FACULTY OF MEDICINE AND HEALTH SCIENCES

Validation of the accuracy of Magnetic Source Imaging based on intracranial recordings and post-operative results

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

Academic year: 2020 – 2021

Preface

First of all, I would like to thank my promotor Prof. Dr. Evelien Carrette for the guidance provided during the last two years. She stood by me with a wonderful mix of confidence invested in me to autonomously let me set foot in the world of academia, while at the same time providing recommendations and feedback whenever in need. The results of this collaboration can be discovered in this master's dissertation.

In addition, I want to thank my parents who have been so patient with me pending my meandering interests and have allowed me the opportunity to discover where these truly lay.

My best friends, Julie and Febe, my brothers, Joachim and Wolfgang, and Margot, who have provided me with feedback, walks, talks and relaxing evenings.

Finally, I would like to thank Sander, who has provided me with so much support, laughter and love over the years, I could not begin to grasp his contribution to the past years in general and this work specifically. As did his perpetually stocked fridge to cater my every craving.

Contents

Summary

Objective: To retrospectively validate the accuracy of Magnetic Source Imaging (MSI) to localize the irritative zone (IZ), seizure onset zone (SOZ) and epileptogenic zone (EZ) defined in the presurgical epilepsy evaluation. Reference localizations were provided by their gold standard: intracranial electroencephalography (ICEEG) for both the IZ and SOZ, and the resection cavity in seizure free patients for the EZ. Qualitative and quantitative comparisons were performed.

Methods: Sixteen patients who underwent magnetoencephalography (MEG), ICEEG and resective surgery were enrolled. MSI cluster localization was performed and concordance with the IZ, SOZ and EZ on a lobar and sublobar level were determined. The accuracy was determined by calculating the mean distance between the MSI cluster and the IZ, SOZ and EZ. Results were compared between patients with good surgical outcome (Engel = I) and poor surgical outcome (Engel > I).

Results: MSI cluster localization showed sublobar concordance with the IZ in 94% of patients, the accuracy to detect the IZ was 18.4mm. MSI cluster localization compared to the SOZ showed concordance in 69% of patients and a mean distance of 28.9mm. This distance was significantly different from the distance between the MSI cluster and the IZ ($p \leq 0.01$). MSI cluster localization with the EZ showed sublobar concordance in 75% of patients and had an accuracy of 14.2mm. No differences in regional sensitivity of MEG could be identified.

Conclusion: Magnetoencephalography can be employed to reliably indicate the IZ, SOZ and EZ, thereby justifying its use in the presurgical epilepsy evaluation.

Introduction

Epilepsy is a common neurological disorder, which can cause highly debilitating seizures. Although many types of anti-epileptic drugs (AEDs) are available, these fail to provide adequate seizure control in about one third of patients[1]; so-called refractory epilepsy patients. For some of these, epilepsy surgery may however be able to provide seizure freedom. The goal of resective surgery is to completely remove or disconnect the epileptogenic zone – the area consisting of tissue indispensable for generating clinical seizures[2]. Its location and extent have to be inferred through approximation, based on the definition of different cortical zones which can be measured. In this thesis, both the irritative zone and the seizure onset zone will be investigated. The irritative zone is the area of cortex responsible for generating interictal spikes or interictal epileptiform discharges (IEDs)[2]. It often overlaps with the seizure onset zone but is generally more extensive. The seizure onset zone is the area of cortex from which clinical seizures arise[2]. However, removal of the seizure onset zone will not necessarily provide seizure freedom: it is possible that a second seizure onset zone with a higher threshold for epileptic activity is present in the same epileptogenic zone. After removal of the primary seizure onset zone, this secondary seizure onset zone may cause seizures[2].

Surgical candidates are assessed in a presurgical epilepsy evaluation to determine suitability for resection and the localization of the epileptogenic tissue. Results of different testing modalities are reviewed at a multidisciplinary staff meeting. If a patient undergoes surgical resection and becomes seizure free, it is concluded that the epileptogenic zone is removed as (part of) the resected area[2].

In some patients, standard testing modalities may not provide sufficient information on the localization of the epileptogenic zone. These may require additional testing. One such a non-invasive modality is magnetoencephalography (MEG), which measures the magnetic fields produced by the electrical activity of the pyramidal neurons[3]. Because magnetic fields are perpendicular to the current by which they are caused, MEG can be used complementary to electroencephalography (EEG) by measuring activity mainly in the sulcal walls as opposed to on top of the gyral crests and in the sulcal depths[3,4]. After recording the MEG data, magnetic source imaging (MSI) can be performed. This is a computational method that attempts to co-localize sources of interictal activity to the patients' MRI. Interictal spikes are identified by a specialist and through single equivalent current dipole (ECD) modelling, a theoretical electrical discharge is calculated which best explains the registered magnetic fields[3]. Multiple ECDs that localize closely together form a cluster.

Intracranial EEG is the gold standard method to measure both the irritative zone and seizure onset zone thanks to its excellent spatial resolution[2,5]. Implantation of depth electrodes and subdural grids and/or strips eliminates distortion of the electric signal by the scalp, skull and dura[6]. Due to the invasive nature of ICEEG, the technique does pose serious medical risks such as hemorrhage, stroke and infections which increase with implantation of more electrodes and prolonged duration of implantation[7]. This limits sampling capacity[7], thereby demonstrating the importance of conveying an appropriate hypothesis for electrode implantation at the multidisciplinary staff meeting. If the seizure onset zone is not covered, the invasive procedure might be unsuccessful[8] or activity at the edge of a grid might be localized unreliably leading to faulty removal of cortical tissue[7]. This demonstrates the need for accurate, non-invasive testing modalities to assess the epileptogenic zone which can either reduce the need for ICEEG or guide electrode placement to ensure optimal sampling.

This master's dissertation will investigate the role of magnetic source imaging in the presurgical evaluation of refractory epilepsy patients. More specifically its accuracy to identify the irritative zone, seizure onset zone and epileptogenic zone will be examined. In addition, it will be investigated whether this accuracy correlates with surgical outcome. To this account, a retrospective study of a clinical patient population in the Reference Center for Refractory

Epilepsy at Ghent University Hospital will be performed. Comparable studies have been carried out in the past, however, the specific aims of this study might provide novel insights into matters on which no consensus exists. Additionally, examining the results obtained at this specific center presents an opportunity to situate these relative to those obtained at analogous specialized centers.

1.1 Epilepsy

The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) defined an epileptic seizure in 2005 as: *"An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain"*[9]. The symptoms produced by this abnormal neuronal activity depend on the site of origin and it's connections[10]. They also formulated a definition for epilepsy[9], which was revised in 2014 by the ILAE to be more suitable for use in clinical practice:

Epilepsy is a disease of the brain defined by any of the following conditions:

1. *At least two unprovoked (or reflex) seizures occurring >24 h apart*
2. *One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years*
3. *Diagnosis of an epilepsy syndrome*

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years[11].

Even with this revised definition, correct diagnosis of epilepsy can be hard to attain. Many forms of epilepsy exist and even though seizures are usually stereotyped within patients, these present very heterogenous between patients. Further complicating diagnosis is the absence of symptoms when the patient is not having a seizure. Therefore, the clinician must often rely on a description of the symptoms by the patient or witnesses, or the accidental observation of a seizure[12]. Another complicating factor is the existence of several acute brain conditions such as stroke or head trauma which may cause epileptic seizures, but do not qualify for a diagnosis of epilepsy[10]. These are termed 'acute symptomatic seizures'[12] and the distinction relies on the difference between unprovoked and provoked non-reflex seizures, with the latter temporarily reducing seizure threshold, but not presenting with an enduring susceptibility for seizures[10].

1.1.1 Epidemiology

In a 2003 review Sander, JW[12] estimated the prevalence of epilepsy based on eleven studies as four to ten cases per 1000 people and the incidence as 50 per 100 000 per year, depending on the geographic and socio-economic setting. Higher rates are reported in rural, resource-poor areas, with an incidence as high as 100 per 100 000 people per year. However, there is a great diagnostic gap and treatment gap in these countries[13]. The lifetime prevalence of epilepsy is a lot higher, with up to five percent of the population worldwide who will experience nonfebrile seizures at a certain point[12]. This disparity between prevalence and lifetime prevalence is mainly due to a good prognosis, with 60-70% of patients achieving long-term remission, usually within five years of diagnosis[12,14].

1.1.2 Classification

According to the ILAE's 2017 update of the classification of epilepsy, three levels can be assessed[15]. First is a classification of the seizure type, which must only be determined after a definite diagnosis of an epileptic seizure. These possible types include: 1) seizures of focal onset, originating within neural networks but limited to one hemisphere, 2) seizures being of generalized onset, arising within and rapidly engaging bilateral cortical or cortical-subcortical networks, and 3) seizures of unknown onset. Next is a classification of the type of epilepsy. This classification must only be performed after a definite diagnosis of epilepsy, as defined in 2014 by the ILAE[11]. Epilepsy can either be 1) focal, 2) generalized, 3) combined generalized

& focal, in patients who have both focal and generalized seizures, or 4) unknown. The third level requires a diagnosis of epilepsy syndromes, however this diagnosis may not be possible in many patients. An epilepsy syndrome may be characterized by a distinct set of traits such as age of onset, seizure type, EEG activity pattern, co-morbidities and prognosis.

A second classification is based on etiology. These include: structural, genetic, infectious, metabolic, immune or unknown etiology. This classification has strong implications for treatment and epilepsies may fall under multiple categories[15].

1.1.3 Risk factors

Risk factors depend both on a person's age and geographical location. Congenital, developmental and genetic risk factors are strongly associated with children and young adults. Cranial trauma, tumors and central nervous system infections can occur at any age. However, tumors are more common over the age of forty. Once over sixty, cerebrovascular accidents (CVA) are the most common risk factor[12]. Epilepsy caused by infection is mainly prevalent in certain resource-poor countries[12].

Genetic influence on epilepsy also varies greatly, with some known rare monogenic Mendelian epilepsies. However, in most epilepsies an intricate interplay between environmental factors, genetic susceptibility variants and common genetic variation is suspected[13].

1.1.4 Treatment

In treatment of epilepsy, anti-epileptic drugs (AEDs) are used to suppress seizures. A lot of different AEDs exist, each with its own mechanism of action. Even though the name contains the word anti-epileptic, current evidence suggests a merely anti-seizure effect[16,17]. It has been suggested that a large number of patients would enter into spontaneous remission, as can be observed in resource-poor countries where 80-94% of patients with active epilepsy do not receive AED treatment[18]. In a house-to-house survey carried out in northern rural Ecuador, 1029 people with definite or probable epilepsy were identified. 386 (37%) of these 1029 cases received anti-epileptic treatment at some point. Of the remaining 643 patients who never received treatment, 314 patients (49%) had inactive epilepsy, indicating seizure freedom in at least the last twelve months[19]. This provides support for the theory that remission may occur independent of AED treatment. Kwan and Sander propose to categorize prognosis into three broad groups of patients: 1) Excellent prognosis: about 20-30% of patients will enter long-term remission, presumably even without AEDs; 2) Remission with treatment only: about 20-30% of epilepsy patients will become seizure-free but only with AED treatment and seizures will recur if treatment is discontinued; 3) Continuing seizures despite treatment: about 30-40% of patients will have insufficient seizure suppression using AEDs, so-called refractory epilepsy patients[14]. Patients in this last category may benefit from non-pharmacological treatments such as surgery, ketogenic diet, vagal nerve stimulation or deep brain stimulation.

1.2 Refractory epilepsy

In 1993 it was estimated that about 30% of all epilepsy patients won't obtain adequate seizure control using AEDs[1]. A study by Kwan and Brodie followed 525 patients diagnosed with epilepsy in the Epilepsy Unit of the Western Infirmary in Glasgow, Scotland between January 1, 1984, and December 31, 1997[20]. 470 of these patients had never received AED treatment before. They observed that of these 470 patients, 222 patients (47%) became seizure free after treatment with a first AED. Another 61 patients became seizure free after monotherapy with a second AED. This number dropped to only 6 patients (1%) becoming seizure free on monotherapy with a third AED and 12 patients (3%) on a two-drug therapy. This so called drug-resistant or refractory epilepsy was more strictly defined in 2010 by a task force appointed by the ILAE:

"Drug resistant epilepsy may be defined 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"[21].

Predictors of refractory epilepsy are: more than ten seizures before treatment initiation, a familial history of epilepsy, febrile seizures, traumatic brain injury as the cause of epilepsy, recreational drug use and psychiatric comorbidity, especially depression[22]. Even though referral for surgical intervention is still rare, this caution is unwarranted as research has shown the immense superiority of resective surgery in seizure-free outcome over continued pharmacological treatment in medically refractory epilepsy patients[23]. Patients with refractory epilepsy have an increased risk of comorbid illness, psychological dysfunction, social stigmatization, overall reduced quality of life, increased risk of mortality and a decreased life expectancy[24]. Some controversy also remains on epilepsy as a progressive disorder. This inconsistency may be related to the heterogeneity of epilepsies, however, in the case of temporal lobe epilepsies, most evidence does suggest a progressive disorder. A rapid recognition of drug-resistant epilepsy and initiation of alternative treatment may thus decrease the risk of progressive structural, cognitive and behavioral damage[24].

1.3 Presurgical epilepsy evaluation

Patients under consideration for epilepsy surgery will undergo a presurgical evaluation to assess whether they are suitable candidates. The evaluation's goal is two-fold: to identify the tissue indispensable for generating seizures, *the epileptogenic zone*, and to identify a possible overlap of this epileptogenic zone with functional tissue, the eloquent cortex[2]. If surgery is pursued, the goal is to completely remove or disconnect this epileptogenic focus, which should provide seizure freedom. However, this zone is a theoretical construct and cannot be assessed directly through any diagnostic modality available[2]. Its location and extent have to be inferred through approximation, based on the definition of five different cortical zones which can be measured. The presurgical evaluation will thus attempt to delineate these cortical areas which can help guide surgical resection of the epileptogenic zone. These zones are: the irritative zone, the seizure onset zone, the symptomatogenic zone, the epileptogenic lesion and the functional deficit zone[2]. Every patient undergoes the following tests which will be described in some more detail below: prolonged video-EEG monitoring, magnetic resonance imaging, [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) and neuropsychological assessment[25].

1.3.1 Prolonged video-EEG monitoring

Prolonged video-EEG monitoring is performed in all surgical candidates and constitutes a very important tool in the presurgical evaluation. Patients are admitted to a specialized unit in the hospital where their neural activity is permanently monitored on an EEG and time-locked video is being recorded[25]. This allows for linking the seizure semiology to the electroencephalogram. Throughout the monitoring both ictal and interictal activity will be assembled, and if necessary, AED intake can be phased out to increase the chance of a habitual seizure. Inspection of the encephalogram allows for classification of the seizures and confirmation of the diagnosis. Based on the activation pattern of the electrodes, two zones described in the presurgical epilepsy evaluation can be identified with prolonged video-EEG monitoring: the irritative zone and the ictal onset zone. The *irritative zone* is the tissue responsible for generating interictal spikes[2]. These encephalographic spikes do not produce any symptoms but are considered the hallmark of epilepsy, even though their neurophysiological origin remains largely unknown[26]. The *seizure onset zone* is the tissue where the seizures originate[2], but is not necessarily equal to the epileptogenic zone. It is possible for the seizure onset zone to be more extensive than the epileptogenic zone. In this case, partial resection of the seizure onset zone may provide seizure freedom. On the other hand, it is also possible that a seizure onset zone with higher threshold for seizing activity is located within the same epileptogenic zone. In this case, the seizure onset zone with low threshold will be responsible for the habitual seizures, and can be measured with EEG. However, after resection of this seizure onset zone, the higher threshold one may become clinically apparent[2]. Finally, because the patient is also being video-recorded during video-EEG monitoring, it may also be possible to get an indication of the *symptomatogenic zone*. This is the tissue responsible for a patient's symptoms during a seizure and depending on its function, seizure semiology may provide considerable

information on localization or none at all. During a seizure, interaction with the patient is important to detect any negative symptoms[25]. It is important to note that the symptomatogenic zone does not necessarily overlap with the epileptogenic zone. In patients where the seizures arise in functionally silent tissue, seizure semiology may be but a reflection of ictal spread to symptomatically apparent regions[2].

1.3.2 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is used to identify structural abnormalities in the brain. Compared to computed tomography (CT) imaging, MRI has excellent sensitivity for soft tissue. This makes the technique suitable for detecting even small lesions. Today, the most common MRI scanners have a 1.5Tesla or 3.0Tesla magnetic field strength. With this increase in magnetic field strength, a higher signal-to-noise ratio is achieved[27]. A 3Tesla MRI scanner was estimated to be 2.57 times as likely to detect structural abnormalities than the 1.5Tesla scanner[27]. Many MRI sequences are available, each suited for visualization of specific interests. In patients with epilepsy, structural abnormalities may be possible *epileptogenic lesions*. However, it is important that MRI results are always considered in light of all results from the presurgical evaluation. A structural abnormality does not necessarily equal epileptogenic lesion, and may even be entirely unrelated[2].

1.3.3 [18F]-fluorodeoxyglucose positron emission tomography

In an FDG-PET scan, a radioactive glucose marker is injected intravenously into the patient's arm. This radioactive glucose will spread throughout the body and brain and allow for visualization of the cortical glucose metabolism. FDG-PET is performed interictally and detection of a hypometabolism shows the *functional deficit zone*[2]. The relationship of this zone to the epileptogenic zone is unclear because the presence of a metabolic deficit does not necessarily indicate epileptogenesis in the lesion[2]. Patients with multiple lesions may show several functional deficit zones despite only one being epileptogenic. Even if a lesion is epileptogenic, the functional deficit zone may extend far beyond the epileptogenic zone: in patients with mesial temporal lobe epilepsy, FDG-PET often shows an extensive hypometabolism reaching beyond the mesial temporal lobe, even if seizure-freedom was attained with resection limited to the mesial temporal lobe[2]. It is however a good indicator for lateralization of the epileptogenic zone and may suggest and help guide implantation of invasive electrodes in the case of strong discrepancies with other test results[25].

1.3.4 Neuropsychological assessment

All patients are subjected to a neuropsychological assessment which will perform an in depth analysis of cognitive functioning. Different subjects being tested include: language, verbal and non-verbal memory, visuo-spatial perception, somatosensory and motor capabilities, attention, cognitive speed and frontal lobe functioning[25]. Deficits may be indicative of the functional deficit zone. Furthermore, a patients presurgical status provides a baseline comparison to their postsurgical functioning for detection of any loss of function or occasionally improved functioning[25].

1.3.5 Multidisciplinary staff meeting

The results of these tests are reviewed at a multidisciplinary staff meeting to try and form a hypothesis about the exact location of the epileptogenic zone. This may result in a proposal for epilepsy surgery or for some patients demonstrate non-suitability for surgery. In more than 50% of patients however, these tests do not provide sufficient information for precise delineation of the epileptogenic zone. This may be due to a lack of abnormal findings, non-localizing, multifocal or incongruent results. In these patients additional techniques may be employed based on their specific results and seizure types[25].

1.3.6 Additional testing

Additional tests performed in light of the presurgical evaluation may include: ictal single photon emission computed tomography (SPECT), magnetoencephalography (MEG), EEG-functional MRI (EEG-fMRI), surface coil imaging, MR spectroscopy (MRS) and Wada test. These results

will often guide placement of intracranial electrodes for invasive EEG monitoring[25]. Both MEG and intracranial EEG (ICEEG) will be discussed in more detail later since they are the subject of this study.

1.4 Intracranial EEG

Some patients may require invasive EEG monitoring to determine localization of the epileptogenic zone. Intracranial EEG is the gold standard method to measure both the irritative zone and seizure onset zone[2,28]. An electrode implantation scheme is designed based on the results of the presurgical evaluation to more precisely check seizure origin. Through implantation of depth electrodes in the brain and placement of subdural grids and strips on the cortical surface, distortion of the electrical signal caused by the scalp, skull and dura can be eliminated[6] (Figure 1). Intracranial EEG therefore excels in spatial resolution. However, due to the invasive nature of the procedure, electrodes must be placed under careful consideration to avoid unnecessary risks. This leads to a limited sampling capacity of the brain and demonstrates the importance of conceiving a convincing hypothesis for electrode implantation at the multidisciplinary staff meeting[7]. If the seizure onset zone is not covered, this might render the invasive procedure fruitless, or activity at the edge of a grid might be localized unreliably leading to faulty or incomplete removal of cortical tissue[7,8]. Due to the invasive nature of ICEEG, the technique also poses serious medical risks such as hemorrhage, stroke and infections which increase with prolonged implantation of the electrodes[7]. During invasive EEG monitoring or intra-operatively, functional mapping may be performed. Using subdural electrodes, a small electrical stimulus is administered to a specific cortical area to see if a response is elicited, thus requiring the patient to be awake for this procedure[25]. This allows for identification of eloquent cortex in proximity of the hypothesized epileptogenic zone. Based on these results the most appropriate treatment can be suggested.

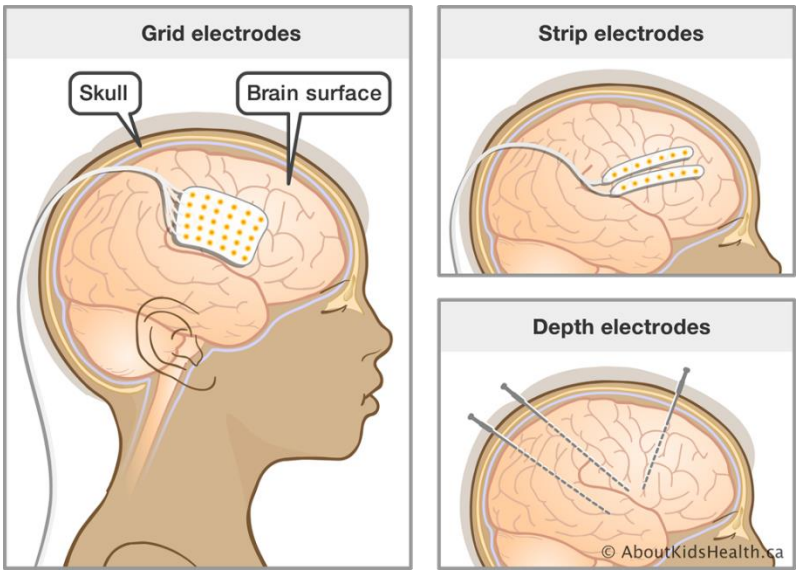

Figure 1 Intracranial electrode placement
Image property of AboutKidsHealth ©

1.5 Magnetoencephalography

Magnetoencephalography (MEG) is a non-invasive functional imaging method which measures magnetic induction generated by electrical activity of the brain. According to Ampère's right hand rule, every electrical current produces a perpendicular magnetic field. This magnetic field can be measured by a pick-up coil, part of the flux transformer in the MEG scanner, in which it will induce an electrical current proportional to its strength[29]. These magnetic fields are extremely small, measurable extracranially in the order of femtoTesla (10^{-15}), or about a factor 10^7 to 10^8 times smaller than the earth's magnetic field[29]. To be able to record this minuscule signal, superconducting quantum interference devices (SQUIDs) are used which are coupled to the brain's magnetic flux by means of the primary flux transformer[30]. These need to be cooled to a few degrees from absolute zero to achieve their superconducting effects and are therefore embedded in liquid helium. This allows electrons to pass the thin insulator in between two superconductors by means of quantum tunneling, thereby eliminating the impedance of the recording coil, which is an application of the Josephson effect[30,31] (Figure 2).

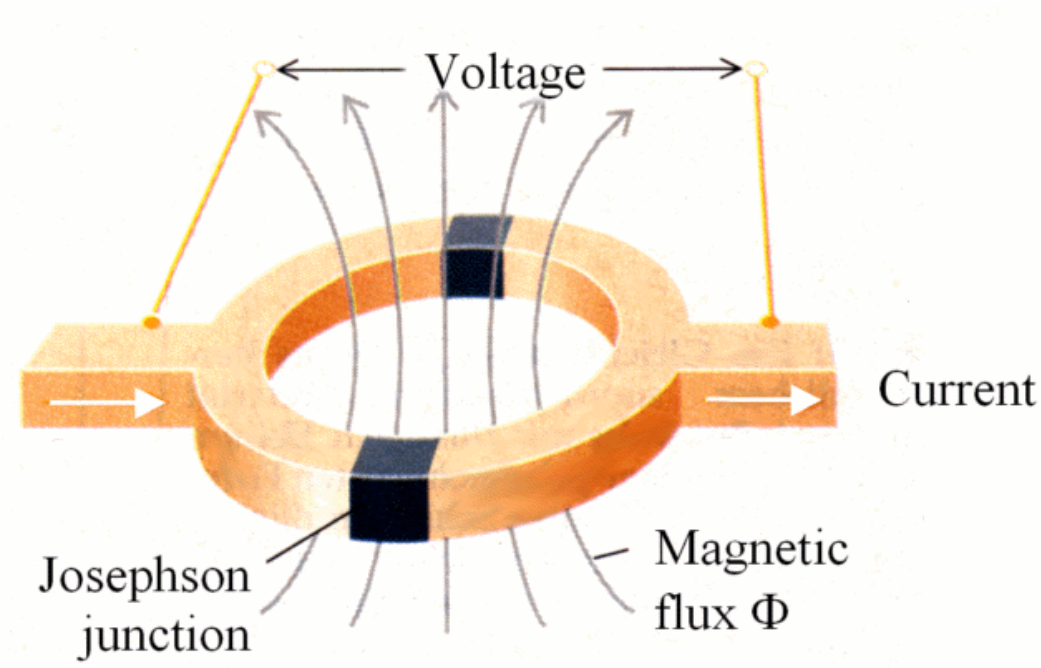

Figure 2 Illustration of the Josephson effect as applied in SQUIDs
Image courtesy of Kwok, Raymond at San José State University

Because the brain's magnetic signals are so small, different types of noise may easily obscure them: sensor noise, brain noise and environmental noise. That is why several solutions exist to reduce this noise. Sensor noise is minimized by the design of the SQUIDs and primary flux transformers, as both do not produce any noise due to their superconductive design[30]. Background brain noise can be countered by spatial filtering methods such as the signal space separation (SSS) method or spatiotemporal signal space separation method (tSSS). Finally, due to the extremely small signal size of the brain's magnetic flux compared to background environmental magnetic noise, Magnetic Shielded Rooms (MSR) have been developed in which the MEG scanner is located.

During MEG acquisition, patients are positioned in a helmet attached to the MEG scanner in sitting or supine position. This helmet contains the SQUIDs embedded in an insulated tank filled with liquid helium, called a dewar[29]. To account for movement in the helmet, Head Position Indicator (HPI) coils are attached to the patients head and digitally registered. These generate small magnetic fields of known strength and thus allow tracking of the patient's head inside the helmet[3].

To appreciate the distinctive benefit of MEG in the presurgical epilepsy evaluation, several characteristics are worth pointing out. First of all, the magnetic permeability of biological tissues is nearly the same as the magnetic permeability of a vacuum[29]. Therefore the MEG signals are not attenuated by the skull and meninges, thus providing a higher spatial resolution than surface EEG whose signals are distorted by varying electrical conductivities in the different biological tissues of the head[2,29]. Secondly, magnetic fields are perpendicular to the electrical current by which they are caused, making MEG highly complementary to EEG. Whereas EEG measures neural activity mainly on top of the gyral crests and in the sulcal depths, MEG measures neural activity arising in the sulcal walls[3,4]. A negative EEG in refractory epilepsy patients should thus not necessarily imply a clear MEG.

On the other hand, the magnetic field strength deteriorates more rapidly than the electric field with increasing distance from the source, limiting MEGs ability to detect deep sources in the brain[3]. To accommodate correct localization of the signal, patients must remain relatively still in the helmet, thus rendering the technique less suitable for ictal localizations[32]. In addition,

prolonged scanning durations analogous to the 24 hour EEG are unattainable in a MEG scanner due to their scarcity and cost. Scanning duration is usually limited to one hour.

1.6 Magnetic Source Imaging

After data acquisition, epileptiform activity such as interictal spikes are identified and magnetic source imaging (MSI) can be performed. The goal is to, as the name indicates, determine the neural sources of the external magnetic field distributions measured at the detectors. This requires solving the forward and inverse problem, both of which are addressed with a component model: a head model and a source model. The head model is used to solve the forward problem: determine the external magnetic signal of a known source in the brain. Usually a homogenous spherical simplification of the head is used to represent volume conduction. Due to the uniform magnetic permeability in biological tissues this homogeneity can be assumed[32]. The inverse problem aims to compute the origin of the magnetic distribution measured at the surface[33]. However, an infinite amount of correct solutions exist for this problem, necessitating assumptions to be made about the sources. The most commonly used model is Equivalent Current Dipole (ECD) modelling, with the ECD representing the center of gravity of a small collection of firing neurons[32]. However, this model cannot account for a complex distribution of epileptic activity as it assumes a single dipole is responsible for the observed magnetic fields.

Based on the definition of fiducial markers (nasion, preauricular points, inion), the MEG localization is co-registered to the patient's MRI, allowing projection of the ECDs on the structural image. Multiple ECDs that localize together are labeled clusters.

1.7 Resective surgery

After delineation of the hypothesized epileptogenic zone, an extensive risk-benefit assessment of surgical outcome should be performed[24]. This includes the possibility to resect the epileptogenic zone without substantial concerns of causing permanent functional deficits[25]. The surgical procedure is based on the type of epilepsy, localization of the epileptogenic zone and proximity of eloquent cortex, and its intent may either be curative or palliative. Resections in the temporal lobe have the highest likelihood of seizure freedom, with just under 70% of patients achieving seizure freedom for at least two years[34]. Patients with extratemporal resections have an increased risk of seizure recurrence[35]. In general, more than 50% of patients undergoing surgical resection of focal epilepsy will experience long-term seizure freedom[35,36]. In patients with overlapping eloquent cortex, multiple subpial transections (MSTs) may be performed. These prevent the spread of ictal activity by disconnecting the epileptogenic zone, but maintain its function by preserving its structure[37]. For patients with generalized, refractory, severe motor seizures such as drop seizures, corpus collosotomies may be indicated[24]. However, these are a palliative measure and not intended to achieve seizure freedom.

1.8 Objectives

This study will validate the results obtained with magnetoencephalography and magnetic source imaging in the presurgical epilepsy evaluation. This validation will be performed against three zones defined in the presurgical epilepsy evaluation, identified by their current gold standard. Magnetic source imaging will be compared to the irritative zone, as identified with intracranial EEG, the seizure onset zone, as identified with intracranial EEG, and the epileptogenic zone, identified as the resection cavity in patients with good surgical outcome (Engel = I). Due to the nature of the signals which are usually registered in magnetoencephalography (interictal epileptiform activity), it can be hypothesized that its accuracy will be optimal to localize the irritative zone. The value of the irritative zone in the presurgical epilepsy evaluation with respect to surgical outcome has often produced conflicting results. A 2010 systematic review by Rathore and Radhakrishnan[38] did however find a correlation between the presence of post-surgical interictal epileptiform discharges and poor surgical outcome. Other studies have found an association between resection of the irritative zone and better surgical outcome[39,40]. Nevertheless, with the seizure onset zone as identified

in intracranial EEG being the main driver in surgical resection, it is important to grasp the relationship of magnetic source imaging with this zone. Finally, a comparison is also made between magnetic source imaging and the resection cavity in seizure free patients, as a true gold standard for removal of the epileptogenic zone and achieving seizure freedom.

Perhaps even more important in its clinical application, is the use of MEG to guide intracranial electrode implantation. Due to the medical risks associated with ICEEG, optimal sampling must be ensured. The validation of MEG to accurately identify the irritative zone and/or seizure onset zone is therefore of utmost importance. In this study, clusters of equivalent current dipoles, identified with magnetic source imaging based on interictal epileptiform discharges will be used for this comparison. To this account, they will be subjected to both qualitative and quantitative analysis to determine their accuracy to localize the irritative zone, seizure onset zone and the epileptogenic zone. In addition, the effect of surgical outcome on the accuracy to identify the irritative zone and seizure onset zone will be investigated.

Materials and methods

The master dissertation consists of a retrospective study of anonymized datasets assembled in light of patients' presurgical epilepsy evaluation. Approval of the ethical committee at Ghent University hospital was obtained before onset of this retrospective study. A description of the methodologies used for data acquisition and analysis in the presurgical evaluation is presented subsequently.

2 Data acquisition

2.1 Magnetoencephalography

MEG scans were recorded using a whole head 306 channel Elekta Neuromag® system (MaxShield; Elekta Neuromag®, Elekta Oy, Helsinki, Finland) in a light-weight MSR. Four head position indicator (HPI) coils were attached to the patients' head to track its position in the detector helmet during recording and allow to correct for head movement afterwards. A virtual 3D head model was created based on digitization of three fiducial points (nasion, left and right trachus), the HPI coils and at least 150-200 additional points on head and face (Fastrak Polhemus® digitizer system) to allow co-registration to MRI. Patients underwent a one-hour recording session of spontaneous neural activity in supine position with closed eyes. Falling asleep was encouraged. However, patients were not sedated during the recording session. AED treatment was unchanged. Sampling frequency was at least 1kHz and acquisition band-pass 0.1-300Hz[41].

2.2 Magnetic Source Imaging

Data were preprocessed offline using the signal space separation (SSS) or spatiotemporal SSS (tSSS) method to eliminate residual artifacts and correct for head movements. Band-pass filter was 0.1-40Hz. IEDs were identified upon visual inspection by two experienced specialists. Source localization was performed using a spherical head model and equivalent current dipole modelling tools (Elekta Neuromag® Oy). ECDs were fitted at the onset and at the peak of the IEDs using a selection of at least 40 channels. Multidipole modelling was used when necessary to discriminate the IED origin from its propagation pathways. The dipole fit was considered valid if the goodness of fit was > 80% and the 95% confidence volume was less than or equal to $20mm^3$. Dipoles were fitted onto the patients' MRI[41].

2.3 Intracranial EEG

Invasive video-EEG monitoring was suggested at the multidisciplinary staff meeting in patients whose non-invasive testing results provided incongruent information or non-localizing results and additional evidence was desired. An electrode implantation schema was designed based on the results of all localizing modalities used, including MEG localization due to its previously established value in the presurgical epilepsy evaluation[3]. Depending on this schema subdural grids, strips and/or depth electrodes were used. Subdural grids were implanted by performing

a craniotomy, depth electrodes were inserted through burr-holes using stereotactic surgery. Subdural strips were implanted by either of the aforementioned techniques depending on their target location. Depth electrodes were used to register activity of deep structures inaccessible to subdural electrodes[42]. Intake of AEDs was gradually phased out during the ICEEG registration period to maximize habitual seizures. Electrodes showing interictal and ictal onset activity were listed in the clinical report, delineating both the gold standard irritative zone and seizure onset zone respectively.

During ICEEG monitoring or intra-operatively functional mapping of eloquent cortex was performed. Small electrical stimuli were administered to a specific cortical area to see if a response was elicited and identify eloquent cortex in proximity of the hypothesized epileptogenic zone.

2.4 Magnetic Resonance Imaging and Computed Tomography

All patients underwent an MRI scan at the start of the presurgical evaluation using a magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence. A second MRI scan was acquired after implantation of the intracranial electrodes, along with a computed tomography (CT) scan with reconstructions in three orthogonal directions. Six months after surgical resection a third MRI or CT scan was acquired visualizing the resection cavity (RS). MRI sequences used in this study vary upon availability.

2.5 Surgical Resection

After successful registration of the intracranial EEG and a clear hypothesis on the localization of the epileptogenic zone, patients underwent surgical resection. During surgery the intracranial electrodes were removed. Extent of the resection cavity depends upon localization and size of the presumed epileptogenic zone and proximity of eloquent cortex. In some patients where eloquent cortex posed a threat to loss of functionality in the case of a resection, multiple subpial transections were made.

3 Study description

In this section, a description follows of the methods used in this master's dissertation.

3.1 Patient selection and data collection

Patient selection for this study was based on the following criteria: 1) suffering from refractory epilepsy, 2) underwent presurgical epilepsy evaluation, 3) MEG scan showing interictal epileptiform discharges, 4) ICEEG registration showing ictal and interictal epileptiform activity, 5) underwent surgical resection of the presumed epileptogenic zone. See Figure 3. Informed consent was obtained from all patients.

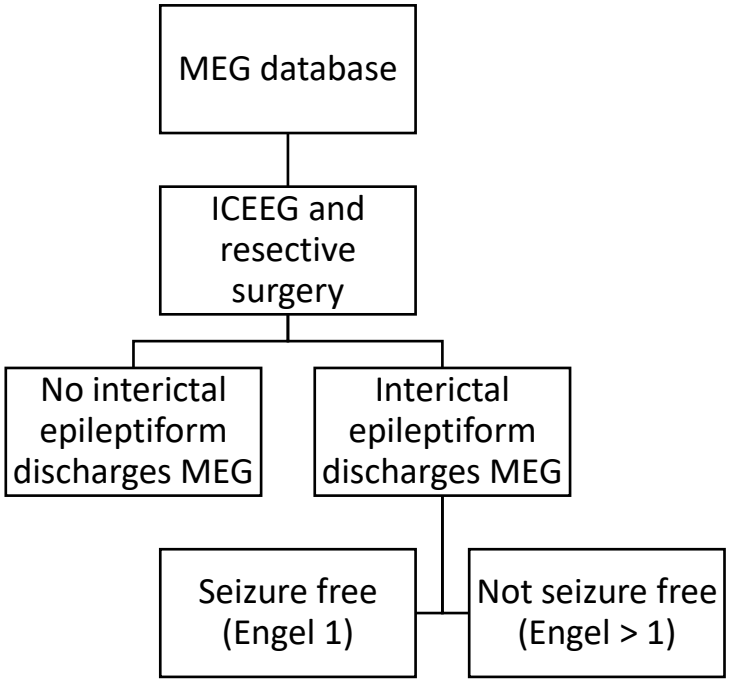

Figure 3 Patient selection flowchart

Based on these criteria, patients were selected from a large anonymized database containing 227 patients who underwent a MEG investigation in the presurgical epilepsy evaluation between 2008 and 2020.

3.2 DICOM creation and data localization

After data collection, the following series of steps was completed for every patient included in the study. This was performed in the EEG/MEG signal processing and neuroimaging software Curry 8 (Compumedics®, Australia).

3.2.1 DICOM I – MSI cluster

The MSI DICOM created in the Elekta Neuromag® software was imported in Curry 8. MSI clusters consist of the collection of ECDs obtained from the IEDs registered during magnetoencephalography. MSI clusters were marked in bright yellow and exported as a collection of points. In patients with multiple clusters, every cluster was saved separately. When defining the MSI clusters, dipole orientation was not taken into account. This projection of MSI clusters on a patients' pre-operative MRI constitutes DICOM I. In patients where this MRI was missing, a post-resection MRI was used to project the MSI cluster on.

All clusters were then assigned to a hemisphere, lobe and sublobar region. Lobar classification: frontal, parietal, temporal, occipital or insular. Sublobar classification: orbitofrontal, inferior frontal gyrus, medial frontal gyrus, superior frontal gyrus, mesial frontal, central, superior parietal lobe, inferior parietal lobe, mesial parietal, lateral temporal, mesial temporal, basal temporal, lateral occipital, mesial occipital and insular. Clusters spanning multiple regions were assigned upon visual inspection to the one containing the most ECDs. In patients with more than one cluster, the cluster containing the most ECDs was appointed as dominant cluster, and only this cluster was used for further analysis.

3.2.2 DICOM II – Intracranial EEG

Patients' MRI and CT scan obtained after implantation of the intracranial electrodes were co-registered in Curry 8 to DICOM I based on four fiducial points (nasion, left and right tragus and inion). A 3D boundary element head model (BEM) was created based on the post-implantation MRI. The CT scan allows for generation of an interactive electrode mesh on the co-registered image. Some patients did not undergo a CT scan during electrode implantation. In these, an

electrode grid was created manually through identification of the electrodes on the post-implantation MRI. Subdural electrodes are shown in Clamshell and depth electrodes in Brown (Figure 4). After creation of the electrode grid, overlap of the grid with the MSI cluster was assessed based on visual analysis. Clusters were classified as Covered, Partially covered or Not covered. Covered was employed for those clusters that were located entirely underneath an intracranial electrode grid or directly surrounding a depth electrode. MSI clusters in which part of the ECDs were located directly underneath the grid or surrounding a depth electrode were labeled Partially covered and MSI clusters which had no direct coverage by intracranial electrodes were labeled Not covered.

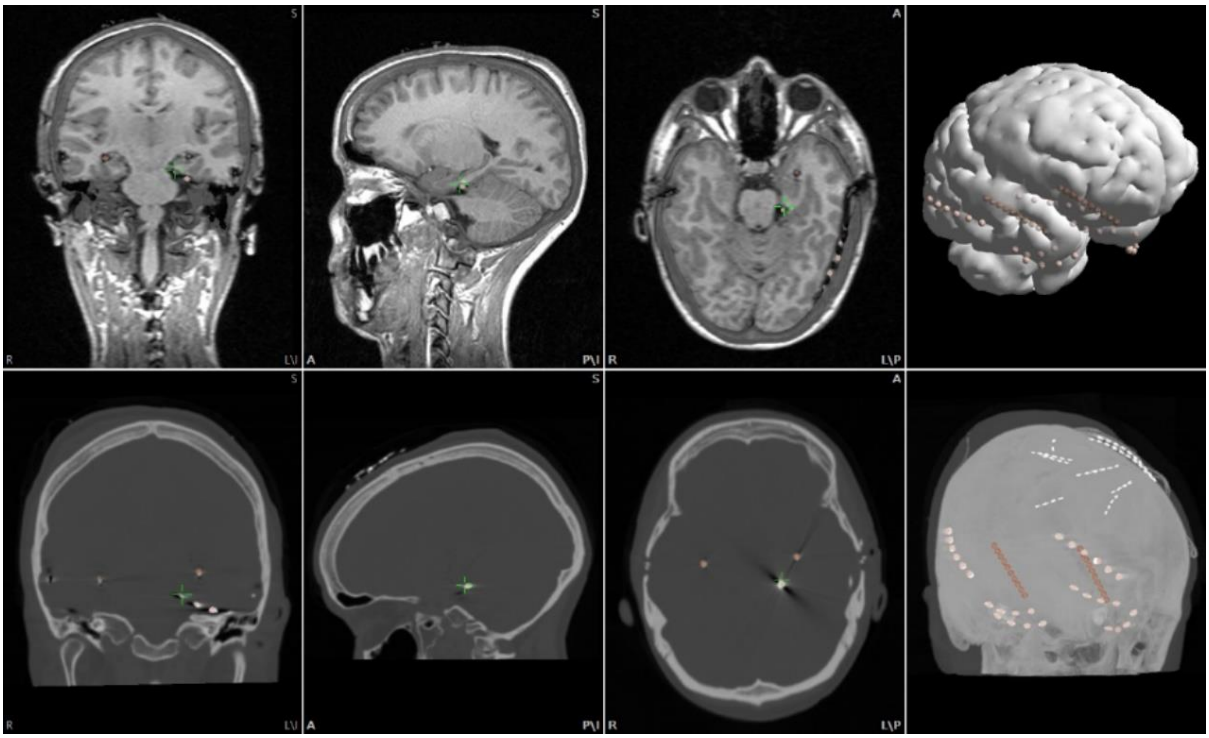

Figure 4 Intracranial electrode mesh created based on a post-implantation CT scan
Depth electrodes are marked in brown, cortical grids and strips are marked in clamshell

3.2.2.1 DICOM IIa – Irritative Zone

Based on the anonymized clinical ICEEG report, registered interictal activity was visualized on the respective electrodes of DICOM II by marking them blue. These localizations constitute DICOM IIa. This allows for visualization of the irritative zone which is defined as all contacts showing interictal activity. The irritative zone was assigned to a lobe and sublobar region, with categories being the same as those used for classification of the MSI clusters (see supra). If spanning multiple regions, the region containing the most important sources of IEDs was assigned.

3.2.2.2 DICOM IIb – Seizure Onset Zone

Ictal onset activity recorded during ICEEG was marked on DICOM II as DICOM IIb using red. This comprehends all electrodes showing the first ictal discharges as described in the clinical evaluation of the intracranial investigation. The seizure onset zone was assigned to a lobe and sublobar region, with categories being the same as those used for classification of the MSI clusters (see supra). If ictal onset was registered in multiple regions, the onset zone inducing habitual seizures was assigned.

3.2.3 DICOM III – Resection cavity

The MRI or CT scan taken six months after resection constitutes DICOM III. This was co-registered to DICOM I based on four fiducial points (nasion, left and right tragus and inion). The resection cavity was isolated through segmentation and marked using volume points in

Curry 8. Resolution of the volume points was 2mm. In those patients with a post-resection CT scan, a histogram window was identified to optimally visualize the soft tissue. In patients with a good outcome (Engel = I), the resection cavity was designated the epileptogenic zone. Patients with Engel > I were used as a negative control in tests comparing good outcome versus poor outcome. The resection cavity was assigned to a lobe and sublobar region, with categories being the same as those used for classification of the MSI clusters (see supra). If spanning multiple regions, the resected area was assigned to the region it overlaps most with.

3.3 Qualitative analysis

DICOM II and DICOM III were co-registered to DICOM I in Curry 8 to create an overlay and allow for accurate comparison. Both qualitative and quantitative analyses were performed.

3.3.1 Concordance of the MSI cluster with the irritative zone

MSI cluster localization compared to the irritative zone as identified with ICEEG. A qualitative comparison was performed on two levels based on the lobar and sublobar regions to which the MSI cluster and IZ were assigned. Each patient was classified according to lobar and sublobar concordance. If the MSI cluster was assigned to the same (sub)lobe as the IZ - (sub)lobar concordance (Figure 5). If the MSI cluster was assigned to a (sub)lobe in which a minority of interictal contacts was present or a minority of ECDs and interictal contacts were present in the same (sub)lobe - partial concordance (Figure 6). If no ECDs were present in a (sub)lobe with interictal contacts – non-concordant (Figure 7). Degree of concordance per lobe and sublobe were calculated based on these results.

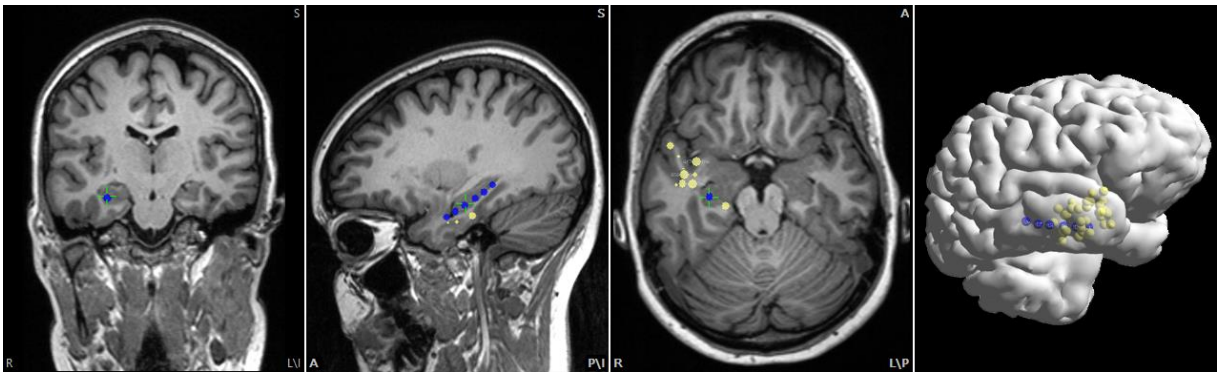

Figure 5 Example of concordance between the MSI cluster and the irritative zone identified with ICEEG; blue = irritative zone, yellow = MSI cluster

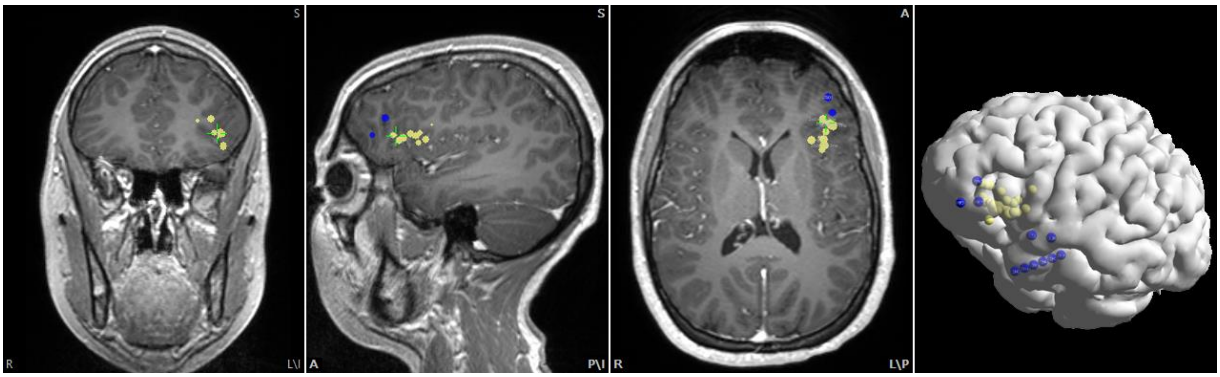

Figure 6 Example of partial concordance between the MSI cluster and the irritative zone identified with ICEEG; blue = irritative zone, yellow = MSI cluster

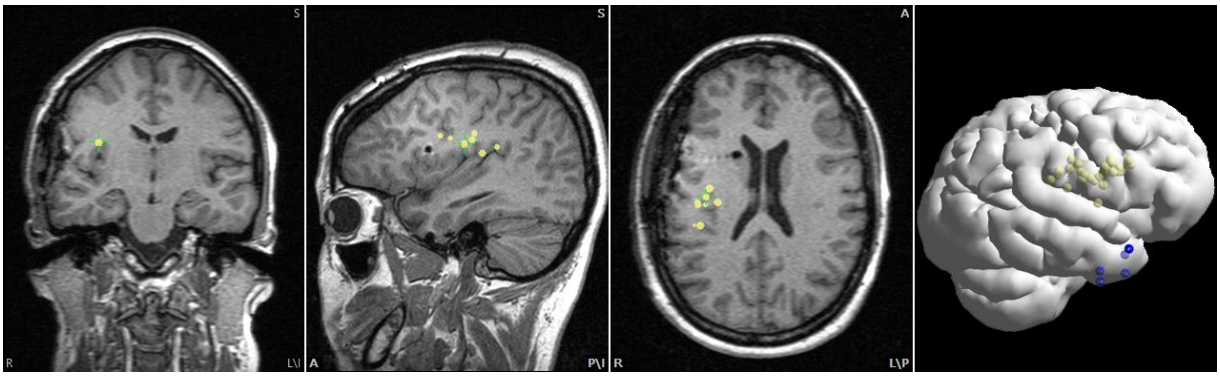

Figure 7 Example of non-concordance between the MSI cluster and the irritative zone identified with ICEEG; blue = irritative zone, yellow = MSI cluster

3.3.2 MSI cluster concordance with the irritative zone compared to surgical outcome

Concordance between the localization of the MSI cluster and the irritative zone was compared to surgical outcome, both on a lobar and sublobar level. Concordance was dichotomized for this analysis into concordance and no concordance. Partial concordance was allocated to the concordance category. Based on the resulting 2x2 table, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

3.3.3 Concordance of the MSI cluster with the seizure onset zone

MSI cluster localization compared to the seizure onset zone as identified with ICEEG. A qualitative comparison was performed on two levels based on the lobar and sublobar regions to which the MSI cluster and SOZ were assigned. Each patient was classified according to lobar and sublobar concordance. If the MSI cluster was assigned to the same (sub)lobe as the SOZ - (sub)lobar concordance. If the MSI cluster was assigned to a (sub)lobe in which a minority of ictal onset contacts were present or a minority of ECDs and ictal onset contacts were present in the same (sub)lobe – partial concordance. If no ECDs were present in a (sub)lobe with ictal onset contacts – non-concordant. Degree of concordance per lobe and sublobe were calculated based on these results.

3.3.4 MSI cluster concordance with the seizure onset zone compared to surgical outcome

Concordance between the localization of the MSI cluster and the seizure onset zone was compared to surgical outcome, both on a lobar and sublobar level. Concordance was dichotomized for this analysis into concordance and no concordance. Partial concordance was allocated to the concordance category. Based on the resulting 2x2 table, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

3.3.5 Concordance of the MSI cluster with the epileptogenic zone

MSI cluster localization compared to the epileptogenic zone, defined as the resection cavity in seizure free patients. A qualitative comparison was performed on two levels based on the lobar and sublobar regions to which the MSI cluster and resection cavity were assigned. Each patient was classified according to lobar and sublobar concordance. If the MSI cluster was assigned to the same (sub)lobe as the resection cavity - (sub)lobar concordance. If the MSI cluster was assigned to a (sub)lobe in which a subsidiary segment of the resection cavity was present or a minority of ECDs and subsidiary segment of the resection cavity were present in the same (sub)lobe - partial concordance. If no ECDs were present in a (sub)lobe where resection took place – non-concordant. Degree of concordance per lobe and sublobe were calculated based on these results.

3.3.6 MSI cluster concordance with the resection cavity compared to surgical outcome

Concordance between the localization of the MSI cluster and the resection cavity was compared to surgical outcome, both on a lobar and sublobar level. Concordance was dichotomized for this analysis into concordance and non-concordance. Partial concordance was allocated to the concordance category. Based on the resulting 2x2 table, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

3.3.7 Comparison of MSI cluster concordance with the IZ, SOZ and EZ

The degree of concordance of the MSI cluster with the irritative zone, seizure onset zone and epileptogenic zone was compared to each other. Both concordance and partial concordance were clustered under concordance.

3.3.8 Comparison of MSI cluster concordance with the IZ and SOZ depending on MSI cluster coverage

All results obtained in this study to validate the accuracy of magnetoencephalography to detect the irritative zone and seizure onset zone are verified against the results of intracranial EEG. Therefore, the degree to which the MSI cluster was covered is of utmost importance for the correct interpretation of these results. Concordance of the MSI cluster with the IZ and SOZ on a lobar and sublobar level was compared to coverage of the MSI cluster. Concordance was dichotomized for this analysis into concordance and non-concordance.

3.4 Quantitative analysis

3.4.1 Comparison of the accuracy of MSI to localize the IZ, SOZ and EZ

For every patient, the distance between each ECD part of the MSI cluster as assessed at the multidisciplinary staff meeting and the nearest interictally activated ICEEG electrode was measured in Curry 8. These results were averaged to calculate the distance between the MSI cluster and the irritative zone per patient. The accuracy of magnetic source imaging to localize the irritative zone was defined as the mean distance between the MSI cluster and the irritative zone. This was calculated by averaging all patients' individual MSI cluster distance to the irritative zone.

Similarly, the accuracy of magnetic source imaging to localize the seizure onset zone was calculated. For every patient, the distance between each ECD part of the MSI cluster as assessed at the multidisciplinary staff meeting and the nearest ictal activated ICEEG electrode was measured in Curry 8. These results were averaged to calculate the distance between the MSI cluster and the seizure onset zone. The accuracy of magnetic source imaging to localize the seizure onset zone was defined as the mean distance between the MSI cluster and the seizure onset zone. This was calculated by averaging all patients' individual MSI cluster distance to the seizure onset zone.

Lastly, the accuracy of magnetic source imaging to localize the epileptogenic zone was calculated. For every patient, the distance between each ECD part of the MSI cluster as assessed at the multidisciplinary staff meeting and the nearest volume point in the resection cavity was measured in Curry 8. These results were averaged to calculate the distance between the MSI cluster and the resection cavity. The accuracy of magnetic source imaging to localize the epileptogenic zone was defined as the mean distance between the MSI cluster and the epileptogenic zone. This was calculated by averaging only the results of MSI cluster distance to the resection cavity from patients with a seizure free outcome after resection.

The accuracy of magnetic source imaging to localize the irritative zone, seizure onset zone and epileptogenic zone was compared to one another.

3.4.2 Comparison of the mean distance between the MSI cluster and the IZ, SOZ and RS in relation to surgical outcome

The mean distance between the MSI cluster and the irritative zone was compared in patients with good surgical outcome (Engel = I) versus poor surgical outcome (Engel > I). Similarly, the mean distance between the MSI cluster and the seizure onset zone was compared based on surgical outcome, and the mean distance between the MSI cluster and the resection cavity.

3.4.3 Comparison of the mean distance between the MSI cluster and the IZ and SOZ depending on MSI cluster coverage

The mean distance between the MSI cluster and the IZ and SOZ was compared to MSI cluster coverage by intracranial electrodes. MSI cluster coverage was divided in fully covered, partial coverage and no direct coverage.

3.5 Statistical analysis

Chi square and Fisher's exact test were performed to assess significance levels in the qualitative analysis. Cochran's Q test was used for assessment of differences between concordance levels of the MSI cluster localization with the IZ, SOZ and EZ. With regard to surgical outcome, four possibilities were defined: true positive (TP) cases: MSI cluster concordance with the IZ/SOZ/RS and good surgical outcome (Engel = I); false positives (FP): concordance of the MSI cluster but poor surgical outcome (Engel > I); false negatives (FN): non-concordance of the MSI cluster with the IZ/SOZ/RS but good surgical outcome; true negatives (TN): non-concordance and poor surgical outcome. To assess the value of concordance between the MSI cluster and the IZ, SOZ and RS with regard to seizure outcome, sensitivity [TP/(TP+FN)], specificity [TN/(TN+FP)], positive predictive value [PPV = TP/(TP+FP)] and negative predictive value [NPV = TN/(FN+TN)] were calculated. Normality of the quantitative results was assessed using the Shapiro-Wilk test to decide between parametric or non-parametric tests. Only in the average distance of the MSI cluster to the epileptogenic zone, a normal distribution was present. Related-samples Wilcoxon Signed rank test was performed to assess the difference in the mean distance from the MSI cluster to the IZ and the SOZ. Mann-Whitney U test was performed to assess differences in the mean distance of the MSI cluster to the IZ, SOZ and RS between surgical outcome groups. A p-value of ≤ 0.05 was considered statistically significant. SPSS 27 was used for statistical analysis. Results are expressed as mean ± standard deviation or mean [min – max].

Results

4.1 Patient selection

Twenty-six patients underwent invasive EEG monitoring and surgical resection subsequently. Five of these patients' MEG scan could not be used for further analysis, either due to a lack of IEDs or because of artefacts obscuring the MEG signal. This results in a useful MEG investigation in twenty-one out of twenty-six patients (81%). Two patients were excluded because of the inability to register habitual seizures on ICEEG or a lack of information on the activation of interictal contacts. In three patients, MRI or CT scans necessitated for further analysis were not available. Sixteen patients were included in the study.

Twelve patients were female and four male. The mean age during the MEG investigation was 25.2 [10 - 38] years. Mean age of onset of the epilepsy was 10.1 ± 8.7 years. The mean seizure frequency was 35.4 ± 73.6 seizures per month. In all patients, structural abnormalities were identified on MRI (Table 1). Patient no. 2 had a vagus nerve stimulator (VNS).

Table 1 Patient description

Patient No.	Sex	Age (years)	Onset (years)	Frequency (/month)	No. AEDs	NMR
1	F	18	7	30	3	Lesion L Postcentral
2	F	31	3.5	30	4	FCD R Lateral ventricle to Insular cortex
3	F	16	5	18	3	Lesion R Frontal operculum
4	M	38	28	30	3	Hemosiderin lesion L Superior Frontal gyrus
5	F	10	9	300	1	DNET L Postcentral
6	F	25	24	6	2	FCD R Inferior Temporal
7	F	36	22	15	3	R Hippocampal sclerosis
8	F	29	0.1	2	5	R Hippocampal sclerosis
9	F	36	7	2	3	Diffuse damage L Parietal
10	M	30	0.7	30	3	Gliosis R Temporal
11	M	16	14	4	3	Cavernoma L Temporal ventricle wall
12	F	22	8	4	3	Hyperintense T2 R Hippocampus
13	M	35	10	6	4	Tissue loss and gliosis R Occipito-Temporal
14	F	22	18	3	3	BL hyperintense FLAIR supratentorial
15	F	17	1.5	84	3	L Frontal FCD and L Hippocampal sclerosis
16	F	22	3	3	3	Sturge-Weber R Occipital and atrophy R Temporal

F = Female; M = Male; BL = Bilateral; L = Left; R = Right; DNET = Dysembryoplastic Neuroepithelial Tumor; FCD = Focal Cortical Dysplasia

4.2 Data localization

4.2.1 Localization Magnetic Source Imaging

In patient no. 1, a single ECD outlier was removed due to its solitary presence in the contralateral hemisphere of the MSI cluster. Thirteen patients (81%) had a single MSI cluster while three patients (19%) had two clusters. None had more than two. In total, nineteen clusters were detected. Eleven out of these nineteen clusters (58%) were located in the right hemisphere. Temporal lobe epilepsy was indicated in eleven clusters (58%), with six (32%) localizing lateral temporal and five (26%) mesial temporal. Five clusters (26%) localized frontal, of which two clusters (11%) were located orbitofrontal, two (11%) in the inferior frontal gyrus and one (5%) in the medial frontal gyrus. Of the three remaining extra-temporal clusters one (6%) was located centrally in the parietal lobe, one (6%) mesial occipital and one (6%) insular (Table 2).

Table 2 Results MSI cluster localization

Patient No.	No. clusters	Hemi-sphere	Lobar localization	Sublobar localization
1	1	L	Frontal	Medial frontal gyrus
2	1	R	Temporal	Lateral temporal
3	1	R	Temporal	Lateral temporal
4	1	L	Frontal	Orbitofrontal
5	1	L	Parietal	Central
6	1	R	Temporal	Mesial temporal
7	2	R	Temporal	Mesial temporal
7	2	L	Temporal	Mesial temporal
8	1	R	Temporal	Lateral temporal
9	1	L	Temporal	Lateral temporal
10	2	R	Frontal	Orbitofrontal
10	2	R	Temporal	Lateral temporal
11	1	L	Temporal	Lateral temporal
12	1	R	Temporal	Mesial temporal
13	1	R	Temporal	Mesial temporal
14	1	R	Frontal	Inferior frontal gyrus
15	2	L	Frontal	Inferior frontal gyrus
15	2	L	Insular	Insular
16	1	R	Occipital	Mesial occipital

L = Left; R = Right

4.2.2 Localization Intracranial EEG

Complete coverage of the MSI cluster by intracranial electrodes was observed in nine patients (56%), partial coverage in six patients (38%). In one patient (Pt. nr. 16; 6%), the intracranial electrode grid or depth electrodes did not overlap directly with the MSI cluster. This patient was however not excluded from analysis due to the proximity of the subdural grid to the MSI cluster, which was smaller than 15mm.

4.2.2.1 DICOM IIa – Irritative Zone

In eight patients (50%), the irritative zone as identified with intracranial EEG was located in the right hemisphere while six patients (38%) had an irritative zone in the left hemisphere. Two patients (13%) had a bilateral irritative zone, located mesial temporal in both hemispheres. Ten patients (63%) had temporal localizations of the irritative zone with eight (50%) of these localized mesial temporal and two (13%) basal temporal. In three patients (19%) the irritative zone was located in the frontal lobe, two patients (13%) had a parietal irritative zone and one patient (6%) insular. On a sublobar level these localized orbitofrontal (one patient, 6%), inferior frontal gyrus (one patient, 6%), central (two patients, 13%), superior parietal lobule (one patient, 6%) and insular (one patient, 6%) (Table 3).

Table 3 Interictal intracranial localizations

Patient No.	Interictal hemisphere	Interictal lobar localization	Interictal sublobar localization
1	L	Frontal	Central
2	R	Insular	Insular
3	R	Frontal	Inferior Frontal gyrus
4	L	Frontal	Orbitofrontal
5	L	Parietal	Central
6	R	Temporal	Mesial temporal
7	BL	Temporal	Mesial temporal
8	R	Temporal	Mesial temporal
9	L	Parietal	Superior parietal lobule
10	R	Temporal	Mesial temporal
11	L	Temporal	Basal temporal
12	BL	Temporal	Mesial temporal
13	R	Temporal	Mesial temporal
14	R	Temporal	Basal temporal
15	L	Temporal	Mesial temporal
16	R	Temporal	Mesial temporal

BL = Bilateral; L = Left; R = Right

4.2.2.2 DICOM IIb – Ictal Onset Zone

Ten patients (63%) had a seizure onset zone in the right hemisphere, six patients (38%) in the left. On a lobar level, ten patients (63%) showed ictal onset in the temporal lobe on intracranial EEG. Two patients (13%) had frontal onset, three patients (19%) parietal and one patient (6%) insular. Five (31%) temporal localizations originated mesial temporally, four (24%) basal temporal and one (6%) lateral temporal. Of the extra-temporal localizations, one patient (6%) showed seizure onset in the inferior frontal gyrus, three patients (19%) centrally, one patient (6%) in the superior parietal lobule and one patient (6%) insular (Table 4).

Table 4 Ictal intracranial localizations

Patient No.	Ictal hemisphere	Ictal lobar localization	Ictal sublobar localization
1	L	Parietal	Central
2	R	Insular	Insular
3	R	Frontal	Inferior Frontal gyrus
4	L	Frontal	Central
5	L	Parietal	Central
6	R	Temporal	Basal temporal
7	R	Temporal	Mesial temporal
8	R	Temporal	Mesial temporal
9	L	Parietal	Superior parietal lobule
10	R	Temporal	Mesial temporal
11	L	Temporal	Basal temporal
12	R	Temporal	Basal temporal
13	R	Temporal	Mesial temporal
14	R	Temporal	Basal temporal
15	L	Temporal	Mesial temporal
16	R	Temporal	Lateral temporal

L = Left; R = Right

4.2.3 Localization Resection cavity

Resections took place in the right hemisphere in ten patients (63%) and in the left hemisphere in 6 patients (38%). Two patients (13%) underwent a resection in the frontal lobe, three patients (19%) in the parietal lobe, ten patients (63%) in the temporal lobe and one patient (6%) in the insula. Mesial temporal resections were performed most frequently, in eight out of sixteen patients (50%), supplemented with resection of the anterior two thirds of the temporal lobe in three patients (19%) and resections in the fusiform gyrus in two patients (13%). Both lateral and basal temporal resections were performed in one patient (6%). Extra-temporal resections (6 patients, 38%) took place in the inferior frontal gyrus (one patient, 6%), superior frontal gyrus (one patient, 6%), central (two patients, 13%), superior parietal lobule (one patient, 6%) and insula (one patient, 6%) (Table 5).

Twelve out of sixteen patients (75%) achieved seizure freedom. It can be concluded that in these patients, the epileptogenic zone has been removed. Four patients (25%) did not become seizure free after surgical resection (Pts. no. 1, 3, 4, 15). Three patients with poor surgical outcome (75%) had extra-temporal resections, with two (50%) located in the frontal lobe (inferior frontal gyrus and superior frontal gyrus) and one (25%) in the parietal lobe (central region) (Table 6 and Table 7) One patient who did not achieve seizure freedom (25%) underwent a mesial temporal resection. The difference in outcome between temporal and extra-temporal resections was not statistically significant ($p > 0.05$). All four patients who did not achieve seizure freedom underwent subtotal resection of the presumed epileptogenic zone due to overlap with eloquent cortex. In all but one, the resection was supplemented with multiple subpial transections in the eloquent cortex. In patient no.1 the epileptogenic lesion could not be removed in its entirety due to proximity of the sensorimotor cortex. Patient no. 3 had subtotal resection of the seizure onset zone due to overlap with eloquent cortex. Patient no. 4 initially achieved a significant improvement in seizure frequency after resection, but seizures started recurring after a fall with bleeding of the resection cavity as a result. Patient no. 15, in whom ictal onset was identified in the left mesial temporal lobe underwent an amygdalotomy but no resection of the hippocampus due to preserved function.

Table 5 Resection cavity localizations and surgical outcome

Patient No.	Resection hemisphere	Resection lobar localization	Resection sublobar localization	Subtotal resection?	Outcome resection
1	L	Parietal	Central	Y	Engel IV
2	R	Insular	Insular	N	Engel I
3	R	Frontal	Inferior frontal gyrus	Y	Engel III
4	L	Frontal	Superior frontal gyrus	Y	Engel IV
5	L	Parietal	Central	N	Engel I
6	R	Temporal	Mesial temporal	N	Engel I
7	R	Temporal	Mesial temporal	N	Engel I
8	R	Temporal	Mesial temporal	N	Engel I
9	L	Parietal	Superior parietal lobule	Y	Engel I
10	R	Temporal	Mesial temporal	N	Engel I
11	L	Temporal	Basal temporal	Y	Engel I
12	R	Temporal	Mesial temporal	N	Engel I
13	R	Temporal	Mesial temporal	N	Engel I
14	R	Temporal	Mesial temporal	N	Engel I
15	L	Temporal	Mesial temporal	Y	Engel II
16	R	Temporal	Lateral temporal	N	Engel I

L = Left; R = Right; Y = Yes; N = No

Table 6 Surgical outcome on a lobar level

	Seizure free	Not seizure free	Total
Frontal	0	2	2
Parietal	2	1	3
Temporal	9	1	10
Insular	1	0	1
Total	12	4	16

Table 7 Surgical outcome on a sublobar level

	Seizure free	Not seizure free	Total
Inferior frontal gyrus	0	1	1
Superior frontal gyrus	0	1	1
Central	1	1	2
Superior parietal lobule	1	0	1
Lateral temporal	1	0	1
Mesial temporal	7	1	8
Basal temporal	1	0	1
Insular	1	0	1
Total	12	4	16

4.3 Qualitative analysis

Detailed results of concordance between the MSI cluster and the reference zones per patient can be reviewed in the addendum (Table S1).

4.3.1 Concordance of the MSI cluster with the irritative zone

MSI cluster localization was concordant with localization of the irritative zone on a lobar level in nine patients (56%) and partially concordant in six patients (36%). In one patient (Pt. no. 14; 6%), the MSI cluster was not concordant with the irritative zone (Table 8). On a sublobar level, concordance was found in six patients (38%), partial concordance in nine patients (56%) and no concordance in one patient (Pt. no. 14; 6%) (Table 9). Figure 8 shows concordance of the MSI cluster with the irritative zone as identified with intracranial EEG on a lobar level. The percentage of concordant results did not differ significantly per lobe or per sublobe ($p > 0.05$). Non-dominant clusters of patients with two clusters were not included in this statistic but are described subsequently. Pt. nr 7 showed lobar and sublobar partial concordance between the non-dominant cluster and the irritative zone. Pt. nr 10 showed lobar concordance and no concordance on a sublobar level with the IZ and pt. nr 15 showed partial concordance both on a lobar and sublobar level.

Table 8 Concordance of the MSI cluster with the IZ per lobe

	Frontal	Parietal	Temporal	Insular	Total
Concordance	2	1	6	0	9
Partial concordance	1	1	3	1	6
No concordance	0	0	1	0	1
Total	3	2	10	1	16

Table 9 Concordance of the MSI cluster with the IZ per sublobe

	Oribto-frontal	Inferior frontal gyrus	Central	Superior parietal lobule	Mesial temporal	Basal temporal	Insular	Total
Concordance	1	0	1	0	4	0	0	6
Partial concordance	0	1	1	1	4	1	1	9
No concordance	0	0	0	0	0	1	0	1
Total	1	1	2	1	8	2	1	16

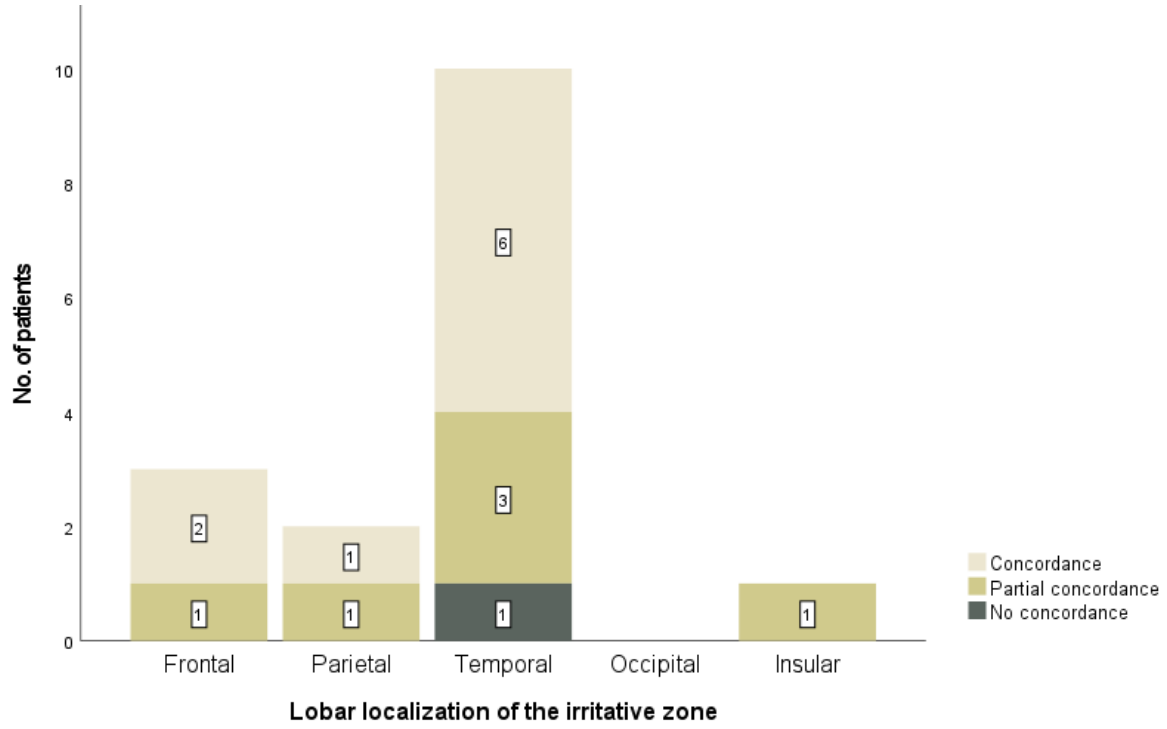

Figure 8 Concordance of MSI cluster localization with interictal ICEEG

4.3.2 MSI cluster concordance with the irritative zone compared to surgical outcome

Concordance of MSI cluster localization with the irritative zone as identified with ICEEG was compared to surgical outcome. On a lobar level, eleven patients (69%) with concordant localizations became seizure free after surgical resection, four patients did not (25%). One patient (6%) with non-concordant localizations of the MSI cluster and the irritative zone became seizure free after surgical resection (Table 10). Sensitivity and specificity of these results were respectively 92% and 0%. The positive predictive value was 73% and negative predictive value 0%. On a sublobar level, the same result was found (Table 11). These results did not prove to be statistically significant ($p > 0.05$).

Table 10 Concordance of the MSI cluster with the irritative zone on a lobar level compared to surgical outcome

	Seizure free	Not seizure free	Total
Concordance	11	4	15
No concordance	1	0	1
Total	12	4	16

Table 11 Concordance of the MSI cluster with the irritative zone on a sublobar level compared to surgical outcome

	Seizure free	Not seizure free	Total
Concordance	11	4	15
No concordance	1	0	1
Total	12	4	16

4.3.3 Concordance of the MSI cluster with the seizure onset zone

MSI cluster localization was concordant with the seizure onset zone as identified with intracranial EEG in eight patients (50%). Five patients (31%) showed partial concordance and

three patients (Pts. no. 9, 14, 15; 19%) showed no concordance at all (Table 12). On a sublobar level, three patients' (19%) MSI cluster was concordant with the SOZ, and eight patients (50%) showed partial concordance. Five patients (Pts. no. 4, 9, 10, 14, 15; 31%) showed no concordance on a sublobar level with the intracranially defined SOZ (Table 13). Figure 9 shows concordance of the MSI cluster with the seizure onset zone as identified with ICEEG per lobe. Concordance did not show any significant differences between lobes or between sublobes ($p > 0.05$). Non-dominant clusters of patients with two clusters were not included in this statistic but are described subsequently. Pt. nr 7 showed no concordance on a lobar and sublobar level between the non-dominant cluster and the seizure onset zone. Pt. nr 10 showed lobar concordance and no concordance on a sublobar level with the SOZ and pt. nr 15 showed partial concordance both on a lobar and sublobar level.

Table 12 Concordance of the MSI cluster with the SOZ per lobe

	Frontal	Parietal	Temporal	Insular	Total
Concordance	1	1	6	0	8
Partial concordance	1	1	2	1	5
No concordance	0	1	2	0	3
Total	2	3	10	1	16

Table 13 Concordance of the MSI cluster with the SOZ per sublobe

	Inferior frontal gyrus	Central	Superior parietal lobule	Lateral temporal	Mesial temporal	Basal temporal	Insular	Total
Concordance	0	1	0	0	2	0	0	3
Partial concordance	1	1	0	1	1	3	1	8
No concordance	0	1	1	0	2	1	0	5
Total	1	3	1	1	5	4	1	16

Figure 9 Concordance of MSI cluster localization with ictal ICEEG

4.3.4 MSI cluster concordance with the seizure onset zone compared to surgical outcome

Concordance of MSI cluster localization with the seizure onset zone as identified with ICEEG was compared to surgical outcome. On a lobar level, ten patients (63%) with concordant results became seizure free after surgical resection. Three patients (19%) did not. Two patients (13%) with non-concordant results became seizure free after surgery, one patient with non-concordant results did not become seizure free (Table 14). The sensitivity for concordant MSI cluster localization with seizure onset zone localization on a lobar level to predict seizure outcome was 83%, specificity was 25%. The positive predictive value was 77% and negative predictive value 33%. On a sublobar level, nine patients (56%) with concordant results achieved seizure freedom after surgical resection, while two patients (13%) had poor surgical outcome. Three patients (19%) with non-concordant results became seizure free and two patients (13%) with a non-concordant result did not achieve seizure freedom (Table 15). The sensitivity was 75% and specificity 50%. Positive predictive value was 82% and negative predictive value 40%. These results were not statistically significant ($p > 0.05$).

Table 14 Concordance of the MSI cluster with the seizure onset zone on a lobar level compared to surgical outcome

	Seizure free	Not seizure free	Total
Concordance	10	3	14
No concordance	2	1	2
Total	12	4	16

Table 15 Concordance of the MSI cluster with the seizure onset zone on a sublobar level compared to surgical outcome

	Seizure free	Not seizure free	Total
Concordance	9	2	11
No concordance	3	2	5
Total	12	4	16

4.3.5 Concordance of the MSI cluster with the epileptogenic zone

Comparison of the MSI cluster with the epileptogenic zone was only possible in patients who became seizure free after resective surgery. Therefore, only patients with Engel = I (12 patients, 75%) were included in this section. Seven patients (58%) showed concordant findings between localization of the MSI cluster and the epileptogenic zone on a lobar level. Two patients (17%) showed partial concordance and three patients (Pts. no. 9, 14, 16; 25%) did not have any concordance between lobar localizations (Table 16). On a sublobar level, five patients' (42%) MSI cluster showed concordance with the epileptogenic zone, four patients (33%) showed partial concordance and three patients (Pts. no. 9, 14, 16; 25%) had non-concordant results (Table 17). The amount of concordant localizations between the MSI cluster and the epileptogenic zone, identified as the resection cavity in seizure free patients, per lobe is shown in Figure 10. Concordance between lobes or between sublobes did not differ significantly ($p > 0.05$). Non-dominant clusters of patients with two clusters were not included in this statistic but are described subsequently. Pt. nr 7 showed no concordance on a lobar and sublobar level between the non-dominant cluster and the epileptogenic zone. Pt. nr 10 showed lobar concordance and no concordance on a sublobar level with the EZ and pt. nr 15 showed partial concordance both on a lobar and sublobar level.

Table 16 Concordance of the MSI cluster with the EZ on a lobar level

	Parietal	Temporal	Insular	Total
Concordance	1	6	0	7
Partial concordance	0	1	1	2
No concordance	1	2	0	3
Total	2	9	1	12

Table 17 Concordance of the MSI cluster with the EZ on a lobar level

	Central	Superior parietal lobule	Lateral temporal	Mesial temporal	Basal temporal	Insular	Total
Concordance	1	0	0	4	0	0	5
Partial concordance	0	0	0	2	1	1	4
No concordance	0	1	1	1	0	0	3
Total	1	1	1	7	1	1	12

Figure 10 Concordance of MSI cluster localization with the epileptogenic zone

4.3.6 MSI cluster concordance with the resection cavity compared to surgical outcome

Concordance of MSI cluster localization with the resection cavity was compared to surgical outcome. On a lobar level, nine patients (56%) with concordant results achieved seizure freedom while three patients (19%) had poor surgical outcome. Three patients (19%) with non-concordant results achieved seizure freedom and one patient (6%) with non-concordant results had poor surgical outcome (Table 18). These results generated a sensitivity of 75% and specificity of 25%. The positive predictive value was 75% and negative predictive value 25%. On a sublobar level, nine patients (56%) with MSI cluster localization concordant with the resection cavity achieved good surgical outcome, two (13%) did not. Three patients (19%) with non-concordant results achieved seizure freedom after resection and two patients (13%) with non-concordant results had poor surgical outcome (Table 19). The sensitivity was 75% and specificity 50%. Positive predictive value was 82% and negative predictive value 40%. These results were not statistically significant ($p > 0.05$).

Table 18 Concordance of the MSI cluster with the resection cavity on a lobar level compared to surgical outcome

	Seizure free	Not seizure free	Total
Concordance	9	3	12
No concordance	3	1	4
Total	12	4	16

Table 19 Concordance of the MSI cluster with the resection cavity on a sublobar level compared to surgical outcome

	Seizure free	Not seizure free	Total
Concordance	9	2	11
No concordance	3	2	5
Total	12	4	16

4.3.7 Comparison of MSI cluster concordance with the IZ, SOZ and EZ

Concordance levels of the MSI cluster with the irritative zone, seizure onset zone and the epileptogenic zone were compared to each other. Both concordance and partial concordance were classified as concordant for this test. In 94% of all patients, MSI cluster localizations on a lobar level were concordant with the irritative zone identified with intracranial EEG. In 81% of all patients, MSI cluster localization showed lobar concordance with the localization of the seizure onset zone and in 75% of patients with a seizure free outcome, there was concordance between the MSI cluster and the epileptogenic zone (Table 20). On a sublobar level, 94% of all patients showed concordance between MSI cluster localization and the irritative zone. For the seizure onset zone, there was concordance with the MSI cluster in 69% of all patients. Concordance between the MSI cluster and the epileptogenic zone was 75% (Table 21). Differences in concordance were not statistically significant on a lobar and sublobar level ($p > 0.05$).

Table 20 Comparison between concordance of the MSI cluster with the IZ, SOZ and EZ on a lobar level

	Concordance	No concordance	Total
Irritative Zone	15	1	16
Seizure Onset Zone	13	3	16
Epileptogenic Zone	9	3	12

Table 21 Comparison between concordance of the MSI cluster with the IZ, SOZ and EZ on a sublobar level

	Concordance	No concordance	Total
Irritative Zone	15	1	16
Seizure Onset Zone	11	5	16
Epileptogenic Zone	9	3	12

4.3.8 Comparison of MSI cluster coverage to concordance with the IZ and SOZ and surgical outcome

Nine patients (56%) with a fully covered MSI cluster had concordant results between the cluster and IZ on a sublobar level, while no patients with full coverage had non-concordant results. Five patients (31%) with a partially covered MSI cluster had concordant results with the IZ as defined with ICEEG on a sublobar level, one patient (Pt. no. 14; 6%) had non-concordant results. One patient (6%) with an MSI cluster not directly covered by intracranial electrodes had concordant results with the IZ on ICEEG (Table 22). Results were not statistically significant ($p > 0.05$).

Eight patients (50%) with fully covered MSI clusters had MSI localizations concordant with localization of the SOZ identified with ICEEG on a sublobar level. One patient (Pt. no. 4; 6%) with a fully covered MSI cluster showed no concordance with the SOZ on a sublobar level. Two patients (13%) with partial coverage of the MSI cluster showed concordant results with the SOZ while four patients (Pts. no. 9, 10, 14, 15; 25%) with a partially covered MSI cluster showed no concordance with the SOZ. One patient (6%) with no direct coverage of the MSI cluster showed concordant results with the SOZ on a sublobar level (Table 23). Results were not statistically significant ($p > 0.05$).

Of twelve patients who obtained seizure freedom following surgical resection, six patients (50%) had a fully covered MSI cluster during intracranial registrations, five patients (42%) had partial coverage and one patient (8%) showed no coverage of the MSI cluster (Table 24).

Table 22 Comparison of concordance between the MSI cluster and IZ defined with ICEEG on a sublobar level with respect to coverage of the MSI cluster

	Concordance	No concordance	Total
Fully covered	9	0	9
Partial coverage	5	1	6
Not covered	1	0	1
Total	15	1	16

Table 23 Comparison of concordance between the MSI cluster and SOZ defined with ICEEG on a sublobar level with respect to coverage of the MSI cluster

	Concordance	No concordance	Total
Fully covered	8	1	9
Partial coverage	2	4	6
Not covered	1	0	1
Total	11	5	16

Table 24 Comparison of surgical outcome depending on coverage of the MSI cluster

	Seizure free	Not seizure free	Total
Fully covered	6	3	9
Partial coverage	5	1	6
Not covered	1	0	1
Total	12	4	16

4.4 Quantitative analysis

Detailed results of the accuracy observed of MSI to localize the reference zones can be found per patient in the addendum (Table S1).

4.4.1 Comparison of the accuracy of MSI to localize the IZ, SOZ and EZ

The mean distance between the MSI cluster and the irritative zone was 18.4 ± 8.7 mm. The mean distance between the MSI cluster and the seizure onset zone was 28.9 ± 16.9 mm. The mean distance between the MSI cluster and the epileptogenic zone was 14.2 ± 12.3 mm (Table 25). The mean distance of the MSI cluster to the irritative zone was found to be significantly different from the mean distance of the MSI cluster to the seizure onset zone ($p \leq 0.01$).

Table 25 Average distances between the MSI cluster and the IZ, SOZ and EZ

	N	Range (mm)	Minimum (mm)	Maximum (mm)	Mean (mm)	Std. Deviation (mm)
Average distance between the MSI cluster and IZ	16	35,9	9,5	45,4	18,4	8,7
Average distance between the MSI cluster and SOZ	16	62,6	14,6	77,2	28,9	16,9
Average distance between the MSI cluster and EZ	12	41,2	,0	41,2	14,2	12,3

4.4.2 Comparison of the mean distance between the MSI cluster and the IZ, SOZ and EZ with respect to surgical outcome

The mean distance between the MSI cluster and the irritative zone as identified with ICEEG was compared to patients' surgical outcome. In patients with good outcome (Engel = I), the mean distance was 19.1 ± 9.8mm. In patients with poor surgical outcome, the mean distance between the MSI cluster and the irritative zone was 16.1 ± 4.4mm (Table 26). Similarly, the mean distance from the MSI cluster to the seizure onset zone was calculated with respect to surgical outcome. In patients with good surgical outcome, the mean distance was 25.4 ± 11.5mm. In patients with poor outcome, this distance was 39.3 ± 27.4mm (Table 27). Lastly, when comparing the distance between the MSI cluster and the resection cavity in patients with good outcome versus poor outcome, a mean distance of 14.2 ± 12.3mm was observed in the former, and 34.1 ± 23.9mm in the latter respectively (Table 28). See Figure 11 for visual representation. The distance of the MSI cluster to the IZ, SOZ and RS was not significantly different in patients with good versus poor surgical outcome ($p > 0.05$).

Table 26 Average distance between the MSI cluster and the IZ depending on surgical outcome

	Mean (mm)	N	Std. Deviation (mm)
Seizure free	19,1	12	9,8
Not seizure free	16,1	4	4,4
Total	18,4	16	8,7

Table 27 Average distance between the MSI cluster and the SOZ depending on surgical outcome

	Mean (mm)	N	Std. Deviation (mm)
Seizure free	25,4	12	11,5
Not seizure free	39,3	4	27,4
Total	28,9	16	16,9

Table 28 Average distance between the MSI cluster and the resection cavity depending on surgical outcome

	Mean (mm)	N	Std. Deviation (mm)
Seizure free	14,2	12	12,3
Not seizure free	34,1	4	23,9
Total	19,2	16	17,4

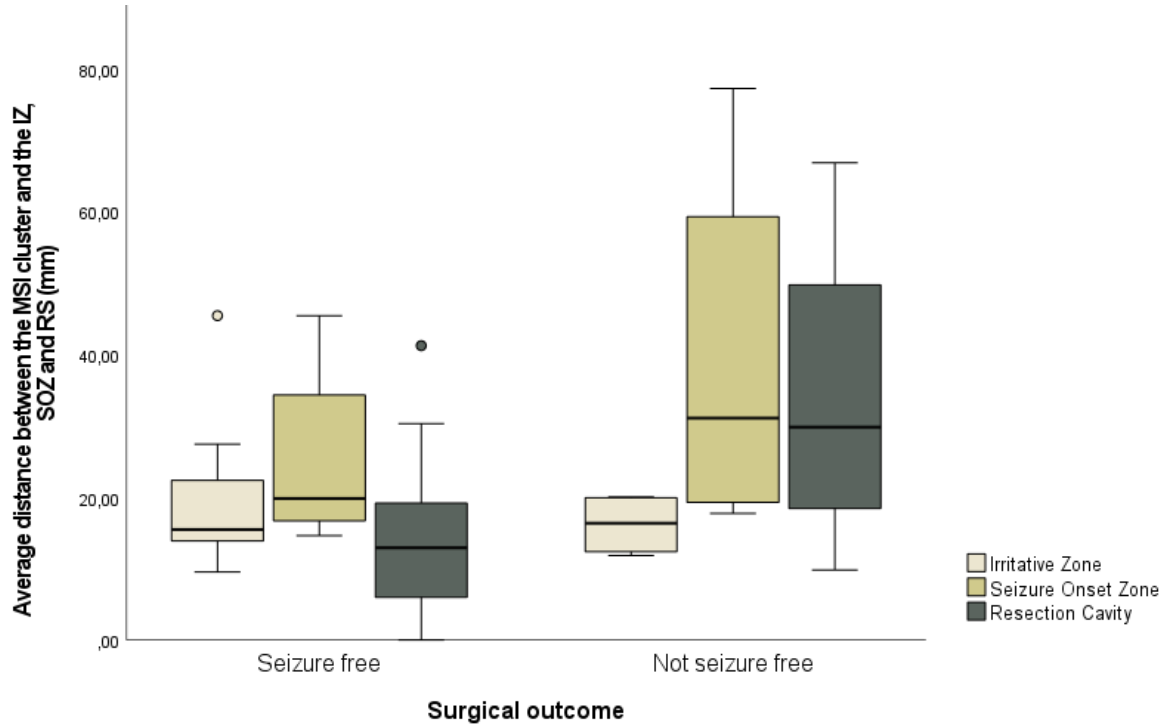

Figure 11 Boxplot showing the difference in mean distance of the MSI cluster to the irritative zone, seizure onset zone and resection cavity depending on surgical outcome

4.4.3 Comparison of the mean distance between the MSI cluster and the IZ and SOZ depending on MSI cluster coverage

The mean distance between the MSI cluster and the IZ in patients with a fully covered cluster was 15.4 ± 4.7mm. The mean distance between the MSI cluster and the IZ in patients with a partially covered cluster was 22.4 ± 12.3mm. The mean distance between the MSI cluster and the IZ in patients with an MSI cluster not directly covered by intracranial electrodes was 20.7mm (Table 29). These results were not statistically significant ($p > 0.05$).

The mean distance between the MSI cluster and the SOZ in patients with full coverage of the cluster by intracranial electrodes was 26.0 ± 20.0mm. The mean distance between the MSI cluster and the SOZ in patients with partial coverage of the MSI cluster was 35.5 ± 10.5mm. The mean distance between the MSI cluster and the SOZ as identified with intracranial EEG in patients with an MSI cluster not directly covered with intracranial electrodes was 15.4mm (Table 30). This distance was significantly different between patients with full coverage and partial coverage ($p \leq 0.05$) and between patients with no coverage and partial coverage ($p \leq 0.05$). However, after Bonferroni correction neither remained statistically significant.

Table 29 Average distance between the MSI cluster and the IZ depending on cluster coverage

	Mean (mm)	N	Std. Deviation (mm)
Fully covered	15,4	9	5,0
Partial coverage	22,4	6	12,3
Not covered	20,7	1	.
Total	18,4	16	8,7

Table 30 Average distance between the MSI cluster and the SOZ depending on cluster coverage

	Mean (mm)	N	Std. Deviation (mm)
Fully covered	26,0	9	20,0
Partial coverage	35,5	6	10,5
Not covered	15,4	1	.
Total	28,9	16	16,9

Discussion

This retrospective study attempted to assess the accuracy of magnetic source imaging to localize the irritative zone, seizure onset zone and epileptogenic zone as defined in the presurgical epilepsy evaluation. The nature of the signal magnetoencephalography generally registers (interictal epileptiform discharges), predicts that the accuracy will be optimal for localizing the irritative zone. These results were also investigated with respect to surgical outcome. Considering the small patient population included in this study, results should be interpreted with caution and extrapolation is unadvisable. They do however provide useful insights into certain tendencies within this patient population and could be informative to situate the results obtained in this specific refractory epilepsy reference center among others.

5.1 Patient selection

After application of extensive selection criteria on a large anonymized database, sixteen patients were included in this study. However, it is noteworthy that out of twenty-six candidate-patients, twenty-one (81%) showed MEG results providing information on the localization of the epileptogenic zone. This result is similar to the 20% negative MSI cases Knowlton et al.[7] observed in their study. All patients included in this study showed structural abnormalities on MRI. This contradicts the usual indication of MEG and ICEEG in those patients without consensus on localization of the epileptogenic zone based on non-invasive standard techniques. The absence of structural lesions on MRI in particular is a large contributor to this indication[2]. Therefore, MRI abnormalities in the entire patient population in the database were examined, 64% of whom showed structural abnormalities possibly related to epilepsy. Patients who underwent both MEG and ICEEG, but not necessarily surgical resection showed structural abnormalities in 91% of cases. A selection bias was likely introduced, favoring inclusion of patients with structural abnormalities due to a higher likelihood of being surgical candidates[34].

5.2 Data localization

5.2.1 Localization Magnetic Source Imaging

Due to the fast deterioration of the magnetic signal with increasing distance, MEG is theorized to have decreased sensitivity for deep sources[29]. This hypothesis has been validated multiple times in experimental settings[43-45], with the sensitivity of MEG for mesial temporal sources ranging between 25% and 60% detection of IEDs. With respect to the present study, three out of 16 patients (19%) presented with two MSI clusters. All three non-dominant clusters were localized in the temporal lobe or insula. One non-dominant cluster (Pt. no. 7) was localized in the contralateral mesial temporal hemisphere. These bilateral IEDs are frequently observed in mesial temporal lobe epilepsy (mTLE), with Ergene et al.[46] reporting their existence in 61% of the mTLE patients observed in a 24h scalp EEG recording. In the present study, one additional patient (Pt. no. 12) showed bilateral IEDs on ICEEG. Nonetheless, only one cluster of ECDs was detected with MEG in the hemisphere of the seizure onset zone. Pt. no. 16 showed IEDs on ICEEG both in the occipital and mesial temporal region, MEG detected a cluster solely in the occipital region. Including only the dominant MSI cluster in analysis of the accuracy of MSI, determined based on the amount of ECDs in the cluster, might provide an underestimation of the true asset of MEG. As reported in the present study, all three non-dominant clusters were localized in the temporal lobe, and intracranial recordings identified the SOZ in all three

patients in the mesial temporal lobe. Taking into account the decreased sensitivity of MEG for mesial temporal sources[43-45], raises the question whether the clusters identified as non-dominant in this study had lower IED activity in the region during MEG recording or presented as non-dominant due to a lower percentage of spikes being recorded. Therefore, results of the MEG investigation should always be interpreted in light of all results obtained during the presurgical epilepsy evaluation and caution is warranted especially in the case of deep sources.

With respect to dipole orientation, Baumgartner et al.[47] report two kinds of MEG dipole orientations in mTLE patients. One is the anterior temporal vertical dipole, which would originate in the mesial-basal temporal lobe, the other is the anterior temporal horizontal dipole, with its origin in the temporal pole. Pataraia et al.[48] reproduced these results, thereby adding the lateral temporal region as source for the anterior temporal horizontal dipole. Analysis of the MSI clusters in the present study did not take into account this orientation. This might have introduced erroneous localizations in patients with anterior temporal ECDs. Two patients with lateral temporal localizations of their respective MSI clusters (Pts. no. 8 and 11) showed anterior, basal and mesial temporal ECDs. Their irritative zone, seizure onset zone and epileptogenic zone were located mesial temporal (Pt. no. 8) and basal temporal (Pt. no. 11) respectively.

5.2.2 Localization Intracranial EEG

According to Lachaux et al.[5] intracranial electrodes register only those sources of IEDs on average no more than 10mm away, depending on the strength of the IEDs and volume conduction properties of the brain. They suggest estimation of the spatial resolution in patients if possible. This disparity in spatial resolution between patients makes it difficult to assign an arbitrary limit for within-coverage ECDs. Tamilia et al.[49] assessed the accuracy of MSI compared to ICEEG and included only those ECDs within ≤ 30mm of the nearest intracranial electrode. The publication did however not state the experimental rationale for this 30mm cutoff value. In the present study, coverage of the MSI clusters by intracranial electrodes was determined based on visual assessment. One patient's MSI cluster was not directly covered with electrodes (Pt. no. 16), but was however included for further analysis. This could be justified by the proximity of the subdural grid to the MSI cluster, the distance of which was smaller than 15mm. All MSI clusters were evaluated in their entirety, resulting in certain clusters only partially covered by intracranial electrodes. This may lead to underestimation of the accuracy of MSI in patients presenting with ECDs in areas not covered by electrodes. Future research should aim at identifying an experimentally determined standard on the spatial resolution of intracranial electrodes, to allow for more precise validation of functional imaging modalities against ICEEG.

With regard to localization of the irritative zone, it is important to note that this was performed based on the IEDs measured with intracranial electrodes. Considering sampling capacity of the brain is limited with ICEEG, it is not possible to proclaim absoluteness of the detected IZ. In certain patients it may prove more extensive in the case of additional electrode coverage.

5.2.3 Localization Resection cavity

Seizure freedom after surgical resection for temporal lobe epilepsy is obtained in about 70% of patients[34,50,51]. In the present study, nine out of ten patients (90%) who underwent surgical resection in the temporal lobe obtained seizure freedom. All nine had structural abnormalities on MRI. Three out of six patients (50%) with extra-temporal resections had good surgical outcome. Holtkamp et al.[52] investigated surgical outcome in 25 patients with frontal lobe epilepsy who underwent ICEEG and surgical resection and observed seizure free outcome in fifteen patients (60%). There was no significant difference in outcome between patients with MRI abnormalities and non-lesional patients. This contradicts the results by Carrette et al.[42] who observed seizure free outcome in 69% of all patients included in the study, while 83% of patients with structural abnormalities overlapping with the SOZ identified with ICEEG obtained seizure free outcome. Téllez-Zenteno et al.[53] reported an odds ratio of 2.5 to achieve seizure

freedom in patients with structural abnormalities. This substantial difference may however result from including all patients who underwent surgical resection versus solely patients who underwent ICEEG during their presurgical evaluation, as was the case in the two previously mentioned studies. Due to its high spatial resolution, ICEEG might substantially improve seizure onset identification, thereby diminishing the improved odds of structural lesions on MRI. Complete resection of the lesion identified on MRI is an important predictor for surgical outcome. Only 21% of patients with partial lesionectomy obtained seizure freedom versus 80% of patients with complete lesionectomy[54]. Similarly, the present study observed that four out of six patients (67%) with subtotal resection of the presumed epileptogenic zone, corresponding with the lesion detected on MRI, did not obtain seizure freedom. Due to this subtotal resection, it was not possible to uncover whether the poor surgical outcome was the result of false localization of the epileptogenic zone, or the result of overlap with eloquent cortex.

5.3 Qualitative analysis

5.3.1 Concordance of MSI with the IZ, SOZ, EZ

Kim et al.[55] investigated ten patients with refractory focal epilepsy to determine the accuracy of MSI. They observed sublobar concordance between ECDs and the irritative zone in 90% of patients. This result is similar to the result obtained in the current study, in which localization of the MSI cluster showed at least partial concordance with the irritative zone in 94% of all patients on a lobar and sublobar level. The role of the irritative zone in the presurgical epilepsy evaluation with respect to surgical outcome has often been debated. In 1987, Wyllie et al.[56] reported that complete resection of the irritative zone and seizure onset zone was associated with good surgical outcome in 86% of patients. Only 51% of those in whom resection did not encompass all areas exhibiting IEDs attained good surgical outcome. Similarly, Rassi-Neto et al.[40] investigated lesional refractory epilepsy patients and observed improved seizure free outcome in patients who underwent resection of both the lesion and adjacent irritative cortex versus those who underwent resection restricted to the lesion (91% vs 60%). On the other hand, Bartolomei et al.[57] quantified spike generation and seizure initiation in thirty-two patients based on stereo-EEG (SEEG) recordings. They reported concordance between regions of maximal spike generation and seizure initiation in eighteen patients (56%). Patients with focal cortical dysplasia (FCD) showed the highest level of concordance, in fifteen out of twenty patients (75%). Patients who did not have FCD showed concordant results in four out of twelve (33%). These results suggest that even though the irritative zone can be a valuable indicator for localizing the seizure onset zone, areas of maximal spiking activity and ictal onset do not necessarily overlap[57]. They do however supply evidence for the role of the irritative zone in guiding intracranial electrode implantation. Similarly, several studies have investigated magnetoencephalography in light of guiding intracranial electrode implantation. De Tiège et al.[41] reported additional intracranial electrode coverage based on MSI results in five out of seventy patients (7%). Three patients (4%) previously rejected for surgical resection were indicated for ICEEG after disclosure of the MSI results and one patient (1%) could undergo surgical resection without intracranial monitoring[41]. Similar results were obtained in other studies[58,59], demonstrating MEG's ability to provide non-redundant localization information. Results observed in the present study verify this ability to detect the IZ as identified by the gold standard intracranial EEG. In previous literature it has been described that MEG is more sensitive to neocortical extra-temporal sources than mesial temporal sources[32,44,45,60]. This difference in regional sensitivity of MEG could not be reproduced in this study, likely due to a limited number of patients.

Santiuste et al.[43] performed simultaneous MEG and intracranial EEG recordings, thereby observing ECDs localized to the sublobe of the seizure onset zone in all four included patients. By performing simultaneous registrations, spikes registered on ICEEG but not on MEG had to be a consequence of restricted sensitivity of MEG to detect the sources. During non-simultaneous investigations, spikes might originate from diverging sources, resulting in a lower number of concordant cases. This can be observed when comparing these results to those obtained in other studies. Almubarak et al.[61] reported 75% concordance on a lobar level with

intracranial EEG but only 36% concordance on a sublobar level. Kim et al.[55] obtained higher results of concordance, with 67% of patients showing sublobar concordance with the SOZ. These results correspond closely to the (at least partial) concordance on a sublobar level obtained in the present study in 69% of all patients. Minassian et al[62] obtained even more superior results with a concordance rate of 91% with the seizure onset zone as identified with intracranial EEG in eleven children with non-lesional extratemporal epilepsy. This higher rate of concordance might be a results of MEG's increased sensitivity for neocortical sources compared to mesial temporal sources[44,45], the latter of which were abundant in the present study. It is important that results observed in the present study are interpreted cautiously due to uncomplete coverage of the MSI cluster in a number of patients.

5.3.2 Magnetic source imaging with respect to surgical outcome

Sensitivity, specificity and positive and negative predictive value of MEG's ability to detect the IZ, SOZ and RS were calculated. Sensitivity of MSI cluster localization to the same sublobe as the irritative zone was 92%, specificity 0%. The PPV was 73% and NPV 0%. This high sensitivity, indicating that patients with a seizure free outcome have an 92% chance of concordance between their MSI cluster and IZ, may mainly be a reflection of high concordance between the MSI cluster and the IZ in general. This becomes apparent when comparing this value to the PPV, which also takes into account the high prevalence of a good surgical outcome in the patient population, and is slightly lower due to concordance both in seizure free and non-seizure free patients. This suggests that overlap between the MSI cluster and IZ does not substantially correlate with surgical outcome. Something similar is observed in the NPV value of 0%, which indicates that non-concordance between the MSI cluster and the IZ is predictive of good surgical outcome. This seems counterintuitive and at most one would expect no relation between concordance of the MSI cluster with the IZ and surgical outcome. A probable explanation is that due to the high percentage of seizure free patients with concordant results, the NPV is based on one single patient and cannot be employed for projections to a wider population.

Knowlton et al.[7], reported a PPV of 82% and a NPV of 44% for concordance between MSI and the SOZ identified with ICEEG. These results were almost identical to the results obtained in the present study, which observed a PPV of 82% and NPV of 40% for both concordance of the MSI cluster with the SOZ and the RS on a sublobar level. RamachandranNair et al.[63] observed a sensitivity of 100% for concordance of the MSI cluster with the resection cavity, which was higher than the sensitivity obtained in this study (75%); and PPV of 72%, lower than the PPV obtained in the present study (82%). In general, overlap of MEG with the SOZ and RS appears to have better positive predictive results than negative predictive results with respect to surgical outcome[64]. Tenney et al.[65] observed an inconsistent result with a PPV of 57% and NPV of 74% for MSI localization concordance with the SOZ. Only sixteen out of thirty-two patients (50%) in their population obtained seizure freedom, which may contribute to the high NPV and low PPV reported.

When comparing the results obtained for concordance between the MSI cluster and the SOZ or RS to the results obtained for concordance between the MSI cluster and the IZ, it was observed that the sensitivity decreased (75% vs 92%) and specificity increased (50% vs 0%) for concordance of the MSI cluster with the SOZ or RS. Due to a lower number of concordant cases, these tests could be performed on a more well-balanced distribution of patients. The PPV (82% vs 73%) and NPV (40% vs 0%) were both higher for MSI cluster concordance with the SOZ or RS than with the IZ. This indicates that concordance between the MSI cluster and the SOZ or RS is more predictive of seizure free outcome than concordance between the MSI cluster and the IZ. A higher NPV indicates that non-concordance between the MSI cluster and the SOZ or RS is more predictive of poor surgical outcome than non-concordance between the MSI cluster and the IZ. It is however important to keep in mind the patients with poor surgical outcome in this study. Due to incomplete resections in all four, it is uncertain whether the poor surgical outcome was the result of false localizations of the epileptogenic zone.

5.3.3 Concordance of the MSI cluster with the IZ and SOZ depending on MSI cluster coverage

When comparing concordance of the MSI cluster with the IZ on a sublobar level in light of cluster coverage, it was observed that the single patient (Pt. no. 14) with non-concordant results showed only partial coverage of the MSI cluster by the intracranial electrodes. These results suggest that even if the MSI cluster is only partially covered with intracranial electrodes, identification of the irritative zone is still possible in certain patients. However, even more importantly, these results indicate that in one patient with non-concordant results and only partial coverage of the MSI cluster, it is impossible to state with certainty whether this non-concordance is the result of no IEDs in the area during ICEEG, or due to IEDs not being registered as a result of non-coverage with electrodes.

Similarly, when comparing results of MSI cluster concordance with the SOZ on a sublobar level depending on cluster coverage, six patients showed only partial coverage of the MSI cluster, four of which (Pts. no. 9, 10, 14, 15; 67%) had non-concordant results with the SOZ defined with ICEEG. In patients with full coverage of the MSI cluster, only one patient showed non-concordant results (Pt. no. 4). These results seem suggestive of a correlation between full MSI cluster coverage and identification of the SOZ with MSI. Without full coverage of the MSI cluster by intracranial electrodes it is impossible to know whether a (secondary) SOZ was present in the area defined by MSI. When attempting to interpret these observations, it is however important to keep in mind additional factors which might influence these results. For instance, the possibility might exist that in certain patients with partial coverage of the MSI cluster, MEG results contradicted a plausible hypothesis of localization of the epileptogenic zone identified with multiple testing modalities. Therefore, this area indicated by MEG should be excluded as SOZ, and therefore sampled, but perhaps sampling was not performed as extensive as in the main region of interest.

When considering the obtained results of MSI cluster coverage in light of surgical outcome, no correlation seems present. One patient (Pt. no. 15) with partial MSI cluster coverage and non-concordant results between MSI localization and localization of the SOZ on a sublobar level had poor surgical outcome. The three remaining patients with partial MSI cluster coverage and non-concordant results between the cluster and SOZ had good surgical outcome.

5.4 Quantitative analysis

5.4.1 Accuracy of MSI to localize the IZ, SOZ, EZ

The mean distance between the MSI cluster and the irritative zone was 18.4 ± 8.7mm. This result is in line with observations by Tamilia et al.[49], who observed a mean distance of 15.4 ± 12.2mm between ECDs and the IZ. Interestingly, they eliminated the obstacle of an inherent distance between the ECDs and the cortical electrodes, due to their restricted presence, by performing source localization on the intracranially obtained IEDs. This was labeled the '*ground-truth*' irritative zone. Their reported result did however not differ tremendously from that observed in the present study. This could be due to the limited sampling capacity of intracranial electrodes[5], as a result of which the sources of IEDs cannot be localized far from the registered signal. Kim et al.[55] observed a mean distance of 9.3 ± 10.8mm between MEG spike sources and intracranially registered IEDs; only half the distance demonstrated in the current study. No explanation could be identified for this discrepancy based on the reported methodology. An important distinction between the present study and both aforementioned studies lies in the approach to calculating the mean distance. The latter averaged the distance of every ECD registered rather than comparing clusters of spikes. By using this approach statistical significance will be obtained more easily due to a larger number of observations. However, patients with a higher spiking frequency will be over-represented in the final result.

Kim et al.[55] reported a mean distance of 21.5 ± 15.6mm between the ECDs and the nearest ICEEG ictal onset contacts. Similar to before, the result obtained in the present study is less accurate, with a mean distance between the MSI cluster and the seizure onset zone of 28.9 ± 16.9mm. This distance was significantly larger than the distance between the MSI cluster and

the irritative zone ($p \leq 0.01$). Considering both MEG and interictal ICEEG measure interictal epileptiform discharges, and the IZ is generally more extensive than the SOZ[2], this greater accuracy is in line with expectations. Results concerning the distance between the MSI cluster and the IZ and SOZ need to be interpreted cautiously. Due to the presence of ECDs which were not directly covered by intracranial electrodes, the obtained results might underestimate the accuracy of MEG to localize these zones.

A mean distance of 13.4 ± 13.8mm between the ECDs and the resection cavity in twenty-four children with epilepsy who became seizure free after surgical resection was reported by Tamilia et al.[49]. This corresponds closely to the distance between the MSI cluster and the epileptogenic zone (14.2 ± 12.3mm) obtained in the present study. This result was slightly smaller than the distance between the MSI cluster and the irritative zone (18.4 ± 8.7mm) and considerably smaller than the distance between the MSI cluster and the seizure onset zone (28.9 ± 16.9mm). This may seem counterintuitive as the seizure onset zone is the main driver for surgical resection. However, it is important to keep in mind that the distance between the MSI cluster and the IZ and SOZ was measured between each ECD and the nearest interictally active or ictal onset electrode, while the distance between the MSI cluster and the epileptogenic zone was measured between each ECD and the nearest volume point in the resection cavity. While the epileptogenic zone will overlap with the seizure onset zone, it will inherently be more extensive as a certain distance is present in between activated intracranial electrodes. In addition, in some patients the resection included removal of tissue beyond the seizure onset zone, based on very active interictal activity or fast spread of ictal activity to nearby regions.

5.4.2 Accuracy of MSI with respect to surgical outcome

The distance between the MSI cluster and the IZ was slightly larger in patients with good surgical outcome than in those with poor outcome. This result is contraindicative, but similar to the one observed when comparing concordance of the MSI cluster and the IZ to surgical outcome (5.3.2). The accuracy in good versus poor outcome groups is a result of the mean distance, therefore, due to a lower amount of observations, the distance in patients with poor outcome will have a stronger effect on the overall result. The result suggests that adjacency of the MSI cluster to the IZ is not an indicator of good surgical outcome.

Tamilia et al. observed a significantly closer localization of ECDs to the resection cavity in patients with good surgical outcome versus patients with poor surgical outcome. This tendency was similarly observed in the present study, in which the accuracy of MSI to localize the SOZ and RS appeared to differ between seizure free and non-seizure free patients. These results did not reach statistical significance. However, a limited amount of patients in the study and loss of statistical power due to the use of non-parametric tests are likely contributors to this non-significance. The mean distance between the MSI cluster and the SOZ or RS was smaller in patients who obtained seizure freedom than in patients with poor surgical outcome. This suggests a correlation between closer localization of the MSI cluster to the SOZ or RS and an increased likelihood of seizure freedom. The range of distances between the MSI cluster and the SOZ or RS in patients with poor surgical outcome is remarkably larger than the range in patients with good surgical outcome, especially considering fewer patients are present in the poor outcome group.

5.4.3 Accuracy of MSI with respect to cluster coverage

The distance between the MSI cluster and the IZ and SOZ was larger in patients with partial coverage of the MSI cluster compared to those with full coverage. This result supports the assumption that various ECDs may have been located outside of coverage of the intracranial electrodes. This confirms that caution should be employed in the interpretation of the results obtained in this study concerning the accuracy of magnetic source imaging based on intracranially recorded data.

5.5 Conclusion

Magnetic source imaging can be deemed a reliable method for localizing the irritative zone, seizure onset zone and epileptogenic zone. This justifies the use of magnetoencephalography in the presurgical epilepsy evaluation, especially in those patients where conventional methods provide non-sufficient information on the localization of the epileptogenic zone. In addition, its results can reliably guide implantation of intracranial electrodes due to its substantial concordance with all three zones reviewed. Nonetheless, it proved most accurate for localizing the irritative zone, which is in line with what was hypothesized based on the nature of the recorded signals. The obtained results likely underestimate the accuracy of MSI to localize the irritative zone and seizure onset zone identified with ICEEG, due to various ECDs located outside coverage of the intracranial electrodes.

5.6 Limitations

A small patient population included in the study prevented drawing strong conclusions with regard to the observed tendencies. For future research aiming to investigate similar subjects, a multicentric study could provide the population necessitated for strong clinical evidence. Another remark is on the comparison of the MSI clusters to ICEEG. By including all ECDs which were part of the MSI cluster, the possibility exists that some IED sources could not be identified with ICEEG as IZ or SOZ due to non-coverage with electrodes. In light of the results obtained in comparing the accuracy of MSI to localize the IZ and SOZ in patients with full coverage versus partial coverage, it became apparent that the accuracy was decreased in the latter. Therefore, results presented in this study on the accuracy of MSI to localize the IZ and SOZ should be interpreted with caution. Future research should aim to identify experimentally established guidelines on intracranial electrode coverage, which could allow for more precise validation of functional imaging modalities against ICEEG. Situation of the obtained quantitative results in the current literature proved difficult due to a lack of quantitatively supported studies. Especially with regard to electrode coverage, a quantitative approach could produce more reliable indications on the accuracy of MSI.

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Poster

VALIDATION OF THE ACCURACY OF MAGNETIC SOURCE IMAGING BASED ON INTRACRANIAL RECORDINGS AND POST-OPERATIVE RESULTS

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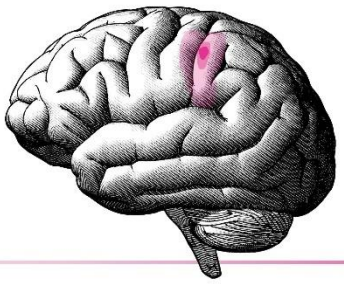
INTRODUCTION

Resective epilepsy surgery can be used to obtain seizure freedom in some patients suffering from refractory epilepsy. This requires removal of the **EPILEPTOGENIC ZONE** - the tissue indispensable for generating seizures, thus designating the resection cavity in seizure free patients its gold standard. The epileptogenic zone cannot be measured directly and has to be inferred from the localization of five cortical zones, identified by multiple diagnostic tools. For both the **IRRITATIVE ZONE** and **SEIZURE ONSET ZONE**, intracranial electroencephalography (ICEEG) is the gold standard reference.

Magnetoencephalography can detect interictal activity. Using magnetic source imaging, the origin of this activity can be estimated. The significance of MEG clusters in the presurgical epilepsy evaluation is often debated. This study will retrospectively compare MEG cluster localizations qualitatively and quantitatively to the **IRRITATIVE ZONE**, **SEIZURE ONSET ZONE** and **EPILEPTOGENIC ZONE** as defined by ICEEG and the resection cavity in seizure free patients.



IRRITATIVE ZONE

SEIZURE ONSET ZONE

EPILEPTOGENIC ZONE

AIM

How does the irritative zone identified with MEG relate to the...

... Irritative zone identified with intracranial EEG

... Seizure onset zone identified with intracranial EEG

... Resected region in seizure free patients (=epileptogenic zone)

METHODS

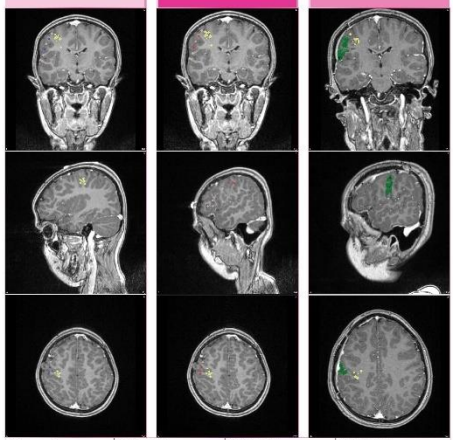
Patient selection and data collection from anonymized MEG patient database

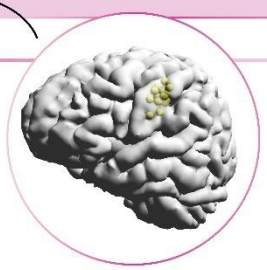
DICOM creation and localizations in Curry 8
- DICOM I – MSI Cluster
- DICOM II – Co-registration post-implantation MRI and CT with intracranial electrodes
  - DICOM IIa – Irritative zone ICEEG
  - DICOM IIb – Seizure onset zone ICEEG
- DICOM III – Resection cavity

Comparison DICOMs and qualitative and quantitative analysis

MEG CLUSTER

IRRITATIVE ZONE ICEEG	SEIZURE ONSET ZONE ICEEG	EPILEPTO-GENIC ZONE





- **MEG cluster**
- **Electrodes showing interictal activity**
- **Electrodes showing ictal onset**
- **Resected region**

RESULTS

227 patients in MEG database
— 20 patients remain

- Engel I
- Engel > I
- Waiting for follow-up

Comparison DICOMs	DICOM I vs DICOM IIa	DICOM I vs DICOM IIb	DICOM I vs DICOM III
Lobe	Concordant	Concordant	Concordant
Sublobe	Concordant	Concordant	Concordant
Average distance (mm)	16,5	16,5	12,6
Median distance (mm)	15,6	15,6	11,7

NEXT STEPS

In the next steps, for all remaining patients, three DICOMs will be created. These will be classified to a lobe and sublobar region to qualitatively evaluate concordance. Quantitatively, both measurements of the average and median distance of the MEG cluster to the irritative zone, seizure onset zone and epileptogenic zone will be determined.

REFERENCES

Rosenow, F. & Lüders, H. Presurgical evaluation of epilepsy. Brain 124, 1683-1700 (2001)

Megevand, P. et al. Electric source imaging of interictal activity accurately localises the seizure onset zone. J Neurol Neurosurg Psychiatry 85, 38-43. doi:10.1136/jnnp-2013-305815 (2014)

Addendum

Results qualitative and quantitative analysis

Table S1 Results of the localizations performed in this study

	MSI cluster			Interictal ICEEG			Ictal ICEEG			Surgical resection				
No.	Lobar	Sublobar	Covered	Lobar	Sublobar	Distance (mm)	Lobar	Sublobar	Distance (mm)	Lobar	Sublobar	Distance (mm)	Subtotal resection	Outcome
1	L Frontal	Medial frontal gyrus	Y	L Frontal	Central	11,8	L Parietal	Central	20,8	L Parietal	Central	27	Y	Engel IV
2	R Temporal	Lateral temporal	Y	R Insular	Insular	15,5	R Insular	Insular	16,6	R Insular	Insular	8,4	N	Engel I
3	R Temporal	Lateral temporal	Y	R Frontal	Inferior frontal gyrus	19,8	R Frontal	Inferior frontal gyrus	17,7	R Frontal	Inferior frontal gyrus	9,8	Y	Engel III
4	L Frontal	Orbitofrontal	Y	L Frontal	Oribtofrontal	20	L Frontal	Central	77,2	L Frontal	Superior frontal gyrus	66,8	Y	Engel IV
5	L Parietal	Central	Y	L Parietal	Central	14,6	L Parietal	Central	14,6	L Parietal	Central	13,4	N	Engel I
6	R Temporal	Mesial temporal	P	RTemporal	Mesial temporal	15,4	R Temporal	Basal temporal	20,8	R Temporal	Mesial temporal	0	N	Engel I
7	R Temporal	Mesial temporal	Y	BL Temporal	Mesial temporal	13,1	R Temporal	Mesial temporal	18,8	R Temporal	Mesial temporal	3,7	N	Engel I
7	L Temporal	Mesial temporal	Y	BL Temporal	Mesial temporal	9,4	R Temporal	Mesial temporal	55,4	R Temporal	Mesial temporal	49,9	N	Engel I
8	R Temporal	Lateral temporal	P	R Temporal	Mesial temporal	27,4	R Temporal	Mesial temporal	25	R Temporal	Mesial temporal	13,6	N	Engel I
9	L Temporal	Lateral temporal	P	L Parietal	Superior parietal lobule	15,4	L Parietal	Superior parietal lobule	45,3	L Parietal	Superior parietal lobule	30,3	Y	Engel I
10	R Frontal	Orbitofrontal	P	R Temporal	Mesial temporal	18,2	R Temporal	Mesial temporal	35,1	R Temporal	Mesial temporal	12,7	N	Engel I
10	R Temporal	Lateral temporal	Y	R Temporal	Mesial temporal	25,8	R Temporal	Mesial temporal	26,7	R Temporal	Mesial temporal	25	N	Engel I
11	L Temporal	Lateral temporal	Y	L Temporal	Basal temporal	24	L Temporal	Basal temporal	33,5	L Temporal	Basal temporal	13,1	Y	Engel I

Table S2 Results of the localizations performed in this study (continued)

	MSI cluster			Interictal ICEEG			Ictal ICEEG			Surgical resection				
No.	Lobar	Sublobar	Covered	Lobar	Sublobar	Distance (mm)	Lobar	Sublobar	Distance (mm)	Lobar	Sublobar	Distance (mm)	Subtotal resection	Outcome
12	R Temporal	Mesial temporal	Y	BL Temporal	Mesial temporal	10	R Temporal	Basal temporal	16,8	R Temporal	Mesial temporal	8,2	N	Engel I
13	R Temporal	Mesial temporal	Y	R Temporal	Mesial temporal	9,5	R Temporal	Mesial temporal	17,6	R Temporal	Mesial temporal	1,2	N	Engel I
14	R Frontal	Inferior frontal gyrus	P	R Temporal	Basal temporal	45,4	R Temporal	Basal temporal	45,4	R Temporal	Mesial temporal	24,7	N	Engel I
15	L Frontal	Inferior frontal gyrus	P	L Temporal	Mesial temporal	12,9	L Temporal	Mesial temporal	41,3	L Temporal	Mesial temporal	32,6	Y	Engel II
15	L Insular	Insular	Y	L Temporal	Mesial temporal	15,5	L Temporal	Mesial temporal	21,1	L Temporal	Mesial temporal	12,9	Y	Engel II
16	R Occipital	Mesial occipital	N	R Temporal	Mesial temporal	20,7	R Temporal	Lateral temporal	15,4	R Temporal	Lateral temporal	41,2	N	Engel I

BL = Bilateral; L = Left; R = Right; N = No coverage of the MSI cluster by intracranial electrodes; P = Partial coverage of the MSI cluster by intracranial electrodes; Y = Full coverage of the MSI cluster by intracranial electrodes; Green indicates concordance with the MSI cluster, orange indicates partial concordance with the MSI cluster, red indicates non-concordance with the MSI cluster; Non-dominant MSI clusters were marked in yellow

Results Curry 8

Pt. no. 1

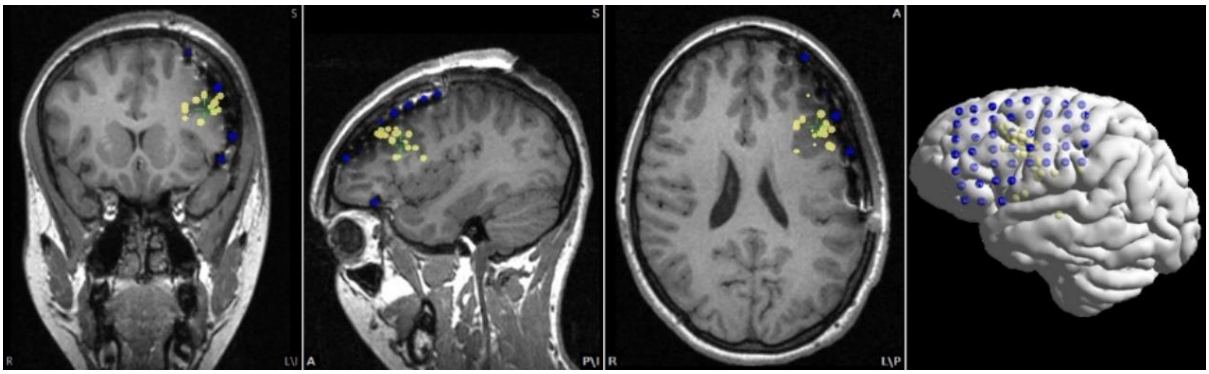


Figure S1 Localization of the MSI cluster compared to the irritative zone

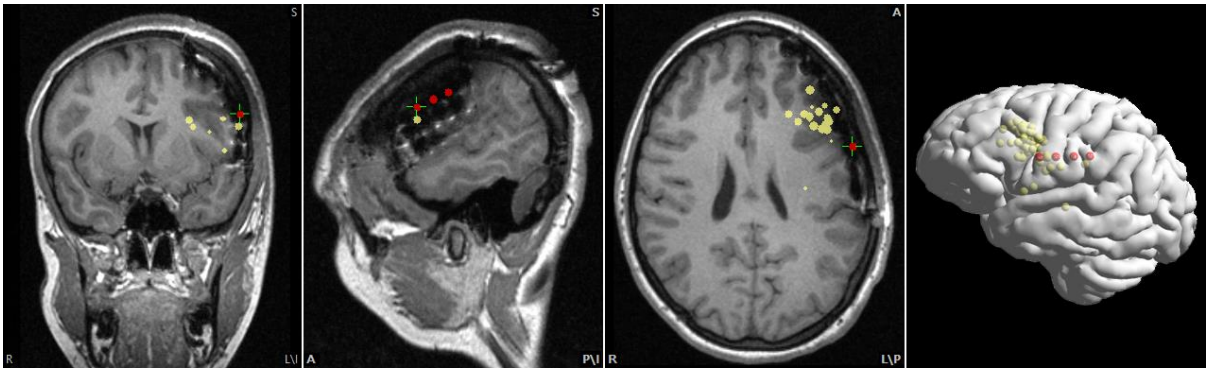


Figure S2 Localization of the MSI cluster compared to the seizure onset zone

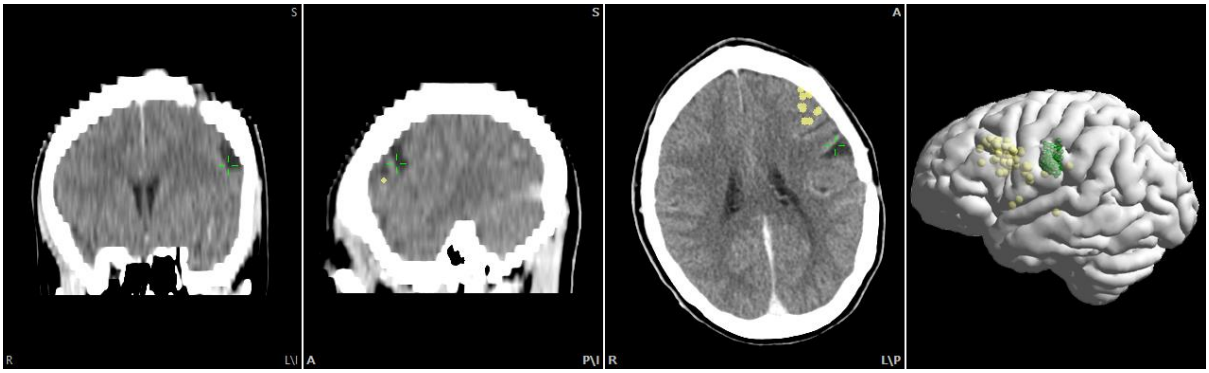


Figure S3 Localization of the MSI cluster compared to the resection cavity

Pt. no. 2

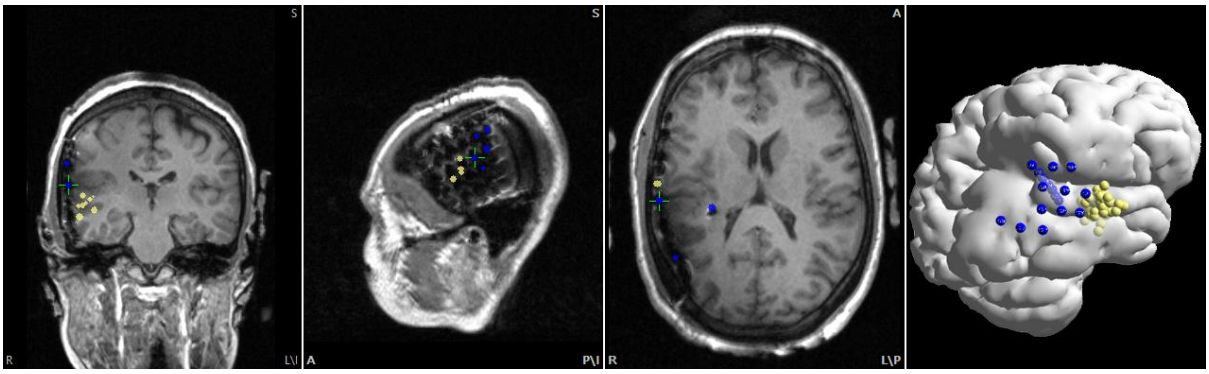


Figure S4 Localization of the MSI cluster compared to the irritative zone

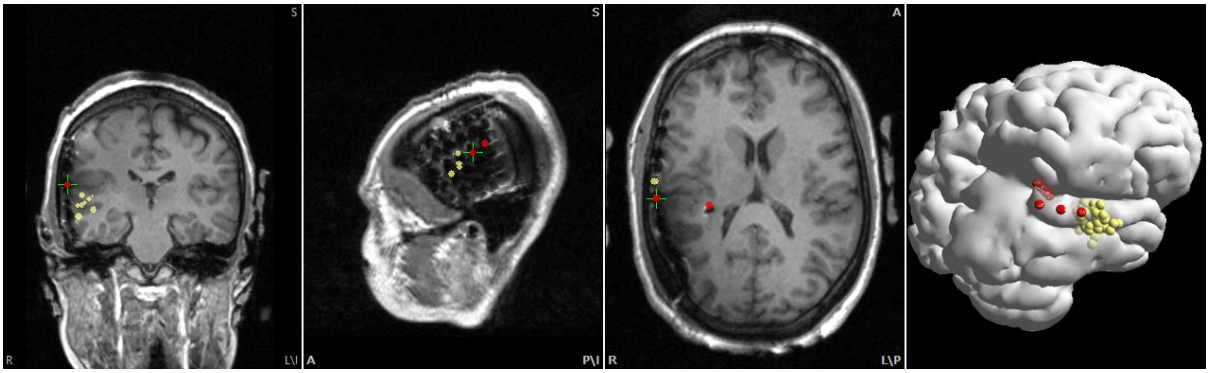


Figure S5 Localization of the MSI cluster compared to the seizure onset zone

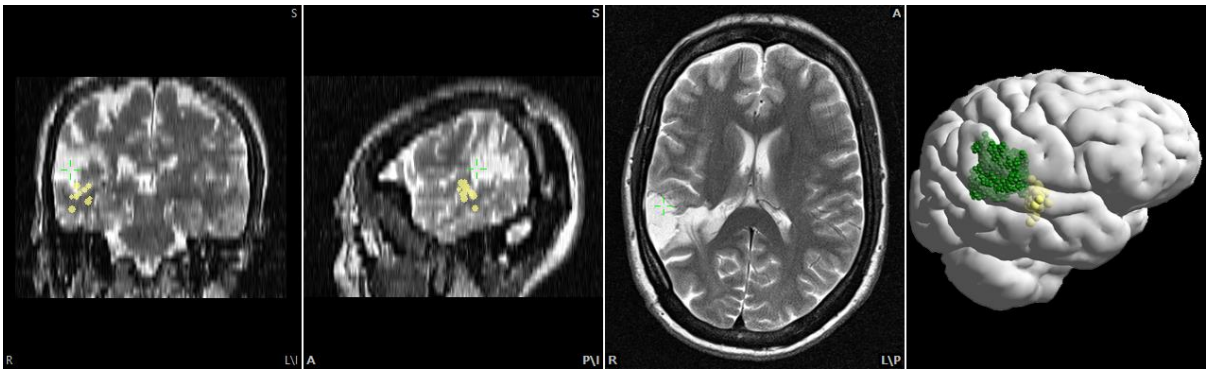


Figure S6 Localization of the MSI cluster compared to the resection cavity

Pt. no. 3

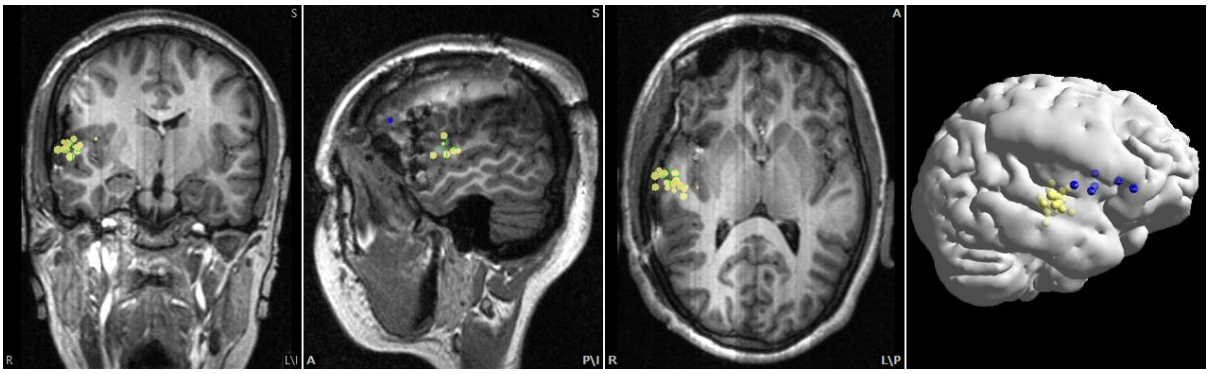


Figure S7 Localization of the MSI cluster compared to the irritative zone

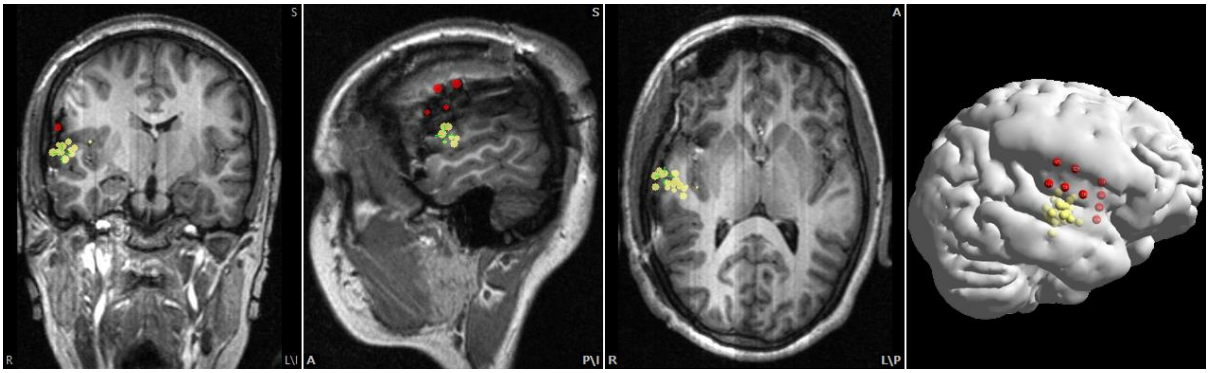


Figure S8 Localization of the MSI cluster compared to the seizure onset zone

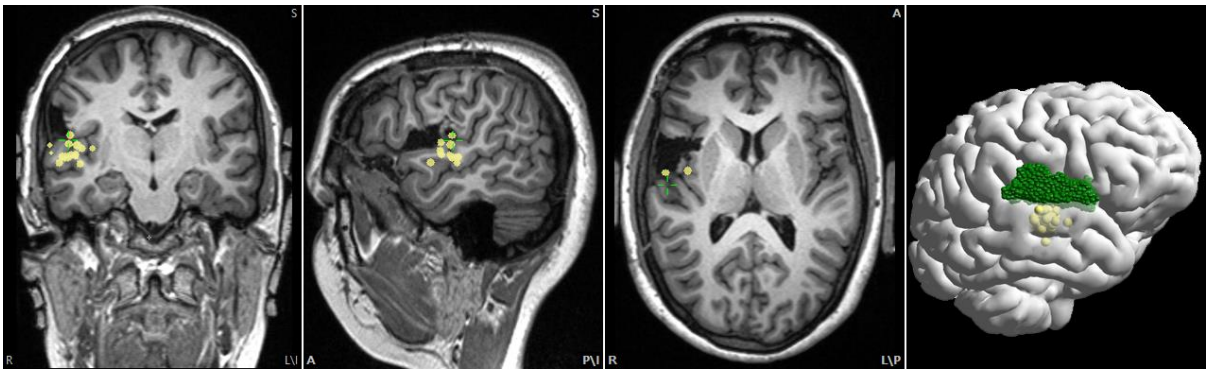


Figure S9 Localization of the MSI cluster compared to the resection cavity

Pt. no. 4

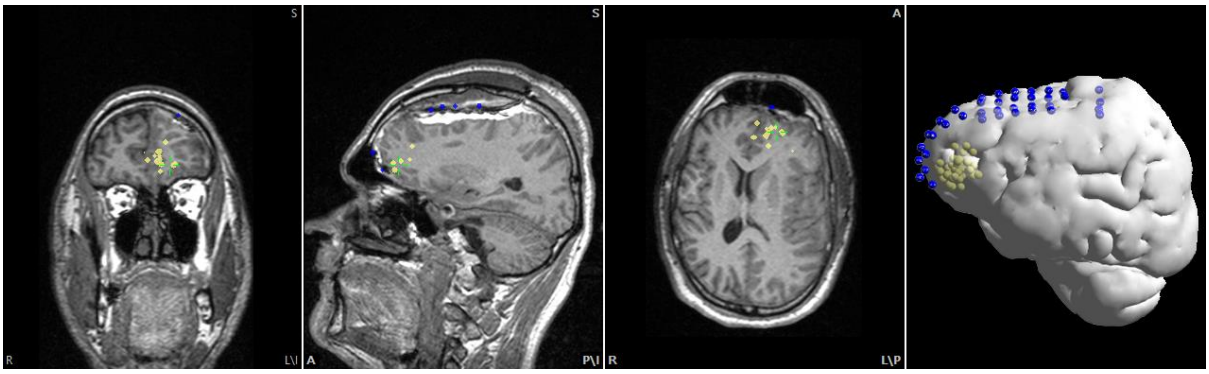


Figure S10 Localization of the MSI cluster compared to the irritative zone

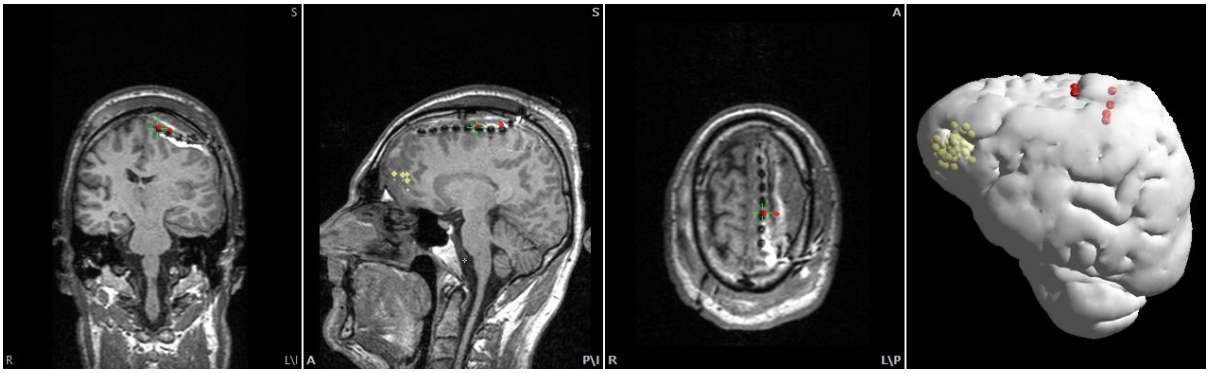


Figure S11 Localization of the MSI cluster compared to the seizure onset zone

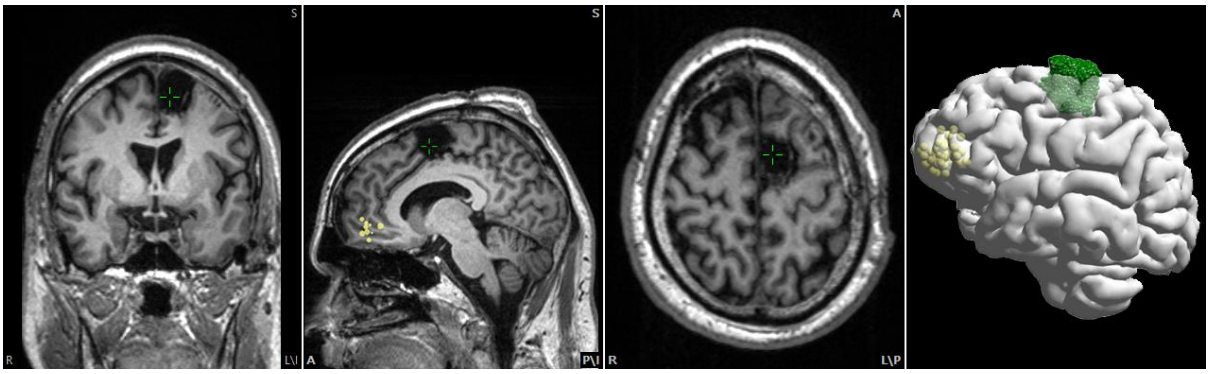


Figure S12 Localization of the MSI cluster compared to the resection cavity

Pt. no. 5

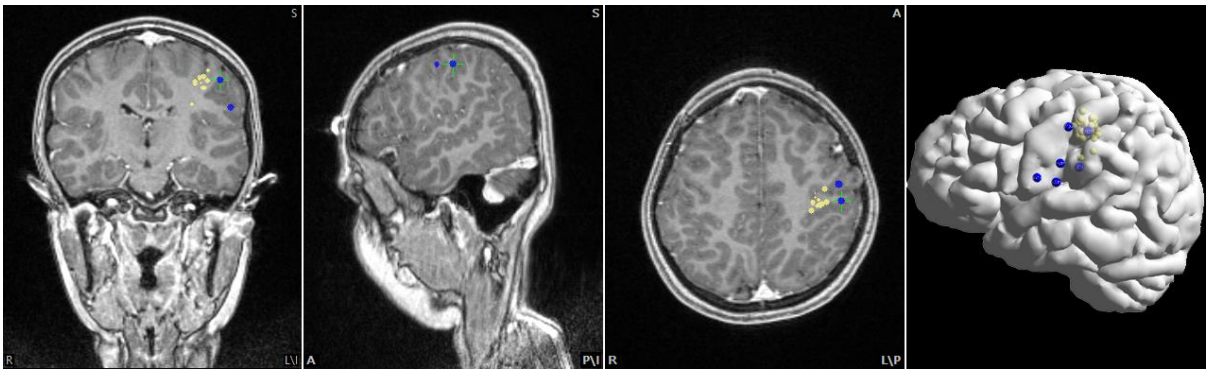


Figure S13 Localization of the MSI cluster compared to the irritative zone

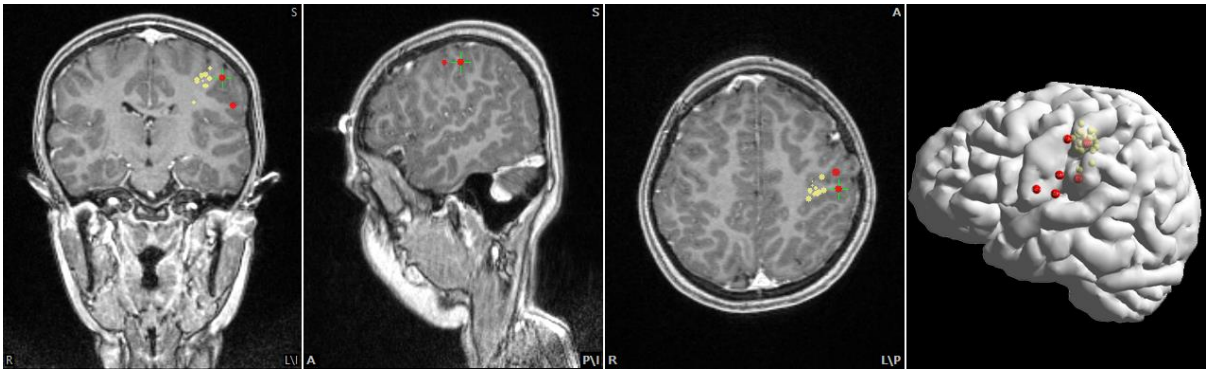


Figure S14 Localization of the MSI cluster compared to the seizure onset zone

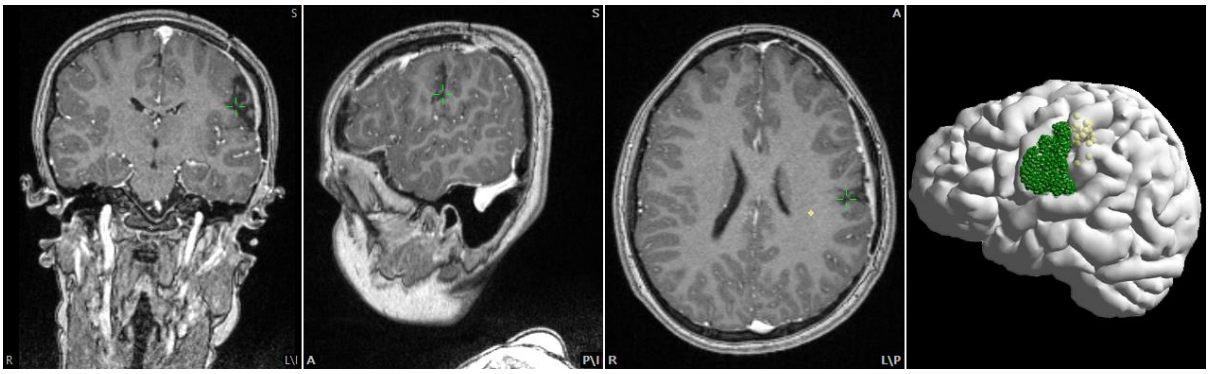


Figure S15 Localization of the MSI cluster compared to the resection cavity

Pt. no. 6

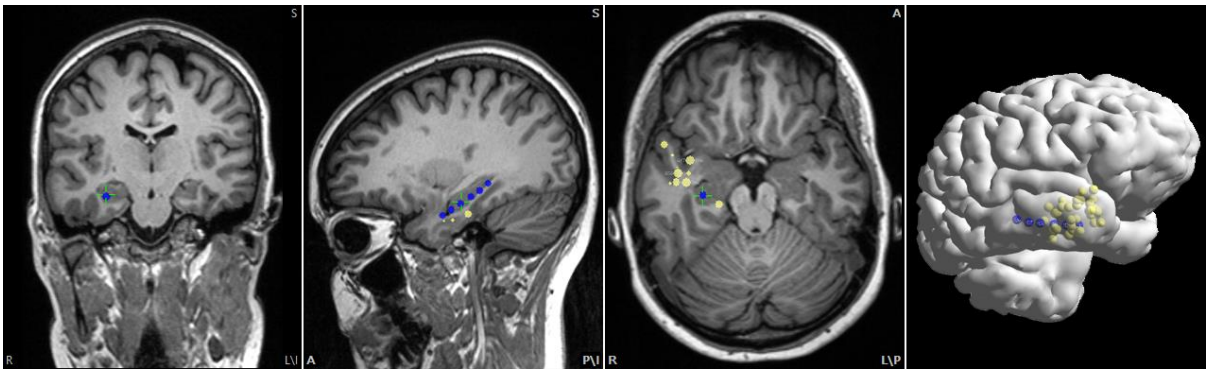


Figure S16 Localization of the MSI cluster compared to the irritative zone

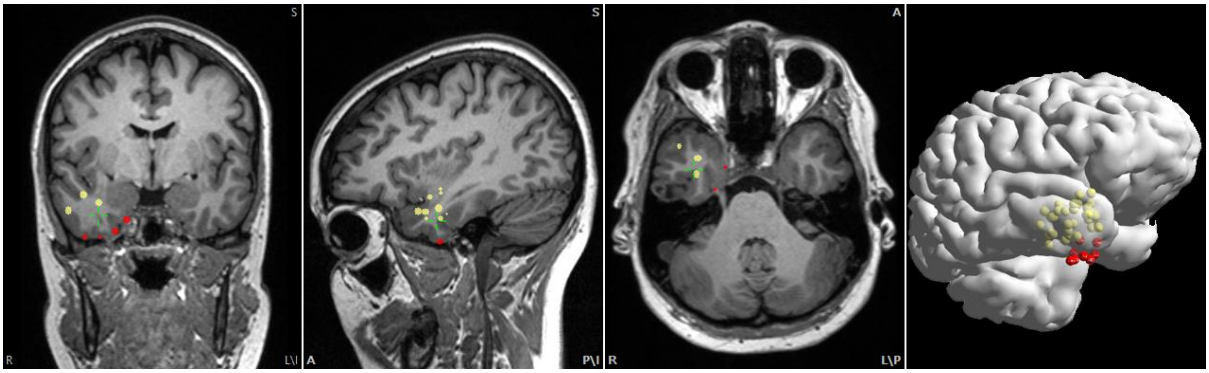


Figure S17 Localization of the MSI cluster compared to the seizure onset zone

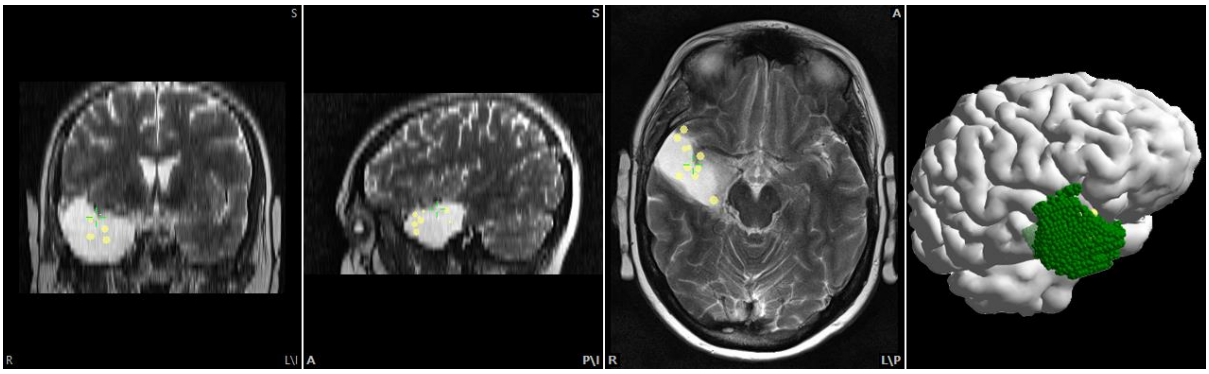


Figure S18 Localization of the MSI cluster compared to the resection cavity

Pt. no. 7

Cluster 1

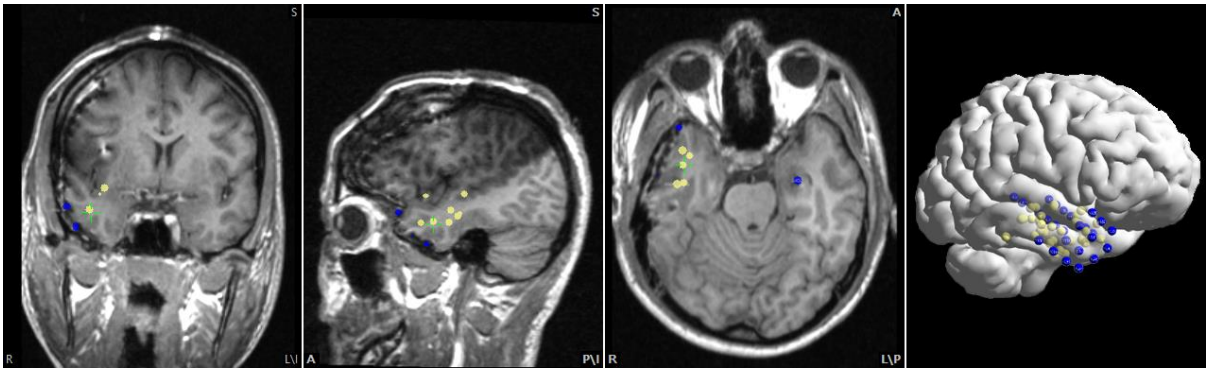


Figure S19 Localization of the MSI cluster compared to the irritative zone

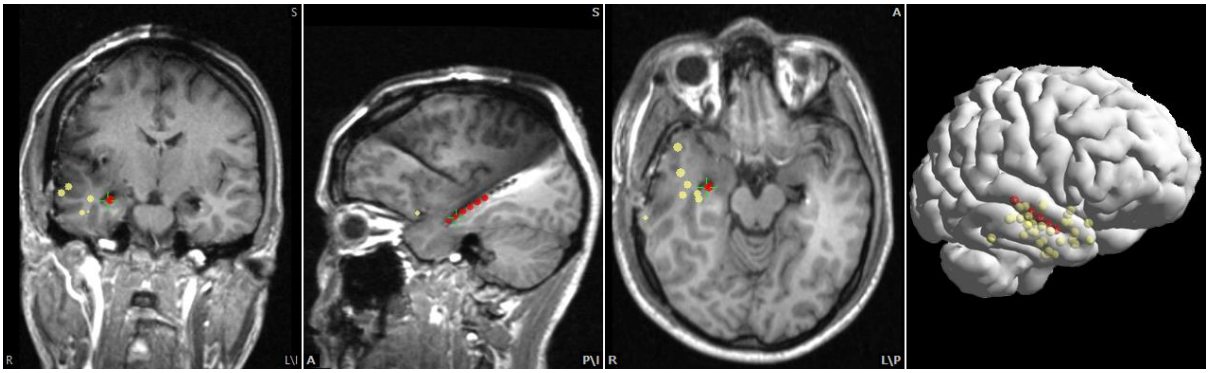


Figure S20 Localization of the MSI cluster compared to the seizure onset zone

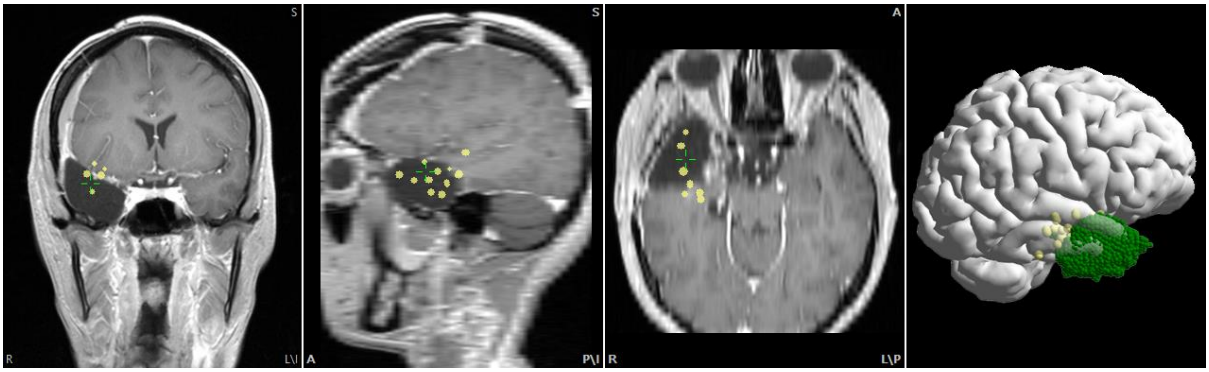


Figure S21 Localization of the MSI cluster compared to the resection cavity

Cluster 2

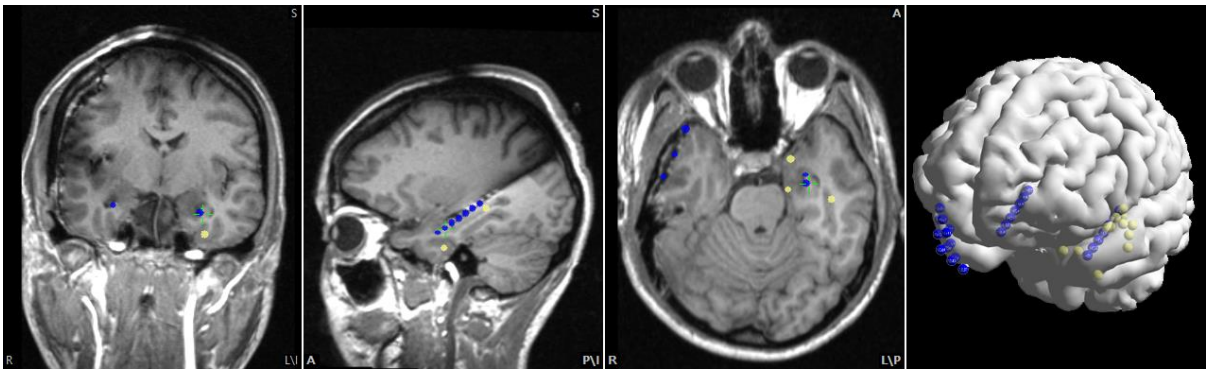


Figure S22 Localization of the MSI cluster compared to the irritative zone

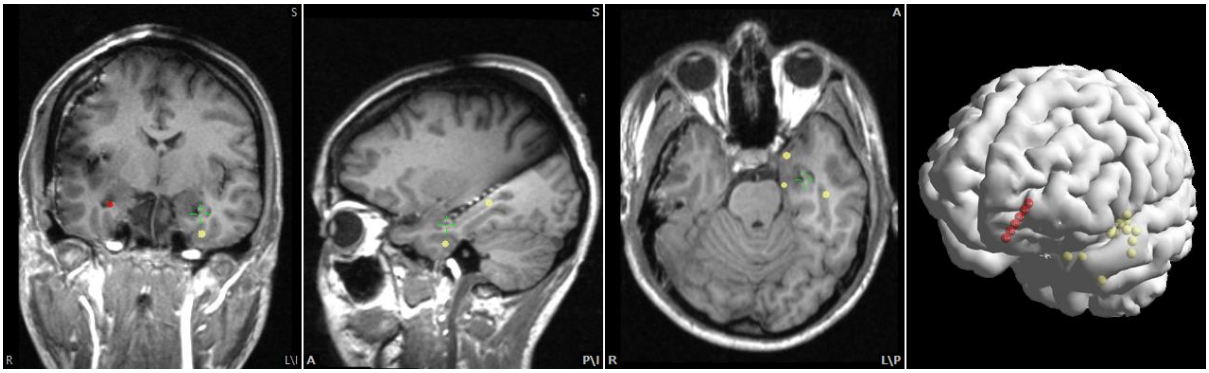


Figure S23 Localization of the MSI cluster compared to the seizure onset zone

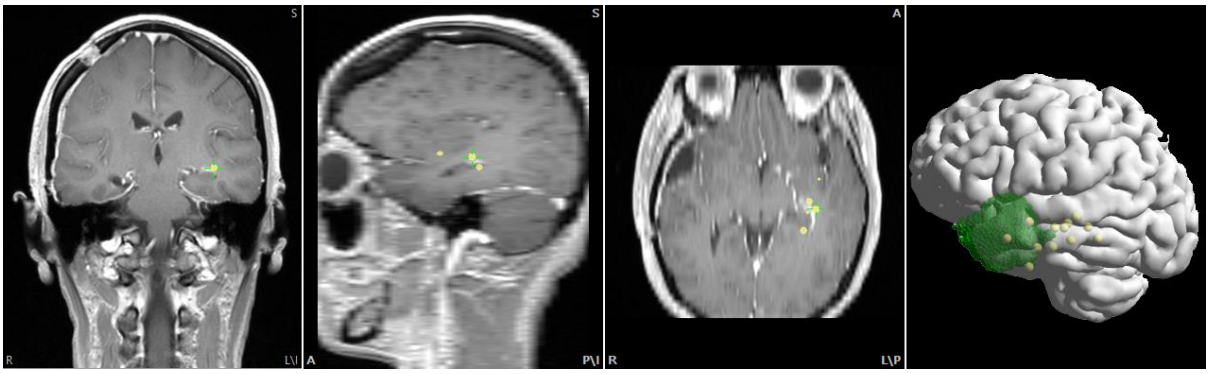


Figure S24 Localization of the MSI cluster compared to the resection cavity

Pt. no. 8

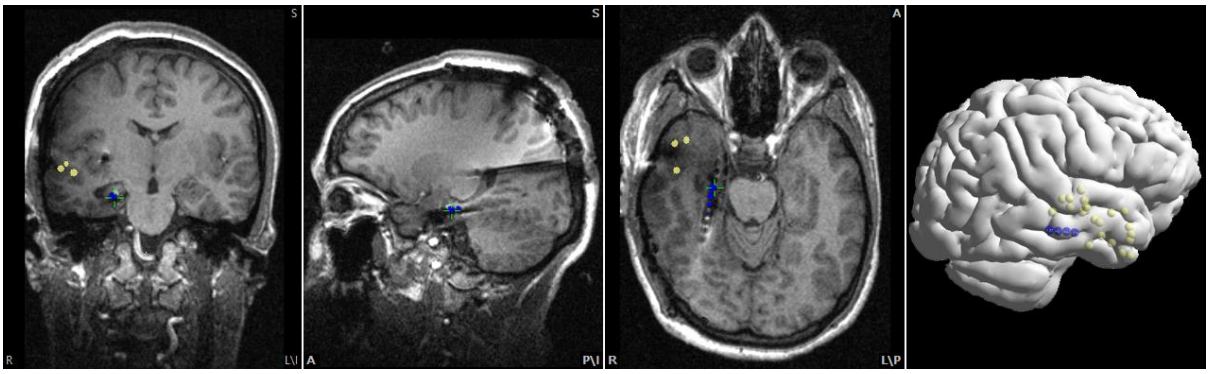


Figure S25 Localization of the MSI cluster compared to the irritative zone

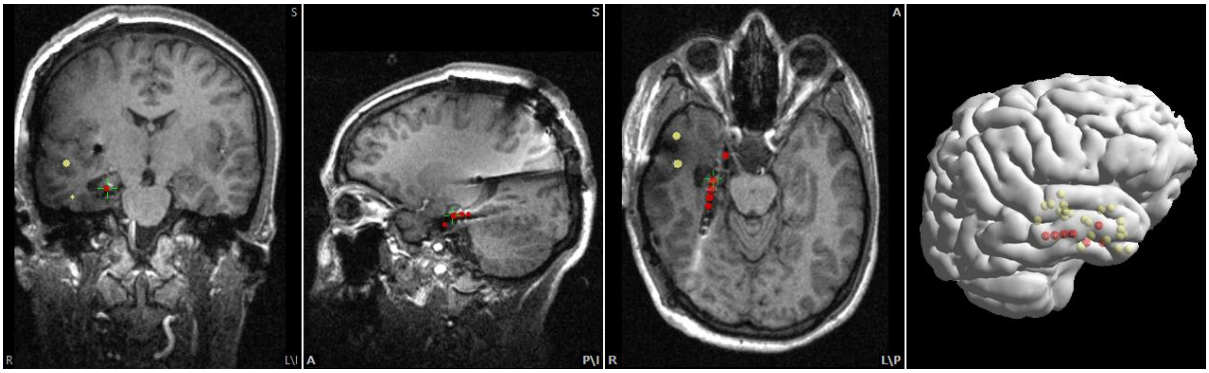


Figure S26 Localization of the MSI cluster compared to the seizure onset zone

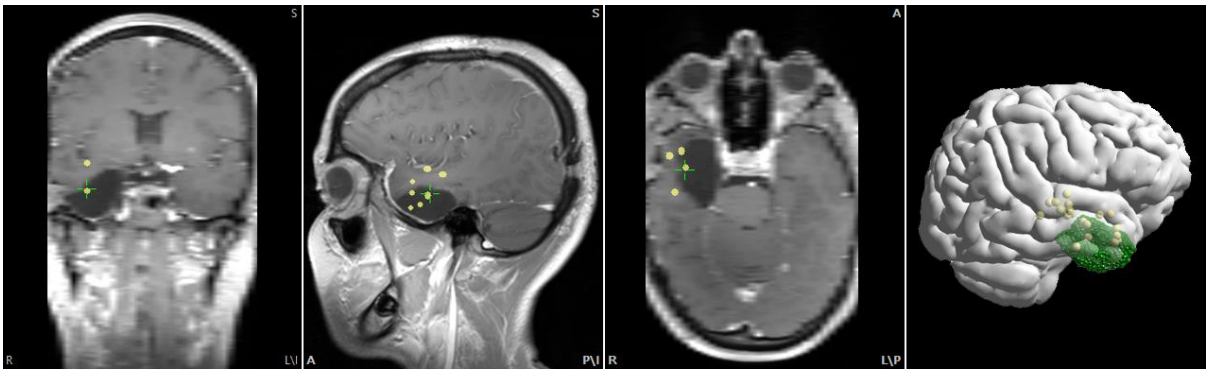


Figure S27 Localization of the MSI cluster compared to the resection cavity

Pt. no. 9

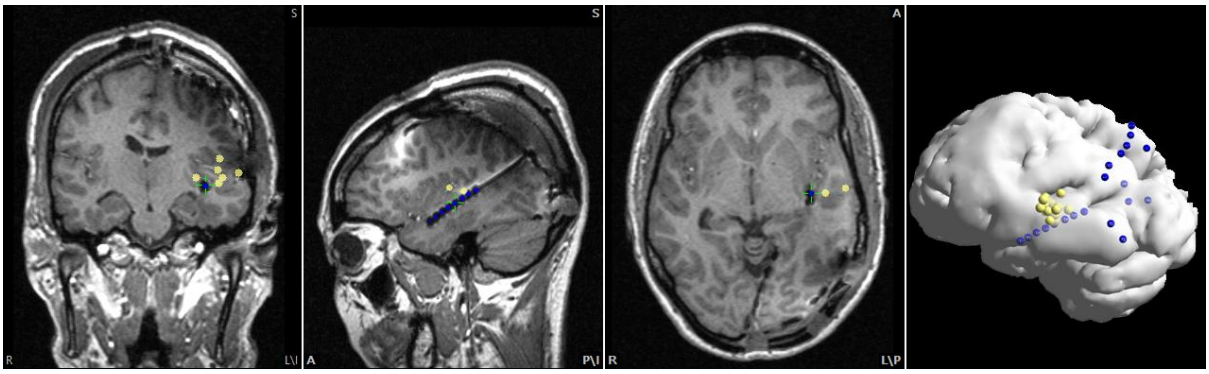


Figure S28 Localization of the MSI cluster compared to the irritative zone

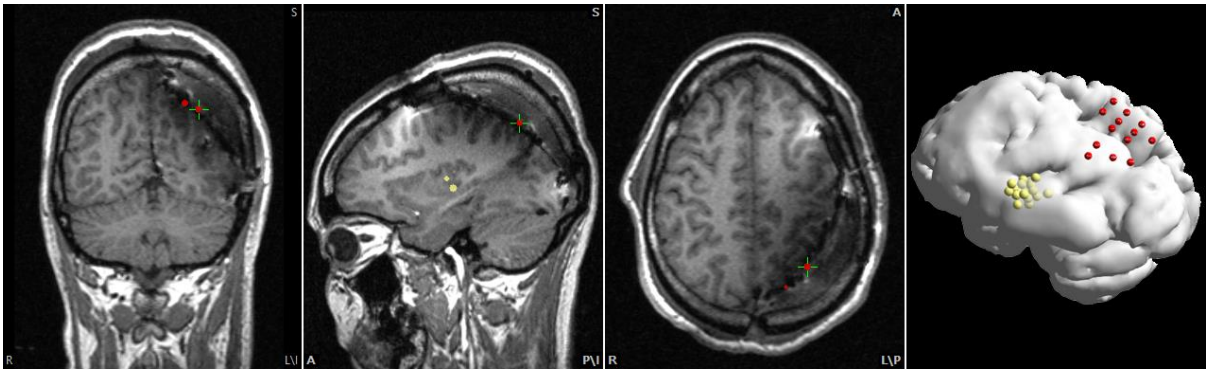


Figure S29 Localization of the MSI cluster compared to the seizure onset zone

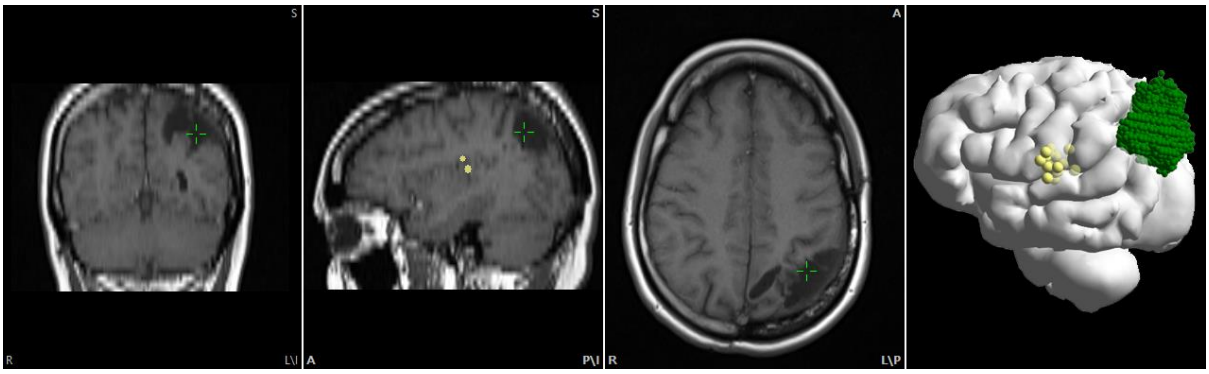


Figure S30 Localization of the MSI cluster compared to the resection cavity

Pt. no 10

Cluster 1

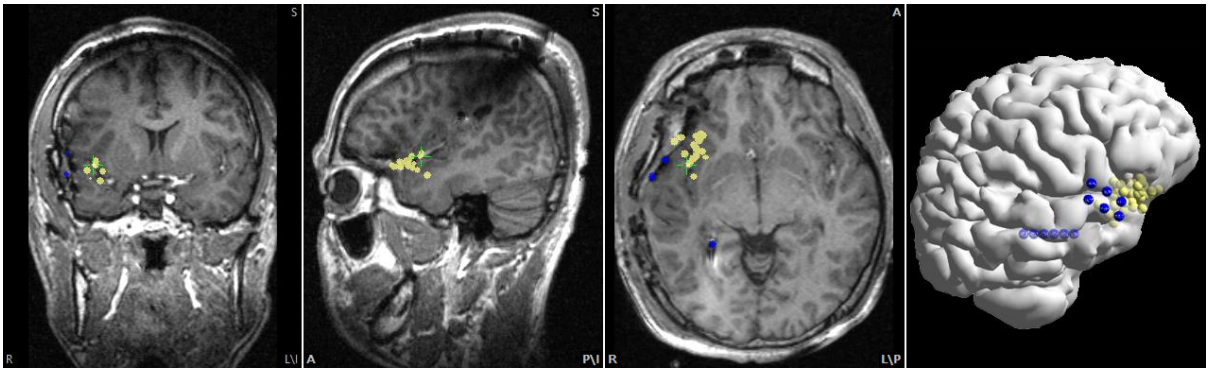


Figure S31 Localization of the MSI cluster compared to the irritative zone

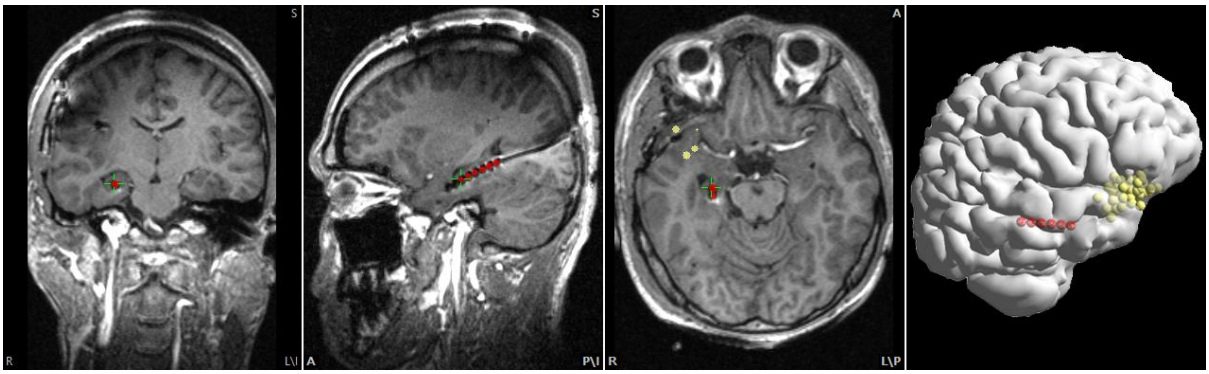


Figure S32 Localization of the MSI cluster compared to the seizure onset zone

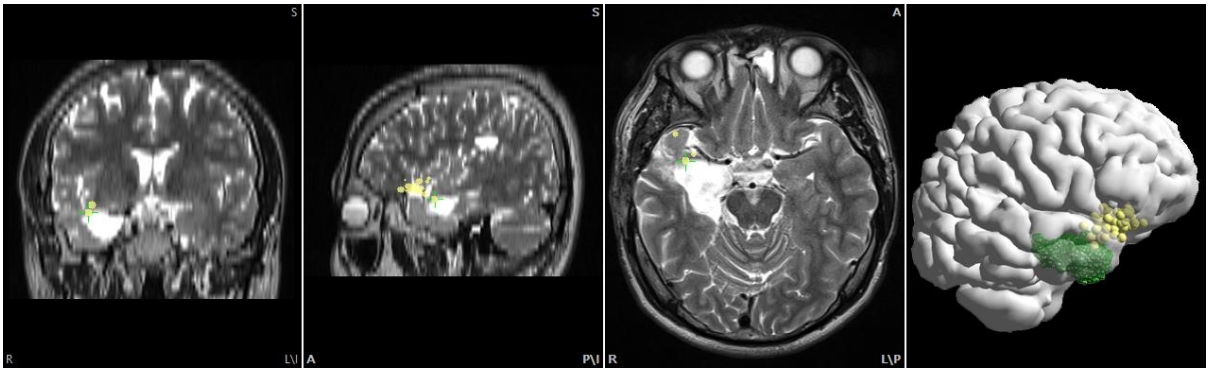


Figure S33 Localization of the MSI cluster compared to the resection cavity

Cluster 2

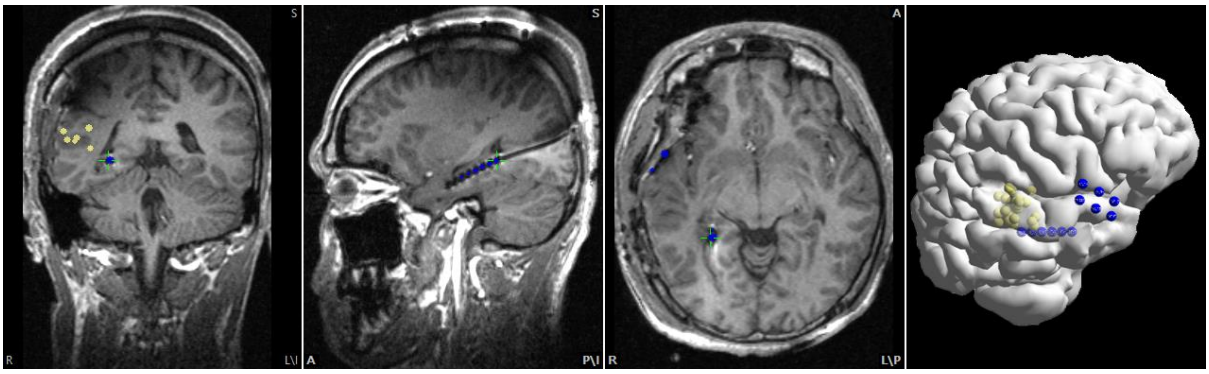


Figure S34 Localization of the MSI cluster compared to the irritative zone

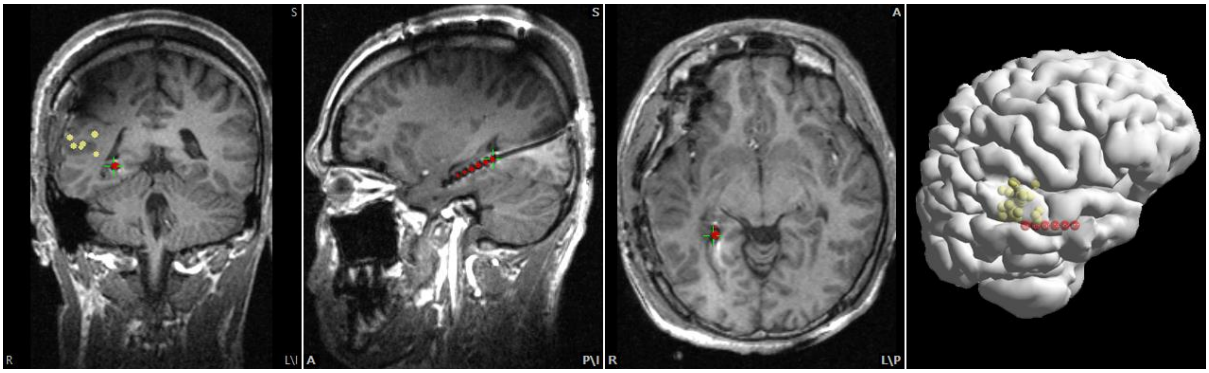


Figure S35 Localization of the MSI cluster compared to the seizure onset zone

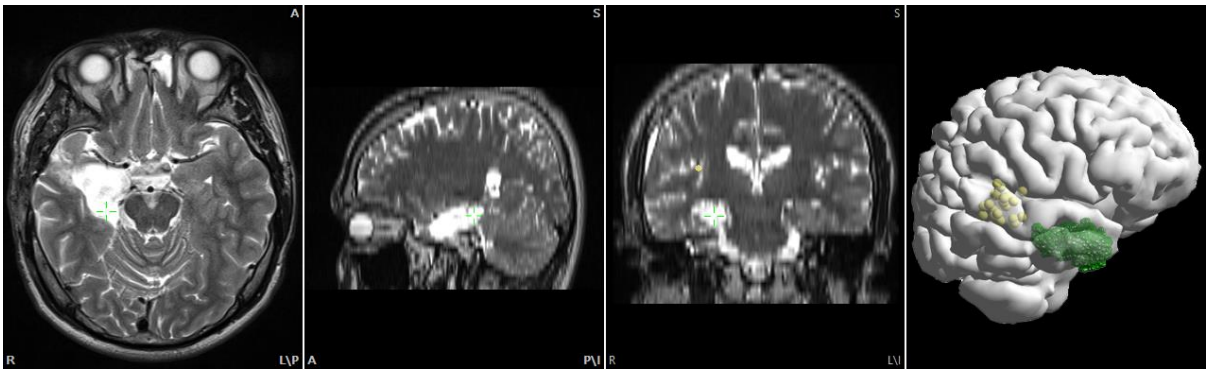


Figure S36 Localization of the MSI cluster compared to the resection cavity

Pt. no. 11

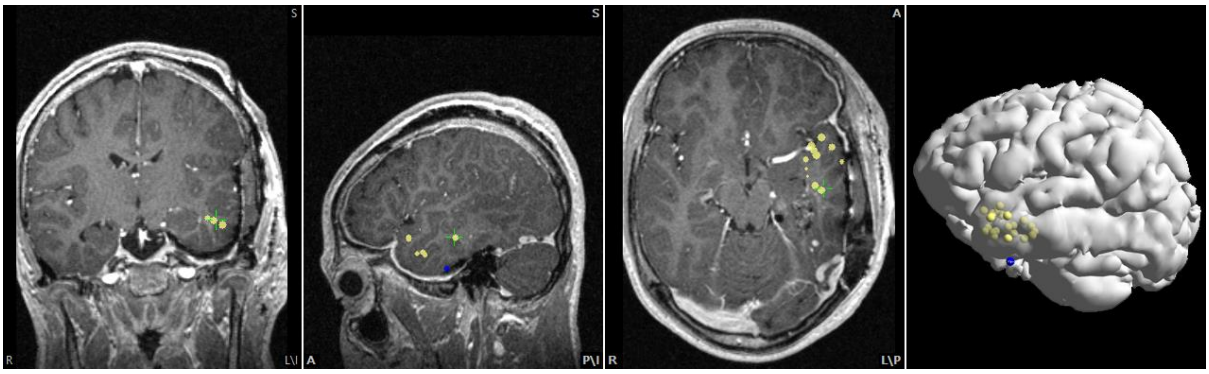


Figure S37 Localization of the MSI cluster compared to the irritative zone

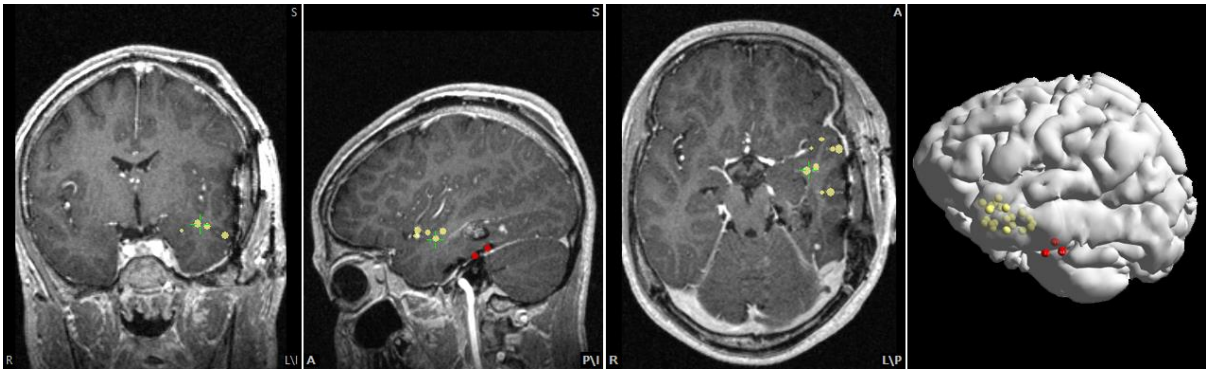


Figure S38 Localization of the MSI cluster compared to the seizure onset zone

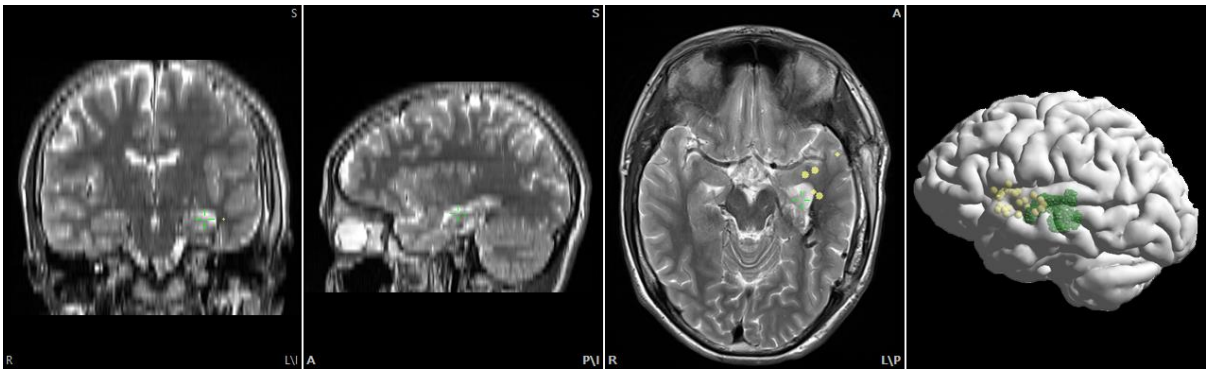


Figure S39 Localization of the MSI cluster compared to the resection cavity

Pt. no. 12

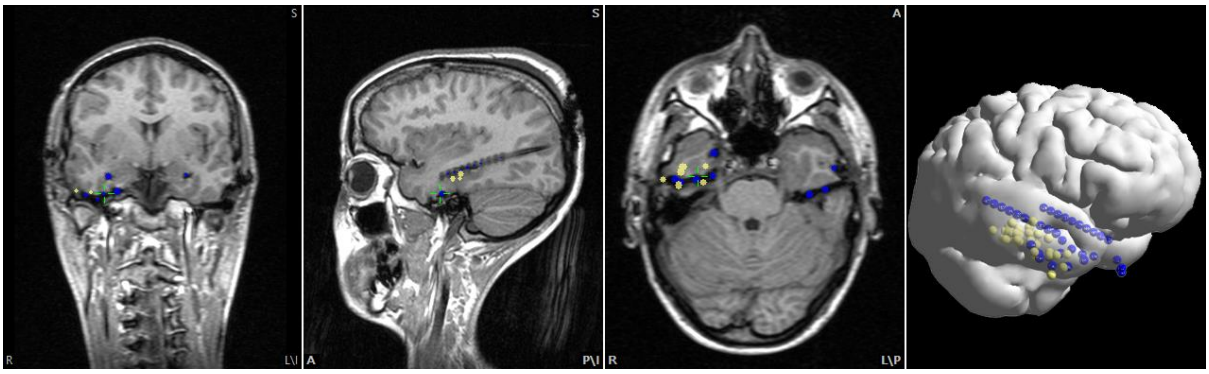


Figure S40 Localization of the MSI cluster compared to the irritative zone

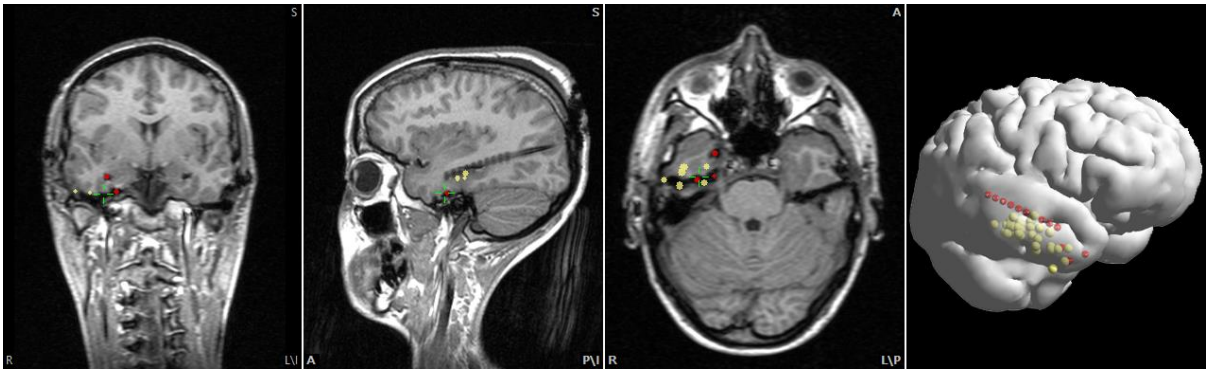


Figure S41 Localization of the MSI cluster compared to the seizure onset zone

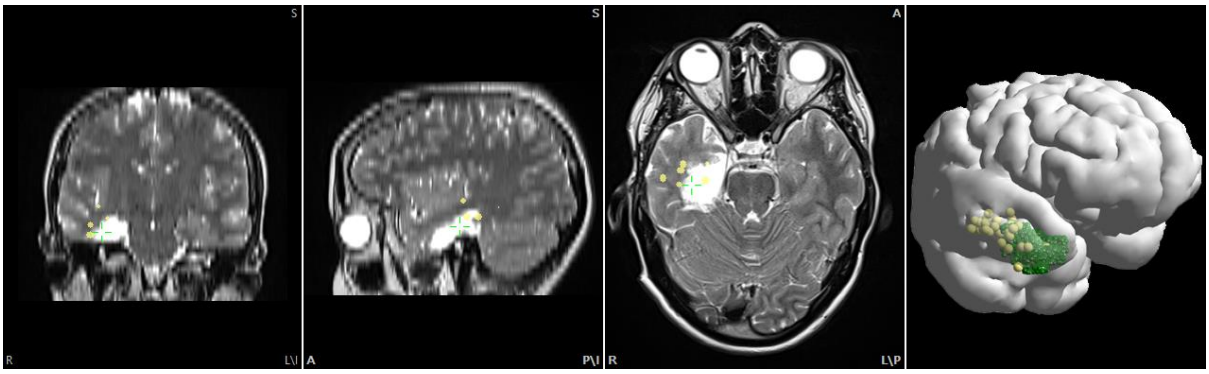


Figure S42 Localization of the MSI cluster compared to the resection cavity

Pt. no. 13

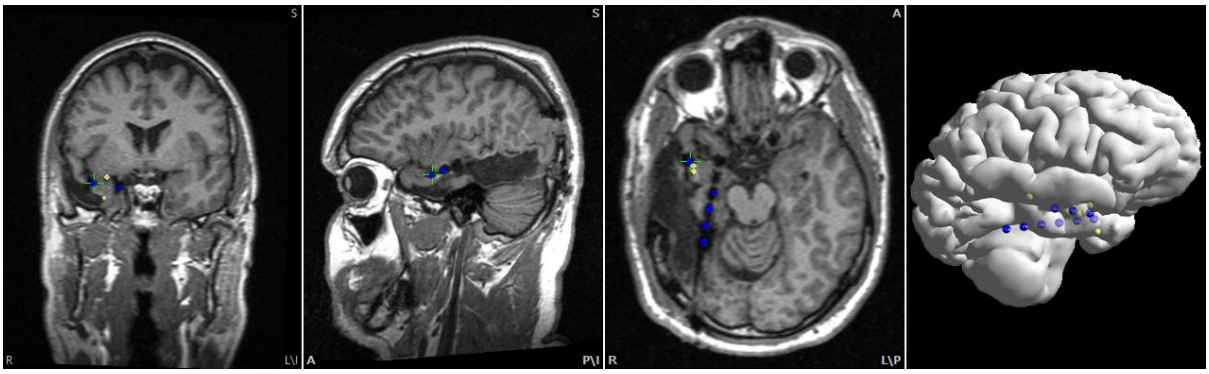


Figure S43 Localization of the MSI cluster compared to the irritative zone

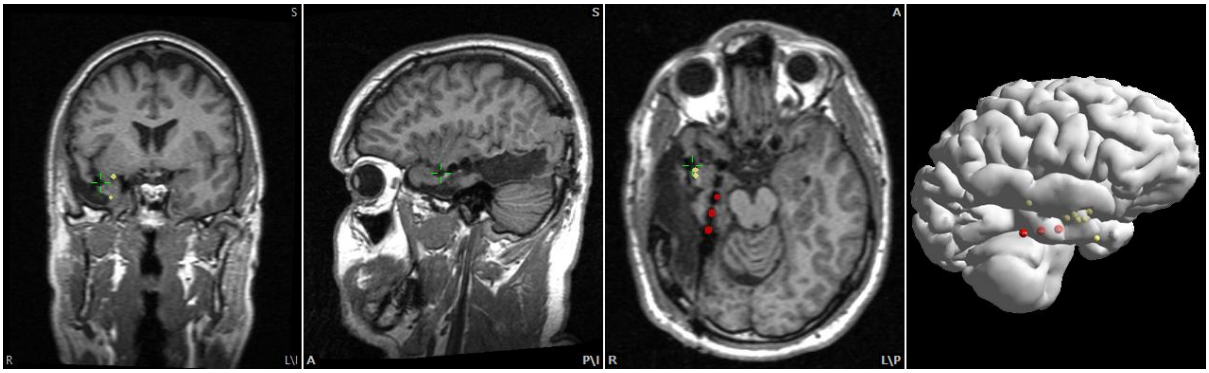


Figure S44 Localization of the MSI cluster compared to the seizure onset zone

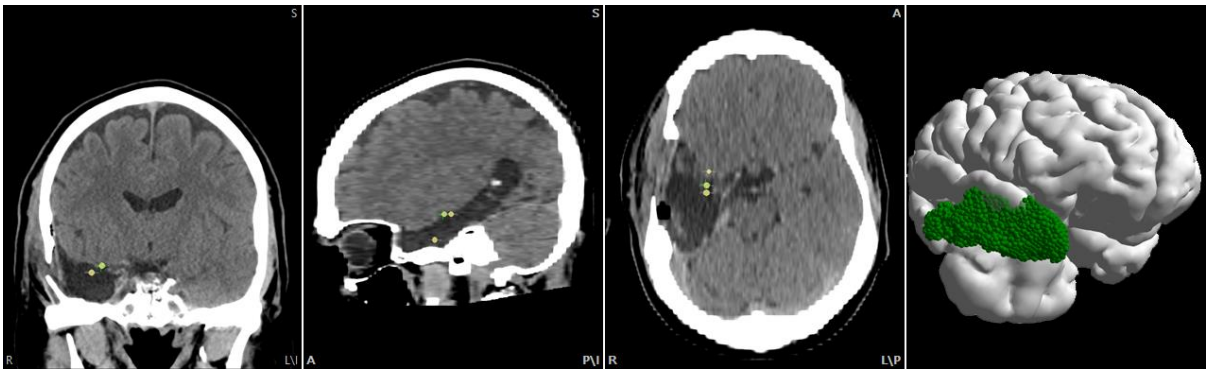


Figure S45 Localization of the MSI cluster compared to the resection cavity

Pt. no. 14

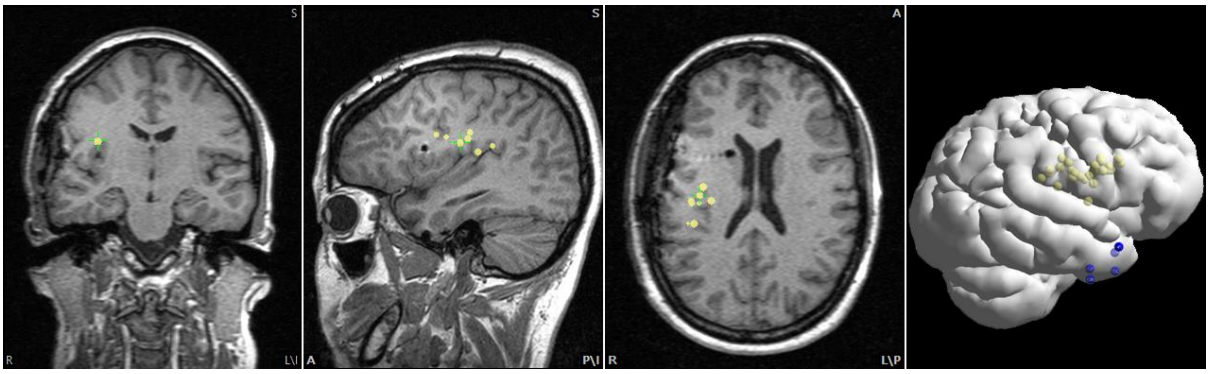


Figure S46 Localization of the MSI cluster compared to the irritative zone

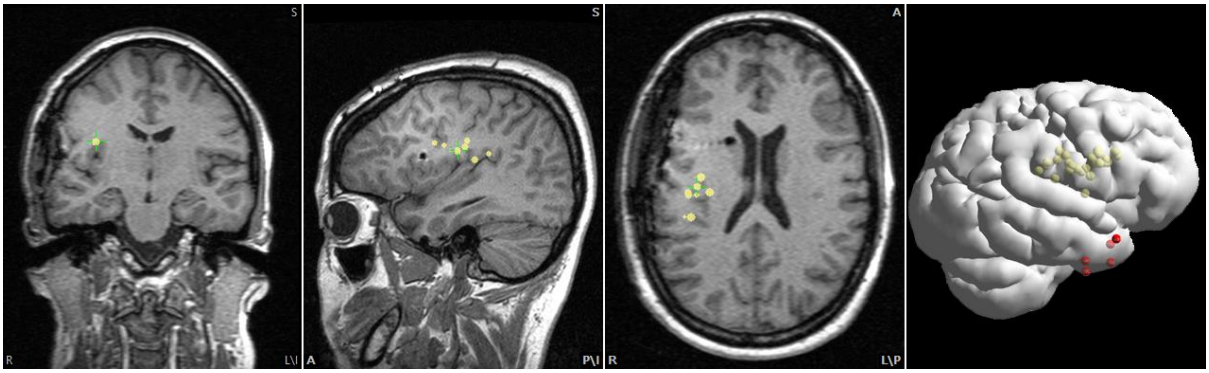


Figure S47 Localization of the MSI cluster compared to the seizure onset zone

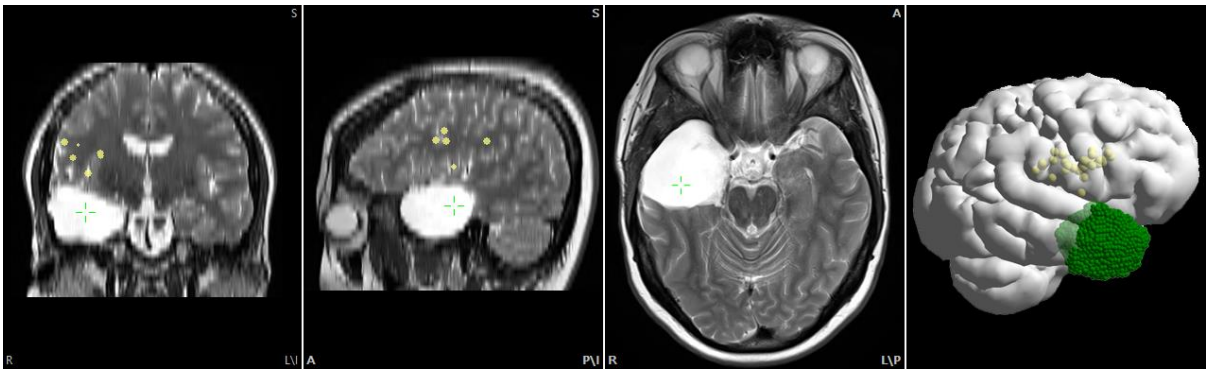


Figure S48 Localization of the MSI cluster compared to the resection cavity

Pt. no. 15

Cluster 1

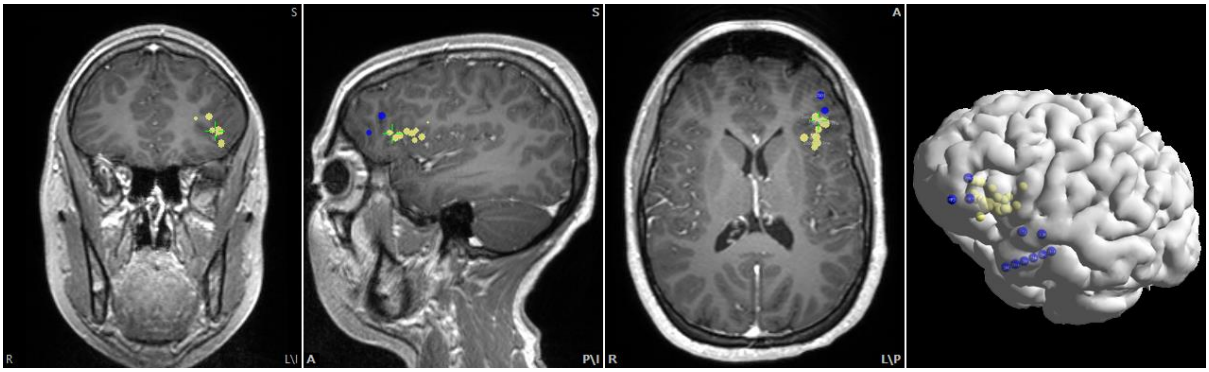


Figure S49 Localization of the MSI cluster compared to the irritative zone

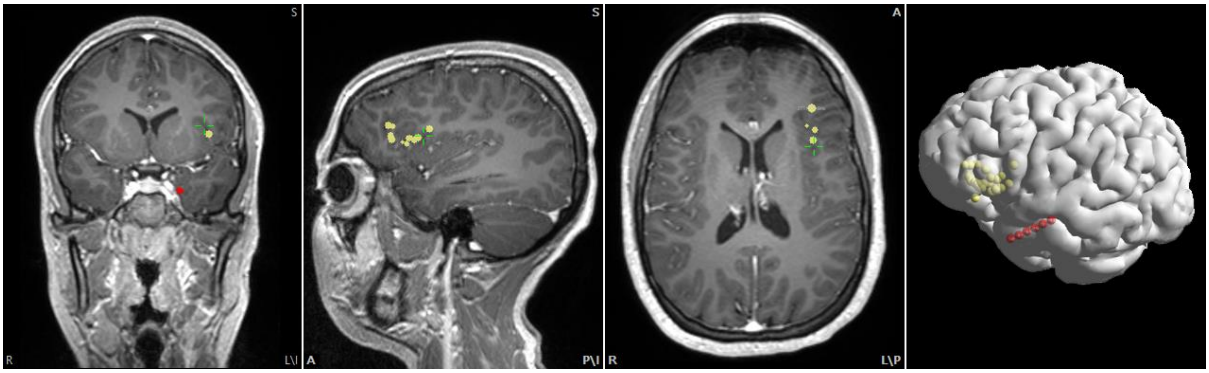


Figure S50 Localization of the MSI cluster compared to the seizure onset zone

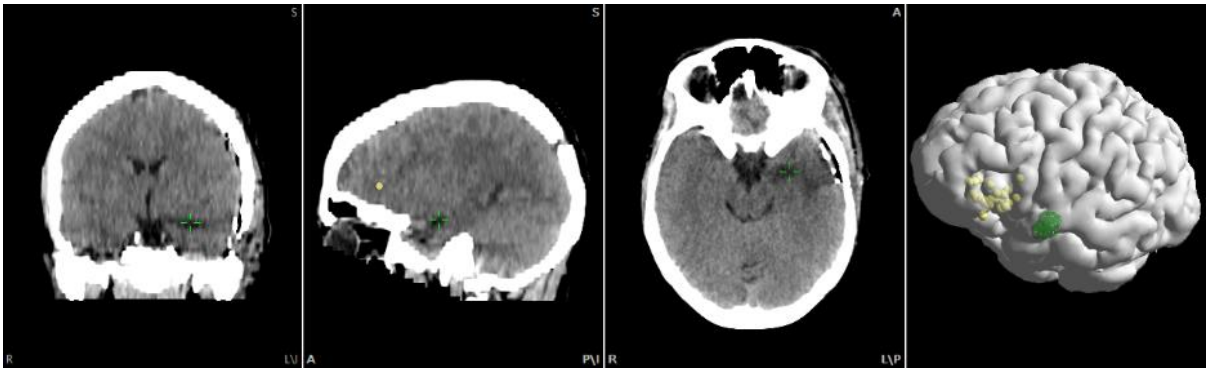


Figure S51 Localization of the MSI cluster compared to the resection cavity

Cluster 2

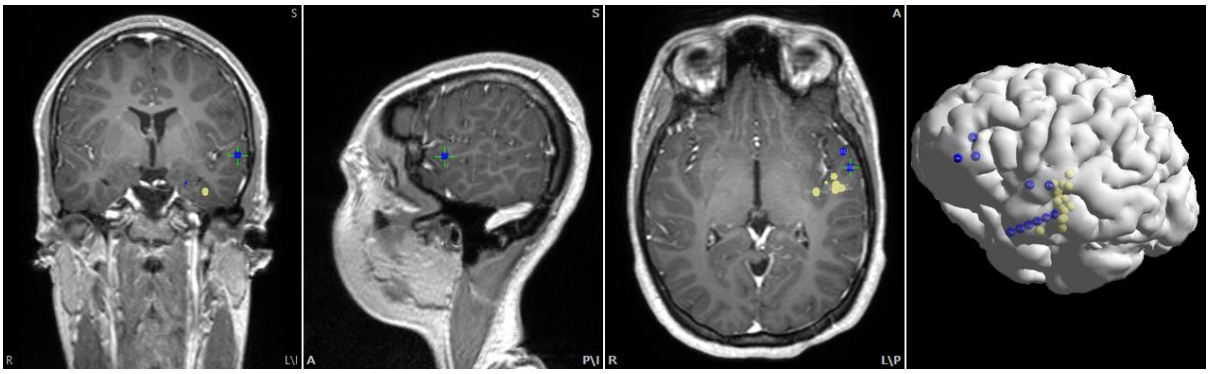


Figure S52 Localization of the MSI cluster compared to the irritative zon

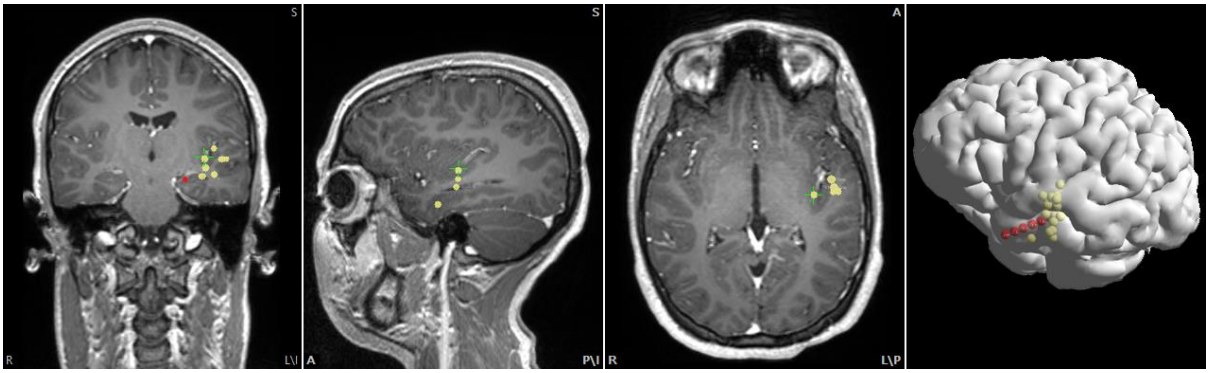


Figure S53 Localization of the MSI cluster compared to the seizure onset zone

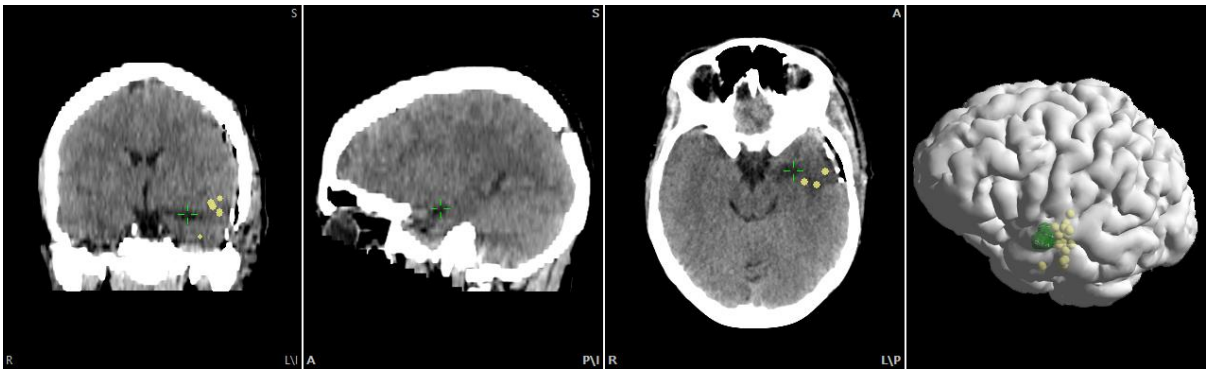


Figure S54 Localization of the MSI cluster compared to the resection cavity

Pt. no. 16

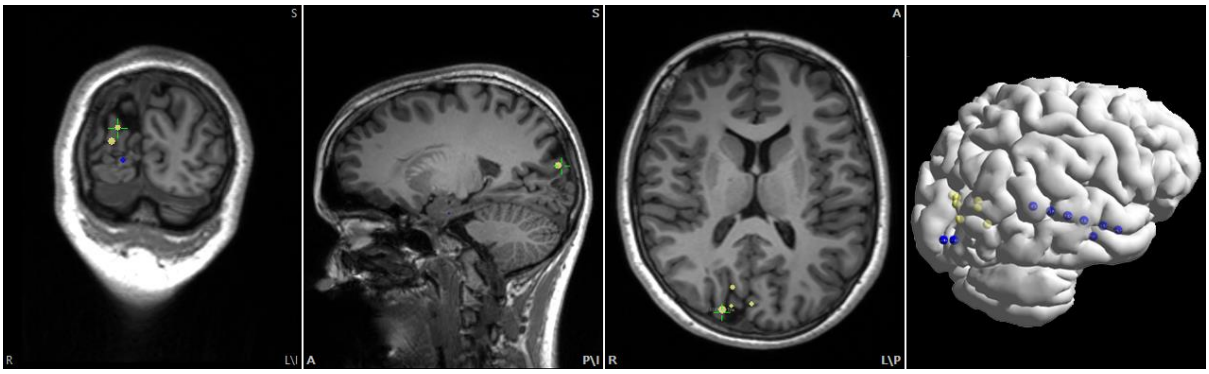


Figure S55 Localization of the MSI cluster compared to the irritative zone

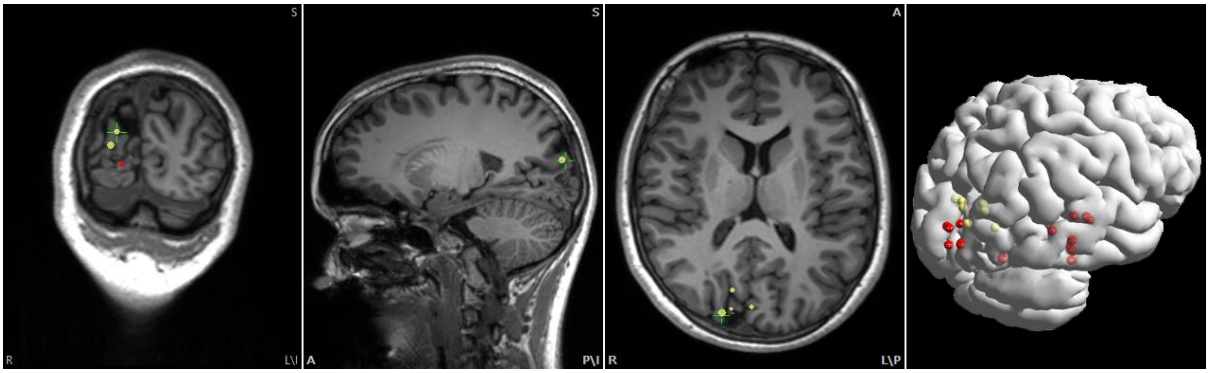


Figure S56 Localization of the MSI cluster compared to the seizure onset zone

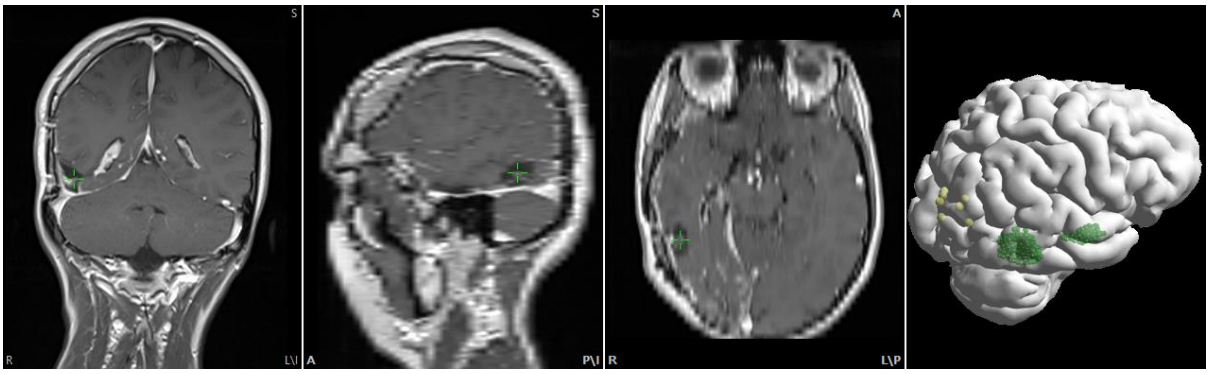


Figure S57 Localization of the MSI cluster compared to the resection cavity