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

Running title: MRI in presurgical epilepsy workup

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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, higher field strength improved lesion detection rate by 18% for 3 T compared to 1-1.5 T, and by 23% for 7 T compared to 1-3 T. Field strengths higher than 1.5 T did not have higher lesion detection rates in patients with hippocampal sclerosis (HS). Lesion detection rate of epilepsy-specific MRI protocols was 83% in temporal lobe epilepsy (TLE) patients. Dedicated MRI protocols and evaluation by an experienced epilepsy neuroradiologist increased lesion detection. In HS, 3DT1, T2, and FLAIR each had a lesion detection rate around 90%. Apparent diffusion coefficient indices had a lateralizing value of 33% in 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.

Keywords: magnetic resonance imaging – lesion – diagnostic imaging – refractory epilepsy

Introduction

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 newer 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 aimed 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 (3 T or 7 T) in detecting an epileptogenic lesion in epilepsy surgery candidates who were considered MRI-negative on scans at lower field strength (3 T versus 1-1.5 T, and 7 T versus 1.5-3 T)?
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 8 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. 3 T or 7 T: index test) to that of a lower field strength (i.e. 1/1.5/3 T: 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 (**Suppl. 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 (**Suppl. 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 (**Suppl. methods**) [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

With 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 1348 matches (**Suppl. Fig. 1**). After removal of duplicates, 1122 articles were screened 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 (**Suppl. Table 4**). Sample sizes varied between ten 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.

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Eight studies compared 3 T MRI with 1/1.5 T in patients with focal epilepsy and variable pathology. Seven studies compared 7 T MRI with 1.5/3 T in patients with focal epilepsy and variable pathology or focal cortical dysplasia (FCD). One study specifically compared 3 T with 1.5 T in patients with hippocampal sclerosis (HS) [29], two compared 7 T with 1.5 T in patients with temporal lobe epilepsy (TLE) and variable pathology [23,25]. Three out of eight 3 T versus 1/1.5 T studies and one of two 1.5 T versus 7 T in TLE studies did not show suitable data to calculate lesion detection rates of higher field strength in those patients in whom the 1/1.5 T 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 (**Suppl. 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) (**Suppl. 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 3 T MRI in MRI-negative patients at 1/1.5 T with focal epilepsy and variable suspected pathology (**Table 1** and **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 7 T MRI of 23% (95%-CI: 18 – 30%) in MRI-negative patients at lower field strengths (**Table 1** and **Figure 1**). In four studies both 1.5 T and 3 T were compared to 7 T [22,28,33,35]. In two of these all new lesions on 7 T were found in those who had previously undergone 3 T [28,33]. In the other two studies halve of the new lesions on 7T were found in those who had previously undergone 3 T [22,35].

MRI at 3 T did not reveal new lesions compared to 1.5 T 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 1.5 T MRI, one study showed a lesion detection rate of 67% for 7 T MRI (**Table 1**) [25].

MRI sequences

Study selection is illustrated in **Supplementary Figure 2**. After removal of duplicates, the search yielded 1266 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].

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 6 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 (**Suppl. Tables 7** and **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 reference standard. The index and/or comparator test were, however, only fully applicable for 4 studies (**Suppl. Tables 7** and **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** and **Figure 2**). Pooled lesion detection rate at 1.5 T 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 3 T (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 7 T 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 – 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 in 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 3 T) 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% of quantitative ADC measurements using a cutoff 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% (cutoff of ±2 SD) [47], 46% (cutoff of ±2 SD) [52] and 81% (cutoff of ±1 SD) [46]. These studies, however, also revealed that asymmetry indices failed to lateralize in 19% (cutoff of ±1 SD) [46] and 72% (cutoff of ±2 SD) [47] of patients with a lesion on conventional epilepsy protocol MRI.

Two studies investigated T2* and SWI sequences at 7 T 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, 7 T T2* revealed abnormalities suggestive of a lesion that was not visible on conventional images [48]. One study found a lesion detection rate of 90% of ASL on 3 T 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 (**Suppl. figure 3**). FA localization was false positive in 20% (95%-CI: 10 – 35%), MD localization was false positive in 36% (95%-CI: 18 – 58%) (**Suppl. 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 1/1.5 T MRI, we show a diagnostic advantage of 18% for 3 T, and in patients with normal 1-3 T MRI, the diagnostic advantage of 7T was of 23% . Epilepsy MRI protocols have a pooled lesion detection rate of 83% in patients with TLE (1.5 T), and on average 51% (3 T) in those with FCD; 35% for FCD type I and 70% for FCD type II. At 7 T this increases to 82% in 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 3 T, or even 7 T MRI in epilepsy surgery candidates with normal lower field MRI, costs and lack of accessibility of 7 T MRI limit its use in routine presurgical evaluation, and the reported added detection rates at 3 T and 7 T may have been too optimistic due to several factors. First, when looking only at 7 T, several studies compared this field strength not only to 3 T but also to 1/1.5 T. 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 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, 3 T MRI did not reveal new lesions compared to 1.5 T. Zijlmans et al. [26] even reported that HS detection at 3 T is hampered by susceptibility artifacts. On the other hand, 3 T could facilitate the detection of dual pathology, e.g. neighboring MCDs, in these patients. Furthermore, the internal structure of the hippocampus may be better visible on 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 1.5-3 T 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. Lateralization value appeared to be optimal in studies using a threshold of ±1 SD of the healthy control population: the lateralizing value was highest and false lateralization (compared to conventional MRI) was lowest. Nevertheless, false lateralization still occurred in 19% of patients [46]. In patients with TLE, 7 T T2* and SWI sequences showed no diagnostic advantage over a 1.5 T 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, so 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. 1.5 T or 3 T) 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 1/1.5 T with 3 T[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 1.5 T scan with direct evaluation of the 7 T scan, also possibly leading to inflated lesion detection rate of 7 T compared to 1.5 T 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 electro-clinical 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 7 T, 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 1.5 T in comparison with 3 T[31] or 7 T[25], possibly inflating the lesion detection rate of the 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, harmonized 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 center 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. 3 T versus 1/1.5 T or 7 T versus 1.5/3 T – may reveal a lesion in one out of five patients. Field strengths higher than 1.5 T, 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.

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References

1. Jobst BC, Cascino GD. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. JAMA 2015; 313: 285-93.
2. Recommendations for neuroimaging of patients with epilepsy. Commission on Neuroimaging of the International League Against Epilepsy. (no authors listed). Epilepsia 1997; 38: 1255-6.
3. Gaillard WD, Chiron C, Cross JH, Harvey AS, Kuzniecky R, Hertz-Pannier L, et al. Guidelines for imaging infants and children with recent-onset epilepsy. Epilepsia 2009; 50: 2147-53.
4. Jayakar P, Gaillard WD, Tripathi M, Libenson MH, Mathern GW, Cross JH. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia 2014; 55: 507-18.
5. Guidelines for neuroimaging evaluation of patients with uncontrolled epilepsy considered for surgery. Commission on Neuroimaging of the International League Against Epilepsy. (no authors listed). Epilepsia 1998; 39: 1375-6.
6. Cross JH, Jayakar P, Nordli D, Delalande O, Duchowny M, Wieser HG, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. Epilepsia 2006; 47: 952-9.
7. 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: 310-8.

8. Bell GS, de Tisi J, Gonzalez-Fraile JC, Peacock JL, McEvoy AW, Harkness WFJ, et al. Factors affecting seizure outcome after epilepsy surgery: an observational series. J Neurol Neurosurg Psychiatry 2017; 88: 933-40.
9. Bhatti L, Hoang JK, Dale BM, Bashir MR. Advanced magnetic resonance techniques: 3 T. Radiol Clin North Am 2015; 53: 441-55.
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: 1054-68.
11. 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: 1977-87.
12. 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: 770-6.
13. Mouthaan BE, Rados M, Boon P, Carrette E, Diehl B, Jung J, et al. Diagnostic value of interictal source imaging in presurgical epilepsy evaluation: A systematic review from the E-PILEPSY consortium. Clin Neurophysiol 2019; 130: 845-55.
14. Kobulashvili T, Kuchukhidze G, Brigo F, Zimmerman G, Höfler J, Leitinger M, et al. Diagnostic and prognostic value of noninvasive long-term video-electroencephalographic monitoring in epilepsy surgery: A systematic review and meta-analysis from the E-PILEPSY consortium. Epilepsia 2018; 59: 2272-83.

15. Schmid E, Thomschewski A, Taylor A, Zimmerman G, Kirschner M, Kobulashvili T, et al. Diagnostic value of functional magnetic resonance imaging, Wada test, magnetoencephalography, and functional transcranial Doppler sonography for memory and language outcome after epilepsy surgery: A systematic review. Epilepsia 2018; 59: 2305-17.
16. ERN EpiCARE. About the e-pilepsy project [Internet]. ERN EpiCARE [cited 2021 Aug 8]. Available from: https://epi-care.eu/therapeutics/e-pilepsy/.
17. PRISMA. PRISMA 2020 Checklist [Internet]. Prisma; 2020 [cited 2021 Aug 8]. Available from: http://www.prisma-statement.org/.
18. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic value studies. Ann Intern Med 2011; 155: 529-36.
19. Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the Gap between Methodologists and End-Users: R as a Computational Back-End. Journal of Statistical Software 2012; 59: 1-15.
20. Rubinger L, Chan C, D'Arco F, Moineddin R, Muthaffar O, Rutka JT, et al. Change in presurgical diagnostic imaging evaluation affects subsequent pediatric epilepsy surgery outcome. Epilepsia 2016; 57: 32-40.
21. Colon AJ, Osch MJPV, Buijs M, Grond JVD, Hilleband A, Schijns O, et al. MEG-guided analysis of 7 T-MRI in patients with epilepsy. Seizure 2018; 60: 29-38.
22. Feldman RE, Delman BN, Pawha PS, Dyvorne H, Rutland JW, Yoo J, et al. 7 T MRI in epilepsy patients with previously normal clinical MRI exams compared against healthy controls. PLoS One 2019; 14: e0213642.

23. Kwan BYM, Salehi F, Ohorodnyk P, Lee DH, Burneo JG, Mirsattari SM, et al. Usage of SWI (susceptibility weighted imaging) acquired at 7 T for qualitative evaluation of temporal lobe epilepsy patients with histopathological and clinical correlation: An initial pilot study. J Neurol Sci 2016; 369: 82-7.
24. 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 Invest Clin 2016; 68: 112-8.
25. Santyr BG, Goubran M, Lau JC, Kwan BYM, Salehi F, Lee DH, et al. Investigation of hippocampal substructures in focal temporal lobe epilepsy with and without hippocampal sclerosis at 7 T. J Magn Reson Imaging 2017; 45: 1359-70.
26. Zijlmans M, de Kort GA, Witkamp TD, Huiskamp GM, Seppenwoolde, JH, van Huffelen AC, et al. 3 T 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: 256-62.
27. Winston GP, Micallef C, Kendell BE, Bartlett PA, Williams EJ, Burdett JL, et al. The value of repeat neuroimaging for epilepsy at a tertiary referral centre: 16 years of experience. Epilepsy Res 2013; 105: 349-55.
28. Bartolini E, Cosottini M, Costagli M, Barba C, Tassi L, Spreafico R, et al. Ultra-High-Field Targeted Imaging of Focal Cortical Dysplasia: The Intracortical Black Line Sign in Type IIb. Am J Neuroradiol 2019; 40: 2137-42.
29. Hashiguchi K, Morioka T, Murakami N, Suzuki SO, Hiwatashi A, Yoshiura T, et al. Utility of 3-T FLAIR and 3D short tau inversion recovery MR imaging in the preoperative diagnosis of hippocampal sclerosis: direct comparison with 1.5-T FLAIR MR imaging. Epilepsia 2010; 51: 1820-8.
30. Liu T, Liang H, Cui J, Sun K, Zhang S, Yuan L, et al. Clinical Application of 7 T Magnetic Resonance Imaging in Patients with Focal Cortical Dysplasia IIa and Epilepsy. Stereotact Funct Neurosurg. 2020 Dec 11:1-9.

31. Knake S, Triantafyllou C, Wald LL, Wiggins G, Kirk GP, Larsson PG, et al. 3 T phased array MRI improves the presurgical evaluation in focal epilepsies: a prospective study. Neurology 2005; 65: 1026-31.
32. Phal PM, Usmanov A, Nesbit GM, Anderson JC, Spencer D, Wang P, et al. Qualitative comparison of 3-T and 1.5-T MRI in the evaluation of epilepsy. Am J Roentgenol 2008; 191: 890-5.
33. Veersema TJ, Ferrier CH, van Eijsden P, Gosselaar PH, Aronica E, Visser F, et al. Seven tesla MRI improves detection of focal cortical dysplasia in patients with refractory focal epilepsy. Epilepsia Open 2017; 2: 162-71.
34. Wang I, Oh S, Blümcke I, Coras R, Krishnan B, Kim S, et al. Value of 7 T MRI and post-processing in patients with nonlesional 3 T MRI undergoing epilepsy presurgical evaluation. Epilepsia. 2020 Nov;61(11):2509-20.
35. De Ciantis A, Barba C, Tassi L, Cosottini M, Tosetti M, Costagli M, et al. 7 T MRI in focal epilepsy with unrevealing conventional field strength imaging. Epilepsia 2016; 57: 445-54.
36. Nguyen DK, Rochette E, Leroux JM, Beaudoin G, Cossette P, Lassonde M, et al. Value of 3.0 T MR imaging in refractory partial epilepsy and negative 1.5 T MRI. Seizure 2010; 19: 475-8.
37. Strandberg M, Larsson EM, Backman S, Källén K. Pre-surgical epilepsy evaluation using 3 T MRI. Do surface coils provide additional information? Epileptic Disord 2008; 10: 83-92.
38. Ahmed R, Rubinger L, Go C, Drake JM, Rutka JT, Snead OC, et al. Utility of additional dedicated high-resolution 3 T MRI in children with medically refractory focal epilepsy. Epilepsy Res 2018; 143: 113-9.

39. Jack CR Jr, Rydberg CH, Krecke KN, Trenerry MR, Parisi JE, Rydberg JN, et al. Mesial temporal sclerosis: diagnosis with fluid-attenuated inversion-recovery versus spin-echo MR imaging. Radiology 1996; 199: 367-73.
40. Kim JH, Tien RD, Felsberg GJ, Osumi AK, Lee N, Friedman AH. Fast spin-echo MR in hippocampal sclerosis: correlation with pathology and surgery. Am J Neuroradiol 1995; 16: 627-36.
41. Kuzniecky RI, Bilir E, Gilliam F, Faught E, Palmer C, Morawetz R, et al. Multimodality MRI in mesial temporal sclerosis: relative sensitivity and specificity. Neurology 1997; 49: 774-8.
42. McBride MC, Bronstein KS, Bennett B, Erba G, Pilcher W, Berg MJ. Failure of standard magnetic resonance imaging in patients with refractory temporal lobe epilepsy. Arch Neurol 1998; 55: 346-8.
43. Meiners LC, van Gils A, Jansen GH, de Kort G, Witkamp TD, Ramos LM, t al. Temporal lobe epilepsy: the various MR appearances of histologically proven mesial temporal sclerosis. Am J Neuroradiol 1994; 15: 1547-55.
44. Tien RD, Felsberg GJ, Campi de Castro C, Osumi AK, Lewis DV, Friedman AH, et al. Complex partial seizures and mesial temporal sclerosis: evaluation with fast spin-echo MR imaging. Radiology 1993; 189: 835-42.
45. Von Oertzen J, Urbach H, Jungbluth S, Kurthen M, Reuber M, Fernández G, et al. Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy. J Neurol Neurosurg Psychiatry 2002; 73: 643-7.
46. Kantarci K, Shin C, Britton JW, Cascino GD, Jack CR Jr. Comparative diagnostic utility of 1H MRS and DWI in evaluation of temporal lobe epilepsy. Neurology 2002; 58: 1745-53.

47. Yoo SY, Chang KH, Song IC, Han MH, Kwon BJ, Lee SH, et al. Apparent diffusion coefficient value of the hippocampus in patients with hippocampal sclerosis and in healthy volunteers. Am J Neuroradiol 2002; 23: 809-12.
48. Veersema TJ, van Eijsden P, Gosselaar PH, Hendrikse J, Zwanenburg JJM, Spliet WGM, et al. 7 Tesla T2*-weighted MRI as a tool to improve detection of focal cortical dysplasia. Epileptic Disord 2016; 18: 315-23.
49. Lam J, Tomaszewski P, Gilbert G, Moreau JT, Guiot MC, Albrecht S, et al. The utility of arterial spin labeling in the presurgical evaluation of poorly defined focal epilepsy in children. J Neurosurg Pediatr. 2020 Dec 25:1-10.
50. Chen X, Qian T, Kober T, Zhang G, Ren Z, Yu T, et al. Gray-matter-specific MR imaging improves the detection of epileptogenic zones in focal cortical dysplasia: A new sequence called fluid and white matter suppression (FLAWS). Neuroimage Clin 2018; 20: 388-97.
51. Wang R, Li SY, Chen M, Zhou C. Diagnostic value of interictal diffusion-weighted imaging in evaluation of intractable temporal lobe epilepsy. Chin Med Sci J 2008; 23: 68-72.
52. Wehner T, Lapresto E, Tkach J, Liu P, Bingaman W, Prayson RA, et al. The value of interictal diffusion-weighted imaging in lateralizing temporal lobe epilepsy. Neurology 2007; 68: 122-7.
53. Eriksson SH, Rugg-Gunn FJ, Symms MR, Barker JG, Duncan JS. Diffusion tensor imaging in patients with epilepsy and malformations of cortical development. Brain 2001; 124: 617-26.
54. Assaf BA, Mohamed FB, Abou-Khaled KJ, Williams JM, Yazeij MS, Haselgrove J, et al. Diffusion tensor imaging of the hippocampal formation in temporal lobe epilepsy. Am J Neuroradiol 2003; 24: 1857-62.

55. Salmenpera TM, Simister RJ, Bartlett P, Symms MR, Boulby PA, Free SL, et al. High-resolution diffusion tensor imaging of the hippocampus in temporal lobe epilepsy. Epilepsy Res 2006; 71: 102-6.
56. Chen Q, Lui S, Li CX, Jiang LJ, Ou-Yang L, Tang HH, et al. MRI-negative refractory partial epilepsy: role for diffusion tensor imaging in high field MRI. Epilepsy Res 2008; 80: 83-9.
57. Rugg-Gunn FJ, Eriksson SH, Symms MR, Barker GJ, Duncan JS. Diffusion tensor imaging of cryptogenic and acquired partial epilepsies. Brain 2001; 124: 627-36.
58. Thivard L, Bouilleret V, Chassoux F, Adam C, Dormont D, Baulac M, et al. Diffusion tensor imaging can localize the epileptogenic zone in nonlesional extra-temporal refractory epilepsies when [(18)F]FDG-PET is not contributive. Epilepsy Res 2011; 97: 170-82.
59. Theysohn JM, Kraff O, Maderwald S, Schlamann MU, de Greiff A, Forsting M, et al. The human hippocampus at 7 T--in vivo MRI. Hippocampus 2009; 19: 1-7
60. Xue H, Cai L, Dong S, Li Y. Clinical characteristics and post-surgical outcomes of focal cortical dysplasia subtypes. J Clin Neurosci 2016; 23: 68-72.
61. Yao K, Duan Z, Zhou J, Li L, Zhai F, Dong Y, et al. Clinical and immunohistochemical characteristics of type II and type I focal cortical dysplasia. Oncotarget 2016; 7: 76415-22.
62. Najm IM, Sarnat HB, Blümcke I. Review: The international consensus classification of Focal Cortical Dysplasia - a critical update 2018. Neuropathol Appl Neurobiol 2018; 44: 18-31.
63. Zhang C, Kwan P. The Concept of Drug-Resistant Epileptogenic Zone. Front Neurol 2019; 10: 558.

64. Awad IA, Rosenfeld J, Ahl J, Hahn JF, Lüders H. Intractable epilepsy and structural lesions of the brain: mapping, resection strategies, and seizure outcome. Epilepsia 1991; 32: 179-86.

Figures and tables

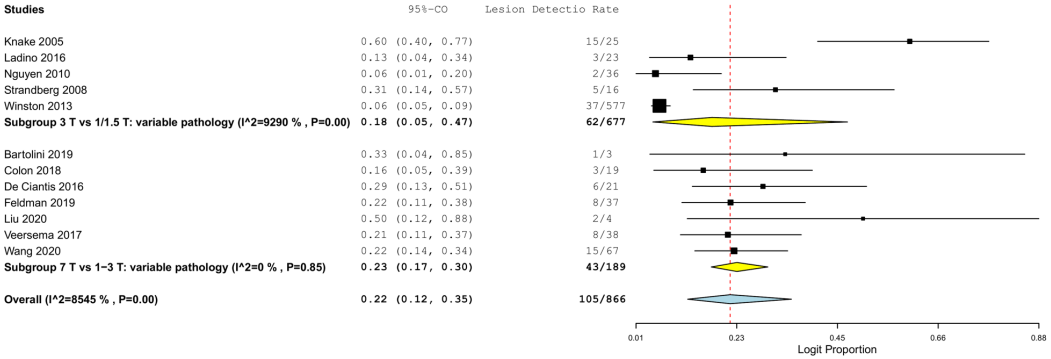
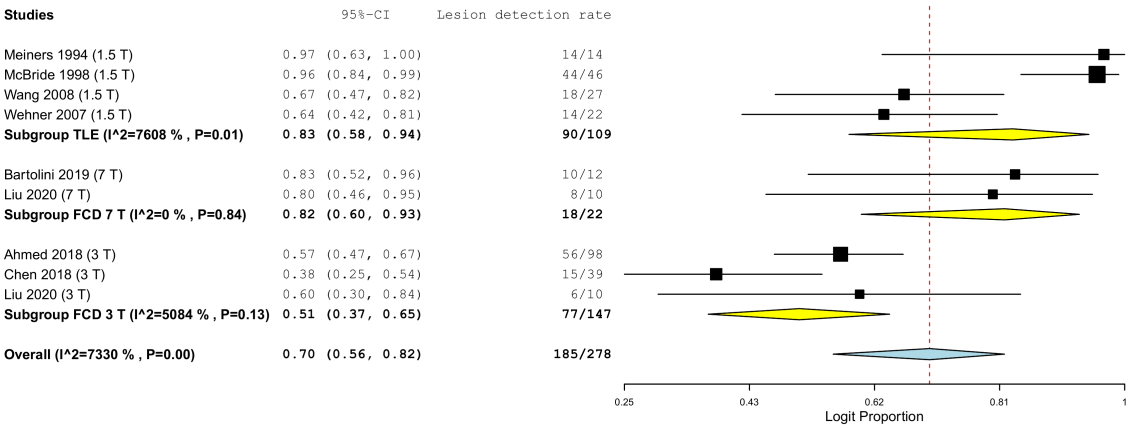
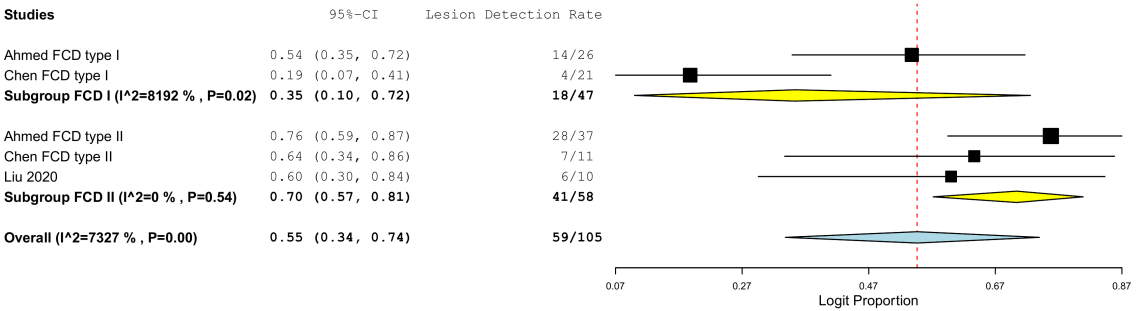


Figure 1: Forest plot of additional lesion detection rate with higher field strength


Studies
95%-CI
Lesion detection rate
Meiners 1994 (1.5 T) 0.97 (0.63, 1.00) 14/14
McBride 1998 (1.5 T) 0.96 (0.84, 0.99) 44/46
Wang 2008 (1.5 T) 0.67 (0.47, 0.82) 18/27
Wehner 2007 (1.5 T) 0.64 (0.42, 0.81) 14/22
Subgroup TLE (I^2=7608 % , P=0.01) 0.83 (0.58, 0.94) 90/109
Bartolini 2019 (7 T) 0.83 (0.52, 0.96) 10/12
Liu 2020 (7 T) 0.80 (0.46, 0.95) 8/10
Subgroup FCD 7 T (I^2=0 % , P=0.84) 0.82 (0.60, 0.93) 18/22
Ahmed 2018 (3 T) 0.57 (0.47, 0.67) 56/98
Chen 2018 (3 T) 0.38 (0.25, 0.54) 15/39
Liu 2020 (3 T) 0.60 (0.30, 0.84) 6/10
Subgroup FCD 3 T (I^2=5084 % , P=0.13) 0.51 (0.37, 0.65) 77/147
Overall (I^2=7330 % , P=0.00) 0.70 (0.56, 0.82) 185/278
0.25
0.43
0.62
0.81
1
Logit Proportion


Studies
95%-CI
Lesion Detection Rate
Ahmed FCD type I 0.54 (0.35, 0.72) 14/26
Chen FCD type I 0.19 (0.07, 0.41) 4/21
Subgroup FCD I (I^2=8192 % , P=0.02) 0.35 (0.10, 0.72) 18/47
Ahmed FCD type II 0.76 (0.59, 0.87) 28/37
Chen FCD type II 0.64 (0.34, 0.86) 7/11
Liu 2020 0.60 (0.30, 0.84) 6/10
Subgroup FCD II (I^2=0 % , P=0.54) 0.70 (0.57, 0.81) 41/58
Overall (I^2=7327 % , P=0.00) 0.55 (0.34, 0.74) 59/105
0.07
0.27
0.47
0.67
0.87
Logit Proportion

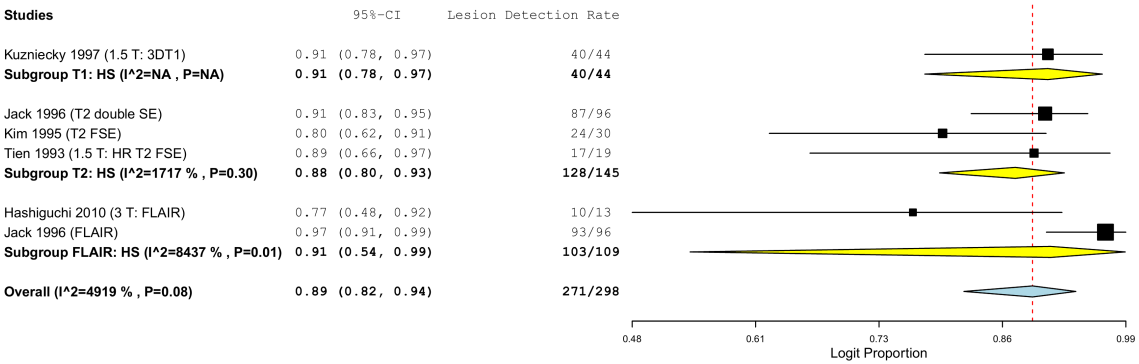

Studies
95%-CI
Lesion Detection Rate
Kuzniecky 1997 (1.5 T: 3DT1) 0.91 (0.78, 0.97) 40/44
Subgroup T1: HS (I^2=NA , P=NA) 0.91 (0.78, 0.97) 40/44
Jack 1996 (T2 double SE) 0.91 (0.83, 0.95) 87/96
Kim 1995 (T2 FSE) 0.80 (0.62, 0.91) 24/30
Tien 1993 (1.5 T: HR T2 FSE) 0.89 (0.66, 0.97) 17/19
Subgroup T2: HS (I^2=1717 % , P=0.30) 0.88 (0.80, 0.93) 128/145
Hashiguchi 2010 (3 T: FLAIR) 0.77 (0.48, 0.92) 10/13
Jack 1996 (FLAIR) 0.97 (0.91, 0.99) 93/96
Subgroup FLAIR: HS (I^2=8437 % , P=0.01) 0.91 (0.54, 0.99) 103/109
Overall (I^2=4919 % , P=0.08) 0.89 (0.82, 0.94) 271/298
0.48
0.61
0.73
0.86
0.99
Logit Proportion

Figure 2: Forest plot of epilepsy protocol and standard MRI sequences lesion detection rate. a: epilepsy-specific MRI protocol, data presented separately for TLE and FCD subgroups; b: epilepsy-specific MRI protocol, data from figure a presented separately for FCD type I and type II (3 T); c: separate standard sequences for patients with HS.

Table 1: MRI field strength lesion detection rate with clinical diagnosis or histopathology as reference standard

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

Liu 2020	Epilepsy patients with a pathologic confirmation of FCD IIa	7 T versus 3 T	60% (6/10)	80% (8/10)	50% (2/4)
Veersema 2017	Epilepsy surgery candidates, suspicion of FCD, with negative 1-3 T MRI or suspected of dual pathology	7 T versus 1-3 T[n]	5.0% (2/40)[o]	25% (10/40)	21% (8/38)[p]
Wang 2020	Epilepsy surgery candidates with negative 3 T MRI	7 T versus 3 T	0.0% (0/67)	22% (15/67)	22% (15/67)
		TLE, variable pathology. 7T versus 1.5 T			
Kwan 2016	Epilepsy surgery candidates with TLE	7 T versus 1.5 T	85% (9/13)	92% (8/13)	NA[q]
Santyr 2017	Epilepsy surgery candidates with TLE	7 T versus 1.5 T	31% (4/13)	77% (10/13)	67% (6/9)

[a] In accordance with the study results, two patients with indeterminate 3 T results were not included as positive MRI results
[b] Patients underwent repeated imaging with both 1.5 T and 3 T
[c] Non-specific abnormalities on 1.5 T 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 3 T MRI. The one patient with a new lesion on 7 T had previously undergone 3T
[k] Two patients with negative 7 T MRI had FCD type Ib
[l] 14/21 (67%) underwent 3 T MRI. Of the 6 patients with a new lesion on 7 T, 3 had previously undergone 3 T
[m] 13/37 (35%) underwent 3 T MRI. Of the 8 patients with a new lesion on 7 T, 4 had previously undergone 3 T
[n] 35/40 (88%) underwent 3 T MRI. Of the 8 patients with a new lesion on 7 T, all had previously undergone 3 T
[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, 7 T MRI confirmed the dual pathology
[q] In patients who were already positive on 1.5 T MRI for another lesion, three additional abnormal 7 T MRI findings which were not detected by the clinical 1.5 T MRI were found

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 2002	Focal epilepsy surgical candidates, operated, variable pathology	Basic head MRI[a]	-	40% (36/90)
		All sequences combined (1.5 T): - 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)	-	89% (80/90)
Focal epilepsy, FCD				
Ahmed 2018	Children with medically refractory epilepsy, FCD suspected, operated[b]	All sequences combined (standard epilepsy protocol) (3 T): - 3D T1 - FLAIR (cor+ax) - PD/T2 (cor+ax)	-	57% (56/98)[c]
		All sequences combined (dedicated HR MRI) (3 T): - FLAIR (cor+ax) - PD/T2 (cor+ax)	-	87% (85/98)[d]
Bartolini 2019	Patients with focal epilepsy who underwent surgery and had a histopathologic diagnosis of FCD	All sequences combined (7 T): -3DT1 -3D FLAIR -3D SWAN (+targeted SWAN) -2D T2* -2D T2 FSE -2D targeted gray-white matter border FSE-IR	-	83% (10/12)[e]
Chen 2018	Patients with pathologically confirmed FCD with surgical outcome Engel 1-2[f]	3D FLAIR (sag) (3 T)	-	47% (8/17)[g]
		All sequences combined (3 T): -FLAIR (cor+ax) -T1 (ax) -T2 (ax)	-	39% (15/39)[h]

		-DWI (ax)		
Liu 2020	Patients with pathologically confirmed FCD IIa	All sequences combined (3 T): -3D T1 MPRAGE -2D T2 TSE -2D T2-FLAIR	-	60% (6/10)
		All sequences confined (7 T): -3D T1 MPRAGE -2D T2 TSE -3D T2 FLAIR -SWI -WMS -GWB	-	80% (8/10)
		HS		
Hashiguchi 2010	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) (1.5/3 T)	-Atrophy -Signal change	77% (10/13) 69% (9/13)
		-3D STIR (parallel to long axis of hippocampus) (3 T)	-Signal change	69% (9/13)
Jack 1996	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 1995	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 1997	Patients with TLE who underwent temporal lobe resection with pathological confirmation of HS	-3DT1 (1.5 T)	-Hippocampal atrophy	91% (40/44)
		-T1 IR (perpendicular to the long axis of hippocampus) (1.5 T)	-Signal change	86% (38/44)
Meiners 1994	Patients with TLE who underwent temporal lobe resection with pathological confirmation of HS	All sequences combined (1.5 T): - 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 1993	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) (1.5 T)	-Hippocampal atrophy -Signal abnormality -Signal change + hippocampal atrophy	84% (16/19) 84% (16/19) 90% (17/19)
		TLE, variable pathology		
McBride 1998	Patients with TLE who underwent temporal lobe resection with variable pathology with MRI from primary center and tertiary center both available	All sequences combined (1.5 T): -T1 (cor)	-	96% (44/46)

		-T2 (cor)		
Wang 2008	Patients with TLE who had undergone temporal lobe resection with with variable pathology[i]	All sequences combined (1.5 T): - T1 FLAIR (ax+sag) - T2 FSE (cor+ax) - T2 FLAIR (ax)	-Hippocampal atrophy AND T2 signal change	67% (18/27)
Wehner 2007	Patients with TLE who had undergone temporal lobe resection with with variable pathology[j]	All sequences combined (1.5 T)	-Hippocampal atrophy	64% (14/22)

[a] Not epilepsy specific protocol and performed outside epilepsy center
[b] Proven in 63/98. Type I FCD in 26/63 and Type II FCD in 37/63
[c] Lesion detection rate in Type I FCD was (14/26) 54%, in Type II FCD (28/37) 76%
[d] Lesion detection rate in Type I FCD was (22/26) 85%, in Type II FCD (36/37) 97%
[e] Lesion detection rate in 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 in Type I FCD was (3/10) 30%, in Type II FCD (2/2) 100%, in type III (3/5) 60%
[h] Lesion detection rate in Type I FCD was (4/21) 19%, in Type II FCD (7/11) 64%, in type III (4/7) 57%
[i] HS 15/27
[j] HS 9/22

Table 3: Additional MRI sequences lesion detection rate 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 in MRI-negatives on conventional MRI = *diagnostic advantage sequence*	Lesion on conventional MRI, but not on sequence
TLE							
Kantarci 2002 (1.5 T)	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 2016 (7 T)	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 2008 (1.5 T)	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 2007 (1.5 T)	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 2002 (1.5 T)	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 2020 (3 T)	Pediatric 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
			FCD				
Chen 2018 (3 T)	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 2016 (7 T)	Patients with histologically confirmed FCD in all[j], either MRI negative on 3 T 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 1.5 T 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 in 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 in Type I FCD was (1/1) 100%, in Type II (2/4) 50%, in mild MCD (1/1) 100%

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-negatives	Lesions on conventional MRI not detected by DTI	Number of patients with irrelevant DTI abnormality[b]
Assaf 2003	Patients with unilateral TLE	8/12	Lat	Asymmetry index[c]	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 2008	Patients with refractory focal epilepsy who were conventional MRI negative	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 2001	Patients with focal epilepsy and suspect 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 conventional MRI-negatives	32% (7/22)	27% (6/22)
					MD↑ total correct	46% (10/22) 36% (8/22)	No conventional MRI-negatives	64% (14/22)	41% (9/22)
Rugg-Gunn 2001	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)
Salmenpera 2006	Patients with unilateral TLE	6/7	Lat	Asymmetry index[d]	FA↓ *total*	0.0% (0/7)	0.0% (0/1)	100% (6/6)	0.0% (0/7)

					correct	0.0% (0/7)	0.0% (0/1)		
					MD↑	100% (7/7)		0.0% (0/6)	14% (1/7)[e]
					total		100% (1/1)		
					correct	86% (6/7)	0.0% (0/1)		
Thivard 2011	Patients with refractory epilepsy who were conventional MRI negative, all underwent sEEG	0/20	Loc	Voxel-based analysis with healthy control group using SPM	TLE+eTLE			All MRI negative	40% (8/20)
					MD↑	60% (12/20)			
					total		60% (12/20)		
					correct	40% (8/20)	40% (8/20)		
					TLE			All MRI negative	39% (5/13)
					MD↑	39% (5/13)			
					total		39% (5/13)		
					correct	15% (2/13)	15% (2/13)		
					eTLE			All MRI negative	42% (3/7)
					MD↑	100% (7/7)			
					total		100% (7/7)		
					correct	86% (6/7)	86% (6/7)		

[a] total: all found lesions; correct: corresponding to the location of the epileptogenic lesion based on the reference standard

[b] this also includes 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 sided abnormal