/40)	75% (30/40)[a]	60% (15/25)
Ladino *et al*. 2016 [24]	Patients with non-conclusive pre-surgical non-invasive evaluation and previous normal/equivocal 1.5T MRI[b]	3T versus 1.5T	23% (7/30)	33% (10/30)	13% (3/23)
Nguyen *et al*. 2010 [36]	Surgical candidates with negative/ initially regarded as non-relevant 1/1.5T MRI	3T versus 1/1.5T	0.0% (0/36)[c]	5.6% (2/36)	5.6% (2/36)
Phal *et al*. 2008 [32]	Epilepsy patients who underwent both 1.5T and 3T MRI due to various reasons[d]	3T versus 1.5T	74% (14/19)[e]	90% (17/19)[f]	NA[g]
Rubinger *et al*. 2016 [20]	Children with refractory epilepsy who had undergone resective surgery	3T versus 1.5T	86% (120/140)	92% (156/169)	NA[h]
Strandberg *et al*. 2008 [37]	Surgical candidates with normal/ unclear 1/1.5T MRI[d]	3T versus 1/1.5T	30% (7/23)	52% (12/23)	31% (5/16)
Winston *et al*. 2013 [27]	Epilepsy patients who underwent both 1.5T and 3T MRI[d]	3T versus 1.5T	22% (161/738)	27% (198/738)	6.4% (37/577)
Zijlmans *et al*. 2009 [26]	Patients with non-conclusive presurgical non-invasive evaluation	3T versus 1.5T	51% (19/37)	49% (18/37)	NA[i]
Hippocampal sclerosis, 3T versus 1.5T					
Hashiguchi *et al*. 2010 [29]	Patients who underwent anterior temporal lobectomy with amygdalohippocampectomy and had HS	3T versus 1.5T			
		-Atrophy	77% (10/13)	77% (10/13)	0.0% (0/3)
		-Hyperintensity	69% (9/13)	69% (9/13)	0.0% (0/4)
Focal epilepsy, variable pathology or FCD. 7T versus 1-3T					
Bartolini *et al*. 2019 [28]	Patients with focal epilepsy who underwent surgery and had a histopathologic diagnosis of FCD	7T versus 1.5/3T[j]	75% (9/12)	83% (10/12)[k]	33% (1/3)
Colon *et al*. 2018 [21]	Epilepsy surgery candidates with negative 3T MRI	7T versus 3T	0.0% (0/19)	16% (3/19)	16% (3/19)
De Ciantis *et al*. 2016 [35]	Epilepsy surgery candidates with a 1.5-3T MRI which was considered negative by the referring centre	7T versus 1.5/3T[l]	0.0% (0/21)	29% (6/21)	29% (6/21)
Feldman *et al*. 2019 [22]	Patients with focal epilepsy and a non-lesional clinical (1.5T or 3T) MRI	7T versus 1.5/ 3T[m]	0.0% (0/37)	22% (8/37)	22% (8/37)

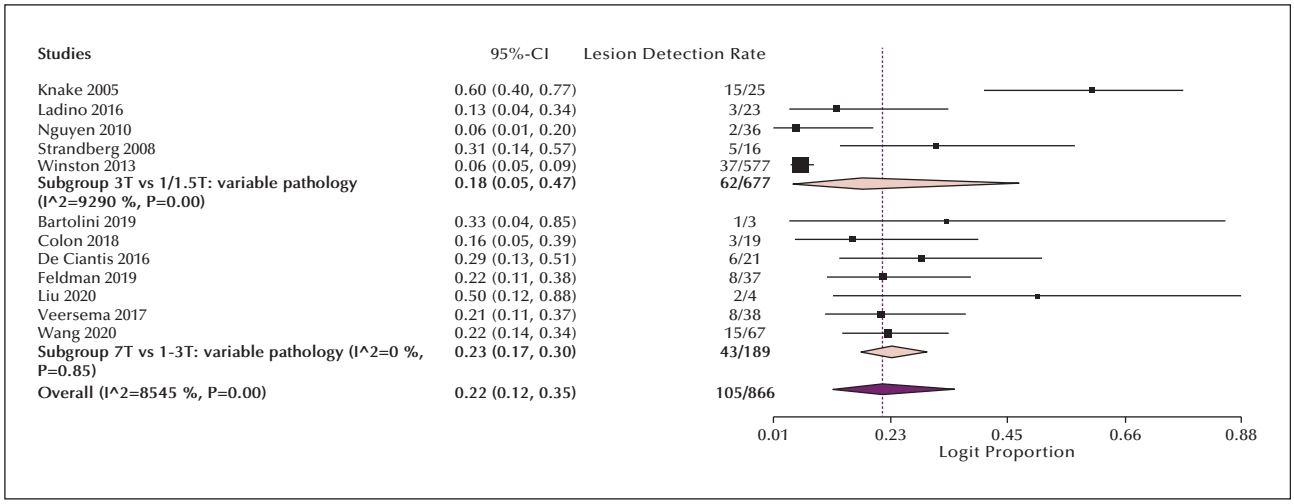
▼ **Table 1.** Lesion detection rate according to MRI field strength, with clinical diagnosis or histopathology as reference standard (*continued*).

Study	Group characteristics	Type of comparison	Lesion detection rate at low-field strength	Lesion detection rate at high-field strength	Lesion detection rate at high-field strength - negative at low-field strength = diagnostic advantage
Liu *et al*. 2020 [30]	Epilepsy patients with a pathological confirmation of FCD IIa	7T versus 3T	60% (6/10)	80% (8/10)	50% (2/4)
Veersema *et al*. 2017 [33]	Epilepsy surgery candidates, suspicion of FCD, with negative 1-3T MRI or suspected of dual pathology	7T versus 1-3T[n]	5.0% (2/40)[o]	25% (10/40)	21% (8/38)[p]
Wang *et al*. 2020 [34]	Epilepsy surgery candidates with negative 3T MRI	7T versus 3T	0.0% (0/67)	22% (15/67)	22% (15/67)
TLE, variable pathology. 7T versus 1.5T					
Kwan *et al*. 2016 [23]	Epilepsy surgery candidates with TLE	7T versus 1.5T	85% (9/13)	92% (8/13)	NA[q]
Santyr *et al*. 2017 [25]	Epilepsy surgery candidates with TLE	7T versus 1.5T	31% (4/13)	77% (10/13)	67% (6/9)

[a] In accordance with the study results, two patients with indeterminate 3T results were not included as positive MRI results
[b] Patients underwent repeated imaging with both 1.5T and 3T
[c] Non-specific abnormalities on 1.5T MRI disregarded by the authors (6 patients), as were non-congruent lesions (4 patients)
[d] Patients with generalized epilepsy not included in calculation
[e] Reported in number of observations: 55/74
[f] Reported in number of observations: 65/74
[g] Data presented in number of lesions, no comparison of individual patients possible, therefore not included in meta-analysis
[h] Different populations scanned, no comparison of individual patients possible, therefore not included in meta-analysis
[i] Insufficient details provided for direct comparison, therefore not included in meta-analysis
[j] 6/12 (50%) underwent 3T MRI. The one patient with a new lesion on 7T had previously undergone 3T
[k] Two patients with negative 7T MRI had FCD type Ib
[l] 14/21 (67%) underwent 3T MRI. Of the 6 patients with a new lesion on 7T, 3 had previously undergone 3T
[m] 13/37 (35%) underwent 3T MRI. Of the 8 patients with a new lesion on 7T, 4 had previously undergone 3T
[n] 35/40 (88%) underwent 3T MRI. Of the 8 patients with a new lesion on 7T, all had previously undergone 3T
[o] Both patients had HS, but were suspect of dual pathology based on the lower field MRI
[p] In one of the two patients who were suspect for dual pathology on lower field MRI, 7T MRI confirmed the dual pathology
[q] In patients who were already positive on 1.5T MRI for another lesion, three additional abnormal 7T MRI findings which were not detected by the clinical 1.5T MRI were found

Study characteristics of the 19 included studies on standard and additional MRI sequences are presented in *supplementary table 6*. Six studies had a prospective and 13 a retrospective design. Sample sizes varied between six and 98 patients. Thirteen studies included both children and adults, two only children [38, 49] and two mostly adults [23, 47]. Two publications did not report the age of the study population [42, 45]. All included studies had histopathology as a reference standard.

None of the included studies were free from bias (*supplementary tables 7, 8*). Risk of selection bias was found in all studies on standard MRI sequences and in all but one study on additional MRI sequences. Thirteen studies did not report sufficient details on the field strength used, the protocol used for conventional MRI or the coils used, and therefore carried an unclear risk of bias regarding index or comparator test. The reference standard was judged to have a high risk of bias in two studies because insufficient data were provided on histopathological results. Seven studies carried a high risk of bias for patient flow and timing due to suspected information bias. There were few concerns regarding applicability of patient selection and



■ **Figure 1.** Forest plot of additional lesion detection rate with higher-field strength.

reference standard. The index and/or comparator test were, however, only fully applicable for four studies (*supplementary tables 7, 8*).

Lesion detection rate

• *Epilepsy protocol and standard MRI sequences* (table 2)

Eight publications presented lesion detection rates of (various) epilepsy MRI protocols with histopathology as a reference standard (*table 2, figure 2*). Pooled lesion detection rate at 1.5T in TLE patients was 83% (95% CI: 58-94%) (*figure 2A*), based on four studies. Only one of these solely included patients who had HS [43]. The pooled estimate of the detection rate of epilepsy MRI protocols in FCD was 51% (95% CI: 37-65%) at 3T (based on three studies) (*figure 2A*), 35% (95% CI: 10-72%) for FCD type I, and 70% (95% CI: 57-81%) for type II (*figure 2B*). At 7T, the pooled estimate of detection rate of epilepsy MRI protocols in FCD was 82% (95% CI: 60-93%) (based on two studies) (*figure 2A*), ranging from 80 to 100% for FCD type II [28, 30]. A dedicated protocol with high-resolution MRI had a lesion detection rate of 87% for FCD, 85% for type I FCD, and 97% for type II FCD [38].

Additionally, one study showed a significantly higher detection rate for its epilepsy protocol, which included interpretation by an experienced epilepsy neuroradiologist, compared to a basic head MRI performed outside an epilepsy centre in the same patients with focal epilepsy with variable pathology (89% versus 40%) (*table 2*) [45].

Six studies reported lesion detection rates for standard MRI sequences separately, five of which were based on patients with TLE and HS (*figure 2C*) in whom T1 sequences (3DT1) had a lesion detection rate of 91% (95% CI: 78-97%), T2 sequences of 88% (95%-CI: 80-93%), and FLAIR of 91% (95% CI: 54-99%). One study additionally reported a lesion detection rate of 3D STIR (short tau inversion recovery) of 69% in patients with mTLE/HS [29]. The diagnostic value of FLAIR as a single 3D acquisition technique (at 3T) in patients with FCD was only reported in one study with 17 patients (30% for type I FCD and 100% for type II) (*table 2*) [50].

• *Additional sequences*

Lesion detection rates for additional MRI sequences with histopathology as a reference standard are presented in *table 3*. Given the limited number of studies, subgroup meta-analysis was not possible.

One study reported a lateralizing value of 33% for quantitative ADC measurements using a cut-off for the asymmetry index calculated as ±1 SD of healthy controls in conventional MRI-negative patients with TLE [51]. The lateralizing value regardless of MRI negativity/positivity in this study was 78%. Three studies, not including conventional MRI-negative patients, showed a lateralizing value of quantitative ADC measurements of 28% (cut-off of ±2 SD) [47], 46% (cut-off of ±2 SD) [52] and 81% (cut-off of ±1 SD) [46]. These studies, however, also revealed that asymmetry indices failed to lateralize in 19% (cut-off of ±1 SD) [46] and 72% (cut-off of ±2 SD) [47] of patients with a lesion on conventional epilepsy protocol MRI.

Two studies investigated T2* and SWI sequences at 7T in a small number of patients [23, 48]. In TLE, these sequences did not reveal new lesions not seen on conventional MRI. In one of two patients with FCD, 7T T2* revealed abnormalities suggestive of a lesion that was not visible on conventional images [48]. One

▼ **Table 2.** Epilepsy protocol and standard MRI sequences. Lesion detection rate with histopathology as a reference standard.

Study	Group characteristics	Type of sequence(s)	Topographical marker	Lesion detection rate
Focal epilepsy, variable pathology				
Von Oertzen *et al*. 2002 [45]	Focal epilepsy surgical candidates, operated, variable pathology	Basic head MRI[a] All sequences combined (1.5T): - T1 SE (sag) - T2 TSE (cor+ax) - T1 IR (cor) -FLAIR (ax, in TLE orientation perpendicular or parallel to the longitudinal axis of the hippocampal body)	- -	40% (36/90) 89% (80/90)
Focal epilepsy, FCD				
Ahmed *et al*. 2018 [38]	Children with medically refractory epilepsy, FCD suspected, operated[b]	All sequences combined (standard epilepsy protocol) (3T): - 3D T1 - FLAIR (cor+ax) - PD/T2 (cor+ax)	-	57% (56/98)[c]
		All sequences combined (dedicated HR MRI) (3T): - FLAIR (cor+ax) - PD/T2 (cor+ax)	-	87% (85/98)[d]
Bartolini *et al*. 2019 [28]	Patients with focal epilepsy who underwent surgery and had a histopathologic diagnosis of FCD	All sequences combined (7T): -3DT1 -3D FLAIR -3D SWAN (+targeted SWAN) -2D T2* -2D T2 FSE -2D targeted grey-white matter border FSE-IR	-	83% (10/12)[e]
Chen *et al*. 2018 [50]	Patients with pathologically confirmed FCD with surgical outcome Engel 1-2[f]	3D FLAIR (sag) (3T)	-	47% (8/17)[g]
		All sequences combined (3T): -FLAIR (cor+ax) -T1 (ax) -T2 (ax) -DWI (ax)	-	39% (15/39)[h]
Liu *et al*. 2020 [30]	Patients with pathologically confirmed FCD IIa	All sequences combined (3T): -3D T1 MPRAGE -2D T2 TSE -2D T2-FLAIR	-	60% (6/10)
		All sequences confined (7T): -3D T1 MPRAGE -2D T2 TSE -3D T2 FLAIR -SWI -WMS -GWB	-	80% (8/10)

▼ **Table 2.** Epilepsy protocol and standard MRI sequences. Lesion detection rate with histopathology as a reference standard (*continued*).

Study	Group characteristics	Type of sequence(s)	Topographical marker	Lesion detection rate
HS				
Hashiguchi *et al*. 2010 [29]	Patients with TLE who underwent temporal lobe resection with pathological confirmation of HS	-FLAIR (oblique along long hippocampal axis and coronal perpendicular to long hippocampal axis) (1.5/3T)	-Atrophy -Signal change	77% (10/13) 69% (9/13)
		-3D STIR (parallel to long axis of hippocampus) (3T)	-Signal change	69% (9/13)
Jack *et al*. 1996 [39]	Patients with TLE who underwent temporal lobe resection with pathological confirmation of HS	-T2 double SE (cor) (field strength not reported)	-	91% (87/96)
		-FLAIR (cor) (field strength not reported)	-	97% (93/96)
Kim *et al*. 1995 [40]	Patients with TLE who underwent temporal lobe resection with pathological confirmation of HS	-T2 FSE (cor) (field strength not reported)	-Signal change	80% (24/30)
Kuzniecky *et al*. 1997 [41]	Patients with TLE who underwent temporal lobe resection with pathological confirmation of HS	-3DT1 (1.5T)	-Hippocampal atrophy	91% (40/44)
		-T1 IR (perpendicular to the long axis of hippocampus) (1.5T)	-Signal change	86% (38/44)
Meiners *et al*. 1994 [43]	Patients with TLE who underwent temporal lobe resection with pathological confirmation of HS	All sequences combined (1.5T): - T1 (sag) - T2 (ax) - T2 (cor, through temporal lobe) - IR (cor, through temporal lobe) - T2 (parallel to the long axis of the hippocampus)	-Signal change -Hippocampal atrophy	100% (14/14) 86% (12/14)
Tien *et al*. 1993 [44]	Patients with the clinical diagnosis of intractable CPS without gross structural extrahippocampal MRI lesion, who underwent temporal lobe resection with pathological confirmation of HS	- HR T2 FSE of the temporal lobes (cor, perpendicular to long axis of hippocampus) (1.5T)	-Hippocampal atrophy -Signal abnormality -Signal change + hippocampal atrophy	84% (16/19) 84% (16/19) 90% (17/19)
TLE, variable pathology				
McBride *et al*. 1998 [42]	Patients with TLE who underwent temporal lobe resection with variable pathology with MRI from primary centre and tertiary centre both available	All sequences combined (1.5T): -T1 (cor) -T2 (cor)	-	96% (44/46)
Wang *et al*. 2008 [51]		All sequences combined (1.5T): - T1 FLAIR (ax+sag)		67% (18/27)

▼ **Table 2.** Epilepsy protocol and standard MRI sequences. Lesion detection rate with histopathology as a reference standard (*continued*).

Study	Group characteristics	Type of sequence(s)	Topographical marker	Lesion detection rate
	Patients with TLE who had undergone temporal lobe resection with with variable pathology[i]	- T2 FSE (coral) - T2 FLAIR (ad)	-Hippocampal atrophy AND T2 signal change	
Wehner *et al*. 2007 [52]	Patients with TLE who had undergone temporal lobe resection with with variable psychology	All sequences combined (1.5T)	-Hippocampal atrophy	64% (14/22)

[a] Not epilepsy specific protocol and performed outside epilepsy centre
[b] Proven in 63/98. Type I FCD in 26/63 and Type II FCD in 37/63
[c] Lesion detection rate for Type I FCD was (14/26) 54%, in Type II FCD (28/37) 76%
[d] Lesion detection rate for Type I FCD was (22/26) 85%, in Type II FCD (36/37) 97%
[e] Lesion detection rate for Type I FCD was (0/2) 0.0%, in Type II FCD 10/10) 100%
[f] Type I FCD in 21/39, Type II FCD in 11/39, Type III FCD in 7/39
[g] Lesion detection rate for Type I FCD was (3/10) 30%, in Type II FCD (2/2) 100%, in type III (3/5) 60%
[h] Lesion detection rate for Type I FCD was (4/21) 19%, in Type II FCD (7/11) 64%, in type III (4/7) 57%
[i] HS 15/27

study found a lesion detection rate of 90% of ASL on 3T in paediatric patients with poorly defined focal epilepsy who underwent presurgical evaluation with variable pathology, however, there was no diagnostic advantage over conventional MRI [49]. Finally, one study assessed the lesion detection rate of the FLAWS (fluid and white-matter suppression) sequence and found a lesion detection rate of 54% (13 of 24 patients with normal conventional MRI) [50].

• ***DTI***

Additionally, we included six studies on DTI in a post-hoc supplementary analysis with clinical diagnosis as a reference standard (*table 4*) [53-58].

Overall, the localizing value of a decreased FA was 8% (95%-CI: 2-26%) and of an increased MD 34% (95% CI: 20-52%) in patients with normal conventional MRI (*supplementary figure 3*). FA localization was false positive in 20% (95%-CI: 10-35%) and MD localization was false positive in 36% (95% CI: 18-58%) (*supplementary figure 4*). One publication was not included in the meta-analysis, as all patients showed a lesion (MCD) on conventional MRI. The authors reported a lesion detection rate of 68% for FA and 36% for MD [53].

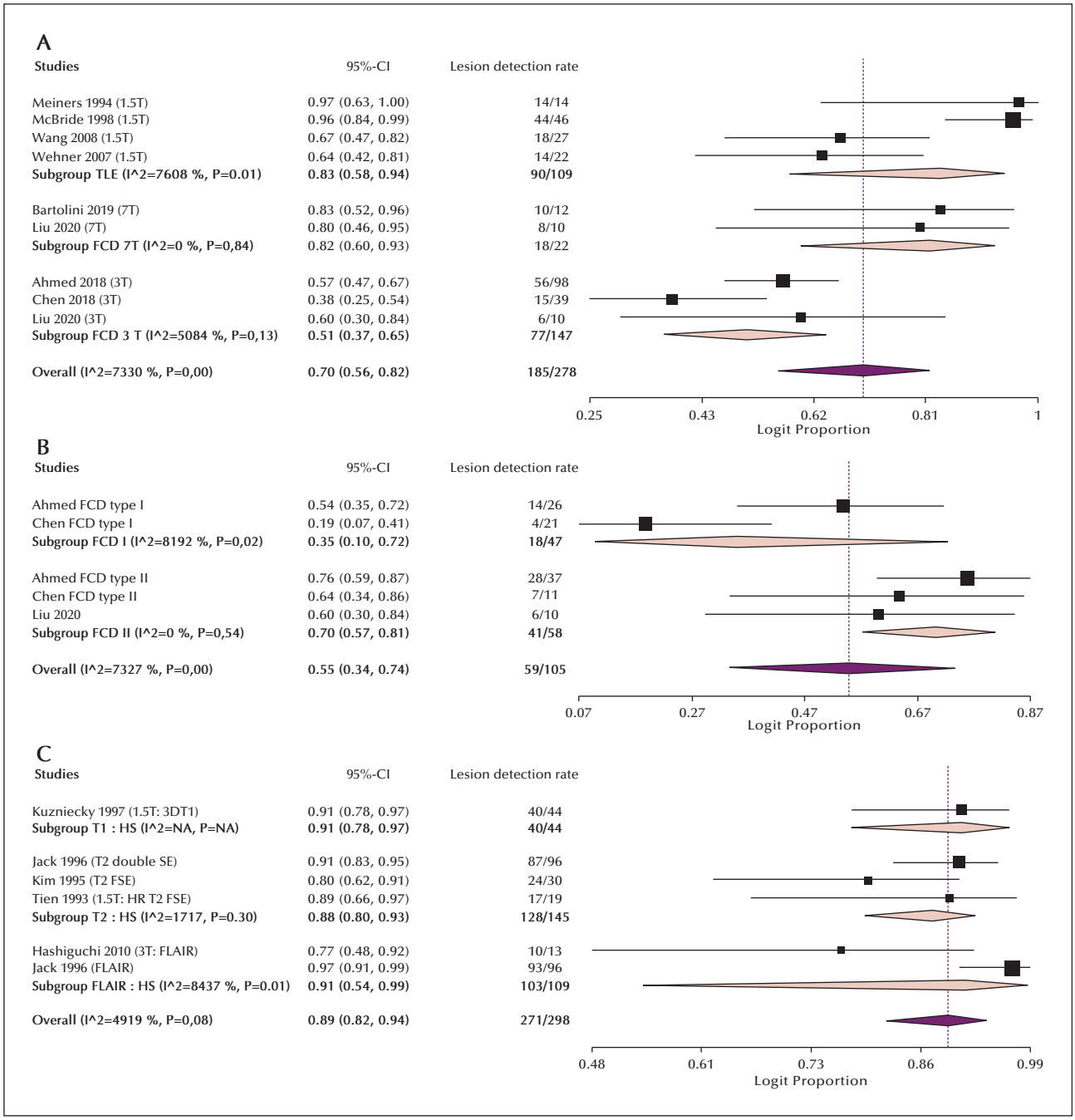
Two studies revealed a lateralizing value in unilateral TLE of 0.0% for FA [54, 55] and of 67% [54] or 86% [55] for MD. In the MRI-negative subgroup, lateralizing values were 0.0% for FA [54, 55] and 0.0% [54] and 50% [55] for MD. ■

Discussion

There is substantial variability in the clinical application of MRI in epilepsy surgery workup, and only 25% of European centres adhere to the applicable guidelines on MRI imaging standards [2-6, 12].

Here, we present a systematic literature review and meta-analysis of the diagnostic value of MRI sequences and of the diagnostic advantage of increased MRI field strength. In patients with normal 1/1.5T MRI, we show a diagnostic advantage of 18% for 3T, and in patients with normal 1-3T MRI, the diagnostic advantage of 7T was 23%. Epilepsy MRI protocols have a pooled lesion detection rate of 83% in patients with TLE (1.5T), and on average 51% (3T) in those with FCD; 35% for FCD type I and 70% for FCD type II. At 7T, this increases to 82% for FCD type II. In patients with HS, standard MRI sequences (*i.e.* 3DT1, T2, or FLAIR) each have a detection rate of around 90%. Additional MRI techniques, such as quantitative ADC measurements and DTI, have some lateralizing or localizing value, but can also show false localizing results or fail to identify lesions that were found on conventional MRI.

Although these results suggest an additional diagnostic role for 3T, or even 7T MRI in epilepsy surgery candidates with normal lower-field MRI, costs and lack of accessibility of 7T MRI limit its use in routine presurgical evaluation, and the reported added detection rates at 3T and 7T may have been too optimistic due to several factors. First, when looking only at 7T, several studies compared this field strength not only to 3T but also to 1/1.5T. This might have led to a higher estimate of diagnostic advantage. Further, high-field MRI is generally applied later in the diagnostic process when additional information from other tests is available and included in the assessment, increasing the risk of information bias. The increased



■ **Figure 2.** Forest plot of epilepsy protocol and standard MRI sequences relative to lesion detection rate. (A, B) Epilepsy-specific MRI protocol; data are presented separately for TLE and FCD subgroups (A) and separately for FCD type I and type II (3T) (B). (C) Separate standard sequences for patients with HS.

detection rate of higher-field MRI may also not apply to specific subcohorts. Because the group of patients with refractory epilepsy is heterogeneous, including both temporal and extratemporal epilepsy with differences in prognosis after epilepsy surgery [1, 8], and distinct underlying (presumed) histopathology with specific imaging characteristics [30, 40, 43, 50, 59], we chose to describe field strength-related differences in detection rates for subgroups separately. Indeed, in patients with HS, 3T MRI did not reveal new lesions compared to 1.5T. Zijlmans *et al*. [26] even reported that HS detection at

▼ **Table 3.** Lesion detection rate according to additional MRI sequences with histopathology as a reference standard.

Study	Group characteristics	Type of sequence(s)	Topographical marker	Conventional MRI lesion detection rate	Additional sequence lesion detection rate	Lesion detection rate sequence on MRI-negative on conventional MRI = *diagnostic advantage sequence*	Lesion on conventional MRI, but not on sequence
TLE							
Kantarci *et al.* 2002 [46] (1.5T)	Patients with TLE who underwent temporal lobe resection with variable pathology[a]	-DWI (cor)	-Increased hippocampal ADC[b] -Increased temporal stem ADC	100% (36/36)	81% (29/36) 70% (25/36)	-	19% (7/36) 31% (11/36)
Kwan *et al.* 2016 [23] (7T)	Patients with TLE who underwent temporal lobe resection with variable pathology[c]	-T2* (cor, perpendicular to long axis of hippocampus) -SWI (cor, perpendicular to long axis of hippocampus)	-	78% (7/9)[d]	67% (6/9) 7% (6/8)	0.0% (0/2) 0.0% (0/2)	11% (1/9) 13% (1/8)
Wang *et al.* 2008 [51] (1.5T)	Patients with TLE who underwent temporal lobe resection with variable pathology[e]	-DWI (ax)	Increased hippocampal ADC[b]	67% (18/27)	78% (21/27)	33% (3/9)	NR
Wehner *et al.* 2007 [52] (1.5T)	Patients with TLE who underwent temporal lobe resection with variable pathology[f]	-DWI (cor)	Increased hippocampal ADC[b]	NA[g]	46% (10/22)	NA[g]	NA[g]
Yoo *et al.* 2002 [47] (1.5T)	Patients with TLE who underwent temporal lobe resection with pathological confirmation of HS in all	-DWI (ax)	-Qualitative assessment -Increased hippocampal ADC[b]	100% (18/18)	0.0% (0/18) 28% (5/18)	-	72% (13/18)
Variable pathology							
Lam *et al.* 2020 [49] (3T)	Paediatric patients with poorly defined focal epilepsy who underwent presurgical evaluation, variable pathology	-ASL (ax)	-	90% (10/11)	90% (10/11)	0.0% (0/1)	None

▼ **Table 3.** Lesion detection rate according to additional MRI sequences with histopathology as a reference standard (*continued*).

Study	Group characteristics	Type of sequence(s)	Topographical marker	Conventional MRI lesion detection rate	Additional sequence lesion detection rate	Lesion detection rate sequence on MRI-negative on conventional MRI = *diagnostic advantage sequence*	Lesion on conventional MRI, but not on sequence
FCD							
Chen *et al*. 2018 [50] (3T)	Patients with pathologically confirmed FCD with surgical outcome Engel 1-2[h]	-FLAWS (sag)	-	39% (15/39)	72% (28/39)[i]	54% (13/24)	0.0% (0/16)
Veersema *et al*. 2016 [48] (7T)	Patients with histologically confirmed FCD in all[j], either MRI negative on 3T or suspect for FCD	-T2*	Superficial hypointensity	67% (4/6)	67% (4/6)[k]	50% (1/2)	17% (1/6)

[a] HS in 28/40 patients, 36/40 patients with abnormal histopathology
[b] Using asymmetry index
[c] HS in 4/9 patients
[d] Only comparison possible with conventional 1.5T MRI
[e] HS in 15/27 patients
[f] HS in 9/22 patients
[g] No direct comparison is made with conventional MRI
[h] Type I FCD in 21/39, Type II FCD in 11/39, Type III FCD in 7/39
[i] Lesion detection rate for Type I FCD was (12/21) 57%, in Type II FCD (11/11) 100%, in type III (5/7) 71%
[j] Type I FCD in 1/6, Type II FCD in 4/6, mild MCD in 1/6
[k] Lesion detection rate for Type I FCD was (1/1) 100%, in Type II (2/4) 50%, in mild MCD (1/1) 100%

3T is hampered by susceptibility to artifacts. On the other hand, 3T could facilitate the detection of dual pathology, *e.g.* neighbouring MCDs in these patients. Furthermore, the internal structure of the hippocampus may be more clearly visible at higher-field strengths, perhaps not leading to an increase in lesion detection rate but potentially adding relevant information [59].

Although several publications have recommended the use of a dedicated epilepsy protocol that includes T1, T2, and FLAIR sequences [2-6, 12], the protocols used in the studies of this systematic review varied. Our meta-analysis shows that the detection rate of these epilepsy-specific protocols at 1.5-3T in patients with FCD is little more than half of that in TLE patients (51% versus 83%). The lesion detection rate was higher in histologically proven FCD type II than type I, an observation that has repeatedly been reported before [60, 61], and has been suggested to be related to the level and type of neuronal disorganization and the appearance of the transmantle sign in type II FCD [60-62]. In FCD, a further increase in the detection rate was achieved by applying a dedicated high-resolution MRI protocol. Overall, detection rate was higher when MRI was performed at an epilepsy centre and evaluated by an experienced neuroradiologist [45].

Only a small number of publications on additional MRI sequences met our inclusion criteria. The majority focused on DWI in patients with TLE and assessed the lateralizing value of quantitative ADC measurements by means of an asymmetry index. The lateralization value appeared to be optimal in studies

▼ **Table 4.** DTI detection rate with clinical diagnosis as a reference standard.

Study	Group characteristic	Conventional MRI positive	Goal of test	DTI method	DTI detection rate[a]		DTI abnormality detection rate in conventional MRI-negative cases	Lesion on conventional MRI not detected by DTI	Number of patients with irrelevant DTI abnormality[b]
Assaf *et al.* 2003 [54]	Patients with unilateral TLE	8/12	Lat	Asymmetry indexc	FA correct	0.0% (0/12)	0.0% (0/4)	100% (8/8)	0.0% (0/12)
					MD correct	67% (8/12)	50% (2/4)	25% (2/8)	0.0% (0/12)
Chen *et al.* 2008 [56]	Patients with refractory focal epilepsy who were negative on conventional MRI	0/15	Loc	Voxel-based analysis with healthy control group using SPM	FA total correct	33% (5/15) 13% (2/15)	33% (5/15) 13% (2/15)	All MRI negative	27% (4/15)
					MD total correct	67% (10/15) 47% (7/15)	67% (10/15) 47% (7/15)	All MRI negative	60% (9/15)
Eriksson *et al.* 2001 [53]	Patients with focal epilepsy and suspicion of MCD on conventional MRI	22/22	Loc	Voxel-based analysis with healthy control group using SPM	FA total correct	77% (17/22) 68% (15/22)	No negative cases on conventional MRI	32% (7/22)	27% (6/22)
					MD total correct	46% (10/22) 36% (8/22)	No negative cases on conventional MRI	64% (14/22)	41% (9/22)
Rugg-Gunn *et al.* 2001 [57]	Patients with cryptogenic/acquired focal epilepsy (past acute, non-progressive cerebral injury)	10/40	Loc	Voxel-based analysis with healthy control group using SPM	FA total correct	28% (11/40) 25% (10/40)	3.3% (1/30) 3.3% (1/30)	10% (1/10)	10% (4/40)
					MD total correct	45% (18/40) 40% (16/40)	27% (8/30) 20% (6/30)	0.0% (0/10)	13% (5/40)

▼ **Table 4.** DTI detection rate with clinical diagnosis as a reference standard (*continued*).

Study	Group characteristic	Conventional MRI positive	Goal of test	DTI method	DTI detection rate[a]		DTI abnormality detection rate in conventional MRI-negative cases	Lesion on conventional MRI not detected by DTI	Number of patients with irrelevant DTI abnormality[b]
Salmenpera *et al*. 2006 [55]	Patients with unilateral TLE	6/7	Lat	Asymmetry index[d]	FA total correct	0.0% (0/7) 0.0% (0/7)	0.0% (0/1) 0.0% (0/1)	100% (6/6)	0.0% (0/7)
					MD total correct	100% (7/7) 86% (6/7)	100% (1/1) 0.0% (0/1)	0.0% (0/6)	14% (1/7)[e]
Thivard *et al*. 2011 [58]	Patients with refractory epilepsy who were negative on conventional MRI, all underwent sEEG	0/20	Loc	Voxel-based analysis with healthy control group using SPM	TLE +eTLE MD total correct	60% (12/20) 40% (8/20)	60% (12/20) 40% (8/20)	All MRI negative	40% (8/20)
					TLE MD total correct	39% (5/13) 15% (2/13)	39% (5/13) 15% (2/13)	All MRI negative	39% (5/13)
					eTLE MD total correct	100% (7/7) 86% (6/7)	100% (7/7) 86% (6/7)	All MRI negative	42% (3/7)

[a] total: all found lesions; correct: corresponding to the location of the epileptogenic lesion based on the reference standard
[b] including patients with DTI lesions concordant with reference standard but with additional non-concordant DTI lesions
[c] asymmetry index calculated by taking the difference between the left and right for each patient, cut-off at 2 SD of the mean of the healthy control group
[d] asymmetry index calculated by taking the difference between the ipsilateral and contralateral mean hippocampal ROI value and dividing by the mean of the ROI values, cut-off at 2 SD of the mean of the healthy control group
[e] not lateralizing, both side abnormal

using a threshold of ±1 SD of the healthy control population; the lateralizing value being at the highest level and false lateralization (compared to conventional MRI) at the lowest level. Nevertheless, false lateralization still occurred in 19% of patients [46]. In patients with TLE, 7T T2* and SWI sequences showed no diagnostic advantage over a 1.5T epilepsy protocol. To evaluate the usefulness of DTI as a tool for detecting epileptogenic lesions – rather than to visualize white matter tracts – in presurgical evaluation, we need to consider that no studies with histopathology as a reference standard were found. We decided to perform a separate analysis using the clinical diagnosis as an alternative reference standard and found that increased MD has higher localizing and lateralizing value than a decreased FA. However, MD also showed more false localizing results than FA. Most of these studies applied a voxel-based comparison with a healthy control group.

Our study has several limitations. For the MRI field strength, only studies that reported a detection rate of both the low and high-field strength scans, acquired in the same centre, were selected. Nevertheless, scans at lower-field strength may have been acquired years before the higher-field strength scans were performed, thus general improvements in acquisition schemes over time may have influenced the comparison. Studies reporting lesion detection at a single-field strength were excluded, as the primary aim of our field-strength analysis was to evaluate the results of scanning at higher-field strength in patients who did not show a lesion at lower-field strength. This provides quantifiable results of the diagnostic advantage of higher-field strength, rather than reliable detection rates of the individual (*e.g.* 1.5T or 3T) field strengths. Pooling this data from the included studies would not have been representative, as patient selection in the included studies was often based on MRI negativity at lower-field strength. For the research question regarding standard and additional MRI sequences, a uniform reference standard was selected, using histopathology as first choice, which limited the number of primary studies that could be included. We chose, however, to present an additional analysis on DTI with a broader inclusion, also considering papers with electro-clinical localization as a reference standard, as no papers with histopathology results as reference were identified. Also, our quality appraisal was mostly designed for interpretation of results, not for incorporation of any quality domains into the calculation of the lesion detection rate. Patient selection bias (*i.e.* MRI-negative or epilepsy surgery candidates), standardization bias (*i.e.* use of diverse MRI hardware such as coils) and information bias (*i.e.* image analysis aided by previous diagnostic results) could have caused over- or underestimation of diagnostic value. An overestimation of the lesion detection rate could have also been caused by the comparison of only radiology reports of lower-field strength MRI, to direct re-evaluation of the higher-field-strength MRI scan, which was the case in four of eight papers that compared 1/1.5T with 3T [27, 31, 36, 37] and in two 7T studies [22, 34]. For patients with TLE, one [25] out of two studies compared the report of the 1.5T scan with direct evaluation of the 7T scan, also possibly leading to inflated lesion detection rate of 7T compared to 1.5T in TLE. Moreover, various other technical parameters such as voxel size, slice thickness, angulation, and coils are known to affect image quality and thus diagnostic test value. Statistically correcting for such factors is desired but remains impossible with the small number of studies included in our review and without performing an individual patient data meta-analysis. We chose to extract the data as presented by the authors and not recalculate the lesion detection rate from the available data in the papers. Studies, however, varied in their interpretation of whether lesions were considered relevant or not. Although histopathology is the best available reference standard to determine MRI lesion detection rate, it disregards the peri-lesional and widespread electroclinical networks involved in seizure generation. Lesion resection does not consistently lead to seizure freedom, and, conversely, it is notable that a proportion of patients with incomplete resection of the lesion can still become seizure-free [63, 64]. Choosing histopathological confirmation as a reference standard may have exaggerated the lesion detection rate, since the chance of proceeding to resection is higher in patients with a lesion on MRI than in MRI-negative patients as these might have been the easy-to-diagnose patients. Some difficult-to-diagnose patients may have escaped inclusion, as their chance to proceed to resection is smaller, thus sensitivity and specificity could also not be calculated. Lastly, with technical developments and the relative novelty of 7T, results must be interpreted with the possible limitations of the technique used in the time period of the published studies.

There was wide heterogeneity between studies, mostly regarding the study populations, MRI parameters, and types of sequences. We believe this reflects the lack of multilateral agreement on the best MRI protocol for epilepsy. This lack of a standardized and uniform epilepsy MRI protocol might have also led to bias when comparing field strengths. This risk of bias was highest for studies which did not report the protocol used for 1.5T in comparison with 3T [31] or 7T [25], possibly inflating the lesion detection rate at higher-field strength. In an effort to reduce clinical variability in MRI practice, the neuroimaging task force of the ILAE recently recommended a new protocol, harmonizing neuroimaging of epilepsy structural sequences (HARNESS-MRI), which includes

1-mm^3 3D T1 and FLAIR, as well as high-resolution 2D submillimetric coronal (perpendicular to the long axis of hippocampus) T2 images, for use in all patients with epilepsy [10].

In spite of the study limitations, the collected data indicate that in epilepsy surgery candidates with refractory focal epilepsy who are referred to an epilepsy surgery centre with a negative MRI, but in whom a focal epileptogenic lesion is suspected, a dedicated epilepsy protocol with image interpretation by an experienced radiologist has the highest diagnostic advantage. In patients with HS, individual detection rates are around 90% for 3DT1, T2, and FLAIR sequences, *i.e.* the sequences recommended in most epilepsy MRI protocols. If patients remain MRI-negative nevertheless, imaging at higher-field strength – *i.e.* 3T versus 1/1.5T or 7T versus 1.5/3T – may reveal a lesion in one out of five patients. Field strengths higher than 1.5T, however, seem of limited value for MRI-negative patients with suspected HS, but applying additional quantitative asymmetry indexes using DWI may lead to lateralization in one third of these patients. DTI can add further information, but can also show false localizing results or fail to identify lesions found on conventional MRI. For other additional sequences, the available studies were insufficient in sample sizes and unconvincing in results. High-quality studies are needed to further support the evidence base of specific MRI sequences and optimal dedicated MRI protocols in candidates for epilepsy surgery. Our findings may be used as evidence base for developing such new studies and supporting recommendations. ■

Supplementary material.
Supplementary data accompanying the manuscript are available at www.epilepticdisorders.com.

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TEST YOURSELF

(1) How many of the included studies on the diagnostic value of MRI were free from bias?

A. Six
B. Three
C. None

(2) Which of the following is true?

A. The lesion detection rate linearly increases with MRI field strength
B. If lower-field MRI (either 1/1.5T or 3T) is normal, repeating MRI at higher field has an additional detection rate of around 20%
C. All epilepsy surgery candidates should undergo 3T MRI

(3) Which statement is correct?

A. In patients with suspected hippocampal sclerosis and normal 1.5T MRI, it is worthwhile repeating MRI at 3T

B. Each MRI sequence (T1, T2, FLAIR) has an identical HS detection rate

C. DWI in MRI-negative patients has a good additional lesion detection rate, with a high specificity

D. None of the above

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.