FACULTY OF MEDICINE AND HEALTH SCIENCES

Evaluation and Comparison of the Value of Source Localization on the Basis of MEG and High-density EEG within the Presurgical Evaluation of Patients with Refractory Epilepsy.

Word count: 16075

Demmy Croes
Student number: 01407821

Supervisor(s): Dr. Evelien Carrette, Drs. Stefanie Gadeyne

A dissertation submitted to Ghent University in partial fulfilment of the requirements for the degree of Master Science in Biomedical Sciences

Academic year: 2018 – 2019

GHENT UNIVERSITY

Preface

First of all, I would like to thank my promotor Dr. Evelien Carrette, who guided me throughout this master dissertation. She helped me whenever she could despite her busy work-schedule. The MEG recordings in Brussels were very pleasant and instructive.

I also want to thank my supervisor Stefanie Gadeyne for the very thorough corrections/suggestions and feedback during the writing and preparations of this master dissertation.

Furthermore, thanks to Dr. Apr. Stefanie De Buyser and Prof. Dr. Ir. Pieter van Mierlo for the help with the statistical analysis and the source localizations difficulties respectively.

Finally, I am also grateful to my parents Nancy and Jean-Marc, my sister Femke and Arno, who supported me during the fulfillment of this master dissertation.

Table of Contents

1 Summary

Background
Magneto-encephalography (MEG) and high-density electroencephalography (HD-EEG) are two investigations that can be used in the presurgical evaluation of patients with refractory epilepsy. These techniques are employed if previous investigations are inconclusive regarding the localization of the epileptogenic zone (EZ). The aim of this study was to investigate the value of MEG and HD-EEG within this presurgical evaluation.

Methods
In this master dissertation, the results of one-hour 306-channel MEG and 128-channel HD-EEG were compared retrospectively in 41 patients with refractory epilepsy. First, the sensitivity for interictal epileptiform discharge (IED) detection between MEG and HD-EEG was examined. Second, the accuracy of source localization on MEG and HD-EEG was investigated. MSI (magnetic source imaging) and ESI (electric source imaging) results were compared to the hypothesis about the localization of the EZ, determined at the epilepsy-surgery staff meeting, and if possible to the resection zone after surgery.

Results
MEG and HD-EEG had respectively a sensitivity of 63.0% (25/41) and 73.2% (30/41) to detect IEDs. IED-detection was not significantly different between both modalities. MSI and ESI were concordant with the EZ-hypothesis on a lobar level in respectively 78.5 % (11/14) and 80.0 % (16/20) of the patients in whom comparison was possible. For sublobar level, this was respectively 70.0 % (7/10) and 81.8 % (9/11). No significant difference was found for concordance rates between MSI and ESI regarding the EZ-hypothesis. Of the few patients who underwent surgery three and four of a total of seven patients had respectively concordant MSI and ESI results compared to the resection zone. All patients with concordant MSI and/or ESI results were seizure free.

Conclusion
No difference was perceived between MEG and HD-EEG in IED detection sensitivity and localization accuracy. A combination of both modalities within the presurgical evaluation remains useful because some individual patients may benefit only from a MEG or HD-EEG investigation.

2 Introduction

2.1 General

Epilepsy is a neurological disorder defined by recurrent and unprovoked epileptic seizures. During these seizures, the normal brain function is disturbed by abnormal excessive or synchronous activity at the level of the brain cortex due to an imbalance between excitation and inhibition [4, 5]. According to the latest adapted definition from the International League Against Epilepsy (ILAE), epilepsy is characterized by: "*1) at least 2 unprovoked (or reflex) seizures occurring greater than 24 hours apart. 2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years 3) the diagnosis of an epilepsy syndrome"* [6]. There are many risk factors that can be the trigger for developing epilepsy. Some potential risk factors are central nervous system (CNS) infection, head trauma, stroke, CNS tumour, developmental or neurodegenerative disorder, chromosomal or genetic syndrome, etc. [5].

2.2 Epidemiology

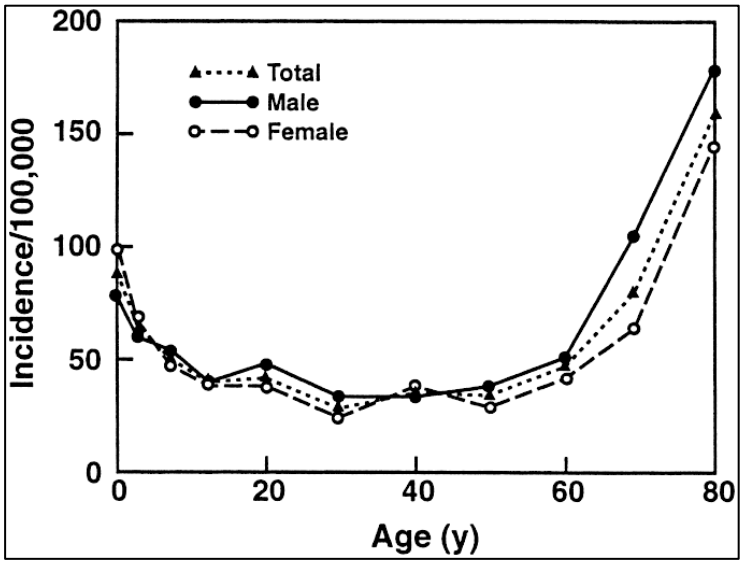

Figure 1 - Incidence of epilepsy by age [3]

Approximately 70 million people suffer from epilepsy worldwide of which 90 percent are found in developing countries. This percentage can be explained by endemic diseases such as malaria and neurocysticercosis, the difference in medical infrastructure, a higher incidence rate of traffic and birth related injuries, etc. In developed countries, the prevalence ranges from 4-10 cases per 1000 in comparison with 14-57 cases per 1000 in developing and tropical countries. The incidence rate in developed countries can be presented by a U-shaped curve with the highest rate during childhood and after the age of 65 (Fig 1). The incidence of epilepsy peaks during early adult years in developing countries [7].

2.3 Classification

The type of onset in the brain determines how epileptic seizures are classified (Fig 2). **Focal onset** seizures originate in a network of neurons limited to one brain hemisphere. These seizures can be classified by level of awareness, non-motor or motor onset and focal to bilateral tonic-clonic. Impaired awareness refers to the loss of awareness during any part of the seizure. The focal to bilateral tonic-clonic seizure alludes rather to a propagation pattern of a seizure than a specific seizure type. **Generalized onset** seizures occur when neuronal networks in both hemispheres are involved. Since the majority of generalized seizures present themselves with impaired awareness, these seizures are only subdivided in motor and non-motor (absence) seizures. Absence seizures occur suddenly with an impaired consciousness and an interruption of activity, especially during childhood. In addition, the seizures can also have an **unknown onset**. This category can be further subdivided in motor or non-motor and

unclassified. The latter is used if there is not enough information to categorize or if the seizures are not suitable with the other categories. There is also a possibility to classify focal seizures on an anatomical level (e.g. mesial temporal, neocortical, etc.). This type of classification is useful during presurgical evaluations (see below) [8].

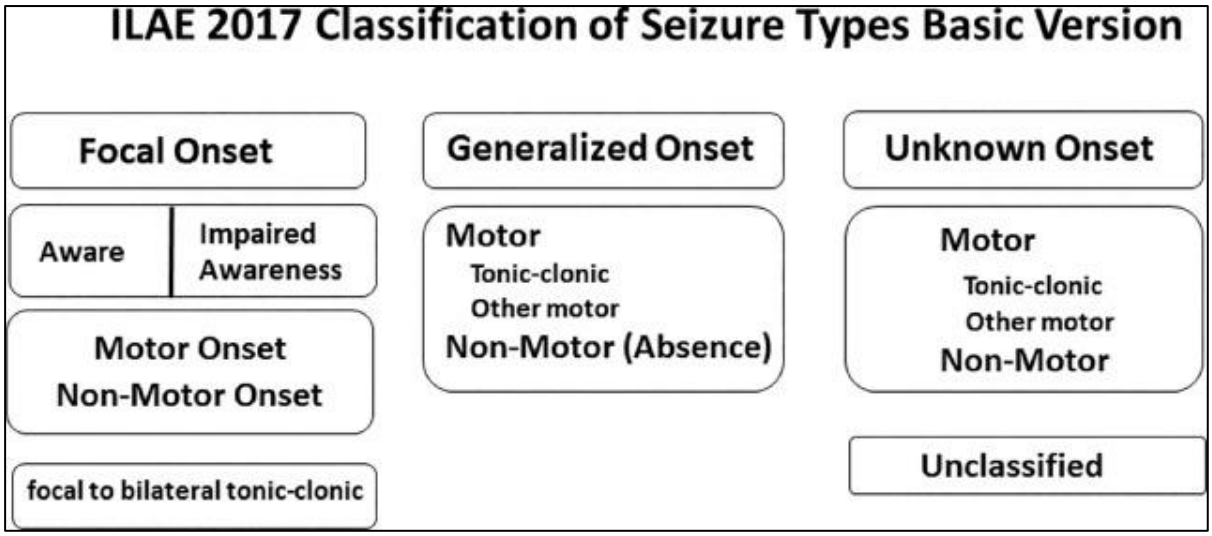

Figure 2 - ILAE 2017 classification of seizure types basic version [7]

2.4 Diagnosis

In order to diagnose a patient with epilepsy, the clinical history is first examined. This part of the diagnosis involves both the personal as the familial history and the identification of risk factors. It is important to identify the context in which the seizures occurred such as the circumstances (e.g. day or night, during illness, the occurrence of specific triggers, etc.) and the semiology. Additionally technical evaluations are executed that consist of a Magnetic Resonance Imaging (MRI) scan, an electroencephalography recording (EEG) and if necessary a video-EEG recording [5].

2.4.1 Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) is used to determine whether there are any CNS structural lesions that can be potentially linked to epilepsy. Different sequences (T1, T2, Flair, etc.) are obtained to capture possible malformations. The 3Tesla (T) MRI is used as a standard because of its higher accuracy and sensitivity in comparison to the 1.5T MRI (new lesions are observed in 20% of patients). Structural lesions that can be detected by MRI are mainly developmental cortical dysplasia, hippocampal sclerosis, low-grade neoplasms and cavernous angiomas. Recently, the 7T MRI was approved by the FDA for clinical use. This ultra-high field MRI rendered promisingly results in terms of higher spatially resolution [5, 9].

2.4.2 Electroencephalography (EEG)

Electroencephalography (EEG) measures the electrical activity of the brain cortex trough electrodes (±20) positioned on the patient's scalp. The most important diagnostic markers of epilepsy are interictal epileptiform discharges (IEDs), which occur between seizures and are visible on the EEG as spikes, sharp-waves or spike-and-waves complexes. A patient experiencing a seizure during the EEG recording and consequently registrating ictal epileptiform activity is very unusual because of very short recording times (20-30 minutes). Besides conforming the diagnosis with a high specificity, EEG often allows classification of the seizures and the possible diagnosis of an epilepsy syndrome [5].

2.4.3 Video-EEG monitoring (VEM)

Some patients will undergo video-EEG monitoring (VEM) in a specialized epilepsy center because the diagnosis and/or seizure classification cannot be confirmed by standard EEG. The investigation is conducted in a monitoring room equipped with a synchronized camera, microphone and EEG recording device. The main advantages of this technique are the prolonged measurement (24hours to 7days) and the character of the simultaneous video and EEG recording. This increases the chance that a seizure will occur, and therefore ictal activity on the EEG and semiology of a seizure on the video will be registered [5].

2.5 Anti-epileptic drugs (AEDs)

When a patient is diagnosed with epilepsy, a treatment with anti-epileptic drugs (AEDs) will be initiated. A whole range of AEDs is currently available with different mechanism of action. There is no optimal treatment for epilepsy in general and therefore the choice of drug(s) is based on patient-specific characteristics such as sex, age, seizure type and comorbidities. 60% to 70% of the patients treated with AEDs will eventually achieve seizure freedom of whom 40% to 60% will retain remission after withdrawal of drugs. A patient is considered sustained seizure-free if the seizures do not occur for at least one year or 3 times the inter-seizure interval before the therapy has started, whichever is greater [5, 10, 11].

2.6 Refractory Epilepsy

One-third of all epilepsy patients cannot control their seizures. These patients suffer from medication-resistant or refractory epilepsy which is defined by the ILAE as *"failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" [11].* Refractory epilepsy is associated with an increased risk for co-morbidity (e.g. migraine, ADHD, etc.), psychological dysfunction (e.g. depression, anxiety disorder, etc.), injuries, social stigmatization, reduced quality of life and mortality, therefor it is important to pursue seizure-freedom [12]. Other evident causes such as non-compliance (e.g. inadequate doses of AEDs and not adjusting unhealthy lifestyle), the prescription of unsuitable AEDs and incorrect diagnose (e.g. syncope, movement disorders, etc.) can lead to failure of the AED-treatment. This pseudo-resistance must first be excluded by a specialized epilepsy clinic before an alternative treatment other than AEDs should be considered. In addition, the seizures need to be classified as focal or generalized to know which treatment will be the most advantageous. When the seizures are focal, resective surgery must be the first treatment being considered because of high chances of seizure freedom (27-80%). When surgery is impossible, other treatment possibilities can be evaluated such as vagus nerve stimulation (VNS), deep brain stimulation (DBS), new AED trials and dietary treatments [5].

2.7 Epilepsy surgery

During epilepsy surgery, the epileptogenic zone (EZ) is removed or disconnected to aim seizure freedom. This region in the brain is necessary and sufficient for the generation of epileptic seizures. Currently, no single diagnostic modality is available that can define the entire EZ with certainty. Therefore, the EZ is more a theoretical region that only is completely eliminated by surgery if the patient is seizure free. Different surgical procedures can be performed based on the type of epilepsy the patient suffers from among which curative (e.g. amygdalohippocampectomy, temporal lobectomy, lesionectonomy, hemispherectomy, etc.) and palliative surgery (e.g. multiple subpial resection and corpus callosotomy and hemispherotomy). The last procedure is exerted to reduce the frequency of epileptic seizures and thereby increasing the quality of life [5, 13].

2.8 Presurgical evaluation

A multidisciplinary team of specialist including neurologists, neurosurgeons, neuroimaging specialists, neuropsychologists, psychiatrists etc. will attempt to determine the location and the extension of the EZ. Furthermore, the potential impact of the surgery will be assessed based on the emotional status and neurological and cognitive functions of the patient. When the EZ is a part of the eloquent cortex (i.e. the region in the brain that provides direct control of function, it is impossible to eliminate the whole EZ because functional deficits could arise. The presurgical evaluation consists of an assembly of non-invasive neurophysiological- and imaging (both structural and functional) investigations. These investigations define different cortical zones of epileptic abnormality (Table 1). High concordance (overlap) between these different cortical zones can lead to an accurate and convincing EZ-hypothesis. All patients undergo a prolonged video-EEG monitoring (see above), a 3T MRI (see above) and a neuropsychological examination. Some patients need further testing if there is discordance between the aforementioned investigations, when the MRI is normal, multiple lesions are found on the MRI-image or there is a more precise hypothesis needed. Additionally, interictal Positron Emission Tomography (PET), ictal Single Photon Computed Tomography (SPECT), **magnetoencephalography (MEG)**, **high-density EEG (HD-EEG)** and/or invasive video-EEG monitoring (iVEM) can be executed [5, 14, 15].

Presurgical evaluations	**Cortical zones**
Video-EEG monitoring	Irritative zone[1], Symptomatogenic zone[2], Ictal onset zone[3]
MRI	Epileptogenic lesion
Neuropsychological examination	Functional deficit zone[4]
FDG-PET	Functional deficit zone[4]
Ictal SPECT	Ictal onset zone[3]
MEG	Irritative zone[1]
HD-EEG	Irritative zone[1]
IVEM	Irritative zone[1], Symtomatogenic zone[2], Ictal onset zone[3], Eloquent cortex
fMRI	Eloquent cortex

Table 1 - Presurgal evaluations localizing different cortical zones of epileptic abnormality; adjusted from [15]

2.8.1 Neuropsychological examination

During the neuropsychological exam, the patient's cognitive abilities are tested for different dominant and non-dominant functions (e.g. language, verbal and non-verbal memory, somatosensory and motor function). Besides localizing the functional deficit zone[4] (Table 1),

[1] The area in the cortex that generates interictal epileptiform discharges.
[2] The area in the cortex that produces the ictal symptoms when activated by epileptiform discharges.
[3] The area in the cortex that generates ictal epileptiform discharges during an epileptic seizure.
[4] The area in the cortex that is characterized by underlying functional deficits during the interictal period that may be the result of a lesion or a deviant neuronal transport which has effect locally or distantly from the epileptogenic tissue.

neuropsychological testing is also important to estimate possible cognitive impairment post-operatively [13, 16, 17].

2.8.2 Positron Emission Tomography (PET)

Positron Emission Tomography (PET) is an imaging technique that measures the accumulation of certain radioactive substances. For epilepsy, 18F-fluorodeoxyglucose (FDG) is the most prevalently injected tracer because interictal epileptic abnormalities usually occur together with a hypometabolisme of glucose. FDG-PET has an added value especially when there are no structural lesions on the MRI-image (e.g. MRI-negative cortical dysplasia and temporal lobe epilepsy) and can be used as a guideline for IVEM. The PET-image should be superimposed on the MRI-images for accurate anatomical interpretation. This investigation defines the functional deficit zone[4] (Table 1) [13, 15, 16].

2.8.3 Single Photon Computed Tomography (SPECT)

An epileptic seizure occurs usually together with an increased cerebral blood-flow. This rise can be measured by ictal Single Photon Computed Tomography (SPECT) especially in patients with frequent seizures (because of the higher success rate). The procedure consists of an injection with a radioactive tracer within seconds after the seizure onset. Consequently, the patient has to be monitored 24h/day by trained personnel for accurate results. If the injection is delayed, only secondary hyperperfusion after seizure spreading can be detected which renders diffuse or non-localizing images. Subtraction ictal-interictal SPECT co-registered to MRI (SISCOM) can be utilized for better delineation of the ictal onset zone. Through specialized computer software the two images can be subtracted from each other and superimposed on the patients co-registered MRI. Ictal SPECT determines the ictal onset zone[3] (Table 1) [13, 17, 18].

2.8.4 Invasive video-EEG monitoring (IVEM)

Invasive video-EEG monitoring (IVEM) is opted when the results from non-invasive examinations are discordant, the eloquent cortex is nearby the potential resection area and/or no lesions can be observed with imaging techniques. This investigation can solely be executed when an EZ-hypothesis is formulated, to place the electrodes. Subdural and/or depth electrodes can be implanted respectively on the brain surface or in deeper brain structures such as sulci, the amygdala, the hippocampus or the insula. Besides recording electrical activity with high spatial resolution, during IVEM the cortex can also be stimulated to determine function. Recent findings, among which high resolution electrode grids and new biomarkers (high frequencies oscillations) have increased the value of IVEM. IVEM localizes the irritative zone[1], the symptomatogenic zone[2], the ictal onset zone[3] and the eloquent cortex (Table 1) [13, 16].

2.8.5 Functional MRI (fMRI)

Functional MRI (fMRI) uses differences in blood oxygen level-dependent (BOLD) contrast to assess certain activity in the brain. Generally, two well-chosen conditions (target and control) are compared with each other to visualize brain areas responsible for specific tasks (e.g. movement, language or memory). The application of fMRI in the presurgical evaluation consists of identifying the eloquent cortex and its relationship to the EZ (Table 1). The Wada test[5] is increasingly being replaced by this investigation because discordance between the two tests has only been reported in 14% of the patients. Simultaneous fMRI-EEG is a recent neuro-

[5] The Wada or intracarotid amobarbital test assesses hemispheric lateralization and possible memory decline after surgery by injecting sodium amobarbital into the internal carotid artery inducing contralateral hemiparesis.

imaging technique that detects BOLD activity linked to interictal spikes on the EEG. This examination is not yet a standard in the presurgical evaluation because only a limited number of data of fMRI-EEG is available in patients with focalized epilepsy [9, 17].

2.9 Magnetoencephalography (MEG)

Magnetoencephalography (MEG) is a non-invasive investigation that is part of the presurgical evaluation. MEG measures the magnetic fields in the brain cortex, which arise from intra- and extracellular ion currents due to postsynaptic potentials in the apical dendrites of pyramidal neurons. These neurons are parallel aligned and activated simultaneously, producing a measurable electrical, and perpendicular thereupon, magnetic signal. The position of the apical dendrites within the folded cortex determines their parallel orientation. Radially orientated sources, located in the top of de gyri, are not captured by MEG because their magnetic fields are evened out. However, MEG is extremely sensitive for tangentially orientated sources, located in the banks of the sulcus that produce measurable magnetic fields outside the skull (Fig 3).

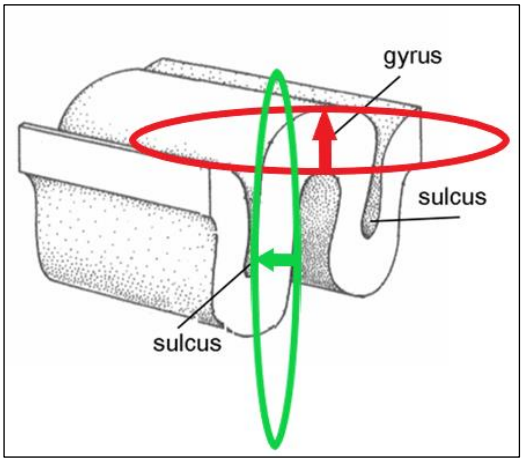

Figure 3 - Brain cortex with gyri and sulci; red = radial source, green = tangential source, arrow = electrical field and circle = magnetic field; adjusted from [2]

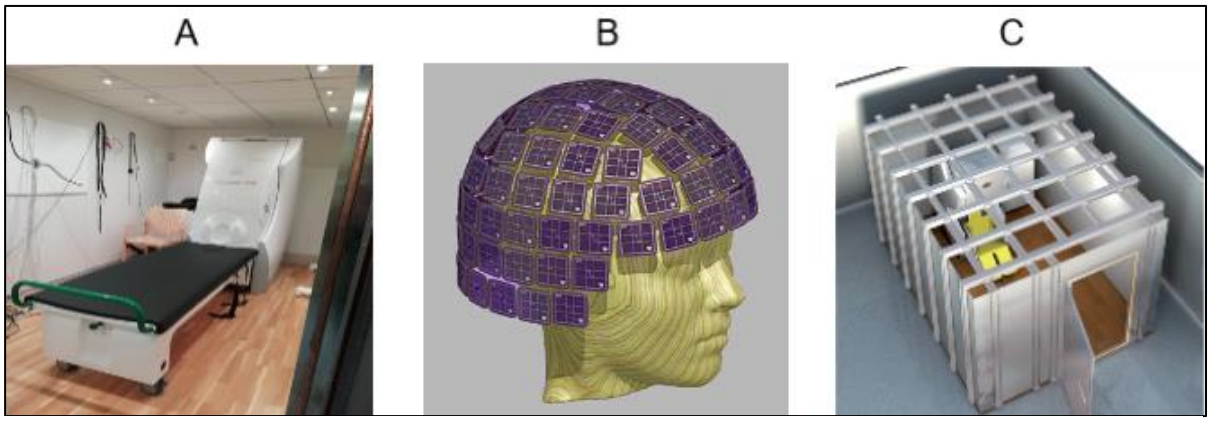

Figure 4 - MEG-equipment: A = MEG device, B = Sensors, C = LMSR [2]

The amplitudes of magnetic signals captured by MEG are in the order of 10^{-15} to 10^{-12} T. Therefore, specific conditions are essential to successfully measure these signals. Superconducting QUantum Interference Devices (SQUIDs) are specifically developed for the MEG apparatus (Fig 4 A-B). These sensors are imbedded in a helmet containing liquid helium because they are superconducting at a temperature of 4,2 K. SQUIDs can detect very fast changes in the magnetic flux through gradiometers and magnetometers, which are respectively sensitive for shallow and deeper sources. Currently, MEG systems exist that have approximately 300 sensors arranged next to each other, which provides a good spatial resolution (lobar-sublobar). In addition, the MEG device is positioned in a magnetic shielded room (MSR) to eliminate the magnetic interference from the environment. The walls of this room consist of several layers of µ-metal and aluminum. Due to technical improvements, there is now also a light weighted MSR (LMSR) available (Fig 4 C). This room actively removes

magnetic interferences by means of an active feedback compensation system[6] and a signal space separation (SSS) method[7], and thereby requires only one layer of µ metal and aluminum. MEG requires an expensive device and demands many logistics, which has led to limited availability [5, 19].

2.10 High-density EEG (HD-EEG)

Figure 5 - 256 HD-EEG-setup [1]

High-density EEG (HD-EEG; Fig 5) measures, like standard EEG, the electrical current originating from the pyramidal neurons in the brain cortex. This non-invasive presurgical technique is more sensitive for radially orientated sources then for tangentially orientated sources because tangentially orientated sources are more prone to background cancelation effects. HD-EEG utilizes a greater number of electrodes (64-256) in comparison to standard EEG (19-31). This increased electrode-number leads to an increased spatial resolution (lobar-sublobar). HD-EEG requires compared to MEG a relatively inexpensive device. During both MEG and HD-EEG, only IEDs are usually registered because of the short-term character (+/- 1 hour) of both recordings, which only makes it possible to define the irritative zone with these investigations. Longer recordings are difficult to achieve due to comfort-reasons for the patient [2, 20, 21].

2.11 Source localization

Source localization (or imaging) is a model-based technique, which attempts to estimate the brain source of the signals captured with MEG or HD-EEG. Only when IEDs are registered on the magneto- or electroencephalogram, source localization can be performed after annotation of these peaks. Magnetic- and electrical source (MSI and ESI) imaging entails the resolving of two problems: the forward and the inverse problem. By utilizing this approach, the source of the electrical and magnetic potentials measured at the level of the scalp can be calculated with a (sub)lobar resolution [22, 23].

2.11.1 Forward problem

The forward problem attempts to predict which signals can be measured at the level of the sensors or electrodes, when a specific source is activated in the brain. Therefore, all possible signals from all possible sources have to be predicted. To solve this problem, a source model that represent neuronal activity and a head model based on the individual MRI of the patient are required. Furthermore, the positions of the sensors/electrodes relative to the brain have to be known. An electromagnetic input-system can measure the exact electrode positions in HD-EEG. For MEG, head positions indicators register the exact position of the head relative to the fixed sensors in the detection-helmet. The electrical/magnetic sources in the brain can be modelled by a current dipole with an orientation, position and intensity. This current dipole forms the basis of more complex source models that define source space (see below). The head model characterizes the anatomical and electrical properties of the head accounting for

[6] The active feedback compensation system produces a compensatory magnetic field to decrease sensor interference.
[7] The SSS-method removes residual sensor interference and active feedback compensations system effects.

geometry and conductivity. MEG usually utilizes a spherical head model that represents the brain in a simplistic way as a sphere consisting of a homogeneous middle (Fig 6 A). Electrical potentials, unlike magnetic fields, are much more sensitive to the differences in conductivity and anisotropy of the tissues (e.g. skull, grey matter, white matter and cerebrospinal fluid) through which they have to propagate to reach the electrodes. Therefore, HD-EEG requires realistic multilayer head models that more accurately reflect the shape and physical properties of the brain and the surrounding tissues. The calculation of realistic head models is complex, so the forward problem can be solved more easily for MEG than for HD-EEG. Examples of realistic head models are the boundary element model (BEM), the finite element model (FEM) and the finite difference model (FDM; Fig 6 B). The BEM divides the head into three layers (skin, skull and brain) and assumes that homogeneous conductivity applies for each layer. The FEM and the FDM divides the head respectively in unequal (tetrahedral or polyhedral) or equal (cubic) voxels that each have their own conductivity. The source space, the assembly of all possible source (or dipole) localisations, can be constructed based on the source and the head model [22, 23].

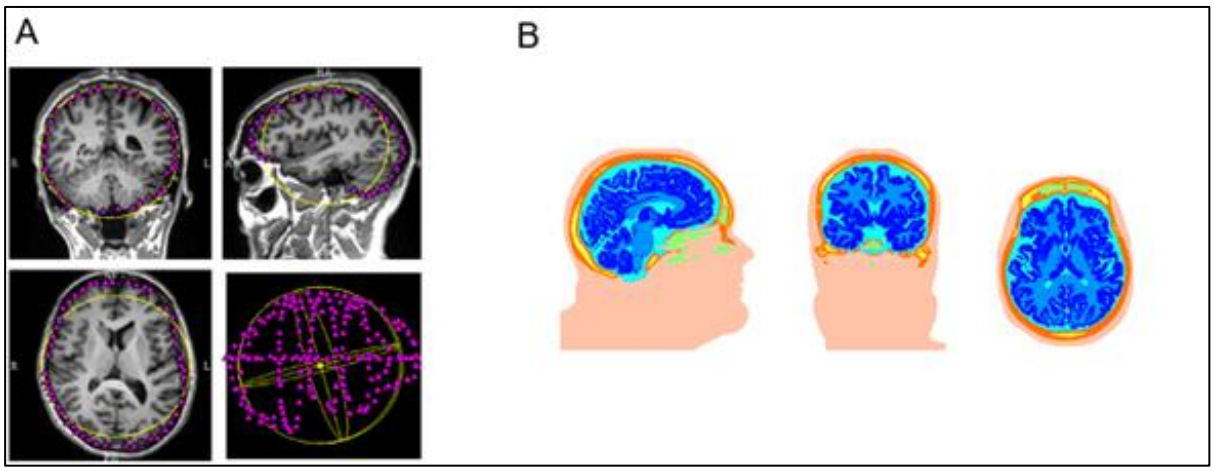

Figure 6 - Head models: A = spherical head model, B = Finite Difference Model (FDM) [2, 24]

2.11.2 Inverse problem

The inverse problem attempts to translate the signals measured at the level of the sensors/electrodes by underlying magnetic or electrical sources. To solve this problem, one or more sources have to be found that minimize the difference between the measured MEG/EEG signal and the via forward modelling calculated MEG/EEG signal. Different models (with different assumptions/constraints) can be used for the reconstruction of the source(s), but there is no unique solution for the problem. The equivalent current dipoles (ECD) model presumes that one or a small number of source(s)

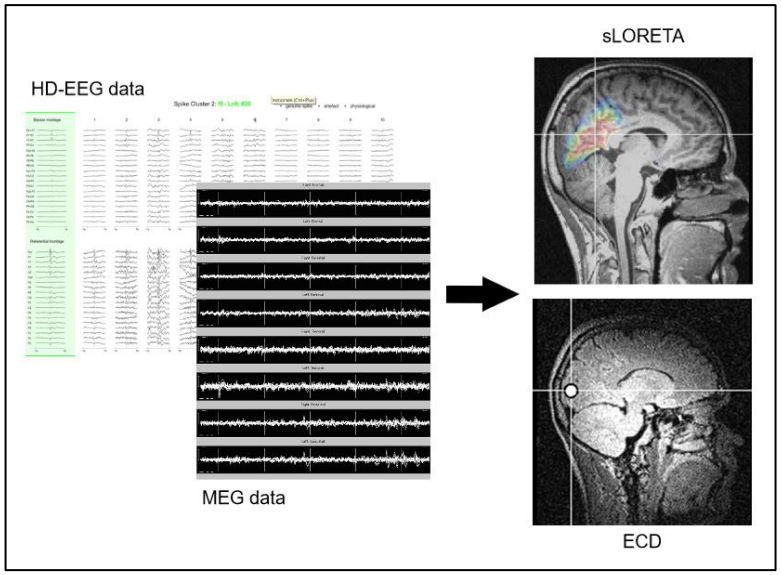

Figure 7 - Inverse problem can be solved by the ECD model or distributed models (sLORETA)

(dipole(s)) are responsible for the generation of the measured MEG/EEG signal. In addition, models that use distributed sources also exist. These models consider the influence of all possible sources and the sources are represented with maximal activity-distribution. Examples of distributed source models are Minimum Norm Estimation (MNE), Weighted MNE (WMNE), Low Resolution Electromagnetic Tomography (LORETA), Standardised LORETA (sLORETA) and Local Auto-Regressive Averages (LAURA). MNE tries to identify the solution with minimum power. The variant WMNE compensates for deeper sources. LORETA assumes spatial smoothness of neurons: if one neuron is active, there is high a probability that surrounding neurons are also active. Biophysical constrains and beamformers[8] are taken in account by sLORETA and LAURA. MEG is only sensitive to tangential sources, so the number of possible solutions for the inverse problem is lower than for HD-EEG [22, 23].

2.12 Problem posing

Literature suggests that MEG and HD-EEG are complementary techniques in the presurgical evaluation of patients with epilepsy. As mentioned above, MEG is only sensitive to tangential oriented sources, whereas HD-EEG is sensitive for both tangentially and radially oriented sources, but the detection of radial sources is superior [2]. Furthermore, MEG captures mainly superficial sources because the magnetic field decreases in strength inversely proportional to the square of the distance from the electrical source [25]. Consequently, the magnetic signal degrades as the source is located deeper. Electrical signals are less distance sensitive; therefore, HD-EEG can better detect deeper sources. Due to the intrinsic properties of these techniques, some signals are better registered by either MEG or HD-EEG. Taking into account that these investigations complement each other, various studies investigated the usefulness of implementing both techniques in the presurgical evaluation.

Some studies examined the difference in the detection of IEDs during simultaneous MEG and EEG registration. These studies showed that MEG is overall equal or slightly more sensitive for the detection of IEDs compared to standard EEG. Although, some IEDs could not be detected by MEG but could by standard EEG [26-29]. For instance, the research group of Heers et al. reported an IED-detection sensitivity of 60.3% and 50.8% for MEG and standard EEG respectively [29]. The few studies that compared HD-EEG to MEG reported the same findings. [30, 31]. For example, Knake et al. found an IED-detection sensitivity of 72% for MEG (306 sensors) and 61% for HD-EEG (70 electrodes). In another study, the signal-to-noise ratios (SNRs) for IEDs were calculated from simultaneous HD-EEG (128 electrodes) and MEG (305 sensors) recordings as function of orientation and depth of the source. Both techniques had different SNRs for different sources in the brain, which again indicates complementarity of the techniques [32].

Other studies investigated the reliability of source localization based on MEG or HD-EEG. A high sensitivity was reported in different studies for both techniques. For example, a sensitivity of 83% and 84% was reported for respectively MEG and HD-EEG, if compared with the surgical outcome. MEG or HD-EEG can sometimes yield additional information crucial for final decision-making concerning the EZ [33, 34].

Furthermore, the added value of MEG or HD-EEG was investigated for specific groups of epilepsy patients in the presurgical evaluation. MEG appears to be clinically relevant especially in patients with extratemporal lobe epilepsy and MRI-negative epilepsy. While HD-EEG appears to be important for patients with temporal lobe epilepsy [35, 36].

A comparison of both techniques within the same patients can be useful. Although, HD-EEG and MEG have already been compared in the field of IED detection, a low number of electrodes

[8] Beamformers are spatial filters that let pass signals from certain sources and attenuates signals from other sources.

was used (≤ 70 electrodes) in the different studies [30, 31]. Research has shown that the use of HD-EEG arrangements with a higher number of electrodes (> 100 electrodes) is better for spatial resolution [37]. Furthermore, there are few studies (with small numbers of patients) comparing MEG and HD-EEG based on accuracy of source localization. Usually these two techniques were compared separately with other presurgical investigations [38]. In addition, the usefulness of MEG and HD-EEG for specific groups of epilepsy patients has to be further investigated. It is important to know which patients benefits most from a MEG and/or HD-EEG investigation.

3 Materials and methods

3.1 Patient population

In this study, refractory epilepsy patients that were eligible for epilepsy surgery within the Gent University Hospital in the period from January 2014 up to and including September 2018 were considered. Patients needed to have undergone both MEG and HD-EEG investigations to be included in the study.

The outcome of the different investigations and the specific type of epilepsy were collected from the pseudonymized patient records. This study was approved by the ethical committee of the Gent University Hospital (EC/2014/0967).

3.2 MEG acquisition and data-analysis

All MEG recordings took place at the Erasmus Hospital in Brussels. Every patient signed an informed consent form before the research started. First, four head position indicators (HPI) coils were glued on the patient's head. These HPI coils made it possible to register the position of the head during the recording so that head movements could be corrected afterwards. Furthermore, a 3D model of the head of the patient was made by an electromagnetic input-system (Fastrak Polhemus® digitizer system). The position of three reference points (nasion, left and right tragus), the HPI coils and 300-400 additional points on the head and face of the patient were digitized consecutively. These coordinates were used afterwards to superimpose the MEG data on the MRI-image. The recording itself was done with a whole-head 306-channel Elekta Neuromag® system consisting of 204 gradiometers and 102 magnetometers. The MEG device was located in a LMSR. During the one-hour recording, the patient attempted to lie still with the eyes closed in the device and to sleep if possible. Afterwards, the MEG data were pre-processed with the SSS-method and band-passed filtered (between 0.1 and 40 Hz). The magneto-encephalogram was visually inspected for IEDs and thereafter MSI was performed per IED. For this, a patient-specific spherical head model was developed based on the patient's MRI images and the 3D head model. Subsequently, an ECD was calculated as early as possible in the peak of each IED in order to obtain a good signal-to-noise ratio. The ECDs were then positioned on the MRI of the patient (only dipoles with a goodness of fit of at least 80%).

3.3 HD-EEG acquisition and data-analysis

All HD-EEG recordings took place at the Gent University Hospital. Before the start of the investigation, the patient signed an informed consent form. The 128-electrode cap (BrainCap® from EasyCap) was first placed on the head of the patient. Next, a 3D model was made of the patient's head with an electromagnetic input system (EEG PinPoint® from Localite). Six reference points (nasion, top of the nose, left and right tragus, left and right exocanthion) and the electrode positions were digitized. Furthermore, a conducting-gel was applied on the electrodes for good contact between the electrodes and the scalp. During the recording, the patient lay in resting supine position and tried to sleep for one hour. Afterwards, the HD-EEG data were filtered with a band-pass filter (between 1 and 70 Hz) and a notch filter (50 Hz). The electro-encephalogram was visually inspected for IEDs and thereafter ESI was performed for the different types of averaged IEDs. A multi-layered realistic head model was composed based on the MRI images of the patient and the 3D head model, for which the FDM method was used. Via the inverse solution sLORETA, an activity distribution was calculated for the peak of each average IED. The maximum of the distribution was displayed on the MRI of the patient.

3.4 Data Analysis

The raw MEG and HD-EEG data were analysed for IEDs by experienced MEG and HD-EEG interpreters (two reviewers for each modality). The reviewers were blinded for the results of the other modality. The reports of these reviewers with the MEG and HD-EEG results were retrospectively analysed for each patient.

3.4.1 IED detection

First, the possible difference in the detection of IEDs was examined between MEG and HD-EEG. The sensitivity for IED detection was determined for each modality. Furthermore, it was investigated whether there were patients in whom IEDs were detected by MEG alone, HD-EEG alone, by none of these two tests or by both modalities. Subsequently, the sensors/electrodes on which the IEDs were captured were compared in terms of lateralisation and localization. This comparison was only possible for patients with IED detection by both MEG and HD-EEG. The IEDs were classified as unique (one type of IEDs), dominant (one dominant type of IEDs that was detected at least twice as high as other type(s) of IEDs) and non-dominant (non-dominant types of IEDs). Only patients with unilateral unique, unilateral dominant or unilateral non-dominant MEG and HD-EEG IEDs could be compared on lateralisation level. Comparison for lobar level could only been executed for patients with unilateral unique or unilateral dominant MEG and HD-EEG IEDs. Concordance between MEG and HD-EEG for IED detection was defined as lateralisation to the same side (left/right) and/or localization to the same lobar region.

3.4.2 Source localization

Second, source localization on the basis of MEG relative to HD-EEG was investigated. MSI results were classified as localized (unique cluster/source, dominant cluster/source, non-dominant clusters/sources) or non-localized (scattered or no IEDs). Localized was defined as more than five ECDs in one sublobar region for MSI. ESI results were classified as localized (unique source, dominant source, non-dominant sources) or non-localized (wide field or no IEDs). For ESI, localized was defined as the localization of the maximum of the activity distribution of the peak in one sublobar region. The sensitivity was examined for both MSI and ESI. Furthermore, the ESI and MSI results were compared for lateralisation and localization. Only in patients in whom both MSI and ESI was performed could be compared. In the case of multiple localized sources, only the dominant source (if there was one) was used for comparison. Unilateral unique and unilateral dominant sources could be compared on all levels. Unilateral non-dominant localized sources could only be compared for lateralization, unless all sources pointed to the same lobar (or sublobar region). Unilateral (lobar) scattered (MSI) result or unilateral (lobar) wide field (ESI) results could be compared for lateralisation (and lobar level). Concordance was defined as lateralisation to the same side, localization to the same lobar region and/or localisation to the same sub-lobar region.

3.4.3 Comparison of source localization with EZ-hypothesis

Thirdly, MEG and HD-EEG source localization was compared to the hypothesis concerning the localization of the EZ made during the epilepsy surgery meeting (i.e. based on the results of the different investigations performed during the presurgical evaluation including video-EEG, 3T MRI, FDG-PET, neuropsychological examination and any other additional test) by a multidisciplinary epilepsy surgery team within Ghent University Hospital. When the EZ-hypothesis was incomplete for sublobar and/or lobar level, the EZ-hypothesis was only compared to the source localization results respectively for lobar and/or lateralization level. MSI and ESI results were only compared to the EZ-hypothesis for the levels (lateralization level and/or lobar level and/or sublobar level) that were possible (see above: 4.4.2). When the EZ-hypothesis was narrower than the irritative zone determined by MSI or ESI (sublobar level),

the EZ hypothesis was still concordant with the MSI or ESI result. Concordance was again defined as lateralisation to the same side, localization to the same lobar region and/or localisation to the same sub-lobar region.

3.4.4 Comparison of source localization with epilepsy surgery

Finally, if surgery was performed it was possible to compare MEG and HD-EEG source localization with the resection zone. The resected region could only been compared on the level the resection took place (lateralization, lobar or sublobar level) MSI and ESI results could only be compared to the resected region for lateralization, lobar level and/or sublobar level, if it was possible (see above 4.4.2). Concordance was defined as described above (4.4.3). The EZ was considered resected if the patient was seizure free after surgery.

3.4.5 Statistics

The generalized estimating equation model was used to evaluate the possible IED-detection difference between MEG and HD-EEG, the possible difference in localization between MSI and ESI and the possible difference in concordance between MSI and ESI when compared to the EZ-hypothesis. Every time the estimated odds ratio with its 95% confidence interval was calculated.

4 Results

4.1 IED detection

41 patients were included in this study, of which 22 (53.7%) females and 19 (46.3%) males. The **sensitivity** for **IED detection** was 61% (25/41 patients) for MEG, 73.2% (30/41 patients) for HD-EEG and for both modalities together 80.5% (33/41 patients) (Table 2).

The estimated odds ratio for IED detection ($\frac{P\ detection\ MEG / P\ no\ detection\ MEG}{P\ detection\ \ HD-EEG / P\ no\ detection\ HD-EEG}$) was 0.573 with a 95% confidence interval of [0.281 - 1.169], which was not significant.

Table 2 - Percentages of patients with or without IED detection by MEG and HD-EEG

IED detection	**MEG**	**HD-EEG**
Yes	61.0 % (25/41)	73.2 % (30/41)
No	39.0 % (16/41)	26.8 % (11/41)

Table 3 - Overview of number of patients per epilepsy type (based on the EZ-hypothesis) for IED detection by MEG alone, HD-EEG alone, by neither of these tests or by both modalities

IED-detection	**ETNE**	**mTLE**	**TLE (INH)**	**mTLE + TNE**	**ETNE + mTLE**	**NLE**	**MFE**	**WHE**	**Total**
MEG + / HD-EEG -	0	2	0	0	0	1	0	0	3
MEG - / HD-EEG +	4	0	1	0	0	3	0	0	8
MEG - / HD-EEG -	3	1	0	0	0	3	1	0	8
MEG + / HD-EEG +	8	3	3	1	1	5	0	1	22
Total	15	6	4	1	1	12	1	1	

ETLE = extra-temporal neorcortical epilepsy; TNE = temporal neocortical epilepsy; mTLE = mesial temporal lobe epilepsy; TLE = temporal lobe epilepsy; INH = incomplete hypothesis; NLE = non-localizing epilepsy; MFE = multifocal epilepsy; WHE = whole hemisphere epilepsy

4.1.1 IED detection by MEG alone

IEDs were detected only by MEG and not by HD-EEG in three of the 41 patients (7.3%) (Table 4). Two of those patients suffered from mesial temporal lobe epilepsy and one from non-localizing epilepsy (Table 3). One of the three patients had a detectable lesion on the MRI (hippocampal sclerosis). The location of this lesion corresponded to the location of the recorded IEDs.

Table 4 - Patients with IED detection only by MEG

Patient	Gender	MEG IEDloc	HD-EEG IEDloc	MRI	Diagnosis
7	F	L P (D)	No	No	NLE (L)
14	M	ND (L FT / R FT)	No	No	R mTLE
15	M	L (F)T	No	HS - L T	L mTLE

IEDloc = localization of the sensors/electrodes on which he IEDs were detected; Diagnosis was based on the EZ-hypothesis; F = female; M = male; L = left; R = right; T = temporal; F = frontal; P = parietal; D = dominant IEDs; ND = non-dominant IEDs; HS = hippocampal sclerosis; NLE = non-localizing epilepsy; mTLE = mesial temporal lobe epilepsy

4.1.2 IED detection by HD-EEG alone

In eight of the 41 patients (19.5%), IEDs were only recorded with HD-EEG (Table 5). One of those patients had temporal lobe epilepsy (incomplete EZ-hypothesis), two had frontal lobe epilepsy, two had occipital lobe epilepsy and three had non-localizing epilepsy (Table 3). In four of the eight patients a lesion was detected on the MRI of which a heterotopia, a MRI status after surgery (ganglioglioma resection) with a fluid filled resection cavity and gliotic changes, a focal cortical dysplasia and a brain development disorder (polymicrogyria or focal cortical dysplasia). The region of the detected IEDs corresponded to the region of the lesion on the MRI in two of the four patients.

Table 5 - Patients with IED detection only by HD-EEG

Patient	Gender	MEG IEDloc	HD-EEG IEDloc	MRI	Diagnosis
2	M	No	R T	HT - R O	R OLE
6	F	No	L T	SAS (FFRC + GL) - L T	L TLE
8	F	No	ND (BL F / L F / R F)	No	NLE
16	F	No	L POS	No	L OLE
19	F	No	L FT	No	L FLE
23	F	No	L F	FCD - L LL	NLE
31	M	No	R CF	DD - R F	R FLE
35	M	No	L T	No	NLE (L)

IEDloc = localization of the sensors/electrodes on which he IEDs were detected; Diagnosis was based on the EZ-hypothesis; F = female; M = male; L = left; R = right; BL = bilateral; T = temporal; F = frontal; O = occipital; C = central; POS = posterior; LL = limbic lobe; ND = non-dominant IEDs; HT = heterotopia; SAS = status after surgery; FFRC = fluid filled resection cavity; GL = gliosis; FCD = focal cortical dysplasia; DD = developmental disorder; NLE = non-localizing epilepsy; TLE = temporal lobe epilepsy; FLE = frontal lobe epilepsy; OLE = occipital lobe epilepsy

4.1.3 No IED detection by MEG and HD-EEG

No IEDS were detected by either MEG or HD-EEG in eight of the 41 patients (19.5%) (Table 6). One of those patients was suffering from mesial temporal lobe epilepsy, one from frontal lobe epilepsy, one from parietal lobe epilepsy, one from insular epilepsy, one from multifocal epilepsy and three from non-localizing epilepsy (Table 3). Three of the eight patients had a MRI lesion of which a hippocampal sclerosis, a MRI status after surgery

(amygdalohippocampectomy) with parenchyma defect and adjacent gliosis and an atrophic insula.

Table 6 - Patients with no IED detection by MEG and HD-EEG

Patient	Gender	MEG IEDloc	HD-EEG IEDloc	MRI	Diagnosis
5	F	No	No	No	NLE
12	M	No	No	No	R PLE
22	F	No	No	HS - L T	L mTLE
28	F	No	No	SAS (PD + GL) - R T	NLE (R)
29	F	No	No	AT - L IN	L INE
34	F	No	No	No	MFE
40	F	No	No	No	NLE
41	M	No	No	No	FLE

IEDloc = localization of the sensors/electrodes on which he IEDs were detected; Diagnosis was based on the EZ-hypothesis; F = female; M = male; L = left; R = right; T = temporal; IN = insula; HS = hippocampal sclerosis ; SAS = status after surgery; PD = parenchyma defect; GL = gliosis; AT = atrophy; NLE = non-localizing epilepsy; mTLE = mesial temporal lobe epilepsy; FLE = frontal lobe epilepsy; PLE = parietal lobe epilepsy; INE = insular epilepsy; MFE = multifocal epilepsy

4.1.4 IED detection by MEG and HD-EEG

In 22 of the 41 patients (53.7%) IEDs were detected by both modalities (Table 8). Seven of those patients were diagnosed with temporal lobe epilepsy (of which three with mesial temporal lobe epilepsy), six with frontal lobe epilepsy, one with parietal lobe epilepsy, one with occipital lobe epilepsy, five with non-localizing epilepsy, one with epilepsy at the level of the whole right hemisphere (atrophic right hemisphere) and one with frontotemporal epilepsy (Table 3).

In 19 patients, both MEG and HD-EEG identified unilateral unique or unilateral (non-)dominant IEDs. The lateralization was never non-concordant in those patients (Table 7). In the other three patients, bilateral IEDs were detected by one (patient #9 and 13) of both modalities (patient #32). 14 patients had unique or dominant unilateral lobe IED detection by MEG and HD-EEG. In 10 of those 14 patients, IED detection was concordant on a lobar level. The four other patients showed lobar non-concordance for IED detection. Five patients had unilateral non-dominant IEDs for MEG (patient #4, 20, 37 and 39) or HD-EEG (patient #21).

A MRI lesion was found in 14 of the 22 patients. In five of the 10 patients with lobar concordance, the location of the MRI lesion corresponded to the location of the recorded IEDs. Four patients with lobar concordance were MRI negative.

Table 7 - Percentages of patients with or without IED detection concordance between MEG and HD-EEG for lateralisation and lobar level

Concordance	Lateralisation	Lobar level
Yes	46.3 % (19/41)	24.4 % (10/41)
No	0 % (0/41)	9.8 % (4/41)
N/A	53.7 % (22/41)	65,9 % (27/41)

N/A = not applicable

Table 8 - Patients with IED detection by both MEG and HD-EEG

Patient	Gender	MEGied	HD-EEGied	Conlat	Conlob	MRI	Diagnosis
1	M	R (F)T	R (F)T	Yes	Yes	GL- R T	R mTLE
3	M	L T (D)	L T	Yes	Yes	GL + PD - L O	L OLE
4	M	L Poly (ND)	L T	Yes	/	No	NLE (L)
9	F	L F	BL C	/	/	No	R PLE
10	F	R (F)T (D)	R TP	Yes	No	AT - R	R WHE
11	M	L FT	L FT (D)	Yes	Yes	No	L TLE
13	M	BL Poly FT (ND)	L Poly FT (ND)	/	/	GL - L FT	L FTE
17	M	R FT (D)	R FT (D)	Yes	Yes	No	R FLE
18	F	R POT (D)	R POT (D)	Yes	Yes	No	NLE
20	F	L Poly FTP (ND)	L F (D)	Yes	/	HT - L F	L FLE
21	M	L (F)PT (D)	L ND (F / T)	Yes	/	Global AT	NLE (L)
24	M	R FT	R FT (D)	Yes	Yes	HR - R T	NLE (R)
25	M	L FT	L CF	Yes	No	FCD + GL - L F	L FLE
26	F	R FT (D)	R FT (D)	Yes	Yes	HSI + CT - R T	R TLE
27	M	R FT	R CP (D)	Yes	No	SAS (HSI) - R F	R FLE
30	F	L T	L FT (D)	Yes	No	No	L TLE
32	F	BL Poly (ND)	BL CF (D)	/	/	PD - L F	L FLE
33	M	R FT	R FT (D)	Yes	Yes	SAS (GL) - R T	R TLE
36	F	R FT	R FT	Yes	Yes	T2 LE - R T	R mTLE
37	F	L ND (F / LH)	L F (D)	Yes	/	SAS (PL + HSI) - L F	L FLE

38	M	L T	L T	Yes	Yes	No	L mTLE
39	F	R ND (FT / TP)	R FT	Yes	/	No	NLE (R)

IEDloc = localization of the sensors/electrodes on which he IEDs were detected; Conlat = concordance on lateralization level; Conlob = concordance on lobar level; Diagnosis was based on the EZ-hypothesis; F = female; M = male; L = left; R = right; BL = bilateral; T = temporal; F = frontal; O = occipital; P = parietal; C = central; Poly = polymorphic IEDs; D = dominant IEDs; ND = non-dominant IEDs; GL = gliosis; PD = parenchyma defect; AT = atrophy; HT = heterotopia; HR = hippocampal residual; FCD = focal cortical dysplasia; HSI = hemosiderosis; CT = cystic transformation SAS = status after surgery; T2 LE = lesion on T2 image; PL = parenchyma loss; DD = developmental disorder; NLE = non-localizing epilepsy; TLE = temporal lobe epilepsy; FLE = frontal lobe epilepsy; PLE = parietal lobe epilepsy; OLE = occipital lobe epilepsy: WHE = whole hemisphere epilepsy; FTE = frontotemporal epilepsy

4.2 Source localization

Source localization could been performed in 33 of the 41 patients for one or both modalities (Table 14). The **sensitivity** for **localization** was 46.3 % (19/41) for MSI, 70.7 % (29/41) for ESI and 78.0 % (32/41) for both modalities together (Table 9).

The estimated odds for localization with MSI was 0.394 times the estimated odds for localization by means of ESI, with a significant 95 % confidence interval of [0.185 - 0.841]. The localization results for each epilepsy type are displayed in table 10.

Table 9 - Percentages of patients with or without localization by MSI and ESI in all patients

Localization	**MSI**	**ESI**
Yes	46.3 % (19/41)	70.7 % (29/41)
No	53.7 % (22/41)	29.3 % (12/41)

Table 10 - Overview of number of patients per epilepsy type (based on the EZ-hypothesis) for localization by MSI alone, ESI alone, by neither of these tests or by both modalities

Localization	**ETNE**	**mTLE**	**TLE (INH)**	**mTLE + TNE**	**ETNE + mTLE**	**NLE**	**MFE**	**WHE**	**Total**
MSI + / ESI -	0	2	0	0	0	1	0	0	3
MSI - / ESI +	5	0	3	0	0	3	0	0	11
MSI - / ESI -	3	1	0	0	0	4	1	0	9
MSI + / ESI +	7	3	1	1	1	4	0	1	18
Total	15	6	4	1	1	12	1	1	

ETNE = extra-temporal neorcortical epilepsy; TNE = temporal neocortical epilepsy; mTLE = mesial temporal lobe epilepsy; TLE = temporal lobe epilepsy; INH = incomplete hypothesis; NLE = non-localizing epilepsy; MFE = multifocal epilepsy; WHE = whole hemisphere epilepsy

In 21 of 22 patients (of who had both MEG and HD-EEG IED detection), source localization was performed for both MEG and HD-EEG. Although patient #20 had detection of IEDs by both modalities, source localization was too complex to be modelled for MEG. MSI and ESI results were concordant on **lateralization** level in 19 patients (Table 11, 12 and 13). In one patient (#9), the source lateralization result was non-concordant. In another patient (#32), the MSI result was bilateral scattered and the ESI result was bilateral dominant localized. **Lobar**

concordance and non-concordance for MSI and ESI was seen in respectively 11 and six of the 21 patients. In two patients (#37 and 39), the MSI results were unilateral non-dominantly clustered. One non-dominant cluster (superior frontal) was concordant with the ESI result (frontal cingulate cortex) on a lobar level (but not on a sublobar level) in patient #37. In patient #39, the ESI (anterior temporal) result was concordant on a sublobar level with the MSI result of one non-dominant cluster. Patient #4 had a unilateral scattered and a unilateral lobar wide field result for MEG and HD-EEG respectively. Concordance testing on a **sublobar** level was possible in 15 of the 21 patients. In seven patients, the source localization results were concordant on this sublobar level. Patient #11 and 33 both had unilateral lobar scattered results for MSI. In five of the seven patients with sublobar concordance, the location of the MRI lesion corresponded to the location of the MSI and ESI result. In patient #24 the location of the MSI and ESI result (insula and superior temporal) were not corresponding with the location of the MRI lesion (hippocampal residual). One patient (#38) suffered from MRI negative epilepsy.

Table 11 - Percentages of patients with or without source localisation concordance between MEG and HD-EEG for lateralisation, lobar level and sublobar level

Concordance	Lateralisation	Lobar level	Sublobar level
Yes	46.3 % (19/41)	26.8 % (11/41)	17.1 % (7/41)
No	2.4 % (1/41)	14.6 % (6/41)	19.5 % (8/41)
N/A	51.2 % (21/41)	58.5 % (24/41)	63.4 % (26/41)

N/A = not applicable

Table 12 - Percentages of patients (only patients in whom both MSI and ESI was performed) with or without source localisation concordance between MEG and HD-EEG for lateralisation, lobar level and sublobar level

Concordance	Lateralisation	Lobar level	Sublobar level
Yes	90.5 % (19/21)	52.4 % (11/21)	33.3 % (7/21)
No	4.8 % (1/21)	28.6 % (6/21)	38.1 % (8/21)
N/A	4.8 % (1/21)	19,0 % (4/21)	28.6 % (6/21)

N/A = not applicable

Table 13 - Percentages of patients (only patients in whom comparison was possible between MSI and ESI) with or without source localisation concordance between MEG and HD-EEG for lateralisation, lobar level and sublobar level

Concordance	Lateralisation	Lobar level	Sublobar level
Yes	95.0 % (19/20)	64.7 % (11/17)	46.7 % (7/15)
No	5 % (1/20)	35.3 % (6/17)	43.3 % (8/15)

Table 14 - Comparison of MSI and ESI results for lateralization, lobar level and sublobar level in patients with MEG and/or HD-EEG source localisation

Patient	MSI	ESI	Conlat	Conlob	Consub
1	R sT + orF (DS)	R mT + aT	Yes	No	No
2	No	R aT	/	/	/
3	L (a-p)T (DS)	L IN (TP)	Yes	No	No
4	L SC (mT / lT / TP junction)	L T (WF)	Yes	/	/
6	No	L lT + (mT)	/	/	/
7	L PO (DS)	No	/	/	/
8	No	NDS (L mT / R mT / BL P CC)	/	/	/
9	L FP SMC	R CP	No	No	No
10	R pT (DS)	R pbT	Yes	Yes	No
11	L T SC	L mT + aT (DS)	Yes	Yes	/
13	L iF	L pmT (NDS - point to the same region)	Yes	No	No
14	R NDS (iF / pT)	No	/	/	/
15	L mT + aT	No	/	/	/
16	No	L mO	/	/	/
17	R iF (DS)	R mT + pIN (DS)	Yes	No	No
18	R pTO + iTO (DS)	R pTO + iTO (DS)	Yes	Yes	Yes
19	No	L IN (FT)	/	/	/
20	No (IED detection but source localization too complex to be modelled)	L F PFC (DS)	/	/	/
21	L pT + iP (DS)	L IN (FT; NDS - point to the same region)	Yes	No	No
23	No	L mT	/	/	/
24	R sT + IN	R sT + IN (DS)	Yes	Yes	Yes
25	L F PMC + SMA	L F PMC + SMA	Yes	Yes	Yes
26	R mT + pT + lT (DS)	R mT + pT + lT (DS)	Yes	Yes	Yes
27	R F (near resection cavity)	R F (near resection cavity; DS)	Yes	Yes	Yes
30	L mT	L aT (DS)	Yes	Yes	No
31	No	L F (at the level of the structural abnormality)	/	/	/
32	BL SC	BL CP (more L than R; DS)	/	/	/
33	R T SC	R mT + (lT) (DS)	Yes	Yes	/
35	No	L mT + aT	/	/	/
36	R mT	R mT	Yes	Yes	Yes
37	L NDS (sF / F SMA + P)	L F CC (DS)	Yes	/	/

38	L mT	L mT	Yes	Yes	Yes
39	R NDS (aT / F operculum + iF gyrus / P)	R aT	Yes	/	/

MSI = magnetic source imaging result; ESI = electric source imaging result; Conlat = concordance on lateralization level; Conlob = concordance on lobar level; Consub = concordance on a sublobar level; L = left; R = right; BL = bilateral; T = temporal; F = frontal; O = occipital; P = parietal; C = central; IN = insula; s = superior; i = inferior; a = anterior; p = posterior; b = basal; or = orbital; m = mesial; l = lateral; CC = cingulate cortex; PFC = prefrontal cortex; PMC = premotor cortex; SMA = supplementary motor area; SMC = sensorimotor cortex; DS = dominant source; NDS = non-dominant source; SC = scattered; WF = wide field

4.3 Comparison of source localization with EZ-hypothesis

In 24 and 30 of the 41 patients source localization was performed for MEG and HD-EEG respectively (Table 24 and 25). Both the MSI and ESI results were concordant with the EZ-hypothesis on **lateralization level** in almost all patients (except for patient #9) in who MSI and ESI could be compared (Table 15, 16 and 17). In patients #9, the MSI and ESI result were respectively non-concordant and concordant with the EZ-hypothesis. In three patients (#8, 18 and 23), no hypothesis could be made based on the presurgical evaluation. Patient #32 had a bilateral scattered MSI result and a bilateral dominant ESI result.

Table 15 - Percentages of patients with or without concordance between the MSI and ESI results and the EZ-hypothesis for lateralization

Concordance lateralization	**MSI-EZ**	**ESI-EZ**
Yes	51.2 % (21/41)	63.4 % (26/41)
No	2.4 % (1/41)	0.0 % (0/41)
N/A	46.3 % (19/41)	36.6 % (15/41)

N/A = not applicable

Table 16 - Percentages of patients (only patients in whom MSI and/or ESI was performed) with or without concordance between the MSI and ESI results and the EZ-hypothesis for lateralization

Concordance lateralization	**MSI-EZ**	**ESI-EZ**
Yes	87.5 % (21/24)	86.7 % (26/30)
No	4.2 % (1/24)	0.0 % (0/30)
N/A	8.3 % (2/24)	13.3 % (4/30)

N/A = not applicable

Table 17 - Percentages of patients (only patients in whom comparison was possible between the EZ-hypothesis and the source localisations results) with or without concordance between the MSI and ESI results and the EZ-hypothesis for lateralization

Concordance lateralization	**MSI-EZ**	**ESI-EZ**
Yes	95.4 % (21/22)	100,0 % (26/26)
No	4.5 % (1/22)	0.0 % (0/26)

MEG and HD-EEG source localization was concordant with the EZ hypothesis on a **lobar level** in respectively 11 and 16 patients (Table 18, 19 and 20). Non-concordance was perceived in three (MSI) and four (ESI) patients. In six patients (#4, 7, 21, 24, 35 and 39), an incomplete hypothesis was only formulated on lateralization level. MSI results were non-localized on a lobar level (unilateral scattered or unilateral NDC) in four patients (#4, 14, 37 and 39). Patient #10 had whole hemisphere atrophy, so both the MSI and ESI could only be compared at lateralization level.

The estimated odds for concordance on a lobar level for MSI was 16.6 % lower than for ESI with a 95 % confidence interval of [0.196 – 3.544], which was not significant.

Table 18 - Percentages of patients with or without concordance between the MSI and ESI results and the EZ-hypothesis for lobar level

Concordance lobar level	**MSI-EZ**	**ESI-EZ**
Yes	26.8 % (11/41)	39.0 % (16/41)
No	7.3 % (3/41)	9.8 % (4/41)
N/A	65.9 % (27/41)	51.2 % (21/41)

N/A = not applicable

Table 19 - Percentages of patients (only patients in whom MSI and/or ESI was performed) with or without concordance between the MSI and ESI results and the EZ-hypothesis for lobar level

Concordance lobar level	**MSI-EZ**	**ESI-EZ**
Yes	45.8 % (11/24)	53.3 % (16/30)
No	12.5 % (3/24)	13.3 % (4/30)
N/A	41.7 % (10/24)	33.3 % (10/30)

N/A = not applicable

Table 20 - Percentages of patients (only patients in whom comparison was possible between the EZ-hypothesis and the source localisations results) with or without concordance between the MSI and ESI results and the EZ-hypothesis for lobar level

Concordance lobar level	**MSI-EZ**	**ESI-EZ**
Yes	78.6 % (11/14)	80.0 % (16/20)
No	21.4 % (3/14)	20.0 % (4/20)

On a **sublobar level**, MSI and ESI were concordant with the EZ hypothesis in seven (MEG) and nine (HD-EEG) patients (Table 21, 22 and 23). Non-concordant results were found in three (MEG) and two patients (HD-EEG). In nine patients (#2, 6, 11, 16, 17, 20, 30, 33 and 37), a hypothesis was only formulated on a lobar level. MSI results were scattered in one lobe (localization only on lobar level) in two patients (#11 and 33).

The estimated odds for concordance on a sublobar level for MSI is 60.4 % lower than for ESI with an insignificant 95 % confidence interval of [0.090 - 1.754].

Table 21 - Percentages of patients with or without concordance between the MSI and ESI results and the EZ-hypothesis for sublobar level

Concordance sublobar level	MSI-EZ	ESI-EZ
Yes	17.1 % (7/41)	22.0 % (9/41)
No	7.3 % (3/4)	4.9 % (2/41)
N/A	75,6 % (31/41)	73.2 % (30/41)

N/A = not applicable

Table 22 - Percentages of patients (only patients in whom MSI and/or ESI was performed) with or without concordance between the MSI and ESI results and the EZ-hypothesis for sublobar level

Concordance sublobar level	MSI-EZ	ESI-EZ
Yes	29.2 % (7/24)	30.0 % (9/30)
No	12.5 % (3/24)	6.7 % (2/30)
N/A	58.3 % (14/24)	63.3 % (19/30)

N/A = not applicable

Table 23 - Percentages of patients (only patients in whom comparison was possible between the EZ-hypothesis and the source localisations results) with or without concordance between the MSI and ESI results and the EZ-hypothesis for sublobar level

Concordance sublobar level	MSI-EZ	ESI-EZ
Yes	70.0 % (7/10)	81.8 % (9/11)
No	30.0 % (3/10)	18.2 % (2/11)

In five of the seven patients (#25, 26, 27, 36, and 38) with **concordant sublobar MSI and ESI results**, the EZ hypothesis was concordant with the source localization on a sublobar level. Three of those patients suffered from temporal lobe epilepsy (of which two with mesial temporal lobe epilepsy) and two from frontal lobe epilepsy. Four patients had corresponding MRI positive epilepsy. One patient had MRI negative epilepsy. Patient #18 and #24 had respectively no or an incomplete hypothesis (only lateralization) despite the concordant MEG and ESI results. Both the MSI and ESI corresponded to the lateralization of the EZ-hypothesis (right) in patient #24.

Patients with **non-concordant sublobar MSI and ESI results** had varying concordance results when compared with the EZ-hypothesis on a sublobar level. In two patients (#1 and 9), the EZ-hypothesis was only concordant with the ESI results. These patients had MRI positive mesial temporal lobe epilepsy and MRI negative parietal epilepsy. In patient #3, who suffered from MRI positive occipital lobe epilepsy, the EZ-hypothesis was non-concordant with both the MSI and ESI result. Patient #10 suffered from whole right hemisphere atrophy (see above). In patient #13 (MRI positive) the MSI (left inferior frontal) and ESI (left posterior mesial temporal) results each pointed to a part of the EZ-hypothesis (left frontal operculum and left posterior mesial temporal). Patient #17, 21 and 30 had all an incomplete hypothesis. In patient #17 (MRI negative) the EZ-hypothesis on a lobar level (left occipital) only corresponded to the MSI result. The EZ-hypothesis was only defined on lateralization level (left) in patient #21 (MRI negative) which corresponded to both the MSI and ESI result. Patient #30 (MRI positive) had an EZ-

hypothesis on a lobar level (left temporal), which was concordant with both the MSI and ESI results.

For patients #7, 14 and 15, **source localization** could **only** be **performed by MEG**. In patient #7, an incomplete hypothesis on lateralization level (left) corresponded to the MSI lateralization. The MSI result was non-dominantly clustered in patient #14. The EZ-hypothesis (right mesial temporal) of this patient was only concordant with one cluster (right posterior temporal) on a lobar level (not on a sublobar level). The MSI result of patient #15 was concordant with the EZ-hypothesis (left mesial temporal) on a sublobar level.

Most of the patients with **source localization only performed by HD-EEG** had an incomplete hypothesis. For patients #8 and 23 no EZ-hypothesis could be formulated. Patient #35 had an incomplete hypothesis on lateralization level (left), which corresponded to the ESI lateralization. In patients #2, 6 and 16, an EZ-hypothesis could only be defined on a lobar level. The ESI-EZ results were concordant in patients #6 (left temporal) and 16 (left occipital). In patient #2 the hypothesis (right occipital) was non-concordant with the ESI result (right anterior temporal). Only patient #19 and 31 had a complete hypothesis on a sublobar level, which was respectively non-concordant (left frontal supplementary motor area vs left insular) and concordant (left frontal around the resection area) with the HD-EEG source localization results.

Table 24 - Concordance between MSI results and EZ-hypothesis for lateralization, lobar and sublobar level in patients with MEG source localization

Patient	MSI	Hypothesis	Conlat	Conlob	Consublob
1	R sT + orF (DS)	R mT	Yes	No	No
3	L (a-p)T (DS)	L O (around calcarine sulcus)	Yes	No	No
4	L SC (mT / lT / TP Junction)	L H (INH)	Yes	/	/
7	L PO (DS)	L H (INH)	Yes	/	/
9	L FP SMC	R CP	No	No	No
10	R pT (DS)	Whole R H	Yes	/	/
11	L T SC	L T (INH)	Yes	Yes	/
13	L iF	L F (operculum) + mpT	Yes	Yes (partially)	Yes (partially)
14	R NDS (iF / pT)	R mT	Yes	/	/
15	L mT + aT	L mT	Yes	Yes	Yes
17	R iF (DS)	R F (INH)	Yes	Yes	/
18	R pTO + iTO	No Hypothesis	/	/	/
21	L pT + iP (DS)	L H (INH)	Yes	/	/
24	R sT + IN	R H (INH)	Yes	/	/
25	L F PMC + SMA	L F SMA	Yes	Yes	Yes
26	R mT + pT + lT (DS)	R T (around post-traumatic injury)	Yes	Yes	Yes
27	R F (near resection cavity)	R F (posterior margin resection cavity)	Yes	Yes	Yes

30	L mT	L T (INH)	Yes	Yes	/
32	BL SC	L F (area of post-traumatic damage)	/	/	/
33	R T SC	R T (INH)	Yes	Yes	/
36	R mT	R mT	Yes	Yes	Yes
37	L NDS (sF / F SMA + P)	L F (INH)	Yes	/	/
38	L mT	L mT	Yes	Yes	Yes
39	R NDS (aT / F operculum + iF gyrus / P)	R H (INH)	Yes	/	/

MSI = magnetic source imaging result; Conlat = concordance on lateralization level; Conlob = concordance on lobar level; Consub = concordance on a sublobar level; L = left; R = right; BL = bilateral; H = hemisphere T = temporal; F = frontal; O = occipital; P = parietal; C = central; IN = insula; s = superior; i = inferior; a = anterior; p = posterior; or = orbital; m = mesial; l = lateral; PMC = premotor cortex; SMA = supplementary motor area; SMC = sensorimotor cortex; DS = dominant source; NDS = non-dominant source; SC = scattered; INH = incomplete hypothesis

Table 25 - Concordance between ESI results and EZ-hypothesis for lateralization, lobar and sublobar level in patients with HD-EEG source localization

Patient	ESI	Hypothesis	Conlat	Conlob	Consublob
1	R mT + aT	R mT	Yes	Yes	Yes
2	R aT	R O (INH)	Yes	No	/
3	L IN (TP)	L O (around calcarine sulcus)	Yes	No	No
4	L T (WF)	L H (INH)	Yes	/	/
6	L lT + (mT)	L T (INH)	Yes	Yes	/
8	NDS (L mT / R mT / BL P CC)	No hypothesis	/	/	/
9	R CP	R CP	Yes	Yes	Yes
10	R pbT	Whole L H	Yes	/	/
11	L mT + aT (DS)	L T (INH)	Yes	Yes	/
13	L pmT (NDS - point to the same region)	L F + pmT	Yes	Yes (partially)	Yes (partially)
16	L mO	L O (INH)	Yes	Yes	/
17	R mT + pIN (DS)	R F (INH)	Yes	No	/
18	R pTO + iTO (DS)	No Hypothesis	/	/	/
19	L IN (FT)	L F (SMA)	Yes	No	No
20	L F PFC (DS)	L F (INH)	Yes	Yes	/
21	L IN (FT; NDS - point to the same region)	L H (INH)	Yes	/	/
23	L mT	No hypothesis	/	/	/
24	R sT + lN (DS)	R H (INH)	Yes	/	/
25	L F PMC + SMA	L F SMA	Yes	Yes	Yes
26	R mT + pT + lT (DS)	R T (around post-traumatic injury)	Yes	Yes	Yes
27	R F (near resection cavity; DS)	R F (posterior margin resection cavity)	Yes	Yes	Yes

30	L aT (DS)	L T (INH)	Yes	Yes	/
31	L F (at the level of the structural abnormality)	L F (at the level of the structural abnormality)	Yes	Yes	Yes
32	BL CP (more L than R; DS)	L F (area of post-traumatic damage)	/	/	/
33	R mT + (lT) (DS)	R T (INH)	Yes	Yes	/
35	L mT + aT	L H (INH)	Yes	/	/
36	R mT	R mT	Yes	Yes	Yes
37	L F CC (DS)	L F (INH)	Yes	Yes	/
38	L mT	L mT	Yes	Yes	Yes
39	R aT	R H (INH)	Yes	/	/

ESI = electric source imaging result; Conlat = concordance on lateralization level; Conlob = concordance on lobar level; Consub = concordance on a sublobar level; L = left; R = right; BL = bilateral; H = hemisphere; T = temporal; F = frontal; O = occipital; P = parietal; C = central; IN = insula; s = superior; i = inferior; a = anterior; p = posterior; or = orbital; m = mesial; l = lateral; b = basal; CC = cingulate cortex; PFC = prefrontal cortex; PMC = premotor cortex; SMA = supplementary motor area; DS = dominant source; NDS = non-dominant source; WF = wide field; INH = incomplete hypothesis

4.4 Comparison of source localization with epilepsy surgery

Seven of the 41 patients underwent epilepsy surgery (Table 26 and 27). Three patients (#25, 26 and 27) with concordant MSI and ESI results had corresponding surgery in the same region (sublobar). All three patients were seizure free after the surgery. Patient #25 underwent a topectomy at the level of the left supplementary motor area (SMA), which was narrower than the concordant MSI and ESI results that included the left premotor cortex and the left SMA. The resection (topectomy of posterior resection border right frontal) in patient #27 was again narrower than the concordant MSI and ESI result (resection border right frontal, but uncertainty about which flank(s) were part of the EZ). Patient #26 had an extensive resection right temporal (partly determined by intraoperative electrocorticography) around the post-traumatic lesion (hemosiderosis and cystic transformation) and a right amygdalohippocampectomy. This resected region corresponded with the location of the concordant MSI and ESI result. In patient #1 only the ESI (right mesial temporal) result was concordant with the resected zone (right amygdalohippocampectomy). This patient was seizure free after surgery. Only HD-EEG source localization could been performed in patient #19. Although the patient was seizure free after surgery, the ESI result (left insular) and resected region (topectomy at the level of the left SMA) were non-concordant on a lobar and sublobar level. Patient #13 and 14 were both not seizure free after the resection. In patient # 13 the MSI (left inferior frontal) and ESI (left posterior mesial temporal) result pointed both to another part of the resected region (left hippocampal resection and left frontobasal topectomy). Patient #14 had a non-dominant clustered result for MSI, and ESI could not been performed. The two clustered (right inferior frontal and right posterior temporal) MSI results were not concordant with the resected zone (right amygdalohippocampectomy) on a sublobar level.

Table 26 - Concordance between MSI results and resected region for lateralization, lobar and sublobar level in patients whom had surgery and MSI

Patient	MSI	Resection region	Seizure free	Conlat	Conlob	Consub
1	R sT + orF (DS)	Right amygdalo-hippocampectomy	Yes	Yes	No	No
13	L iF	Left hippocampal resection + left frontobasal topectomy	No	Yes	Yes (partially)	Yes (partially)
14	R NDS (iF / pT)	Right amygdalo-hippocampectomy	No	Yes	/	/
19	No	Topectomy at the level of the left SMA	Yes	/	/	/
25	L F PMC+ SMA	Topectomy at the level of the left SMA	Yes	Yes	Yes	Yes
26	R mT + pT + lT (DS)	Resection right temporal around lesion + right amygdalo-hippocampectomy	Yes	Yes	Yes	Yes
27	R F (near resection cavity)	Topectomy at the level of the posterior border of the resection cavity right frontal	Yes	Yes	Yes	Yes

MSI = magnetic source imaging result; Conlat = concordance on lateralization level; Conlob = concordance on lobar level; Consub = concordance on a sublobar level; L = left; R = right; T = temporal; F = frontal; s = superior; i = inferior; p = posterior; or = orbital; m = mesial; l = lateral; PMC = premotor cortex; SMA = supplementary motor area; DS = dominant source; NDS = non-dominant source

Table 27 - Concordance between MSI results and resected region for lateralization, lobar and sublobar level in patients whom had surgery and MSI

Patient	ESI	Dissected region	Seizure free	Conlat	Conlob	Consub
1	R mT + aT	Right amygdalo-hippocampectomy	Yes	Yes	Yes	Yes
13	L pmT	Left hippocampal resection + frontobasal topectomy	No	Yes	Yes (partially)	Yes (partially)
14	No	Right amygdalo-hippocampectomy	No	/	/	/
19	L IN (FT)	Topectomy at the level of the left SMA	Yes	Yes	No	No
25	L F PMC + SMA	Topectomy at the level of the left SMA	Yes	Yes	Yes	Yes
26	R mT + pT + lT (DS)	Resection right temporal around lesion + right amygdalo-hippocampectomy	Yes	Yes	Yes	Yes
27	R F (near resection cavity; DS)	Topectomy at the level of the posterior border of the resection cavity right frontal	Yes	Yes	Yes	Yes

ESI = electric source imaging result; Conlat = concordance on lateralization level; Conlob = concordance on lobar level; Consub = concordance on a sublobar level; L = left; R = right; T = temporal; F = frontal; IN = insula; a = anterior; p = posterior; m = mesial; l = lateral; PMC = premotor cortex; SMA = supplementary motor area; DS = dominant source

5 Discussion

MEG and HD-EEG are two investigations that can be used in the presurgical evaluation of patients with refractory epilepsy. They both detect IEDs by picking up the electrical or magnetic fields generated by abnormal epileptic activity in the brain. Subsequently, source localization can be performed to determine the irritative zone [39]. In this study, the sensitivity for IED detection and source localization accuracy was assessed retrospectively between one-hour 306-channel MEG and 128-channel HD-EEG in 41 patients with refractory epilepsy. The main advantage of the design of this study in comparison to other studies was the use of a higher number of electrodes for HD-EEG, because higher spatial sampling leads to a more accurate source localization [37]. Consequently, MEG and HD-EEG could be compared in a more correct way.

MEG and HD-EEG showed no significant difference in **sensitivity** for **detection of IEDs**. However, more patients had unique IED-detection by HD-EEG than with MEG. Previous studies also reported that MEG and (HD-) EEG had similar sensitivity for IED-detection [26, 29, 30]. Iwasaki et al. compared a 122-channel MEG to a 23-channel EEG and found no significant difference for IED-detection. IEDs were detected in both EEG and MEG in 31, in MEG alone in eight, in EEG alone in one, and in neither modality in three of a total of 43 patients [26]. Heers et al. made a comparison between a 74-channel MEG and a 32-channel EEG after sleep deprivation (EEGsd) and showed an insignificant difference in detection of IEDs. MEG recorded IEDs in 38/63 patients, while EEGsd recorded IEDs in only 32/63 patients [29]. Knake et al. used a 306-channel MEG in comparison to a 70-channel HD-EEG set-up. Again, the IED detection results were not significantly different between MEG and HD-EEG. The overall sensitivity to detect IEDs was 72% for MEG and 61% for EEG [30]. In contrast to the IED-detection results of this study, more patients had MEG only IED-detection than HD-EEG only IED-detection in all of these studies. Unique detection of IEDs by MEG or HD-EEG can be explained by a difference in characteristics. As mentioned earlier, (HD-)EEG is much more prone to distortion caused by differences in conductivity [22]. On the other hand, MEG detects mainly superficial sources, because magnetic signals degrade as they are located deeper in the brain [25]. Furthermore, MEG detects exclusively tangential sources, while (HD-) EEG is more sensitive to radial sources. However, a broad range of sources have an orientation that has both a tangential and radial part, which makes it possible that both MEG and (HD-) EEG can detect these sources [26]. Among the 41 patients in this study, three patients had MEG only detection and eight patients had HD-EEG only detection. Two of the three patients with MEG-only detection had presumed mesial temporal lobe epilepsy. Previous literature is inconsistent regarding MEG sensitivity for IEDs in patients with mesial temporal lobe epilepsy. Some authors indicate that mesial temporal sources are difficult to detect, while other authors contradict this finding [36]. In the patients with HD-EEG only detection, four had presumed extra-temporal epilepsy of whom two with frontal lobe epilepsy and two with occipital lobe epilepsy. Potentially, IEDs in these regions were radial in orientation, which could explain why MEG did not detect those sources. One patient with HD-EEG only detection had presumed temporal lobe epilepsy with uncertainty about the precise location of the EZ within this temporal lobe. Literature suggest that HD-EEG can better detect lateral temporal sources than mesial temporal sources [36]. IEDs were detected by MEG and HD-EEG in more than half of the patients in this study. Only 14 patients could be compared for concordance on a lobar level, of whom 10 patients showed **lobar concordance** for **IED detection**. This result can be interpreted as indicating that MEG and HD-EEG can detect the same IEDs despite the difference in detection properties, as previously discussed. Other studies with simultaneous MEG and HD-EEG reported the same phenomena. One of the limitations of this study was that MEG and HD-EEG were not simultaneously recorded (see below) [30, 31].

The **MSI** results were **concordant** with the **ESI** results on a **lobar level** in 26.8% of all patients. This low percentage can be explained by a high number of patients (58.5%) in whom MSI

results and ESI results could not been compared or where missing. In patients in whom comparison was possible, 64.7% had concordant MSI and ESI results. On a **sublobar level**, 46.6% of the patients in whom source localization could been compared showed concordant ESI and MSI results (17.1% in all patients). Furthermore, the **sensitivity for localization** on a sublobar level was significantly different between MSI (19/41) in comparison to ESI (29/41). Park et al. compared a 153-channel MEG to a 70-channel HD-EEG (simultaneous) in terms of source localization. MSI and ESI results where concordant on a lobar level in 90.0% of the patients in whom source localization could been compared [38]. This percentage (90.0%) is much higher than the result (64.7%) of this study. This discrepancy could been explained by difference in methods such as the use of the same or different source localization models for MEG and HD-EEG and whether or not MEG and HD-EEG where simultaneously recorded.

No significant difference was found between concordance rates of MSI and ESI when compared to the EZ hypothesis both at a lobar and sublobar level. **MSI** results were concordant with the **EZ hypothesis** in 78.5% (11/14 patients; 26.8% in all patients) of the patients in whom the MSI results could be compared with the EZ hypothesis at the **lobar level**. On a **sublobar level**, the MSI and the EZ-hypothesis were concordant in 70% (7/10 patients: 17.1% in all patients) of the patients in whom comparison was possible. Park et al. found that 100.0% of the patients in whom the MSI results were compared with presurgical evaluation had concordant results on a lobar level. However, in patients with temporal lobe epilepsy, the distribution of the dipoles was wider over lateral and whole temporal regions. Furthermore, they found a concordance rate of 80% for MSI (4/5 patients) at the sublobar level when compared only with intracranial EEG results (part of the presurgical evaluation) [40]. Other studies also reported high concordance rates between intracranial EEG and MSI [41, 42]. The **EZ hypothesis** was concordant with the **ESI** result on a **lobar level** in 80.0% (16/20 patients; 39.0% in all patients) of the patients in whom comparison was possible. For the **sublobar level**, this was 81.8% (9/11 patients; 22.0% in all patients). A concordance rate at the lobar level of 96.3 % between the result of the presurgical evaluation and ESI was perceived by Park et al [38]. Other studies with fewer electrodes reported similar concordance rates [43, 44]. Park et al. found a concordance rate at the sublobar level between ESI and intracranial EEG of 88.9% (8 of 9 patients) [38]. Again, other studies reported similar concordance rates between ESI and intracranial EEG [45, 46]. In this study, it was not possible to compare MSI and ESI to intracranial EEG because there were only a few patients who underwent this investigation. Therefore, MSI and ESI could only be compared to the EZ hypothesis that was determined also by the MSI and ESI results together with results of other presurgical investigations. This limitation could lead to an important bias. A recent study investigated clinical utility of combined electromagnetic source localization. This study renders promisingly results in localization accuracy in comparison with other presurgical techniques [47].

Patients (#1, 3 and 9) with sublobar **non-concordant MSI** results in comparison to the **EZ-hypothesis** had presumed mesial temporal lobe epilepsy, occipital lobe epilepsy and centroparietal epilepsy respectively. As mentioned before, literature is contradictory about MSI and the possibility to detect mesial temporal sources. In addition, some studies suggest that horizontal anterior temporal ECDs present mesial temporal sources [48]. In patient #3, who had presumable occipital epilepsy, the non-dominant cluster (left occipital) was well concordant with the EZ-hypothesis, in contrast to the dominant cluster (left temporal). In patient #9, who had presumable centroparietal epilepsy, the pathophysiological character of the discharges was not entirely clear, so the MEG result should be interpreted with caution. Two patients (#2 and 3) with presumable occipital lobe epilepsy had on a sublobar level **non-concordant ESI** results compared to the **EZ-hypothesis.** In patient #3, however, a burst was perceived left occipital. Two other patients (#17 and 19) with presumable frontal lobe epilepsy had also non-concordant results when comparing the ESI results to the EZ-hypothesis.

Patients with sublobar **concordant MSI** results when compared to the **EZ-hypothesis** had presumable temporal lobe epilepsy (four), of which three mesial temporal epilepsy, frontal lobe

epilepsy (two) and frontotemporal lobe epilepsy (one). Of the nine patients with sublobar **concordant ESI** results in comparison to the **EZ-hypothesis,** four had presumable temporal lobe epilepsy of which three with mesial temporal lobe epilepsy, three had frontal lobe epilepsy, one had frontotemporal epilepsy and one had centroparietal epilepsy. Ossenblok et al. found that MSI (151 channel-MEG) is superior in localizing the possible epileptogenic zone in comparison to ESI (71 channel-EEG) in frontal lobe epilepsy patients. In this study, ESI had one concordant result (patient #31) more than MSI in patients with frontal lobe epilepsy when compared to the EZ-hypothesis on a sublobar level. MEG could not detect IEDs in this patient. Two patients (#36 and 38) with mesial temporal lobe epilepsy had concordant results in both MSI and ESI when compared to the EZ-hypothesis on a sublobar level. Two other patients (#1 and 15) had concordant results either in MSI or in ESI. These results indicate that both techniques can be useful in patients with frontal lobe epilepsy and mesial temporal lobe epilepsy.

In three of the seven patients who had **surgery**, the **MSI** result was concordant with the resection area on a sublobar level. All of these three patients were seizure free after surgery. However, one patient with non-concordant MSI (right superior temporal and orbitofrontal) and resected area (right amygdalo-hippocampectomy) was seizure free. **ESI** was concordant with the resected region in four patients on a sublobar level. Again, all of these four patients were seizure free after surgery. One patients was seizure free, in which the ESI (left insula) and resected area (topectomy at the level of the left SMA) were non-concordant. Another patient in whom MSI and ESI were both partially concordant with the resected area was not seizure free after surgery. As mentioned before MSI (left inferior frontal) and ESI (left posterior mesial temporal) pointed both to another part of the resected zone (left hippocampal resection and frontobasal topectomy) in this patient. Therefore, concordance between MSI/ESI results and the surgical region could indicate seizure freedom. In three of the four patients who were seizure free the MSI and ESI results were concordant with each other. This result indicates that concordant MSI and ESI results could even better predict seizure freedom. Comparison to the resection area is considered the ultimate standard for localization accuracy, because if patients are seizure-free after surgery it is certain that the epileptogenic zone was resected. Therefore, several studies compared MSI and ESI to the resected region taking into account the surgical outcome. Mouthaan et al. performed a systematic review about the diagnostic accuracy of MSI and ESI (HD-EEG). Eleven studies were included among which eight MSI studies and three ESI studies. They found a sensitivity 87% and 79% respectively for MSI and ESI. These sensitivities did not show statistical difference. However, a statistical difference between the concordant and non-concordant group regarding good surgical outcome probability was found for both MSI and ESI [39]. The results of this review correspond to the findings of this study.

Several **limitations** should be considered in this study. First of all, MEG and HD-EEG data were recorded separately. Therefore, the exact correspondence of the IEDs could not been in investigated in time. Moreover, the detection of IEDs in one modality can sometimes lead to the detection in the other modality [49]. Further research is necessary to examine high channel MEG and high channel HD-EEG but then simultaneously. Secondly, the used source localization models were different for MEG and HD-EEG. In the future, studies should compare MSI and ESI using the same source localization models, so that the comparison can be more accurate. Thirdly, only patients with both MEG and HD-EEG investigations were included in this study. MEG and HD-EEG testing occurs often only in patients in whom it is difficult to formulate an EZ hypothesis, which could lead to selection bias. Fourthly, only seven patients underwent epilepsy surgery, so no statistical analysis could be performed for MSI and ESI in comparison to the resection area and the surgical outcome. The other statistical analyses were also performed on a relative small number of patients. Finally, the recordings of both MEG and HD-EEG lasted only one hour (standard in practice), so patients with infrequent IEDs could have no detection or detection of only a few IEDs.

6 Conclusion

MEG and HD-EEG can both detect IEDs with a relatively high sensitivity. In this study, no difference was found between MEG and HD-EEG for IED detection. Although, some patients had IED-detection only by MEG or HD-EEG. Furthermore, MSI and ESI results were well concordant with the EZ-hypothesis. Again, no difference was found between MSI and ESI for localization accuracy on lobar and sublobar level. In certain patients, only MSI or ESI was concordant with the EZ-hypothesis. In the few patients that underwent surgery, good surgical outcomes were linked to MSI/ESI results that were concordant with the resection zone.

Based on the results of this study, it is shown that a combination of MEG and HD-EEG within the presurgical evaluation remains useful because some individual patients may benefit only from a MEG or HD-EEG investigation. Nevertheless, within this study-population it was not possible to specify which modality for which patient group is best suited. Larger, prospective, studies are needed to examine the usefulness of MEG and HD-EEG for specific groups of epilepsy patients.

7 Reference list

1. Spinoza Centre (2018) 256-channel EEG. https://www.spinozacentre.nl/resources/eeg/
2. Carrette E, Vonck K, Boon P (2014) Magentoencefalografie en epilepsie. *(2014) TIJDSCHRIFT VOOR NEUROLOGIE EN NEUROCHIRURGIE*
3. Rowan AJ (1998) Reflections on the treatment of seizures in the elderly population. *Neurology* **51**: S28-33
4. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J, Jr. (2005) Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* **46**: 470-2
5. Carette E (2011) The Optimization of the Presurgical Evaluation of Patients with Refractory Epilepsy. In Faculty of Medicine and Health Sciences, Ghent University
6. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J, Jr., Forsgren L, French JA, Glynn M*, et al.* (2014) ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* **55**: 475-82
7. Singh A, Trevick S (2016) The Epidemiology of Global Epilepsy. *Neurol Clin* **34**: 837-847
8. Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, Hirsch E, Jansen FE, Lagae L, Moshé SL*, et al.* (2017) Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia* **58**: 531-542
9. Middlebrooks EH, Ver Hoef L, Szaflarski JP (2017) Neuroimaging in Epilepsy. *Current Neurology and Neuroscience Reports* **17**: 32
10. Das N, Dhanawat M, Shrivastava SK (2012) An overview on antiepileptic drugs. *Drug Discov Ther* **6**: 178-93
11. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshe SL, Perucca E, Wiebe S, French J (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* **51**: 1069-77
12. Laxer KD, Trinka E, Hirsch LJ, Cendes F, Langfitt J, Delanty N, Resnick T, Benbadis SR (2014) The consequences of refractory epilepsy and its treatment. *Epilepsy Behav* **37**: 59-70
13. Rosenow F, Lüders H (2001) Presurgical evaluation of epilepsy. *Brain* **124**: 1683-1700
14. Lopez Gonzalez FJ, Rodriguez Osorio X, Gil-Nagel Rein A, Carreno Martinez M, Serratosa Fernandez J, Villanueva Haba V, Donaire Pedraza AJ, Mercade Cerda JM (2015) Drug-resistant epilepsy: definition and treatment alternatives. *Neurologia* **30**: 439-46
15. Iwasaki M, Jin K, Nakasato N, Tominaga T (2016) Non-invasive Evaluation for Epilepsy Surgery. *Neurologia medico-chirurgica* **56**: 632-640
16. Schulze-Bonhage A, Zentner J (2014) The preoperative evaluation and surgical treatment of epilepsy. *Deutsches Arzteblatt international* **111**: 313-319
17. Tripathi M, Ray S, Chandra PS (2016) Presurgical evaluation for drug refractory epilepsy. *International Journal of Surgery* **36**: 405-410
18. Ryvlin P, Rheims S (2008) Epilepsy surgery: eligibility criteria and presurgical evaluation. *Dialogues in clinical neuroscience* **10**: 91-103
19. Rathore C, Radhakrishnan K (2015) Concept of epilepsy surgery and presurgical evaluation. *Epileptic Disord* **17**: 19-31; quiz 31
20. Wang G, Worrell G, Yang L, Wilke C, He B (2011) Interictal spike analysis of high-density EEG in patients with partial epilepsy. *Clin Neurophysiol* **122**: 1098-105
21. Chu CJ (2015) High density EEG-what do we have to lose? *Clin Neurophysiol* **126**: 433-4
22. Staljanssens W (2018) EEG Source Connectivity for Seizure Onset Zone Localisation in Epilepsy In Faculty of Engineering and Architecture, Ugent
23. He B, Yang L, Wilke C, Yuan H (2011) Electrophysiological imaging of brain activity and connectivity-challenges and opportunities. *IEEE Trans Biomed Eng* **58**: 1918-31
24. Montes-Restrepo V, Carrette E, Strobbe G, Gadeyne S, Vandenberghe S, Boon P, Vonck K, Mierlo Pv (2016) The Role of Skull Modeling in EEG Source Imaging for Patients with Refractory Temporal Lobe Epilepsy. *Brain Topography* **29**: 572-589
25. Kharkar S, Knowlton R (2015) Magnetoencephalography in the presurgical evaluation of epilepsy. *Epilepsy & Behavior* **46**: 19-26
26. Iwasaki M, Pestana E, Burgess RC, Luders HO, Shamoto H, Nakasato N (2005) Detection of epileptiform activity by human interpreters: blinded comparison between electroencephalography and magnetoencephalography. *Epilepsia* **46**: 59-68
27. Lin YY, Shih YH, Hsieh JC, Yu HY, Yiu CH, Wong TT, Yeh TC, Kwan SY, Ho LT, Yen DJ*, et al.* (2003) Magnetoencephalographic yield of interictal spikes in temporal lobe epilepsy. Comparison with scalp EEG recordings. *Neuroimage* **19**: 1115-26

28. Ramantani G, Boor R, Paetau R, Ille N, Feneberg R, Rupp A, Boppel T, Scherg M, Rating D, Bast T (2006) MEG versus EEG: influence of background activity on interictal spike detection. *J Clin Neurophysiol* **23**: 498-508
29. Heers M, Rampp S, Kaltenhauser M, Pauli E, Rauch C, Dolken MT, Stefan H (2010) Detection of epileptic spikes by magnetoencephalography and electroencephalography after sleep deprivation. *Seizure* **19**: 397-403
30. Knake S, Halgren E, Shiraishi H, Hara K, Hamer HM, Grant PE, Carr VA, Foxe D, Camposano S, Busa E*, et al.* (2006) The value of multichannel MEG and EEG in the presurgical evaluation of 70 epilepsy patients. *Epilepsy Res* **69**: 80-6
31. Ossenblok P, de Munck JC, Colon A, Drolsbach W, Boon P (2007) Magnetoencephalography is more successful for screening and localizing frontal lobe epilepsy than electroencephalography. *Epilepsia* **48**: 2139-49
32. Hunold A, Funke ME, Eichardt R, Stenroos M, Haueisen J (2016) EEG and MEG: sensitivity to epileptic spike activity as function of source orientation and depth. *Physiol Meas* **37**: 1146-62
33. Nissen IA, Stam CJ, Citroen J, Reijneveld JC, Hillebrand A (2016) Preoperative evaluation using magnetoencephalography: Experience in 382 epilepsy patients. *Epilepsy Res* **124**: 23-33
34. Brodbeck V, Spinelli L, Lascano AM, Wissmeier M, Vargas M-I, Vulliemoz S, Pollo C, Schaller K, Michel CM, Seeck M (2011) Electroencephalographic source imaging: a prospective study of 152 operated epileptic patients. *Brain* **134**: 2887-2897
35. De Tiège X, Carrette E, Legros B, Vonck K, Op de beeck M, Bourguignon M, Massager N, David P, Van Roost D, Meurs A*, et al.* (2012) Clinical added value of magnetic source imaging in the presurgical evaluation of refractory focal epilepsy. **83**: 417-423
36. Gavaret M, Maillard L, Jung J (2015) High-resolution EEG (HR-EEG) and magnetoencephalography (MEG). *Neurophysiologie Clinique/Clinical Neurophysiology* **45**: 105-111
37. Lantz G, Grave de Peralta R, Spinelli L, Seeck M, Michel CM (2003) Epileptic source localization with high density EEG: how many electrodes are needed? *Clin Neurophysiol* **114**: 63-9
38. Park CJ, Seo JH, Kim D, Abibullaev B, Kwon H, Lee YH, Kim MY, An KM, Kim K, Kim JS*, et al.* (2015) EEG Source Imaging in Partial Epilepsy in Comparison with Presurgical Evaluation and Magnetoencephalography. *J Clin Neurol* **11**: 319-30
39. Mouthaan BE, Rados M, Boon P, Carrette E, Diehl B, Jung J, Kimiskidis V, Kobulashvili T, Kuchukhidze G, Larsson PG*, et al.* (2019) Diagnostic accuracy of interictal source imaging in presurgical epilepsy evaluation: A systematic review from the E-PILEPSY consortium. *Clin Neurophysiol* **130**: 845-855
40. Boroujeni ME, Gardaneh M, Shahriari MH, Aliaghaei A, Hasani S (2017) Synergy Between Choroid Plexus Epithelial Cell-Conditioned Medium and Knockout Serum Replacement Converts Human Adipose-Derived Stem Cells to Dopamine-Secreting Neurons. *Rejuvenation Res* **20**: 309-319
41. Almubarak S, Alexopoulos A, Von-Podewils F, Wang ZI, Kakisaka Y, Mosher JC, Bulacio J, González-Martínez J, Bingaman W, Burgess RC (2014) The correlation of magnetoencephalography to intracranial EEG in localizing the epileptogenic zone: A study of the surgical resection outcome. *Epilepsy Res* **108**: 1581-1590
42. Englot DJ, Nagarajan SS, Imber BS, Raygor KP, Honma SM, Mizuiri D, Mantle M, Knowlton RC, Kirsch HE, Chang EF (2015) Epileptogenic zone localization using magnetoencephalography predicts seizure freedom in epilepsy surgery. *Epilepsia* **56**: 949-958
43. Michel CM, Lantz G, Spinelli L, De Peralta RG, Landis T, Seeck M (2004) 128-channel EEG source imaging in epilepsy: clinical yield and localization precision. *J Clin Neurophysiol* **21**: 71-83
44. Sperli F, Spinelli L, Seeck M, Kurian M, Michel CM, Lantz G (2006) EEG source imaging in pediatric epilepsy surgery: a new perspective in presurgical workup. *Epilepsia* **47**: 981-90
45. Abdallah C, Maillard LG, Rikir E, Jonas J, Thiriaux A, Gavaret M, Bartolomei F, Colnat-Coulbois S, Vignal JP, Koessler L (2017) Localizing value of electrical source imaging: Frontal lobe, malformations of cortical development and negative MRI related epilepsies are the best candidates. *NeuroImage: Clinical* **16**: 319-329
46. Rikir E, Koessler L, Gavaret M, Bartolomei F, Colnat-Coulbois S, Vignal JP, Vespignani H, Ramantani G, Maillard LG (2014) Electrical source imaging in cortical malformation-related epilepsy: A prospective EEG-SEEG concordance study. *Epilepsia* **55**: 918-932
47. Duez L, Tankisi H, Hansen PO, Sidenius P, Sabers A, Pinborg LH, Fabricius M, Rásonyi G, Rubboli G, Pedersen B*, et al.* (2019) Electromagnetic source imaging in presurgical workup of patients with epilepsy. *Neurology* **92**: e576
48. Carrette E, Op De Beeck M, Bourguignon M, Boon P, Vonck K, Legros B, Goldman S, Van Bogaert P, De Tiège X (2011) Recording temporal lobe epileptic activity with MEG in a light-weight magnetic shield. *Seizure* **20**: 414-418

49. Zijlmans M, Huiskamp GM, Leijten FS, Van Der Meij WM, Wieneke G, Van Huffelen AC (2002) Modality-specific spike identification in simultaneous magnetoencephalography/electroencephalography: a methodological approach. *J Clin Neurophysiol* **19**: 183-91