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

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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 post-processing procedures in participating centers.

Methods:

A survey on the clinical use of imaging, electromagnetic source localization and post-processing methods in epilepsy surgery candidates was distributed amongst 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 MRI protocols are acquired at 3 Tesla by 15 centers and at 1.5 Tesla by nine. Three perform 3T MRI only by indication. 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 post-processing methods are used in 16 centers. Interictal PET is available in 22 centers; all using 18F-FDG. Seventeen centers perform PET post-processing. SPECT is used by 19 centers, of which 15 perform post-processing. Four centers perform neither PET nor SPECT in children. Seven centers apply MEG source localization, and nine EEG source localization. Fourteen combinations of inverse methods and volume conduction models are used.

Significance:

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

Key words: epilepsy surgery; MRI; SPECT; PET; electromagnetic source imaging

Key point box:

- The current use of presurgical imaging, electromagnetic source localization, and imaging post-processing methods in Europe was investigated
- A survey was distributed amongst 25 European epilepsy surgery centers
- There is a large variation in the presurgical diagnostic work-up between epilepsy surgery centers across Europe
- This stresses a need for high quality systematic reviews, evidence-based recommendations and harmonization of presurgical diagnostic work-up

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 from 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 post-processing methods, and electromagnetic source localization.

Only few recommendations on the use and specifications of these techniques for presurgical evaluation are available in the English literature. MRI is considered mandatory as primary imaging modality.[1] Although consensus among experts has not been reached on specific protocols, all recommendations include an anatomical 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.[2-6]

Pediatric epilepsy specialist units are recommended to have access to interictal PET and/or ictal SPECT.[1] FDG-PET is considered most valuable for so-called “MRI negative” patients or in case 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 useful.[7] 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.[7; 8]

Electromagnetic source localization, using MEG or EEG data, has been recognized as a useful and accurate clinical tool awaiting further validation.[1; 9-11] Official epilepsy-specific guidelines on electromagnetic source localization are lacking, but there are several general recommendations on hardware requirements and technique.[12-15]

The aim of this study was to catalog the diagnostic imaging, post-processing, and electromagnetic source localization techniques currently used by the E-PILEPSY centers, as a first step towards harmonization of presurgical assessment and diagnostic tools. Additionally, 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 asked 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 standard MRI epilepsy protocol (7), additional MRI sequences and MRI post-processing procedures (10), interictal PET (4), ictal SPECT (4), PET/SPECT post-processing procedures (8), EEG and MEG hardware and source localizations methods (38) (see supplementary materials for survey questions). Since 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 supplied 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, USA). 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. As 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 post-processing

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. 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 either 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 the supplementary materials Figure 1.

Only 12 centers (50%) perform all MRI sequences with slice orientation as recommended in the guidelines. Only six centers (25%) also meet the criteria for recommended slice orientation and slice thickness for each sequence (Figure 1); for five centers this applies to their adult protocol, for six to their pediatric protocol.

Use of additional MRI sequences is reported by 22 centers; 21 perform these in adults and 19 in children (Table 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 mostly reported to be indicated when lesions, or the suspected epileptogenic zone, are in close proximity to eloquent cortex.

Sixteen centers (67%) apply MRI post-processing, which is outsourced to other centers by four. Fourteen centers use post-processing in adults, nine in children, either for the purpose of clinical care or scientific research. Eight centers have the ability to perform morphometric analysis.[16] 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, while 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 multi-planar 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 planning.[18] In general, the most important indication for post-processing 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 even though 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 work-up (eight centers). All centers use the 18F-FDG ligand, only two use additional ligands.

PET post-processing 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 post-processing procedures.

Ictal SPECT is available in 19 centers and is applied to adult patients by 17 centers and in children by 11. SPECT is mostly indicated for MRI negative patients and patients with discordant semiology, imaging or electrophysiology results. The 99mTC-HMPAO marker is used by 17 centers, 99mTC-ECD by four. Post-processing 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 center's standard SPECT analysis.

With respect to published guidelines for children[1], four out 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 out of 19 centers (37%) performing SPECT, did not report a comparison of ictal with interictal SPECT as recommended.

Electromagnetic source localization

Electromagnetic source localization is performed by 12 centers; exclusively MEG in three, exclusively EEG in five, and four centers perform both. All seven that use MEG source localization do so in adults, six in children. Eight centers perform EEG source localization in adults, six in children. A total of 14 different combinations of inverse methods and volume conduction models are used: seven for MEG and 13 for EEG (supplementary materials Table 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.[19; 20] Jayakar et al.[6] 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 or not certain tests should be recommended in certain etiologies. These studies, however, did not address specific details regarding the diagnostic techniques neither did they 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.[1-8]

Standard epilepsy MRI protocols vary largely between centers. While there is some level of disagreement between different guidelines and recommendations on the exact details of the MRI protocol (as detailed in supplementary materials Table 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 from the fact that there is no consensus that higher-field strength MRI has additional value in the detection or delineation of epileptogenic lesions.[6; 21-23] 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 post-processing methods are performed by two-thirds of centers and consist mostly of morphometric methods and image reformatting or reconstruction methods. The limited use of post-processing can, to some extent, be attributed to a lack of local experience, lack of resources and lack of guidelines.[6]

The value of PET and SPECT in the presurgical work-up of epilepsy patients has been well explored.[24-27] 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.[24; 28] 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 limited use of novel markers. The clinical role of other markers and their precise contribution to the presurgical evaluation remains to be established.[7; 26; 28] PET post-processing methods are acknowledged to allow more precise anatomic localization of the hypometabolic area than conventional visual analysis.[8; 9] Most centers perform MRI co-registration. Few use SPM, probably because this technique has not yet been proven to have superior sensitivity over visual detection.[24]

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-slot.[26] Although 99mTC-HMPAO is the most popular ligand[29], 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.[7; 8] The post-processing method used most often is SISCOM, which has been proven to improve sensitivity of SPECT to visualize hyper perfused epileptogenic areas.[26] 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[1; 6], its clinical potential seems promising.[30] Formal epilepsy-specific guidelines on electromagnetic source localization are lacking, although there are several general recommendations elaborating important aspects that may influence its accuracy.[12-15] 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 here demonstrate 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 less “MRI-negative” patients and only operate on those with clear-cut identifiable MRI lesions. Alternatively, lack of availability of non-invasive diagnostic tools might lead to more frequent – and possibly unnecessary – invasive EEG recording procedures.

The relation between presurgical diagnostic work-up and surgical outcome was not 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[25; 31], 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 valuable.[32-34] 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 post-processing 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.

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Disclosure of conflicts of interest

The authors disclose no financial conflict of interest.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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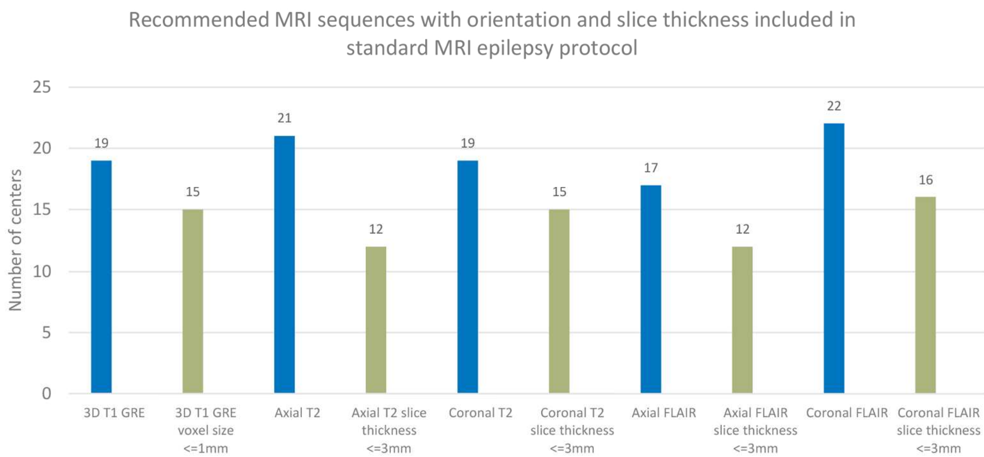
Figure legends

Figure 1. *Number of centers that include guideline recommended MRI sequences with the correct slice orientation (blue bars), and recommended slice thickness (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.*

Tables

Table 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 # centers	% of total (n=22)	# Centers for adult	% of total (n=21)	# 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%



Number of centers that include guideline recommended MRI sequences with the correct slice orientation (blue bars), and recommended slice thickness (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.
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