



PRESURGICAL FOCUS LOCALIZATION IN EPILEPSY

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Presurgical focus localization in epilepsy

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Presurgical focus localization in epilepsy

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CHAPTER 1

General introduction, aims and thesis outline

Introduction

Epilepsy surgery

Epilepsy is one of the most common neurological diseases. It is characterized by an enduring predisposition to generate epileptic seizures. Worldwide, the overall life time prevalence is 7.60 per 1,000 persons¹. Epilepsy has a damaging effect on social, physical and psychological wellbeing. Anti-seizure drugs are the mainstay of seizure treatment. In approximately 30-40% of focal epilepsy patients seizures are insufficiently controlled with anti-seizure medication. In such pharmacoresistant – or ‘refractory’ – focal epilepsy patients surgery is considered. Success of surgery is based primarily on adequate seizure control but neuropsychological development, neurological deficits, quality of life and psychosocial adjustment are also important outcome measures. A recent Cochrane systematic review found an average proportion of good surgical outcome after one year in 64% of patients, with a between-study range of 13.5-92.5%². Patients’ cognitive functioning remains stable over many years following surgery, with a chance of cognitive improvement when seizures are well-controlled and anti-seizure drugs are reduced³. In 76% of patients clinically important improvement in quality of life is achieved one year after surgery⁴, particularly when complete seizure-freedom is reached⁵.

The presurgical workup

Epilepsy surgery is based on the premise that a focal brain area is responsible for generating seizures. This so-called epileptogenic zone (EZ) is a theoretical construct, defined as the minimum amount of cortex that must be resected to give seizure freedom⁶. Success of surgery depends on adequate EZ identification. Pre-surgical evaluation aims to identify potential candidates for surgery and determine the surgical approach. Moreover, it determines which patients are not expected to benefit from surgery and should be rejected. During this pre-surgical trajectory the EZ is delineated, and its relationship with eloquent brain areas is established. This process involves the use of numerous imaging and neurophysiological diagnostic methods (figure 1.1). Usually this starts with an attempt to identify structural abnormalities using magnetic resonance imaging (MRI), and interpreting semiological and neurophysiological biomarkers by means of long-term monitoring with video-EEG (LTM-VEEG). After this initial workup, a collective comprehensive analysis of diagnostic data is performed during a multidisciplinary team conference. In case of an uncertain EZ hypothesis – due to indeterminate, non-localizing, discordant or incongruent results – additional evaluation with ancillary tests may be indicated with subsequent multidisciplinary team discussions. Ancillary tests include noninvasive techniques such as non-standard MRI sequences, fluorodeoxyglucose–positron emission tomography (FDG-PET), hexamethylpropylene amine oxime (HMPAO)/ethylcysteinate dimer (ECD) single photon-emission computed tomography (SPECT), magnetoencephalography (MEG), electric or magnetic source localization or imaging (MSI, ESI), and post-processing

techniques. Invasive procedures, such as extra-operative invasive EEG monitoring with stereotactic depth electrodes or subdural grid electrodes, may be performed in a later stage of the presurgical workup. Wada testing, functional MRI, or diffusion tensor imaging (DTI) are techniques that are used to map eloquent areas that may be at risk for surgical damage. Although no single modality provides a full portrait of the EZ, their collective information can form a sufficient base to determine the surgical target area⁶. Also, a re-review of previous individual diagnostic test results in light of newly acquired information from clinical and diagnostic tests is often done during multidisciplinary team conferences, to optimize the localizing value of the diagnostic data. When there is certainty regarding the EZ location patients may undergo disconnection or resection of the presumed EZ, sometimes with the use of intra-operative electrocorticography (ECoG) to tailor the surgical strategy.

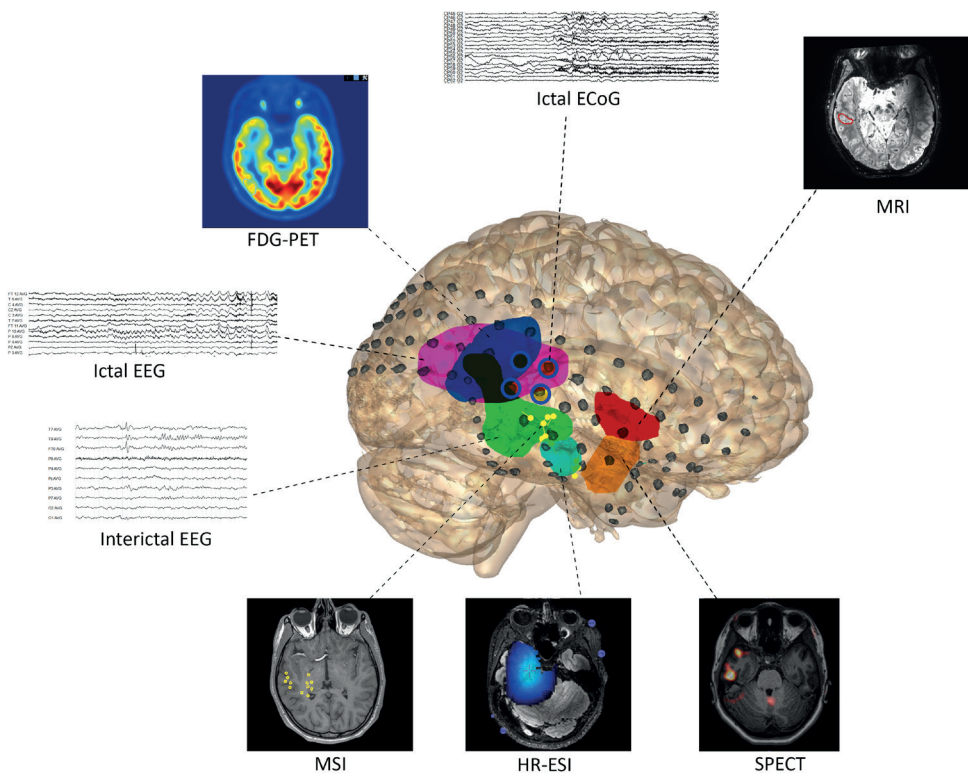


Figure 1.1. Illustrative example of the various diagnostic techniques involved in epileptogenic zone localization. ECoG: electrocorticography; EEG: electroencephalography; FDG-PET: fluorodeoxyglucose–positron emission tomography; HR-ESI: high-resolution electric source imaging; MRI: magnetic resonance imaging; MSI: magnetic source imaging; SPECT: single photon-emission computed tomography. Diagnostic test results are presented as reviewed during the multidisciplinary team conference with the dashed line connecting to the representative area in the centrally located 3D brain model. Each colored entity in the 3D brain reflects the presumed epileptic source as estimated by interictal EEG (green area), ictal EEG (purple area), MSI (yellow dots), HR-ESI (cyan area), MRI (red area), SPECT (orange area), FDG-PET (blue area) and ictal ECoG (blue circles surrounding grey dots). Grey dots represent the ECoG electrodes covering a large brain region that is suspected to include the epileptogenic zone (Figure courtesy of Nicole van Klink, University Medical Center Utrecht).

Presurgical diagnostic tests: which, when and how?

The large number of different available diagnostic methodologies raises the question how the presurgical workup should be organized. The answer to this question is not simple as was demonstrated by Jayakar and coworkers⁷. A broad-based global panel of experts was unable to agree upon the utility of almost all diagnostic tests. Only for three modalities unanimous agreement was achieved: MRI, interictal EEG and LTM-VEEG were considered mandatory or strongly recommended⁷. With MRI and neurophysiological techniques being the only modalities with undisputed utility, interest may be directed into adequate implementation and optimization of these – broadly accepted – techniques in order to improve presurgical workup.

Adequate implementation may focus on each method's technical specifics. However, the few available recommendations and guidelines on MRI reveal that consensus on specific sequences and protocols has not been reached⁸⁻¹¹. Published EEG guidelines and recommendations mostly focus on electro-diagnostic facilities such as personnel and in-hospital safety procedures, because technical and methodological aspects have been largely matured^{12, 13}. Therefore, recommendations are limited to aspects of data handling, seizure-provocation methods, software packages with spike and seizure detection functionality, and prevention of postoperative infections or other complications in patients studied with intracranial electrodes^{12, 13}. Potential for workup optimization may lie in the use of combinations of different techniques. MRI and neurophysiological data can be combined by means of electric or magnetic source imaging which includes an additional mathematical procedure for increased epileptic source localization accuracy. As an alternative to combining ordinary data, research may also focus on novel strategies where new diagnostic information is actively sought – rather than passively acquired – by means of single pulse electrical stimulation. Further background about these methods will be addressed in detail in the following subsections.

Magnetic resonance imaging

Magnetic resonance imaging is considered the driving force in the presurgical epilepsy workup. MRI identifies structural brain abnormalities in patients. Some of these abnormalities disrupt cortical or hippocampal integrity and give rise to epileptic seizures. Common abnormalities associated with epileptic seizures are hippocampal sclerosis, developmental tumors, ischemic or hemorrhagic brain lesions and cavernomas, and a large group of malformations of cortical development, such as focal cortical dysplasia and tubers. The identification of an epileptogenic lesion with MRI significantly increases the chance of postoperative seizure-freedom with an odds ratio of 2.5^{14, 15}. Whether epileptogenic lesions are detected depends on the quality of the applied MRI technique and its interpretation. Technological 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 and potentially lead to improved detection rates of structural brain lesions. Of these, MR field strength and specific MR sequences used are considered to contribute most to lesion detection sensitivity and accuracy.

Higher field strength results in higher signal-to-noise ratio, contrast-to-noise ratio and spectral resolution that fundamentally facilitates higher spatial and temporal image resolution. However, full realization of these benefits is hampered by technological limitations that include field inhomogeneity and necessity for improved gradient and radiofrequency array coil performance. Moreover, at high field strength there is a change in relaxation kinetics resulting in lower contrast and signal-to-noise ratio and there is enhancement of susceptibility artifacts¹⁶. Sequence selection establishes a variety of images, each with a different focus on certain tissue properties and anatomy, such as gyral pattern, gray-white matter differentiation, and vascular abnormalities. Advanced post-processing techniques – including hippocampal volumetry, statistical parametric mapping, voxel-based morphometry and curvilinear reformatting – can be used as a final attempt to uncover a so far unrevealed lesion^{17,18}.

Electroencephalography and source imaging

Electroencephalography (EEG) is another cornerstone in epilepsy diagnosis and surgical evaluation. EEG records electric signal changes from synchronous excitation of a large number of neurons. In epilepsy such signal changes can be observed during seizure periods (ictal) or between seizure periods (interictal). Long-term monitoring with video EEG (LTM-VEEG) enables the capture of seizures and corresponding ictal EEG data during a recording period of several days. Localizing information from seizure semiology is reflected in the so-called symptomatogenic zone and ictal EEG data translates to the so-called ictal onset zone⁶. A disadvantage of LTM-VEEG is that one needs to wait until seizures occur. Furthermore, it requires hospital admission and intensive supervision from a nurse or specialist, although there are some early developments with respect to home monitoring¹⁹. Standard EEG recordings of 30 minutes are not focused on seizure data but aim to capture interictal epileptiform discharges. The brain area covered by the electrodes showing interictal epileptic activity is defined as the irritative zone⁶. EEG offers a high temporal resolution but limited spatial resolution due to volume conduction of electric currents. This makes LTM-VEEG alone not sufficiently accurate – as reflected by a moderate sensitivity and low specificity – for identification of the epileptogenic zone²⁰.

High resolution electric source imaging (HR-ESI) and magnetic source imaging (MSI), the magnetic counter-part of ESI using magnetoencephalographic (MEG) data, are additional electrophysiological methods using 64-350 sensors for non-invasive interictal localization of epileptogenic regions. By reconstructing the electric or magnetic potentials as identified

by EEG or MEG, locations of underlying source currents are estimated and subsequently combined with structural imaging. Patients undergoing HR-ESI are able to move around freely; MSI requires a patient to lay still in the MEG device thus making it less suitable for young children. Although source imaging is historically based on interictal epileptic activity, ictal source imaging is also possible and is currently receiving growing interest. Nevertheless its main focus is still directed to interictal source imaging and each year, several reviews and opinion papers are published as its role within the presurgical workup is not fully established.

Single pulse electrical stimulation

In selected surgical candidates chronic intracranial EEG evaluation is needed to better delineate a presumed EZ. Recordings mainly focus on the identification of the SOZ, which requires capture of seizures. Waiting for seizures may result in a recording duration of days to weeks and successful monitoring often requires the withdrawal of anti-seizure medication – with its associated risk of serious medical complications. Single pulse electrical stimulation (SPES) offers an alternative in that it actively probes the covered brain in the interictal state with brief electrical pulses of 1 ms duration to evoke responses across different frequency bands²¹⁻²³. Some of these responses have been suggested to serve as biomarkers for the epileptogenic region, since they are associated with the SOZ and the resected area in good-surgical outcome patients²¹⁻²³. Delayed responses – both low and high frequency oscillations – have shown most value as clinical biomarker of epileptic tissue. The appearance of early responses is considered a physiological phenomenon of effective connectivity²⁴. However, higher amplitude early responses are observed when stimulated in the seizure onset zone, suggesting that these may also reflect an increased excitability of the epileptogenic cortex²⁵. This opens opportunity for further exploration of the use of early responses in the EZ delineation.

Aims and thesis outline

The overall aim of the studies described in this thesis was to improve our knowledge of presurgical diagnostic approaches in epilepsy surgery by evaluating the use and accuracy of current and novel diagnostic methods for focus localization. Specifically, we aimed to determine the clinical practice of presurgical epilepsy workup approaches across Europe; to review the evidence-base for the detection of epileptogenic lesions with MRI and for the localization of the epileptic source with electric and magnetic source imaging; to describe the application of high-resolution electric source imaging in a specific subgroup of surgical candidates, those with tuberous sclerosis complex; and to further explore the use of invasive single pulse electrical stimulation (SPES) techniques.

With the survey reported in **chapter 2** we investigated which diagnostic imaging, post-processing, and electromagnetic source imaging techniques are currently used by the centers that are member of a large European epilepsy surgery consortium – the pilot European Reference Network E-PILEPSY. We determined to what extent these methods related to available guidelines and practice recommendations.

In **chapters 3 and 4**, we present systematic literature reviews to provide the best available evidence of diagnostic accuracy and value of two major presurgical investigations. The study described in **chapter 3** addressed the diagnostic value and potential of higher field strength MRI and specific MRI sequence selection to detect and localize epileptogenic lesions of interest in epilepsy surgery candidates. The literature was systematically reviewed and meta-analyses were performed, when possible. **Chapter 4** focusses on the diagnostic value of interictal HR-ESI and MSI to detect the epileptogenic zone in surgical candidates. A critical appraisal of previously published studies enabled the calculation of summary sensitivity and specificity estimates – reflecting diagnostic accuracy – of both techniques.

Chapter 5 reports on a retrospective analysis of the diagnostic accuracy and clinical value of HR-ESI in a rare subset of surgery candidates; tuberous sclerosis complex. In this particular cohort of patients, inherently having multiple potentially epileptogenic brain lesions, we compared the localizing value of HR-ESI with that of seizure semiology and interictal and ictal LTM-VEEG results. Finally, **chapter 6** describes how we explored the use of SPES as a novel tool to identify and localize on-demand the epileptogenic cortex during interictal state in patients who underwent chronic subdural grid monitoring as part of their presurgical evaluation.

Chapter 7 provides a summary of the work presented in this thesis. **Chapter 8** provides a general discussion of our findings and recommendations for future research.

CHAPTER 2

Current use of imaging and electromagnetic source localization procedures in epilepsy surgery centers across Europe

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Objective

In 2014 the European Union–funded E-PILEPSY project was launched to improve awareness of, and accessibility to, epilepsy surgery across Europe. We aimed to investigate the current use of neuroimaging, electromagnetic source localization, and imaging postprocessing procedures in participating centers.

Methods

A survey on the clinical use of imaging, electromagnetic source localization, and postprocessing methods in epilepsy surgery candidates was distributed among the 25 centers of the consortium. A descriptive analysis was performed, and results were compared to existing guidelines and recommendations.

Results

Response rate was 96%. Standard epilepsy magnetic resonance imaging (MRI) protocols are acquired at 3 Tesla by 15 centers and at 1.5 Tesla by 9 centers. Three centers perform 3T MRI only if indicated. Twenty-six different MRI sequences were reported. Six centers follow all guideline-recommended MRI sequences with the proposed slice orientation and slice thickness or voxel size. Additional sequences are used by 22 centers. MRI postprocessing methods are used in 16 centers. Interictal positron emission tomography (PET) is available in 22 centers; all using 18F-fluorodeoxyglucose (FDG). Seventeen centers perform PET postprocessing. Single-photon emission computed tomography (SPECT) is used by 19 centers, of which 15 perform postprocessing. Four centers perform neither PET nor SPECT in children. Seven centers apply magnetoencephalography (MEG) source localization, and nine apply electroencephalography (EEG) source localization. Fourteen combinations of inverse methods and volume conduction models are used.

Conclusion

We report a large variation in the presurgical diagnostic workup among epilepsy surgery centers across Europe. This diversity underscores the need for high-quality systematic reviews, evidence-based recommendations, and harmonization of available diagnostic presurgical methods.

Introduction

In January 2014 the European Union–funded E-PILEPSY project was launched, with the primary aim of improving awareness and accessibility of epilepsy surgery across Europe. E-PILEPSY has established a consortium of 25 epilepsy surgery centers with the goal of increasing the number of patients in Europe cured of their refractory epilepsy by improving delivery of optimal epilepsy surgery (<http://www.e-pilepsy.eu/>).

Harmonization and improvement of presurgical tools and diagnostic procedures are important aims of the project. A first objective was to gain insight into presurgical diagnostic procedures across participating centers, specifically magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), corresponding postprocessing methods, and electromagnetic source localization.

Only few recommendations on the use and specifications of these techniques for presurgical evaluation are available in the English-language literature. MRI is considered mandatory as a primary imaging modality²⁶. Although consensus among experts has not been reached on specific protocols, all recommendations include an anatomic three-dimensional (3D) T_1 -weighted gradient-recalled-echo, axial and coronal T_2 -weighted sequences, and axial and coronal fluid-attenuated inversion recovery (FLAIR). For 3D T_1 , voxel size should not exceed 1 mm. For T_2 and FLAIR, slice thickness should not exceed 3 mm^{7–11}.

It is recommended that pediatric epilepsy specialist units have access to interictal PET and/or ictal SPECT²⁶. F18-fluorodeoxyglucose (FDG)–PET is considered most valuable for so-called “MRI negative” patients or in cases of nonspecific abnormalities. Co-registration with MRI is highly recommended, and (semi)quantitative analysis—such as left-to-right asymmetry indices and statistical parametric mapping (SPM) analysis—is acknowledged as useful²⁷. Ictal SPECT should be compared with interictal SPECT to detect subtle changes. Co-registration with MRI, Subtraction Ictal SPECT CO-registered to MRI (SISCOM), and statistical comparisons are recognized to improve results^{27,28}.

Electromagnetic source localization, using MEG or EEG data, has been recognized as a useful and accurate clinical tool awaiting further validation^{26,29–31}. Official epilepsy-specific guidelines on electromagnetic source localization are lacking, but there are several general recommendations on hardware requirements and technique^{32–35}.

The aim of this study was to catalog the diagnostic imaging, postprocessing, and electromagnetic source localization techniques currently used by the E-PILEPSY centers, as a first step toward harmonization of presurgical assessment and diagnostic tools. In

addition, we investigated how the implementation of these methods relates to currently available guidelines and recommendations.

Methods

A survey was designed targeting the primary contacts of the E-PILEPSY consortium. This group consisted of neurologists, neurophysiologists, and neurosurgeons. When necessary, primary contact collaborators obtained additional and more detailed information from neuroradiologists, physicists, or researchers in their institution to complete the survey. The topics and corresponding number of queries included in the survey were the following: the standard MRI epilepsy protocol (7), additional MRI sequences and MRI postprocessing procedures (10), interictal PET (4), ictal SPECT (4), PET/SPECT postprocessing procedures (8), and EEG and MEG hardware and source localizations methods (38) (see supplementary data 2.1 for survey questions). Because this study does not include patient data, approval of the ethics board was not required.

All E-PILEPSY consortium centers were invited to provide data. Data were collected from January 2014 to May 2014. First results of this survey were discussed at a consortium meeting in June 2014, where it was decided to further refine the Supporting Information. An additional request was then sent to the centers with a summary of the information already supplied for verification. Additional questions were included on modality specifications, clinical indications, and patient group characteristics. These data were collected from June 2014 to July 2015. If data had omissions or errors, the responsible investigator of the corresponding center was contacted for clarification.

Data was processed using Microsoft Excel and IBM SPSS version 22.0 (IBM Corp, Armonk, NY, U.S.A.). Analysis was restricted to procedures performed for clinical purposes. First, the number of centers performing a certain procedure and a broad overview of indications were presented, separately for adult and pediatric populations where relevant. Second, data were evaluated in light of existing epilepsy-specific guidelines and recommendations. Standard MRI protocols reported by centers were compared with the MRI sequences included in most guidelines, as summarized in the introduction. The requirement to perform at least PET or SPECT (on site or by collaboration) as suggested in pediatric guidelines was evaluated for each center. Because there are no epilepsy-specific guidelines or recommendations on electromagnetic source localization, no comparison could be made.

Results

Response rate was 96% (24 centers). Twenty-one centers (88%) perform epilepsy surgery both in children and adults, two centers exclusively in adults, another exclusively in children.

Magnetic resonance imaging and postprocessing

Fifteen centers (63%) perform their standard MRI epilepsy protocol using a 3T MRI scanner. Nine centers use a 1.5T system; three of those perform additional sequences at 3T only in patients who are MRI negative at lower field strength. In one center, 7T MRI is available for clinical purposes.

Nineteen centers (79%) use identical MRI protocols for adults and children. Two centers include an additional sequence in the pediatric protocol: T_2 -weighted by one and T_1 -weighted inversion recovery by the other. The three remaining centers perform epilepsy surgery only on children or adults and inherently reported their protocols only for that specific population. A total of 26 different MRI sequences are used in the standard protocols. A general overview of these sequences is given in supplementary figure 2.1.

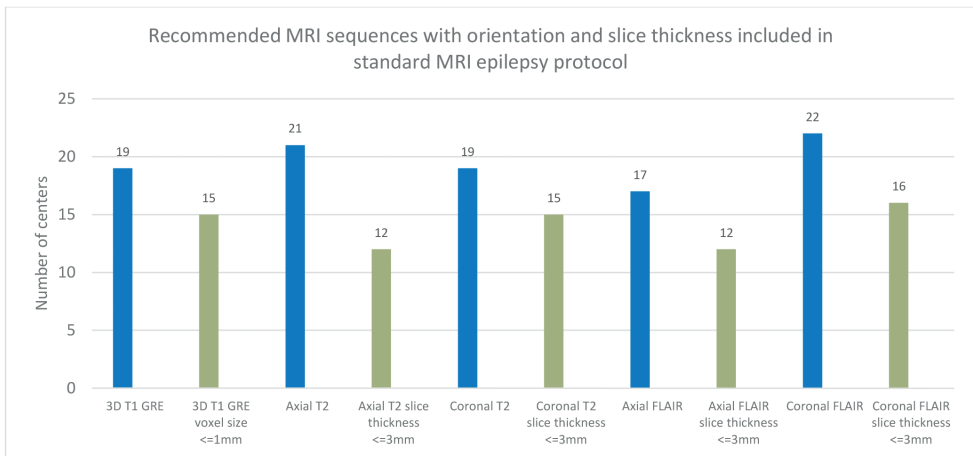


Figure 2.1. Number of centers that include guideline recommended MRI sequences with the correct slice orientation (blue bars), and recommended slice thickness/voxel size (olive green bars), in their standard MRI protocol. 2D type sequences also include 3D type sequences, as the former can be reconstructed from the latter.

Use of additional MRI sequences is reported by 22 centers; 21 perform these in adults and 19 in children (table 2.1). Sequences mostly comprise diffusion-based MR techniques (dMRI; primarily for the investigation of optic and pyramidal tracts) and fMRI (primarily for language and motor function). These sequences were reported to be indicated primarily when lesions, or the suspected epileptogenic zone, are in proximity to eloquent cortex.

Table 2.1. Use of additional MRI sequences on standard field strength in epilepsy surgery centers, subdivided into adult and pediatric populations

Use of additional MRI sequences	Total no. centers	% of total (n = 22)	No. centers for adult	% of total (n = 21)	No. centers for pediatric	% of total (n = 19)
fMRI	20	90	19	90	17	89
fMRI-language	18	82	17	81	13	68
fMRI-motor	18	82	17	81	15	79
fMRI-other (Visual, auditory, memory, emotion)	12	55	12	57	8	42
Diffusion-based MR techniques	15	68	14	67	12	63
Pyramidal tracts	12	55	11	52	9	47
Optic tracts	10	45	9	43	8	42
Arcuate fasciculus	6	27	5	24	5	26
Other	3	14	3	14	2	11
MR spectroscopy	5	23	5	24	4	21
Hemosiderin-sensitive sequence (SWI/T2*)	4	18	4	19	4	21
EEG-fMRI	3	14	2	9.5	2	11
3D T1	2	9	2	9.5	2	11
Higher field strength structural MRI at 3T	2	9	1	4.8	2	11
Higher field strength structural MRI at 7T	1	4.5	1	4.8	1	5.3
Surface coil imaging	1	4.5	1	4.8	1	5.3
T2 PROPELLER	1	4.5	1	4.8	0	0
T1 SPAIR/IR	1	4.5	1	4.8	1	5.3

Sixteen centers (67%) apply MRI postprocessing, which is outsourced to other centers by four. Fourteen centers use postprocessing in adults and nine in children, for the purpose of clinical care or scientific research. Eight centers have the ability to perform morphometric analysis³⁶. Two of those centers use hippocampal volumetry and one center also performs volumetry of the cortex. Another center performs quantitative analysis of FLAIR signal to distinguish between unilateral and bilateral hippocampal abnormalities, whereas another uses its own in-house developed software for quantification of signal alterations. Seven centers utilize image reformatting/reconstruction methods on 3D MRI data, such as multiplanar reconstruction or curvilinear reformatting as proposed by Huppertz et al.¹⁷. Four centers use multimodal image integration or visualization of different modalities to aid epilepsy surgery planning³⁷. In general, the most important indication for postprocessing methods is a normal conventional MRI in patients who are suspected of underlying localized malformations of cortical development.

Positron emission tomography and single-photon emission computed tomography

Twenty-two centers have interictal PET available, of which two redirect patients to a collaborating center. Sixteen centers use PET in both adults and children, another four use it exclusively in adults, although they also perform epilepsy surgery in children. Two centers that only perform epilepsy surgery in either adults or children perform PET in that

specific group. PET is mostly indicated for MRI-negative patients (14 centers), or applied standardly in the presurgical workup (eight centers). All centers use the 18F-FDG ligand; only two use additional ligands.

PET postprocessing is performed by 17 of 22 centers. PET-MRI co-registration is performed by 13 centers. SPM is used by six centers, of which four apply SPM routinely to all interictal PET scans, and two only when visual inspection of PET fails to identify localized hypometabolism or provides abnormalities that are discordant to other modalities. Two centers report the use of other not-further-specified postprocessing procedures.

Ictal SPECT is available in 19 centers and is applied to adult patients by 17 centers and in children by 11. SPECT is indicated primarily for MRI-negative patients and patients with discordant semiology, imaging, or electrophysiology results. The technetium-99m hexamethyl propylene amine oxime (99mTc-HMPAO) marker is used by 17 centers, and technetium-99m ethyl cysteinate dimer (99mTc-ECD) by 4 centers. Postprocessing is applied by 15 centers. Ten use SISCOM. Two centers use ictal-interictal SPECT analyzed by SPM (ISAS), of which one performs an MRI co-registration additionally. Two centers perform only MRI co-registration and one center performs only CT co-registration. All procedures are part of the centers' standard SPECT analysis.

With respect to published guidelines for children²⁶, 4 of 22 centers performing epilepsy surgery in children (18%), do not meet the recommendations, as they perform neither PET nor SPECT in children. In three of those, one of these modalities is used in adults. Seven (37%) of 19 centers performing SPECT did not report a comparison of ictal with interictal SPECT as recommended^{27,28}.

Electromagnetic source localization

Electromagnetic source localization is performed by 12 centers: exclusively MEG in 3, exclusively EEG in 5, and 4 centers perform both. All seven centers that use MEG source localization do so in adults; six in children. Eight centers perform EEG source localization in adults and six in children. A total of 14 different combinations of inverse methods and volume conduction models are used: 7 for MEG and 13 for EEG (supplementary table 2.1). For both EEG and MEG, dipole model is the most popular inverse method and individual MR-based methods are the most popular volume conduction model (six centers). Centers did not report for which specific indications these techniques were applied.

Discussion

This survey on the presurgical diagnostic procedures among 25 epilepsy surgery centers in Europe shows a large variation in the imaging and source localization techniques and their specific implementation.

Only two surveys reported on the frequency of use of different diagnostic modalities and surgical procedures^{38, 39}. Jayakar et al.⁷ addressed the utility of different presurgical diagnostics in an attempt to reach consensus among epilepsy surgery specialists, nicely illustrating the large variation in the experts' opinions on whether certain tests should be recommended in certain etiologies. These studies, however, did not address specific details regarding the diagnostic techniques, and they did not compare the use and availability of tests with published guidelines and recommendations.

We found that only a minority of centers conduct their presurgical diagnostic pathway entirely in accordance with the few available international guidelines or recommendations on structural MRI, PET, and SPECT in candidates for epilepsy surgery^{7-11, 26-28}.

Standard epilepsy MRI protocols vary largely between centers. Although there is some level of disagreement between different guidelines and recommendations on the exact details of the MRI protocol (as detailed in supplementary table 2.2), the main outline is well established. Only 25% of centers meet these standards. When asked, however, many centers judged their MRI protocol to be in accordance with guidelines and recommendations, as became evident during a consortium discussion.

Only three of the nine centers that base their standard MRI protocol for surgical candidates on 1.5T, perform additional 3T scanning in MRI-negative patients. This may be explained by the fact that there is no consensus that higher field strength MRI has additional value in the detection or delineation of epileptogenic lesions^{7, 40-42}. Logistical aspects such as limited time slots or available scanner types force centers to make choices in their applied MRI sequences. All recommendations advise tailoring of protocols according to the clinical information, which is inevitably subject to the opinion and experience of the responsible clinician and may further explain protocol variations.

MRI postprocessing methods are performed by two thirds of centers and consist mostly of morphometric methods and image reformatting or reconstruction methods. The limited use of postprocessing can, to some extent, be attributed to a lack of local experience, lack of resources, and lack of guidelines⁷.

The value of PET and SPECT in the presurgical workup of patients with epilepsy has been well explored⁴³⁻⁴⁶. In current recommendations, however, the only requirement for epilepsy surgery centers is to have at least one of the two modalities available in the presurgical diagnostic trajectory in children. This is, however, not the case for 18% of consortium centers performing epilepsy surgery in children.

Use of the FDG marker by all 22 centers reflects the general belief that the FDG marker is the ideal radiopharmaceutical to study focal epilepsy^{43, 47}. Most other PET tracers need an on-site cyclotron and radiochemistry facility to be produced in real time. This environment is available only at very few sites, hence the limited use of novel markers. The clinical role of other markers and their precise contribution to the presurgical evaluation remains to be established^{27, 45, 47}. PET postprocessing methods are acknowledged to allow more precise anatomic localization of the hypometabolic area than conventional visual analysis^{28, 29}. Most centers perform MRI co-registration. Few use SPM, probably because this technique has not yet been proven to have superior sensitivity over visual detection⁴³.

SPECT is used by fewer centers compared to PET, probably as a result of the higher cost of resources and the necessity to capture a seizure during a limited time-slot⁴⁵. Although 99mTc-HMPAO is the most popular ligand⁴⁸, differences in ligand selection might be explained by availability issues. Ictal SPECT is not compared with interictal SPECT in 37% of the centers, despite the fact that the usefulness of comparison is emphasized^{27, 28}. The postprocessing method used most often is SISCOM, which has been proven to improve sensitivity of SPECT to visualize hyperperfused epileptogenic areas⁴⁵. Few studies support the use of SPM analysis of ictal SPECT, which is reflected by the limited use in the consortium (two centers).

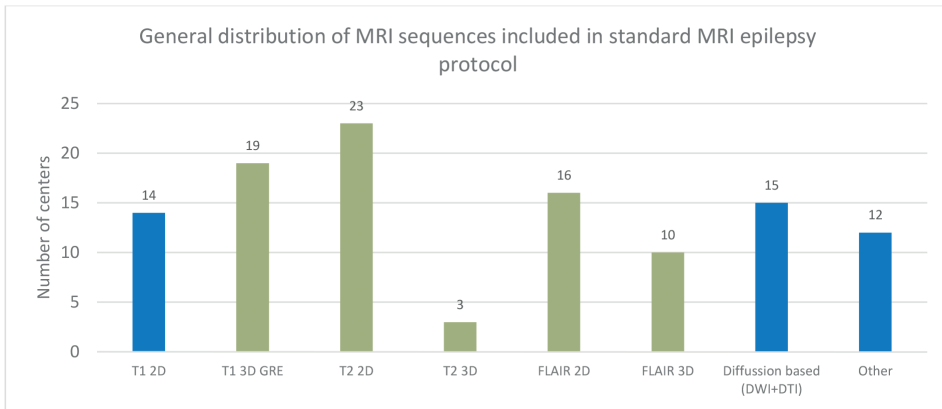
Electromagnetic source localization is employed by half of centers. Although it is not yet considered a required part of the diagnostic approach in surgical candidates and needs to be further validated,^{7, 26} its clinical potential seems promising⁴⁹. Formal epilepsy-specific guidelines on electromagnetic source localization are lacking, although there are several general recommendations elaborating important aspects that may influence its accuracy³²⁻³⁵. A consortium discussion revealed that technical constraints, logistic constraints, and limited reimbursement prevent widespread use of MEG.

Gaining insight into the current use of imaging and electromagnetic source localization procedures in epilepsy surgery centers across Europe is the first step to achieve harmonization. We demonstrate herein that there are considerable differences between centers. In some centers there seems to be a lack of awareness of, or disagreement with, currently available guidelines and recommendations. In others, limited resources may limit the availability of recommended tools. This can have important consequences for health care costs, the selection of patients, the need for invasive recordings, and eventually for surgical outcome. As an example; centers that do not have access to functional imaging techniques probably select fewer "MRI-negative" patients and operate only on patients with clear-cut identifiable MRI lesions. Alternatively, lack of availability of noninvasive diagnostic tools might lead to more frequent, and possibly unnecessary, invasive EEG recording procedures.

The relation between presurgical diagnostic workup and surgical outcome was not a subject of this survey. It remains unexplored to what extent the reported variations in availability of presurgical diagnostics influence surgical outcome. The E-PILEPSY consortium offers a unique opportunity to investigate such relations in the future.

High-quality systematic reviews and evidence-based recommendations on the use, specifics, and minimum standards of imaging and source localization techniques are highly needed. Unfortunately, strong evidence for their effectiveness is lacking^{44,50} because diagnostic accuracy studies are observational by nature and in current evidence-based medicine regarded as weak. Systematic reviews using methodologies that are more tolerant to well-designed observational studies or cohort studies, such as the GRADE method, are more likely to reveal a higher level of evidence and can be valuable⁵¹⁻⁵³. The establishment of systematic reviews and emerging evidence-based recommendations will therefore be an important task of the E-PILEPSY consortium. Furthermore, E-PILEPSY aims to increase centralized availability of various postprocessing methods and electromagnetic source localization procedures, expertise, and shared databases through the project's IT-platform. This may ultimately help to improve the delivery of optimal presurgical diagnostics and the selection of surgical candidates in Europe.

Supplementary material



Supplementary figure 2.1. Number of centers that include particular MRI sequences in their standard MRI protocol. A total 26 different MRI sequences were reported that are classified into eight categories. Olive green bars represent sequences satisfying guideline recommendations, i.e. T1 3D GRE, T2 and FLAIR. The category “Other” includes sequences such as T2*, Susceptibility Weighted Imaging (SWI), Time of Flight (TOF), Arterial Spin Labeling (ASL), and Susceptibility Weighted Angiography (SWAN).

Supplementary table 2.1. Use of combination of inverse methods and volume conduction models for EEG and MEG source localization. LORETA: low-resolution brain electromagnetic tomography. eLORETA: exact LORETA. sLORETA: standardized LORETA. LAURA: Local AUtoRegressive Average. MUSIC: Multiple Signal Classification. (L) SMAC: (Locally) Spherical Model with Anatomical Constraints³²⁻³⁵.

Inverse method & volume conduction model combination	# Centers for EEG (total n=9)	# Centers for MEG (total n=7)
Dipole	5 (56%)	5 (71%)
- Individual MR based	3 (33%)	5 (71%)
- Realistic	1 (11%)	0
- Spherical/Ellipsoid	2 (22%)	1 (14%)
sLORETA	3 (33%)	1 (14%)
- Individual MR based	3 (33%)	1 (14%)
- Realistic	1 (11%)	0
LORETA	3 (33%)	1 (14%)
- Individual MR based	1 (11%)	1 (14%)
- Realistic	2 (22%)	0
LAURA	2 (22%)	0
- Individual MR based	1 (11%)	0
- (L)SMAC	1 (11%)	0
MUSIC - Individual MR based	2 (22%)	1 (14%)
Dynamic imaging of coherent sources- Individual MR based	1 (11%)	1 (14%)
eLORETA- Individual MR based	1 (11%)	0
beamformers- Multi spherical	0	1 (14%)
Current source density - Spherical/Ellipsoid	1 (11%)	0

Supplementary table 2.2. Summary of MRI sequences included in guideline recommendations. Each row includes a different sequence with slice orientation presented. If reported by the respective guideline, recommended slice thickness is noted between brackets (). Ax: axial, cor: coronal, sag: sagittal, X: specific sequence with orientation is reported by guideline, /: sequence is reported by guideline but without specific slice orientation.

	Jayakar et al., 2014	Gaillard et al., 2009	Wellmer et al., 2013	Deblaere & Achten, 2008	Jackson & Badaway, 2011
	Pediatric	Pediatric	Adult+pediatric	Adult+pediatric	Adult+pediatric
(HR)3D T1	X (<=1-1.5 mm)	X (<=1-2 mm)	X (<=1mm)	X	X
T1 ax	-	X (<=2-3mm)	-	-	X
T1 cor	-	X (<=2-3mm)	-	-	X
T1 sag	-	X (<=2-3mm)	-	-	X
T2 ax	X (<= 2-4 mm)	X (<=2-3mm)	X (<=3mm)	X	/
T2 cor	X (<= 2-4 mm)	X (<=2-3mm)	X (<=3mm)	X	/
FLAIR ax	X (<= 2-4 mm)	X (<=2-3mm)	X (<=3mm)	-	X
FLAIR cor	X (<= 2-4 mm)	X (<=2-3mm)	X (<=3mm)	X	
HR T2 oblique/cor	X (<= 2-4 mm)	X (<=2-3mm)	-	-	-
Hemo/calc ax	-	-	X (<=3mm)	/	-
DWI (no specific orientation)	-	-	-	X	-

Supplementary data 2.1. Survey on current use of imaging and source localization procedures in epilepsy surgery that was distributed among centers across Europe.

I. Acquisition and post-processing of imaging in surgical candidates

1. For routine MRI please indicate:

- MR Field strength:
- System (brand, e.g. Siemens, Philips etc.):
- SENSE used? If so please indicate SENSE factor:
- Approximate total duration of MR scan:
- Sequences used:

Sequence	Plane (sag/trans/cor)	Resolution (mm X,Y,Z)

2. Do you do perform additional functional or structural MRI sequences in specific patient groups (e.g. DTI for optic tracts, language (or other) fMRI, High field [e.g. 7T] MRI in MR-negative patients etc.)?

If so please indicate patient group, sequence and rationale:

Patient group/Indication	Sequence/Field Strength	Rationale

4. Do you use ictal SPECT?

If so please indicate patient group, tracer and rationale:

Patient group/Indication	Tracer	Rationale

5. Do you use interictal PET?

If so please indicate patient group, tracer and rationale:

Patient group	Tracer	Rationale

6. Do you use post-processing techniques for PET or SPECT (e.g. SPM) or post-processing techniques that combine PET, SPECT and/or MRI (SISCOM, STATISCOM etc.)?

If so please indicate patient group, tracer and rationale:

Patient group/Indication	Technique	Rationale

In case you use a database of control patients for (automated) comparison purposes:
If so, please indicate:

- Source of the control datasets:
- Characteristics of this dataset:
- Number of subjects in the control database:

II. Acquisition and post-processing of EEG/MEG in surgical candidates

A: access to EEG system (yes,no)

-
- 1: brand & model: (e.g. Micromed LTM, Nihon Kohden Neurofax, Nicolet V32,, NA)
-
- 2: max #channels EEG: (e.g. 19,32, 64, 128, ... ,NA)
-
- 3: max sampling rate EEG: (e.g. 256 Hz, 512 Hz, 1024 Hz,, NA)
-
- 4: access to EEG raw data (yes/no)
-
- 5: data format (e.g. propriety, EDF, ASCII,, NA)
-
- 6: access to EEG processed data only (yes/no)
-
- 7: type of processed data (e.g. picture, annotated image data, report,, NA)
-
- 8: EEG cap (yes/no)
-
- 9: #channels in cap (e.g. 21, 32, 64,, NA)
-
- 10: fiducial marker / electrode position tracker (yes/no)
-
- 11: brand (e.g. Polhemus, Stealth, Xensor, ..., NA)
-

12: EEG used for: *(clinical/research/both)*

.....

B: access to MEG system (yes/no)

.....

1: brand & model *(e.g. CTF omega, Neuromag TRIUX, BTI 4D, ..., NA)*

.....

(sampling rate, sensor type, max# sensors should be clear from brand and model)

2: access to MEG raw data (yes/no)

.....

3: data format MEG raw data *(e.g. propriety, EDF, ASCII,..., NA)*

.....

4: access to MEG processed data only (yes/no)

.....

5: type of processed data *(e.g. picture, annotated image data, reports,..., NA)*

.....

6: MEG used for: *(clinical/research/both)*

.....

C: access to individual 3D MRI (yes,no)

.....

1: image data files available (yes,no)

.....

2: data format *(e.g. DICOM, NIFTI, Analyze, ...,NA)*

.....

3: typical voxel size *(e.g. 1 x 1 x 1 mm, ..., NA)*

.....

4: fiducial markers applied during MRI (yes/no/NA)

.....

D: commercial source localization software (yes,no)

.....

1: product name *(e.g. Besa, Curry, ASA, ..., NA)*

.....

2: favorite source localization method(s) *(e.g. dipole, MUSIC, sLORETA, CSD,..., NA)*

.....

3: headmodel(s) used *(e.g. spherical/realistic/individual MR based, ..., NA)*

.....

4: used for: *(clinical/research/both)*

.....

5: user: (e.g. physician, technician, physicist, researcher, ..., NA)

.....

E: public domain source localization software (yes/no)

.....

1: name: (e.g. brainstorm, Fieldtrip, NUTMEG, MNI, EEGLAB, ..., NA)

.....

2: platform: (e.g. Windows, Unix, MacOS, Matlab,, NA)

.....

3: favorite source localization method(s) (e.g. dipole, MUSIC, sLORETA, CSD, ..., NA)

.....

4: headmodel(s) used (e.g. spherical/realistic/individual MR based,, NA)

.....

5: used for: (clinical/research/both)

.....

6: user: (e.g. physician, technician, physicist, researcher, ..., NA)

.....

F: Person that completed this survey / main contact for the topic of source localization:

.....

1: position (e.g. physician, technician, engineer, researcher,...)

.....

3: affiliation

.....

3: email address:

.....

CHAPTER 3

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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*Authors contributed equally

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%.

Conclusion

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.

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 resected⁵⁴. The cornerstone in formulating such hypotheses for individual patients is structural imaging with magnetic resonance imaging (MRI)^{7, 9, 26, 27, 55}.

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^{15, 56}.

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 epilepsy⁵⁷. 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^{7, 9, 11, 26, 27, 55, 58}. 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 Europe⁵⁹.

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^{20, 60-62}. 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 statement⁶³.

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 EpiCARE⁶². By producing systematic reviews, the Consortium sought to provide a firm evidence basis for harmonization and improvement of diagnostic procedures in epilepsy surgery^{20, 60, 61}. 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 3.1.

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 (supplementary table 3.2). 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 3.3). 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 (supplementary methods 3.1)⁶⁴. 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 software⁶⁵.

Results

MRI field strength

The search yielded 1348 matches (supplementary figure 3.1). 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^{40-42, 66-80}.

Ten studies had a prospective and eight a retrospective design (supplementary table 3.4). Sample sizes varied between ten and 738 patients. Eleven studies included both children and adults, one included only children⁶⁶, and six mostly adults^{42, 67-71}. One study did not report age⁴⁰.

The reference standard in three studies was histopathology⁷²⁻⁷⁴. Four studies used surgical confirmation in a subset of the patients, and intracranial EEG or non-invasive diagnostics in the others^{41, 75-77}. In two articles, both reporting large cohort studies, the reference standard was not clearly specified; instead, the frequency of MRI lesions was given^{40, 66}. The remaining studies used the clinical diagnosis as a reference standard.

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)⁷³, two compared 7 T with 1.5 T in patients with temporal lobe epilepsy (TLE) and variable pathology^{69, 71}. 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 3.1). In one of these studies, distinct cohorts of patients were scanned at the two field strengths and compared⁶⁶.

None of the included studies were free from bias (supplementary table 3.5). 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 3.5).

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 3.1 and figure 3.1). 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 3.1 and figure 3.1). In four studies both 1.5 T and 3 T were compared to 7 T^{68, 72, 76, 78}. In two of these all new lesions on 7 T were found in those who had previously undergone 3 T^{72, 76}. In the other two studies half of the new lesions on 7T were found in those who had previously undergone 3 T^{68, 78}.

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 3.1). 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 3.1)⁷¹.

MRI sequences

Study selection is illustrated in supplementary figure 3.2. 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^{69, 72-74, 81-107}.

Eleven studies evaluated standard MRI sequences^{72-74, 81-88}, five evaluated additional MRI sequences^{69, 89-92}, and three contained data on both standard and additional sequences^{93, 94}. Six studies were on DTI⁹⁶⁻¹⁰¹.

Table 3.1. 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 1.5 T					
Knake 2005 ⁴¹	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 ⁷⁰	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 ⁷⁹	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 ⁷⁵	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 ⁶⁶	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 ⁸⁰	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 ⁴⁰	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 ⁴²	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 ⁷³	Patients who underwent anterior temporal lobectomy with amygdalohippocampectomy and had HS	3 T versus 1.5 T -Atrophy -Hyperintensity	77% (10/13) 69% (9/13)	77% (10/13) 69% (9/13)	0.0% (0/3) 0.0% (0/4)
Focal epilepsy, variable pathology or FCD, 7 T versus 1-3 T					
Bartolini 2019 ⁷²	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 ⁶⁷	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 ⁷⁸	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 ^j	0.0% (0/21)	29% (6/21)	29% (6/21)

Feldman 2019⁶⁸	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 2020⁷⁴	Epilepsy patients with a pathologic confirmation of FCD IIa	7 T versus 3 T	60% (6/10)	80% (8/10)	50% (2/4)
Veersema 2017⁷⁶	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 2020⁷⁷	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 2016⁶⁹	Epilepsy surgery candidates with TLE	7 T versus 1.5 T	85% (9/13)	92% (8/13)	NA ^a
Santyr 2017⁷¹	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 3 T

^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

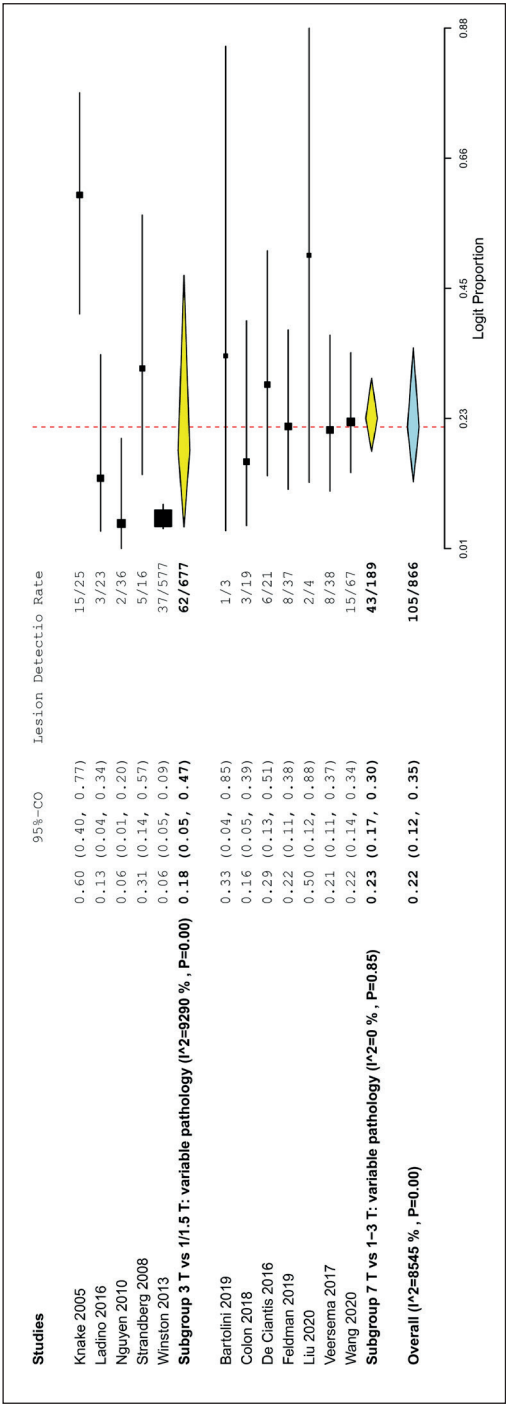


Figure 3.1. Forest plot of additional lesion detection rate with higher field strength

Study characteristics of the 19 included studies on standard and additional MRI sequences are presented in supplementary table 3.6. 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^{81, 92} and two mostly adults^{69, 90}. Two publications did not report the age of the study population^{85, 88}. All included studies had histopathology as a reference standard.

None of the included studies were free from bias (supplementary table 3.7 and 3.8). 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 four studies (supplementary table 3.7 and 3.8).

Lesion detection rate

Epilepsy protocol and standard MRI sequences

Eight publications presented lesion detection rates of (various) epilepsy MRI protocols with histopathology as a reference standard (table 3.2 and figure 3.2). Pooled lesion detection rate at 1.5 T in TLE patients was 83% (95%-CI: 58 – 94%; figure 3.2a), based on four studies. Only one of these solely included patients who had HS⁸⁶. 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 3.2a); 35% (95%-CI: 10 – 72%) for FCD type I and 70% (95%-CI: 57 – 81%) for type II (figure 3.2b). 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 3.2a); ranging from 80 – 100% for FCD type II^{72, 74}. 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 FCD⁸¹.

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 3.2)⁸⁸.

Table 3.2. 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 ⁸⁸	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 T1E orientation perpendicular or parallel to the longitudinal axis of the hippocampal body)	-	89% (80/90)
		Focal epilepsy, FCD		
Ahmed 2018 ⁸¹	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 ⁷²	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
		3D FLAIR (sag) (3 T)	-	47% (8/17) ^g
		All sequences combined (3 T): -FLAIR (cor+ax) -T1 (ax) -T2 (ax) -DWI (ax)	-	39% (15/39) ^h
Chen 2018 ⁸³	Patients with pathologically confirmed FCD with surgical outcome Engel 1-2 ⁱ			

Liu 2020 ⁷⁴	Patients with pathologically confirmed FCD IIa	All sequences combined (3 T): -3D T1 MPRAGE -2D T2 TSE -2D T2-FLAIR All sequences confined (7 T): -3D T1 MPRAGE -2D T2 TSE -3D T2 FLAIR -SWI -WMS -GWB	- - -	60% (6/10) 80% (8/10)
HS				
Hashiguchi 2010 ⁷³	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)
Jack 1996 ⁸²	Patients with TLE who underwent temporal lobe resection with pathological confirmation of HS	-3D STIR (parallel to long axis of hippocampus) (3 T) -T2 double SE (cor) (field strength not reported) -FLAIR (cor) (field strength not reported)	-Signal change - -	69% (9/13) 91% (87/96) 97% (93/96)
Kim 1995 ⁸³	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 ⁸⁴	Patients with TLE who underwent temporal lobe resection with pathological confirmation of HS	-3DT1 (1.5 T) -T1 IR (perpendicular to the long axis of hippocampus) (1.5 T)	-Hippocampal atrophy -Signal change	91% (40/44) 86% (38/44)
Meiners 1994 ⁸⁶	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 ⁸⁷	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 1998⁸⁵	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) -T2 (cor)	96% (44/46)
Wang 2008⁹⁴	Patients with TLE who had undergone temporal lobe resection with variable pathology ⁱ	All sequences combined (1.5 T): - T1 FLAIR (ax+sag) - T2 FSE (cor+ax) - T2 FLAIR (ax)	67% (18/27)
Wehner 2007⁹⁵	Patients with TLE who had undergone temporal lobe resection with variable pathology ^j	All sequences combined (1.5 T)	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

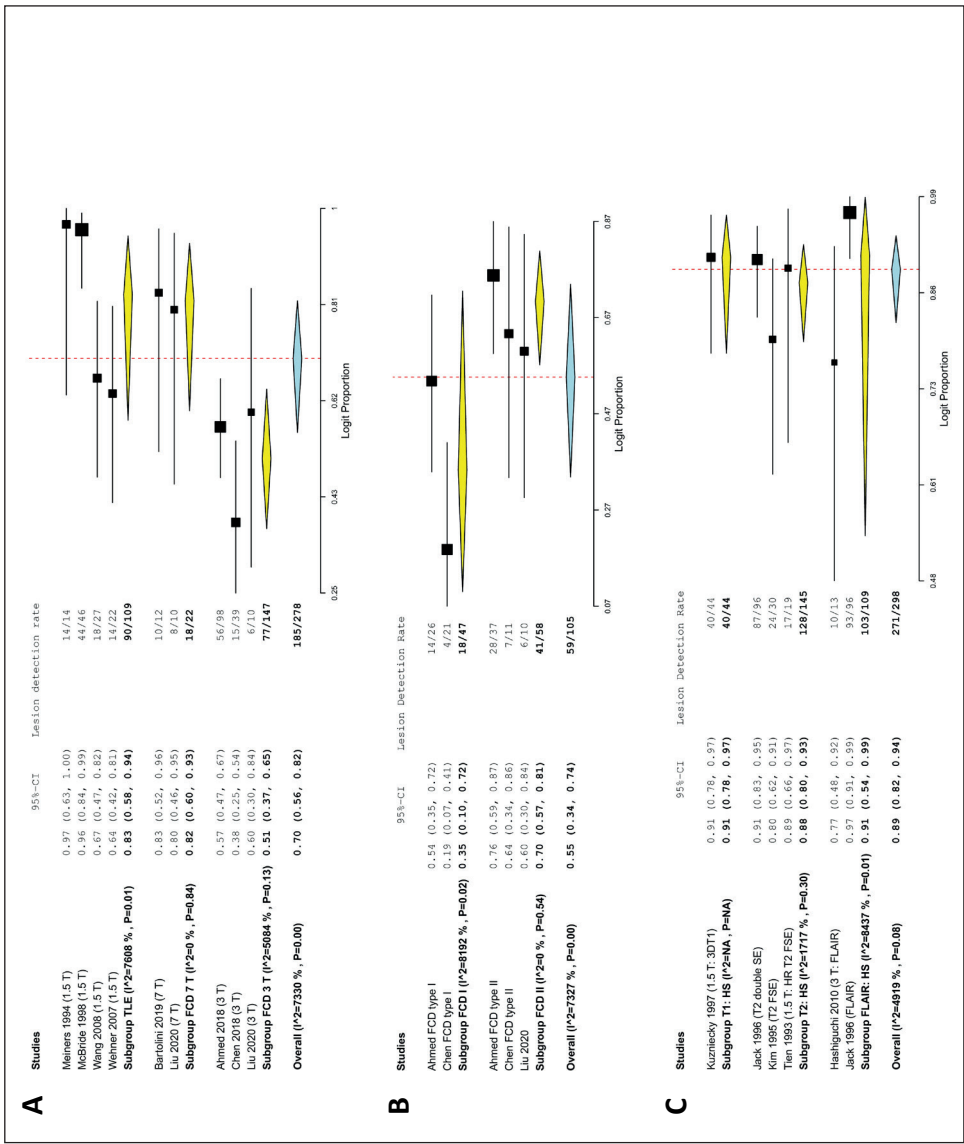


Figure 3.2. Forest plot of epilepsy protocol and standard MRI sequences lesion detection rate. A: epilepsy-specific MRI protocol, data presented separately for TLE and FCD subgroups; B: epilepsy-specific MRI protocol, data from figure A presented separately for FCD type I and type II (3 T); C: separate standard sequences for patients with HS.

Table 3.3. 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 = <i>diagnostic advantage</i> sequence	Lesion on conventional MRI, but not on sequence
TLE							
Kantarci 2002⁸⁹ (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 2016⁶⁹ (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 2008⁹⁴ (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 2007⁹⁵ (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 2002⁹⁰ (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 2020²² (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 2018²³ (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)
Veersema 2016⁹¹ (7 T)	Patients with histologically confirmed FCD in all, either MRI negative on 3 T or suspect for FCD	-T2*	Superficial hypointensity	67% (4/6) ^k	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 3.4. 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 2003⁹⁷	Patients with unilateral TLE	8/12	Lat	Asymmetry index ^c	FA ↓ correct	0.0% (0/12)	100% (8/8)	0.0% (0/12)
					MD ↑ correct	0.0% (0/4)	25% (2/8)	0.0% (0/12)
Chen 2008⁹⁹	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)	All MRI negative	27% (4/15)
					MD ↑ total correct	67% (10/15) 47% (7/15)	All MRI negative	60% (9/15)
Eriksson 2001⁹⁶	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)	32% (7/22)	27% (6/22)
					MD ↑ total correct	46% (10/22) 36% (8/22)	64% (14/22)	41% (9/22)
Rugg-Gunn 2001¹⁰⁰	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)	10% (1/10)	10% (4/40)
					MD ↑ total correct	45% (18/40) 40% (16/40)	0.0% (0/10)	13% (5/40)
Salmenpera 2006⁹⁸	Patients with unilateral TLE	6/7	Lat	Asymmetry index ^d	FA ↓ total correct	0.0% (0/7) 0.0% (0/7)	100% (6/6)	0.0% (0/7)
					MD ↑ total correct	100% (7/7) 86% (6/7)	0.0% (0/6)	14% (1/7) ^e

Thivard 2011 ¹⁰¹	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)		
					TLE		All MRI negative	39% (5/13)
					MD ↑	39% (5/13)		
					total	15% (2/13)		
					correct	15% (2/13)		
					eTLE		All MRI negative	42% (3/7)
					MD ↑	100% (7/7)		
					total	86% (6/7)		
					correct	100% (7/7)		

^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

Six studies reported lesion detection rates for standard MRI sequences separately, five of which in patients with TLE and HS (figure 3.2c), 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/HS⁷³. 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 3.2)⁹³.

Additional sequences

Lesion detection rates for additional MRI sequences with histopathology as a reference standard are presented in table 3.3. 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 TLE⁹⁴. 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)⁹⁰, 46% (cutoff of ± 2 SD)⁹⁵ and 81% (cutoff of ± 1 SD)⁸⁹. These studies, however, also revealed that asymmetry indices failed to lateralize in 19% (cutoff of ± 1 SD)⁸⁹ and 72% (cutoff of ± 2 SD)⁹⁰ 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^{69, 91}. 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 images⁹¹. 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 MRI⁹². 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)⁹³.

DTI

Additionally, we included six studies on DTI in a post-hoc supplementary analysis with clinical diagnosis as a reference standard (table 3.4)⁹⁶⁻¹⁰¹.

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 3.3). FA localization was false positive in 20% (95%-CI: 10 – 35%), MD localization was

false positive in 36% (95%-CI: 18 – 58%) (supplementary figure 3.4). 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 MD⁹⁶.

Two studies revealed a lateralizing value in unilateral TLE of 0.0% for FA^{97, 98} and of 67%⁹⁷ or 86%⁹⁸ for MD. In the MRI negative subgroup, lateralizing values were 0.0% for FA^{97, 98} and 0.0%⁹⁷ and 50%⁹⁸ 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^{7, 9, 26, 27, 55, 59}. 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^{54, 56}, and distinct underlying (presumed) histopathology with specific imaging characteristics^{74, 83, 86, 93, 102}, 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.⁴² 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 information¹⁰².

Although several publications have recommended the use of a dedicated epilepsy protocol that includes T1, T2, and FLAIR sequences^{7, 9, 26, 27, 55, 59}, 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^{103, 104}, 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 FCD¹⁰³⁻¹⁰⁵. 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 neuroradiologist⁸⁸.

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 patients⁸⁹. 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, one²⁵ 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 perilesional 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^{106, 107}. 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 T⁴¹ or 7 T⁷¹, 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 mm³ 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 epilepsy⁵⁸.

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.

Supplementary material

Supplementary methods 3.1: QUADAS-2

The risk of bias was rated high or low for the following domains: patient selection, index/comparator test, reference standard and flow and timing. Only when there was insufficient data was the risk of bias rated unclear. Applicability was the degree to which the studies were applicable to our research question. This was rated high or low, referring to concerns regarding applicability for patient selection, the index/comparator test and the reference standard.

The risk of bias for the patient population could be rated high when selection bias was suspected or when the population did not consist of only epilepsy surgery candidates.

For the index and comparator tests, there could be a risk of standardization bias when they were not conducted in a standardized way (e.g. non-comparable sequences, head/surface coils or field strengths).

When histopathology was chosen as a reference standard, the risk of bias regarding the reference standard could be rated high when not all patients underwent histopathologic confirmation within a study.

Multiple factors could lead to a high risk-of-bias rating for patient flow and timing. Information bias might occur when the radiologist had more information available when judging the imaging than in regular clinical practice at the moment a patient would undergo imaging at a (tertiary) epilepsy surgery centre. The risk of bias was also rated high when the index and comparator tests were not fully comparable. Timing between the index and comparator test was not taken into consideration as most epileptogenic lesions (e.g. FCD or HS) are not expected to change over time.

Applicability concerns were rated high when the patient population was not part of our target population of epilepsy surgery candidates. Index test and comparator test applicability concerns were rated high when a tertiary epilepsy surgery centre would not be likely to use the specific MRI technique (e.g. when special head coils were used). When coils, field strength (for question 2) or sequences (for question 1) were not reported, this was judged as unclear.

The same was applied for the reference standard. If histopathology was used as a reference, this could be rated high i.e. when a specific immunohistochemistry technique was used for pathologic confirmation.

Supplementary table 3.1. Search strings

Research question 1	
Pubmed	("epilepsy"[Title/Abstract] OR "epilepsies"[Title/Abstract] OR "epilepsy"[MeSH Terms]) AND (("magnetic resonance"[Title/Abstract] OR "mri"[Title/Abstract] OR "mrimaging"[Title/Abstract] OR "mr imaging"[Title/Abstract] OR "MR"[Title/Abstract] AND ("3 0 t"[Title/Abstract] OR "3 0 tesla"[Title/Abstract] OR "3 t"[Title/Abstract] OR "3 tesla"[Title/Abstract] OR "3t"[Title/Abstract] OR "3tesla"[Title/Abstract] OR "1 5 t"[Title/Abstract] OR "1 5 tesla"[Title/Abstract] OR "1 5t"[Title/Abstract] OR "1 5tesla"[Title/Abstract] OR "7 0 t"[Title/Abstract] OR "7 0 tesla"[Title/Abstract] OR "7 t"[Title/Abstract] OR "7 tesla"[Title/Abstract] OR "7t"[Title/Abstract] OR "7tesla"[Title/Abstract] OR "field strength"[Title/Abstract] OR "high field"[Title/Abstract] OR "highfield"[Title/Abstract] OR "ultrahigh field"[Title/Abstract] OR "higher resolution"[Title/Abstract] OR "higher resolution"[Title/Abstract]) AND ("epileptogenic"[Title/Abstract] OR "epileptic"[Title/Abstract] OR "lesion"[Title/Abstract] OR "lesions"[Title/Abstract] OR "zone"[Title/Abstract] OR "zones"[Title/Abstract] OR "focus"[Title/Abstract] OR "dysplasia"[Title/Abstract] OR "dysplasias"[Title/Abstract] OR "dysplastic"[Title/Abstract] OR "abnormality"[Title/Abstract] OR "abnormalities"[Title/Abstract] OR "anomaly"[Title/Abstract] OR "anomalies"[Title/Abstract] OR "fcd"[Title/Abstract] OR "fcds"[Title/Abstract] OR "malformation"[Title/Abstract] OR "malformations"[Title/Abstract] OR "sclerosis"[Title/Abstract] OR "heterotopia"[Title/Abstract] OR "location"[Title/Abstract] OR "localization"[Title/Abstract] OR "map"[Title/Abstract] OR "mapping"[Title/Abstract] OR "surgical target"[Title/Abstract] OR "surgical outcome"[Title/Abstract] OR "pathology"[Title/Abstract] OR "sensitivity"[Title/Abstract] OR "specificity"[Title/Abstract] OR "value"[Title/Abstract] OR "accuracy"[Title/Abstract] OR "yield"[Title/Abstract] OR "assessment"[Title/Abstract] OR "diagnostic techniques, neurological"[MeSH Terms] OR "diagnostic imaging"[MeSH Terms] OR "sensitivity and specificity"[MeSH Terms] OR ("presurgical"[Title/Abstract] OR "pre surgical"[Title/Abstract]) AND ("plan"[Title/Abstract] OR "planning"[Title/Abstract] OR "evaluation"[Title/Abstract])) NOT ("animals"[MeSH Terms:noexp] OR "animal"[All Fields])
Embase	epilepsy:ab,ti OR epilepsies:ab,ti AND (magnetic:ab,ti AND resonance:ab,ti OR mri:ab,ti OR mrimaging:ab,ti OR (mri:ab,ti AND imaging:ab,ti) OR MR:ab,ti) AND (3.0t:ab,ti OR 3t:ab,ti OR 1.5t:ab,ti OR 7.0t:ab,ti OR 7t:ab,ti OR (3.0:ab,ti OR 3:ab,ti OR 7:ab,ti AND (t:ab,ti OR tesla:ab,ti)) OR (field:ab,ti AND strength:ab,ti) OR (high:ab,ti AND field:ab,ti) OR highfield:ab,ti OR (ultrahigh:ab,ti AND field:ab,ti) OR (high:ab,ti AND resolution:ab,ti) OR (higher:ab,ti AND resolution:ab,ti)) AND (epileptogenic:ab,ti OR epileptic:ab,ti OR lesion:ab,ti OR lesions:ab,ti OR zone:ab,ti OR zones:ab,ti OR focus:ab,ti OR dysplasia:ab,ti OR dysplasias:ab,ti OR dysplastic:ab,ti OR abnormality:ab,ti OR abnormalities:ab,ti OR anomaly:ab,ti OR anomalies:ab,ti OR fcd:ab,ti OR fcds:ab,ti OR malformation:ab,ti OR malformations:ab,ti OR sclerosis:ab,ti OR heterotopia:ab,ti OR location:ab,ti OR localization:ab,ti OR map:ab,ti OR mapping:ab,ti OR (surgical:ab,ti AND target:ab,ti) OR (surgical:ab,ti AND outcome:ab,ti) OR pathology:ab,ti OR sensitivity:ab,ti OR specificity:ab,ti OR value:ab,ti OR accuracy:ab,ti AND r AND yield:ab,ti OR assessment:ab,ti OR (presurgical:ab,ti OR (pre surgical:ab,ti AND (plan:ab,ti OR planning:ab,ti OR evaluation:ab,ti))) AND [embase]/lim AND [english]/lim NOT 'suppl' NOT 'conference abstract' NOT 'animal'
Cochrane	(epilepsy:ab,ti or epilepsies:ab,ti) AND (MRI:ab,ti or "magnetic resonance":ab,ti)

Research question 2**PubMed**

('epilepsy'[Title/Abstract] OR 'epilepsies'[Title/Abstract] OR 'epilepsy'[MeSH Terms]) AND (('magnetic resonance'[Title/Abstract] OR 'mri'[Title/Abstract] OR 'mrimaging'[Title/Abstract] OR 'mr imaging'[Title/Abstract] OR 'MR'[Title/Abstract] AND (('sequence'[Title/Abstract] OR 'sequences'[Title/Abstract] OR 'protocol'[Title/Abstract] OR 'guideline'[Title/Abstract] OR 'guidelines'[Title/Abstract] OR ('t1'[Title] OR '3DT1'[Title] OR 't2'[Title] OR '3DT2'[Title] OR 'flair'[Title] OR 'FLAWS'[Title] OR 'dwi'[Title] OR 'diffusion weighted'[Title] OR 'ir'[Title] OR 'inversion recovery'[Title] OR 'tir'[Title] OR 'stir'[Title] OR 'dir'[Title] OR 'se'[Title] OR 'spgr'[Title] OR 'spgr'[Title] OR 'spoiled gradient echo'[Title] OR 'gre'[Title] OR 'gradient recalled echo'[Title] OR 'FSE'[Title] OR 'GE'[Title] OR 'MPRAGE'[Title] OR 'MP-RAGE'[Title] OR 'MP2RAGE'[Title] OR 'FFE'[Title] OR 'FSPGR'[Title] OR 'gadolinium'[Title] OR 'contrast'[Title] OR 'pd'[Title] OR 'proton density'[Title] OR 'mpri'[Title] OR 'swi'[Title] OR 'swan'[Title] OR 'susceptibility weighted'[Title] OR 'tof'[Title] OR 'time of flight'[Title] OR 'artrial spin labeling'[Title] OR 'dti'[Title] OR 'diffusion tensor'[Title] OR 'magnetic transfer'[Title] OR 'magnetization transfer'[Title] OR 'mt'[Title])) AND ('epileptogenic'[Title/Abstract] OR 'epileptic'[Title/Abstract] OR 'lesion'[Title/Abstract] OR 'lesions'[Title/Abstract] OR 'zone'[Title/Abstract] OR 'zones'[Title/Abstract] OR 'focus'[Title/Abstract] OR 'dysplasia'[Title/Abstract] OR 'dysplasias'[Title/Abstract] OR 'dysplastic'[Title/Abstract] OR 'abnormality'[Title/Abstract] OR 'abnormalities'[Title/Abstract] OR 'anomaly'[Title/Abstract] OR 'anomalies'[Title/Abstract] OR 'fcd'[Title/Abstract] OR 'malformation'[Title/Abstract] OR 'malformations'[Title/Abstract] OR 'sclerosis'[Title/Abstract] OR 'heterotopia'[Title/Abstract] OR 'location'[Title/Abstract] OR 'localization'[Title/Abstract] OR 'map'[Title/Abstract] OR 'mapping'[Title/Abstract] OR 'surgical target'[Title/Abstract] OR 'outcome'[Title/Abstract] OR 'pathology'[Title/Abstract] OR 'pathologic'[Title/Abstract] OR 'sensitivity'[Title/Abstract] OR 'specificity'[Title/Abstract] OR 'value'[Title/Abstract] OR 'accuracy'[Title/Abstract] OR 'yield'[Title/Abstract] OR 'assessment'[Title/Abstract] OR 'diagnostic techniques, neurological'[MeSH Terms] OR 'diagnostic imaging'[MeSH Terms] OR 'sensitivity and specificity'[MeSH Terms] OR (('presurgical'[Title/Abstract] OR 'pre surgical'[Title/Abstract] AND ('plan'[Title/Abstract] OR 'planning'[Title/Abstract] OR 'evaluation'[Title/Abstract])) NOT ('animals'[MeSH Terms:noexp] OR 'animal'[All Fields]))

Embase

'epilepsy'.ab,ti OR 'epilepsies'.ab,ti OR 'epilepsy'.de AND ('magnetic resonance'.ab,ti OR 'mri'.ab,ti OR 'mrimaging'.ab,ti OR 'mr'.ab,ti) AND ('sequence'.ab,ti OR 'sequences'.ab,ti OR 'protocol'.ab,ti OR 'guideline'.ab,ti OR 'guidelines'.ab,ti OR 't1'.ti OR '3DT1'.ti OR 't2'.ti OR '3DT2'.ti OR 'flair'.ti OR 'FLAWS'.ti OR 'dwi'.ti OR 'diffusion weighted'.ti OR 'ir'.ti OR 'inversion recovery'.ti OR 'tir'.ti OR 'stir'.ti OR 'se'.ti OR 'spin echo'.ti OR 'tse'.ti OR 'spgr'.ti OR 'spoiled gradient echo'.ti OR 'gre'.ti OR 'gradient recalled echo'.ti OR 'FSE'.ti OR 'GE'.ti OR 'MPRAGE'.ti OR 'MP-RAGE'.ti OR 'MP2RAGE'.ti OR 'FFE'.ti OR 'FSPGR'.ti OR 'gadolinium'.ti OR 'contrast'.ti OR 'gre'.ti OR 'pd'.ti OR 'proton density'.ti OR 'mpri'.ti OR 'swi'.ti OR 'swan'.ti OR 'susceptibility weighted'.ti OR 'tof'.ti OR 'time of flight'.ti OR 'artrial spin labeling'.ti OR 'dti'.ti OR 'diffusion tensor'.ti OR 'magnetic transfer'.ti OR 'magnetization transfer'.ti OR 'mt'.ti) AND ('epileptogenic'.ab,ti OR 'epileptic'.ab,ti OR 'lesions'.ab,ti OR 'zone'.ab,ti OR 'zones'.ab,ti OR 'focus'.ab,ti OR 'dysplasia'.ab,ti OR 'dysplasias'.ab,ti OR 'dysplastic'.ab,ti OR 'abnormality'.ab,ti OR 'abnormalities'.ab,ti OR 'anomaly'.ab,ti OR 'anomalies'.ab,ti OR 'fcd'.ti OR 'fcds'.ab,ti OR 'malformation'.ab,ti OR 'malformations'.ab,ti OR 'sclerosis'.ab,ti OR 'heterotopia'.ab,ti OR 'location'.ab,ti OR 'localization'.ab,ti OR 'map'.ab,ti OR 'mapping'.ab,ti OR 'surgical target'.ab,ti OR 'outcome'.ab,ti OR 'pathology'.ab,ti OR 'pathologic'.ab,ti OR 'sensitivity'.ab,ti OR 'specificity'.ab,ti OR 'value'.ab,ti OR 'accuracy'.ab,ti OR 'yield'.ab,ti OR 'assessment'.ab,ti OR 'presurgical'.ab,ti OR 'surgical'.ab,ti AND ('plan'.ab,ti OR 'planning'.ab,ti OR 'evaluation'.ab,ti))) AND (embase)/lim AND [english]/lim NOT 'suppl' NOT 'conference abstract' NOT 'animal'

Cochrane

(epilepsy:ab,ti or epilepsies:ab,ti) AND (MRI:ab,ti or "magnetic resonance":ab,ti)

Supplementary table 3.2. Exclusion criteria title/abstract screening

Exclusion reason		Details
general study characteristics		
insufficient information to fully assess eligibility		not available in English abstract or full text not available
not original research articles		e.g. letters, commentaries, supplementary material, conference abstracts, poster presentations
insufficient sample size		case reports with ≤5 cases
per domain		
population	not on epilepsy or on non-focal or non-structural epilepsy	e.g. rolandic epilepsy or idiopathic generalized epilepsy
	other	studies on transient lesions in patients with status epilepticus
		studies specifically focusing on tumors
		studies on imaging in patients with tuberous sclerosis complex with multiple lesions, as the goal of these studies was not lesion detection, but either identification of the epileptogenic tuber or descriptive
index/comparator test	studies focusing on other diagnostic tests in patients with epilepsy	e.g. EEG, PET, SPECT, MEG, WADA, invasive recordings
	studies focusing on other techniques of MRI	e.g. MR spectroscopy, MRI postprocessing techniques, automated lesion detection techniques, functional MRI, MRI neuronavigation, intra- or postoperative MRI or ex-vivo studies
outcome	studies on MRI, however not mentioning a lesion detection rate	describing a specific MRI technique, MRI safety, techniques of reduction of (motion) artifacts or MRI characteristics of specific epileptic lesions
	studies mentioning MRI, however focus not on lesion detection	e.g. on seizure semiology or seizure propagation, language lateralization or cognitive functioning, cerebral development, disease progression or prognosis or brain networks
	studies on treatment of epilepsy	on surgical technique, seizure outcome after epilepsy surgery or other treatment(s) of epilepsy (e.g. AEDs, VNS, thermocoagulation)

Supplementary table 3.3. Eligibility checklist for full text screening

	MRI field strength	MRI sequences
Study objective	Asses the diagnostic advantage of MRI at a field strength of 3/7 T in detecting an epileptogenic lesion in epilepsy surgery candidates who were non-lesional on lower field strength (1/1.5/3 T) MRI	Asses the diagnostic value of individual MRI sequences and/or their combination in detecting an epileptogenic lesion in epilepsy surgery candidates
Study design	Prospective/retrospective original research articles, sample size >5 patients	
Population	Adult and/or pediatric epilepsy surgery candidates with medically refractory focal epilepsy	
Index test	Clinical brain MRI at a field strength of 3/7 T, either conventional protocol or epilepsy specific protocols	Individual MRI sequences or combined in (epilepsy specific) protocol: <ul style="list-style-type: none"> Standard MRI sequences (T1, T2, FLAIR) Additional MRI sequences (e.g. DWI, DTI, ASL, T2*)
Comparator test	Clinical brain MRI at a lower field strength (1/1.5/3 T), either conventional brain protocol or epilepsy specific protocols	<ul style="list-style-type: none"> For standard MRI sequences: none For additional MRI sequences: standard brain MRI (protocol)
Diagnostic setting	Compare the diagnostic advantage of a higher field strength to that of a lower field strength	<ul style="list-style-type: none"> Standard MRI sequences: lesion detection rate Additional MRI sequences: compare diagnostic advantage of additional sequences to lesion detection rate of standard sequences
Reference standard	<ul style="list-style-type: none"> Histopathology Clinical diagnosis defined as agreement on the location of the epileptogenic zone in a multidisciplinary epilepsy surgery meeting based on multiple diagnostic modalities 	
Type of outcome measure	Lesion detection rate calculated as the number of patients with a lesion on MRI divided by the total number of patients studied	

Supplementary table 3.4. Study characteristics of the included studies on MRI field strength

Study	Data collection	Study objective	Age	Sample size	Population characteristics	Sequence(s)	Field strength	Coils	Visual analysis
Bartolini 2019 ⁷²	Retrospective	Asses the diagnostic advantage of 7 T in patients with histologically proven FCD	Mean 23 (range 9-40) years	12	Patients with focal epilepsy who underwent both 1.5/3 T and 7 T MRI and who underwent surgery and had a histopathology diagnosis of FCD	1.5 T and 3 T; optimized protocol for focal epilepsy, including at least: -3DT1 -T2 (cor+ax) -FLAIR (cor+ax) 7 T: -3DT1 -3D FLAIR -3D SWAN (+targeted SWAN) -2D T2* -2D T2 FSE -2D targeted gray-white matter border FSE-IR	1.5 T and 3 T	NR	One experienced neuroradiologist and one neurologist with expertise in advanced imaging, blinded to histopathologic diagnosis and epilepsy outcome
Colon 2018 ⁶⁷	Prospective	Explore role of visual and MEG guided visual 7 T MRI analysis in improving detection of a possible epileptogenic lesion	Range 19-65 years	19	Epilepsy surgery candidates with a negative 3 T MRI and with MEG results showing epileptiform abnormalities concordant with semiology	3 T ^a -3D-T1 -T2 -T2* -IR -3D-FLAIR 7 T ^a -3D T1 -3D FLAIR -T2* -T2TSE	3 T	NR	Two experienced neuroradiologist and one epileptologist. Semiology data available. ^b

De Ciantis 2016 ⁷⁸	Prospective	Assess the diagnostic yield of 7 T MRI in detecting and characterizing structural lesions in intractable focal epilepsy patients with unrevealing 1.5 T or 3 T MRI	Mean 24 (range 9-42) years	21	Epilepsy surgery candidates with a 1.5-3 T MRI which was considered negative by the referring center	1.5 T: ^a -3D T1 FFE -T2 FLAIR -T2 TSE -T1 IR 3 T: ^a -3D T1 FSPGR -T2 FLAIR -T2 FSE -T2 wm-suppressed FSE-IR 7 T: ^a -3D T1 FSPGR -3D SWAN -T2* targeted dual echo GRE -T2 FSE -TBE (tissue border enhancement) FSE-IR (-In those after July 2014: 3D MP FLAIR)	1.5 T	NR	Three experts in epilepsy imaging, aided by clinical and EEG findings ^c
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Feldman 2019 ⁶⁸	Prospective	Compare 7 T MRI in patients with focal epilepsy who had non-lesional clinical (1.5 T or 3 T) MRI scans with healthy controls	Mean 36 (range 19- 78) years	37 (epilepsy patients)	Patients with focal epilepsy (based on clinical history and EEG) with a non-lesional clinical (1.5 T or 3 T) MRI	1.5 T and 3 T: -No details provided though mentioned that all met or exceeded "minimum recommended imaging" in epilepsy	1.5 T and 3 T	NR	Two expert neuroradiologists, initially blind to clinical data
						7 T: -MP-RAGE -MP2RAGE -T2 TSE -FLAIR (all four coronal-oblique perpendicular to long axis of hippocampus) -SWI (ax) -T2 TSE (ax)	7 T	Single channel transmit/32- channel receive head coil	
Hashiguchi 2010 ⁷³	Retrospective	-Compare diagnostic utility of FLAIR at 3 T and 1.5 T -Assess clinical utility of 3DSTIR for HS diagnosis -Assess relationship of 3DSTIR hypointense hippocampal areas with severity of HS	Mean 33 (range 13- 58) years	13	Patients who underwent anterior temporal lobectomy with amygdalohippocampectomy and had HS	1.5 T: -FLAIR (coronal and oblique along long axis of hippocampus) 3 T: -FLAIR (coronal and oblique along long axis of hippocampus) -3DSTIR (parallel to long axis of hippocampus)	1.5 T 3 T	16-channel phased array coils 8-channel phased array coils	Two experienced neuroradiologists unaware of patient information; unclear how consensus was reached

Knake 2005 ⁴¹	Prospective	Evaluate detection rate, discriminative ability and impact on clinical management of 3 T phased array surface coil MRI	Mean 29 (range 9-57) years	40	Candidates for invasive phase 2 evaluation due to non-conclusive phase 1 findings	1.5 T: -not reported 3 T: -3D T1 MPRAGE -T2 TSE (cor) -T2 TSE (ax) -FLAIR (cor)	1.5 T 3 T	Head coil	Experienced unblinded review by epilepsy radiologist and neurologist. All clinical and previous presurgical evaluations/imaging data available
Kwan 2016 ⁶⁹	Prospective	-Determine the ability of 7 T MRI (particularly SWI) to detect hippocampal and mesial temporal lobe abnormalities -Evaluate the concordance between these findings and histopathology	Total cohort: 13 range 16-65 years Operated: Mean 33 (range 18-50) years	13	Epilepsy surgery candidates with TLE	1.5 T: -T2 (ax) -FSEIR (cor) -GE (cor) -3D FLAIR (cor) -3D T1 (ax) -DWI (ax) 7 T: -T1 MPRAGE -T2* (cor) perpendicular to long axis of hippocampus) -SWI	1.5 T 7 T	NR 16 channel transmit-receive phased array head coils	Neuroradiologist blinded for clinical data
Ladino 2016 ⁷⁰	Prospective	Assess the value of re-imaging patients with refractory focal epilepsy who were negative/nonconclusive at 1.5 T MRI with 3 T MRI	Mean 30 (SD: 11.4) years	30	Patients with non-conclusive pre-surgical non-invasive evaluation and previous normal/equivocal 1.5 T MRI	Both field strengths: -3D FLAIR (sag) -T1 IR (cor) -HR DWI (ax) -3D T2 (sag)	1.5 T 3 T	Both field strengths: 8 channel PA coil	Two independent neuroradiologist blinded for prior imaging with only a short clinical description of seizure semiology and EEG results

Liu 2020 ⁷⁴	Retrospective	Explore the diagnostic value of 7 T MRI in epilepsy patients with FCD-IIa	Range 11-48 years	10	Patients with suspicious focal lesions on 3 T MRI or on MRI-PET co-registration or with focal discharges on scalp EEG who underwent resective epilepsy surgery with 1-year follow-up and had a histopathologic finding of FCD-IIa	3 T: ^a -3D T1 MPRAGE -2D T2 TSE -2D T2-FLAIR 7 T: ^a -3D T1 MPRAGE -2D T2 TSE -3D T2 FLAIR -SWI -WMS -GWB	3 T	NR	Unblinded review by a neuroradiologist and 2 neurosurgery specialists
Nguyen 2010 ⁷⁹	Retrospective	Explore the potential value of reimaging at 3 T of patients with refractory partial epilepsy and negative 1/1.5 T MRI	Median 31 (range 13-56) years	36	Surgical candidates with negative/initially regarded as non-relevant 1/1.5 T MRI	1/1.5 T: -epilepsy protocol, no further details reported 3 T: -3DT1 GRE -T2 (ax) -FLAIR (ax) -FLAIR (perpendicular to hippocampal long axis)	1/1.5 T	Head coil	Experienced neuroradiologist unblinded for clinical information
Phal 2008 ⁷⁵	Retrospective	Compare 1.5 T and 3 T MRI with respect to: -image quality -lesion detection rate -lesion characterization	Mean 24 years (range 10 mnth-70 y)	19 ^d	Patients with epilepsy with variable suspected underlying pathology who had undergone both 1.5 T and 3 T MRI for various reasons: -no lesion on 1.5 T -lesional follow up -surgical planning -scheduling constrains regarding MRI availability	Both field strengths: -3DT1 SPGR (cor) -T2 FSE (ax) -Fast multiplanar IR (ax) -FLAIR (cor) 3 T Six-channel sensitivity-encoding head coil	1.5 T	Transmit-receive single-channel head coil	Four independent experienced neuroradiologists, blinded for clinical results (e.g. seizure signs, EEG). Not blinded to view both 1.5 T and 3 T results at the same time.

Rubinger 2016 ⁶⁶	Retrospective	Evaluate the effectiveness of a change in imaging practice (amongst other 3 T versus 1.5 T) on epilepsy surgery outcome in children	Mean 11 +/- 5 years 309	Children with medically refractory epilepsy who had undergone resective surgery	1.5 T: -3D T1 (-T1 (sag)) -PD/T2 (ax+cor) -FLAIR (ax) (-postcontrast 3D T1 if indicated)	1.5 T	Quadrature head coil or 8-channel head coil	Retrospective review of the MRI report
					HR 3 T: -3D T1 -PD/T2 (ax+cor) -FLAIR (ax+cor) (-postcontrast 3D T1 if indicated)	3 T	8-channel head coil	
Santyr 2017 ⁷¹	Prospective	To assess the value of 7 T in the identification of hippocampal sclerosis in patients with drug-resistant TLE	Mean 33 (range 18-50) years 13	Epilepsy surgery candidates with TLE, suspect for HS	1.5 T: -not reported	1.5 T	NR	Mesial temporal size and architecture graded on a 4-point scale by 2 (neuro) radiologists blinded for clinical data
					7 T: -T1 MPRAGE (perpendicular to long axis of hippocampus in a coronal oblique orientation)	7 T	16-channel transmit-receive head coil array	
Strandberg 2008 ⁸⁰	Retrospective	Asses if lesion detection and characterization of 3 T MRI can be further improved by adding surface coil imaging in patients with drug resistant epilepsy	Median 15 (range 4-51) years 23 ^e	Surgical candidates with normal/unclear 1/1.5 T MRI	1/1.5 T: -not reported	1/1.5 T	NR	Experienced neuroradiologist re-evaluated 3 T with knowledge of only the lateralization of the suspected epileptogenic zone
					3 T head coil: -T2 FLAIR (cor) -T1 3D GRE (cor) -T1 IR (2 planes, covering the region of the suspected EZ)	3 T	-head coil -additional surface coil	
					3 T surface coil: -T1 IR (2 planes, covering the region of the suspected EZ)			

Veersema 2017 ⁷⁶	Prospective	To determine whether use of 7 T MRI in clinical practice leads to higher detection rates of FCD in possible candidates for epilepsy surgery	Median 18 (range 7-48) years	40	Epilepsy surgery candidates, 7 T indicated because of suspicion of FCD but normal lower field strength MRI or suspect for dual pathology	1.5 T: -T1 SE (sag) -Dual SE (ax) -DW SSH (ax) -T2 FLAIR TSE (cor) -T1 FFE (sag) -T1 FFE+gado (sag) 3 T: -T1 SE (sag) -Dual TSE SPAIR (ax) -DWI (ax) -FLAIR (cor) -3D T1 FFE -3D T1 FFE+gado	1-3 T	3 T: -eight channel head coil	Neuroradiologist aware of all previous data and during ESM with all disciplines
						7 T: -3D T1 TFE -3D T2 TSE -3D FMP-LAIR -3D T2* -3D WMS	7 T	16 or 32-channel receive head coil and dual channel transmit coil +additional dielectric pads	

Wang 2020 ⁷⁷	Prospective	Asses the clinical value of 7 T MRI in patients with focal pharmacoresistant epilepsy who underwent presurgical evaluation and had a nonlesional 3 T MRI	Mean 27.5 years (median 26, range 10-55 years)	67	Patients with focal pharmacoresistant epilepsy who underwent presurgical evaluation and had a nonlesional 3 T MRI based on previous radiology reports	3 T: -3D T1 MPRAGE (cor) -2D T2 TSE (obl cor) -2D FLAIR (ax) -2D FLAIR (obl cor) -2D SWI (ax)	3 T	32-channel phased array receive coil	Unaided, unblinded, visual review by a board-certified neuroradiologist with 12 years of experience in epilepsy imaging
						7 T: -3D T1 MP2RAGE (sag) -2D T2*-GRE (ax) -2D T2*-GRE (obl cor) -2D FLAIR (ax) -2D FLAIR (obl cor) -3D SWI	7 T	Head-only circularly polarized transmit and 32-channel phased array receive coil	
Winston 2013 ⁴⁰	Retrospective	Evaluate the role of repeated imaging with improved MRI technology – field strength and head coils – in detecting pathology not previously seen	NR	738 ^f	Patients attending a tertiary epilepsy referral center who had undergone both 1.5 T and 3 T MRI Not only/necessarily epilepsy surgery candidates	1.5 T: -T1 FLAIR (sag) -FSPGR 3D (cor) -T2 FLAIR (cor) -PD/T2 SE (cor) -HR FSPGR (cor, temporal lobe only)	1.5 T	Quadrature coils	Review of the clinical radiology reports written by experienced neuroradiologists with knowledge of the clinical details
						3 T: -T1 FLAIR (sag) -FSPGR 3D (cor) -T2 FLAIR (cor) -PD/T2 FRFSE (cor) -FGRE T2* (cor) -T2 FSE (ax) -PROPELLER (cor, selected patients only)	3 T	8-channel phased array receive coil	

Zijlmans 2009 ^{a,2}	Prospective	Study 3 T compared to 1.5 T phased array MRI in the presurgical work- up of patients with epilepsy with complex focus localization	33 +/- 15 years	37	Patients with partial epilepsy evaluated but not considered eligible for surgery due to unclear seizure focus 3 T MRI because of ambiguity about the epileptic focus	Both field strengths: -T1 SE (sag) -T1 HR iso (sag) -Dual T2 TSE (ax) -DWI (axial) -FLAIR (cor)	1.5 T 3 T	Both field strengths: 8-channel phased array head coil	Experienced neuroradiologists blinded for prior imaging and patient-specific information, provided with brief clinical information regarding the presumed site of the EEG focus and seizure semiology to simulate the normal situation
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^a Orientation not reported

^b MEG guided evaluation was not included

^c 1.5 T or 3 T MRI which were deemed unrevealing at the referral center, were also re-reviewed by the expert radiologists

^d Total sample included 25 patients, 19 had focal epilepsy and were included

^e Total sample included 25 patients, 23 had focal epilepsy and were included

^f Total sample included 804 patients, 738 had focal epilepsy and were included

Supplementary table 3.5. Quality appraisal for the studies included for MRI field strength

Population	Study	RISK OF BIAS				APPLICABILITY CONCERNS					
		PATIENT SELECTION	INDEX TEST (HIGHER FIELD STRENGTH)	COMPARATOR TEST (LOWER FIELD STRENGTH)	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST (HIGHER FIELD STRENGTH)	COMPARATOR TEST (LOWER FIELD STRENGTH)	REFERENCE STANDARD	
3 T focal epilepsy, variable pathology	Knake 2005 ⁴¹	- ^a	+	+	- ^h	- ^j	+	- ^j	?	+	
	Ladino 2016 ⁷⁰	- ^a	+	+	?	+	+	+	+	?	
	Nguyen 2010 ⁷⁹	- ^a	+	- ^f	+	+	+	?	+	+	
	Phal 2008 ⁷⁵	- ^b	+	+	- ^h	- ^j	?	+	+	+	
	Rubinger 2016 ⁶⁶	- ^c	+	+	?	?	+	+	+	?	
	Strandberg 2008 ⁸⁰	- ^a	+	- ^f	?	- ^j	+	- ^m	?	?	
	Winston 2013 ⁴⁰	- ^b	+	+	?	- ^j	- ^k	+	+	?	
	Zijlmans 2009 ⁴²	- ^a	+	+	+	?	- ^k	+	+	+	
3 T mTLE with HS	Hashiguchi 2010 ⁷³	- ^c	+	+	+	+	+	+	+	+ ^o	
Bartolini 2019 ⁷²	- ^c	+	- ^f	+	- ^j	+	- ^m	?	?	+ ^o	
Colon 2018 ⁶⁷	- ^a	+	?	+	+	+	+	?	?	+	
7 T focal epilepsy, variable pathology or FCD	De Ciantis 2016 ⁷⁸	- ^a	+	- ^f	+	- ^j	+	- ^m	?	+	+
Liu 2020 ⁷⁴	- ^c	+	?	+	+	- ^j	+	+	?	?	+ ^o
Feldman 2019 ⁶⁸	- ^a	+	- ^f	+	+	+	+	+	?	?	+
Veersema 2017 ⁷⁶	- ^a	- ^e	- ^f	- ^h	- ^j	+	- ^j	+	+	+	+
Wang 2020 ⁷⁷	- ^a	+	+	- ^h	- ^j	+	+	+	+	+	+

7 T TLE	Kwan 2016 ⁶⁹	? ^d	+	? ^g	+	?	+	?	+
	Santyr 2017 ⁷¹	? ^d	+	? ^g	+	- ^j	+	?	+

+ Low risk of bias or low concerns regarding applicability; - High risk of bias or high concerns regarding applicability; ? unclear

^a High risk of selection bias due to inclusion of only those patients who had an inconclusive presurgical evaluation and/or who were non-lesional or inconclusive at lower field strength MRI

^b High risk of selection bias due to inclusion of only those patients who underwent both field strengths

^c High risk of selection bias due to inclusion of only those patients who underwent resection

^d Selection criteria for patients to undergo 7 T MRI not described

^e High risk of standardization bias due to use of different head coils and because some patients had an additional dielectric pad

^f High risk of standardization bias due to use of different field strengths

^g Coils not reported

^h Different reference standards used: surgical confirmation in part of patients; iEEG or noninvasive diagnostics in the others

ⁱ Reference standard not clearly stated

^j Suspected information bias

^k Inclusion criteria not restricted to epilepsy surgery candidates

^l Applicability concerns due to coils used

^m Applicability concerns due to use of a focused scan area

ⁿ Sequences not reported

^o All patients underwent resection

Supplementary table 3.6. Study characteristics of the included studies on standard and additional MRI sequences

Study	Data collection	Study objective	Age	Sample size	Sequence(s)	Field strength	Coils	Visual analysis
Ahmed 2018 ⁸¹	Retrospective	Asses improvement in lesion detection using additional HR dedicated 3 T MRI in children with medically refractory epilepsy who had normal 3 T epilepsy protocol MRI or suspected FCD	Mean 9.7 years \pm 0.5 years	98 ^a	All sequences combined (standard epilepsy protocol): - 3D T1 - FLAIR (cor+ax) - PD/T2 (cor+ax) All sequences combined (dedicated HR MRI) (targeting the lobe of the putative EZ): ^{a,b} - FLAIR (cor+ax) - PD/T2 (cor+ax)	3 T	8 channel head coil	Pediatric epilepsy neuroradiologist, unblinded
Bartolini 2019 ⁷²	Retrospective	Asses the diagnostic advantage of 7 T sequences in patients with histologically proven FCD	Mean 23 (range 9-40) years	12	7 T: -3DT1 -3D FLAIR -3D SWAN (+targeted SWAN) -2D T2* -2D T2 FSE -2D targeted gray-white matter border FSE-IR	7 T	2-channel quadrature transmit/32-channel receive head coil	One experienced neuroradiologist and one neurologist with expertise in advanced imaging, blinded to histopathologic diagnosis and epilepsy outcome
Chen 2018 ⁹³	Retrospective	Evaluate diagnostic value and characteristic features of FCD using FLAWS sequence	Mean 23 (range 8-48) years	39 (FLAWS+ conventional MRI) 17 (3D FLAIR)	-FLAWS (sag) -3D FLAIR (sag) All sequences combined: -FLAIR (cor+ax) -T1 (ax) -T2 (ax) -DWI (ax)	3 T	12 channel head-neck coil (for all sequences)	Two experienced radiologists blinded for clinical information. Disagreement resolved by consensus

Hashiguchi 2010 ⁷³	Retrospective	-Compare diagnostic utility of FLAIR at 3 T and 1.5 T -Assess clinical utility of 3DSTIR for HS diagnosis -Assess relationship of 3DSTIR hypointense hippocampal areas with severity of HS	Mean 33 (range 13-58) years	13	FLAIR (oblique along long hippocampal axis and coronal perpendicular to long hippocampal axis) -FLAIR (oblique along long hippocampal axis and coronal perpendicular to long hippocampal axis) -3DSTIR (parallel to long axis of hippocampus)	1.5 T 3 T 8-channel phased array coils	16-channel phased array coils	Two experienced neuroradiologists unaware of patient information; unclear how consensus was reached
Jack 1996 ⁸²	Retrospective	Compare FLAIR with double SE T2 in the identification of increased hippocampal signal intensity in HS patients	Mean 36 (range 11-57) years	32 ^b (x3=96 observations)	-T2 double SE (cor) -FLAIR (cor)	NR	NR	Three independent, experienced neuroradiologists, aware of temporal lobectomy but unaware which side and eventual histology results
Kantarci 2002 ⁸⁹	Prospective	Evaluate lateralizing value of interictal DWI (quantitative ADC) in patients with intractable TLE	Mean 37 ± 12 years	36 ^c	-DWI (cor)	1.5 T	NR	Right/left ADC ratio: cutoff calculated as ± 1 SD of healthy controls ROI placement and ADC calculations done by researcher blinded for the patients' diagnosis
Kim 1995 ⁸³	Retrospective	-Identify the extent or topographical distribution of hippocampal sclerosis by fast spin-echo MR -Correlate hippocampal sclerosis extent with histopathological results and seizure outcome after surgery	Mean 32 (range 13-57) years	30	-T2 FSE (cor)	NR	NR	Based on consensus by three neuroradiologist, unclear blinding

Kuzniecky 1997 ⁸⁴	Prospective	Determine the relative sensitivity of 3DT1, T1 IR and HT2 for the detection of HS	Mean 32 (range 11-57) years	44	-3DT1 -T1 IR (perpendicular to long axis of hippocampus)	1.5 T	NR	Two independent observers analyzed each MRI twice at different times (at 1- and 3- month intervals), disagreement resolved by consensus. Blinded for epileptic syndrome or EEG results. Each sequence separately analyzed
Kwan 2016 ⁶⁹	Prospective	-Determine the ability of 7 T MRI (particularly SWI) to detect hippocampal and mesial temporal lobe abnormalities -Evaluate the concordance between these findings and histopathology	Total cohort: range 16-65 years Operated: Mean 33 (range 18-50) years	9 ^d	1.5 T: -T2 (ax) -FSEIR (cor) -GE (cor) -3D FLAIR (cor) -3D T1 (ax) -DWI (ax) 7 T: -T1 MPRAGE -T2* (cor perpendicular to long axis of hippocampus) -SWI (cor perpendicular to long axis of hippocampus)	1.5 T	NR	Neuroradiologist blinded for clinical data
Lam 2020 ⁹²	Prospective	Assess the utility of ASL perfusion 3 T-MRI for the presurgical evaluation of poorly defined epilepsy in pediatric patients	Total cohort: Mean 10 (range 2-18) years	11 ^e	Conventional 3 T, sequences not clearly stated, combined: -3D-T1 -FLAIR -T2 -ASL	3 T	NR	Blinded to any hypotheses regarding the epileptogenic zone

Liu 2020 ⁷⁴	Retrospective	Explore the diagnostic value of 7 T MRI in epilepsy patients with FCD-IIa	Range 11-48 years	10	3 T:	3 T	NR	Unblinded review by a neuroradiologist and 2 neurosurgery specialists
					-3D T1 MPRAGE -2D T2 TSE -2D T2-FLAIR	7 T		
McBride 1998 ⁸⁵	Retrospective	Comparison between standard MRI protocol (outside epilepsy center) with epilepsy specific protocol (epilepsy center)	NR	46 ⁱ	7 T:	7 T	NR	Re-review using 5-point rating scale by two independent physicians experienced with temporal lobe abnormalities and blinded to patient identities, previous studies or side of surgery
					-3D T1 MPRAGE -2D T2 TSE -3D T2 FLAIR -SWI -WMS -GWB	Volume transmit/32-channel receive head coil		
Meiners 1994 ⁸⁶	Retrospective	Assess MRI features of histologically proven HS	Median 32 (range 14-43) years	14	All sequences combined:	1.5 T	Regular head coils	Three radiologists aware of temporal lobectomies but unaware on which side and blinded for the EEG. Final judgement reached by consensus
					-T1 (sag) -T2 (ax+cor through temporal lobe+ parallel to the long axis of the hippocampus) -IR (cor, through temporal lobe)			
Tien 1993 ⁸⁷	Retrospective	Determine the sensitivity and specificity of FSE in lateralizing HS	Total cohort: mean 31 (range 13-55) years	19 ⁹	-HR T2 FSE of the temporal lobes (cor, perpendicular to long axis of hippocampus)	1.5 T	NR	Three experienced neuroradiologists blinded to patient history. Patient and control images reviewed blinded and randomized. Discrepancy resolved by majority opinion.

Veersema 2016 ⁹¹	Retrospective	Localizing value of 7 T conventional sequences and T2* in patients with histologically proven FCD/mMCD	Mean 21 (range 7-45) years	6	-T2* All sequences combined: -3D FLAIR -3D DIR -3D T1 -3D T2	7 T	Volume transmit and 16- or 32-channel receive head coil	Unblinded review
Von Oertzen 2002 ⁸⁸	Retrospective	Compare sensitivity and specificity of standard MRI versus epilepsy-dedicated MRI in patients with focal epilepsy	NR	90 ^h	Basic head MRI (no details provided) All sequences combined: - T1 SE (sag) - T2 TSE (cor+ax) - T1 IR (cor) - FLAIR (ax)	NR	NR	Standard head MRI evaluated by non-expert radiologists and re-assessed by "expert" neuroradiologists informed of seizure semiology, blinded for other patient data, in particular previous MRI reports
Wang 2008 ⁹⁴	Prospective	Evaluate lateralizing value of conventional MRI and interictal DWI (quantitative ADC) in patients with intractable TLE	Mean 32.2 (range 6-51) years	27	-DWI (ax) All sequences combined: -T1 FLAIR (ax+sag) -T2 FSE (cor+ax) -T2 FLAIR (ax)	1.5 T	Standard head coil	Standard clinical MRI review by (neuro) radiologist Right/left ADC ratio: cut-off calculated as ± 1 SD of healthy controls
Wehner 2007 ⁹⁵	Retrospective	Evaluate lateralizing value of interictal DWI (quantitative ADC) in patients with intractable TLE	Median 39 (range 6-56) years	22	-DWI (cor)	1.5 T	NR	ADC (contralateral-resected/both) cut-off calculated as ± 2 SD of healthy controls NR if the radiologist judged the ADC with knowledge of the side of surgery

Yoo 2002 ⁹⁰	Prospective	Evaluate lateralizing value of interictal DWI (qualitative DWI/ADC and quantitative ADC) in patients with intractable TLE	Mean 30 (range 16-42) years	18 ⁱ	-DWI (ax)	1.5 T	NR	Qualitative DWI/ADC: consensus by two experienced neuroradiologists without knowledge of any clinical or conventional MRI data
					All sequences combined: -T1 SE (sag) -T2 FSE (ax) -T2 FSE (oblique coronal plane perpendicular to long axis of hippocampus) -FLAIR (idem) -3D T1 SPGR (idem)			Quantitative ADC: (right-left) / (right + left) / 2 Cut-off calculated as ± 2 SD of healthy controls

^a 98/101 with abnormal histopathology
^b 32/36 with histopathologically confirmed HS
^c 36/40 with abnormal histopathology
^d 9/13 with abnormal histopathology
^e 11/25 operated
^f The total number of patients in whom histopathology did not show an abnormality is unclear
^g 19/21 with histopathologically confirmed HS
^h 90/123 with abnormal histopathology
ⁱ In TLE patients sequences were oriented perpendicular or parallel to the longitudinal axis of the hippocampus
^j 16/18 underwent resection and had histopathology available, however no separate data for the resected patients presented

Supplementary table 3.7. Quality appraisal for the studies included for standard MRI sequences

Study	RISK OF BIAS			APPLICABILITY CONCERNS		
	PATIENT SELECTION ^a	INDEX TEST	REFERENCE STANDARD	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Variable pathology	-	? ^b	+	+	? ^b	+
	vonOertzen 2002 ⁸⁸					
	Ahmed 2018 ⁸¹	? ^b	+	+	? ^b	+
FCD	-	+	+	+	- ^f	+
	Bartolini 2019 ⁷²					
	Chen 2018 ⁹³	+	+	+	+	+
	Liu 2020 ⁷⁴	? ^b	+	+	? ^b	+
	Hashiguchi 2010 ⁷³	+	+	+	+	+
	Jack 1996 ⁸²	? ^b	+	+	- ^{bg}	+
HS	-	? ^b	+	+	? ^b	+
	Kim 1995 ⁸³					
	Kuzniecky 1997 ⁸⁴	? ^b	+	+	? ^b	+
	Meiners 1994 ⁸⁶	+	+	+	+	+
	Tien 1993 ⁸⁷	? ^b	+	+	? ^b	+
TLE, variable pathology	-	? ^b	+	+	? ^b	+
	McBride 1998 ⁸⁵					
	Wang 2008 ⁹⁴	+	- ^c	+	? ^b	+
	Wehner 2007 ⁹⁵	? ^b	+	+	? ^b	+

+ Low risk of bias or low concerns regarding applicability; - High risk of bias or high concerns regarding applicability; ? unclear

^a High risk of selection bias in all studies^b Field strength and/or coils not reported^c Total number of patients who had normal histopathology not reported^d Suspected information bias^e Results not mentioned per individual patient but as numbers of observations with multiple observations per patient^f Applicability concerns due to use of a focused scan area^g Used film prints of MRI

Supplementary table 3.8. Quality appraisal for the studies included for additional MRI sequences

Study	RISK OF BIAS					APPLICABILITY CONCERNS			
	PATIENT SELECTION ^a	INDEX TEST	COMPARATOR TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	COMPARATOR TEST	REFERENCE STANDARD
TLE	Kantarci 2002 ⁸⁹	-	? ^c	+ ^d	+	+	? ^c	? ^c	+
	Kwan 2016 ⁶⁹	? ^b	+	? ^c	+	+	+	? ^c	+
	Wang 2008 ⁹⁴	-	+	+	? ^{g,h}	+	+	+	+
	Wehner 2007 ⁹⁵	-	? ^c	NA ^e	+	+	? ^c	NA ^e	+
	Yoo 2002 ⁹⁰	-	? ^c	? ^c	- ^f	+	+	? ^c	+
Variable pathology	Lam 2020 ⁹²	-	? ^c	? ^c	+	+	? ^c	? ^c	+
FCD	Chen 2018 ⁹³	-	+	+	+	+	- ⁱ	+	+
	Veersema 2016 ⁹¹	-	+	+	- ^g	+	+	+	+

+ Low risk of bias or low concerns regarding applicability; - High risk of bias or high concerns regarding applicability; ? unclear

^a High risk of selection bias in all studies, but one

^b Patient selection unclear

^c Field strength and/or coils not reported

^d Details on conventional MRI not presented

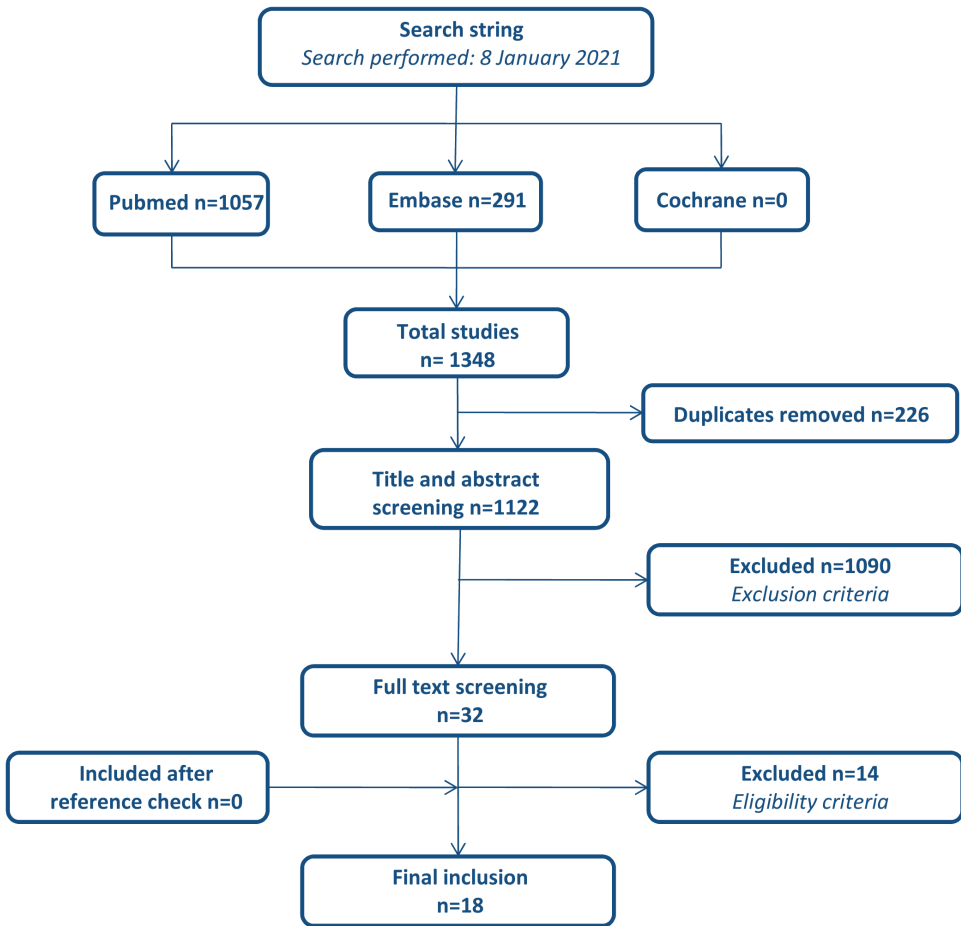
^e No comparator test included

^f No separate data provided for patients with histopathologically confirmed HS

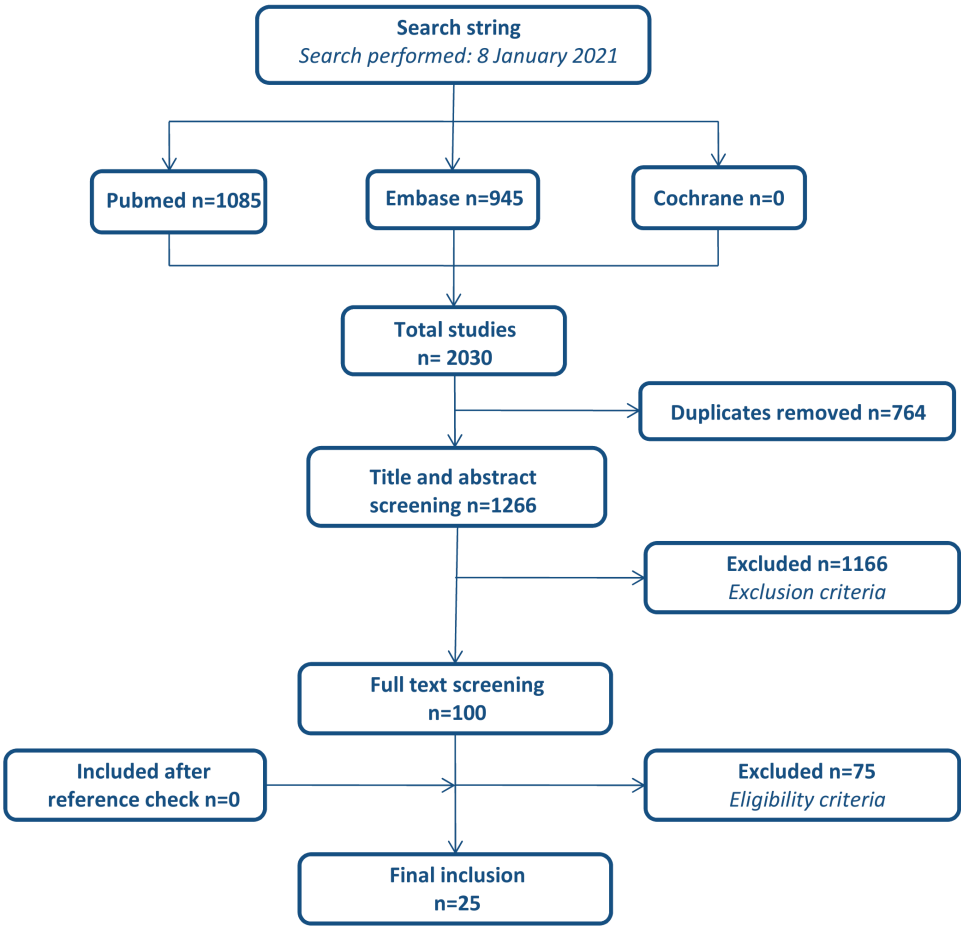
^g Suspected information bias

^h Index and comparator test at different field strengths

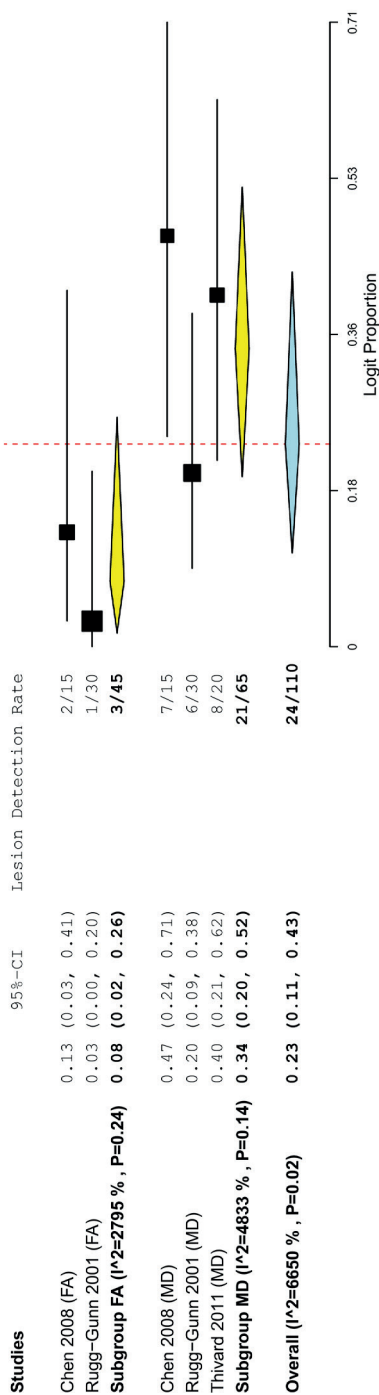
ⁱ Studied a sequence not widely available



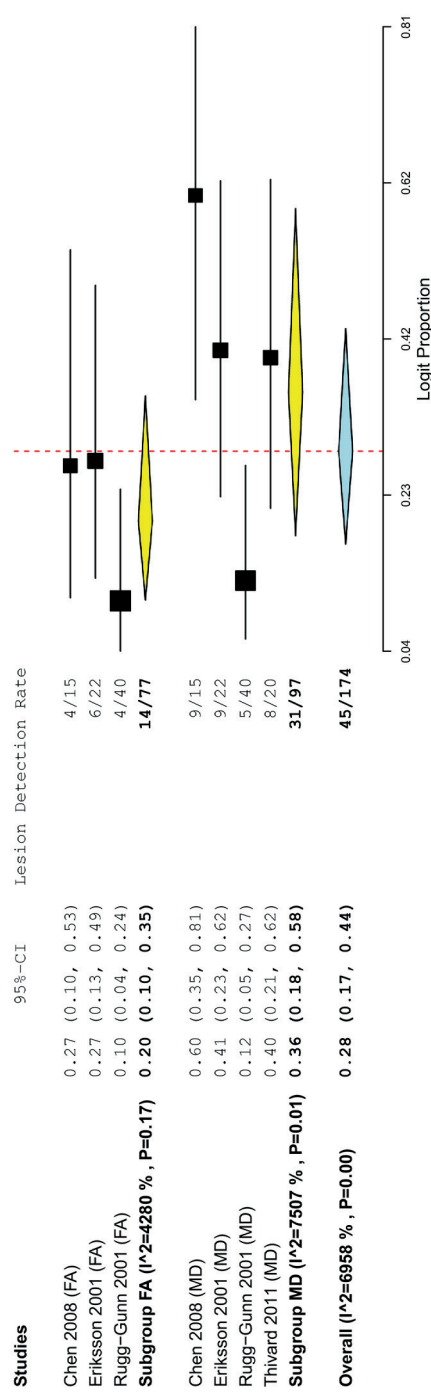
Supplementary figure 3.1. Flow of studies through review process for MRI field strength



Supplementary figure 3.2. Flow of studies through review process for MRI sequences



Supplementary figure 3.3. Forest plot additional DTI lesion detection rate in patients with normal conventional MRI



Supplementary figure 3.4. Forest plot false lesion detection on DTI

CHAPTER 4

Diagnostic accuracy of interictal source imaging in presurgical epilepsy evaluation: a systematic review from the E-PILEPSY consortium

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Objective

Interictal high resolution (HR-) electric source imaging (ESI) and magnetic source imaging (MSI) are non-invasive tools to aid epileptogenic zone localization in epilepsy surgery candidates. We carried out a systematic review on the diagnostic accuracy and quality of evidence of these modalities.

Methods

Embase, Pubmed and the Cochrane database were searched on 13 February 2017. Diagnostic accuracy studies taking post-surgical seizure outcome as reference standard were selected. Quality appraisal was based on the QUADAS-2 framework.

Results

Eleven studies were included: eight MSI ($n = 267$), three HR-ESI ($n = 127$) studies. None was free from bias. This mostly involved: selection of operated patients only, interference of source imaging with surgical decision, and exclusion of indeterminate results. Summary sensitivity and specificity estimates were 82% (95% CI: 75–88%) and 53% (95% CI: 37–68%) for overall source imaging, with no statistical difference between MSI and HR-ESI. Specificity is higher when partially concordant results were included as non-concordant ($p < 0.05$). Inclusion of indeterminate test results as non-concordant lowered sensitivity ($p < 0.05$).

Conclusion

Source imaging has a relatively high sensitivity but low specificity for identification of the epileptogenic zone. We need higher quality studies allowing unbiased test evaluation to determine the added value and diagnostic accuracy of source imaging in the presurgical workup of refractory focal epilepsy.

Introduction

Epilepsy surgery can be a curative treatment option in patients with refractory focal epilepsy. Success of surgery depends on accurate delineation of the epileptogenic zone (EZ). The EZ is a theoretical construct describing the minimum volume of cortical tissue, that is responsible for generation of habitual seizures, and that has to be resected to produce seizure-freedom⁶. Clinical semiology, imaging and electrophysiological data yield important localizing information about the EZ. Video-EEG monitoring (vEEG), magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission tomography (SPECT) and intracranial EEG (iEEG) are frequently used modalities in the presurgical workup⁷.

High resolution electric source imaging (HR-ESI) and magnetic source imaging (MSI) are additional electrophysiological techniques to non-invasively localize epileptogenic brain regions. By reconstructing the electric or magnetic potentials as identified by EEG or MEG, locations of underlying source currents are estimated and subsequently combined with structural imaging. Source localization is often based on interictal epileptic discharges (IED), which are frequently observed during EEG or MEG recording. Because IEDs mark the irritative zone and may not always be concordant with the seizure onset zone^{108,109}, source localization based on ictal data has been proposed in patients with high seizure frequency¹¹⁰⁻¹¹³. So far most experience has been acquired with interictal ESI and MSI, but complete clinical integration across all epilepsy surgery centers has not been established yet^{59, 114, 115}. A number of epilepsy-specific clinical practice guidelines and general recommendations have been published^{32, 116-118}. Yet, disparities in current practice among users on aspects such as the number and positions of sensors, and the selection of inverse and volume conduction models remain^{59, 114}. This may be due to the various technical complex and non-intuitive aspects involved in source localization¹¹⁹. MSI and HR-ESI appear to be complementary techniques that differ in their sensitivity for various neural generators: fundamentally MSI is more accurate than ESI in detecting superficial tangentially orientated sources and involves no signal distortion (volume conduction) while EEG allows recording of all source orientations, is more sensitive to deep sources and is less affected by motion artefacts¹²⁰. One previous systematic review on MSI reported that there is insufficient evidence on the use of MSI in the presurgical evaluation¹²¹. This review did not evaluate HR-ESI and was published nearly a decade ago. In light of the E-PILEPSY network [<http://www.e-epilepsy.eu/>], which aims to harmonize and optimize presurgical diagnostic procedures across European countries, we carried out a systematic review to assess the diagnostic accuracy of interictal HR-ESI and MSI to localize epileptogenic regions of interest in epilepsy surgery candidates.

Methods

Establishment of task force and protocol

As a first step we conducted a broad literature search to allow an orientation on the available literature. Based on this, we established a systematic review protocol containing research questions and study inclusion criteria. A task force was formed of 14 E-PILEPSY members (corresponding co-authors) to allow a broad acceptance of the systematic review protocol and to aid other review tasks (e.g. paper screening, data extraction). Members were familiar with both the field of source imaging and epilepsy surgery, having different educational backgrounds (physicists and physicians) and varying experience (PhD students to professors). Consensus was reached among task force members on the final systematic review protocol.

Search strategy

PubMed, Embase and Cochrane were last searched on 13 February 2017 for articles on the diagnostic value of EEG and MEG source localization in epilepsy. We included synonyms and abbreviations for the terms of interest, and used subject headings (i.e. MeSH, EmTree). The search syntaxes are provided in supplementary material A. The search strategy was limited to humans, English language, and publication date after 1995. Duplicates were eliminated.

Study selection

Title and abstract screening of the studies was done by one of two author couples (BM & MR, GH & FL). Discrepancies in eligibility were discussed and final agreement was reached through a consensus meeting. References found in source imaging review papers were screened. Studies were excluded if there was insufficient information to fully assess their eligibility (e.g. full text not available in English, unavailable abstract, unavailable full text). Letters, commentaries, conference abstracts, poster presentations and supplementary materials were also excluded, as were articles focusing on epilepsy not amenable to surgery (i.e. rolandic epilepsy or idiopathic generalized epilepsy), and EEG-fMRI. Other procedures, such as connectivity analysis^{122, 123}, source volume estimation¹²⁴, beta-band activity source imaging¹²⁵, slow wave interictal MSI¹²⁶ and analysis of high frequency oscillations¹²⁷, were not subject of the review due to their limited clinical utilization compared to traditional interictal source imaging.

Studies were then screened on full text by couples of two independent taskforce members. Full text inclusion criteria were: epilepsy surgery candidates, interictal MSI or interictal ESI, diagnostic accuracy based on level of concordance between ESI or MSI source location and the resected area taking seizure outcome as reference standard.

We consulted authors in the case of unavailable full-text. Studies needed to report on sensitivity or specificity including confidence intervals and/or absolute numbers that allow calculation of these statistics. If this was not the case the study was excluded. The full eligibility checklist is provided in Supplementary material B. Disagreement was discussed and final agreement was reached between the members of each couple before they submitted their full text screening results.

Critical appraisal and data extraction

An online quality appraisal and data extraction form was created that was first piloted before use. Studies were assessed for methodological quality against modified QUADAS-2 (quality assessment of diagnostic accuracy studies) criteria⁶⁴. Certain aspects of the QUADAS-2 framework were thought to be irrelevant and thus left out from the quality appraisal, such as avoidance of disease progression bias. Results between reviewers of a couple were compared and, if necessary, a web-meeting or email conversation was initiated with a third person to resolve disagreement.

Studies were excluded during data extraction in the case of: 1-sample size less than 10 participants, 2-patients included with less than 6 months follow up, 3-not categorizing surgical outcome by means of Engel¹²⁸ or ILAE classification¹²⁹, 4-no classification of concordant and non-concordant ESI or MSI results, 5-low resolution ESI (<64 channels), 6-not presenting results for low resolution (<64 channels) and high resolution (≥64 channels) ESI separately, 7-absence of patients in any of the four groups of the 2 × 2 contingency table (i.e. zero values).

Data analysis

We considered diagnostic accuracy as the ability of source localization (HR-ESI or MSI) to detect and localize an epileptogenic source within a brain region that is subsequently validated as epileptogenic based on resection and surgical outcome. Concordance between source location and resected volume was considered as 'test positive' and may represent source localization within resection volume or sublobar co-localization of the source estimate with resection volume. Non-concordance was defined as 'test negative'. Post-surgical outcome was taken as reference standard, discriminating between good and poor surgical outcome (figure 4.1).

In accordance with most studies, sensitivity was defined as the proportion of good-outcome patients with concordant classification (i.e. test positive), relative to the total number of good-outcome patients. Specificity was defined as the proportion of poor-outcome patients with non-concordant classification (i.e. test negative), relative to the total number of poor-outcome patients.

		Surgery		Non-surgery
		Good surgical outcome	Poor surgical outcome	Unclear
Localizing	Concordant	True positive	False positive	
	Partially concordant	↑ Sensitivity increase ↓ Sensitivity decrease	↑ Specificity decrease ↓ Specificity increase	
	Non-concordant	False negative	True negative	
Non-localizing		↑ Sensitivity decrease	↑ Specificity increase	
		Unclear	Unclear	

Figure 4.1. Diagnostic accuracy 2 × 2 contingency table for source localization. Concordant: MSI or ESI source within resection volume or sublobar concordancy with resection volume. Sensitivity: true positives/ (true positives + false negatives). Good surgical outcome: Engel 1/ILAE 1–2. Poor surgical outcome: Engel ≥ 2/ILAE ≥ 3. Indeterminate test results: e.g. too low number of IEDs, artefacts. Specificity: true negatives/(true negatives + false positives). Allocation of partially concordant (i.e. partially resected) to concordant or non-concordant group affects sensitivity and specificity. Allocation of indeterminate test results tot the non-concordant group affects sensitivity and specificity.

Positive and negative predictive values (PPV, NPV) were not considered in this study. Since the proportion of patients with either non-localizing source localization results, or those not proceeding to surgery after source localization procedure, was unknown in most studies the calculation of positive and negative predictive values was deemed unreliable. Moreover, predictive values are expected to vary strongly among studies due to different presurgical workup strategies (comprehensive versus limited workup), surgical strategies (liberal versus conservative resection) and patient characteristics (e.g. lesional versus non-lesional, TLE versus ETLE). Results from patients undergoing hemispherectomy, hemispherotomy, or re-resection (second stage surgery) were excluded from analysis.

To establish homogeneity among studies, we defined “good outcome” as Engel I or ILAE 1-2. Results from studies classifying Engel II or ILAE 3 as good outcome were manually corrected to our proposed definition, if data was provided. If not, the definition as proposed in the study was adopted. For studies quantitatively reporting level of overlap between resection area and source (e.g. 90% of dipoles within resected area) the dichotomization threshold as used in the study was selected- discriminating concordant from non-concordant - to account for the effect of source localization parameters on threshold definition only known by study authors. We selected the concordance definition (i.e. sublobar co-localization or location within resection volume) that the primary study used for sensitivity and specificity calculation and included this in our analysis.

Allocation of partially concordant categories theoretically affects sensitivity and specificity calculations (figure 4.1). For those studies that provided information, we allocated partially concordant results as normal concordant results to ensure homogeneity across all studies regarding classification. Patients with multiple sources (either within one lobe or across multiple lobes) were also handled as concordant, even when only one source was partially resected. Indeterminate test results (i.e. no source localization possible due to insufficient numbers of IEDs, too many artefacts or scattered sources) were handled as a separate category and reported as a percentage from study sample size for each study^{130, 131}.

We calculated mean proportions (including 95% confidence intervals) for good-surgical outcome in each concordance group using a weighted binary random-effects model. We calculated a summary estimate of sensitivity and specificity by means of the bivariate linear mixed model by Reitsma to account for the two-dimensional trade-off between sensitivity and specificity^{132, 133}. Subgroup analysis was performed for the selection of studies that provided surgical outcome information for indeterminate and partial concordance test results. Subgroup analysis for epilepsy location (TLE versus ETLE) and MRI results (lesional versus non-lesional) was performed. Statistical programming was done using the program Open-Meta Analyst and the mada package used in .R¹³⁴.

Results

Study selection

Figure 4.2 visualizes the flow of studies through the review process. Our search yielded 1964 papers after removal of duplicates. After title/abstract screening 96 papers were selected for full text assessment. Reference checking of review papers revealed two new studies. Fifty one studies proceeded to data extraction and quality appraisal, of which twelve were prospective. Seven of these were excluded for reason of different study objectives ($n = 5$)¹³⁵⁻¹³⁹, not concerning the population of interest ($n = 1$)¹⁴⁰ or for not using a reference standard of interest¹⁴¹. In total, forty studies were excluded during data extraction (see supplementary material C for list of excluded studies in this phase and their exclusion reasons). This led to a total of 11 studies that were included in the review: eight on MSI, three on HR-ESI^{149, 142-151}.

Study characteristics

All studies were cross-sectional cohort studies, of which five were prospective (table 4.1). The number of included patients with positive source localization (sample size) ranged from 14 to 52 (median 36). Seven studies reported the proportion of patients with indeterminate test results: one HR-ESI study (16%) and six MSI studies (7–36%, median 17%). Four of these six MSI studies additionally provided surgical outcome results for this group^{142, 145, 147, 148}.

Table 4.1. A: adult; EZ: epileptogenic zone; (F) CD: (focal) cortical dysplasia; MLR: multi-lobar resection; P: paediatric; SLR: single lobe resection; SR: surgical resection sim EEG: simultaneously recorded EEG; ^a: one patient with scattered source result excluded; ^b: eight second stage surgery patients excluded; ^c: surgical outcome for partial concordance category provided; ^d: insufficient details on Engel classification to reclassify; ^e: nine patients with scattered source results excluded, 9 patients with repeated surgery excluded ^f: two thresholds reported by study (10% and 25%), highest threshold selected by reviewers; ^g: patients with less than 6 months follow-up excluded ^h: type of source estimate (e.g. single dipoles, clusters) not specified. ⁱ: study classifies partially/non-concordant results with poor outcome as indeterminate test result. For data analysis purposes these were considered true negatives by reviewers; ^j: post-op MRI available, but study did not report its role in resection volume estimation; ^k: thirteen indeterminate test results excluded; ^l: 6/38 did not undergo surgery and were excluded; ^m: When one of the solution points directly neighbouring the source maximum was inside the resection volume, this was considered concordant.

Study	Data collection	Sample size ^a	Age group	Population characteristics	Type of test	Type of resective surgery	% multiclusters	Resection volume estimation	Study's concordance definition	Minimum follow up (years)	Good outcome definition
Jeong et al., 2012 ¹⁴²	Retrospective	24 ^a	A	FCD (histologically confirmed)	MEG (+sim EEG)	SLR (23), MLR (1)	50	Post-op MRI	Complete or partial cluster resection	1	Engel 1
Kim et al., 2013 ¹⁴³	Retrospective	14 ^b	P	Neocortical epilepsy	MEG (+sim EEG)	SLR (13), MLR(1)	79	Post-op MRI	>70% of all dipoles within resection volume	1	Engel 1
Schneider et al., 2012 ¹⁴⁴	Retrospective	18	A+P	Neocortical MRI negative epilepsy	MEG (+sim EEG)	SLR (16), MLR (2)	39	Post-op MRI	Complete or partial resection of unifocal cluster ^c	2	Engel 1a ^d
Wilenius et al., 2013 ¹⁴⁵	Retrospective	16 ^e	A+P	FCD (histologically confirmed)	MEG	SLR (14), MLR(2)	6	Post-op MRI	>25% of source clusters within resection volume ^f	0,5	Engel 1 ^g
Papanicolaou et al., 2005 ¹⁴⁶	Prospective	41	A+P	Mixed group	MEG (+sim EEG)	Not specified	unclear	Not specified	Complete source estimate resection ^{ch,i}	1	ILAE class 1-2
Mu et al., 2014 ¹⁴⁷	Retrospective	38	A+P	FLE	MEG	Not specified	24	Not specified ^j	Complete cluster resection ^c	0,5	Engel 1

Knowlton et al., 2008 ¹⁴⁸	Prospective	49 ^k	A+P	Inconclusively localizing MRI and vEEG with seizures recorded on ICEEG	MEG (+sim EEG)	Not specified	Unclear	Not specified	Sublobar co-localization of cluster and resection volume	1	Engel 1
Almubarak et al., 2014 ¹⁴⁹	Retrospective	36	A+P	Mixed group with localizing ICEEG	MEG (+sim EEG)	Not specified	Unclear	Post-op MRI	Complete cluster resection	0,5	Engel 1a ^d
Brodbeck et al., 2011 ⁴⁹	Prospective	52	A+P	Mixed group	HR-EEG	SLR (41), MLR(11)	NA	Not specified	Complete source maximum resection	1	Engel 1
Megevand et al., 2014 ¹⁵⁰	Prospective	32 ^l	A+P	Mixed group, all underwent ICEEG	HR-EEG	Not specified	NA	Post-op MRI	Complete source maximum resectionm	1	Engel 1
Feng et al., 2016 ¹⁵¹	Prospective	43	A+P	TLE which did not require ICEEG	HR-EEG	Not specified	NA	Post-op MRI	Sublobar co-localization of source maximum and resection volume	0,58	Engel 1-2 ^d

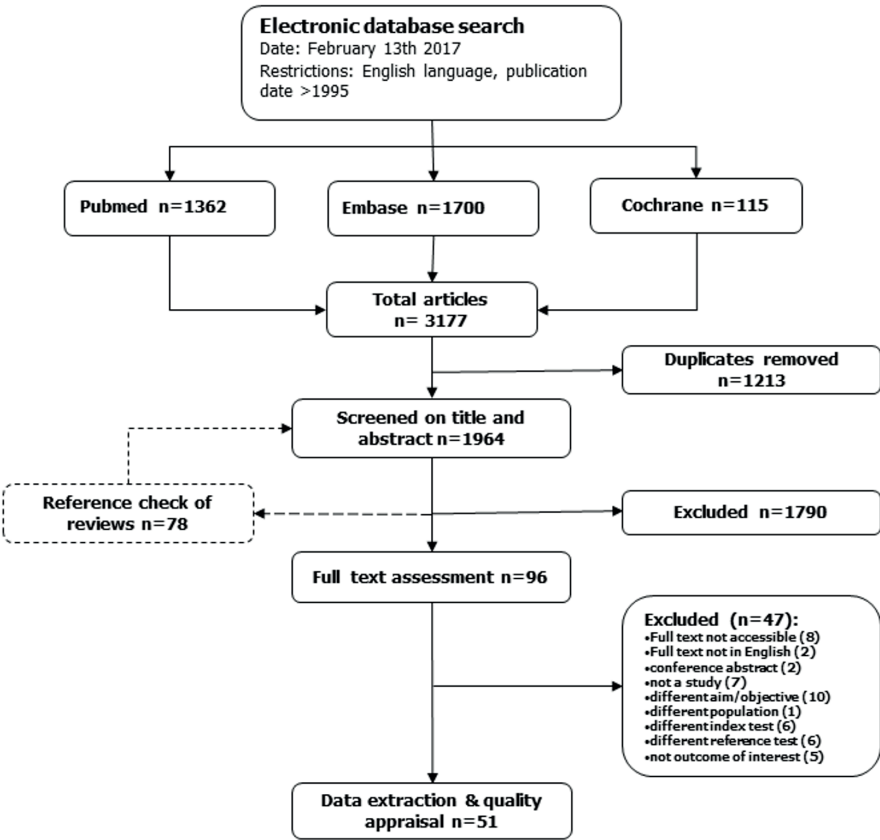


Figure 4.2. Flow of studies through review process.

Three studies reported that indeterminate test results may be resulting from their source localization procedure but did not specify the amount of patients to which this applied^{144, 146, 151}. One study did not mention indeterminate test results at all⁴⁹.

Regarding population characteristics, one study focused on adults, one on children, and nine included both age groups. Inclusion criteria varied among studies. Indications to perform ESI or MSI were not always explicitly stated, but could be derived from inclusion criteria. Five studies provided information whether resection included single lobe or multiple lobes for each patient.

Seven studies used post-operative MRI to assess the resection volume. Three studies did not mention use of post-op MRI. One study reported that post-op MRI was available, but did not further specify if this was applied to assess resection volume¹⁴⁷. Concordance with resection volume was defined as sublobar by two and as 'source estimate within resection volume' by nine studies.

Concordance definition varied among studies. Six studies specified how partially concordant results were handled. Three studies separately reported surgical outcome for patients with partially concordant results^{144, 146, 147}. Three studies did not: two included patients with partial concordance in the complete concordance group^{142, 150}, and one considered this as non-concordant¹⁴⁹. Multifocal source estimates were reported by five MSI studies; their occurrence ranged between 6% and 79% (median, 39%) of the patients^{142-145, 147}. Three studies classified resection of only one source in a multifocal source patient as concordant. One study classified such cases as non-concordant. One study presented data for multi-cluster cases but did not state its classification, and was therefore considered non-concordant by our reviewers.

All but one study used Engel class to define outcome. Definition of good outcome varied between Engel 1a and Engel 1–2. Minimum follow up period ranged from 6 months to one year. Study duration ranged between 2–11 years.

All HR-ESI studies used sensor nets with whole-head coverage consisting of 128-256 EEG electrodes. One study used a realistic head model (FDM)¹⁵¹ and two a spherical head model (SMAC)^{49, 150}. Linear distributed inverse solution based on averaged spikes was used in all studies. One used LORETA¹⁵¹, one LAURA⁴⁹ and one used an unspecified distributed inverse solution¹⁵⁰.

All MSI studies used whole-head MEG. In one study the applied technique varied between double-probe (74 channels) and whole-head (306 channels) MEG¹⁴⁷. Six out of eight studies used simultaneous EEG to aid IED identification. No averaging was performed in any study. All studies used equivalent current dipole (ECD) as inverse solution. Overall, cluster definition varied among studies.

Methodological quality

Study quality was generally assessed as "poor" according to QUADAS-2; no study was free from bias (table 4.2). Studies scored badly on disease spectrum bias, partial verification bias and inappropriate exclusions from data analysis. All studies enrolled a consecutive sample of patients, none were of case-control design.

Table 4.2. Quality appraisal of individual studies. + low risk, - high risk, ? unclear risk.

Type of test	Study	Risk of bias			Applicability concerns			
		Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
MSI	Jeong et al., 2012 ¹⁴²	-	?	+	-	+	?	+
	Kim et al., 2013 ¹⁴³	+	?	+	-	+	?	+
	Schneider et al., 2012 ¹⁴⁴	-	+	-	-	+	+	+
	Wilenius et al., 2013 ¹⁴⁵	-	-	+	-	+	+	+
	Papanicolaou et al., 2005 ¹⁴⁶	+	+	+	-	+	+	+
	Mu et al., 2014 ¹⁴⁷	-	+	-	-	+	+	+
	Knowlton et al., 2008 ¹⁴⁸	-	+	-	-	+	+	+
	Almubarak et al., 2014 ¹⁴⁹	-	+	-	-	+	+	+
	Brodbeck et al., 2011 ⁴⁹	+	+	-	?	+	+	+
	Megevand et al., 2014 ¹⁵⁰	-	+	+	-	+	+	+
HR-ESI	Feng et al., 2016 ¹⁵¹	-	+	+	-	+	+	+

Selection bias (i.e. disease spectrum bias) was applicable to eight studies. This was the case for studies selecting specific populations such as patients undergoing or not undergoing intracranial EEG, patients with frontal lobe epilepsy or patients with histologically proven focal cortical dysplasia. A consequence of our inclusion criteria was an additional general disease spectrum bias across all studies. It was believed that exclusion of patients that were considered non-eligible for surgery based on presurgical workup, most likely resulted in an over-estimation of diagnostic accuracy. We did not visualize this in the quality summary to permit between-study difference in selection bias to be noticeable.

One study was biased for the index test based on data-driven threshold selection¹⁴⁵. Two retrospective studies did not report information on blinding from reference standard information, and were judged as unclear for index test bias.

Reference standard bias was observed in five studies. Good surgical outcome was defined as only Engel 1a by two studies^{144, 149} or only Engel 1–2 by one¹⁵¹. Three studies included patients with follow up period between 6–12 months^{147, 149, 151}. Two studies classified concordance based on sublobar co-localization^{148, 151}. Bias regarding study flow was observed in ten studies. In six studies, source localization results were considered in the decision to proceed to surgery (partial verification bias), the decision for coverage/ placement of ICEEG, or the area/extend of resection (differential verification bias)^{143-145, 147-149, 151}. Six studies did not report surgical outcome data for indeterminate test results^{142-144, 146, 149, 151}. All factors possibly led to over-optimistic diagnostic accuracy. Insufficient data was reported by one study to permit bias judgment⁴⁹.

Variations among studies with respect to population, index test specifics, and reference standard specifics were not considered a concern regarding applicability as all these represented part of general clinical practice.

Diagnostic accuracy

Diagnostic accuracy analysis of MSI and ESI accuracy included a total of 394 patients, 267 on MSI and 127 on HR-ESI, of whom surgical outcome data was available. In 363 patients a localizing source was found: 236 MSI and 127 HR-ESI (figure 4.3). For all MSI studies, good surgical outcome was reached in 130/236 patients (mean: 54%, 95% CI: 45–63%). For HR-ESI this was 86/127 patients (mean: 67% 95% CI 49–85%). No statistical difference on the probability of good surgical outcome between MSI and HR-ESI studies was observed.

In total, the number of patients with good surgical outcome in the concordant group was higher (172/226 patients, mean: 76%, 95% CI: 67–86%) than the number of patients in the non-concordant group (36/111 patients, mean: 28%, 95% CI: 19–36%). Statistical

difference between the concordant and non-concordant group regarding good surgical outcome probability was found for MSI and HR-ESI (table 4.3).

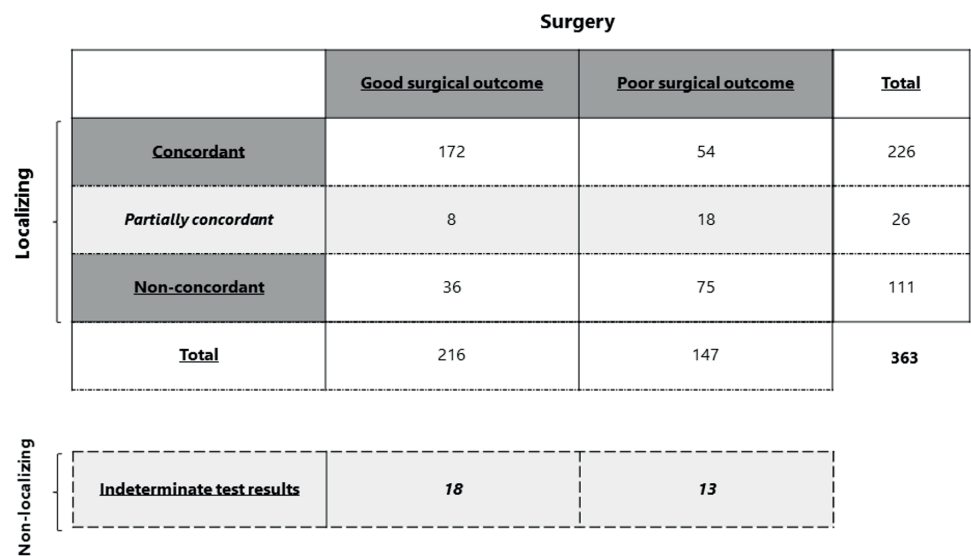


Figure 4.3. 2x2 contingency table for patient total in all studies (both MSI and HR-ESI).

Table 4.3. Odds ratio of level of concordance for surgical outcome. HR-ESI: High resolution electric source imaging. MSI: magnetic source imaging. ^a based on studies reporting surgical outcome for partially concordant cases, three MSI studies in total.

Concordance category per type of test	Good surgical outcome probability in patients (mean, 95% CI)	Odds ratio	95% Confidence interval	P-value
HR-ESI				
Concordant	75/91 (82%, 67-98%)	9.6	3.8 – 24.0	<0.001
Partially concordant	Not applicable	-	-	-
Non-concordant	11/36 (30%, 15-45%)	Ref	-	-
MSI				
Concordant	97/135 patients (74%, 63-85%)	4.7	1.7- 12.9	0.002
Partially concordant ^a	8/26 patients (30%, 12-47%)	1.7	0.35-8.4	0.512
Non-concordant	25/74 patients (25%, 13-37%)	Ref	-	-

Surgical outcome data of indeterminate test results was available in four MSI studies; 18/31 patients (mean 56%, 95% CI:33–79%) had good surgical outcome. Sensitivity ranged between 50–96% for MSI and 80–91% for HR-ESI. Specificity ranged between 17–80% for MSI and 56–75% for HR-ESI (supplementary material D).

Summary estimates based on the bivariate linear mixed model showed sensitivity and specificity of 82% (95% CI: 75–88%) and 53% (95% CI: 37–68%) for overall source localization. For HR-ESI, summary sensitivity and specificity were 87% (95% CI: 77–93%) and 61% (95% CI: 45–74%) respectively (figure 4.4). For MSI, summary sensitivity and specificity were 79% (95% CI: 69–87%) and 46% (95% CI: 25–70%) respectively. HR-ESI and MSI sensitivity/specificity estimates did not show statistical difference ($p > 0.05$).

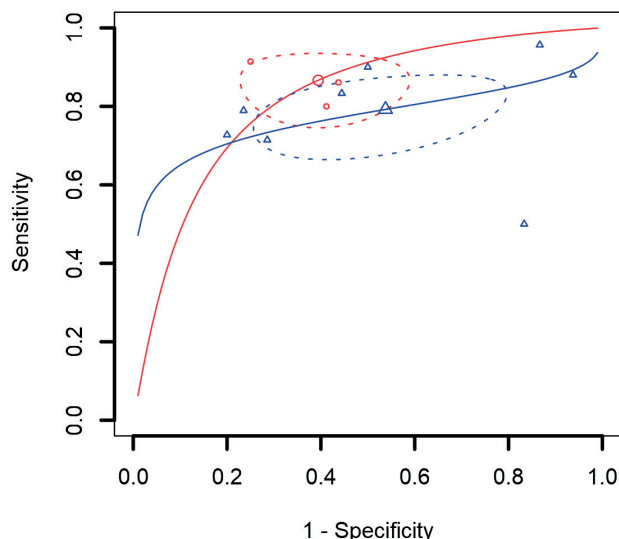


Figure 4.4. Summary ROC curve with summary estimates for HR-ESI (red) and MSI (blue). Individual studies are shown as small symbols. Summary points shown as large symbols, representing sensitivity and specificity estimates pooled using the bivariate linear mixed model. The 95% CI is represented by dotted line (---).

Sensitivity and specificity estimations based on single source locations were based on five MSI studies and were 83% (95% CI: 63–93%) and 22% (95% CI: 20–72%) respectively. No statistical differences regarding sensitivity and specificity estimates were observed when multifocal sources were included in the estimation (supplementary material E). Analysis for the allocation of partially concordant results was based on three studies. A statistically significant higher specificity estimate was observed when partially concordant results were categorized as non-concordant, compared to concordant categorization (69% versus 20%, $p < 0.05$). Based on four studies reporting surgical outcome of patients with indeterminate source imaging results, statistically significant lower summary sensitivity was observed when indeterminate test results were included in the estimates and considered non-concordant (61% versus 76%, $p < 0.05$).

Subgroup analysis showed good surgical outcome in 11/14 lesional patients (mean: 80%, 95% CI: 61–99%) and 46/68 non-lesional patients (mean: 60%, 95% CI: 43–85%) with concordant results. For non-concordant results these were 2/12 in lesional patients (mean: 16%, 95% CI: –1–34%) and 8/18 in non-lesional patients (mean: 42%, 95% CI: 19–66%). Summary sensitivity for lesional and non-lesional patients was similar, and specificity showed no apparent difference ($p = 0.059$, supplementary material E).

Subgroup analysis for lobar location showed that a good surgical outcome was achieved in 64/96 TLE patients (mean: 61%, 95% CI: 33–89%) and 47/92 ETLE patients (mean: 43%, 95% CI: 21–65%) with concordant results. Good surgical outcome was achieved in 9/24 TLE patients (mean: 37%, 95% CI: 19–54%) and 12/34 in ETLE patients (mean: 42%, 95% CI: 16–68%) of the non-concordant group. Summary sensitivity and specificity for TLE and ETLE subgroup were comparable and no statistically significant differences were observed (supplementary material E).

Discussion

Electric and magnetic source localization are believed to be valuable techniques in the diagnostic workup of epilepsy surgery candidates. We performed a systematic review and included eight studies on MSI and three on HR-ESI that used seizure outcome after surgery as a reference standard. All studies were highly biased on various aspects, with considerable heterogeneity among studies regarding the included population and test methodology. Bivariate meta-analysis estimated a summary sensitivity and specificity of 82% (95% CI: 75–88%) and 53% (95% CI: 37–68%) for overall source localization and no statistical difference between HR-ESI and MSI was found.

The only previous systematic review on source localization included more studies (17 in total) and reported a higher MSI sensitivity (84% versus 79%) and higher specificity (52% versus 46%) than our study¹²¹. Separate pooling of sensitivity and specificity permitted authors to include more studies, even when sensitivity or specificity measures were missing in individual studies due to zero values in the 2×2 contingency tables. However, separate pooling of sensitivity and specificity fails to account for the trade-off between these two measures, the more so when either one is not calculable for all studies. Therefore, we decided to include only studies without zero values in the 2×2 contingency tables and calculated sensitivity and specificity by means of bivariate modelling, at the cost of the number of included studies^{152, 153}. Other outcomes also provide information on the clinical value of a test; of which several have been published for MEG. Changes in clinical management after MEG following previous conventional non-invasive presurgical workup, were seen in 21–35% of patients, in whom 11–75% of these changes were considered as crucial or

of clear impact^{139, 154}. In 23–33% of surgical candidates who required ICEEG, a change in clinical management after MEG was observed, of which 26–39% was classified ‘beneficial’ according to the authors^{136, 155}. The level to which clinical management is changed by HR-ESI remains uncertain as such studies were not discovered by our literature search.

Heterogeneity among studies regarding the included population was observed. It has been proposed that MSI and ESI should preferentially be applied in extratemporal rather than temporal lobe epilepsy, as - in the latter - an epileptic focus may easily propagate through a well-developed and complex limbic network, leading to a more wide-spread irritative zone^{32, 156}. None of the individual studies reported statistical differences in test performance between temporal, extratemporal, lesional and non-lesional epilepsy patients, which was also not found by our pooled subgroup analysis^{49, 146, 150}.

The underreporting of surgical outcome data for patients with indeterminate source imaging results, and the inconsistency in reporting partially concordant results, were an important finding of our study. Indeterminate test results were more frequently reported in MSI studies (six studies) than in HR-ESI studies (one study). Unexpectedly, the majority of patients with indeterminate MSI test results had good outcome. The importance of these results was highlighted; a statistically significant lower sensitivity was observed when indeterminate test results were included in the analysis of diagnostic accuracy. We further showed that categorizing partially concordant results as non-concordant significantly affects specificity. An explorative analysis showed a statistically significant higher sensitivity for HR-ESI over MSI only when indeterminate test results and partially concordant results were calculated as non-concordant. HR-ESI studies showed, as compared to MSI studies, a very low number of indeterminate and partially concordant results, and they were all prospective and based on distributed inverse methods. Therefore, this result is likely confounded and therefore not reported as a definite result. As addressed by Papanicolaou and colleagues, cases of partial concordance between source estimate and resected area do not have the same significance as cases of complete or non-concordance¹⁵⁷. In the context of other imaging modalities, partially concordant results may be clinically valuable.

The ability to record epileptic activity from deep midline structures (e.g. mesial temporal regions) is much debated, as such measures are hampered by cortical propagation and relative low signal compared to background brain activity^{138, 158-160}. It often occurs that source localization records only the neocortically (anterio-temporal) propagated hippocampal spikes, not the hippocampal spikes themselves. As surgical strategy aims to resect the underlying hippocampal pathology, the source localization result are left out of the resection volume. From a strict localization perspective, such spatially distinct source solutions do not contribute to identification of the true EZ over other possible EZ's. The

high variation among studies on dealing with such results calls for consensus within the community¹⁶¹.

Our study has several limitations. First, strict inclusion criteria resulted in few primary studies. A higher number of MSI studies was found compared to HR-ESI and the number of MSI patients outnumbered those with HR-ESI (267 versus 127) reflecting the novelty of HR-ESI relative to MSI.

Second, the quality appraisal was mostly designed for illustrative purposes and the degree to which each quality domain contributes to over- or underestimation of diagnostic accuracy is not quantified. Yet, it is certain that our self-induced patient selection bias, resulting from not taking into account patients who were rejected after presurgical workup, promotes both MSI and HR-ESI diagnostic accuracy over-optimistically. When verification bias (i.e. inclusion of source localization results in the presurgical workup) is present, diagnostic accuracy is corrupted by clinical decision making; surgical resection might easily be expanded after consideration of the source localization results.

Third, inclusion criteria were restricted to ESI studies using 64 EEG electrodes, as this is considered to be the minimum number of channels necessary for accurate localization^{32, 162, 163}. Yet, several studies on surgical candidacy have applied ESI based on more widely clinical available long term EEG systems and report sensitivity and specificity ranging between 50–62% and 17–50%^{164, 165}. The number of electrodes should not be considered the sole criterion. Adequate coverage of the head, especially inferior temporal regions, is of importance. Although this was not an inclusion criteria, all of our included HR-ESI studies used whole-head electrode coverages, including subtemporal regions therefore improving localization accuracy¹⁶⁶⁻¹⁶⁸.

We further excluded studies that did not dichotomize their results into concordance categories. A large difference between dichotomization thresholds was observed in the studies by Wilenius et al., and Kim et al., (25% versus 70%)^{143, 145}. This proves that a manual dichotomization would have probably disregarded methodological considerations that are often familiar only to those involved in the source localization procedure, and on which threshold selection generally is based¹⁶⁹⁻¹⁷². In many of the studies there was underreporting on technical specifics such as artefact handling, spike criteria and selection of the spike interval. Such specifics are important to allow adequate interpretation of study results. Liberal spike criteria and inappropriate artefact handling may be responsible for less accurate localizations. Source localization based on spike peaks have higher SNR compared to spike onset but could possibly be contaminated by propagation effects resulting in different localizations on sublobar level¹⁷³. If such information was available, subgroup analysis could have aided recommendations on these technical aspects.

Fourth, surgical outcome as reference standard – though considered to be the ultimate standard for localization¹⁴⁸ – is not free from uncontrollable variables.

The Engel classification does not allow straightforward comparison between epilepsy surgery centers due to its considerable subjective judgement using terms as “some disabling seizures” and “worthwhile improvement” in seizure frequency¹²⁹. Neither outcome classification (Engel or ILAE classification) includes post-surgical use of anti-epileptic drugs. Absolute proof of removal of the epileptogenic zone might ideally be established by complete seizure freedom off all anti-epileptic drugs following epilepsy surgery. Further, resection is often limited by eloquent cortex, and seizure recurrence after initial postsurgical seizure freedom can occur due to newly evolved epileptogenic tissue^{148, 156}. The definition of a true positive is based on the unambiguous proof that resection of a source estimate results in good surgical outcome. However, an important issue emerges when we attempt to compare studies with different definitions of ‘concordant localization’. A first concern is that sublobar regions are defined according to anatomical landmarks and may differ widely in size and shape depending on their location and among patients¹⁵⁰. In the case of resection volume concordance, the resected area can still be sometimes too large to discriminate between different localizations, especially for multilobar resections¹⁷⁴. A second aspect is that the size of the source estimate partly depends on the quality of the source solution. A liberal acceptance of weak dipoles with low SNR might result in widespread dipole solutions or excessive large clusters. Yet, they also might just reflect large epileptogenic areas. Also, clusters can be defined as a number of dipoles localized within the same sublobar region^{144, 148, 175} or within a region of fixed dimensions¹⁴⁵. Specificity might be even more unreliable: surgical failure does not necessarily rule out epileptogenicity of resected tissue, as a more widespread epileptogenic network can be present¹⁷⁶. Also the consideration of a source estimate beyond the resection volume in cases of surgical failure as a ‘true’ localization is debatable as non-resected areas encompass both epileptogenic and non-epileptogenic regions¹⁷⁷. Although surgical outcome as reference standard might not be ideal, different reference standards, such as ICEEG^{138, 178-184}, MRI lesion^{51, 185, 186} or presumed EZ¹⁸⁷ suffer from limitations as well. It is known that peri-lesional areas are often marked as epileptogenic and good surgical outcome might not always necessitate complete removal of the SOZ^{147, 188}. The presumed EZ remains a theoretical construct up to the point of resection^{147, 188}.

Considering all issues discussed above, future diagnostic accuracy studies require improvements on bias and transparency. Investigators may use the Standards for Reporting of Diagnostic Accuracy checklist for their study^{130, 131, 189}. Emphasis should be given on prospective study designs, and cohorts should include all patients in whom presurgical source localization procedures are performed and apply alternative reference standards (e.g. seizure onset zone based on ICEEG, lesion location) on those not eventually

submitted for surgery. Ideally, decisions to proceed to surgery and the area of resection should be independent from source localization results, but is probably unethical. As an alternative, the presurgical team may be exposed to the source imaging results after they have made the initial decision on surgery so that the influence on clinical decision making can be accounted for to a maximum degree. A normalization algorithm, which accounts for resection size, source estimation size, and differences in procedural approaches should be developed to allow fair comparison between patients and studies. EEG and MEG contain complementary information due to their distinct technical properties. Its combined use is demonstrated to have superior diagnostic accuracy over use of ESI or MSI alone¹⁹⁰. More studies are needed to further explore the accuracy and feasibility of EEG-MEG fusion source localization¹⁹¹.

Once an appropriate level of diagnostic accuracy is established, the integrative approach of HR-ESI and MSI within the presurgical workup should be studied by evaluating various combinations with other tests (e.g. MRI with HR-ESI, MSI with PET)¹⁹² and which patient groups (e.g. non-lesional, multilesional) benefit most.

In this systematic review and meta-analysis, diagnostic accuracy of MSI and HR-ESI to localize the epileptogenic regions of interest is strongly affected by poor study quality and likely biased towards an overestimation of diagnostic accuracy. Results from HR-ESI and MSI should therefore be interpreted with caution and independent support from other diagnostic tools is required to proceed to resective surgery. High quality studies, that allow unbiased MSI and ESI evaluation and judge results in light of source estimate size and resection size are needed to obtain high quality evidence.

Supplementary material

Supplementary material A: Search queries

SOURCE:EMBASE	(epilepsy'/exp OR epilepsies:ab,ti OR epilepsy:ab,ti) AND ((('source localization':ab,ti OR 'source localisation':ab,ti OR 'source imaging':ab,ti OR 'inverse method':ab,ti OR 'inverse solution':ab,ti OR 'dipole':ab,ti OR 'inverse modelling':ab,ti OR 'inverse modeling':ab,ti OR 'spike source':ab,ti OR 'source reconstruction':ab,ti) AND ('electroencephalography'/exp OR eeg:ab,ti OR electroencephalography:ab,ti)) OR ('magnetoencephalography'/exp OR meg:ab,ti OR magnetoencephalography:ab,ti)) AND [english]/lim AND [1995-2017]/py NOT 'suppl' NOT 'conference abstract'
RESULTS:	1655 (after duplicate removal n=45)
SOURCE:PUBMED	("epilepsy"[MeSH Terms] OR "epilepsy"[tiab] OR "epilepsies"[tiab]) AND ((("source localization"[tiab] OR "source localisation"[tiab] OR "source imaging "[tiab] OR "inverse method "[tiab] OR "inverse solution"[tiab] OR "dipole "[tiab] OR "inverse modeling"[tiab] OR "inverse modelling"[tiab] OR "spike source"[tiab] OR "source reconstruction"[tiab]) AND ("Electroencephalography"[Mesh] OR "EEG"[tiab] OR "electroencephalography"[tiab])) OR ("Magnetoencephalography"[Mesh] OR "MEG"[tiab] OR "magnetoencephalography"[tiab])) AND ("1995/01/01"[PDat] : "3000/12/31"[PDat]) AND English[lang]
RESULTS:	1357 (after duplicate removal n=5)

SOURCE: Cochrane library	#1	MeSH descriptor: [Epilepsy] explode all trees
	#2	MeSH descriptor: [Electroencephalography] explode all trees
	#3	MeSH descriptor: [Magnetoencephalography] explode all trees
	#4	((('source localization') or ('source localisation') or ('source imaging') or ('inverse method') or ('inverse solution') or ('dipole') or ('inverse modeling') or ('inverse modelling') or ('spike source') or ('source reconstruction'))
	#5	#3 or MEG or magnetoencephalography
	#6	#2 or EEG or electroencephalography
	#7	#1 or epilepsy or epilepsies
	#8	#4 and #6
	#9	#8 or #5
	#10	#7 and #9 Publication Year from 1995 to 2017
RESULTS:	112 (after duplicate removal n=3)	
<hr/>		
EMBASE +		
PUBMED+		
COCHRANE		1964 (after duplicate removal n=1213)

Supplementary material B: Eligibility checklist MEG and EEG source localization

name:.....

Author+year of paper:.....

Study Characteristics	Eligibility criteria	Location in text (optional) (pg & ¶/fig/table)		
		Yes	No	Unclear
1. Study objective (the study objective as stated by the authors)	Assess the clinical value or diagnostic accuracy of interictal MEG or interictal EEG source localization in the presurgical evaluation of epilepsy surgery candidates.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Study design (for information on study design see appendix)	Systematic review, meta-analysis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	(Randomised) Controlled Trial	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Cohort study	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Case-control	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Cross-sectional study	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Case series	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Case reports	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Narrative review	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Expert opinion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Population/ subpopulation (participants in the study, or subgroups of participants)	adult and/or pediatric human epilepsy surgery candidates	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Type of diagnostic test	Interictal MEG or interictal EEG source localization/source imaging	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Diagnostic test settings/characteristic	Goals of test: detect/estimate location of epileptogenic source in brain and/or incorporate diagnostic test results in presurgical workup and surgical planning	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. Reference standard/ gold standard	Any of the following:			
	· Change in clinical management/surgical plan (i.e. decision to go to surgery, determining resection area)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	· Seizure outcome after surgery	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

7. Types of test outcome measures	Any of the following:			
	· Any type of association or correlation measure between index test results and change in clinical management	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	· Number or % of patients, with certain seizure outcome	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	· Any type of association or correlation measure between index test results and seizure outcome	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

All sections (1- 7) contain at least one YES? → INCLUDE ☐

→ Proceed to next paper

Study design = Review? → Perform reference check ☐

→ Proceed to next paper

In all other cases → EXCLUDE ☐

Supplementary material C: Data extraction inclusions/exclusions

Study	Primary exclusion reason	Additional comments
Schneider, 2013 ¹⁶¹	Subset of a study	Concordance level of MSI with SR not in patient table. Only reported combined with ICEEG. Therefore absolute numbers of TP, FN, TN, FP cannot be reconstructed. Further, level of concordance not explicitly described (is this sublobar or resection?). Sens/spec cannot be reconstructed from patient data table, as CI do not match. Overall reported data is dubious. Lastly this is a subset of Almubarak et al. (2014) ¹⁴⁴ .
Fischer, 2005 ¹⁷¹	Not outcome measure of interest	Resection of MEG source cannot be determined, They provide two measures, distance between source-center and resection-center and coverage of source ellipsoid with resected area. Based on the measure it cannot be concluded if source maximum was resected since this depends on resection size.
		Fischer et al., confirms in a commentary to Lau et al., that available data for sensitivity and specificity analysis by means of concordance level is not published ¹⁷² .
Albert, 2014 ¹⁹³	Not outcome measure of interest	Only results of resected MEG sources included.
Kim, 2012 ¹⁹⁴	Not outcome measure of interest	No quantitative concordance rule (unclear if dipoles were resected).
Iida, 2005 ¹⁹⁵	Absence of TP, NP, FP or FN	No true negatives reported, specificity is –inf.
Vadera, 2013 ¹⁵⁶	Not absolute numbers reported	They do provide a seizure freedom rate for ETLE patients with incomplete and complete removal of source focus but they do not provide the n of these groups so no confidence interval can be calculated.
Smith, 2003 ¹⁹⁶	Not a study	conference paper with incomplete data, impossible to translate to 2x2 table.
Stefan, 2011 ¹⁹⁷	Not outcome of interest	They use distance to MRI lesion as outcome measure. Dichotomization of this is performed considering <3cm from lesion as congruent. However this does not imply any level of congruence with resected area.
Sutherling, 2008 ¹⁵⁵	Different study aim/objective	Change in clinical management by MEG.
Wheless, 1999 ¹⁷⁴	Not reference standard of interest	They do not use Engel or Wiesner score.
Wu, 2010 ¹³⁷	Absence of TP, NP, FP or FN	2x2 contingency table had zero values.
Wu, 2013 ¹⁹⁸	Absence of TP, NP, FP or FN	2x2 contingency table had zero values.
De Tiege, 2012 ¹³⁹	Different study aim/objective	Change in clinical management by MEG.
Assaf, 2004 ¹⁴⁰	Not population of interest	reporting of only True positives, all good outcome.
Bowen, 2012 ¹⁹⁹	Different study aim/objective	Change in clinical management by MEG.
Brodbeck, 2009 ²⁰⁰	Absence of TP, NP, FP or FN	2x2 contingency table had zero values (after removal of Hemispherectomies.)
Brodbeck, 2010 ¹⁹	Absence of TP, NP, FP or FN	2x2 contingency table had zero values.

Coutin-Churchman, 2012 ¹⁶⁴	Not index test of interest	Low resolution ESI.
Englot, 2015 ²⁰¹	Not population of interest	Hemispherectomy patients included and not reported separately.
Carrette, 2011 ¹³⁵	Different study aim/objective	Change in clinical management by MEG.
Widjaja, 2013 ¹⁴¹	Not reference standard of interest	Do not report a minimum duration for follow-up. Follow-up not provided for individual patients so extraction of only those with at least 6 months follow up is impossible.
Widjaja, 2008 ²⁰²	Absence of TPNP,FP or FN	2x2 contingency table had zero values.
RamachandranNair, 2007 ²⁰³	Absence of TPNP,FP or FN	2x2 contingency table had zero values.
Paulini, 2007 ²⁰⁴	Not population of interest	No outcome data for patients with non-resected sources.
Iwasaki, 2002 ¹⁶⁹	Not outcome of interest	They do not perform a dichotomization.
Tanaka, 2014 ²⁰⁵	Different study aim/objective	Focusses on propagation patterns of MEG. Not a standard way to source imaging. Also zero values in the contingency table.
Zhang, 2011 ²⁰⁶	Not index test of interest	Only assessment of MEG combined with other imaging modality (e.g. MRI).
Knowlton, 2006 ¹³⁸	Not reference standard of interest	Inappropriate reference standard (IEEG).
Ito, 2015 ²⁰⁷	Not index test of interest	Not objective of interest, not setting of interest: MEG used to stratify patients to redirect to tertiary center.
Jung, 2013 ¹⁷⁸	Not reference standard of interest	No reporting of information on whether MEG source is resected and whether this correlates to surgical outcome. They do report in which patients MEG source was focal (within same lobe), lateralized (multi lobe) or non-lateralized (contra-lateral hemisphere) and for these patients if there was overlap with SOZ. They report for these patients the resected area, but it is unknown to what extend the MEG source was resected. In conclusion, the study does not evaluate if the MEG source was resected.
Tenney, 2014 ¹⁸²	Not reference standard of interest	Inappropriate reference standard (IEEG-based SOZ).
Kaiboriboon, 2010 ²⁰⁸	Not outcome of interest	Evaluates concordance with side of surgery in temporal lobectomy patients.
Kargiotis, 2014 ²⁰⁹	Absence of TPNP,FP or FN	2x2 contingency table had zero values.
Knowlton, 2009 ¹³⁶	Different aim/study objective	Change in clinical management by MEG.
Elschoff, 2012 ²¹⁰	Not population of interest	Very high selection bias (only good outcome selected, manual adding of 1 bad outcome insufficiently justified).
Oliva, 2010 ¹⁶⁵	Not index test of interest	Uses low resolution EEG (LT-EEG).
Lascano, 2016 ¹⁹²	Subset of a study	Subset of Brodbeck et al. (2011) ⁴⁹ . Reports only lobar co-localization.
Murakami, 2016 ¹⁷⁵	Not population of interest	Consists for 20% of second stage surgery. Does not provide separate information of these patients.
Russo, 2016 ²¹¹	Absence of TPNP,FP or FN	2x2 contingency table had zero values.
Russo, 2016 ²¹²	Absence of TPNP,FP or FN	2x2 contingency table had zero values.

Total count for each exclusion reason	
Exclusion reason	Number of studies
Absence of TP/NP/FP or FN	10
Different aim/study objective	6
Not a study	1
No absolute numbers reported	1
Not index test of interest	4
Not outcome measure of interest	6
Not population of interest	5
Not reference standard of interest	5
Subset of a study	2
Total	40

Supplementary material D: Diagnostic accuracy outcome data

Type of test	Study	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)
MEG	Jeong et al., 2012 ¹⁴²	5	1	8	10	83 (44 – 97)	566 (34 – 75)
MEG	Kim et al., 2013 ¹⁴³	4	4	5	1	50 (22 – 79)	17 (3 – 56)
MEG	Schneider et al., 2012 ¹⁴⁴	9	1	4	4	90 (60 – 98)	50 (22 – 79)
MEG	Wilenius et al., 2013 ¹⁴⁵	8	3	1	4	73 (43 – 90)	80 (38 – 96)
MEG	Papanicolaou et al., 2005 ¹⁴⁶	22	3	15	1	88 (70 – 96)	6 (1 – 28)
MEG	Mu et al., 2014 ¹⁴⁷	22	1	13	2	96 (79 – 99)	13 (4 – 38)
MEG	Knowlton et al., 2008 ¹⁴⁸	20	8	6	15	71 (53 – 85)	71 (50 – 86)
MEG	Almubarak et al., 2014 ¹⁴⁹	15	4	4	13	79 (57 – 92)	77 (53 – 90)
HR-EEG	Brodbeck et al., 2011 ⁴⁹	31	5	7	9	86 (71 – 94)	57 (33 – 77)
HR-EEG	Megevand et al., 2014 ¹⁵⁰	12	3	7	10	80 (55 – 93)	59 (36 – 78)
HR-EEG	Feng et al., 2016 ¹⁵¹	32	3	2	6	91 (78 – 97)	75 (41 – 93)

Supplementary material E: Bivariate sensitivity and specificity estimates of subgroups

<i>covariate</i>	<i>Type of test</i>	<i>Category (number of studies)</i>	<i>Sensitivity</i>	<i>95% CI</i>	<i>P-value</i>	<i>Specificity</i>	<i>95% CI</i>	<i>P-value</i>
Partial concordant	MSI	Non-concordant (3)	77%	65-87	-	69%	33-91	-
		Complete concordant (3)	91%	80-96	0.066	20%	5-54	0.049*
Handling indeterminates	MSI	Included in estimates (4)	61%	49-71	-	75%	59-86	-
		Excluded from estimates (4)	76%	64-85	0.040*	69%	56-80	0.585
Single source versus multisource	MSI	Multiclust. excluded (5)	83	63-93	-	22	20-72	-
		Multiclusters included (5)	80	58-92	0.610	42	20-67	0.929
Lesional and non-lesional	MSI + HR-ESI	Lesional (4)	75	48-90	-	69	43-87	-
	MSI + HR-ESI	Non-lesional (5)	73	54-87	0.905	46%	30-64	0.173
	MSI	Lesional (3)	71	14-90	-	79	48-94	-
		Non-lesional (4)	68	42-86	0.795	43	24-64	0.059
	HR-ESI	Lesional (1)	88	27-99	-	50	15-85	-
		Non-lesional (1)	85	68-94	0.85	58	31-81	0.77
TLE and ETLE	MSI + HR-ESI	TLE (7)	86	77-92	-	47	27-68	-
		ETLE (7)	76	60-87	0.121	39	22-60	0.608
	MSI	TLE (5)	78	57-91	-	43	19-71	-
		ETLE (6)	75	55-88	0.726	34	17-55	0.643
	ESI	TLE (2)	91	80-96	-	54	12-91	-
		ETLE (1)	80	53-93	0.241	66	38-87	0.718

Note. Sensitivity and specificity based on bivariate linear mixed model by Reitsma; TLE: temporal lobe epilepsy; ETLE: extra temporal lobe epilepsy; *statistically significant ($p<0.05$)

CHAPTER 5

High-resolution electric source imaging for presurgical evaluation of tuberous sclerosis complex patients

Brian E. Moushaan, Floor E. Jansen, Albert J. Colon, Geertjan M. Huiskamp, Pieter van Eijsden, Frans S. S. Leijten, Kees P. J. Braun

Objective

We retrospectively assessed the localizing value of patient-history-based semiology (PHS), video-based semiology (VS), long-term monitoring video electroencephalography (LTM-VEEG) and interictal high resolution electric source imaging (HR-ESI) in the presurgical workup of patients with tuberous sclerosis complex (TSC).

Methods

Data from 24 consecutive TSC surgical candidates who underwent both HR-ESI and LTM-VEEG was retrospectively collected. PHS and VS were analyzed to hypothesize the symptomatogenic zone localization. LTM-VEEG and HR-ESI localization results were extracted from the diagnostic reports. Localizing value was compared between modalities, taken the resected/disconnected area of surgical patients in consideration. HR-ESI's impact on the epileptogenic zone hypothesis and surgical workup was evaluated.

Results

Semiology, interictal EEG, ictal EEG and HR-ESI were localizing in 25%, 54%, 63% and 79% of patients. Inter-modality concordance ranged between 33–89%. In good surgical outcome patients, PHS, VS, interictal EEG, ictal EEG and HR-ESI showed concordance with resected area in 1/9 (11%), 0/9 (0%), 4/9 (44%), 3/9 (33%) and 6/9 patients (67%). HR-ESI positively impacts clinical management in 50% of patients.

Conclusion

In presurgical evaluation of TSC patients, semiology often has limited localizing value. Presurgical work-up benefits from HR-ESI. Our findings may advice future presurgical epilepsy workup of TSC patients with the ultimate aim to improve outcome.

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem disorder with multiple hamartomas that manifest most commonly in the skin, retina, heart, kidney and brain. In the central nervous system TSC gives rise to cortical tubers that may cause neurological symptoms, including epilepsy and neurodevelopmental disorders such as autism and intellectual disability. Early seizure onset and poor seizure control are related to the level of neurodevelopmental deficit^{213, 214}. With anti-seizure medication adequate seizure control may be achieved but studies show high variability in the number of patients in whom seizure freedom is achieved (17–100%)²¹⁵. For medically intractable epilepsy patients surgery is considered and postoperative seizure freedom can be achieved in 55–65% of cases^{216–218}.

The cornerstone of feasibility of epilepsy surgery is accurate localization of the epileptogenic zone (EZ), which is defined as the area of cortex that is necessary and sufficient for initiating seizures and which needs to be removed (or disconnected) for complete elimination of seizures²¹⁹. Unfortunately, in TSC patients multiple potentially epileptogenic lesions (i.e. tubers) are scattered throughout the brain. Not all tubers contribute to epilepsy and removal of a single or of a few tubers may render a patient seizure-free. The challenge is therefore to identify the epileptogenic tuber(s) involved in seizure generation. Even with functional neuroimaging techniques such as α [¹¹C]-methyl-L-Tryptophan-Positron Emission Tomography (AMT-PET) it remains challenging to distinguish epileptogenic from non-epileptogenic tubers, apart from the fact that the tracer is not available in most facilities²²⁰.

As a result, the presurgical workup of TSC patients is different from that in most patients with other etiologies; it aims to identify the single epileptogenic lesion among many, rather than attempting to visualize a lesion and determine its concordance with semiology and electroencephalography (EEG) findings. For most etiologies, long-term video-EEG monitoring (LTM-VEEG) is the center-piece neurophysiological evaluation in EZ identification²⁰. In TSC patients, focality in interictal or ictal EEG has been found predictive of good surgical outcome^{217, 221}. Still, using ictal EEG to localize the seizure onset zone, related to an epileptogenic tuber, may be problematic. Tubers may show abnormal, diffusive connectivity with other tubers and perituberal cortices and propagated ictal rhythms are often indistinguishable from seizure onset^{222, 223}. Thus, renewed interest has surged for interictal electric source imaging (ESI), particularly because in surgical TSC candidates dominant interictal foci often remain unaltered over long periods of time²²⁴.

With high resolution interictal electric source imaging (HR-ESI) locations of underlying source currents are estimated using 64 or more scalp EEG electrodes (HR-EEG) and

subsequently combined with structural high-resolution magnetic resonance imaging (MRI). Prospective studies have shown that HR-ESI accurately estimates the EZ in the presurgical epilepsy workup of lesional and non-lesional epilepsy surgery candidates^{49, 60, 150, 151}.

A comparison of LTM-VEEG and HR-ESI findings in the presurgical work-up of TSC patients has not yet been performed. In this retrospective cohort study we selected patients who underwent both LTM-VEEG and HR-ESI and assessed the localizing value of each modality in the presurgical workup. We analyzed the lobar co-localization of semiology taken from patient or relatives (patient history-based semiology, PHS) with video-based semiology (VS) from LTM-VEEG. We compared the localizing value of ictal and interictal EEG data from LTM-VEEG with HR-ESI. Furthermore, we assessed the localizing value of the modalities by using the ultimate gold standard, which is the resected area in seizure-free patients. Finally, we evaluated the impact of HR-ESI on the EZ hypothesis, its clinical consequences and how this translated to positive surgical outcome.

Methods

Patients

We retrospectively collected clinical data from consecutive patients with a definite diagnosis of TSC who underwent both HR-ESI and LTM-VEEG as part of epilepsy surgery evaluation between 2011–2019. The Dutch epilepsy surgery program consists of a national collaboration between the University Medical Center Utrecht (UMCU) and two other Dutch epilepsy institutes (ACE Kempenhaeghe/MUMC, Heeze; SEIN, Heemstede). The UMCU is a nationally and internationally (EpiCARE) endorsed expertise center for patients with rare and complex epilepsies. We have approximately 200 children and 500 adults with TSC in active clinical care, some of whom will undergo an epilepsy surgery diagnostic work-up, based on clinical criteria. We collected demographic information, including sex, age, as well as epilepsy related characteristics, such as age at seizure onset, seizure frequency, seizure semiology, and epilepsy treatment. Initial pre-operative evaluation included semiology, 3T MRI and LTM-VEEG. If in subsequent multidisciplinary team meetings focus localization was uncertain, a second stage evaluation was performed including HR-ESI and in some patients interictal and ictal Single Photon Emission Computed Tomography (SPECT), or magnetoencephalography (MEG). When indicated, subsequent functional evaluation was done with Wada testing, functional MRI, or diffusion tensor imaging (DTI). Patients that were considered eligible for surgery underwent disconnection or resection including intra-operative tailoring with Electrocorticography (ECoG).

At the time of data collection, patients had been either operated, rejected for surgery, presurgical workup was ongoing, or patients had been withdrawn from workup. No informed consent was required under Dutch law for this retrospective observational study on available and pseudonymized data from routine clinical care.

Semiology

PHS and VS from LTM-VEEG were extracted from medical records separately. Two independent clinical neurophysiologists from two centers with each at least 15 years of experience within the field (FL, AC), were instructed to hypothesize the symptomatogenic zone location from either modality²²⁵. Seizure descriptions were presented in a randomized fashion blinded for the source of the description (i.e. PHS or VS). Discrepancies between reviewers were resolved in an organized meeting to achieve consensus and obtain final results.

LTM-VEEG

Continuous video and simultaneous 21–32 channel EEG was recorded. Electrodes were positioned according to the 10–10 system or to the 10–20 system with additional coverage of lateral frontal and/or temporal regions. Patients were recorded for at least 21 hours up to 2 weeks, sometimes preceded by tapering of medication. If multiple LTM-VEEG recordings were performed in a patient, the recording with recorded ictal epileptic activity that was closest to the date of the HR-ESI was selected. Interictal focus, or foci, and the presumed ictal onset zone were extracted from the LTM-VEEG report that was written by the clinical neurophysiologist at the time of evaluation. In case of multifocal interictal activity, localization of the predominant focus – defined as the focus that showed a prominent high spike frequency among other foci – was also extracted from the report.

HR-ESI

High resolution EEG was recorded using a 85-channel EEG electrocap (BioSemi Mark-6, Brainstar system 4.0) from 2011–2013 and an 84-channel TinCap custom (Easycap) from 2013 onwards both using a LTM 128 amplifier with SystemPlus Evolution software (Micromed). Electrode positions relative to the skull were registered by using a magnetic tracking device (Polhemus, Colchester, VT, U.S.A.). Spontaneous activity was recorded during a 40–60 minute session, sometimes after sleep deprivation. Interictal epileptic spikes were visually marked and subsequently inspected for their spatiotemporal consistency by an automatic clustering program according to Van 't Ent et al.²²⁶. Spikes from each cluster were averaged and standard deviations were calculated. Clusters showing a standard deviation smaller than one-third of the spike maximum, were considered consistent¹⁸³. Only consistent clusters were selected for forward modeling using individual patient 3D T1 MRI with CURRY 7.0 software (Compumedics, Victoria, Australia). Inverse solution was applied using two algorithms: multiple signal classification (MUSIC) and standardized low-

resolution brain electromagnetic tomography (sLORETA). Clusters showing consistency between the two inverse solutions were considered representative of a focal source and formed the net-result of the source localization. Clusters showing inconsistency between MUSIC and sLORETA were rejected because of the invalidity of a focal assumption. The source location was extracted from the reports written by the physicist involved in the source imaging procedure at the time presurgical workup.

Data analysis

Anatomical location results of modalities – PHS, VS, interictal EEG (LTM-VEEG), ictal EEG (LTM-VEEG), HR-ESI – and the resected area were defined by lateralization and lobar localization. Lateralization was defined as: left, right or midline. Lobar regions were defined as: frontal (including fronto-central), central, temporal, parietal (including parieto-central) and occipital. A result was considered multifocal in case of bilateral localizations or multiple unilateral localizations in different lobes. A result was considered non-localizing if the modality showed an unclear focus or suggested a deep non-localizing focus.

Localization concordance

Localization of modalities was evaluated for their lobar concordance with each other (inter-modality) and with the resected or disconnected area in patients who underwent surgery. Concordance was expressed in terms of:

- 1- Concordant: sources co-localized in the ipsilateral lobe
- 2- Discordant: sources localized contra-laterally or in different ipsilateral lobes
- 3- Indeterminate: either one of the modalities was non-localizing or multifocal
- 4- Partially concordant: (a) one source localized in midline and the other to the left/right in the same lobar region (e.g. midline parietal with right parietal); (b) one source localized in the border region between lobes and the other source in one of the lobes (e.g. parieto-occipital with parietal); or (c) in case of multiple resected areas, the source localized in only one of the resected areas (e.g. a right parietal focus with right parietal and central resection)

A fronto-central or parieto-central localization was considered to be concordant with frontal and parietal localizations respectively. A central localization that was unknown to be on the parietal or frontal side was considered concordant with a fronto-central or parieto-central location and partially concordant with a frontal or parietal localization. Data was analyzed descriptively and presented as proportions of concordance levels and surgical outcome within patient groups.

Impact of HR-ESI on epilepsy surgery workup

The impact of HR-ESI on the diagnostic epilepsy surgery workup was assessed by reviewing multidisciplinary meeting records. We collected the hypothesized EZ formulated during the initial pre-operative evaluation (prior to evaluation of HR-ESI results) and the newly defined EZ hypothesis that was formulated (after review of HR-ESI results) during the subsequent second multidisciplinary meeting. If hypotheses were not in the minutes of the meeting records, the study authors attempted to formulate hypotheses by means of deduction using the available diagnostic information. Patients were excluded from this analysis if HR-ESI was performed prior to the first multidisciplinary meeting or if new information from other diagnostics was discussed in the second meeting. In these cases we deemed the newly formed hypothesis biased and not a representative for HR-ESI's impact on clinical management.

Details of the HR-ESI results, with respect to tuber correspondence or intra-lobar/sublobar location, were extracted from medical records to evaluate the basis of a hypothesis change. We then classified the level of EZ hypothesis modification as follows:

1. EZ discarded: the old hypothesis was considered unreliable and the new information not sufficient to constitute a novel hypothesis
2. EZ enlarged: the new hypothesis encompassed a wider region surrounding the old hypothesis
3. EZ unaffected: the hypothesis was unaltered due to non-contributing HR-ESI results
4. EZ confirmed: the old hypothesis was confirmed by contributing HR-ESI results
5. EZ narrowed: the new hypothesis encompassed a more targeted region of the old hypothesis
6. EZ changed: the hypothesis was changed to a different lobar region
7. EZ generated: the old hypothesis was non-localizing, HR-ESI resulted in a new localizing hypothesis

Subsequently, we noted the decisions – for additional (non)invasive testing or neurosurgical procedures – made in the second multidisciplinary meeting. In patients who underwent surgery the impact of HR-ESI on the clinical management was based on the EZ modification, whether the HR-ESI source was part of the resected area and the surgical outcome. Clinical contribution of HR-ESI was categorized as critically valuable, critically misleading, opposing, positively supportive, negatively supportive, disruptive, indeterminate (figure 5.1).

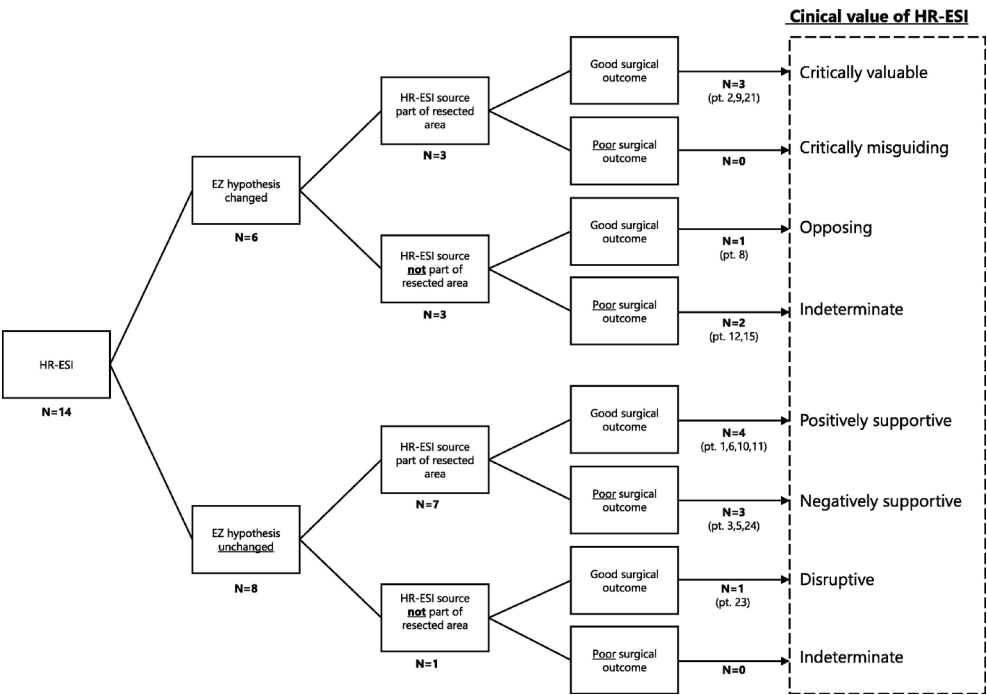


Figure 5.1. Framework and results for clinical value evaluation of HR-ESI. Pt.: patient; HR-ESI: high-resolution electric source imaging; EZ: epileptogenic zone; Good surgical outcome: Engel 1; Poor surgical outcome: Engel 2–4.

Results

Patient characteristics

Twenty-four patients (16 male) were included in this study. Median age at seizure onset was 0.5 years (range 0.08–12 years). Median age at the start of presurgical evaluation was 5 years (range 1–35 years). Seizure types at the start of presurgical workup were focal epileptic spasms in seven, other focal motor in seven and focal non-motor seizures in eleven patients. Three patients had two or more types of seizures (supplementary table 5.1). Sixteen patients had daily seizures, four patients had daily to weekly seizures, three patients had weekly seizures and one patient monthly seizures.

Presurgical workup

Median time between recording of LTM-VEEG and HR-ESI was 4 months (range 1–24 months). Non-invasive ancillary or repeated tests were performed in seven patients: SPECT in three, MEG in two and repeated LTM-VEEG in two. Four patients (4/24, 17%) were rejected for surgery: in three, workup did not result in a clear and consistent EZ hypothesis;

in one, stereo depth EEG (SEEG) was considered but contra-indicated as the child was too young. Additionally, 4/24 patients (17%) were withdrawn from further surgical workup of whom three were withdrawn due to seizure reduction and in one patient parents decided to cancel further investigations. One patient is still awaiting planned ECoG-guided surgery. Thus, at the time of data collection, a total of fifteen patients had undergone surgery. In 14/15 patients (93%) surgery was guided by ECoG. Additional presurgical intracranial EEG monitoring with SEEG was performed in two and with grid electrodes in four children. Median follow up was 12 months (range 4–73 months). Good outcome (Engel 1, assessed at the end of follow up) was achieved in 9/15 patients (60%).

Semiology

PHS was presumed localizing to a single (unilateral) lobar region in 6/24 (25%) patients. In none of the subgroup of seven patients with epileptic spasms, localization was achieved. In 6/24 patients (25%) it was only possible to either lateralize to a hemisphere, or to localize to a lobar region but with uncertain lateralization. Clinical seizures were captured on video during LTM-VEEG in all patients. VS was presumed to localize to a single (unilateral) lobar region in 6/24 patients (25%). For the subgroup of patients with epileptic spasms localization was achieved in 1/7 (14%) patients versus 5/17 patients (29%) with other seizure types. In 5/24 (21%) VS was only able to localize to the temporal or frontal lobe with uncertain lateralization.

In patients with both localizing ictal EEG and localizing PHS, PHS was concordant in one out of three patients. This patient also showed concordance with interictal EEG, HR-ESI and resected area (patient 9). There were no patients showing concordance between VS and other modalities. In six patients both PHS and VS were non-localizing and in only one patient PHS and VS were both localizing to the same unilateral lobar region. In this particular patient however ictal EEG and HR-ESI localized to the contra-lateral parietal lobe and surgery in this area resulted in good outcome after 7 months (patient 6; supplementary table 5.2).

LTM-EEG

Ictal EEG was available in all patients. Clinical seizures showed simultaneous – not necessarily concordant – seizure activity in all patients. Number of seizures ranged from 2 to 16 (median 7). Mean LTM-VEEG duration was 67 hours (range 21–100 hours). In four patients no information on anti-seizure medication reduction was registered. In 12 of 20 patients (57%) dosage was decreased before and during recording.

Interictal EEG localized to a single lobe in 13/24 patients (54%). In 10/24 patients (42%) multifocal interictal EEG abnormalities were recorded. In six of these patients multifocal EEG suggested a predominant unilateral focal area. In the remaining patient interictal EEG

was non-localizing. With respect to patients with epileptic spasms interictal EEG localized in 2/7 patients (29%) which was lower than in patients with other seizure types (12/17, 71%).

Ictal EEG was localizing in 15/24 patients (63%) and non-localizing in 7/24 patients (29%). In the remaining two patients multifocal sources were seen (patient 18, 7) (supplementary table 5.2). For the subgroup of patients with epileptic spasms ictal EEG localized in 4/7 patients (57%) compared to 11/17 patients (65%) with other seizure types.

In patients with both localizing ictal EEG and localizing interictal EEG, inter-modality concordance was found in 8/9 patients (89%) and partial concordance in the remaining patient. In patients with multifocal interictal EEG showing a predominant unilateral focus and a localizing ictal EEG, concordance was found in one half and partial concordance in the other half of patients (patient 1, 10, 17, 19).

HR-ESI

HR-ESI recording duration was scheduled for 60–120 min (dependent on patient cooperation). Interictal epileptic activity was observed in all but one patient. This patient had indistinct spikes that could not be differentiated from artefacts. HR-ESI localized to an unilateral single lobe in 19/24 (79%) of patients. HR-ESI was bilaterally multifocal in 4/24 patients (17%) (supplementary table 5.2). In patients with epileptic spasms HR-ESI was localizing in 4/7 (57%) compared to 15/17 (88%) patients with other seizure types. Figure 5.2 shows an example of a HR-ESI result in a patient with a left frontal focus.

In patients with both localizing interictal EEG and HR-ESI, intermodality concordance was seen in 7/10 (70%) and partial concordance in 2/10 patients (20%). Intermodality concordance between ictal EEG and interictal HR-ESI was seen in 7/13 patients (54%), partial concordance in 4/13 (31%).

From the six patients with multifocal interictal EEG showing a predominant unilateral focus one was concordant with HR-ESI (17%), three were partial concordant (50%), one was discordant, and in the remaining patient HR-ESI was multifocal.

Localization concordance with resected area and surgical outcome

Concordance with the resected area was seen in one patient for PHS and in none for VS (table 5.1a&b). Both interictal and ictal EEG were concordant with resected area in 5/15 patients (33%) compared to 9/15 patients (60%) for HR-ESI. Partial concordance was seen in 2/15 (13%), 5/15 (33%) and 2/15 patients (13%) for interictal EEG, ictal EEG and HR-ESI. Nine patients (60%) had good surgical outcome with median follow up of 9 months (range 4–73). Median follow up in poor surgical outcome patients was 19 months (range 7–39).

Table 5.1.

A. Modality concordance with resected area per surgical patient.

Patient	PHS	VS	Interictal EEG (LTM-VEEG)	ictal EEG (LTM-VEEG)	HR-ESI	Surgical outcome
1	indet	indet	indet	pc	c	Good
2	indet	indet	c	c	c	Good
3	d	indet	indet	pc	c	Good
4	d	indet	pc	indet	d	Good
5	d	indet	c	indet	c	Good
6	d	d	indet	pc	pc	Good
7	indet	indet	indet	pc	d	Good
8	indet	d	c	c	c	Good
9	c	indet	c	c	c	Good
10	indet	d	indet	c	c	Poor
11	indet	indet	pc	pc	pc	Poor
12	indet	indet	indet	indet	c	Poor
13	indet	indet	d	d	indet	Poor
14	indet	d	c	c	c	Poor
15	indet	indet	d	indet	indet	Poor

B. Modality concordance with resected area of all surgical patients.

Modality	PHS		VS		Interictal EEG (LTM-VEEG)		ictal EEG (LTM-VEEG)		HR-ESI	
Surgical outcome	Good	Poor	Good	Poor	Good	Poor	Good	Poor	Good	Poor
Level of concordance	Concordant	1	0	0	0	0	4	1	3	2
	Partially Concordant	0	0	0	0	0	1	1	4	1
	Discordant	4	0	2	2	2	0	2	0	1
	Indeterminate	4	6	7	4	4	2	2	2	0

PHS; patient-history based semiology; VS; video-based semiology; LTM-VEEG; long term monitoring video electroencephalography; HR-ESI; high-resolution electric source imaging. Surgical outcome: Good (Engel 1), Poor (Engel 2-4), c: concordant; pc: partially concordant; d: discordant; indet: indeterminate.

In the patients with good surgical outcome, PHS, interictal EEG, ictal EEG and HR-ESI were concordant with the resected area in 1/9 (11%), 4/9 (44%), 3/9 (33%) and in 6/9 patients (67%). Partial concordance was seen in 1/9 (11%), 4/9 (44%) and 1/9 patients (11%).

In poor outcome patients, concordance with resected area was seen in 1/6 (17%), 2/6 (33%) and 3/6 patients (50%) for interictal, ictal EEG and HR-ESI respectively. Partial concordance was seen in 1/6 patients (17%) for each modality.

When excluding non-localizing and multifocal test results, concordance with the resected area in patients with good surgical outcome was seen in 4/5 (80%) for interictal EEG and 3/7 patients (42%) for ictal EEG. Partial concordance was seen in 1/5 (20%) and 4/7 (58%) of patients. HR-ESI maintained the same concordance rate due to absence of non-localizing or multifocal results in this subgroup.

In patients showing concordance with resected area, good outcome was achieved in 4/5 (80%), 3/5 (60%), 6/9 (67%) for interictal, ictal EEG and HR-ESI respectively. Partial concordance had good outcome in 1/2 patients (50%) for interictal EEG and HR-ESI and in 4/5 (80%) for ictal EEG. Discordance had good outcome in no patients for interictal EEG and ictal EEG and in all patients for HR-ESI. In the case of an indeterminate concordance level, good outcome was seen in 4/6 (67%) and 2/2 patients (50%) for interictal EEG and ictal EEG, and in none for HR-ESI.

Impact of HR-ESI on epilepsy surgery workup

Three patients were excluded from this analysis (supplementary table 5.3). In one patient the MRI result – a nearby transmantle sign – was included in post-HR-ESI hypothesis as decided in the second multidisciplinary meeting (patient 24). In patient 12, HR-ESI was indicated prior to review of LTM-VEEG results and both results were simultaneously reviewed during the multidisciplinary meeting. In patient 20 LTM-VEEG was performed after evaluation of HR-ESI results.

In the remaining 21 patients HR-ESI modified the hypothesized EZ in eleven (52%), in four of whom HR-ESI discarded the presumed EZ. HR-ESI did not change the hypothesis in 10/21 patients (48%): in eight HR-ESI confirmed the hypothesis and in two HR-ESI was not contributory and the EZ remained unaffected. After HR-ESI evaluation in the second multidisciplinary meeting 9/21 patients (43%) proceeded directly to surgery, 10/21 (48%) underwent additional testing and 2/21 (10%) were directly rejected for surgery. In most patients in whom HR-ESI confirmed the EZ (6/8, 75%), it was decided to directly proceed to surgery. In the other two patients additional testing was performed (table 5.2).

Of the 21 patients included in the analysis, fourteen underwent surgery. In 7/14 patients (50%) HR-ESI contributed positively to the presurgical decision making process. In three, this contribution was critically valuable suggesting that without HR-ESI they would not have been operated and become seizure free. In 5/14 (36%) patients HR-ESI contributed negatively to the presurgical workup but this was never considered critically misleading (figure 5.1).

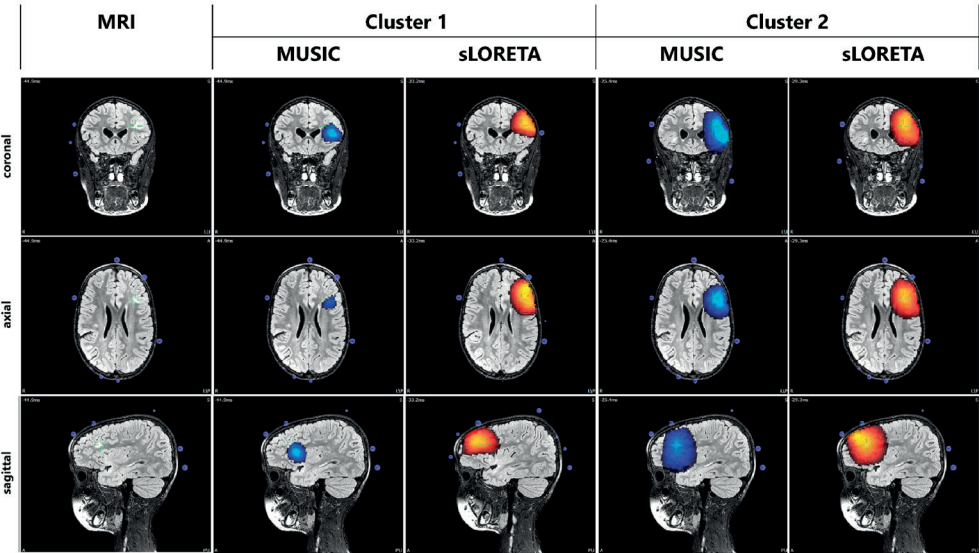


Figure 5.2. HR-ESI results from patient 3 indicating a left frontal focus. HR-ESI: high resolution electric source imaging; MUSIC: multiple signal classification; sLORETA: standardized low-resolution brain electromagnetic tomography. Fluid attenuated inversion recovery (FLAIR) MRI shows multiple bilateral subcortical tubers. A large tuber is located in the left fronto-lateral region (marked with crosshair). HR-ESI resulted in two spike clusters. MUSIC and sLORETA results for each cluster are depicted by blue and red blobs and were all located in or near the tuber region with varying spatial accuracy. Interictal EEG was multifocal by showing bilateral frontal and temporal activity with a predominant left fronto-temporal focus. Ictal EEG suggested a widespread left fronto-centro-parietal focus. Resection of two tubers in the left frontal area resulted in seizure freedom (Engel 1a) at 13 months follow up.

Table 5.2. Number of patients with HR-ESI related EZ modification and resulting clinical consequences.

EZ modification	Clinical consequence				Total (%)
	Rejected	Additional non-invasive testing	Additional non-invasive and invasive testing	Additional invasive testing	Proceed to surgery
EZ discarded	2	1	-	1	-
EZ enlarged	-	-	2	-	-
EZ unaffected	-	1	-	-	1
EZ confirmed	-	1	-	1	6
EZ narrowed	-	-	-	2	1
EZ changed	-	-	-	-	1
EZ generated	-	-	-	1	-
Total (%)	2 (10%)	3 (14%)	2 (10%)	5 (24%)	9(43%)
					21 (100%)

EZ: epileptogenic zone.

Discussion

In this retrospective cohort study including 24 TSC patients, we evaluated the localizing value of HR-ESI in the presurgical workup and compared this with semiology and LTM-VEEG results. HR-ESI was more often localizing compared to semiology, interictal EEG and ictal EEG (79% versus 25%, 54% and 63%). When localizing, interictal and ictal EEG have a high inter-modality concordance (89%), while HR-ESI was concordant with interictal and ictal EEG in 70% and 55% of patients respectively. Inter-test concordance for semiology was poor and was seen in only one patient. Localization was achieved less often in patients with epileptic spasms, especially using semiology and interictal EEG and to a lesser degree using ictal EEG and HR-ESI.

Concordance with resected area was best for HR-ESI. In seizure-free patients, HR-ESI is more often concordant (67%) with resected than ictal EEG (33%) while ictal EEG is more often partially concordant than HR-ESI (44% versus 11%). However, non-localizing and multifocal test results were seen often with interictal and ictal EEG and excluding these from the calculation affected the concordance rate by increasing this to 80% for interictal EEG, and 42% for ictal EEG while not altering the concordance rate for HR-ESI.

When HR-ESI results were discussed in the second multidisciplinary meeting, it had a strong impact on epilepsy surgery workup by modifying or confirming the hypothesized EZ in 52% and 38% of patients respectively. In 50% of patients HR-ESI positively impacts presurgical decision making process; in three this was critically valuable to achieve seizure freedom.

Video-based semiology has been reported to be often subtle in TSC patients but investigations into the localizing value of semiology in surgical TSC patients have not been performed yet²²⁷. History-based seizure semiology classification often agreed with video-based seizure semiology classification in general epilepsy surgery cohorts²²⁸. However, correct localization in focal epilepsy is lower for PHS than for VS; showing 20–38% PHS concordance versus 50–56% VS concordance when using seizure conference conclusion or non-invasive diagnostics as reference standard^{229, 230}. In 77% of seizure-free patients VS co-localized with resected area on lobar level²³¹.

Our data did not confirm a superior localizing value of VS over PHS. Fundamentally, seizure semiology is an interpretation that is dependent on the experience and recall of the observer²³². It solely reflects symptomatogenic zone activation, which may only be part of – or even not be included in – the EZ. Seizures arising from different EZ could activate the same symptomatogenic zone or vice-versa²³². The complex and numerous brain abnormalities involved in TSC and our center's liberal inclusion criteria (i.e. poorly localizing

semiology and non-localizing epileptic spasms) for presurgical evaluation, might govern the poor localizing accuracy of semiology reported here. Also, our population consisted mostly of young patients – sometimes with cognitive disabilities – who are often unable to communicate their symptoms to caretakers. Semiology in the context of EZ identification in determining surgical candidacy in TSC might be considered of limited value.

In a previous small study on HR-ESI for EZ identification, all five postoperative seizure-free TSC patients had the HR-ESI source maximum included within the resected area though all poor outcome patients HR-ESI was partially concordant²⁰⁹. The authors used a higher number of electrodes (i.e. 128–256 electrodes) and concordance was determined post-operatively using post-operative MRI and unblinded for surgical outcome²⁰⁹. In a selection of patients in whom ESI changed the clinical management, a 67% sensitivity and 50% specificity was demonstrated when taking resected area and the postoperative outcome as reference standard²³³. This compares to our demonstrated concordance in 67% of good outcome patients and in 50% patients of poor outcome patients²³³.

A meta-analysis on LTM-VEEG by Kobulashvili and coworkers reported a sensitivity of 70% -based on complete and partial concordance – that compares to our 78% (partial) concordance rate in our good surgical outcome group²⁰. A comparative analysis between ictal EEG and magnetic source imaging (MSI), the magnetic counterpart of HR-ESI, demonstrated superior sensitivity of interictal MSI over ictal EEG (100% versus 56%) in predicting the resected area in six seizure-free TSC patients²³⁴.

A prospective study showed a clinical management plan change in 34% of 82 consecutive TSC patients based on new and non-redundant information from ESI²³³. The used classification of new non-redundant information compares to our outcome of EZ modification that showed an HR-ESI-related change of the EZ in 11/21 patients (52%). Change of management is however difficult to assess retrospectively; additional non-invasive testing could still have been performed even without HR-ESI result. This could explain the high proportion of EZ modification in our cohort.

Many patients had multifocal interictal epileptiform EEG abnormalities, but a predominant unilateral focus was often identified. Unexpectedly, we found predominant foci and the ictal EEG in all patients with localizing ictal EEG to be at least partially concordant. This supports what earlier studies demonstrated; surgical candidates with TSC have dominant and consistent interictal epileptogenic foci over the course of many years that are often concordant with the ictal onset zone^{224, 235}. A dominant interictal EEG focus as surrogate for the region of ictal onset, combined with HR-ESI findings, may be favored for localization purposes over ictal EEG recordings.

The finding of multifocal HR-ESI results in two patients with unifocal interictal LTM-VEEG appears counter-intuitive (patient 17, 13). However, when reviewing the diagnostic reports of the individual patients, HR-ESI captured bilateral interictal activity that was previously not seen during interictal LTM-EEG (patient 13). In patient 17, interictal LTM-EEG was concluded as a midline central focus although it regularly showed bilateral spread. This spread was registered in the HR-ESI resulting in a multifocal source estimate. Inter-observer differences may have resulted in dissimilar classification and selection of interictal epileptic discharges for localization purposes.

Unexpectedly, the localizing results from the individual diagnostic tests did not always reflect the resected area, and seizure-outcome did not always relate to the degree of concordance or discordance of different presurgical investigations as was seen in patient 14, 4 and 7. This displays that studying localizing accuracy of the presurgical epilepsy workup is challenged by specific nuances and the selected geometric level of co-localization (i.e. lobar or sub-lobar) involved in a complex clinical decisional process.

Our study included only data from official diagnostic reports. We anticipated that the evaluation of diagnostics results in light of other clinical and diagnostic information, which is common in presurgical multidisciplinary meetings, could potentially introduce bias. We found in some patients that initial diagnostic reports were in disagreement with the evaluation by the multidisciplinary team. In patient 12 the LTM-VEEG official report concluded an unclear localization, while the team agreed on a right frontal focus which was included into the surgical plan. Unfortunately, in this patient surgery resulted in poor outcome. In another patient (patient 7) the team concluded that the bilateral multifocal interictal EEG, as concluded in the official report, actually showed two consistent foci of which one supported partly the equivocal left temporal ictal EEG localization. The left temporal lobe was subsequently selected as area to be resected which resulted in a good postsurgical outcome.

This study has several limitations. First, there is a patient selection bias. Patients undergoing HR-ESI are more likely to have inconclusive or non-congruent presurgical workup results and should be considered as a population with difficult to localize seizures. Second, lower localization value of LTM-VEEG relative to HR-ESI may be partially the result of LTM-VEEG's contribution to an inconclusive workup. Yet, we had a non-localizing ictal EEG in 7/24 patients (29%) that is in reasonable agreement with a non-localization rate of 22% found in a large series of TSC patients²²⁷. To minimize bias, we selected only LTM-VEEG's with seizure data and included HR-ESI results even with artefacts or without epileptic activity. Third, due to the retrospective nature of this study, the reporting epileptologists and physicist were not fully blinded for the clinical history, seizure semiology and MRI data during the review of HR-ESI and LTM-VEEG. The two experts analyzed semiology based

on descriptions taken from the charts blinded for other data. This always lacks finesse. Fourth, the lobar co-localization is affected by differences in size and shape of brain lobes; the larger frontal lobe likely to be more often concordant than the smaller occipital lobe. Therefore, we presented partially concordant results separate from concordant results as a lobar concordance level may be considered already liberal. Alternatively, measures such as Euclidean distance or surface overlap between source localization and resected area are more objective but are difficult to establish in the non-ESI modalities studies here, such as standard LTM-VEEG and semiology. Nevertheless, partially concordant results may still be clinically valuable in the context of other imaging modalities. Fifth, source localization based on LTM-VEEG data was not part of standard practice. It is recognized that ictal ESI provides additional localizing information over interictal ESI²³⁶. More diagnostic potential may be reached when source localization is performed on the collected interictal and ictal EEG from LTM-VEEG^{237, 238}. Sixth, the selection criteria for spike clusters used for source localization were largely based on strict signal quality standards that do not necessarily correlate with the epileptic tuber. Moreover, altered intracranial geometry and tuber-specific conductivity may violate some assumptions of the forward model that may cause a small localization error. An alternative approach might be to constrain source solutions to perituberal regions while simultaneously allowing a more liberal acceptance regarding signal quality²³⁹. Seventh, our reference standard – the resected area in seizure free patients – has its limitations. Seizure recurrence may be caused by incomplete resection – due to eloquent area vicinity – or it may be explained by newly evolved epileptogenic tissue^{148, 156}. To increase sample size we included all operated patients regardless of postoperative follow-up duration. The concept of the epileptogenic zone is based on a focal assumption, yet it is increasingly acknowledged that epilepsy also behaves as a complex network²⁴⁰. For TSC specifically, focal seizures and interictal epileptiform discharges may arise in the centre of epileptogenic tubers, propagating to the tuber rim, perituberal cortex and other (epileptogenic) tubers^{223, 241, 242}. Epileptic activity may also start independently from different tubers^{243, 244}. Complex and widespread epileptic zones and networks have also been demonstrated by various methodologies and biomarkers such as EEG-functional MRI²⁴⁴ and high frequency oscillations²⁴⁵. These zones are sometimes located with spatial distance from spike topography²⁴⁴. Tuber locations associated with epileptic spasms show functional connection to the globi pallidi and cerebellar vermis²⁴⁶. Thus, removal of the cortical tuber (tubectomy) alone may not be sufficient to interrupt the complex epileptic network completely. Surgical failure may not necessarily rule out epileptogenicity of resected tissue but is also no proof that non-resected source estimates are epileptogenic¹⁷⁷. Lastly, our small sample size prevented statistical analysis and computation of reliable sensitivity and specificity. A larger cohort is needed for more robust and reliable outcomes.

Conclusions

This study demonstrates that HR-ESI is more often localizing compared to semiology, interictal EEG and ictal EEG in presurgical evaluation of TSC patients. Semiology has limited localizing value. Interictal and ictal EEG have often non-localizing and multifocal test results that impact the overall localization value of these methods. HR-ESI is more concordant with proven epileptogenic zone, with ictal EEG being more partial concordant. HR-ESI has a predominantly positive impact on clinical management without ever being critically misleading. Presurgical workup of TSC might benefit from less emphasis on semiology and more on HR-ESI results. Employing HR-ESI initial presurgical workup modality might complement LTM-VEEG results by improving localization accuracy, guiding ancillary (non) invasive testing or confirming the EZ hypothesis when there is hesitance to undertake surgery. Future studies should prospectively explore the added value of HR-ESI early in the presurgical epilepsy evaluation of TSC patients.

Supplementary material

Supplementary table 5.1. Patient characteristics.

Patient	Sex	Age*	Seizure type
1	F	9	Epileptic spasm
2	M	2	Other focal motor
3	F	9	Other focal motor
4	M	3	Other focal motor
5	M	16	Focal non-motor
6	M	2	Other focal motor
7	F	5	Focal non-motor
8	F	13	Focal non-motor
9	F	2	Other focal motor
10	F	7	Epileptic spasm
11	M	5	Focal non-motor
12	M	1	Epileptic spasm
13	M	2	Epileptic spasm
14	F	26	Focal non-motor
15	M	6	Epileptic spasm
16	M	9	Focal non-motor
17	M	3	Focal non-motor
18	F	13	Other focal motor
19	F	3	Type 1: focal non-motor Type 2: focal non-motor
20	M	35	Type 1: focal non-motor Type 2: focal non-motor
21	M	7	Focal non-motor
22	M	1	Other focal motor
23	M	3	Epileptic spasm
24	M	1	Type 1: focal non-motor Type 2: Epileptic spasm

*At the onset of presurgical workup. M: male; F: female.

Supplementary table 5.2. Presurgical modality localizations and consecutive surgical workup per patient.

Patient	PHS	VS	Interictal EEG (LTM-VEEG)	Ictal EEG (LTM-VEEG)	HR-ESI	Ancillary tests	Decision	Resected area	Follow up (months)	Surgical outcome (Engel)
1	F	T	MF (predom. LC)	LC	LP	-	ECoG guided surgery	LP	73	1a
2	x	x	LP	LP	LP	GRID	Surgery	LP	29	1b
3	LT	x	MF (predom. LFT)	LFCP	LF	GRID	ECoG guided surgery	LF (2 tubers)	13	1a
4	LF	x	MP	x	LP ^a	GRID ^b	ECoG-guided lesionectomy	RP	12	1b
5	LT	x	RT	x	RT	-	ECoG guided surgery	RT	9	1a
6	LF	LF	MF (bilateral)	RP	RP	SEEG; RP	ECoG guided surgery	RP, RC	7	1a
7	T	T	MF (predom. Bilat T)	MF (LFT, LC)	RO ^c	-	ECoG-guided lesionectomy	LT	6	1a
8	x	RF	RT	RT	RT	SPECT: RT, R TO	ECoG guided surgery	RT	4	1a
9	RF	x	RF	RF	RF	-	ECoG guided surgery	RF	4	1
10	x	LF	MF (bilateral)	RF	RF	-	ECoG guided surgery	RF (disconnection)	39	3
11	x	T	LT	LT	LO	GRID	ECoG guided-surgery	L TPO	10	3a
12	x	x	MF (predom. RF)	x	RF	-	ECoG guided surgery	RF	7	3a
13	x	x	LT	LT	MF (LF, LT, RF)	New LTM-VEEG: MF (interictal), L FT (ictal) ^d ; SEEG: L F	ECoG-guided surgery	LF (disconnection) ^e	30	4b
14	T	LT	LF	LF	LF	SPECT ^f ; L F	ECoG guided surgery	LF (2 tubers)	23	4 ^g
15	x	F	LT	x	MF	MEG ⁱ ; LC	ECoG-guided surgery ^h	LCP	15	4c
16	x	x	LFC	LF	LF	-	ECoG-guided surgery planned	-	-	-
17	C	RF	MCP	MC	MF (LF, RCP)	-	Withdrawn (by parents)	-	-	-

18	L F	x	L T	MF (L FT, L PO, L TO)	L T	-	Withdrawn (seizure frequency reduction)	-	-
19	x	x	L PO	L PO/L O ⁱ	L TPO	-	Withdrawn (seizure reduction, surgical risk of language impairment)	-	-
20	P	x	x	x	L F	GRID proposed	Withdrawn (seizure reduction)	-	-
21	x	L F	MF (predom. R)	x	x	New LTM-VEEG: no seizures	Rejected	-	-
22	x	x	MF (predom. R PC)	R C	R F	-	Rejected	-	-
23	x	F	MF (predom. R T)	x	M F	SPECT ^f : MF (L P, L T, R P); MEG ^g : MF (predom. R FT)	Rejected	-	-
24	F	x	MF (predom. R TO)	R TPO	R F ^j	SEEG proposed ^k	Rejected	-	-

PHS: patient-history based semiology; VS: video-based semiology; LTM-VEEG: long term monitoring video electroencephalography; HR-ESI: high-resolution electric source imaging; SEEG: stereo depth EEG; GRID: intracranial GRID EEG; ECoG: electrocorticography; SPECT: single photon emission computed tomography; MEG: magnetoencephalography; L: left; R: right; Bilat: bilateral; F: frontal; T: temporal; C: central; O: occipital; M: midline CP: centro-parietal; FT: fronto-temporal; PO: parieto-occipital; TO: temporo-occipital; FCP: fronto-centro-parietal; - : non-localizing; MF: multifocal; predom: predominantly; x: no hypothesis or not localizing.

^a HR-ESI localized to the left mesial parietal area near the precuneus.

^b GRID electrodes with bilateral midline coverage encompassing the HR-ESI focus and a contra-lateral located tuber – as identified by MRI.

^c Focus was considered not to be involved in generation of the targeted clinical seizures and was therefore not included into the surgical plan.

^d LTM showing multifocal interictal epileptic discharges and ictal suppression of epileptic activity left fronto-temporal.

^e Surgical approach was to start with a tubectomy and based on presence of GRID-recorded post-resection epileptic activity, resection was enlarged up to a frontal disconnection.

^f preceded HR-ESI.

^g In a post-surgical multidisciplinary meeting it was hypothesized that seizure were generated from smaller tubers located in the frontopolar and mesiofrontal regions, or from a larger tuber in the frontal operculum. Resection of all these tuber was considered not feasible.

^h Initially rejected because of multifocality (non-localizing LTM-VEEG and multifocal HR-ESI) and no clear target area for invasive monitoring. Because of clinical worsening years later GRID recording was started following ECoG-guided surgery for palliative purposes.

ⁱ Left parieto-occipital localization resulting from seizure type 1, left occipital localization resulting from seizure type 2.

^j alternative hypothesis suggests a deep source.

^k SEEG proposed in central area, but rejected because patient was too young.

Supplementary table 5.3. HR-ESI related influence on clinical decisions and clinical value.

Patient	Pre-EZ	HR-ESI	Localization specifics	Post-EZ	EZ modification	Clinical decision	Resected area	HR-ESI concordance with resected area	Surgical outcome	Clinical value
1	LC	LP	Confirms suspected tuber	LP	4 = EZ confirmed	4=Proceed to surgery	LP	Yes	Good	Positively supportive
2	LP	LP	More accurate localization in/near functional	LP	5 = EZ narrowed	3=Additional invasive testing	LP	yes	Good	Critically valuable
3	LP ^a	LF	Confirms suspected tuber	LF [*]	4 = EZ confirmed	3=Additional invasive testing	LF (2 tubers)	yes	Good	Positively supportive
4	x	LP ^b	New suspected area	LP [*]	7 = EZ generated	3=Additional invasive testing	RP	no	Good	Opposing
5	RF ^c	RT	New suspected area	RT	6 = EZ changed	4=Proceed to surgery	RT	yes	Good	Critically valuable
6	RP	RP	More wide spread focus	RP	2 = EZ enlarged	2=Additional non-invasive and invasive testing	RP, RC	Yes	Good	Critically valuable
7	LT ^d	RO	Contra-hemispheric focus	LT	3 = EZ unaffected	4=Proceed to surgery	LT	no	Good	Disruptive
8	RT	RT	Not able to tailor a tuber	RT	4 = EZ confirmed	1=Additional non-invasive testing	RT	yes	Good	Positively supportive
9	RF	RF	Confirms lobar location	RF	4 = EZ confirmed	4=Proceed to surgery	RF	yes	Good	Positively supportive
10	RF	RF	Taylorized surgery not possible	RF	4 = EZ confirmed	4=Proceed to surgery	RF (disconnection)	yes	Poor	Negatively supportive
11	LT	LO	Confirms suspected tuber	LTPO	4 = EZ confirmed	4=Proceed to surgery	LTPO	yes	Poor	Negatively supportive
12	NA ^e	-	-	-	-	-	-	-	-	-
13	LT [*]	MF (LF, LT, RF)	Gives more suspected areas	LF / LT	2 = EZ enlarged	2=Additional non-invasive and invasive testing	LF (disconnection) ^f	no	Poor	Indeterminate
14	LF	LF	Confirms suspected tuber	LF	4 = EZ confirmed	4=Proceed to surgery	LF (2 tubers)	yes	Poor ^a	Negatively supportive

15	LT/LC ^a	MF	No meaningful localization	X	1 = EZ discarded	0=Rejected (but years later GRID with palliative surgery)	LCP	no	Poor	Indeterminate
16	LF	L F	Changes target tuber intralobar	LF	5 = EZ narrowed	4=Proceed to surgery	NA (resection planned)	-	-	-
17	M C	MF (LF, R CP)	More accurate localization in/near functional area	RCP	5 = EZ narrowed	3=Additional invasive testing	NA (withdrawn)	-	-	-
18	x	L T	No tuber or other pathological imaging characteristics surrounding tuber	x	3 = EZ unaffected	1=Additional non-invasive testing	NA (withdrawn)	-	-	-
19	L TPO/L PO	L TPO	Confirms suspected tuber	L TPO	4 = EZ confirmed	4=Proceed to surgery	NA (withdrawn)	-	-	-
20	NA ^b	-	-	-	-	-	-	-	-	-
21	F	x	No meaningful localization	X	1 = EZ discarded	1=Additional non-invasive testing	NA (rejected)	-	-	-
22	R FC	R F	Not able to localized to a tuber	X	1 = EZ discarded	0=Rejected	NA (rejected)	-	-	-
23	RT and/ or RTP	MF	No meaningful localization	X	1 = EZ discarded	0=Rejected	NA (rejected)	-	-	-
24	NA ^c	-	-	-	-	-	-	-	-	-

HR-ESI: high-resolution electric source imaging. Pre-EZ: presumed epileptogenic zone prior to HR-ESI evaluation. Post-EZ: presumed epileptogenic zone after evaluation of HR-ESI results. Surgical outcome: Good (Engel 1), Poor (Engel 2-4). L: left; R: right; Bilat: bilateral; F: frontal; T: temporal; C: central; P: parietal; O: occipital; M: midline CP: centro-parietal; FT: fronto-temporal; PO: parieto-occipital; TO: temporo-occipital; TPO: temporo-parieto-occipital. FCP: fronto-centro-parietal; - : non-localizing; MF: multifocal; predom: predominantly; x: no hypothesis or not localizing. NA: not applicable.

^a: hypothesis deduced by study author (BM).

^a mostly based on MRI showing that the two largest tubers were located L F.

^b HR-ESI localized to the left mesial parietal area near the precuneus.

^c Multidisciplinary team re-reviewed LTM-VEEG and concluded a R frontal suspected focus.

^d Focus was considered not to be involved in generation of the targeted clinical seizures and was therefore not included into the surgical plan.

^e LTM-VEEG and HR-ESI were simultaneously indicated and evaluated in the same multidisciplinary team meeting. This patient was therefore excluded from clinical decisions analysis.

^f surgical approach was to start with a tuberectomy and based on presence of post-resection epileptic activity registered by GRID EEG resection was extended, if necessary

to a frontal disconnection.

^aIn a post-surgical multidisciplinary team meeting it was hypothesized that seizures were generated from smaller tubers located in the frontopolar and mesiofrontal regions, or from a larger tuber in the frontal operculum. Resection of all these tuber was considered not feasible.

^bHR-ESI results preceded LTM-VEEG and were discussed in a prior meeting. This patient was therefore excluded from clinical decisions analysis.

^c novel MRI results reviewed during second multidisciplinary team meeting. MRI results might have affected the post EZ. Patient excluded from clinical decisions analysis.

CHAPTER 6

Single pulse electrical stimulation to identify epileptogenic cortex: clinical information obtained from early evoked responses

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Objective

Single Pulse Electrical Stimulation (SPES) probes epileptogenic cortex during electrocorticography. Two SPES responses are described: pathological delayed responses (DR, >100 ms) associated with the seizure onset zone (SOZ) and physiological early responses (ER, <100 ms) that map cortical connectivity. We analyzed properties of ERs, including frequencies >80 Hz, in the SOZ and seizure propagation areas.

Methods

We used data from 12 refractory epilepsy patients. SPES consisted of 10 pulses of 1 ms, 4–8 mA and 5 s interval on adjacent electrodes pairs. Data were available at 2048 samples/s for six and 512 samples/s (22 bits) for eight patients and analyzed in the time–frequency (TF) and time-domain (TD).

Results

Electrodes with ERs were stronger associated with SOZ than non-SOZ electrodes. ERs with frequency content >80 Hz exist and are specific for SOZ channels. ERs evoked by stimulation of seizure onset electrodes were associated with electrodes involved in seizure propagation.

Conclusion

Analysis of ERs can reveal aspects of pathology, manifested by association with seizure propagation and areas with high ER numbers that coincide with the SOZ. Not only DRs, but also ERs could have clinical value for mapping epileptogenic cortex and help to unravel aspects of the epileptic network.

Introduction

Cortical Single Pulse Electrical Stimulation (SPES) and its responses yield information about the epileptic tissue in the brain. SPES was first described by Valentín et al. (2002) in focal refractory epilepsy patients who underwent chronic electrocorticography (ECoG) preceding surgery. The stimulation protocol consists of ten brief pulses of 1 ms and 4–8 mA amplitude with a 5 s interval given over two neighboring electrodes²². SPES evokes two types of responses: early responses (ERs) within 100 ms after stimulation and delayed responses (DRs) after 100 ms up to 1 s after stimulation^{22, 23, 247}. SPES research has mainly focused on DRs. DRs are associated with the seizure onset zone (SOZ) and contain pathological high frequency (80–500 Hz) information. These high frequency DRs are more specific for the seizure onset zone compared to DRs in the low frequency band (<80 Hz)²¹. ERs are assumed to be a physiological phenomenon originating from stimulation of cortico-cortical association fibers (u-fibers). ERs resemble the N1 potential in cortico-cortical evoked potentials (CCEP; general settings 0.3 ms pulses, 1 Hz, 1–15 mA, 20–70 stimuli averaged). The N1 potential provides information regarding cerebral functional connectivity^{25, 248–254}. It has been suggested as a method for the identification of functional areas during surgery²⁵⁵. As such, CCEPs, and ERs, may reveal regions of rich network connectivity. On the other hand, it has been shown that seizure propagation proceeds locally through neocortical cells as well as over longer distances through the deeper lying u-fibers that are stimulated by CCEP^{256, 257}. ERs might mirror these seizure propagation pathways, thus revealing an important aspect of the pathology of epilepsy.

We investigated ERs, including higher frequency responses above 80 Hz, evoked by stimulation out- and inside the seizure onset zone (SOZ) and analyzed their properties in the SOZ and in areas of seizure propagation, respectively. We used two approaches; analysis in the time–frequency (TF) domain of high temporal resolution data and analysis in the time-domain (TD) of high dynamic range data.

Methods

Patients

Data from 12 patients (5 males, mean age 19.7 years, range 8–42 years) with refractory epilepsy who underwent chronic ECoG preceding epilepsy surgery were used. All patients were admitted to the intensive epilepsy monitoring unit of the UMC Utrecht in the Netherlands in the period 2008–2012. SPES was routinely performed as a clinical protocol. SPES results were included in the medical decision making after visual inspection in line with recommendations of Valentín et al. (2002).

Monitoring time ranged from 3 to 8 days. All 12 patients underwent resective surgery of a presumed epileptic focus. Five patients had temporal, three had frontal, two had frontocentral, and two had parietal lobe epilepsy. Most patients were on multiple anti-epileptic drugs that were tapered during the registration. Patient information is summarized in table 6.1.

The institutional ethical committee indicated that no explicit approval was necessary because of the retrospective character of this study, provided that data were coded and handled anonymously.

Electrocorticography data

Subdural grids and strips (Ad-Tech, Racine, Wisconsin, USA) were placed under general anesthesia, after craniotomy. The circular platinum electrodes, imbedded in silicon, had a contact surface of 4.2 mm² and an inter-electrode spacing of 1 cm. In two patients, additional depth electrodes were implanted with eight cylindrical contacts with 7.9 mm² contact surface and 5 mm inter-electrode distance. Electrode placement was based on clinical pre-operative diagnostics, covering both the suspected epileptogenic region(s) and eloquent areas. Electrode positions on the cortex were obtained by co-registration of post-implantation CT with preoperative 3D MRI images²⁵⁸. The median number of implanted electrodes was 96 (range 88–120) per patient (table 6.1).

Clinical information

Per patient a recording of a typical spontaneous clinical seizure was analyzed retrospectively by two neurologists (chosen from CF/FL/MZ). They were asked to mark independently; (1) the one electrode with the first ictal activity as the seizure onset electrode (SO-electrode), (2) all electrodes on which seizure propagation was found (SP-electrodes) within the first 30 s after initial onset. Ictal activity was defined as the first ECoG pattern consisting of rhythmic spikes, rhythmic sharp waves, recruiting gamma activity, regular or low-amplitude activity in the beta range prior to or coinciding with the clinical manifestation of the seizure²⁵⁹. In case of a generalizing seizure, observers marked all electrodes showing ictal activity up to the point of generalization. Disagreement in the marked onset or propagation between two observers was solved in a consensus meeting. Additionally, a clinical SOZ area was defined, based on all recorded seizures from the total monitoring period (by FL/CF). This SOZ typically contained multiple electrodes.

Single pulse data acquisition

Single Pulse Electrical Stimulation (SPES) was performed using a manually controlled cortical stimulator (IRES 600 surgical, Micromed, Treviso, Italy). Monophasic SPES stimuli were given, ten pulses with a duration of 1 ms, separated by 5 s intervals, on pairs of adjacent electrodes. Stimulation was performed at an intensity of 8 mA and only in

Table 6.1. Patient characteristics.

Pt	TD/TF	M/F	Age (y)	Region	Side	Pathology	Total # electrodes	Monitoring period (days)	# Seizures (onset activity, types)	SOZ resected?	Outcome (1y) Engel class
1	TD + TF	M	42	T	L	MTS	96	7	2 (focal gamma onset, 1 type)	Complete	I
2*	TD + TF	F	23	T	L	Glioneural heterotopia	96	6	6 (gamma burst onset, 1 type)	Complete	I
3	TF	M	9	Fr	L	FCD	96 (16 depth)	5	12 (focal beta-gamma onset, 1 type)	Incomplete	IV
4	TF	F	31	T	R	MCD	88	8	1 (gamma onset)	Complete	I
5	TF	F	13	FrC	L&R	TS	96	8	6 (gamma burst onset, 1 type)	Incomplete (multiple tubers bilateral)	IV
6	TF	M	8	FrC	L	Tumor	96	5	>100 (gamma onset, 1 type)	Complete	I
7	TD	F	17	Fr	R	FCD	120	3	6 (gamma onset, 1 type)	Complete	I
8	TD	M	8	P	R	FCD	94 (6 depth)	5	1 (gamma onset, 1 type)	Incomplete (eloquent regions)	I
9	TD	F	18	Fr	L	Reactive changes	112	7	19 (gamma onset, 1 type)	Complete	I
10	TD	F	15	P	L	FCD	96	5	3 (gamma onset, 1 type)	Incomplete	IV
11	TD	M	26	T	L	MTS	120	6	6 (gamma onset, 1 type)	Complete	I
12**	TD	F	27	T	L	MCD	96	6	4 (gamma onset, 2 types)	Incomplete	IV

TD/TF = analysis performed; TD = time domain analysis, TF = time-frequency analysis, F = female, M = male, Fr = frontal, T = temporal, C = central, FrC = fronto-central, P = parietal, L = left, R = right, TS = tuberous sclerosis, MCD = malformation of cortical development, FCD = focal cortical dysplasia, MTS = mesial temporal sclerosis. # Seizures = number of spontaneous clinical seizures, outcome (1y) = post-operative outcome after 1 year using the Engel classification. *Patient 2 had a number of different electrodes on a single strip from which the clinically identical seizures originated. We choose one of these electrodes as SO-electrode, this could explain the poorer results in this patient compared the other patients. **In patient 12 two separate onset zones were found. Only one seizure onset zone could be resected, therefore we selected a seizure of that type.

stimulation pairs where twitches or pain occurred the intensity was gradually reduced to as low as 4 mA. In six patients SPES was available at a high sampling rate of 2048 Hz and a hardware anti-aliasing filter of 538 Hz in a subset of 64 electrodes simultaneously (SD128, Micromed, Treviso, Italy). Subset selection was based on the monitoring result of previous days, and included the clinical SOZ. In eight patients SPES was sampled at 512 Hz (anti-aliasing filter 134 Hz) with a high dynamic range at 22 bits resolution, simultaneously in all implanted electrodes. In two patients both types of recordings were available. Data were recorded with respect to an extra-cranial reference. All recordings showed stimulus artifacts in most electrodes that needed to be dealt with. Electrodes with other artifacts were excluded from analysis.

Time–frequency processing of SPES

We used the same SPES datasets and a similar analytical approach as in our previous study on time–frequency analysis of evoked DRs²¹. The aim of the current study is time–frequency analysis of evoked ERs instead of evoked DRs. To enable analysis of ERs we made the following methodological changes: (1) the time-interval of interest was changed to <100 ms, (2) time–frequency decomposition was based on Hilbert-Huang Transformation instead of Wavelet transform in order to create a higher time resolution, and (3) additional processing was required in order to obtain images similar to the Event Related Spectral Perturbation images (ERSPs) in the previous study²¹. Further details are provided in the following sections.

Preprocessing

Time frequency (TF) analysis was done only on data sampled at 2048 Hz. Preprocessing of the data files was performed in Matlab® (The MathWorks, Natick, MA) as described in our previous study²¹. Preprocessing steps included: stimulus detection, epoching of the data and re-referencing to average reference. Re-referencing was performed in order to exclude contamination of the data by frequencies above 70 Hz, mostly muscle artifacts, which could be present in the extra-cranial common reference. Epochs with interval of $[-1 \text{ s}; 1 \text{ s}]$ covering pre-stimulus baseline were selected. This resulted into ten epochs for each stimulated electrode pair and all recorded response electrodes. An additional steep low-pass finite impulse response filter with a cut-off frequency of 500 Hz ($f_{\text{stop}} = 520 \text{ Hz}$, $f_{\text{pass}} = 500 \text{ Hz}$, attenuation >60 dB/octave) was applied to limit any interference of higher frequencies.

Time–frequency decomposition

The Hilbert-Huang transform (HHT) was used to detect ERs in the proximity of the stimulus artifact. HHT allows time–frequency analysis with a high time resolution that prevents overlap of the artifact with the ER time-window <100 ms we are interested in²⁶⁰. The Hilbert-Huang transform provides a decomposition of the signal into a finite number of

components. These so-called “modes” are not directly related to a specific frequency band, but when combined they result in a coverage, albeit incomplete, of the time–frequency matrix. Frequencies not present in the modes are absent in this matrix and their power is automatically set to zero.

HHT was implemented in Matlab® (The MathWorks, Natick, MA) using a customized script that is freely available online (<http://perso.ens-lyon.fr/patrick.flandrin/emd.html>)²⁶¹. Default values for stop criteria and number of iterations were used as described there. HHT time–frequency analysis (range 5–500 Hz) was performed for each epoch of each stimulus pair. The frequency and time resolution were set at 1 Hz and 0.488 ms. Each analysis resulted in a time–frequency matrix of 496 rows by 4096 columns.

Construction of time–frequency images

Color coded ERSP images were constructed from the time–frequency matrix²⁶². First, the data were smoothed using a 15×15 weighted Gaussian filter. ERSP images were then calculated by averaging each set of ten stimulus epochs, generating one ERSP image for each stimulus pair for each set of response electrodes (total # ERSP images = # pairs of stimulated electrodes \times 64 recorded electrodes). Significance ($p < 0.05$) of spectral perturbations was determined by bootstrapping based on a pre-stimulus baseline interval [–1 s:–0.2 s]. Intensity values were expressed in power on a logarithmic power scale [–20 dB:20 dB]. Additional stimulus masking was performed, by constructing a template based on the symmetry of the HHT of the stimulus artifact. The template was subtracted in each image to mask the artifact and enable better visualization of ERs. A schematic overview of the TF analysis can be found in figure 6.1A.

Visual analysis of ERSP images

ERSP images were visually classified for events in three frequency bands, spike (S) <80 Hz, ripple (R) 80–250 Hz and fast ripple (FR) band (250–500 Hz)²¹. The time interval of interest for ERs was defined as [0 s:0.1 s] after stimulation, based on the latency definitions by Valentín et al. (2002). To avoid bias in interpretation, the DR interval [0.15–1 s] was removed from the final image. ERs were defined as clusters of increased power (coded orange-red) that stand out from the baseline for the same frequency band. Classification of the ER responses in all ERSP images for all stimulus electrode pairs was performed independently by two observers (chosen from CF/JH/GH/BM) for each patient. Inter-observer agreement was calculated by Cohen’s kappa (κ) using SPSS 21 software (IBM SPSS Statistics, Rel. 21.0 2012, Chicago; SPSS Inc.). The κ -scores were calculated separately for the S, R and FR events. A $\kappa > 0.4$ was considered as reasonable agreement^{21, 263}. Final counts of ERs in the spike, ripple and fast ripple band were based on consensus events of two observers. Datasets with $\kappa < 0.4$ for all frequency bands were excluded from analysis.

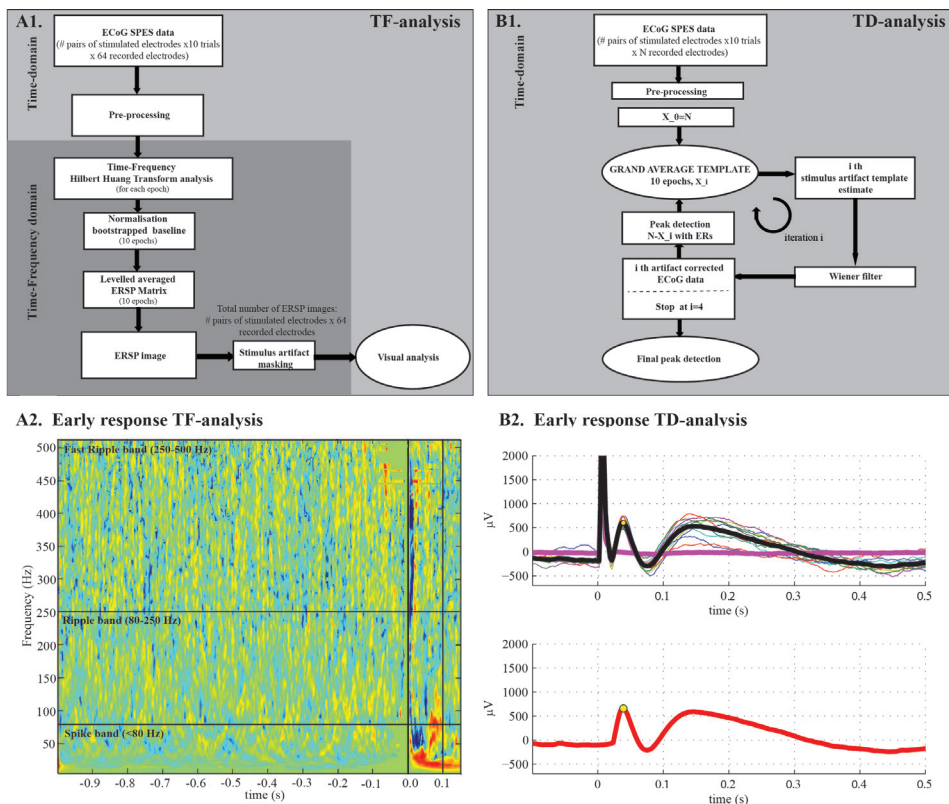


Figure 6.1. Schematic representation of two analyses performed. (A1) TF analysis based on HHT constructed ERSP images. (A2) Resulting HHT based ERSP image of TF analysis, as presented to the observers. Red colors indicate enhanced power compared to the pre-stimulus baseline on a power scale of $[-20:20]$ dB. Intense red (significantly increased power) = 20 dB, green (not significant) = 0 dB, and intense blue (significantly decreased power) = -20 dB. The vertical axis represents frequency, with the horizontal lines separating the S, R and FR frequency band. The horizontal axis is time, with the stimulus at $t = 0$. A pronounced spike and ripple event is shown around 50 ms after stimulation. (B1) TD analysis based on iterative Wiener filtering and peak detection of ER responses. (B2) TD analysis, thin lines are raw data for one electrode of responses evoked by 10 consecutive stimuli. The average is shown in black, the purple line shows the optimal Wiener filter estimate of the stimulus artifact. In the lower panel the artifact corrected average response (red) with the ER detected by the peak detection (yellow dot).

Time-domain processing of SPES

Preprocessing

Time domain (TD) analysis was done only for data recorded with high dynamic range (22 bits). These recordings contain all implanted electrodes, and include both the SOZ and the seizure propagation area. Preprocessing consisted of stimulus detection and epoching as described above, but no re-referencing was performed. For TD analysis, as opposed to TF analysis, contamination of frequencies above 70 Hz present in the extra-cranial common reference does not pose a problem.

Artifact correction and event detection

An algorithm was developed to detect ERs in the time-domain consisting of two steps (Matlab®, The MathWorks, Natick, MA). Step 1 is removal of the stimulus artifact. This was based on Wiener filtering, assuming that the shape of the artifact is the same in all response electrodes for a given stimulus pair. A major determinant of the shape of the stimulus artifact in our data is cross-talk of the leads carrying the stimulus current to leads of recording channels in the same connecting cable. Therefore the stimulus artifact has generally the same shape, however, the amplitude may differ per electrode. First, a grand average over 10 pulses and over each response electrode was taken. Note that the large number of electrodes ($X_0 = N$, which ranges 80–120 electrodes) provides that the number of electrodes without ERs exceeds the number of electrodes with ERs, implying that this average is dominated by artifact data. Therefore it was used as the first template to construct a Wiener filter, which, when applied, removed the main part of the stimulation artifact. Next, ER responses were detected automatically in the filtered data by a quick peak detection algorithm (PeakFinder, N. Yoder, Matlab file-central). A more accurate template artifact was then constructed by excluding electrodes with ERs ($N - X_1$) from a new grand average over the original data. The new template was then again used for Wiener filtering. This process is repeated four times (iteration $i = 1:4$) to further refine the template artifact. Step 2 of the algorithm is the final ER peak detection in the interval 0.02–0.1 s after stimulation. This interval was chosen to avoid potential bias for incomplete artifact correction that interferes with the onset of the ER. For final peak detection the same algorithm as mentioned above was used, but now with an adaptive amplitude threshold determined by visual inspection. The choice of amplitude threshold was made by favoring over-detection over under-detection; when visually clear responses were not adequately detected due to an inadequate threshold setting this was lowered by 10 μV steps. A schematic overview of the TD analysis can be found in figure 6.1B. ER response electrodes were those that exceeded the threshold for a particular stimulus electrode pair. For the TD analysis of ERs and seizure propagation, stimulation of a single electrode pair was considered: one electrode was the electrode marked as SO-electrode (see section clinical information) and the other a neighboring electrode that was located on the same gyrus. In cases of ambiguity, the stimulation pair that showed the largest total number of responses was chosen.

Statistical analysis

Statistical analysis was performed in IBM SPSS Statistics 21 (IBM Corp., Armonk, NY, USA). For all tests we considered p -values < 0.05 significant. TF analyses were done for the spike, ripple and fast ripple band separately. The following analyses were done for TF and TD, when appropriate.

Early response counts

For the TF analysis we counted the number of ERs per electrode (ER_{count}) for the total of all stimulus pairs. We normalized the number of ERs in each response electrode with respect to the maximal count (ER_{max}) found, expressed as percentage:

$$ER_{norm} = (ER_{count} / ER_{max}) \times 100\% \quad (\text{Eq 6.1})$$

We then defined electrodes with a high occurrence of ERs, $ER_{norm} > 50\%$, as ER_{50} electrodes.

So while the detection of a single ER in a particular band reflects the excitability of the underlying tissue with respect to the stimulus, high values of ER_{norm} will reflect the richness of connections to that electrode.

Association of ER counts with SOZ and ERs with propagation

We tested for differences in the value of ER_{norm} between SOZ and non-SOZ channels using a non-parametric Mann–Whitney U test (two-tailed). Differences between association of ER_{50} electrodes with SOZ and with non-SOZ channels was assessed using Fisher's exact test (two-tailed) (TF analysis). We tested for differences in association between ERs, following stimulation of SO-electrode, in SP-electrodes and non-SP-electrodes using Fisher's exact test (two-tailed) (TD analysis).

Sensitivity and specificity of ERs

To further quantify results, sensitivity, specificity, positive and negative predictive value (PPV and NPV) of ER_{50} for the clinical SOZ (TF analysis) and ER for seizure propagation (TD analysis) was determined. Sensitivity was calculated as $tp/(tp + fn)$, specificity as $tn/(tn + fp)$, PPV as $tp/(tp + fp)$ and NPV as $tn/(tn + fn)$.

For TF analysis an electrode was considered as:

- a true positive electrode (tp) if involved in the SOZ and classified as ER_{50} electrode,
- a false positive electrode (fp) if NOT involved in the SOZ but classified as ER_{50} electrode,
- a true negative electrode (tn) if NOT involved in the SOZ and NOT classified as ER_{50} electrode, and
- a false negative electrode (fn) if involved in the SOZ but NOT classified as ER_{50} electrode.

For TD analysis an electrode was considered as:

- a true positive electrode (tp) if marked as SP-electrode and showing ERs,
- a false positive electrode (fp) if NOT marked as SP-electrode but showing ERs,

- a true negative electrode (tn) if NOT marked as SP-electrode and NOT showing ERs, and
- a false negative electrode (fn) if marked as SP-electrode but NOT showing ERs.

Cross-check TD and TF analysis

Finally, we performed a cross-check of the ER results found by the TD and TF analysis in the patients for which SPES data of both types, high temporal resolution data and high dynamic range, were available. This includes: (a) association between ERs marked in the spike band in TF analysis with SP-electrodes when stimulating the SO-electrode, (b) calculation of the ER_{50} electrodes for the total number of stimulus pairs of the TD data, and determining their association with the clinical SOZ electrodes. We computed sensitivity, specificity, PPV and NPV for seizure propagation and seizure onset zone, respectively.

Results

Overall patient results

For six patients (pt 1–6) SPES data were sampled at 2048 Hz in 64 channels allowing the TF analysis and association of ER counts with SOZ for different frequency bands. For eight patients (pt 1, 2, 7–12) data were recorded in up to 120 channels recorded at high dynamic range (22 bits) that allowed the TD analysis and association of ERs with seizure propagation. In two patients (pt 1, 2) both SPES data types were available.

For the six patients recorded at 2048 Hz the mean number of analyzed channels was 62 (± 2). The median number of stimulated electrode pairs was 46 (range 16–55). The median number of electrodes in the SOZ was 5 (range 2–30). For the eight patients recorded at 22 bits a mean of 92 (± 13) channels was analyzed. All patients had seizures with a focal gamma onset. For each patient a SO-electrode was marked. For detailed patient characteristics we refer to table 6.1.

TF and TD analysis

In figure 6.1A a TF-domain ERSP image based on HHT is shown for one response electrode as presented to the observers. In figure 6.1B, the TD analysis of ERs for one electrode of ten responses to consecutive stimuli is shown. ERs were found in all patients, irrespective of the used analysis method.

ER findings and association with SOZ and propagation

TF analysis for the six patients resulted in a kappa > 0.4 in five patients (pt 1–4, and 6) for the spike band, in six patients (pt 1–6) for the ripple band but in only one patient (pt 2) in the FR-band (four ERs in the FR-band on three electrodes), therefore the FR-band

was excluded from further analysis. In figure 6.2 an example of the ER_{norm} distribution in relation to the clinical SOZ is represented. Note that the SOZ is characterized by high values of ER_{norm} (figure 6.2).

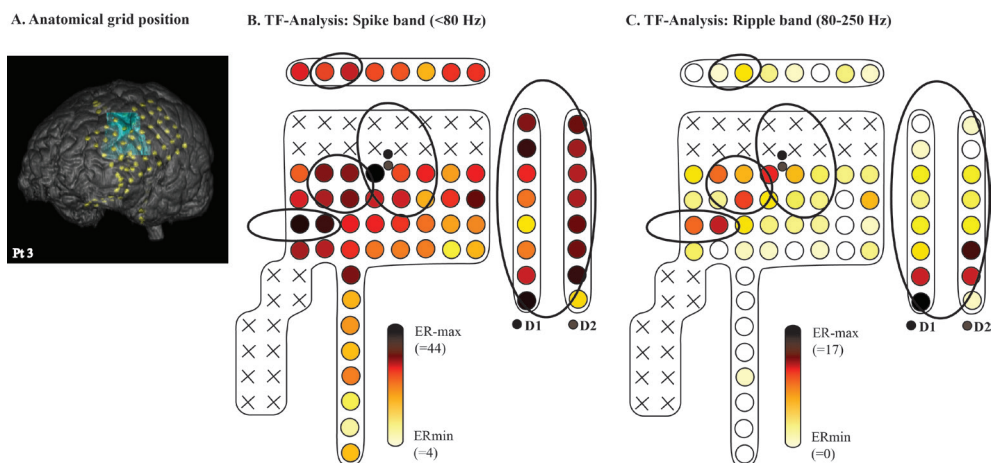


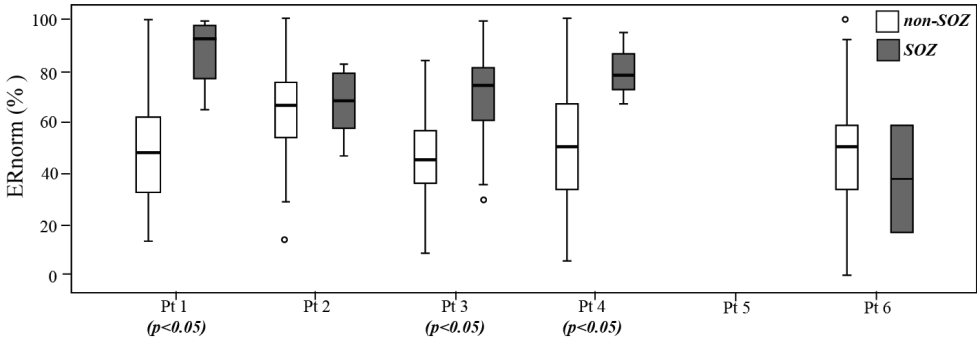
Figure 6.2. Patient example (pt 3) of ER_{norm} distribution. (A) MRI and CT merged images depicting the anatomical grid positions. (B) ER_{norm} distribution in the spike band (<80 Hz) and relation with the SOZ (encircled areas). (C) ER_{norm} distribution in the ripple band (80–250 Hz) and relation with the SOZ. Note: D1 and D2 are depth electrodes.

In three out of five patients with $k > 0.4$ (pt 1, 3 and 4) there was a significant difference between ER_{norm} counts in- and outside the SOZ ($p < 0.05$, Mann–Whitney U) for the S-band and in three out of five patients (pt 1, 3 and 5) for the R-band ($p < 0.05$, Mann–Whitney U). See figure 6.3.

Similar results were found at individual patient level for electrodes marked as ER_{50} electrodes. ER_{50} electrodes were significantly associated with SOZ electrodes in the spike band in two patients (pt 1 and 3; $p < 0.05$, Fisher exact) and in three patients in the ripple band (pt 1, 3 and 5; $p < 0.05$, Fisher exact). At group level the association of ER_{50} and the SOZ was significant for both the spike and ripple band ($p < 0.05$, Fisher exact) (table 6.2).

In figure 6.4 an example is given for an individual patient (pt 1) of ERs detected using the TD method when stimulated in the SO-electrodes. Note that ERs are mostly present in SP-electrodes. ERs detected when stimulating in SO-electrodes were significantly associated with SP-electrodes in four patients (pt 8, 9, 10 and 12; $p < 0.05$, Fisher exact), and at group level ($p < 0.05$, Fisher exact) (table 6.3).

A. Spike-band (<80 Hz)



B. Ripple-band (80-250 Hz)

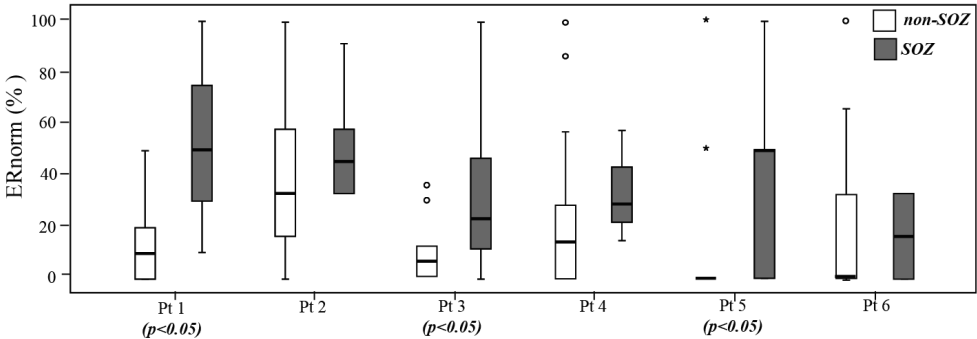


Figure 6.3. Boxplots for difference in ER_{norm} between channels in- and outside SOZ for (A) the spike band (<80 Hz); three patients (pt 1, 3 and 4) had a significant higher ER_{norm} in the clinical SOZ. (B) The ripple band (80–250 Hz). In the ripple band a significant higher ER_{norm} in the clinical SOZ was found for three patients (pt 1, 3 and 5).

Sensitivity and specificity of ER counts for SOZ and ERs for propagation

In the TF analysis group of six patients, we found a median sensitivity and specificity of ER_{50} in the spike band for the SOZ of 87% and 44%, respectively. For the ripple band this sensitivity and specificity was 42% versus 91% (table 6.2). Median sensitivity and specificity of ERs for the SP-electrodes was 32% and 94%, respectively in the TD analysis group of eight patients (table 6.3).

Table 6.2. Results of ER analysis in time–frequency (TF) domain and their relation with seizure onset.

#Pt	TF/TD	# Elec	SOZ (ER ₅₀)		Spec (%)		PPV (%)		NPV (%)		p-Value	
			S-band	R-band	S-band	R-band	S-band	R-band	S-band	R-band	S-band	R-band
1	TF	61	100	75	56	95	14	50	100	98	0.046	0.002
2	TF	62	83	50	18	63	10	13	91	92	1.000	0.661
3	TF	64	87	23	56	100	63	100	83	60	0.001	0.003
4	TF	58	100	33	47	94	9	25	100	96	0.245	0.195
5	TF	64	x	55	x	83	x	40	x	90	x	0.015
6	TF	64	50	0	42	87	3	0	96	96	1.000	1.000
Mean (±SD)/median (range)		62 (±2)	87 (50–100)	42 (0–75)	44 (18–57)	91 (63–100)	9 (3–63)	33 (0–100)	96 (83–100)	95 (60–98)	<0.001	<0.001

Pt = patient, TF = time–frequency analysis, TD = time-domain analysis, # elec = the number of electrodes included in the analysis, Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value, S-band = spike band (<80 Hz), R-band = ripple band (80–250 Hz), SD = standard deviation. *Tested for association ER₅₀ with SOZ, using Fisher exact test (two-tailed), with *p* < 0.05 considered significant (in italic bold). Note: results for the FR-band in TF analysis are not reported because of the single finding in only one patient (pt 2).

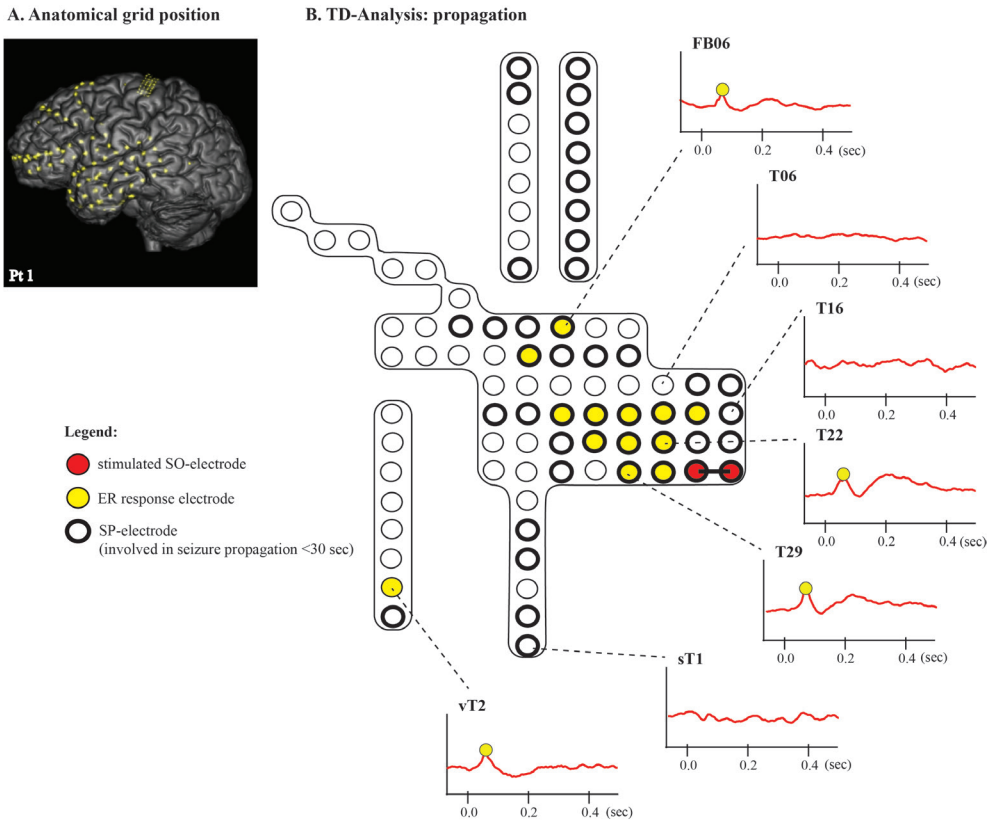


Figure 6.4. Patient example (patient 1) of ER electrodes for stimulation in the SO-electrode (TD analysis) and the correlation with propagation (SP-electrodes). Included are examples of the ER waveforms in selected electrodes. Sensitivity here is 42%, specificity is 86%, and PPV and NPV are 40% and 87%, respectively.

Cross-check TD and TF analysis

In two patients (pt 1 and 2) we compared the results of both TD and TF analysis. Note that comparisons were for different datasets of the same patients. We found that:

- Association of evoked ERs with seizure propagation is significant for ER detected by TD analysis but not for ERs detected in the spike band by TF analysis in patient 1 ($p_{TD} = 0.011$ vs. $p_{TF} = 0.435$, Fisher exact). The opposite was found for the relation between evoked ERs counts and the SOZ; a significant association between ER_{50} and the SOZ was found by TF analysis but not in TD analysis ($p_{TF} = 0.046$ vs. $p_{TD} = 1.000$, Fisher exact). Results for patient 2 were not significant (propagation: $p_{TD} = 0.103$ vs. $p_{TF} = 0.263$, Fisher exact; SOZ: $p_{TF} = 1.00$ vs. $p_{TD} = 0.509$, Fisher exact). TD and TF analysis showed similar, low, sensitivity of ERs for propagation (range: 24–42%).

- ERs detected by TD analysis had a higher specificity for SP-electrodes than ERs detected by TF analysis (figure 6.5).
- Sensitivity values of ER_{50} for the clinical SOZ were lower in both patients for TD (47% and 43%) compared to TF analysis (100% and 83%). Specificity values were comparable in patient 1 (54% vs 56%), but higher for the TD analysis in patient 2 (66% vs 18%) (supplementary table 6.1).

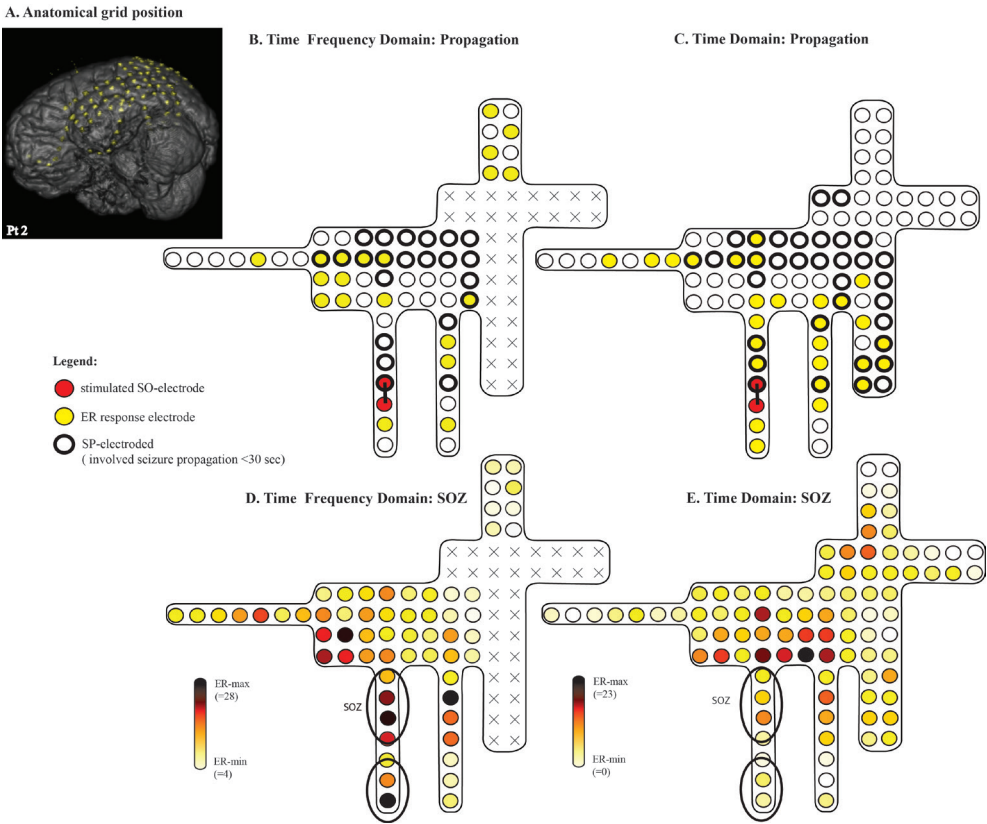


Figure 6.5. Results of the cross-check of TF and TD analysis in one of the two patients (patient 2). (A) MRI and CT merged images depicting the anatomical grid positions. (B and C) TD and TF analysis show similar, low, sensitivity of ER responses for propagation. ERs detected by TD analysis had a higher specificity for SP-electrodes than ERcounts detected by TF analysis. (D and E) Sensitivity of ER_{norm} for the clinical SOZ (encircled areas) are comparable for TD and TF analysis, but specificity is higher for the TD analysis.

Table 6.3. Results ER analysis in time-domain (TD) and relation with seizure propagation.

#Pt	TD/TF	Propagation		Mean latency (ms)	Mean amplitude (µV)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	p-Value*
		# Elec	Threshold (µV)							
1	TD	102	120	46	301	42	86	40	87	0.011
2	TD	91	120	64	378	40	77	52	67	0.103
7	TD	88	90	35	262	24	93	44	84	0.066
8	TD	86	140	47	355	22	98	89	64	0.003
9	TD	77	120	44	443	60	84	47	90	0.001
10	TD	94	120	59	299	36	100	100	72	0.000
11	TD	118	140	44	286	19	94	55	76	0.067
12	TD	82	130	39	206	28	97	92	55	0.002
Mean (±SD)/median (range)		92 (±13)	123 (±16)	47 (±10)	316 (±73)	32 (19–60)	94 (77–100)	54 (40–100)	74 (55–90)	<0.001

Pt = patient, TD = time-domain analysis, TF = time-frequency analysis, # elec = number of electrodes included in analysis, threshold = amplitude threshold used (see methods Section 2.6.2, step 2), mean amplitude = mean amplitude of ERs (baseline to peak), Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value, S-band = spike band (<80 Hz), R-band = ripple band (80–250 Hz), SD = standard deviation. *Tested for association ER response electrodes with SP-electrodes, using Fisher Exact test (two-tailed), with *p* < 0.05 considered significant (in italic bold).

Discussion

The SOZ is more likely to be located in areas showing high counts of ERs evoked by SPES. ERs evoked by stimulation in seizure onset electrodes are more likely to occur in electrodes that show seizure propagation. ERs in the ripple band (80–250 Hz) exist and electrodes with high ER counts in the ripple band have a high specificity for SOZ channels. So, the analysis of ERs evoked by SPES can reveal aspects of pathology, even if the underlying stimulus–response relation is purely physiological. ERs, besides DRs, could assist in unraveling aspects of the epileptic network.

Based on our results, we cannot suggest a preferred general method of analysis for SPES early responses, as each method has its pro's and con's. For the detection of high frequency content time–frequency analysis is necessary, but results for the cross-check patients show that the TF method lacks specificity in the detection of lower frequency responses resulting from a single stimulation site like the SOZ. TD analysis of SPES yields robust responses with high specificity, but lacks the sensitivity needed to extract useful clinical information about the SOZ from the overall statistics of early responses.

Methodological aspects

We showed that SPES evokes ERs [0.0–0.1 s] with frequency features above the traditional 80 Hz. We used a HHT time–frequency analysis instead of a wavelet analysis as used in our previous study²¹. A strength of time–frequency analysis is that it allows averaging in the frequency domain while retaining time information. The time resolution of wavelet analysis proved to be sufficient for DRs, since their relevant time interval lies between 0.15 s and 1.0 s after stimulation, and interference of the stimulus artifact is not an issue. The advantage of HHT is that it enables the detection of early ripple responses at a high time resolution, close to the stimulus artifact. HHT was successfully used in an earlier study by Kalitzin et al. (2012) to determine 'rippleness' of a signal²⁶⁴.

We are the first to find that SPES, with its low number of stimuli and low repetition rate, evokes ERs that can be associated with areas of seizure propagation, when stimulating the SOZ. The artifact removal algorithm applied in the time domain allowed us to detect ERs in a semi-automatic way, in spite of the low signal-to-noise ratio (SNR) of an average of only ten stimuli.

We were able to show an association between overall counts of ERs (ER_{norm}) and the SOZ at group level, and at individual level in four out of six patients. This finding seems to contradict the general finding of Valentín and coworkers (2002,2005) that early responses cannot localize epileptogenic cortex. In contrast to the studies of Valentín et al., in our study we count how often an electrode shows an ER response to stimulation throughout

the SPES protocol and we relate this measure for the richness of connections to the underlying area to the SOZ^{22, 23, 247}.

Does this mean that we can propose ER analysis as a clinical tool? When it comes to predicting seizure propagation it should be noted that clinically identical seizures in semiology can originate from different foci. Our study is limited by the fact that we studied only one seizure per patient and looked at the resulting ERs when stimulating the corresponding SO-electrode. Including more data or more seizures per patient would have increased the statistical robustness and thus clinical usefulness of our results.

When it comes to predicting the SOZ the sensitivity and specificity, based on ER_{50} , are insufficient for reliable prediction of the SOZ in individual patients. When we thresholded the ER_{norm} values to obtain ER_{50} electrodes, the sensitivity for the SOZ was relatively high (87%) for the spike band, but low for the ripple band (42%). Conversely, specificity is low (44%) for the spike band and high (91%) for the ripple band. Nevertheless information derived from ER counts can be added to that of pathological delayed responses, that have a high specificity and sensitivity and can be established during the same SPES session^{21-23, 247}.

Unlike ripples, fast ripples are described as primary pathological events^{244, 265-268}. We found only ERs in the fast ripple band in one patient. This low number of ERs in the fast ripple band cannot refute the assumption that ERs are purely physiological^{22, 252, 269}, although the lack of fast ripples could be explained by the fact that HHT is less suitable for the noisy high frequency content above 250 Hz²⁶⁰. Hardware requirements and the retrospective nature of this study resulted in small patient groups. Data suitable for both TF and TD analysis were not available. Acquiring high frequency data at 2048 Hz meant a sacrifice of recorded ECoG channels to a maximum of 64. The choice of channels to retain was made during the clinical registration and was based on information about the SOZ then available. Capturing seizure propagation over the grid up to 30 s after onset was not considered when the selection of the 64 electrodes for 2048 Hz recordings was made. Interpretation of the comparison between the TF- and TD-based method is therefore hampered if propagation took place in sacrificed channels for the cross-check patients (see figure 6.5). Additionally, incomplete ECoG coverage of the cortex limits interpretation of results of TF and TD based methods in general.

All patients in the TD analysis showed propagation of both the seizure and the ER responses, not only local but also remote from the SOZ, several sulci and gyri away. We observed that seizures often showed substantial secondary propagation around the site they were initially propagated to. For ERs this was less often the case (see figure 6.4 and 5D; in the supplementary material a video of an example where secondary ERs do occur is

provided). As a result, sensitivity values of ERs for SP-electrodes are relatively low. Probably seizure activity produces more massive secondary activation of connecting fibers than SPES stimulation does. It could be worthwhile exploring local responses to additional SPES stimulation in the electrode where earliest ERs appear when stimulated in the SOZ.

Another limitation is that SPES recordings were not performed in a drug-free state for most patients, although AEDs were tapered during the ECoG monitoring session. Since AEDs may contain the spread of ERs across the cortical mantle, medication may have lowered the sensitivity of both the time-domain and the time-frequency domain method.

Both TD and TF approaches rely pre-dominantly on computational signal processing. These methods are, however, not fully automated as they still involve identification by a trained observer as a last step.

Relation with findings in literature

SPES relates to the CCEP stimulation protocol. In Enatsu et al. (2012) CCEPs were used to investigate the relation between evoked cortical responses and seizure propagation. Their CCEP protocol uses more stimuli (50–70) at a higher repetition rate (1 Hz) with pulses of shorter duration (0.3 ms), but an amplitude comparable to SPES (1–15 mA)²⁵³. Effectively, the injected charge would be equal to using 0.3–4.5 mA in SPES. Although this is lower (~50%), the signal-to-noise ratio for CCEPs is probably higher than for SPES, given the substantially higher amount of averages. Enatsu et al. (2012) found no robust relation between seizure propagation and evoked responses. As in most CCEP studies, focus lied on amplitude and latency rather than occurrence and count of evoked responses. They found no significant difference between amplitude in electrodes with CCEPs and seizure propagation, compared to electrodes where only CCEPs without seizure propagation were observed²⁵³. Their conclusion that ictal propagation is not necessarily associated with functional connectivity is in contrast to our finding of a high specificity. An explanation could be that the lower SNR of SPES responses results in fewer detections, so fewer false positives with respect to seizure propagation compared to CCEP. On the other hand, the more powerful SPES stimulus current could ensure that a SPES response is more likely a true than a false positive with respect to seizure propagation, compared to CCEP.

On the matter of identification of the SOZ the CCEP literature shows a clear relation between enhanced CCEP response amplitudes when stimulation is inside the SOZ (called iCCEPs) compared to those when stimulating outside the SOZ (called nCCEPs)^{25, 253, 254}. There have been no reports on the association of the location of CCEP responses with the SOZ, independent of stimulation side. CCEP studies are characterized by a directional, functional connectivity analysis, whereas our SPES-study is characterized by a cumulative response analysis, rather the sum of all iCCEPs and nCCEPs. The CCEP directionality approach could

be of interest in future SPES studies on delayed responses. Valentín et al. (2002, 2005), e.g., showed that a focus in the temporal lobe is represented by tissue showing evoked delayed responses to a stimulus elsewhere, while in the frontal lobe stimulating the focus results in evoked delayed responses elsewhere^{22, 23, 247}.

Recently, Boido et al. (2014) looked specifically at directionality, using a different CCEP protocol (30 pulses at 1 Hz, 2 ms, 4 mA; delivered in depth electrodes (SEEG) with 1.5 mm separation)²⁷⁰. Note that here current density values exceed those of the CCEP studies mentioned earlier, and also of SPES. They defined electrodes as primarily receivers, activators or bidirectional contacts. Their receivers resemble roughly the ER₅₀ electrodes in our study. They did not find, however, an association between primary receiver electrodes and SOZ. Their activators did not show an association with SOZ, nor seizure propagation. However, bidirectional connectivity was a prevalent feature for contacts included in the epileptogenic focus²⁷⁰. The large differences in stimulus parameters and detection thresholds hamper interpretations of the mismatch between their and our results. Therefore, studies that combine CCEP and SPES protocols and analysis methods will be important to better understand the underlying physiological mechanisms of the responses each protocol evokes. Evaluating both CCEP and SPES early and delayed responses, including directionality, in the same epilepsy patient could increase the clinical yield of intracranial electrical stimulation.

Conclusions

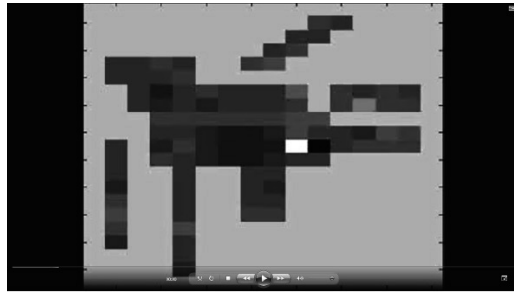
To conclude, we found that analysis of ERs evoked by SPES reveals information about the pathology, manifested by the localization of the SOZ in areas of high ER counts and by the ability of ERs to predict seizure propagation. ERs information could be added to that of DRs to improve pre-operative mapping of epileptogenic cortex and the epileptic network. Larger studies, including prospective studies, are needed to establish the full clinical potential of SPES.

Supplementary material

Supplementary table 6.1. Results cross-check time-domain (TD) and time-frequency (TF)-analysis

#Pt	TF/TD	Propagation					SOZ (ER ₅₀)								
		# elec	Thresh (μV)	Mean latency (ms)	Meanampl (uV)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	p- value*	Sens (%)	Spec (%)	PPV (%)	NPV (%)	p- value**
1	TD	102	120	46	301	42	86	40	87	0.011	47	54	54	47	1.000
	TF	61	—	—	—	38	50	46	41	0.435	100	56	14	100	0.046
2	TD	91	120	64	378	40	77	52	67	0.103	43	66	43	66	0.509
	TF	62	—	—	—	24	52	25	41	0.263	83	18	10	91	1.000

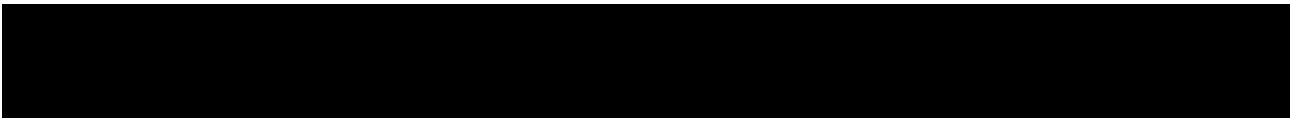
Pt=patient, TD=Time-Domain analysis, TF=Time-Frequency analysis, # elec= number of electrodes included in the analysis, Thresh=amplitude threshold used (see methods section 2.6.2, step 2), Mean latency= mean time of occurrence after stimulus, Mean ampl= mean amplitude of ER response (baseline to peak), Sens=sensitivity, Spec= specificity, PPV=positive predictive value, NPV=negative predictive value, S-band= spike band (<80Hz), R-band=ripple band (80-250 Hz) * Tested for association ER response- electrodes with SP-electrodes, using Fisher Exact test (two-tailed), with p <0.05 considered significant. ** Tested for association ER₅₀ with SOZ, using Fisher exact test (two tailed), with p<0.05 considered significant. Note: Results are only reported for the S-band because of the limited sampling rate of the TD data.



Supplementary video 6.1. Video showing single pulse early responses in pt 12. ECoG Grid coverage is left temporal frontal, with additional strips covering parts of the frontal, central and parietal regions. Time range is from 100 ms before to 500 ms after stimulation. Stimulus is at $t=0$ when black flash appears in the video. Stimulus electrodes are near Wernicke's area, indicated by the neighboring black (+) and white (-) squares. Response amplitude is coded from white ($-300 \mu\text{V}$) to black ($+300 \mu\text{V}$). Note early local propagation near the stimulating electrodes, followed by propagation to Broca's area, in the middle of the display. There, responses show additional local spread propagation.

CHAPTER 7

Summary



Success of epilepsy surgery depends on adequate identification of the epileptogenic zone. The presurgical workup involves the use of numerous diagnostic methods such as MRI, EEG, PET, SPECT, MSI, ESI and invasive procedures such as stereo depth EEG or intracranial GRID EEG. All methods try to localize the EZ but no single one provides a full reflection of the EZ. The aim of this thesis was to improve our knowledge of presurgical diagnostic approaches in epilepsy surgery by evaluating the use and accuracy of current and novel diagnostic methods for focus localization. This work has been performed for a large part in the context of the European-Union funded E-PILEPSY network (now continuing within the European Reference Network for rare and complex epilepsies [EpiCARE]), which aimed to optimize and harmonize epilepsy surgery practice across Europe with the ultimate goal to increase the number and proportion of children and adults cured of their refractory epilepsy.

Practice variation between European epilepsy surgery centers

A first step was to determine the clinical practice of the presurgical epilepsy workup across European epilepsy surgery centers that were part of the E-PILEPSY consortium. In **chapter 2** we surveyed the used diagnostic imaging, post-processing, and electric and magnetic source localization techniques throughout the consortium and found a large variation between the centers. Only 15 out of 24 centers (63%) standardly performed 3 T MRI and three performed 3T MRI only on indication. All other centers used 1.5 T MRI. There was large variety in the used MRI sequences: a total of 26 different sequences was reported. Less disparity was seen on the use of PET and SPECT. Almost all centers (22/24; 92%) performed interictal PET. Use of the 18F-fluorodeoxyglucose (FDG) marker by all reflected the general belief that this marker is the ideal radiopharmaceutical to study focal epilepsy. Ictal SPECT is used by fewer centers (19/24; 79%) - compared to PET- which may result from higher resource cost and the necessity to capture a seizure during a limited time-slot. Half of the centers performed either ESI (n=9) or MSI (n=7). Between these centers a large variety of used inverse methods and volume conduction models was observed. We found that MRI, PET and SPECT post-processing methods are applied by the majority of centers.

Few centers conducted their presurgical diagnostic pathway entirely in accordance with the at that time available international guidelines or recommendations. Twenty-five percent of the centers followed all guideline-recommended MRI sequences with the proposed slice orientation and slice thickness or voxel size. Eighteen percent of the centers performing epilepsy surgery in children did not meet the recommendation to have either PET or SPECT available for workup. Ictal SPECT was not compared with interictal SPECT in 37% of the centers, despite the fact that its usefulness is advised ^{27, 28}.

Evidence-base for diagnostic modalities

The disparity between epilepsy surgery centers and their poor adherence to the limited number of available guidelines – afflicted by low levels of expert consensus – facilitated the need for more evidence-base regarding the diagnostic methods that should be part of the workup and how these should be implemented. An objective of the E-PILEPSY project was to perform several systematic reviews and meta-analyses on various diagnostic tests applied in the pre-surgical work-up for epilepsy surgery. Our objective was to review the evidence-base for epileptogenic lesion localization with MRI and for epileptic source localization with electric and magnetic source imaging.

In **chapter 3** we performed a systematic review and meta-analysis on MRI that was focused on the influence of higher field strength, and on MRI sequence selection. The review included a total of 18 studies for field strength and 25 for sequences. An important finding was that no study was free from bias. Second, higher field strength may improve lesion detection. Not taking aspects of bias into consideration, we calculated that the added lesion detection rate of 3 T and 7 T in patients with normal lower field MRI (i.e. MRI negative patients) is 18% and 22%, respectively. Another finding was that not all patient groups benefited equally from higher field strength MRI. In patients with hippocampal sclerosis (HS) 1.5 T MRI seemed sufficient: scanning at field strengths higher than 1.5T did not contribute to higher lesion detection rate. Standard MRI sequences (3DT1, T2, FLAIR) had a good detection rate of around 90% in HS. Also, epilepsy-specific MRI protocols at 1.5-3 T had a pooled lesion detection rate of 83% in patients with TLE, and 51% in those with FCD. Dedicated MRI protocols and evaluation by an experienced epilepsy neuroradiologist appeared important for lesion detection. The value of additional techniques, such as quantitative DWI and DTI, may be disputed. These methods have some lateralizing or localizing value, but also often fail to identify lesions found on conventional MRI or have false positive or irrelevant findings.

The results from the systematic review and meta-analysis on HR-ESI and MSI for epileptic source localization are presented in **chapter 4**. We included eight MSI studies and three HR-ESI studies of which all had risk of bias. This mostly involved selection of operated patients only, interference of source imaging with surgical decision, and exclusion of indeterminate results. Despite bias, bivariate meta-analysis estimated a summary sensitivity and specificity of 82% (95% CI: 75–88%) and 53% (37–68%) for overall source imaging. MSI or HR-ESI were not superior to the other: there was no statistical difference regarding sensitivity and specificity. Importantly, surgical outcome data for patients with indeterminate source imaging results were underreported, and the reporting of partially concordant results was inconsistent, both influencing accuracy. We demonstrated that specificity was higher when partially concordant results were classified as discordant

($p < 0.05$). Inclusion of indeterminate test results into the discordant category lowered sensitivity ($p < 0.05$).

The results from the meta-analyses presented in **chapter 3 and 4** were affected by poor study quality and were likely biased towards overestimation of diagnostic accuracy. These studies highlight the need for high quality studies, that allow unbiased and transparent evaluation of diagnostic tests so they could further serve the constitution of clinical guidelines.

Novel approaches for EZ localization in presurgical workup

Novel approaches to estimate the EZ may aid presurgical workup in other ways than described previously. In **chapter 5** we explored the localizing value of semiology, long-term monitoring video electroencephalography (LTM-VEEG) and interictal high resolution electric source imaging (HR-ESI) in the presurgical workup, specifically for patients with tuberous sclerosis complex (TSC). TSC patients are different from patients with other etiologies as they are characterized by multiple potentially epileptogenic tuber lesions that are scattered throughout the brain. Removal of a single or of a few tubers may result in seizure freedom, thus presurgical workup aims to identify the single or few epileptogenic lesion(s) among many. In a retrospectively collected cohort of 24 consecutive TSC surgical candidates who underwent both HR-ESI and LTM-VEEG we demonstrated that semiology is of limited value in TSC patients. Patient-history-based and video-based semiology was often non-localizing, and even when it was localizing it did so poorly. HR-ESI was more often localizing than interictal EEG or ictal EEG (79% versus 54% and 63%), due to a smaller number of non-localizing and multifocal test results. Also, HR-ESI was more often lobar concordant with the proven EZ in seizure-free patients compared to ictal EEG (67% versus 33%). Contrarily, ictal EEG was more often partially concordant than HR-ESI (44% versus 11%). Not only localization accuracy was considered important. The impact of a diagnostic test on clinical management is also of value. We observed that when HR-ESI results were discussed in the second multidisciplinary meeting, it had a strong impact on epilepsy surgery workup by modifying or confirming the hypothesized EZ in 52% and 38% of patients respectively. When determining the validity of such modifications by taking surgical outcome into consideration we showed that HR-ESI positively impacts clinical management in 7/14 patients (50%). In three this contribution was critically valuable, suggesting that without HR-ESI these patients would not have been operated and become seizure free. In the remainder of patients, HR-ESI's contribution was indeterminate or had a negative contribution, and in not a single case HR-ESI's contribution was critically misleading. Presurgical workup of TSC patients might benefit from less emphasis on semiology and more on HR-ESI results. Employing HR-ESI in the initial presurgical workup might complement or replace LTM-VEEG localization results. Future prospective studies –

with consideration of the impact on clinical management – may further contribute to the evidence-base for this method.

Being the most invasive diagnostic method used in epilepsy surgery, intracranial EEG monitoring is considered the final modality to be used in case of diagnostic uncertainty about the EZ location. Single pulse electrical stimulation (SPES) by means of intracranial GRID-EEG offers an additional or alternative method for EZ localization in that it actively probes the covered brain with brief (1 ms duration) electrical pulses to evoke responses across different frequency bands. **In chapter 6** we explored the use of this method for the on-demand identification of epileptogenic cortex. We found that early responses (ERs) mirror seizure onset zone connectivity and seizure propagation pathways. Electrodes with ERs were stronger associated with SOZ than with non-SOZ electrodes; at group level and at individual level in four out of six patients the SOZ was more likely to be located in areas showing high counts of ERs. Electrodes with high ER counts in the so-called ripple band (80–250 Hz) had an even higher specificity for SOZ channels than in the lower frequency spike band (<80 Hz). ERs evoked by stimulation in seizure onset electrodes are more likely to occur in electrodes that show seizure propagation. Thus, ERs can reveal aspects of pathology, even if the underlying stimulus–response relation is purely physiological and have clinical value for mapping epileptogenic cortex. Larger and prospective studies are needed to establish the full clinical potential of SPES.

CHAPTER 8

General discussion and future perspectives

General discussion

The aim of this thesis was to improve our knowledge of presurgical diagnostic approaches in epilepsy surgery by evaluating current and novel diagnostic methods for focus localization on aspects of use and accuracy, with the overall goal to increase the chance of post-surgical seizure freedom. The studies described in this thesis demonstrate practice variation between epilepsy surgery centers in the use of imaging and electric and magnetic source localization procedures and a poor adherence to the – limited number of – available guidelines. Furthermore, we have shown that these procedures have limited evidence-base due to factors of bias and lack of transparency. The studies investigating novel approaches demonstrated how high resolution electric source imaging, an advanced and under-utilized diagnostic method, may help in the presurgical workup and how single pulse electric stimulation may on-demand delineate epileptogenic brain areas.

Consensus on presurgical workup

How do we explain the large disparity between European epilepsy surgery centers as described in **chapter 2**? First, we may consider how recommendations and guidelines on diagnostic epilepsy surgery care were formed over the past decennia. The first guidelines were set up by ILAE working groups and started with recommendations primarily based on the expert consensus of the working group^{26, 27, 55}. Years later, guideline groups also performed an updated narrative review of the literature^{7, 9} and evidence assessment²⁷¹, and included previous opinion reports or earlier guidelines to support their recommendations⁵⁸. These guidelines may be, however, criticized for the limited level of transparency regarding their literature review and value assessment. Moreover, there may be concerns for bias towards working group member preferences. Regardless, these endeavors were unanimous on the fact that there was a lack of high-quality studies.

To tackle the bias towards working group member preferences, groups with a more diverse member selection were formed^{7, 51}. This revealed that establishing consensus among practitioners in a broad-based global expert panel is difficult^{7, 271}. Unanimous agreement was achieved only for three diagnostic modalities: MRI and interictal EEG, being considered mandatory across all epilepsy etiology and patient groups, and LTM-VEEG being strongly recommended in general and considered mandatory in selected patients^{7, 271}. This was the basis for an ILAE-endorsed protocol advising that initial presurgical evaluation requires interictal EEG, HR epilepsy protocol MRI and LTM-VEEG. Ancillary tests remain reserved for specific indications and patient groups at the discretion of the treating physician or – preferably – multidisciplinary team⁷.

The lack of agreement on the use of methods other than MRI, interictal EEG and LTM-VEEG was reflected by our survey results (**chapter 2**). Twenty-one percent of centers did not use

SPECT, 18% of pediatric centers performed neither PET nor SPECT, and half of centers did not perform interictal ESI or MSI. A world-wide survey, conducted years later, confirmed this between-center variation²⁷².

More advanced methods were needed to establish a harmonized approach between epilepsy surgery centers. In another effort to achieve broad consensus-based guidelines, Gaillard and coworkers tried a more sophisticated process²⁷³. More than 60 international pediatric epilepsy centers participated in a modified Delphi process: a method of repeated surveying of experts in several rounds and providing feedback response and answer adjustment based on the group response. Recommendations for each level of pediatric epilepsy surgery care were formulated based on patient complexity (e.g age, etiology) and center competencies (i.e. technology, personnel). Recommendations were then specified according to the center's expertise level: basic epilepsy surgery centers (level 1) and advanced centers (level 2)²⁷³. Level 1 centers may care for children of 9 year or older, with a single defined lesion, utilizing video-EEG and 1.5 T MRI. Level 2 centers care for children of all ages utilizing a collection of advanced diagnostic modalities (i.e. 3T MRI, fMRI, PET, or SPECT), having invasive EEG monitoring capacity, conducting surgery in MRI negatives and at locations near or in eloquent cortex or in deep lesions²⁷³. These recommendations, however, did not address the use of each individual test modality during the presurgical evaluation trajectory.

Regarding the European E-PILEPSY consortium, we should acknowledge that this group included centers from both low-income and high-income countries. Among the group, several centers may be viewed as level 1 basic epilepsy surgery centers. Re-analysis of our survey results (**chapter 2**) with consideration of the centers' expertise level and the unequal availability of resources, will most likely result in more adherence to guidelines.

Recommendations resulting from consensus-based methods may always be subject to debate. Even the Delphi process by Gaillard et al. was not without limitations – as the authors pointed out themselves. Their survey was conducted mainly by experienced epilepsy center directors, or senior members of established epilepsy programs, who may carry a bias for particular technologies, etiologies, or procedures²⁷³. This was clearly demonstrated for MSI and ESI. Gaillard et al. concluded: “any newer technologies such as MEG are deemed to be not essential or standard of care”²⁷³. However, a position statement by the American Clinical MEG society (ACMEG) claimed that MSI has “sufficient evidence-base and should be part of routine clinical use”^{116, 274}. The International Federation of Clinical Neurophysiology (IFCN) guideline argued that there is good evidence for the accuracy of ESI in presurgical evaluation of both temporal and extra temporal foci²⁷⁵. Austrian, German and Swiss ILAE working groups considered MEG and 64-256 channel EEG with source imaging to be part of the minimum equipment in epilepsy surgery centers²⁷⁶. The

discussion on the importance of its use was also reflected in a survey among USA epilepsy centers. They found that only 27% of centers had MEG available, similar to the proportion (29%) found by our European survey as demonstrated in **chapter 2**²⁷⁷. Years later, a repeated survey concluded that MEG still had not become part of the standard care in spite of published clinical practice guidelines²⁷⁴. All the above-mentioned impediments clearly point how recommendation and guideline formulation is frustrated and hinder harmonization of diagnostic epilepsy surgery care amongst centers.

Consensus on technical specifics of tests

Beyond selecting the appropriate diagnostic methods and tests, choices are to be made on their technical aspects. In the case of MRI, diagnostic accuracy and yield depend on field strength, type of head coil, selected sequences, resolution and expertise of the reader. 3T MRI appears to have been accepted as standard practice⁷ but 1.5 T is also acceptable for level 1 centers²⁷³. On the aspect of protocol and sequence selection, guidelines and recommendations show some variation, but they all include an anatomic three-dimensional (3D) T1-weighted gradient-recalled-echo, axial and coronal T2-weighted sequences, and axial and coronal fluid-attenuated inversion recovery (FLAIR). For 3D T1, voxel size should not exceed 1 mm. For T2 and FLAIR, slice thickness should not exceed 3 mm^{7-11, 26}. In **chapter 2** we showed that that only 25% of European epilepsy centers adhere to all of these recommendations. In **chapter 3** we demonstrated a wide between-study heterogeneity regarding MRI parameters and types of sequences. Both of these findings constitute and reflect the lack of multilateral agreement on the best MRI protocol for epilepsy. In an effort to further reduce clinical variability in MRI practice, the neuroimaging task force of the ILAE published a – more stringent – “Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNESS-MRI)” protocol that consists of isotropic millimetric 3D T1 and 3D FLAIR images, and high-resolution coronal (perpendicular to hippocampal long axis) 2D submillimetric T2 images with no interslice gap⁵⁸. As the HARNESS protocol can be obtained at 1.5 T, it may serve as a standard across all – high and low-level – epilepsy surgery centers. In case of a MRI negative result, diagnostic optimization can be stepped-wise achieved firstly by re-reviewing the data by a more experienced epilepsy neuroradiologist, secondly by increasing field strength, and thirdly by means of post-processing procedures. Whether epilepsy surgery centers adhere to the HARNESS protocol needs to be studied in the future.

Regarding interictal PET, published guidelines adhere to FDG ligands because at the time of guideline formulation there was limited experience and data from alternative ligands, such as α -methyl tryptophan (AMT)^{7, 26}. Systematic reviews and meta-analyses on PET are infrequent, and until recently only focused on the FDG ligand^{278, 279}. This was also reflected by our survey results: all centers used the FDG ligand.

For ictal SPECT, the guidelines report only hexamethylpropylene amine oxime (HMPAO) and ethylcysteinate dimer (ECD) as ligands of choice⁷. Subtraction of ictal and interictal SPECT co-registered with MRI (SISCOM) is being favored over standard ictal SPECT; systematic reviews and meta-analyses on presurgical epilepsy evaluation have only focused on SISCOM^{272, 280}. Our survey showed however that ictal SPECT is still not compared with interictal SPECT in 37% of the centers.

Technical specifics on MSI are published by the American Clinical MEG Society (ACMEGS) and are reasonably straightforward¹¹⁷. The equivalent current dipole (ECD) is advocated as most appropriate inverse solution and is used by 93% of US centers and by 71% of European MEG centers²⁷⁴ (**Chapter 2**). Contrarily, ESI allows much more freedom on the selection of technical specifics and some publications provide technical guidance^{32, 34, 35}. Official IFCN EEG guidelines refrain from specific recommendations on technical criteria for ESI²⁷⁵. More recent studies did not show significant difference in accuracy between various inverse solutions^{238, 281}. This may explain the large number of different combinations of inverse methods and forward models – particularly in ESI – used by the European centers (**Chapter 2**).

It may be concluded that reaching consensus among practitioners on the use of diagnostic tests in the presurgical epilepsy workup appears to be problematic. There are large inherent differences between epileptogenic etiologies and age groups, concerning the use, accuracy and added value of diagnostic techniques and of candidate selection. Guideline working groups are faced with limited available evidence that is often regarded as low-quality. This permits practitioners to develop personal opinions that are largely based on their personal experience acquired at their institution. Therefore, expert opinions vary between regions, organizations and advocacy groups. Moreover, unequal availability of resources with regard to logistics, technology, local expertise, and reimbursement further force centers to shape the presurgical workup on its own merits. Consequently, presurgical diagnostic workup between centers is variable with respect to the selected diagnostic tests and to their technical settings as we have demonstrated in **chapter 2**. This diversity brings into question to what extent centers vary with respect to surgery success rate and stresses out the need for further systematic evidence-based evaluation of diagnostic tests.

Diagnostic value of presurgical diagnostic tests

Diagnostic accuracy studies

Diagnostic accuracy studies in presurgical epilepsy workup are designed to discriminate between epileptogenic and non-epileptogenic brain areas and are generally considered to be important in evidence-based care. In **chapter 3 and 4** we demonstrated that diagnostic accuracy studies on MRI and source imaging show large heterogeneity between studies on aspects of population selection and test method. Lack of transparency was also seen, especially for studies on MRI (**chapter 3**): thirteen studies did not report sufficient details on the used field strength, protocol or coils. Appraisal of study quality focused on aspects of risk of bias and the relevance of study results for clinical practice. We demonstrated that no single study was free from bias due to several methodological issues.

A first issue arises when diagnostic test results need expression in terms of a reference standard. Many studies have used a variety of reference standards such as the presence of a structural lesion on MRI, histopathological findings of resected tissue, ictal onset or irritative zone as determined by scalp and intracranial EEG, or – being least objective – the multidisciplinary team consensus on the presumed EZ. Studies show that the odds of seizure freedom after surgery are two to three times higher in the presence of a lesion on histopathology or MRI¹⁵. However, not all structural abnormalities cause seizures and not all epileptogenic lesions are MRI-visible. Lesion resection does not consistently lead to seizure-freedom, and, conversely, some patients with incomplete lesion resection can still become seizure-free^{106, 107}. Peri-lesional areas can be marked as epileptogenic and good surgical outcome might not always necessitate complete removal of the SOZ^{147, 188}. Therefore, all these standards represent a proxy for the true EZ and are by definition not completely precise⁶. Therefore, the resected area in good postsurgical outcome patients is being increasingly considered the most appropriate gold standard.

Still, with the selection of the resected area in seizure-free patients as the preferred reference standard, a second issue emerges: an unavoidable patient selection bias. Patient inclusion is restricted to eligible epilepsy surgery candidates who underwent surgery. This disregards the non-eligible surgical candidates of whom presurgical workup concluded uncertain focus localization or high risk of (post-)surgical complications. Diagnostic estimates may therefore be overoptimistic in relation to the overall (i.e. non-eligible and eligible) surgical candidate population.

When considering sensitivity of a test we refer to a ‘true positive’ as a case in which there is concordance between diagnostic test localization and resected area in a patient with good post-surgical outcome. A third problem arises with the definition of concordance. Concordance may refer to either sublobar or lobar co-localization of diagnostic test localization and resected area. Sublobar and lobar regions differ widely in size within and

between patients. Lobar concordance is inherently easier reached in larger lobes such as the frontal lobe. Concordance may also be defined as localization of the test result in – at least part of – the resection volume, or it can be expressed as the Euclidian distance between resected area and diagnostic test localization. Larger resections are more likely to achieve seizure freedom and are more likely to be concordant with, or in proximity of, diagnostic test localization. This increases the probability of a true positive result. Moreover, the utility of the resected area in good surgical outcome patients as reference standard is based on the assumption that surgery is always without complications. A true positive result might be improperly regarded as false positive when seizure recurrence is caused by (peri)-surgical complications such as gliosis, infection, bleeding, by newly evolved remote epileptogenic tissue.^{148, 156}

Specificity as a measure may also be criticized: a test localization outside the resection volume in the case of surgical failure cannot be automatically defined as ‘true negative’ as the non-resected areas encompass both epileptogenic and non-epileptogenic regions¹⁷⁷. Moreover, surgical failure does not rule out epileptogenicity of resected tissue because it may have involved a partial resection of epileptogenic tissue or a more widespread epileptogenic network may be present. Also, the post-surgical Engel classification is subjective by nature and both the Engel and ILAE classification do not consider post-surgical use of anti-seizure medication.

Another issue is the handling of partially concordant, multifocal, and indeterminate or non-relevant test results. In **chapter 3** we found a heterogeneity between studies on whether an MRI lesion was considered relevant. In **chapter 4** we noted a large underreporting of surgical outcome data for patients with indeterminate source imaging results and showed between-study heterogeneity on the reporting and handling of partially concordant results. Both indeterminate and partially concordant results significantly affected the calculated sensitivity and specificity. Resection of a single source in case of a multifocal test result is classified as concordant by one study whilst considered non-concordant by the other.

In general, diagnostic accuracy studies are susceptible to so-called verification bias. Verification bias occurs when only a proportion of the study participants receive confirmation of the diagnosis by the reference standard test, or when some participants receive a different reference standard test, as it may be unethical, unpractical or expensive to obtain a (uniform) reference test in every patient. In epilepsy surgery workup it is inevitable that index test results influence clinical decisions: some patients do not receive the reference standard because they are excluded from surgery (partial verification bias); in others a different combination of tests during their presurgical workup is performed which alters the reference standard, i.e. the area and extent of resection (differential

verification bias)⁵⁰. When an index test enjoys wide acceptance from a clinical team and it is included in the presurgical workup, concordance between index test localization and resected area is also more likely. This may increase sensitivity and lower specificity of a test.

The use of diagnostic test results in epilepsy surgery workup is non-typical. Rather than taking the diagnostic test result as a definitive localization, collective re-review of individual tests in light of all other clinical and prior diagnostic information during multidisciplinary meetings is part of standard practice. Whether a diagnostic test is used early or late in the presurgical workflow may therefore affect its diagnostic potential. Tests performed in a late stage of the presurgical workup are aided by additional supporting information from previous tests. For example, in MRI negative patients re-review of the MRI after availability of other localization data is recommended⁷. However, if attention is only focused on a suspected location and no thorough investigation of other brain areas at similar thresholds for test positivity is performed, sensitivity may be elevated at the cost of specificity⁷. MRI negative patients may also be submitted for high-field MRI. However, because high field-MRI is applied later in the diagnostic process, it has the advantage of having more additional information from other tests. This risk of information bias may result in an overestimation of diagnostic accuracy for high field MRI.

The role of systematic reviews and meta-analyses

Systematic reviews and meta-analyses rank highest in the evidence hierarchy pyramid and are considered of essential importance in the establishment of clinical practice guidelines²⁸². They aim to pool the evidence from available studies and assess study quality with the ultimate goal to answer the research question of interest. There have been several systematic reviews on presurgical diagnostic epilepsy workup undertaken by the epilepsy community. They all describe to a certain degree the above mentioned limitations of patient selection bias, small study sizes and between-study heterogeneity with respect to test technology and included populations^{44, 50, 121, 283, 284}.

Unfortunately, results and conclusions from systematic reviews and meta-analyses are not indisputable per se as they have their own methodological approach. Some provide no information on how they handled inconclusive or indeterminate diagnostic results^{121, 283, 284}. Others do not dichotomize data, neglecting the fact that similar test results could lead to very different management strategies across different patient groups⁵⁰. Used reference standards may vary and not all reports provide technical details on aspects such as type of MRI sequence^{44, 50}.

Is the impact on clinical management an appropriate alternative measure?

Diagnostic accuracy studies are based on the assumption that diagnostic test localizations match the epileptogenic tissue location. This may be true in theory but may not represent clinical practice. Each diagnostic modality is hampered by technical limitations that may – when being familiar with these limitations – justify a more liberal interpretation of diagnostic test results. For example, in case of a hippocampal pathology electric or magnetic source imaging may record only antero-temporal propagated hippocampal spikes – caused by limited cortical propagation and low SNR – that positions the source solution outside the hippocampus^{45, 158-160}. Also, cases of partial concordance between source estimate and resected area do not have the same significance as cases of complete or non-concordance¹⁵⁷. In the context of other imaging modalities, partially concordant results may be clinically valuable.

Further, methods with a more sensitive detection threshold may also reveal irrelevant abnormalities, which was demonstrated for quantitative DWI and DTI (**chapter 3**). Although 3 T MRI did not reveal new lesions compared to 1.5 T in patients with HS (**chapter 3**), higher field strength may facilitate the detection of dual pathology (e.g. neighboring MCDs) or delineate internal structure of the hippocampus and thereby adding potentially relevant information¹⁰².

Thus, rather than focusing on diagnostic accuracy alone, the effect of diagnostic methods on clinical decision-making and patient outcomes should also be of consideration. Such a clinical-decision analysis was done by Uijl and coworkers²⁸⁵. They concluded that FDG-PET, as a single test, can form the basis for deciding whether a patient with TLE is eligible for surgery or not, especially in the case of non-localizing MRI or LTM-VEEG²⁸⁵. An important element that was not addressed in that study was the effect of decisions on post-surgical outcome. In **chapter 5** we performed a comparable, albeit smaller, retrospectively analysis and determined the degree to which HR-ESI test results changed the presumed EZ as formulated during the multidisciplinary team meeting. We found that in most cases a change of clinical management induced by HR-ESI resulted in good post-surgical outcome.

It is important to note that the added value of a single test is also subject to its position in the context of the overall diagnostic workup. Part of the diagnostic information from an index test could be already incorporated in results from previous tests²⁸⁶. This has been shown by a study on surgical candidates with TLE. A reduced test battery – encompassing MRI and long-term EEG – evenly contributed to the decision to perform surgery as a test battery that additionally incorporated patient history and routine EEG findings²⁸⁷.

Improving presurgical workup: two specific novel examples

High resolution electric source imaging in patients with Tuberous sclerosis

In epilepsy diagnosis, attention has been mostly devoted to acquire ictal localizing information. In **chapter 5** we demonstrated that ictal information is of small relevance in TSC patients; semiology has poor localizing accuracy for the EZ and interictal EEG and HR-ESI are more accurate than ictal EEG. These findings highlight known general pitfalls regarding the localizing value of ictal data. Not all brain regions produce recognizable symptoms and first symptoms may represent an area of seizure spread rather than onset²⁸⁸. In the pediatric population, assessment of semiology is difficult as young children are often unable to explain their symptoms. Ictal EEG recording and evaluation may also be hampered by muscle artefacts during seizures.

In most TSC patients, dominant and consistent interictal epileptogenic foci are found. These foci are demonstrated to be concordant with ictal onset in the majority of patients^{224, 235}. Thus, a dominant interictal EEG focus could act as surrogate for the region of ictal onset. This may promote the use of interictal EEG only, at least when TSC patients are concerned.

Our findings in **chapter 4** suggested a good localizing value of interictal HR-ESI in general epilepsy surgery patients (high sensitivity of 87%, moderate specificity of 61%), although the findings should be interpreted in light of several factors of bias. A more recent meta-analysis by Sharma and coworkers reported a comparable sensitivity and specificity of 81 % and 45% respectively²⁸³. Sensitivity and specificity calculations were not performed in **chapter 5** due to the small sample size, but we observed a lobar concordance between interictal HR-ESI and resected area in 67% of good-outcome TSC patients. This was also found by another study on source imaging in surgical TSC patients²³³. This study and ours also showed a clinical management plan or EZ change due to the results of ESI in 34-52% of patients. With HR-ESI showing more often localizing results, which are also more accurate compared to LTM-VEEG, surgical workup of TSC patients may be improved by performing HR-ESI in the initial presurgical workup. It may allow early identification of patients benefiting from surgery with use of less diagnostic tests. Future studies should prospectively study two diagnostic arms, being a combination of MRI and interictal HR-ESI alone in the experimental arm, and current diagnostic evaluation in the reference arm, with an outcome measure focus on the number of patients undergoing surgery, outcome after surgery and number of diagnostic tests required.

Single pulse electrical stimulation

Rather than waiting for seizures during invasive monitoring, probing of cortex with electrical stimuli may reveal epileptogenic networks. The first SPES studies focused on delayed evoked responses occurring about 100-1000 ms after stimulation that proved to be pathological^{22, 23, 247}. Delayed responses also contain HFO's that are known to be

biomarkers for the SOZ²¹. Although SPES induced HFO's are similar to spontaneous HFO's seen during invasive monitoring, it is not able to distinguish pathological from physiological activity²⁸⁹. Thus, there is a need for a further refinement of pathological information derived from SPES. Early responses – occurring more frequently – may contribute to an increase of sensitivity of evoked responses, including high frequency activity.

In **chapter 6** we showed that SPES evokes early responses (ER's) that are associated with areas of seizure onset and propagation. This suggests that the SOZ is embedded in more densely or strongly connected networks. Similar studies, i.e. cortico-cortical evoked potential (CCEP) studies, investigated the role of the N1 potential which is the equivalent of an ER. It was demonstrated that stimulation of the ictal onset zone results in larger N1 amplitudes than when normal cortex is stimulated²⁵. In addition, N1 amplitudes turned out to be significantly larger in ictal propagation areas than outside those areas^{253, 254}. Also, within propagation areas, early seizure spread regions showed significantly greater evoked CCEP responses after stimulation than late-spread regions. Moreover, early-spread regions showed evoked gamma band activity that was coherent with the SOZ²⁹⁰. Our results from **chapter 6** are also supported by other studies demonstrating that a high frequency power increase in the ripple and fast ripple band during early responses is significantly more pronounced in SOZ channels compared to non-SOZ channels,^{291, 292}. Post ER power decrease has also been described both as physiological phenomenon^{108, 173, 291} and as biomarker for the SOZ²⁹³. The complex of ER activity and subsequent suppression is suggested to most likely reflect cortical excitation of epileptic tissue and inhibitory activity from interneurons surrounding the SOZ²⁹³.

These findings on effective connectivity directed analysis to the field of network measures. A SPES-network study found a significantly higher amount of in-degree connections – similar to our ERs – in epileptogenic tissue (i.e. SOZ, resected area) of patients with good-surgical outcome²⁹⁴. Additionally, they showed a high out-degree, a higher percentage of bidirectional connections, and a lower percentage of receiving connections. This suggests that directionality of connectivity plays an important role in epileptic networks. SPES-derived networks also seem superior to traditional network methods; they are better able to disclose physiological connections compared to networks derived from non-evoked ECoG data²⁹⁵.

Combined analyses of SPES-induced early and delayed responses of both low and high-frequency activity and suppression may improve epileptogenic zone localization. Unfortunately no standardized stimulation protocols exist²⁹⁶. A recent study showed that CCEP responses are variable and depend on anatomical location, stimulation amplitude, and stimulation-response distance²⁹². Consideration of these differences is important

to optimize stimulation parameters and to increase method reproducibility. SPES may further form a basis for research on network studies to allow the identification of patient-specific networks characteristics. SPES may contribute to a shift in the concept of focal epilepsy from a localized region of abnormality into one of diseased cortical networks with nodes and connections with affected regions away from the SOZ.

Future perspective

In this thesis we showed that we need more consensus and evidence-base on presurgical diagnostic methods. The goal to improve presurgical epilepsy workup is burdened by expert preferences, methodological barriers, and imperfect – but evolving – concepts of epilepsy localization. Novel approaches may hold potential to improve surgical work up and understanding of epilepsy and need further exploration.

The concept of the epileptic brain is evolving and the consideration of focal epilepsy as a network disease is growing. Some even suggest that the notion of network structure and connections may be more important than localizing the pathological ‘hyper-excitable node’²⁹⁷. In a computational network model, resection of a so-called ‘driver’ node, characterized by unidirectional connectivity to other nodes, led to more seizure reduction than resection of the hyper-excitable node²⁹⁷. Although such network models seem to explain the epileptic brain best, they are impractical as surgical resection is ultimately focal. Thus, when neurosurgical procedures are involved, diagnostic test studies will adhere to a focal epileptic origin.

Novel tests that have not acquired a position within the presurgical workup are suitable for diagnostic accuracy studies. Based on previously discussed issues on bias and transparency, the ideal study is a cohort study with prospective consecutive selection of epilepsy surgery candidates (both eligible and non-eligible). The index test should be evaluated blinded for clinical and other diagnostic data. Test results covering a large brain area should be considered of less accuracy compared to more focal solutions, and may even allow a normalization factor. The resected area in post-surgical seizure free patients is the primary reference standard and should be determined independent from index test results. A normalization with respect to resection size is required as larger resections would probably increase a patient’s chance to become seizure free. A secondary reference standard applicable to all patients, including those non-eligible for surgery, is needed to reduce patient-selection bias. The most appropriate secondary reference standard would be the multidisciplinary team consensus on the presumed epileptogenic zone location, provided that it is determined independent from the index test information. Utilized diagnostic tests, on which the team consensus is based, may vary between patients.

Thus, pooling of patients who have undergone the same diagnostic tests could reduce heterogeneity. Investigators may use the Standards for Reporting of Diagnostic Accuracy checklist for their study^{130, 131, 189}.

Once reliable conclusions about the index test's diagnostic accuracy are drawn, analysis should proceed to study the integrative use of the test within the presurgical workup as this represents clinical practice. This includes a review and re-review of the index test results during the multidisciplinary team meeting with all available diagnostic information taken in consideration. In case of reasonable accuracy, diagnostic randomized controlled trials, comparing the experimental presurgical workup – that includes the novel test(s) – to the standard practice, with the decision to proceed to surgery and post-surgical outcome as outcome measures, need to be undertaken for a definite evaluation of the technology²⁹⁸.

An alternative study approach is required for diagnostic tests that are already standard use in the presurgical workup. For such tests reasonable accuracy has long been assumed and withholding patients from such methods may be unethical. The true value of a test should be determined by the influence it has on the decision to proceed to surgery and its consequence on surgical outcome. This may require statistical techniques such as multivariate logistic regression modelling or ROC curves²⁸⁷. Also, the likelihood that a test may frustrate clinical decision making, by falsely rejecting patients from surgery or commencing unnecessarily ancillary testing, should be of consideration. Decision curve analysis may be valuable as it accounts for the consequences of the false positive and negative classifications and allows the clinicians to set their own desired concordance threshold for the initiation of further actions such as additional testing or surgery^{286, 299}.

After sufficient evidence-base is reached, health economic data should be collected to examine cost-effectiveness. Differences between basic (level 1) and advanced (level 2) epilepsy surgery centers should be considered. Awareness of alternative patient-specific outcome measures, such as patient discomfort of procedures, adverse events and quality of life, is important in risk–benefit discussions with family members²⁶. Clinicians, patient groups, policy makers and healthcare research funders may meet and debate on the most appropriate way to investigate diagnostic technologies. Output of such gatherings can then be integrated in the guideline development methods such as the GRADE framework⁵³.

Appendices

Abbreviations

ADC: apparent diffusion coefficient

AED: anti-epileptic drugs

AMT-PET: α [^{11}C]-methyl-L-tryptophan PET

CCEP: cortico-cortical evoked potentials

DR: delayed response

DTI: diffusion tensor imaging

DWI: diffusion weighted imaging

(99mTC-) ECD-SPECT: ethylcysteinate dimer SPECT

ECoG: electrocorticography

EEG: electroencephalography

ER: early response

ERSP: event related spectral perturbation

ESI: electric source imaging

ETLE: extra temporal lobe epilepsie

EZ: epileptogenic zone

FA: fractional anisotropy

FCD: focal cortical dysplasia

(18-) FDG-PET: fluorodeoxyglucose PET

FLAIR: fluid-attenuated inversion recovery

fMRI: functional MRI

GRID: intracranial GRID EEG

HFO: high frequency oscillations

HHT: Hilbert-Huang transform

(99mTC-) HMPAO-SPECT: hexamethylpropylene amine oxime SPECT

HS: hippocampal sclerosis

HR-ESI: high resolution electric source imaging

ICEEG: intracranial EEG

IED: interictal epileptic discharges

iEEG: see ICEEG

ILAE: International League Against Epilepsy

LTM-VEEG: long-term monitoring with video-EEG

MCD: malformation of cortical development

MD: mean diffusivity

MEG: magnetoencephalography

MRI: magnetic resonance imaging

MSI: magnetic source imaging

mTLE: mesial TLE

MUSIC: multiple signal classification

NPV: negative predictive values
PHS: patient-history-based semiology
PPV: positive predictive value
SEEG: stereo depth intracranial EEG
SISCOM: subtraction ictal SPECT co-registered to MRI
sLORETA: standardized low-resolution brain electromagnetic tomography
SNR: signal to noise ratio
SPECT: single photon emission computed tomography
SPM: statistical parametric mapping
SO-electrode: seizure onset electrode
SOZ: seizure onset zone
SP-electrode: seizure propagation electrode
SPES: single pulse electrical stimulation
TD: time-domain
TF: time-frequency
TLE: temporal lobe epilepsy
TSC: tuberous sclerosis complex
VS: video-based semiology

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Nederlandse samenvatting – Dutch summary

Achtergrond

Epilepsie is een van de meest voorkomende neurologische aandoeningen. Het wordt gekenmerkt door een kwetsbaarheid voor het krijgen van herhaaldelijke epileptische aanvallen die van grote invloed zijn op de kwaliteit van leven. De belangrijkste behandeling is medicatie, maar in 30-40% van de patiënten met epilepsie van het focale type is de aanvalsreductie onvoldoende. Voor dergelijke patiënten kan epilepsiechirurgie een effectieve behandeling zijn waarmee het aantal aanvallen sterk of volledig afneemt.

Epilepsiechirurgie is gebaseerd op de veronderstelling dat er een epileptische haard is in de hersenen waar de aanval zijn oorsprong in vindt, ook wel epileptogene zone genoemd. Het succes van epilepsiechirurgie is grotendeels afhankelijk van het nauwkeurig lokaliseren van deze epileptogene zone. Om dit te bereiken wordt er een prechirurgisch diagnostisch traject gestart. Dit bestaat uit verscheidene beeldvormende en neurofysiologische diagnostische onderzoeken. Een eerste analyse betreft meestal een MRI-scan die de anatomie van de hersenen gedetailleerd in kaart brengt en plaatselijke structurele oorzaken van de epilepsie zichtbaar maakt. Daarnaast vindt er een langdurige elektro-encefalografie (EEG) registratie met video (LTM-VEEG) plaats. Een EEG meet hersenactiviteit door middel van aangebrachte elektrodes op de hoofdhuid. Zowel tijdens de aanvallen (ictaal) alsook in periodes tussen de aanvallen door (interictaal) kan het EEG epileptische activiteit laten zien. De video-opname geeft informatie over het karakter van de aanval, ook wel semiologie genoemd. De verzamelde informatie wordt vervolgens in een multidisciplinair team geanalyseerd om zo een eerste hypothese te vormen over de locatie van de epileptogene zone. In veel gevallen is deze eerste hypothese onvoldoende nauwkeurig, waardoor extra onderzoeken ingezet worden. Deze betreffen onder andere specifieke type MRI-scans, nucleaire onderzoeken zoals PET (positron emission tomography) of SPECT (single-photon emission computed tomography) en elektrische of magnetische bronlokalisatie. Soms wordt besloten tot invasieve procedures. Zoals EEG met elektroden direct op, of diep in, de hersenen geplaatst, respectievelijk intracranieel grid-EEG en stereo-EEG genoemd. Nieuwe informatie uit deze onderzoeken wordt vervolgens weer multidisciplinair besproken om de hypothese over de epileptogene zone te versterken. Dit proces van hypothesevorming en nieuwe diagnostiek kan zich meerdere malen voltrekken.

Door het grote aantal keuzemogelijkheden van diagnostische methoden bestaat al langere tijd de vraag hoe prechirurgische trajecten precies vormgegeven dienen te worden. Een peiling onder epilepsiechirurgie specialisten van over de hele wereld toonde aan dat er alleen overeenstemming is over het gebruik van MRI en EEG, en niet voor alle andere technieken. Elke diagnostische methode biedt daarnaast verschillende keuzes wat betreft

technische instellingen die van invloed zijn op het eindresultaat. Alhoewel hier enkele richtlijnen voor bestaan, zijn deze schaars. Het prechirurgische diagnostische traject biedt daarom ruimte voor verbetering door het optimaliseren van individuele methoden, inzet van een combinatie van technieken, of ontwikkelingen van nieuwe technieken.

MRI heeft een belangrijke rol in het prechirurgische traject. Als met MRI een epilepsie-veroorzakende afwijking (laesie) gevonden wordt, neemt de kans op aanvalsvrijheid na epilepsiechirurgie toe met een factor 2.5. Factoren die de kans op het detecteren van een laesie vergroten zijn voornamelijk optimale magnetische veldsterkte, uitgedrukt in Tesla (T), en gekozen sequenties die elk een eigen karakteristiek hebben wat betreft visualiseren van weefseleigenschappen. EEG vervult ook een dominante rol in het prechirurgische proces. Het heeft een hoge tijdsresolutie waardoor het begin van de epileptische aanval makkelijk waargenomen kan worden, echter is de locatie niet met grote nauwkeurigheid te bepalen door de elektrische geleidbaarheid van het hoofd. Bij LTM-VEEG duurt de registratie vaak enkele dagen omdat een voldoende aantal epileptische aanvallen geregistreerd moet worden voor een betrouwbaar resultaat. Hoge resolutie elektrische bronlokalisatie (HR-ESI) en magnetische bronlokalisatie (MSI) zijn aanvullende technieken waarin een hoog aantal sensoren (64-350) gebruikt worden om epileptische hersenactiviteit te meten tijdens interictale periodes. Elke jaar worden er meerdere artikelen gepubliceerd over deze technieken, omdat hun rol binnen het prechirurgische traject nog niet volledig duidelijk is. Er zijn ook patiënten waarbij langdurige intracraniale EEG-monitoring toegepast wordt om een betere hypothese over de epileptogene zone te verkrijgen waarbij, vergelijkbaar met LTM-VEEG, de registratie enkele dagen duurt. Een alternatief voor deze methode is het zogenaamde *single pulse electrical stimulation* (SPES) waarbij tijdens interictale periodes via de elektrodes elektrische stimulaties gegeven worden en vervolgens gekeken wordt naar reacties, of responsies, in het EEG. Deze responsies lijken samen te hangen met epileptische gevoeligheid van het onderliggende hersenweefsel, wat mogelijkheden biedt voor verder onderzoek.

Het doel van dit proefschrift was om de kennis van prechirurgische diagnostische technieken in het kader van epilepsiechirurgie te vergroten door middel van een evaluatie van het gebruik en de nauwkeurigheid van huidige en nieuwe diagnostische technieken.

Bevindingen in dit proefschrift

Verskil tussen Europese epilepsiechirurgiecentra

Een eerste stap betrof het vaststellen van de klinische praktijk van prechirurgische diagnostiek onder epilepsiechirurgiecentra van het E-PILEPSY consortium. In **hoofdstuk 2** worden de resultaten van een peiling onder de consortiumcentra beschreven betreffende het gebruik van diagnostische beeldvorming, *post-processing* (nabewerking) procedures en elektrische en magnetische bronlokalisatie technieken. Wij vonden een grote variatie

tussen centra in het gebruik van dergelijke technieken. In slechts 15 van de 24 centra (63%) wordt standaard gebruik gemaakt van 3 T veldsterkte MRI, in slechts drie centra wordt dit op indicatie toegepast terwijl de overige centra 1.5 T MRI toepassen. Er was een grote verscheidenheid in de typen gebruikte MRI sequenties: er werden 26 verschillende sequenties gerapporteerd. Minder verschil was er op het gebied van PET en SPECT. Bijna alle centra (22/24; 92%) gebruiken interictale PET. Gebruik van 18F-fluorodeoxyglucose (FDG) door alle centra weerspiegelt een algemene acceptatie dat dit de ideale marker is in focale epilepsie onderzoek. Ictale SPECT wordt, vergeleken met PET, door minder centra gebruikt (19/24; 79%) wat mogelijk het gevolg is van hogere kosten en de beperking dat een aanval geregistreerd dient te worden binnen het gereserveerde tijdslot. De helft van de centra passen ESI (n=9), dan wel MSI (n=7) toe. Binnen deze groep van centra is er een groot verschil in de gebruikte technische instellingen. We stelden vast dat MRI, PET en SPECT *post-processing* methoden door de meerderheid van centra gebruikt worden.

Er waren weinig centra die hun prechirurgisch diagnostisch traject volledig conform de beschikbare internationale richtlijnen en aanbevelingen uitvoerden. Vijfentwintig procent van de centra gebruikten de door de richtlijnen aanbevolen MRI sequenties met de benodigde snijvlakoriëntatie, snijvlakdikte en voxelgrootte. Achttien procent van de centra die epilepsiechirurgie bij kinderen toepassen, volgden niet de aanbevelingen tot het gebruik van PET of SPECT. Ictale SPECT-scans werden niet vergeleken met interictale SPECT-scans door 37% van de centra, ondanks dat dit wel geadviseerd wordt.

Wetenschappelijk bewijs voor diagnostische methoden

De verschillen tussen epilepsiechirurgiecentra wat betreft de gebruikte diagnostiek en de beperkte naleving van het spaarzame aantal richtlijnen onderschrijven de noodzaak tot meer wetenschappelijke onderbouwing over enerzijds welke diagnostische methoden in de prechirurgische diagnostiek horen en anderzijds hoe deze uitgevoerd dienen te worden. Ons doel was het onderzoeken van de wetenschappelijke evidentie van MRI voor epileptogene laesielokalisatie, en van HR-ESI en MSI voor epileptische bronlokalisatie.

In **hoofdstuk 3** hebben we een systematische beschouwing van de literatuur en een meta-analyse uitgevoerd naar de invloed van magnetische veldsterkte en sequentieselectie op het vermogen een laesie te vinden op MRI. We includeerden 18 studies op het gebied van veldsterkte en 25 op het gebied van sequenties. Alle studies bevatten belangrijke methodologische fouten die de uitkomsten fundamenteel kunnen beïnvloeden. Een tweede bevinding was dat een hogere veldsterkte detectie van laesies kan verbeteren. Methodologische problemen buiten beschouwing gelaten, vonden we bij patiënten waar de standaard-veldsterkte MRI geen afwijkingen aangaf (MRI-negatieve patiënten) een toegevoegde waarde van hogere veldsterkte: 18% meer detectie van laesies voor 3 T en 22% voor 7 T. We constateerden tevens dat niet alle patiënten evenveel profiteren

van hogere veldsterkte. Bij patiënten met de hersenafwijking hippocampale sclerose (HS) bleek 1.5 T MRI voldoende; hogere veldsterkte leidde niet tot detectie van meer laesies. Standaard MRI sequenties (3DT1, T2, FLAIR) vertoonden een goede detectiegraad van ongeveer 90% bij patiënten met HS. Voor epilepsie-specifieke MRI protocollen met 1.5-3T veldsterkte was de totale detectiegraad 83% bij temporaalkwabepilepsie en 51% bij patiënten met focale corticale dysplasie. Epilepsie-specifieke MRI protocollen en visuele beoordeling door neuroradiologen die ervaring hebben met epilepsie bleken ook belangrijk te zijn voor een hogere detectiegraad. De waarde van aanvullende technieken zoals diffusie gewogen beeldvorming (Diffusion Weighted Imaging, DWI; Diffusion Tensor Imaging, DTI) staat ter discussie. Deze methoden vertonen enige toegevoegde waarde door het aanwijzen van een hersenhelft waar een potentieel epileptisch focus zou kunnen zitten. Echter, zij missen ook vaak laesies die op conventionele MRI wel gezien worden, hebben vals positieve resultaten of detecteren irrelevante afwijkingen.

In **hoofdstuk 4** presenteren we de resultaten van onze systematische literatuurbeschuiving en meta-analyse naar HR-ESI en MSI voor epileptische bronlokalisatie. Acht studies over MSI en drie studies over HR-ESI werden geïncludeerd. Alle studies hadden veel methodologische problemen, en mogelijk zelfs fouten. Deze betroffen een beperkte patiëntenselectie, oneigenlijke beïnvloeding van de chirurgische besluitvorming door de bronlokalisatie resultaten en het excluseren van ESI/MSI bevindingen die geen eenduidige bron toonden.

Wanneer deze methodologische beperkingen niet meegewogen werden vonden we een hoge gevoeligheid van in totaal 82% voor het correct aanmerken van de epileptogene zone (sensitiviteit) en een redelijke gevoeligheid van in totaal 53% voor het correct aanmerken van niet-epileptogene regio's (specificiteit). Tussen MSI en HR-ESI was er geen statistisch verschil in deze gevoeligheid. Een belangrijke observatie was de onderrapportage van chirurgische uitkomsten bij patiënten met een niet-richtinggevend bronlokalisatie resultaat. Daarnaast was de rapportage van resultaten met gedeeltelijke concordantie tussen bronlokalisatie en gereseceerd hersengebied inconsistent. Deze factoren zijn echter van invloed op de diagnostische nauwkeurigheid. Wij vonden dat de specificiteit hoger werd wanneer gedeeltelijk concordante resultaten geclassificeerd werden als discordant ($p < 0.05$). Het toeschrijven van niet-richtinggevende resultaten aan de discordante categorie verlaagde de sensitiviteit ($p < 0.05$).

De resultaten van onze meta-analyses uit **hoofdstuk 3 en 4** worden beïnvloed door slechte kwaliteit van de beschikbare studies en overschatten daarom mogelijk de diagnostische nauwkeurigheid. Dit onderstreept de behoefte aan studies van hoge kwaliteit, zonder vertekening van resultaten en met een transparante analyse van de onderzochte diagnostische methode zodat richtlijnen verder verbeterd kunnen worden.

Nieuwe benaderingen voor het lokaliseren van de epileptogene zone

Het beter lokaliseren van de epileptogene zone zou ook op andere dan de hierboven beschreven manieren bereikt kunnen worden. In **hoofdstuk 5** onderzochten we de lokaliserende waarde van semiologie, LTM-VEEG en interictale HR-ESI in het prechirurgische diagnostische traject voor een specifieke patiëntencategorie, namelijk patiënten met tubereuze sclerose. Deze hebben verspreid in de hersenen talrijke, potentieel epileptogene gezwellen (tubers). Resectie van een enkele of een paar tubers kan al resulteren in aanvalsvrijheid. De uitdaging is daarom om die enkele epileptogenic tuber(s) te vinden in het scala van niet-epileptogene tubers.

In een retrospectief cohort van 24 epilepsiechirurgiekandidaten met tubereuze sclerose die zowel HR-ESI als LTM-VEEG ondergingen, toonden wij aan dat semiologie vaak van beperkte waarde is. Semiologie op basis van aanvalsbeschrijvingen verkregen vanuit (hetero) anamnese of op basis van video-opname is vaak niet lokaliserend, of foutief lokaliserend. HR-ESI geeft vaker een lokaliserend resultaat dan interictaal of ictaal EEG (79% versus 54% en 63%), door het lagere aantal niet-lokaliserende of multi-lokaliserende test resultaten. Tevens is HR-ESI vaker op het niveau van de hersenkwabben (lobair) concordant met de bewezen epileptogene zone in aanvalsvrije patiënten dan ictaal EEG (67% versus 33%). Daartegenover staat dat ictaal EEG vaker gedeeltelijk concordant is dan HR-ESI (44% versus 11%).

Lokalisatie nauwkeurigheid is niet het enige dat belangrijk is. De invloed van een diagnostische test op de klinische besluitvorming dient ook beschouwd te worden. Onze observatie was dat HR-ESI een sterke invloed had op het epilepsiechirurgie traject door het aanpassen of bevestigen van de hypothese over de epileptogene zone in 52% en 38% van de patiënten. Wanneer de validiteit hiervan werd bepaald door chirurgische uitkomst mee te wegen, constateerden we dat HR-ESI de klinische besluitvorming positief beïnvloedde in 7/14 patiënten (50%). In drie van deze patiënten werd de invloed van kritische waarde geacht; zonder HR-ESI zouden deze patiënten niet geopereerd en aanvalsvrij geworden zijn. In de resterende patiënten was de bijdrage van HR-ESI negatief of niet vast te stellen. In geen gevallen was een negatieve bijdrage kritisch misleidend.

Het prechirurgische diagnostische traject van patiënten met tubereuze sclerose zou baat kunnen hebben bij minder nadruk op semiologie en meer nadruk op HR-ESI resultaten. Toepassing van HR-ESI in het initiële traject zou daarom LTM-VEEG kunnen aanvullen of zelfs vervangen. Toekomstige studies die ook invloed op klinische besluitvorming meewegen, kunnen bijdragen aan de wetenschappelijke onderbouwing van deze methode.

Intracranieel EEG, de meest invasieve methode in het prechirurgische traject, wordt beschouwd als een laatste diagnostische stap bij onduidelijkheid over de epileptogene zone. SPES toegepast bij grid-EEG is een aanvullende en alternatieve methode voor de lokalisatie van de epileptogene zone doordat het actief het brein onderzoekt met kortdurende (1ms) elektrische pulsen die reacties opwekken binnen verschillende signaalfrequentiebanden. In **hoofdstuk 6** onderzochten we deze methode voor het op afroep identificeren van epileptogene hersengebieden. We vonden dat vroege responsies (<100 ms na stimulatie) de verbindingsstructuur van het aanvalsbegin (*seizure onset zone*, SOZ) en de voortgeleiding van een aanval in beeld kunnen brengen. Elektrodes met vroege responsies waren sterker geassocieerd met de SOZ-elektrodes dan met niet-SOZ elektrodes. Op groepsniveau en bij vier van de zes patiënten op individueel niveau was de SOZ vaker gelokaliseerd in gebieden met een hoog aantal vroege responsies. Elektrodes met een hoog aantal vroege responsies in de frequentieband 80-250 Hz vertoonden zelfs een hogere specificiteit voor SOZ-elektrodes dan vroege responsies in de lagere frequentieband (<80 Hz). Vroege responsies opgewekt door stimulatie in SOZ-elektrodes komen vaker voor in elektrodes waar voortgeleiding van de aanval te zien is. Kortom, vroege responsies kunnen pathologische aspecten blootleggen en hebben daardoor klinische waarde voor het in kaart brengen van epileptogeen hersenweefsel. Grotere en prospectieve studies zijn nodig om SPES tot zijn volledige klinisch potentieel te laten komen.

A

Algemene discussie

Hoe verklaren we de grote praktijkvariatie tussen Europese epilepsiechirurgiecentra zoals beschreven in **hoofdstuk 2**? Een eerste verklaring is te vinden in de totstandkoming van richtlijnen. Ondanks dat richtlijnen zich in de loop der jaren meer hebben gebaseerd op een beschouwing van de literatuur, zijn deze alsnog beperkt door het lage aantal studies en de matige kwaliteit. Dit creëert speelruimte voor subjectieve interpretatie die zich vertaalt tot 'expert opinion' vanuit bepaalde instituties of belangengroepen. Elke diagnostische methode biedt daarnaast speelruimte betreffende technische specificaties en instellingen. Er worden pogingen ondernomen tot harmonisatie van methoden, zoals door de ILAE neuroimaging werkgroep in de vorm van het HARNESS protocol (Harmonized Neuroimaging of Epilepsy Structural Sequences). In hoeverre dit door de epilepsiechirurgie gemeenschap nageleefd wordt dient nog onderzocht te worden.

Studies naar diagnostische nauwkeurigheid van prechirurgische methoden zijn erop gericht epileptogene van niet-epileptogene hersengebieden te onderscheiden. Dit gaat, zoals in **hoofdstuk 2 en 3** beschreven, gepaard met methodologische problemen. Een belangrijk punt is dat het gebruik van diagnostische testresultaten binnen de epilepsiechirurgie niet typisch is. In plaats van dat het testresultaat op zichzelf staat wordt deze in multidisciplinaire bijeenkomsten collectief herbeoordeeld in de context van

reeds beschikbare klinische en diagnostische informatie. Diagnostische tests die laat in het traject ingezet worden genieten daardoor de voordelen van meer ondersteunende informatie. Wat betreft invloed op de klinische besluitvorming is de positie van een test in het traject ook van belang: een deel van de diagnostische informatie uit de onderzochte test kan zich al bevinden in de resultaten uit voorgaande testen en kan dus ten overvloede zijn.

In de epilepsiediagnostiek ligt de nadruk vaak op het verkrijgen van ictale informatie, echter blijkt dit, zoals in **hoofdstuk 5** beschreven, niet per se nodig te zijn bij patiënten met tubereuze sclerose. Het sonderen van de cortex met elektrische stimuli heeft een praktisch voordeel doordat het op aanvraag het epileptogene netwerk bloot legt (**hoofdstuk 6**), maar biedt ook een theoretische bijdrage aan de verandering van het conceptuele epilepsiemodel; van een lokale hersenafwijking naar een pathologisch hersennetwerk. Ook al zouden netwerken een beter verklaringsmodel bieden voor het epileptische brein, de neurochirurgische behandeling is praktisch gezien altijd lokaal. Studies over diagnostische testen zullen zich daarom altijd baseren op een focale hypothese. De werkelijke waarde van een test wordt dan bepaald aan de hand van de invloed die het heeft op de klinische besluitvorming tot het ondergaan van chirurgie én de daaropvolgende uitkomst. Wanneer er voldoende wetenschappelijk bewijs is verzameld zullen uiteindelijk, door middel van kosteneffectiviteitsanalyses en focusgroepen, nieuwe richtlijnen opgesteld dienen te worden met als doel een brede acceptatie in de klinische praktijk.

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List of publications

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**these authors contributed equally*

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Curriculum Vitae

Brian Mouthaan was born on 13 May 1988 in Heemskerk, the Netherlands. He grew up in Beverwijk with his parents and his two older brothers. After graduating secondary school, he decided to move to Enschede to study Technical Medicine at the University of Twente. He became interested in neurology and signal analysis, and decided to follow the track 'medical signaling'. During his studies he had the opportunity to do a research internship at prof. Jean Gotman's EEG epilepsy research group at the Montreal Neurological Institute (McGill University, Montreal, Canada). When he returned from Canada, he finished his master study with a project on intracranial electrical stimulation for epilepsy surgery at the Clinical Neurophysiological department at the University Medical Center Utrecht. After that, in 2014, he started the accelerated medicine course at the Utrecht University. Parallel to medicine, he worked as a researcher for the European Union-funded E-epilepsy project, under supervision of Professor Kees Braun, Frans Leijten and Pieter van Eijsden at the department Neurology & Neurosurgery of the University Medical Center Utrecht. In the following years, the work evolved into this PhD thesis. After graduating as physician in December 2017, he decided to expand his horizon by working as a physician in a nursing home (zorggroep Charim, Veenendaal) and at an acute psychiatric ward (Altrecht, Utrecht). He then worked as a general physician in training (UMC Utrecht), but decided after a little more than one year that he was more interested in psychiatric patients and disease. In October 2022 he started his training at the University Medical Center Utrecht to become a psychiatrist. Brian lives with Daniëlle in Utrecht, and they are planning to move to their new home in Amersfoort in 2023.



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