Burnett School of Medicine at Texas Christian University

Children with Drug Resistant Epilepsy Referred for Resective Surgery: Characteristics Delaying Surgical Referral and Advanced Neuroimaging in Improving Outcome

Thesis

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Abstract

Research Question: Two questions will be addressed: "Are there certain characteristics in children with DRE in the US that delay their evaluation for epilepsy surgery despite failing three or more ASMs?" and "In children with DRE, does information derived from magnetoencephalography (MEG) advance presurgical localization of the epileptogenic zone (EZ) and improve the surgical outcome in those who have failed prior epilepsy surgery?"

Background, Significance, and Rationale: Anti-seizure medications (ASM) do not achieve seizure control in 30% of children with epilepsy. For these patients, epilepsy surgery is considered the best treatment. Children are considered to have drug resistant epilepsy (DRE) once they have failed two ASMs and should be referred for surgical evaluation. However, many patients fail more than two ASMs before referral. The characteristics of these children compared to children failing less than two AMSs have not been thoroughly investigated. These characteristics are critical to better understand variables that may interfere with surgical referral. Patients evaluated for surgery undergo an evaluation procedure which involves several neuroimaging techniques. The goal of this process is to identify the EZ. However, oftentimes the localization of this area is unsuccessful or inconclusive. In these cases, intracranial electroencephalography (iEEG) recordings are required which presents limitations due to invasiveness. The utility of MEG in guiding a second surgical workup after previous iEEG-guided surgery has failed has not been investigated. By determining the utility of MEG in aiding in seizure freedom, we would improve surgical management of patients.

Materials and Methods: We prospectively enrolled children ≤ 18 years of age undergoing epilepsy surgery evaluation at 21 US pediatric epilepsy centers participating in the Pediatric Epilepsy Research Consortium Epilepsy Surgery Database. We compared sociodemographic and epilepsy variables of patients failing ≤ and >2 ASMs at the time of epilepsy surgery evaluation. For characteristics of significance, we compared seizure outcome (Favorable: Engel 1 or 2; Unfavorable: Engel 3 or 4) after surgery between those failing ≤2 and >2 ASMs prior to referral. Statistical analyses was performed with SPSS. For the second question, a group of patients who had an unsuccessful prior iEEG-directed epilepsy surgery followed by a MEG-augmented surgery will be identified. MEG data from these children will be analyzed and the two areas of surgical resection will be compared to the dipoles identified from the MEG data. We will compare the localization findings between the two surgeries to assess how MEG augments the surgical outcome.

Results and Conclusion: Additional ASM trials prior to surgical referral are associated with younger age at seizure onset and delay to evaluation. Patients failing >2 ASMs more often have abnormal neurological exam and daily seizures, while also failing treatments other than ASMs prior to surgical referral. Importantly, abnormal exam and seizure frequency do not predict outcome, suggesting delay of surgical evaluation because of these characteristics may be unnecessary. Similarly, children less likely to be rendered seizure free from surgery more often trial >2 ASMs, despite palliative surgical outcomes superior to that expected with additional ASM trials. Recognizing patient characteristics which lead to delayed surgical referral may shorten the duration to surgical therapy with potential for improved outcomes. Finally, MEG seems to augment the surgical workup and aid in favorable outcomes after a previously unsuccessful iEEG-directed surgery.

Research Question & Specific Aims

When referring a child for epilepsy surgery, many characteristics are used to determine if a child is a good candidate for surgery. Our first question we will address is, "Are there certain characteristics in children with DRE in US that delay their evaluation for epilepsy surgery?".

We **hypothesize** that certain characteristics like age at onset, age at surgical referral, and other variables found in **Table 1** are important in referral for epilepsy surgery and some of these characteristics may play a role in delaying referral for children with DRE.

Characteristics		
Gender	Distance from Surgical Center	MRI Results
Ethnicity	Age at Onset	Age at Failure of 2nd ASM
Race	Etiology	Referral Source
Insurance Type	Seizure Characteristics	Age at Surgical Referral

***Table 1**: Characteristics to be Investigated in Aim 1.*

We will address this hypothesis with the following specific aims:

Specific Aim 1: Define characteristics of children with DRE that lead to more than two ASM failures prior to surgical evaluation to help identify opportunities to shorten duration to surgical evaluation.

In order to address this aim we plan to use retrospective data from the Pediatric Epilepsy Research Consortium Epilepsy (PERC) Database to investigate characteristics like those seen in **Table 1** and their impact on the likelihood of these children being referred for surgical evaluation.

Additionally, we would address the following question: "In children with DRE who have failed prior iEEG-directed surgery, does MEG advance the presurgical localization of the EZ and improve the surgical outcome?"

We **hypothesize** that MEG localizes the EZ with high precision, and provides higher additive value compared to other presurgical evaluation techniques in predicting the surgical outcome.

We will address this hypothesis with the following aim:

Specific Aim 2: Estimate the localization precision MEG to localize the EZ in children with DRE.

In order to address the above aim, we will identify patients with DRE who had a iEEG-directed surgery and did not have a successful outcome after one-year post-op, who then had a subsequent surgery with the utilization of MEG which augmented their second surgical workup.

Specific Aim 3: Define the additive value of MEG to achieve seizure freedom after already failing an initial epilpesy surgery.

In order to address the above aim, we will estimate the sensitivity and specificity of the magnetic source imaging to localize the EZ and compare it with other presurgical evaluation techniques for patients who had a successful second surgery.

Introduction, Significance, and Rationale

Introduction

Epilepsy is a group of diseases in which an individual may experience one of a wide variety of seizures. The strict definition involves one of the following: two unprovoked seizures that occur more than 24 hours apart, a single unprovoked seizure with a probability of another seizure after two unprovoked seizures occurring over a time span of 10 years, or the diagnosis of an epilepsy syndrome[1]. An epileptic seizure is one in which there is neuronal activity occurring in the brain that is excessive, abnormal, and synchronous[2]. Based upon clinical and EEG data, there are several categories of seizures that a child may experience. These categories include focal, generalized, unknown, and unclassified[3,4]. Focal seizures will begin in one part of the brain and impact that same part[4]. Generalized seizures begin in and impact both hemispheres of the brain at once with no warning[4]. Unknown seizures are those in which doctors are unsure where in the brain the seizure begins[4]. Finally, unclassified seizures are those in which there is not enough information to classify the seizure or the seizure has a nature that is unusal[4]. Additionally, many causes have been shown to lead to epilepsy like immune, infectious, metabolic, genetic, and structural causes[3,4]. Genetic causes are the most common cause of childhood epilepsy and structural causes are second most common[5].

The treatment of epilepsy is difficult but has tremendously improved over the past two decades. The first line of treatment for children with epilepsy are anti-seizure medications (ASMs). Other treatments include a ketogenic diet in which increasing ketogenesis has shown to have antiepileptic effects[4]. Additionally, neuromodulation therapies like vagal stimulation, deep brain stimulation, and transcranial magnetic stimulation have shown promising results for some individuals[6]. Unfortunately, 20-30% of children develop DRE in which their epilepsy fails to sustain seizure freedom after using two ASMs for an adequate amount of time[7]. Typically, after failing two ASMs, surgery is often considered to represent a viable option as defined by the International League Against Epilepsy (ILAE)[7]. This is deemed the next best option since trialing another medication is less likely to be successful in achieving seizure freedom as only about 24% of patients will achieve seizure freedom with trailing of a third ASM[8, 9]. In order to perform surgery, children must undergo a tremendous amount of presurgical evaluation[10]. This evaluation is two-fold. First, several characteristics are identified to determine if a child is a good surgical candidate, however these characteristics have not been properly defined and more research is needed to define them. Second, in-depth evaluation is needed in order to localize the area of brain that contains the EZ that will be removed by the surgeon.

Characteristics that may determine if a patient is a good surgical candidate are still being investigated, but things that are considered include etiology of the seizures, focality of the seizures, frequency of the seizures, comorbidities, MRI findings, among several other factors. Generally, patients with focal epilepsy or lesional MRIs are considered to be better surgical candidates than patients with generalized epilepsy or nonlesional MRIs[11]. Furthermore, neurologists are more likely to refer patients for epilpesy surgery if they have more frequent seizures (daily or weekly compared to yearly)[11]. Regardless of the patient's epilpesy characteristics, it is vital for a patient to be evaluated for epilepsy surgery once they have failed two ASMs as DRE poses significant

threats to these patients. Patients with DRE can experience delayed development, increased mortality due to sudden unexpected death in epilepsy (SUDEP), negative impacts on their quality of life, social isolation, and psychological concerns[12,8]. Unfortunately, despite failure of two ASMs many children are continually trialed on more than two ASMs before they are referred for epilepsy surgery. A study done in 2015 examining the knowledge of Canadian neurologist's on epilepsy surgery found that only 51.4% of neurologists knew that patients only had to fail two ASM to be referred for epilepsy surgery and in 2022 a study performed on Italian neurologists showed only 17.6% referred patients for surgical evaluation after two ASMs [11,13]. These findings identify the gap of knowledge neurologists may have when it comes to when to refer their patients for surgical evaluation, but it may not show the whole picture as there may be other characteristics physicians consider when determining if they should refer their patients for evaluation. Characteristics of children who have delayed surgical referral have not been identified and thus is one of the focuses of this research. It is important to determine what factors may delay surgical referral in patients who have DRE to determine if there are any areas to improve a timely referral for these children. It is important for children with epilepsy to be referred for epilepsy surgery evaluation once they are deemed to be drug resistant since earlier intervention can result in better surgical outcomes, a decreased chance for poor neurodevelopmental outcomes and psychological and behavioral comorbidities, and a decreased risk for SUDEP[8].

For the second part of the surgical evaluation, there are several imaging modalities that are utilized in order to delineate several areas in the child's brain. The areas in the brain that are important to consider in a child with epilepsy can be seen in **Figure 1**[14]. First is the EZ, or the area that is necessary for seizures, and thus is important to remove during epilepsy surgery. This zone, however, cannot be directly measured and is instead an estimation based on data of other zones collected by neuroimaging[14]. The zone that can be easily found using neuroimaging is the irritative zone, which will generate interictal discharges measured by several devices (e.g. MEG, EEG)[14]. Though the irritative zone is large and very easy to capture, it is not specific, and in some cases does not even include the EZ[15,16]. Additionally, there is the ictal onset zone which is where the seizures begin. This zone is regarded as a good estimator of the EZ, but it is very difficult to measure as the child must have a seizure while they are being assessed using a neuroimaging device (iEEG, SPECT, MEG, or EEG)[14]. This is difficult to obtain as seizures in children may not occur every day, every week, or even every month. Finally, one must assess the eloquent cortex where a patient's language, memory, motor, sensory and high cortical functions reside[14]. It is important to determine where this is located in a patient and how that location is related to the location of the zones discussed above. If a patient were to have an overlap between these areas, removing brain invovled in the epilepsy may place the patient at risk of also losing one of the many important functions listed above. By knowing where the eloquent zone is, surgeons can make informed decisions knowing the deficits a patient may experience after surgery.

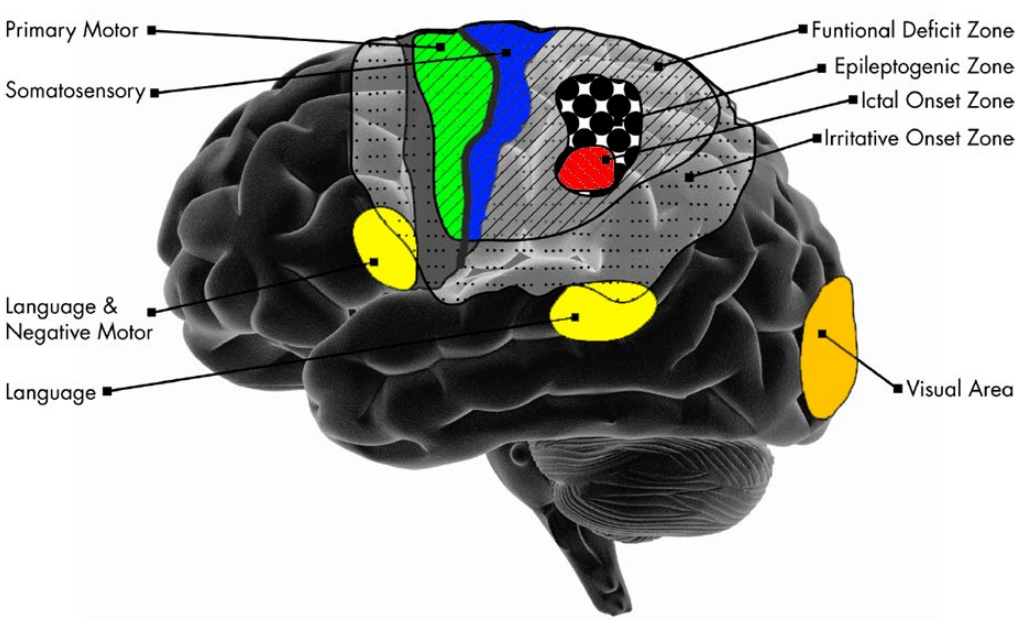

Figure 1*: Cortical zones that are important in an epilepsy patient. Of note, the EZ is the zone that is necessary for a seizure to occur, but cannot be located, so the other zones are located instead. The ictal onset zone is where the seizure begins and is highly specific but is hard to locate as the child must have a seizure while being assessed by neuroimaging. The irritative zone is where epileptogenic discharges are produced, but it is large and not specific. Finally, the eloquent cortex are the areas in the brain that are important for everyday normal functions.*

Several neuroimaging techniques have been used to map the EZ, evaluate the child's neuroanatomy, and study the neuronal connectivity[6,17,18]. Traditionally, physicians have relied on MRI and iEEG as the best method to localize the EZ. However, there are issues with both imaging techniques. MRI can be problematic when results are negative and thus are inconclusive as the imaging shows normal or non-focal findings. These patients often are not considered good surgical candidates and are thus less likely to be offered surgical treatments[19,20]. Additionally, iEEG involves surgical placement, so it may not be the best method as it is costly, carries the risk for bleeding and infection, and may induce unintended neurological damage[21,22]. Thus, the use of a noninvasive technique would be favored and better tolerated by patients and parents.

MEG is a neuroimaging device that is currently being used as a supplement to iEEG in surgical planning. MEG is a non-invasive neuroimaging tool that localizes interictal epileptic spikes to define the epileptogenic zone (**Figure 2**). It has high temporal and spatial resolution that measures magnetic fields in the brain created by neuronal intracellular electrical currents instead of the extracellular electrical currents that EEG measures[23]. Active neurons produce electrical currents in the brain by electromagnetic induction, and the purpose of MEG is to pick up and record the magnetic activity of these neurons. Magnetic fields can be measured from electrical activity since every electrical current is associated with a perpendicular magnetic field and biological tissue is similar to empty space so magnetic fields are not impacted by the scalp or skull[23]. Because the magnetic waves produced by the brain are weak, the imaging must be performed in a magnetically

shielded room to ensure no other electromagnetic noises are picked up by the machine (**Figure 3**)[24]. The recording is performed by having a patient sit or lay down while placing their head in a helmet that contains all the MEG sensors. At Cook Children's Medical Center, the MEG has 306 sensors, 204 that are planar gradiometers and 102 that are magnetometers. These sensors are coils and are able to detect changes in the magnetic fields created by neurons in the brain and will convert these magnetic fields into voltage changes. The coils are coupled to superconducting quantum interference devices (SQUIDs) which are sensitive to magnetic field changes.

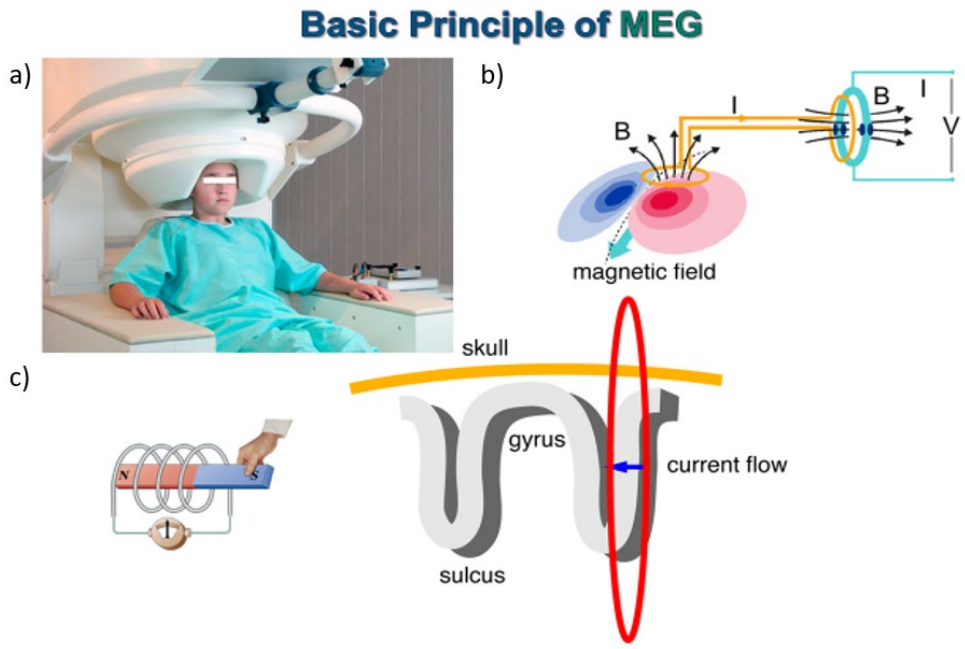

Figure 3: *Basic Principle of MEG. (a) The child sits comfortably in a specially designed armchair during the recording and places their head inside the MEG helmet; (b) MEG recordings are based on electromagnetic induction which dictates that any changing magnetic field can generate a measurable electrical current in a nearby coil; (c) thousands of neurons, which are simultaneously active at the same time, generate a local current that secondarily generates a magnetic field that is measurable outside the scalp through magnetometers.*

Figure 4*: Magnetically Shielded Room where the MEG is located. The patient is inside the room accompanied by his/her caregiver while the rest of the personnel are located outside. The room is equipped with an intercom system to ensure the patients safety, along with audio-visual components and adjustable lighting*[24].

The magnetic fields are sensed by magnetometers and gradiometers and the results are mapped onto each individual patient's MRI to provide magnetic source imaging which helps surgeons map out vital brain areas discussed above (EZ, irritative zone, eloquent cortex, etc.)[23]. To co-register the MEG findings with the patient's MRI scan, four head position indicator (HPI) coils are placed on the patient's head. The relative locations of the HPI coils with respect to the anatomical landmarks on patient's head is determined using a 3D digitizer. This allows aligning the MEG and MRI coordinate systems. Additional electrodes are also placed to measure horizontal and vertical electrooculography (EOG) and electrocardiography (ECG). These measurements serve as extra measurements for removing biological artifacts from the MEG recordings. Images of an example MEG set up are shown below in **Figure 5**.

Figure 5*: MEG and HD-EEG set up. (a) The Philips EGI 400 (256 electrodes) is easy to put on kids because it does not require the use of a conductive gel. Instead of using gel, you soak the net with the attached sponges in water which allows the sponges to become conductive. This procedure quick and easy, especially for children with attention deficits. (b) Co-registration procedure in order to determine the relative localization of the HD-EEG sensors with respect to the child's head anatomy. (c) The child sits comfortably in the MEG with their head placed in the MEG helmet while they sit upright.*

Currently, iEEG is still the gold standard for surgical workup in patients undergoing epilpesy surgery, but MEG is often used prior to iEEG to help guide the lead placements for iEEG. The utility of MEG without iEEG in surgical planning for epilepsy patients has not been established. Furthermore, the utility of MEG for patients who previously failed an epilepsy surgery without the use of MEG in their initial surgical workup who went on to have another surgery with guidance from MEG has yet to be investigated.

Significance and Rationale

Currently, there is little research that has been done to define characteristics that may lead to delayed surgical referral for patients with DRE. There seems to be a large cohort of patients who will fail three or more ASMs before being referred for epilepsy surgery despite their diagnosis of DRE. Based on prior studies, this may be due to a general lack of knowledge that patients failing two ASM should be immediately referred for epilpesy surgery based on the guidelines set in place by the ILAE [7,11,13]. Furthermore, there is a general idea that only patients with focal epilepsy, lesional MRIs, or frequent seizures should be referred for epilepsy surgery despite no guidelines suggesting this[11]. Consequently, there is a paucity of evidenced-based guidelines for when to refer a patient for epilepsy surgery (besides the guidelines after failing two ASM) which may reduce the number of children being evaluated for epilepsy surgery. Additionally, there has been no studies looking at the patient's characteristics that may be delaying their surgical evaluation for

patients failing three or more ASMs compared to less than two ASMs since most studies have focused solely on the physician's perspective of when the refer for surgery. Thus, there is a need to define these characteristics to ensure that all children who are eligible for surgical evaluation are being evaluated for surgery. It is important to keep in mind that surgical evaluation does not mean a patient will undergo surgery, it just indicates that a team will determine if a patient is a good surgical candidate. Thus, there is no reason to trial more medications after a patient has already failed two ASMs prior to being referred for surgical evaluation. Accordingly, the first aim of this research will be to **define characteristics of children with DRE that lead to more than two ASM failures prior to surgical evaluation to help identify opportunities to shorten duration to surgical evaluation**. This will be important since children who are regarded as good surgical candidates are traditionally considered children who have failed two ASMs. Yet, many children are failing three or more ASMs before being evaluated. So far, there is a lack of studies determining specific characteristics (**Table 1**) that differentiate children failing 0-2 ASMs and children failing more than three ASMs before being referred for surgery. Such information is necessary to establish guidelines for properly evaluating children who may benefit from epilepsy surgery and reduced the time for surgical referral.

Finally, there are no widely accepted guidelines for physicians to follow using pre-surgical neuroimaging techniques to determine the need for and outcomes related to surgery. A new, highly precise non-invasive biomarker is needed to identify the EZ. The use of MEG shows great potential for localizing the epileptogenic foci without needing to use an invasive technique[27]. There have been no studies that have investigated the use of MEG in augmenting the second surgical work up for children who have previously failed an epilepsy surgery with the use of iEEG, but without the guidance from MEG. Thus, the final aim of this research is to **define the additive value of MEG neuroimaging methods to achieve seizure freedom in children who previously failed epilpesy surgery**. Such a biomarker will have a significant impact in children who have DRE and are undergoing second surgical evaluation by precisely localizing the seizure onset zone (SOZ) without using an invasive technique. This research will investigate whether the information derived from recordings of MEG can advance the presurgical localization of the EZ and eventually improve the surgical outcome of children with DRE who have already failed an iEEG-directed epilepsy surgery.

METHODS

Research Question 1: Are there certain characteristics in children with DRE in the US that delay their evaluation for epilepsy surgery despite failing three or more ASMs?

Patient Cohort

We retrospectively analyzed the data from the Pediatric Epilepsy Research Consortium (PERC) Database, a collaboration of 21 US pediatric epilepsy centers prospectively collecting data on children ≤ 18 years of age being referred for epilepsy surgery. Two groups of patients were identified for comparison to determine characteristics that may delay referral for surgical evaluation. The first group contained patients who failed less than two ASM prior to surgical referral and the second group of patients were those who failed more than three ASM before referral for surgical evaluation. To be included in the study, children had to have undergone presurgical evaluation. W excluded children who did not have data on the number of failed ASMs at time of surgical referral and children who had prior phase I referral or prior epilepsy surgery. We compared sociodemographic and epilepsy variables of patients failing ≤ and >2 ASMs at the time of epilepsy surgery evaluation. Time to referral was defined as duration from age at DRE diagnosis to age at referral for presurgical evaluation. For characteristics of significance, we compared seizure outcome (Favorable: Engel 1 or 2; Unfavorable: Engel 3 or 4) after surgery between those failing ≤2 and >2 ASMs prior to referral. Statistical analyses were performed with SPSS (Table 1). The details of the characteristics that were investigated and outcomes are explained below.

Data Analysis

<u>Specific Aim 1:</u>

Define characteristics of children with DRE that lead to more than two ASM failures prior to surgical evaluation to help identify opportunities to shorten duration to surgical evaluation

Using data from the PERC database we investigated the characteristics of children with DRE who were referred for surgery after failing two or less ASM and discriminated between children who failed three or more ASM prior to surgical referral. The variables that were investigated include, but are not limited to: gender, race, ethnicity, type of insurance, distance from surgical center, etiology of epilepsy, age at epilepsy onset, MRI results, epilepsy characteristics, age at failure of 2nd ASM, and age at surgical referral. The full list of the variables that were investigated are presented in **Table 2**.

Surgical Referral Characteristics		
Gender	Distance from Surgical Center	Age at Surgical Referral
Ethnicity	Age at Onset	Age at Failure of 2nd ASM
Race	Seizure Etiology	Referral Source
Insurance Type	Type of First Seizure	Frequency of Seizure
MRI Results	Neurological Exam	Neurological Deficit
Source of Surgical Referral	Other Failed Treatments	

***Table 2**: Characteristics to be investigated to determine how they may impact if a patient is referred for surgery or not.*

Once a patient was referred for surgery, we looked at characteristics of the surgical evaluation to determine if those factors may have played a role in delay of surgical referral for those failing three or more ASM. We also investigated surgical details and outcome of the children who did have surgery. These characteristics are listed in **Table 3**. For determining those who had poor versus good surgical outcomes, we used the Engel Surgery Outcome Score seen in **Table 4**[26]. This score is used by physicians to determine the surgical outcome two years after a patient has had epilepsy surgery. It contains major Engel Score categories (e.g. Class I), and subcategories (e.g. Class Ia). For this study utilized major categories. Children with good surgical outcomes are considered to have an Engel score of 1 or 2, and children with poor surgical outcomes have an Engel score of 3 or 4.

Surgical Outcome Characteristics		
Was Surgery Offered?	Why Surgery was not Offered	Was Surgery Performed?
Procedure Performed	Intent of Surgery	Why Surgery wasn't Performed

***Table 3**: Characteristics during surgical referral and surgery characteristics and outcomes.*

Engel Surgery Outcome Score	
Engel Class I	**Free of Disabling Seizures**
Class IA	Completely seizure-free
Class IB	Non disabling simple partial seizures remain
Class IC	Some disabling seizures, but free of disabling seizures for 2 years
Class ID	Generalized convulsions with ASM withdrawal
Engel Class II	**Almost Seizure-Free – Rare Disabling Seizures**
Class IIA	Initially free of disabling seizures, but now have rare seizures
Class IIB	Rare disabling seizures
Class IIC	More than rare disabling seizures
Class IID	Nocturnal seizures only
Engel Class III	**Worthwhile Improvement**
Class IIIA	Worthwhile seizure reduction
Class IIIB	Prolonged seizure-free intervals
Engel Class IV	**No Worthwhile Improvement**
Class IVA	Significant seizure reduction
Class IVB	No appreciable change
Class IVC	Seizures are worse

***Table 4**: Engel Surgery Outcome Scores*

The difference in these variables between the groups (those who were referred for surgery after failing two or less ASMs and those who were not) were statistically analyzed using independent t-tests for continuous data and Pearson's Chi-Square Test for independence and Fisher's Exact Test

for categorical data. All data was analyzed within a 95% confidence interval. Prior to evaluating the statistical significance in the difference of means, assumptions of independence, normality, and homogeneity of variance were first evaluated. If a given variable is found to be not normally distributed, the appropriate non-parametric test was used to assess statistical significance. For categorical data, equal variances were assumed due to Lavene's test being insignificant for all characteristics being investigated. Thus, pooled sample variances were utilized. Multicollinearity effects between independent and dependent variables were explored to determine if any independent variables were correlated with one another that may result in a weakened test statistic due to redundancy. To investigate these effects only continuous and dichotomous variables were tested since categorical variables with more than two dimensions cannot be calculated. The correlation values were obtained using a Pearson correlation matrix. A multivariate linear regression was then performed with the two ASM groups (<2 ASMs versus ≥2 ASMs) being the dependent variables and the remaining continuous and dichotomous variables being the independent variables. This was done to analyze tolerance and variation inflation factor values of the independent variables on the dependent variable. In order to compare the effectiveness of various predictor variables on the outcome of the two ASM groups a binary logistic regression was performed. Data was analyzed using SPSS[25].

Research Question 2: In children with DRE, does information derived from magnetoencephalography (MEG) advance presurgical localization of the epileptogenic zone (EZ) and improve the surgical outcome in those who have failed prior epilepsy surgery?

Patient Cohort

Retrospective data was collected and evaluated from Cook Children's Medical Center at Fort Worth, TX. We identified patients who had an initial epilepsy surgery with the use of iEEG, but the surgery was deemed unsuccessful after one year and subsequently underwent a second surgical evaluation with the use of MEG and analyzed the outcomes of the second surgery **(Figure 6).**

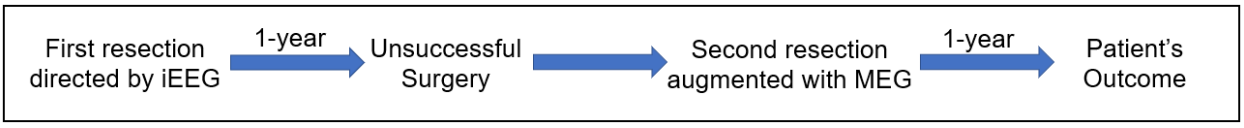

Figure 6*: Timeline of patients included for second research question.*

Patients who had MEG during their initial surgical evaluation were excluded from the study. Patients with no outcomes from the first and/or second surgery were excluded from the study. Patients must be <18 years old prior to their first surgery. MRIs after the first and second surgery along with MEG data were required to be included in the study in order to delineate the surgical volumes from both surgeries.

MEG Analysis

Prior to analysis of the MEG recordings, each patient's structural MRI was uploaded into *Brainstorm*[27] and then processed to create a realistic head model using the CAT12 toolbox[28] which utilizes projection-based thickness in order to better estimate the patient's cortical thickness to generate the patient's cortical surface. This realistic head model was constructed using the patient's MRI obtained prior to the second surgery. The recordings were then reviewed by two independent readers to look for interictal activity in the MEG recordings. The results were analyzed using *Brainstorm* which is documented and freely available for download online under the GNU general public license (http://neuroimage.usc.edu/brainstorm)[27]. First, we excluded any noise or artifacts that showed up on the recordings as those are often cardiac in nature (heartbeats). Interictal epileptogenic discharges (IEDs) were identified and filtered by MEG experts or epileptologists (**Figure 7**). The reviewers were blind to the patient's history and markings from other reviewers. In order to breakup the 306 sensors used in the MEG imaging, the sensors were broken up into eight sections containing 38-39 channels and then the reviewer looked for IEDs in each of those eight sections by finding the main spike deflection and then marking its peak. These eight sections include: right and left frontal, right and left parietal, right and left temporal, and right and left occipital. Like mentioned previously, any eye movements or heartbeats that may have been picked up on the recording were carefully picked out and excluded from the analysis. Once the reviewers finished marking the IEDs, only the IEDs that were picked by all reviewers were kept for analysis.

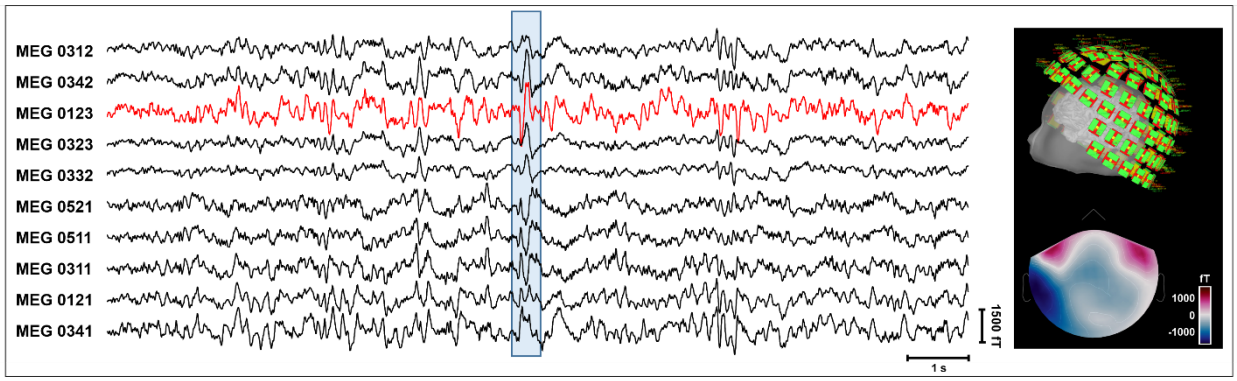

Figure 7: Identification of interical epileptiform discharges (IEDs) on magnetoencephalography (MEG) recordings. *Data from an 18 year old female child with DRE who failed initial left frontal cortical resection guided by iEEG followed by seizure freedom after undergoing left frontal cortical resection of identified MEG dipoles. The area in the blue box highlights an IED identified on MEG. Topographic maps indicate a possible underlying generator in the left frontal regions.*

In order to map the data of the location of the IEDs, we used the patient's MRI with *OpenMEEG* software[29] for more surface level recordings and used *Brainstorm*[27] to account for recordings that may be in subcortical or deep brain regions. We used the ECD model[30] to localize the generator

for each IED and the IEDs with a goodness-of-fit higher than 70% moved on to further analysis. From there, we performed an in-house dipole clustering method (**Figure 8**).

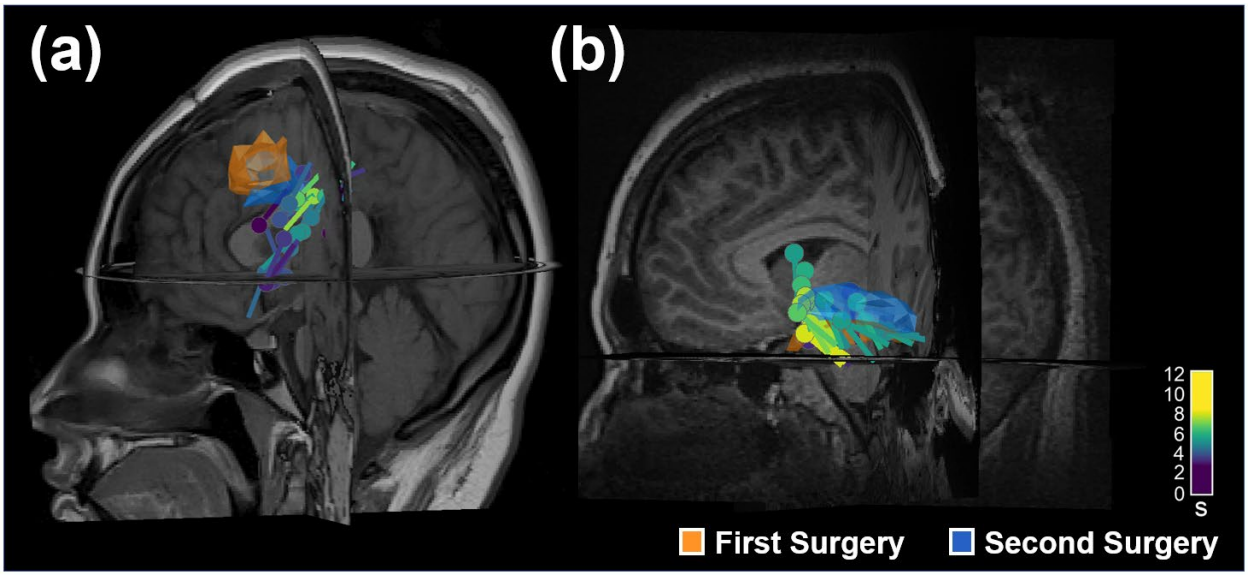

Figure 8: Dipole clustering and distance of dipoles from ablations. *The magnetic resonance imaging (MRI) of an 18-year-old female* ***(a)*** *and 18-year-old male* ***(b)*** *who were seizure free after second resection guided by magnetoencephalography. Cluster of equivalent current dipoles (ECDs) from surgical volumes are displayed. ECDs are color-coded according to their clusterness: from low- (purple) to high-clusterness (yellow) values. The initial resection volume is orange-colored and the second resection volume is blue-colored.*

In order to delineate the surgical resections for each patient we used their MRI after the first surgery and after the second surgery. The first surgical resection was determined using the MRI from after the first surgery. The surgical resection from the first surgery was manually delineated using volume scouts in *Brainstorm*[27]. We then used this 3-D volume and projected it onto the MRI after the second surgical resection to manually delineate the surgical resection of the second surgery (**Figure 8**). After both the surgical volumes were created, we calculated the distance from the ECDs to the surgical resections.

Postsurgical Outcomes

The outcomes of these patients help to determine the precision and accuracy of these neuroimaging techniques. This allowed us to determine the therapeutic significance of using MEG for a patient who previously failed an epilepsy surgery without MEG. The surgical outcome will be monitored using the Engel Surgery Outcome Score show in Table 1.

Statistical Analysis

To identify the difference between the two surgical resections and their distance from the ECDs, we calculated the distance from each dipole to the nearest point of each resection. We then calculated the mean distance for each resection to the dipoles. From there we compared them with *Wilcoxon signed rank test* using a statistical significance of $p<0.05$. All analysis was performed using SPSS[25].

Results

Research Question 1: Are there certain characteristics in children with DRE in the US that delay their evaluation for epilepsy surgery despite failing three or more ASMs?

Study Group

There were 399 patients that met the inclusion/exclusion criteria. Of those patients, 200 patients failed ≤2 ASMs prior to surgical referral and 199 patients failed >2 ASMs prior to referral. The range of failed ASMs prior to surgical evaluation referral ranged from 0 to 14 ASMs (**Figure 9**). The patients included came from 15 of the 21 sites enrolled in the PERC Database (**Figure 10**).

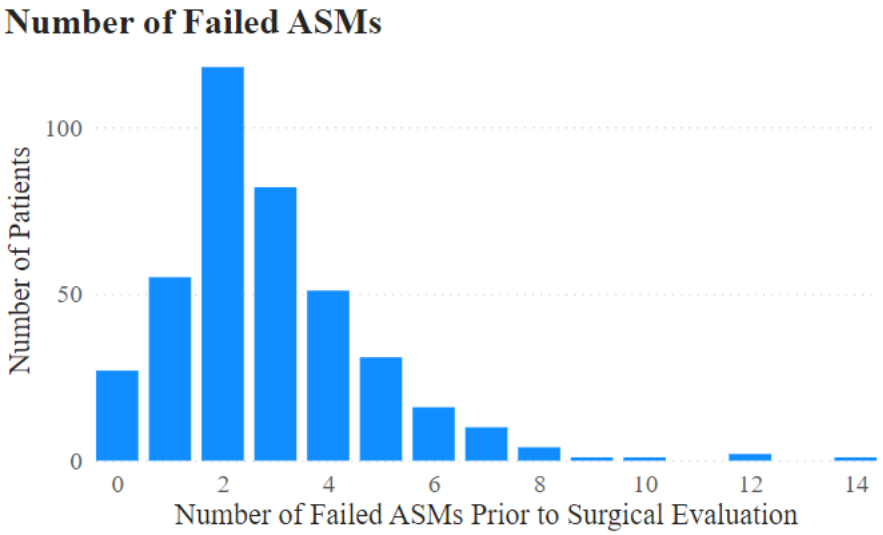

Figure 9: *The range of the number of failed ASMs prior to surgical evaluation. Data is normally distributed if outliers (ASMs≥8) are removed.*

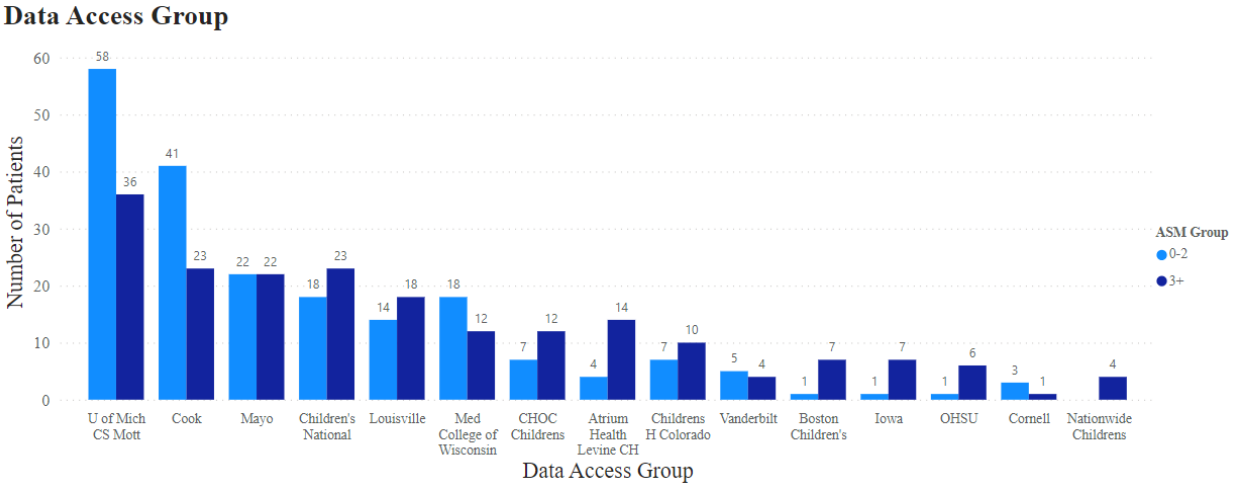

Figure 10: *The hospitals the patients used in this study were from. Most patients came from the University of Michigan CS Mott Children's Hospital in Ann Arbor, MI with the second most patients coming from Cook Childrens Medical Center in Fort Worth, TX.*

Gender, Race, Ethnicity, Type of Insurance, and Distance from Surgical Center

There was no significant difference between failed ASM group with gender, race, or ethnicity (**Figure 11**), type of insurance (**Figure 12**), or distance from surgical center (**Figure 13**). Thus, we failed to identify a relationship between the ASM group and gender, race, ethnicity, type of insurance, or distance from surgical center.

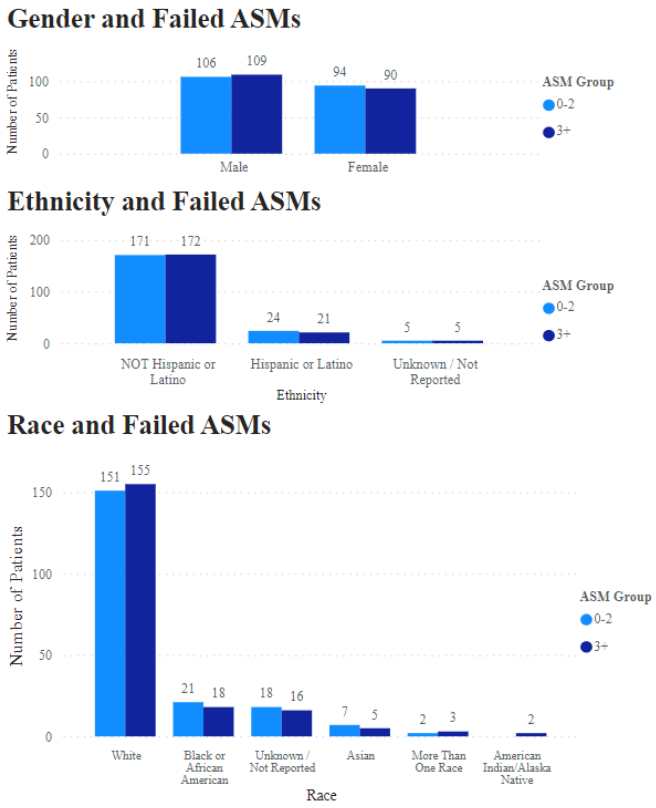

Figure 11*: The difference between the two ASM groups and gender, ethnicity, and race were not statistically significant (p>0.05).*

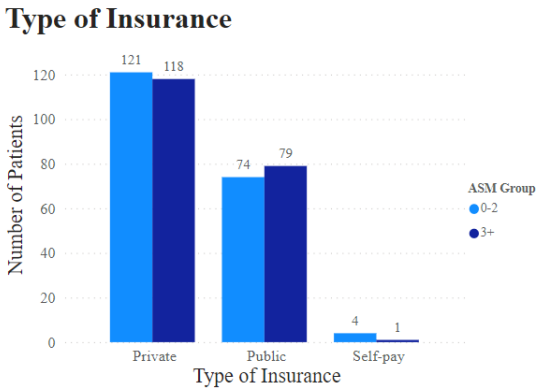

Figure 12*: Chi-squared test was insignificant (p=0.368) and Fisher's Exact test was insignificant (p=0.395), thus we failed to identify an association between type of insurance and ASM group.*

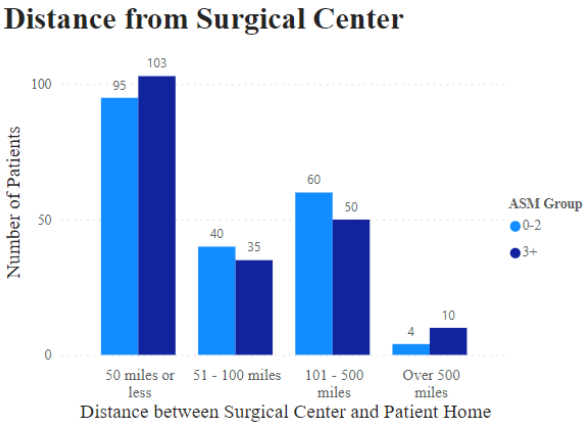

Figure 13*: Chi-squared test was insignificant (p=0.171) and Fisher's Exact test was insignificant (p=0.174), thus we failed to identify an association between distance from surgical center and ASM group.*

Source of Referral for Surgical Evaluation

Based on chi-squared test (*p*=0.700) and Fisher' Exact test (p=0.758), there was no statistically significant association between source of referral for surgical evaluation and ASM group (**Figure 14**).

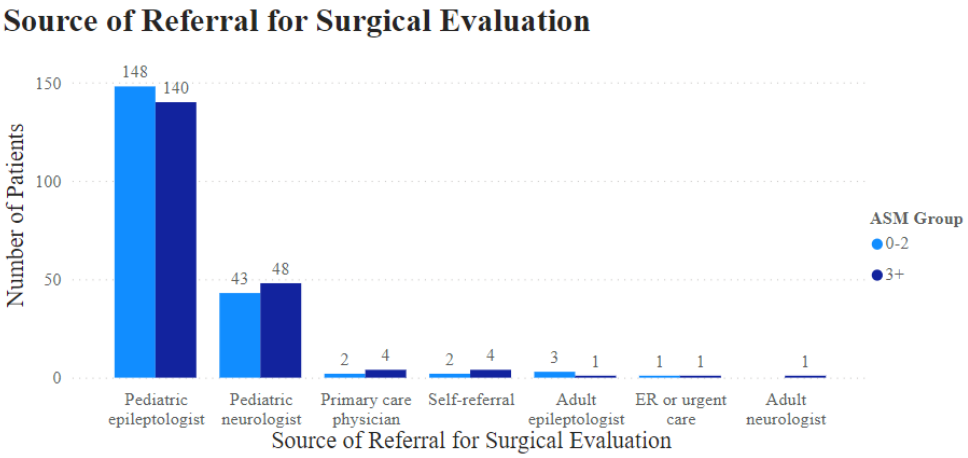

Figure 14*: There was no association between surgical referral source and ASM group*

Age at Epilepsy Onset

There was a statistically significant difference (p = 0.006) when comparing age at epilepsy onset between ASM groups. The average age at epilepsy onset for children failing ≤ 2 ASMs was 5.84 years old, where the average age at epilepsy onset for children failing > 2 was 4.25 years old. The mean difference in age at epilepsy onset between the two ASM groups was 1.59 years with children failing >2 ASMs prior to referral being younger at epilepsy onset (**Figure 15**). Additionally, children failing >2 ASMs had onset of seizures at younger age (median 3y, IQR 0.6-7) compared to children failing ≤2 ASMs (median 5.1, IQR 1-10.9; p<0.001).

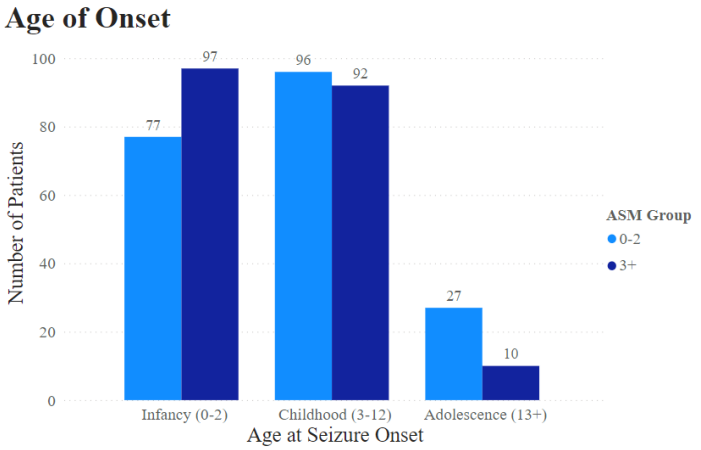

***Figure 15**: The difference between age of epilepsy onset and the two ASM groups was statistically significant (p=0.006) with children failing >2 ASMs having the onset of their epilepsy on average 1.59 years earlier than children failing ≤ 2 ASMs prior to surgical evaluation.*

Age at Failure of 2nd ASM

The difference of the age at failure of the 2nd ASM and the ASM group was statistically significant (n=266; *p*= 0.006). Children failing ≤ 2 ASMs failed their second ASM at 8.50 years old on average compared to children who failed >2 ASMs failed their second ASM at 6.75 years old on average (**Figure 16**). The mean difference between the two groups was 1.75 years.

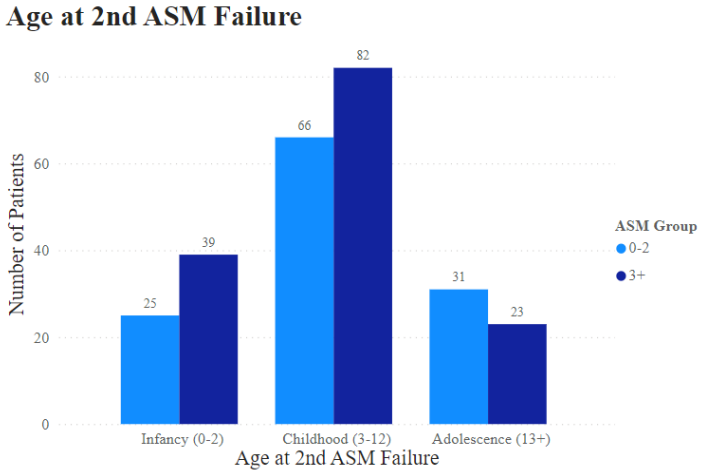

***Figure 16**: Patients failing >2 ASMs failed their 2nd ASM 1.75 years earlier on average compared to children failing ≤2 ASMs (p=0.006).*

Age at Surgical Referral

The difference between ASM groups and the age at surgical referral was not statistically significant (*p*=0.615). The mean age at surgical referral for children failing ≤ 2 ASMs was 9.25 years old compared to 8.93 year old for children failing >2 ASMs (**Figure 17**). Surgical referral was delayed

for those failing >2 ASMs (median 1.4y, IQR 0.3-3) compared to those ≤2 (median 0.3y, IQR 1-1.03; p=0.005).

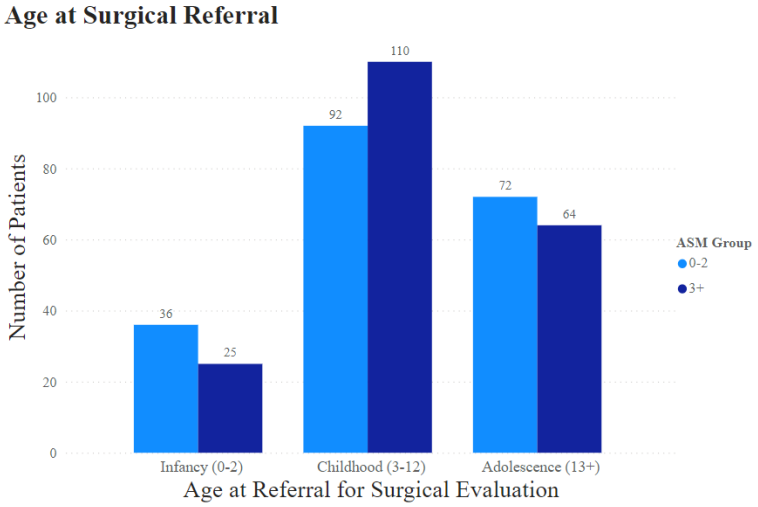

***Figure 17**: There is no significant difference between the mean age at surgical referral for ≤2 ASMs and mean age at surgical referral for >2 ASMs (p=0.615).*

Time Between Failure of 2nd ASM and Surgical Referral

The difference in the time between failure of the second ASM and surgical referral compared to the ASM group was statistically significant (n=265; $p < 0.001$). The average amount of time between failure of the second ASM and surgical referral for patients in the ≤ 2ASM group was 1.00 years, where the average among of time between failure of the second ASM and surgical referral for patients in the >2ASM group was 2.26 years. The mean difference between the two groups was 1.25 years.

Type of 1st Seizure

Based on the chi-squared test, the type of 1st seizure was not associated with ASM group (p=0.054), however, based on the Fisher's Exact test, there was a significant association (p=0.021). And based on a dichotomous logistic regression, generalized onset of the first seizure was the only variable that had a statistically significant impact on the categorization of ASM group (p=0.009) (**Table 5**)..

Frequency of 1st Seizure

Based on the chi-squared test, the frequency of the 1st seizure was associated with the ASM group (p=0.001) (**Figure 18**). Based on a dichotomous logistic regression, seizures occuring more than monthly and daily seizures had a statistically significant impact on the ASM categorization.

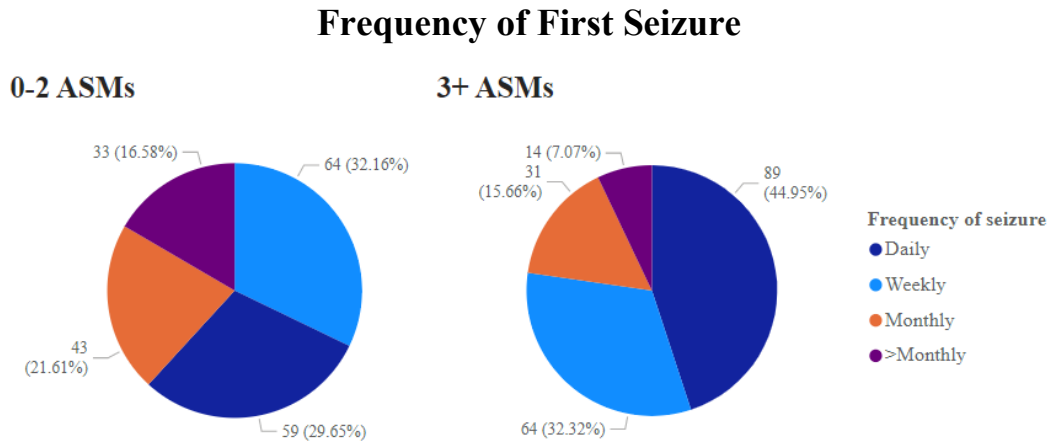

Figure 18: *The frequency of the first seizure is associated with the ASM group (p=0.001).*

Epilepsy Etiology

Based on the chi-sqaured test (p=0.53) there was not a significant association between epilepsy etiology and ASM group, but the Fisher's Exact test found a significant association (p=0.037) (**Figure 19**).

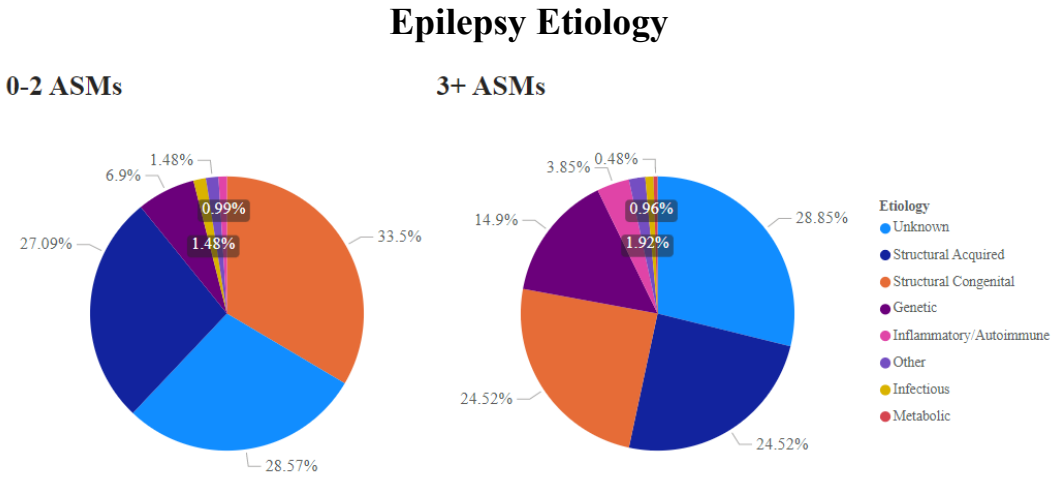

Figure 19: *There was a significant association between etiology of the epilepsy and ASM group based on the Fisher's Exact Test (p=0.037).*

Neurological Exam Findings

Based on the chi-squared test there was a significant association between neurological exam outcome (normal or abnormal) and the ASM group (p<0.001). A dichotomous logistic regression shows an abnormal neurological exam had a statistically significant impact on the ASM group (p=0.004) (**Table 5**).

Neurological Deficit

Of the 399 patients, 268 of them had a neurological deficit. Neurological deficits include cognitive/developmental delay, focal motor deficits, visual deficits, focal sensory deficits, or other deficits not lister. The difference in neurological deficit and the ASM group was insignificant based on Chi-squared test ($p = 0.294$) and Fisher's Exact test ($p = 0.332$). Thus, no association between neurological deficit and ASM group was identified.

MRI Result

The difference in MRI results (normal vs. abnormal) and the ASM group was insignificant based on Chi-squared test ($p = 0.387$) and Fisher's Exact test ($p = 0.427$). Thus, no association between MRI results and ASM group was identified (**Figure 20**).

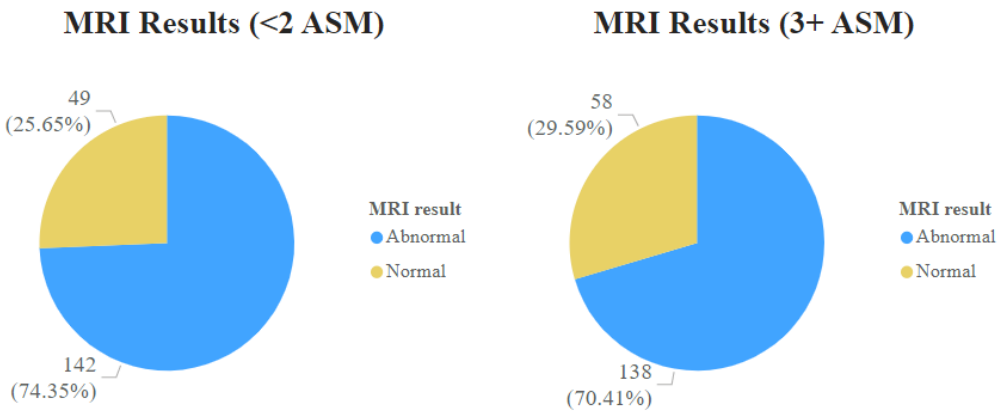

Figure 20: *There was no association between MRI results and ASM group.*

Other Failed Treatments (Non-ASMs)

Both the chi-squared test and Fisher's Exact test found a significant association between other failed non-ASM treatments and ASM group ($p < 0.001$ for both tests) (**Figure 21**).

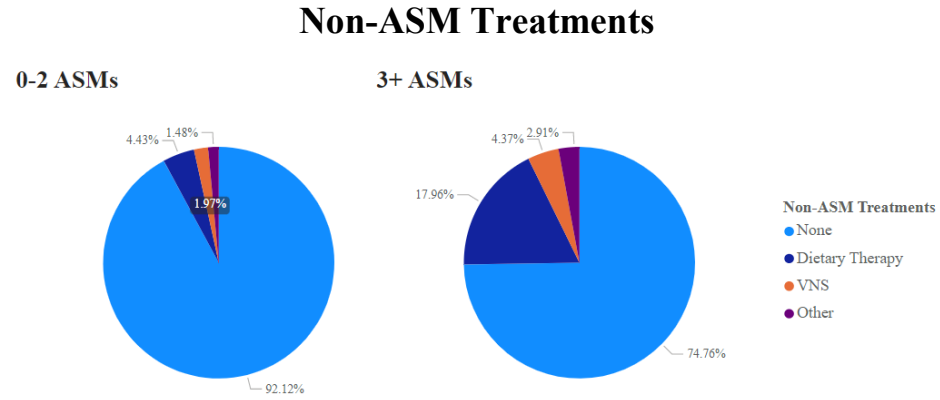

Figure 21*: There was a significant association between types of other non-ASM treatments trialed and ASM group (p<0.001).*

Was Surgery Performed?

Of the 399 patients in this study, only 181 patients had information on if surgery was performed or not. Based on the Chi-squared test (p=0.018) and the Fisher's Exact test (p=0.02), there was a significant association between if surgery was performed and the ASM group (**Table 5**).

Type of Procedure Performed?

Based on the chi-squared test and Fisher's Exact test there was a significant association between the type of procedure performed (neuromodulation, lobectomy, hemispherectomy, lesionectomy, callosotomy, thermal ablation, and other) and the ASM group (p=0.001 for both tests) (**Figure 22**).

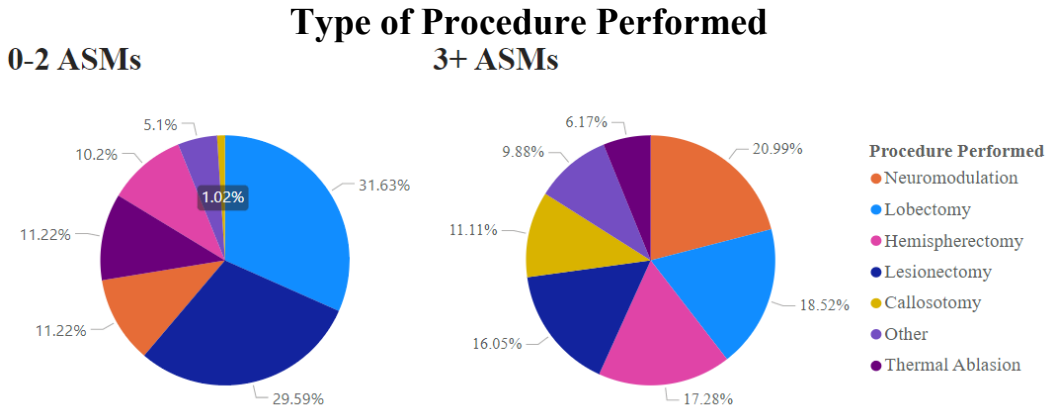

***Figure 22**: There was a significant association between procedure performed and ASM group (p=0.001).*

Intent of Surgery

Of the 399 patients, only 226 patients had the intent of their surgery mentioned. Based on chi-squared test (p<0.001) and Fisher's Exact test (p=0.001), there was a significant association between the intent of the surgery (definitive versus palliative) and the ASM group (**Figure 23**).

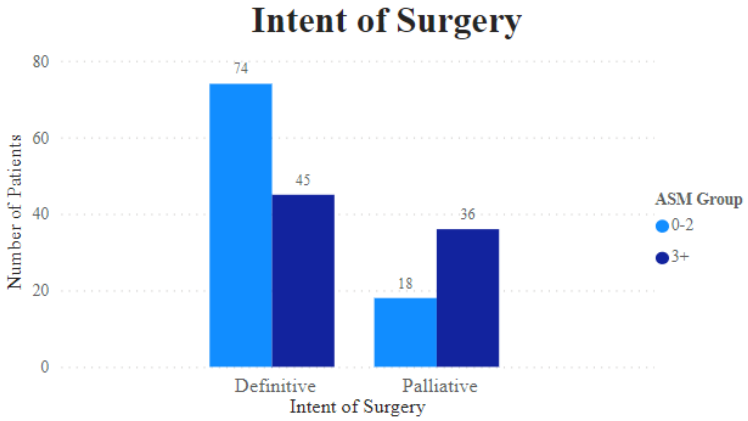

***Figure 23**: The association between intent of surgery and ASM group was significant (p<0.001).*

Was Surgery Offered?

Out of the 399 patients, 238 were offered surgery and 71 were not (90 patients had no information on if surgery was offered. Based on chi-squared test, there was no significant association between if surgery was offered and ASM group (p=0.929) (**Figure 24**).

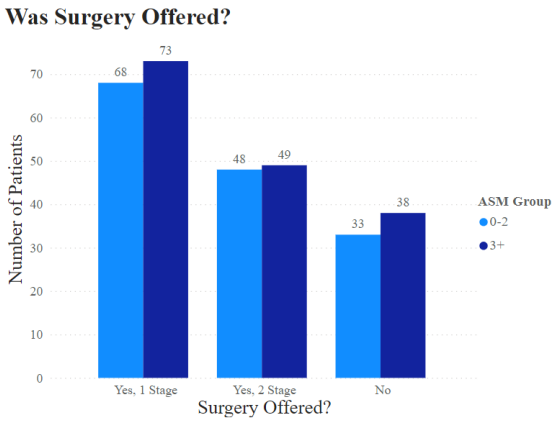

Figure 24*: There was so significant association between if surgery was offered and ASM group.*

Why Surgery Was Not Offered

The difference in why surgery was not offered (inadequate localization, multifocal onset, risk of functional injury, nonepileptic events, or other) and the ASM group was insignificant based on Chi-squared test (p = 0.100) and Fisher's Exact test (p = 0.069). Thus, no association between why surgery was not offered and ASM group was identified.

Why Surgery Was Not Performed

The difference in why surgery was not performed (Stage 1 monitoring did not localize the seizures, patient declined surgery, benefits were not greater than risks, patient declined stage to, or other) and the ASM group was insignificant based on Chi-squared test (p = 0.171) and Fisher's Exact test (p = 0.141). Thus, no association between why surgery was not performed and ASM group was identified.

Surgical Outcomes

Of the 399 patients, 138 children (35%) had surgery and at least one post-op outcome recorded. The median time from surgery to outcome report was 6 months and the mean duration was 6.7 months. The range for the duration was 0-23 months and the IQR was 2-10 months. Favorable outcomes were considered patients who had an Engel score of 1 or 2 and unfavorable outcomes were considered patients who had an Engel score of 3 or 4 or needed an additional surgery (**Table 4).** Of the patients failing ≤2 ASMs prior to surgical referral that had surgery, 66 patients had favorable outcomes and 14 patients had unfavorable outcomes. Of the patients failing >2 ASMs prior to surgical referral that had surgery, 52 patients had favorable outcomes and 20 patients had unfavorable outcomes. There was no significant association between surgical outcome and number of failed ASMs prior to surgical referral based on Fisher's Exact test (p>0.05). There was a

significant correlation between type of first seizure and surgical outcome based on Fisher's Exact test (p<0.001) with 85% of patients who had focal onset of their seizures had favorable outcomes compared to only 32% of patients who had generalized onset seizures having favorable outcomes. Furthermore, there was a significant correlation between frequency of the first seizure and surgical outcome based on Fisher's Exact test (p=0.033) with 66% of patients with daily seizures having favorable outcomes, 84% of patients with weekly seizures having favorable outcomes, 97% of patients with monthly seizures having favorable outcomes, and 93% of those having seizures less than monthly having favorable outcomes (**Table 5)**. There was no significant association between surgical outcome and the etiology of epilepsy ($p=0.$108). Finally, there was a statistically significant correlation between intent of surgery (definitive versus palliative) and surgical outcome based on Fisher's Exact test (p<0.001). Of the definitive procedures performed, 93% had favorable outcomes, and of the palliative procedures performed, 48% had favorable outcomes.

	Daily	Weekly	Monthly	>Monthly
Favorable Outcomes	66%	84%	97%	93%
Unfavorable Outcomes	34%	16%	3%	7%

Table 5*: Frequency of seizures and outcome had a significant correlation (p=0.033).*

Table 6 shows the list of characteristics that were found to be significant.

Variables	<2 Failed ASMs	>2 Failed ASMs	Significance (Fisher's Exact)
Type of 1st Seizure (n=397)			
Focal Onset	89.5% (178)	81.3% (161)	
Generalized Onset	6.5% (13)	15.7% (31)	p=0.021
Unknown Onset	3.5% (7)	3% (6)	
Subclinical Onset	0.5% (1)		
Frequency of 1st Seizure (n=397)			
Daily	29.7% (59)	45% (89)	
Weekly	32.2% (64)	32.3% (64)	p<0.001
Monthly	21.6% (43)	15.7% (31)	
>Monthly	16.6% (33)	7% (14)	
Etiology (n=410, some had >1 selected)			
Structural Congenital	33.5% (68)	24.5% (51)	
Structural Acquired	27.1% (55)	24.5% (51)	
Genetic	6.9% (14)	14.9% (31)	p=0.037
Infectious	1.5% (3)	1% (2)	
Inflammatory/Autoimmune	1% (2)	3.8% (8)	
Metabolic	0% (0)	0.5% (1)	
Unknown	28.5% (58)	28.8% (60)	
Other	1.5% (3)	2% (4)	
Neurological Exam (n=392)			
Normal	61.6% (122)	40.2% (78)	p<0.001
Abnormal	38.4% (76)	59.8% (116)	
Other Failed Treatments (n=409, some failed >1)			
None	92.1% (187)	74.7% (154)	p<0.001
Dietary Therapy	4.4% (9)	18% (37)	
Vagal Nerve Stimulator	2% (4)	4.4% (9)	
Other	1.5% (3)	2.9% (6)	
Was Surgery Performed? (n=218)			
Yes	87.6% (92)	73% (81)	p=0.02
No	12.4% (15)	27% (30)	
Procedure Performed (n=179, some had >1)			
Lobectomy	31.6% (31)	18.5% (15)	
Lesionectomy	29.6% (29)	16% (13)	
Neuromodulation	11.2% (11)	21% (17)	p=0.001
Thermal Ablation	11.2% (11)	6.2% (5)	
Hemispherectomy	10.2% (10)	17.3% (14)	
Callosotomy	1.1% (1)	11.1% (9)	
Other	5.1% (5)	9.9% (8)	
Intent of Surgery (n=173)			
Definitive	80% (74)	55.5% (45)	p=0.001
Palliative	20% (18)	44.5% (36)	

***Table 6**: Patient Characteristics of Significance comparing patients failing ≤ 2 and >2 ASMs prior to referral for surgical evaluation*

Research Question 2: In children with DRE, does information derived from magnetoencephalography (MEG) advance presurgical localization of the epileptogenic zone (EZ) and improve the surgical outcome in those who have failed prior epilepsy surgery?

General Results

We identified seventeen children with DRE (7 males; mean: 12.3 years old at second surgery +/- 5.9 years) who failed an epilepsy surgery with iEEG and then went on to have a second epilepsy surgery with guidance from MEG. Of the 17 children, 53% were seizure free after the second surgery. Only 12% of patients had no significant reduction in their seizures (Engel 4) and 88% of patients had an improvement in their Engel score after their second surgery (**Table 7**). 82% had an abnormal MRI prior to their first surgery. The average Engel score after the first surgery was 3.3 +/- 0.8 and the average Engel score after the second surgery was 1.9 +/- 1.1.

Patient	Gender	Age at Onset (years)	MRI	Age at 1st Surgery (years)	Type of 1st Surgery	Engel Score post-op Surgery 1	Age at 2nd surgery (years)	Type of 2nd Surgery	Engel Score 1-year post-op
1	Male	5	Abnormal	15	Right ATL	3	16	Extension of previous resection	1
2	Female	12	Normal	16	Left frontal cortical resection	3	19	Posteriorly extended previous resection	1
3	Female	2	Abnormal	17	Right frontal lesionectomy	2	20	Right frontal lobectomy	1
4	Male	4	Abnormal	12	Left ATL	2	18	Extension of previous resection	1
5	Male	5	Abnormal	11	Right insular cortex lesionectomy	3	13	Right insular cortex laser ablation	1
6	Female	1	Abnormal	2	Right frontal lobectomy	4	4	Extension of previous resection	1
7	Female	0.5	Abnormal	8	L functional hemispherectomy	2	10	Left frontal lobectomy	1
8	Male	0.6	Abnormal	4	Total resection of cortical dysplasia	4	9	Right occipital gliosis resection	1
9	Female	5	Abnormal	11	Right ATL + hippocampectomy	2	17	Visualase of right insular cortex	1
10	Male	6	Normal	10	Right ATL	4	17	Visualase of right STG and insula	2
11	Female	0.3	Abnormal	2	Left parieto-occipital resection	3	2	Extension of previous resection	2
12	Female	9	Abnormal	10	Visualase of right frontal lobe	4	15	Visualase of right frontal lobe	3
13	Male	5	Abnormal	13	Laser ablation of left middle frontal gyrus	4	16	Visualase of left posterior frontal lobe	3
14	Female	2	Abnormal	5	Removal of right hemisphere cortical dysplasia	4	7	Visualase of right medial temporal lobe	3
15	Female	0.7	Abnormal	1	Left frontal lobectomy	4	1	Extension of previous resection	3
16	Female	10	Normal	10	Right frontal lobe resection	4	11	Right frontal lobe hemispherectomy	4
17	Male	4	Abnormal	12	Right ATL	4	17	Extension of previous resection	4

***Table** 7: Patient demographics, epilepsy characteristics, and surgical history.*

ATL = Anterior Temporal Lobectomy; STG= Superior temporal gyrus

Engel 1

There were 9 patients (53%) who were seizures free (Engel score of 1) after their second surgery which was guided by MEG. Example data that was used to calculate the distance from dipole clusters to the two resections are shown in **Figures 25-27**. On average, the distance from the clustered ECDs from the first resection was 20.5 mm ± 16.9. The average distance from the clustered ECDs from the second resection was 8.4 mm ± 8.0. The Wilcoxon Signed Ranked Test signified there was a significant difference in these average distances from the clusters (p=0.008) (**Figure 28**).

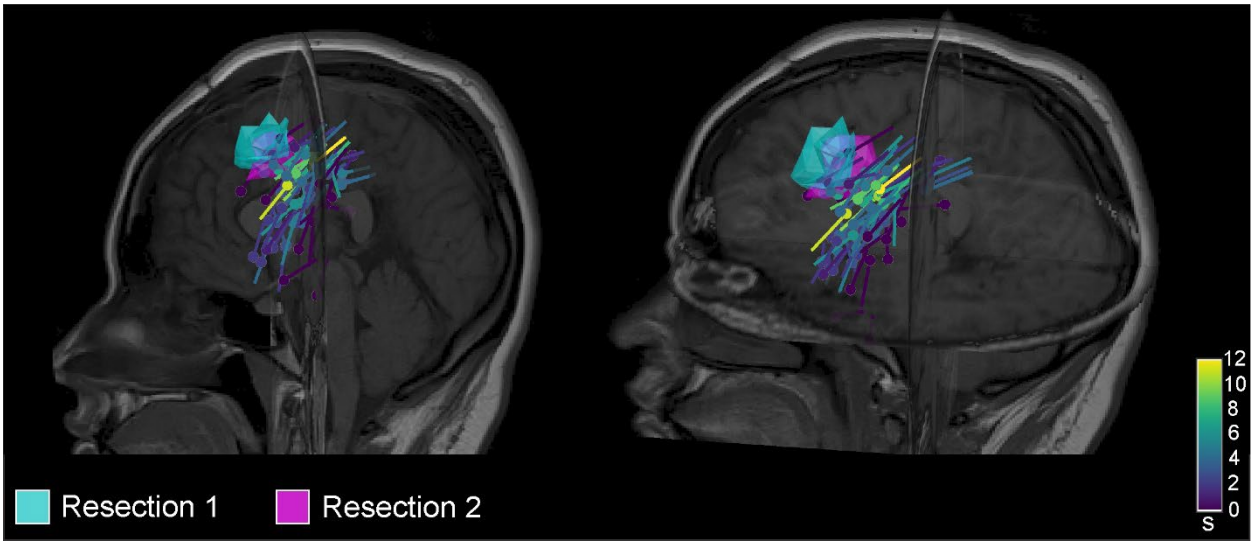

***Figure 25**: **Dipole clustering and distance of dipoles from resections.** The magnetic resonance imaging (MRI) of a 19-year-old female who had resections in the left frontal lobe area (Patient 2 in **Table 7**) who was seizure free after second resection guided by magnetoencephalography. Cluster of equivalent current dipoles (ECDs) from surgical volumes are displayed. ECDs are color-coded according to their clusterness: from low- (purple) to high-clusterness (yellow) values. The initial resection volume is cyan-colored and the second resection volume is magenta-colored. The ECDs are closer on average to the second resection (8.7 mm away) compared to the first resection (15.0 mm away).*

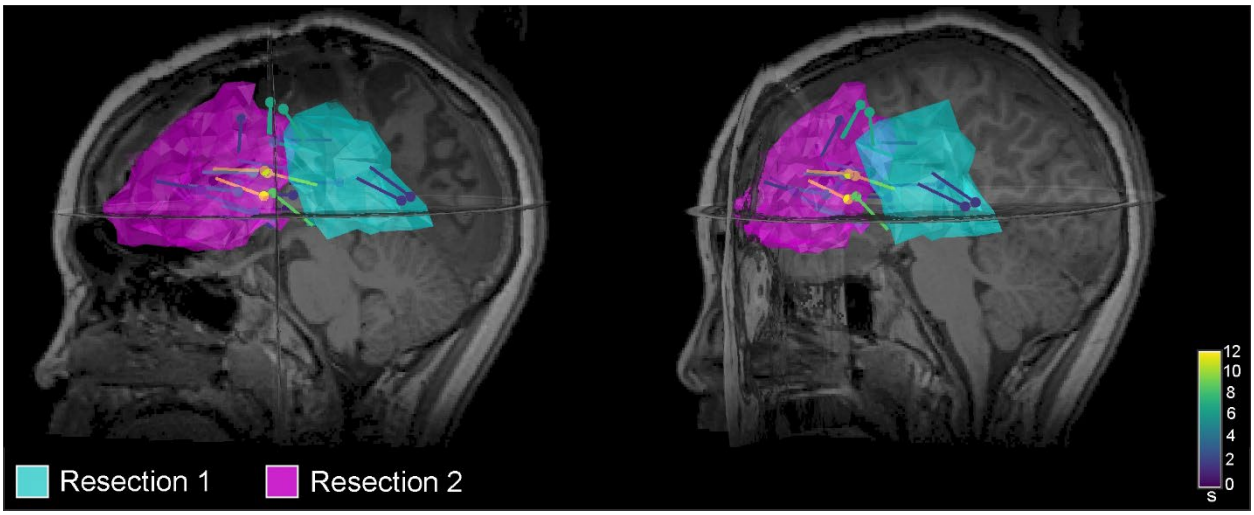

***Figure 26**: **Dipole clustering and distance of dipoles from resections.** The magnetic resonance imaging (MRI) of a 10-year-old female who had resections in the left frontal lobe area (Patient 7 in **Table 7**) who was seizure free after second resection guided by magnetoencephalography. The ECDs are closer on average to the second resection (0.5 mm away) compared to the first resection (9.3 mm away).*

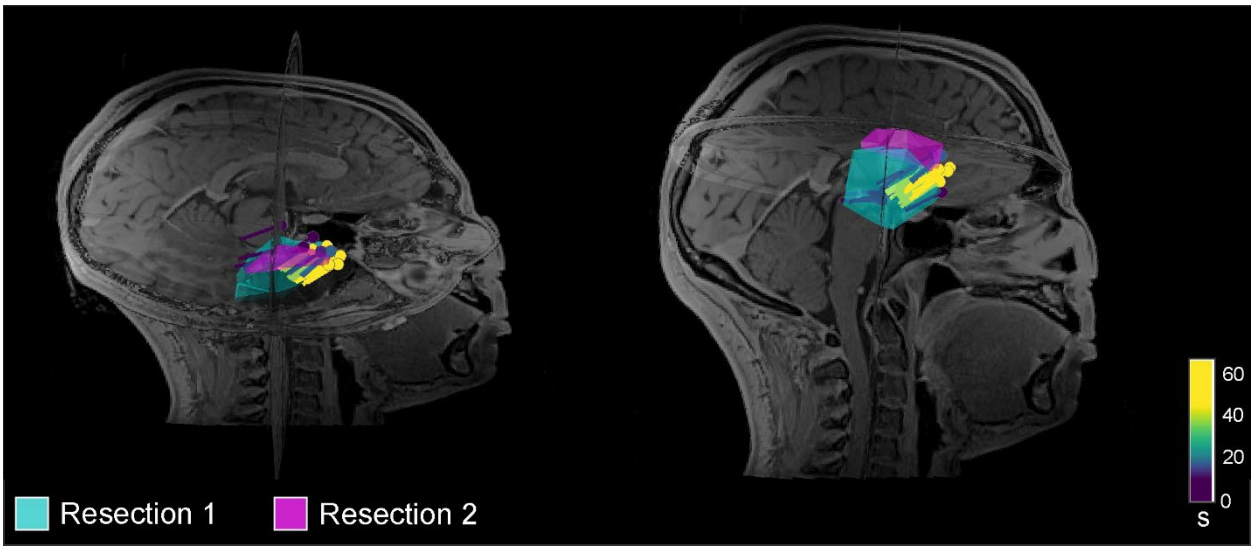

***Figure 27**: **Dipole clustering and distance of dipoles from resections.** The magnetic resonance imaging (MRI) of a 17-year-old female who had resections in the right temporal region (Patient 9 in **Table 7**) who was seizure free after second resection guided by magnetoencephalography. The ECDs are closer on average to the second resection (1.5 mm away) compared to the first resection (2.4 mm away).*

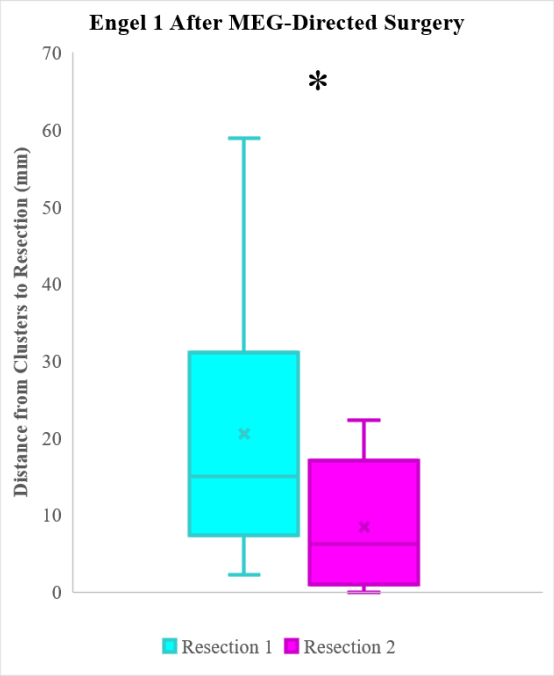

***Figure 28**: Distance of clustered ECDs (in mm) computed from initial resection (cyan-colored); distance of clustered ECDs (in mm) computed from repeated resection (i.e., magnetoencephalography-guided surgery) (magenta-colored). The significant difference ($p < 0.05$) is marked with the asterisk ($p = 0.008$, Wilcoxon signed-rank test).*

Engel 2

There were 2 patients (12%) who had ≥90% reduction in their seizures, but were not seizure free (Engel score of 2) after their second surgery which was guided by MEG. Example data that was used to calculate the distance from dipole clusters to the two resections are shown in **Figure 29**. On average, the distance from the clustered ECDs from the first resection was 13.0 mm. The average distance from the clustered ECDs from the second resection was 11.5 mm. The Wilcoxon Signed Ranked Test signified there was a significant difference in these average distances from the clusters (p=0.008).

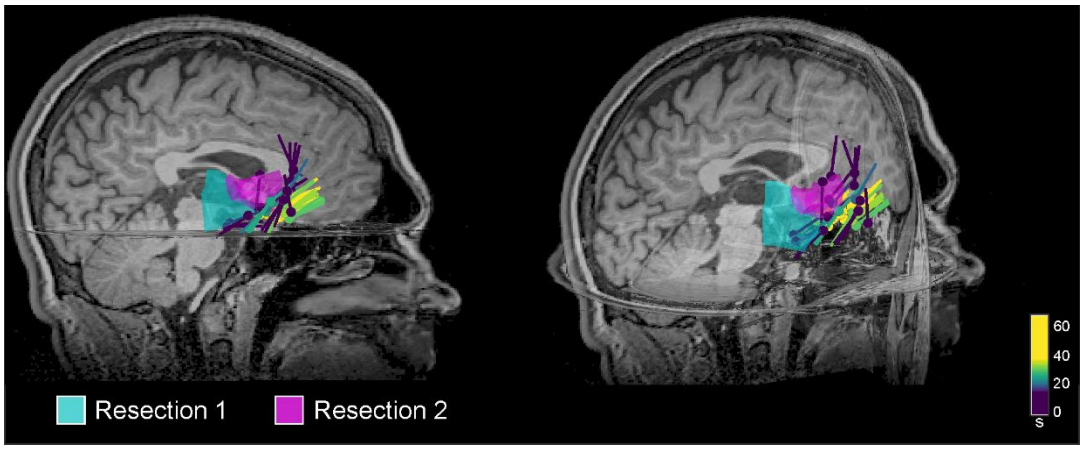

***Figure 29**: **Dipole clustering and distance of dipoles from resections.** The magnetic resonance imaging (MRI) of a 17-year-old male who had resections in the right temporal region (Patient 10 in **Table 7**) who had an Engel score of 2 after second resection guided by magnetoencephalography. The ECDs are closer on average to the second resection (2.5 mm away) compared to the first resection (8.3 mm away).*

Engel 3

There were 4 patients (24%) who had >50% but <90% reduction in their seizures (Engel score of 3) after their second surgery which was guided by MEG. Example data that was used to calculate the distance from dipole clusters to the two resections are shown in **Figures 30-31**. On average, the distance from the clustered ECDs from the first resection was 32.1 mm. The average distance from the clustered ECDs from the second resection was 19.8mm. The Wilcoxon Signed Ranked Test signified there was no significant difference in these average distances from the clusters (p=0.068) (**Figure 32**).

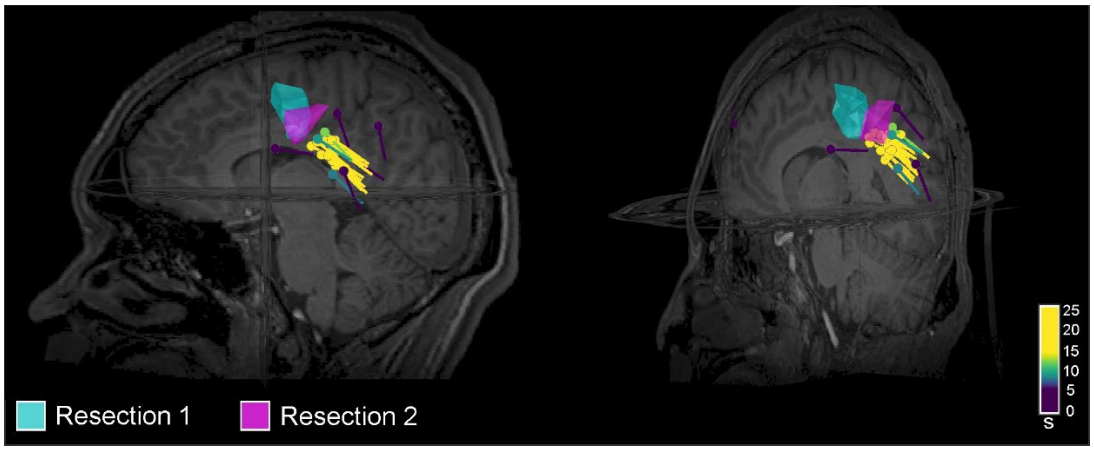

***Figure 30**: **Dipole clustering and distance of dipoles from resections.** The magnetic resonance imaging (MRI) of a 16-year-old male who had resections in the left frontal lobe (Patient 13 in **Table 7**) who had an Engel score of 3 after second resection guided by magnetoencephalography. The ECDs are closer on average to the second resection (12.9 mm away) compared to the first resection (15.4 mm away).*

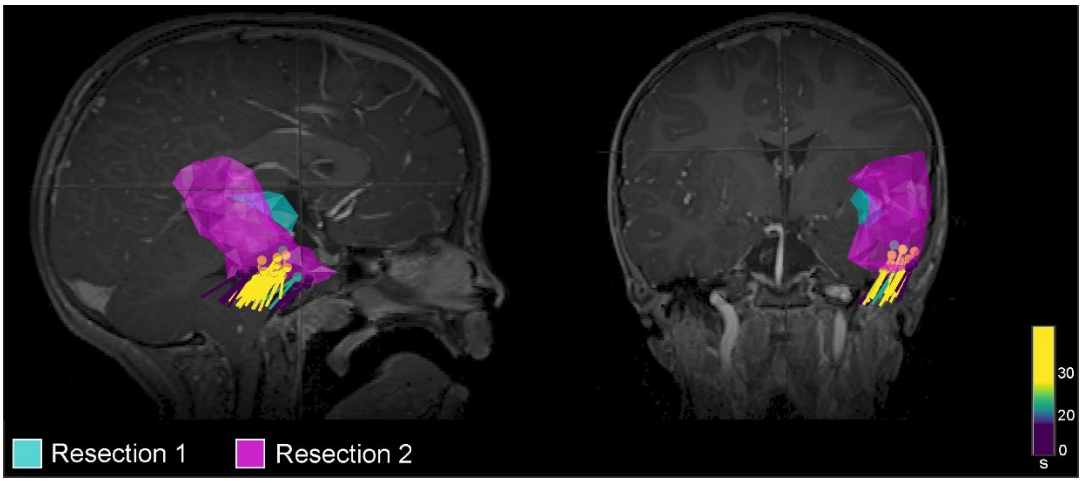

***Figure 31**: **Dipole clustering and distance of dipoles from resections.** The magnetic resonance imaging (MRI) of a 7-year-old female who had resections in the right temporal region (Patient 14 in **Table 7**) who had an Engel score of 3 after second resection guided by magnetoencephalography. The ECDs are closer on average to the second resection (0.0 mm away) compared to the first resection (21.6 mm away).*

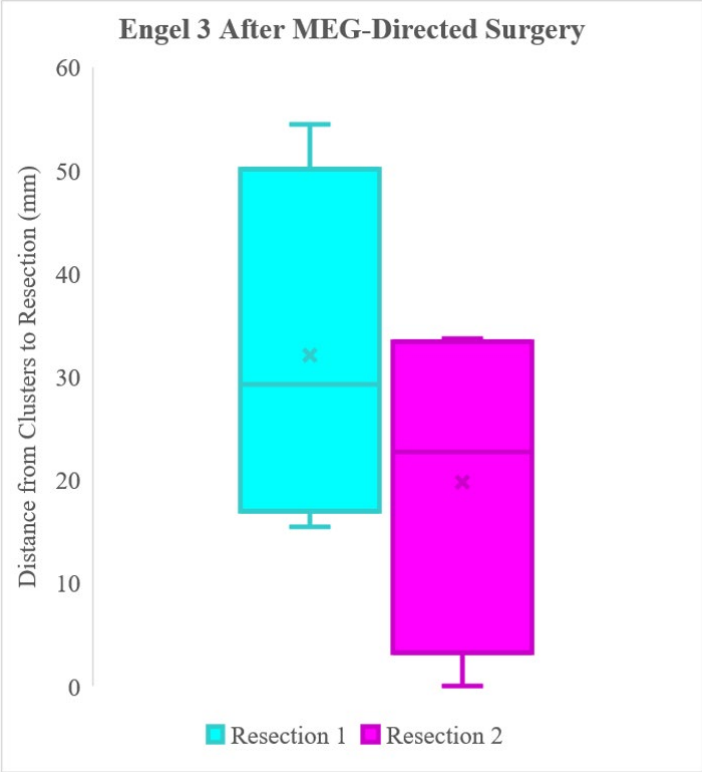

***Figure 32**: Distance of clustered ECDs (in mm) computed from initial resection (cyan-colored); distance of clustered ECDs (in mm) computed from repeated resection (i.e., magnetoencephalography-guided surgery) (magenta-colored). However, there was no significant difference between the two resections ($p = 0.068$, Wilcoxon signed-rank test).*

Engel 4

There were 2 patients (12%) who had <50% reduction in their seizures after their second surgery which was guided by MEG. Both patients had no improvement in their Engel score between the two surgeries. On average, the distance from the clustered ECDs from the first resection was 32.1 mm. The average distance from the clustered ECDs from the second resection was 8.6 mm. However, the Wilcoxon Signed Ranked Test signified there was no significant difference in these average distances from the clusters (p=0.18).

Improved Outcomes

There were 15 patients (88%) who had an improvement in their Engel score after the second surgery. On average, for the patients who had improved Engel scores the distance from the clustered ECDs from the first resection was 22.6 mm. The average distance from the clustered ECDs from the second resection was 11.9 mm. The Wilcoxon Signed Ranked Test signified there was a significant difference in these average distances from the clusters (p=0.001) (**Figure 33**). Additionally, when comparing the difference in the distance between the two resections to the ECDs there was a significant difference based on a Paired Samples t-Test with the average difference in distance being 10.7 mm ± 10.7 (p=0.001).

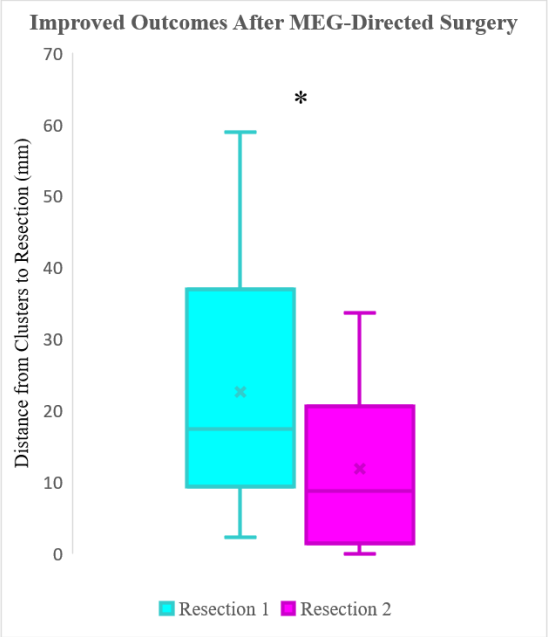

Figure 33*: Distance of clustered ECDs (in mm) computed from initial resection (cyan-colored); distance of clustered ECDs (in mm) computed from repeated resection (i.e., magnetoencephalography-guided surgery) (magenta-colored). The significant difference (p< 0.05) is marked with the asterisk (p = 0.001, Wilcoxon signed-rank test).*

Favorable versus Unfavorable Outcomes

We defined favorable outcomes at patients who had an Engel score of 1 or 2 after their second surgery and those who had an Engel score of 3 or 4 after their second surgery had unfavorable

outcomes. There were 11 patients with favorable outcomes and 6 patients with unfavorable outcomes. On average, for the patients who had favorable outcomes the distance from the clustered ECDs from the first resection was 19.1 mm and the average distance from the clustered ECDs from the second resection was 8.9 mm. The Wilcoxon Signed Ranked Test signified there was a significant difference in these average distances from the clusters for patients with favorable outcomes (p=0.008) (**Figure 34**). On average, for the patients who had unfavorable outcomes the distance from the clustered ECDs from the first resection was 32.1 mm and the average distance from the clustered ECDs from the second resection was 16.1 mm. The Wilcoxon Signed Ranked Test signified there was a significant difference in these average distances from the clusters for patients with favorable outcomes (p=0.028) (**Figure 35**).

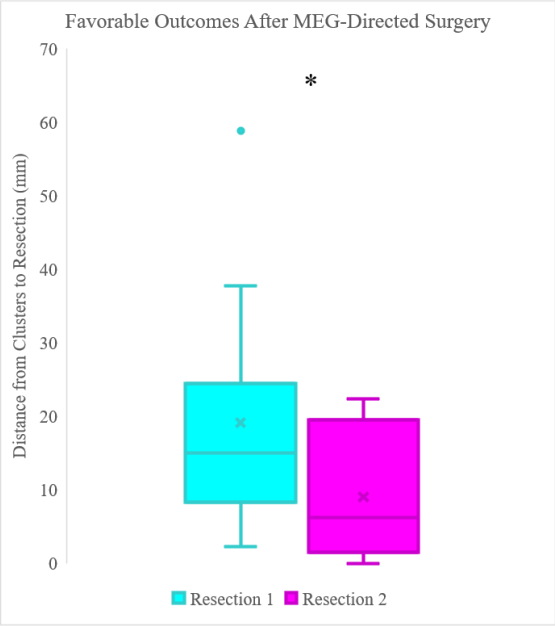

***Figure 34**: Distance of clustered ECDs (in mm) computed from initial resection (cyan-colored); distance of clustered ECDs (in mm) computed from repeated resection (i.e., magnetoencephalography-guided surgery) (magenta-colored). The significant difference ($p < 0.05$) is marked with the asterisk ($p = 0.008$, Wilcoxon signed-rank test).*

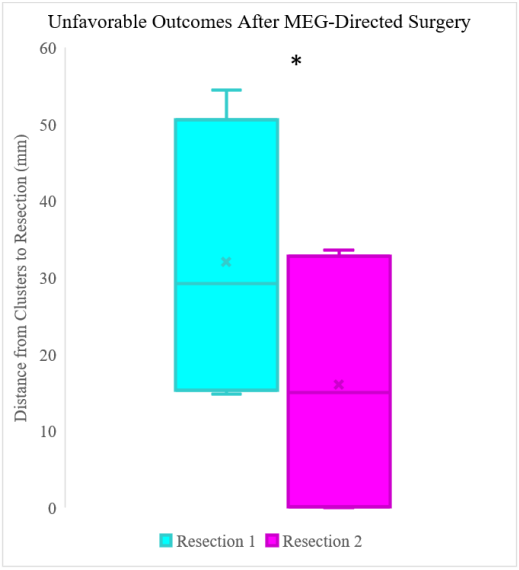

***Figure 35**: Distance of clustered ECDs (in mm) computed from initial resection (cyan-colored); distance of clustered ECDs (in mm) computed from repeated resection (i.e., magnetoencephalography-guided surgery) (magenta-colored). The significant difference ($p < 0.05$) is marked with the asterisk ($p = 0.028$, Wilcoxon signed-rank test).*

For the favorable outcomes, when comparing the difference in the distance between the two resections to the ECDs (Average Difference in Distance = Distance of ECDs from Resection 1 – Distance of ECDs from Resection 2) there was a significant difference based on a Paired Samples t-Test with the average difference in distance being 10.1 mm ± 10.8 (p=0.011). For the unfavorable outcomes, when comparing the difference in the distance between the two resections to the ECDs there was a significant difference based on a Paired Samples t-Test with the average difference in distance being 16.1 mm ± 11.6 (p=0.020). When comparing these two average difference in distances (10.1 mm for favorable outcomes compared to 16.1 mm for unfavorable outcomes) there was no significant difference between them based on an independent Samples t-Test (p=0.650).

Discussion and Innovation

Research Question One

Characteristics that may delay surgical evaluation for children failing >2 ASMs have not been defined, however, this research provided the insight needed to understand these characteristics. This study identified that gender, ethnicity, and race were not associated with whether children would fail ≤ 2 or >2 ASMs prior to surgical referral. This is important to highlight as it shows there is likely no bias based on these patient demographics that would delay a child's surgical referral. Additionally, type of insurance did not play a role in the delay of surgical evaluation for children failing >2 ASMs. Patients who were traveling further to get to a surgical center compared to patients located very close to the hospital had no significant association with the amount of ASMs failed prior to surgical evaluation. This highlights that despite patients being further away from the surgical center, they were not trialed on more ASM due to the distance compared to

children who lived closer to the surgical center. Furthermore, there was not an association between what type of physician referred the patient to surgical evaluation and ASM group. Most referrals (72%) came from pediatric epileptologists.

Children who were younger at epilepsy onset were more likely to trial >2 ASM prior to being referred for epilepsy surgery. In fact, children failing >2 ASMs were on average 1.59 years younger at their epilepsy onset compared to children failing ≤2 ASMs. Additionally, children failing >2 ASMs were on average 1.75 years younger at the failure of their 2nd ASM compared to the children who failed ≤2 ASMs. The ASM group and the age at when the patient was referred had no significant correlation. Finally, the time between when they failed their 2nd ASM and when they were referred for surgical referral was 1.25 years longer for children failing >2 years compared to children failing ≤2 ASMs. This shows that children failing >2 ASMs were not only younger at seizure onset and failure of their 2nd ASM, they had to wait longer for their surgical referral. This is important to recognize since children at younger ages tend have better surgical outcomes, surgery is safe, and these patients are more likely to avoid developmental delays if surgery is performed at a younger age[31]. One study found that seizure freedom was achieved in 89.5% of patients under the age of 3, while other studies have found seizure freedom in children <3 to range from 48% to 76.4%[31]. This is in part due to the plasticity of their brains and the fact important regions in their brains like the speech area, visual area, and motor cortex have not been fully formed[32]. Thus, there should be no reason to continually trial children on ASMs if they are young, since surgery at a younger age result in better surgical outcomes, better developmental outcomes, and it is safe. Additionally, waiting longer from failure of 2nd ASM to surgical evaluation is not beneficial as the longer the patient is experiencing seizures the more likely they will have poor cognitive outcomes, some which may become irreversible, and their surgical outcomes may be poorer[33]. One study focusing on children with intractable frontal lobe epilepsy found 66% of those who had surgery within 5 years of their epilepsy onset were seizure free after surgery compared to only 31% of the children who waited >5 years for surgery from their epilepsy onset[34]. Thus, waiting longer for surgery while being trailed on more ASMs is not beneficial to the patient.

In regards to seizure characteristics and ASM group, there were significant correlations. The type of seizure the patient had was significantly correlated with what ASM group they were in. This was true for patients with generalized onset epilepsy. These patients were more likely to fail >2ASMs prior to surgical referral. This is likely due to the idea that it is much harder to find a seizure onset zone in children with generalized onset epilepsy compared to children with focal onset epilepsy[35]. In focal onset epilepsy, it is much easier to find the seizure onset zone and these children are more likely to have lesional MRIs in which the neurosurgeon can target during resection[35]. As a result, patients with generalized epilepsy likely trialed more medications due to the assumption that it would be harder to localize where in the brain the neurosurgeon would resect to improve these patient's outcomes. Even though this study found that 68% of patients with generalized epilepsy had unfavorable outcomes, 32% of them had favorable outcomes with 16% of those patients became seizure free after surgery. This shows that even though patients with generalized epilepsy have poorer outcomes, there is still a chance that they would have favorable outcomes and even become seizure free. However, it may not be unreasonable to trial more ASM

medications as surgery for patients with generalized epilepsy is unlikely to result in seizure freedom.

Additionally, this study found that the frequency of the seizures was correlated with the ASM group. It specifically showed that patients who had daily seizures were more likely to fail >2ASMs prior to surgical referral, where children who had a seizure frequency greater than every month were more likely to fail ≤2 ASMs before surgical referral. This is important to pay attention to because as mentioned earlier, the longer the patients have seizures and the more frequent these seizures have been shown to result in poorer developmental outcomes[31]. However, patients with daily seizures were found to only have 66% favorable outcomes once surgery was performed compared to patients with more than monthly seizures which showed 93% favorable outcomes. Thus, it may not be unreasonable to consider further ASM trials as surgical outcomes are less likely to be favorable.

When it comes to the etiology of epilepsy there was an association with the ASM group. Patients who had structural causes (both acquired and congenital) of epilepsy were more likely to fail ≤2 ASMs, where patients with genetic epilepsies were more likely to fail >2 ASMs. This finding corresponds to studies showing that patients with genetic epilepsies are less likely to be referred for surgical evaluation and are instead trialed on more ASMs[36]. When comparing surgical outcomes to epilepsy etiology, there was no significant association. So even though 55% of patients with genetic epilepsy had unfavorable outcomes, the association was not significant. Thus, our findings did not show that patients with genetic epilepsies had poorer outcomes compared to patients with structural epilepsies. As a result, children with genetic epilepsies could have done just as well if the surgeries were done earlier which would have also avoided more years of seizure exposure.

Neurological exam findings were associated with ASM group with an abnormal neurological exam more often being seen in patients failing >2 ASMs. However, when comparing surgical outcome to neurological exam findings, there was no significant correlation. Thus, even though an abnormal neurological exam may play a role in the delay of surgical evaluation, an abnormal neurological exam is not necessarily associated with a poor surgical outcome. Thus, the findings on neurological exam should not dictate if a patient is referred for epilepsy surgery or not. Furthermore, the type of neurological deficit found in patients with abnormal neurological exams was not correlated with ASM group.

Surprisingly MRI results (normal vs. abnormal) were not associated with ASM group. It is often felt that patients with normal MRIs are not as good of surgical candidates compared to patients with abnormal MRIs and we expected to find patients failing >2ASMs were more likely to have a normal MRI[20]. Thus, the result of the MRI did not delay surgical referral.

Patients failing >2ASMs were also more likely to have failed other non-ASM treatments like dietary therapy (i.e., ketogenic diet), VNS, or other non-ASM therapies. This shows that the patients who failed >2 ASMs also failed other treatment modalities prior to being referred for surgical evaluation which could have been a factor in delaying the evaluation.

There was no association between ASM group and if surgery was offered or not. Additionally, why surgery was not offered was not associated with ASM group. However, there was an association between ASM group and if surgery was performed or not. Children failing >2 ASMs were less likely to undergo surgery compared to patients failing ≤2 ASMs. But there was no association between ASM group and why surgery was not offered for these patients. Thus, patients failing >2 ASMs were not less likely to be offered surgery compared to patients failing ≤2 ASMs, but they were less likely to undergo surgery.

If patients had a procedure performed, the intent of the surgery was correlated with the ASM group. For patients failing >2 ASMs, the intent of the procedure was more often palliative versus definitive. Furthermore, there was an association between the type of procedure performed and ASM group with patients failing >2 ASMs more likely to undergo larger procedures (i.e. hemispherectomy or callosotomies). Yet, 48% of palliative procedures had favorable outcomes. Given the chance of seizure reduction with trailing of a third ASM is 23.6% after the first two medications failed, palliative procedures are better by offering 90% or better seizure control in 48% of patients[9]. So even though children trialing more ASMs more often underwent palliative procedures, the wait and trials of more ASMs were not necessarily worth it compared to the predicted outcomes.

Finally, the surgical outcome (Engel score) was not correlated with ASM group. So even though patients in the >2 ASM group continued to trial medications, they were not more likely to have poor surgical outcomes. Thus, it is important to consider every child for epilepsy surgical evaluation after they fail two ASMs regardless of their expected outcome. With earlier referral, patients may have less exposure to seizures, better neurodevelopmental outcomes, and even better surgical outcomes.

Research Question Two

Based on the results, the use of MEG has shown to be useful in augmenting the surgical workup for children who previously failed an epilepsy surgery without the use of MEG and underwent a second surgery with the use of MEG. For patients who were rendered seizure free (Engel 1) after their MEG-directed surgery, that surgery was on average 12.1 mm closer to the ECD clusters found on MEG. This was also true for patients who were Engel 2 in which their MEG-directed resection was 1.5 mm closer to the ECDs compared to the initial resection. When looking at the patients who were Engel 3 or 4 after their MEG-directed surgery, the difference in the distances between the two resections was not significant. This may signify that MEG was not useful in these patients, or MEG was unable to accurately identify where seizures were coming from in these patients. The analysis of patients who were Engel 3 or 4 was more difficult to identify ECDs compared to patients who were Engel 1 or 2. Thus, MEG did not augment the surgical work up as much for patients who were Engel 3 or 4 after their second surgery.

When looking at the 15 patients who had an improved Engel score from their initial surgery, their second surgery was on average 10.7 mm closer to the ECDs which was a significant difference. The two patients who did not have an improved outcome in their Engel score did not show any

significant difference in the average distance between the two resections and the ECDs, again suggesting that MEG may not have been useful in augmenting surgical outcome for these patients.

When grouping patients into favorable outcomes (Engel 1 or 2) and unfavorable outcomes (Engel 3 or 4), 69% of patients had favorable outcomes after the MEG-directed surgery whereas only 31% had unfavorable outcomes. For patients with favorable outcomes, the ECDs were statistically significantly closer to the second MEG-directed surgery compared to the first surgery (10.1 mm closer). The same was true for the unfavorable outcomes (16.1 mm closer). It is important to note that the distances from the resections and ECDs were closer for favorable outcomes (19.1 mm for the first resection and 8.9 mm for the second resection) compared to the unfavorable outcomes (32.1 mm for the first and 16.1 mm for the second). So even though the difference was bigger in the unfavorable outcomes, on average the ECDs were further away from the resections compared to the favorable outcomes. Furthermore, when comparing the difference in distance between these two groups, the difference was not statistically significant. This suggests that even though the differences in the resections were smaller for the unfavorable outcomes, the difference compared to the favorable outcomes was not significant and did not lead to a favorable or unfavorable result.

It is important to realize that the children who did have favorable outcomes did have a significant difference in distances between the ECDs and the resections where the difference was not significant for the patients who had unfavorable results. This suggests that MEG did not aid in unfavorable outcomes as the results were not significant. This supports the idea that MEG does augment the surgical workup and aids in favorable surgical outcomes, but did not result in the unfavorable outcomes.

These results are important as it shows MEG has the ability to locate the epileptogenic zone in a precise and accurate way. The use of MEG could lower the need for children to have invasive techniques like iEEG prior to surgery which would decrease the risk for infection, bleeding, and neurological trauma. The use of MEG could also allow children to have one less surgical procedure since MEG is noninvasive.

Future Directions

Future studies are needed to define characteristics that make a good surgical candidate compared to a poor surgical candidate to help create guidelines that would shorten the duration to surgical referral. This study helped identify some of those characteristics that create good surgical candidates such as focal seizures and seizures occuring more than every month. Additionally, we found that patients with generalized seizures and daily seizures may not be good surgical candidates. However, more studies are needed to look at other characteristics not studied in this research such as results of other neuroimaging studies (PET, MEG, fMRI, etc.) and other co-morbidities such as congenital heart malformations which may play a role in children not being good surgical candidates.

Furthermore, this study did not investigate the physician's perspective on when they refer their patients for epilepsy surgery. Due to other studies showing some physicians are unaware that failure of two ASMs should result in surgical evaluation, it would be interesting to see if that also played a role in this patient population[11,13]. To expand on this idea, it would be interesting to see if providing more education to neurologists and epileptologists about the ILAE guidelines would result in more patients being referred for surgery after failure of two ASMs.

Finally, with the recent advancements in neurosurgical procedures for epilepsy patients (like more targeted ablation procedures) and the advancement of neuroimaging techniques (like MEG), it would be interesting to see if there have been less patients failing more than 2 ASMs before they were referred.

With all these findings, and the potential future studies, it would be possible to make clearer guidelines for physicians on when to refer these patients for surgery and once they are referred, what characteristics may predict better surgical outcomes. With these guidelines, we would be able to have better conversations with patients and their families to set better expectations on if an epilepsy surgery may result in favorable or unfavorable results.

Based on the results of the second question of this research, there is evidence that MEG was important in patients who previously had an unsuccessful surgery without the use of MEG. Because this was a retrospective study, there is need for a prospective study. Because MEG has shown to be useful in surgical workup, patients should not be denied a MEG study if they are undergoing their first surgical evaluation. Instead, the study focus on patients who have previously had surgery without MEG and the prospective part of the study would be for the second surgical workup. Additionally, because some of these studies were done over 10 years ago, we were unable to determine how much of the surgical planning was based on the MEG findings, so to be able to do a study prospectively, we would be able to better determine the use of MEG for the surgical workup.

It may also be beneficial to expand upon this study by analyzing the iEEG data and mapping the dipoles found with iEEG for the initial surgery. This was the dipoles from iEEG could be compared to the dipoles from MEG to compare the difference in distance from both the resections

to the iEEG dipoles versus the MEG dipoles. This may help support that iEEG may not have been as accurate in identifying the epileptogenic zone in patients with poor outcomes who went on to having favorable outcomes after MEG was used for the second surgery. It may also help explain why some patients had unfavorable outcomes after the MEG-directed surgery.

Finally, most MEG studies are done simultaneously with high density EEG, so it may be helpful to also analyze that data and compare the dipoles identified with high density EEG to the MEG dipoles. This may also allow us to compare ictal (the time during a seizure) and interictal (the time between seizures) activity and how identifying dipoles in both of those instances may help augment surgical outcomes in these patients.

Conclusion

This research has helped define characteristics that may delay surgical referral and cause children to fail >2 ASMs prior to surgical referral despite the ILAE guidelines suggestion surgical referral once two ASMs have been failed[7]. This research identified that children who are younger at seizure onset and younger when they fail their 2nd ASM are more likely to fail >2 ASMs before they are referred for epilepsy surgery. However, several studies have shown that children <3 years of age have great surgical outcomes especially due to the neuroplasticity resulting in better neurodevelopmental outcomes if surgery is performed sooner[31,32]. That being said, delaying surgical referral due to age is not advisable and all children regardless of age should be referred for surgical evaluation once they fail two ASMs.

Additionally, children with generalized seizures or genetic epilepsies are more likely to fail >2 ASMs compared to patients with focal seizures or structural epilepsies. However, delaying surgical referral due to concerns that genetic epilepsies result in poorer surgical outcomes was not supported in our findings as there was no association between genetic epilepsies and poor surgical outcomes. Thus, delaying surgical referral for children with genetic epilepsies is not advisable. However, there was an association between generalized seizures and unfavorable surgical outcomes, so trialing more medications for patients with generalized seizures may not be unreasonable.

Furthermore, children failing >2 ASMs often fail other non-ASM treatments prior to referral and often wait longer for surgical referral. This group more often have abnormal neurological exams, but an abnormal neurological exam does not predict surgical outcome, thus should not delay surgical referral.

Children failing >2 ASMs were more likely to undergo more extensive surgeries such as callosotomies or hemispherectomies. Additionally, the intent of these surgeries were often palliative. However, regardless of the palliative intent, 48% of these patients had favorable surgical outcomes which a better outcome than trialing a third ASM[9]. Thus, even if a patient would undergo a palliative procedure for their epilepsy, this procedure is more likely to result in better outcomes than trialing another ASM so these children should be referred for surgical evaluation once they have failed two ASMs.

Factors such as gender, race, ethnicity, type of insurance, and distance from surgical center did not play a role in delaying surgical referral. However, it is important to continue to keep an eye on these trends to ensure we are providing unbiased medical care for each patient regardless of their background.

In conclusion, additional ASM trials prior to surgical referral are associated with younger age at seizure onset and delay to evaluation. Patients failing >2 ASMs more often have abnormal neurological exam and daily seizures, while also failing treatments other than ASMs prior to surgical referral. Importantly, abnormal exam and seizure frequency do not predict outcome, suggesting delay of surgical evaluation because of these characteristics may be unnecessary.

Similarly, children less likely to be rendered seizure free from surgery more often trial >2 ASMs, despite palliative surgical outcomes superior to that expected with additional ASM trials. Recognizing patient characteristics which lead to delayed surgical referral may shorten the duration to surgical therapy with potential for improved outcomes.

Additionally, the second part of this research has helped define the utility of MEG in the surgical workup of patients who previously failed a surgery without the use of MEG. The results signified that MEG was useful in aiding in the surgical workup for these patients and helped patients have favorable outcomes (Engel 1 or 2). However, the patients who had unfavorable outcomes after the surgery that utilized MEG, the difference was not significant. This suggests that MEG did not lead to unfavorable outcomes, and instead was just not as useful as it was for the favorable outcomes.

It is important to recognize that MEG did not cause unfavorable outcomes in these patients. Additionally, for these patients, the MEG data was not as useful and there were less ECDs making it harder to identify the epileptogenic zone. However, when MEG is able to identify the epileptogenic zone, it greatly improved the outcomes for patients. Thus, MEG can be useful in aiding in the surgical work up for patients with DRE, but it does not guarantee seizure freedom in every patient. Because MEG was not related to unfavorable outcomes, but instead seemed to aid in favorable outcomes, MEG should be utilized in the surgical workup for all patients undergoing surgical referral in addition to other commonly used neuroimaging techniques (MRI, EEG, etc.).

Based on these results, we cannot suggest that MEG should be used in place of iEEG as this study did not compare the two imaging techniques to each other. Further work should be done to compare the two in order to determine if iEEG can be replaced with MEG. However, this study does show that for now MEG can be used to help aid in the surgical workup for patients, especially ones who did not have a successful first surgery.

Resources

This research was conducted under the supervision and guidance of my mentor, Dr. Christos Papadelis who is the Director of Research at the Jane and John Justin Neurosciences Center of Cook Children's Health Care System, Professor of Pediatrics at the Burnett School of Medicine at TCU, Adjunct Associate Professor of Pediatrics in the University of Texas at Arlington, and Assistant Professor of Pediatrics in Harvard Medical School. All protected health information was stored and analyzed in a HIPAA-compliant computer at Cook Children's. Analysis of the neuroimaging results was analyzed by Dr. Papadelis' research team and myself using *Brainstorm* software that is open-access and free[27].

Compliance

This research study had IRB approval from Cook Children's Health Care System and North Texas Regional IRB. The IRB protocol numbers are: 2017-059 and 2010-068. Approval from IACUC is not needed. Completion of CITI, EPIC, and RedCap training was maintained throughout this project.

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