MEG FOR EPILEPTIC FOCUS LOCALIZATION: A SERIES OF 1000 CASES

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ABSTRACT

The aim of epilepsy surgery in patients with focal, pharmacoresistant epilepsies is to remove the complete epileptogenic zone to achieve long-term seizure freedom. In addition to a spectrum of diagnostic methods, magnetoencephalography (MEG) focus localization is utilized for planning of epilepsy surgery. We present results from a retrospective observational cohort study of 1000 patients, evaluated using MEG at the University Hospital Erlangen over the time span of 28 years.

A total of 1000 consecutive cases were included in the study, evaluated at the University Hospital Erlangen between 1990 and 2018. All patients underwent MEG as part of clinical workup for epilepsy surgery. Of these, 405 underwent epilepsy surgery after MEG, with postsurgical follow-ups of up to 20 years. Sensitivity for interictal epileptic activity was evaluated, in addition to concordance of localization with the consensus of presurgical workup on a lobar level. We evaluate MEG characteristics of patients who underwent epilepsy surgery vs. patients who did not proceed to surgery. In operated patients, resection of MEG localizations were related to postsurgical seizure outcomes, including long-term results after several years. In comparison, association of lesionectomy with seizure outcomes was analyzed. Measures of diagnostic accuracy were calculated for MEG resection and lesionectomy.

Sensitivity for interictal epileptic activity was 72% with significant differences between temporal and extra-temporal lobe epilepsy. MEG was concordant with the presurgical consensus in 51% and showed additional or more focal involvement in an additional 32%. Patients who proceeded to surgery showed a significantly higher percentage of monofocal MEG results. Complete MEG resection was associated with significantly higher chances to achieve seizure freedom in the short and long-term. Diagnostic accuracy was significant in temporal and extra-temporal lobe cases, but was significantly higher in extra-temporal lobe epilepsy (positive likelihood ratio of 2.5 and 7.6, diagnostic odds ratio of 4.4 and 41.6).

The results show that MEG provides non-redundant information, which significantly contributes to patient selection, focus localization and ultimately long-term seizure freedom after epilepsy surgery. In extra-temporal lobe epilepsy, MEG provides excellent accuracy, also compared to interictal or ictal scalp EEG.

Keywords: Epilepsy, epilepsy surgery, magnetencephalography, long-term outcome, magnetic source imaging

INTRODUCTION

In about 30% of patients suffering from focal epilepsies, pharmacotherapy with anti-epileptic drugs (AED) is insufficiently effective (Kwan *et al.*, 2010). Persisting seizures, AED side effects, as well as psychiatric comorbidities considerably impact quality of life (Taylor *et al.*, 2011). Furthermore, the associated direct and indirect costs generate a significant burden for society (Strzelczyk *et al.*, 2017). A safe and cost-effective alternative therapy option in appropriately selected patients is epilepsy surgery (Picot *et al.*, 2016; West *et al.*, 2016). Depending on the specific etiology, seizure-freedom rates of approx. 70% one year after surgery can be achieved in contrast to around 6% with further AED therapy (Brodie *et al.*, 2012; Blumcke *et al.*, 2017).

However, there are considerable unresolved issues. Although current consensus advises prompt referral (Wiebe and Jette, 2012), delays between first diagnosis of epilepsy and evaluation for surgery remain in the range of one to two decades (Benbadis *et al.*, 2003; Martínez-Juárez *et al.*, 2017). Furthermore, success of epilepsy surgery is limited in specific populations, such as patients with normal MRI findings (Blumcke *et al.*, 2017). Probably the most significant issue is the recurrence of seizures within two to five years after surgery in more than 40% of patients (de Tisi *et al.*, 2011).

As an advanced diagnostic modality, Magnetoencephalography (MEG) may contribute to resolve some of these issues. The clinical utilization of MEG especially in the field of epileptology and epilepsy surgery has significantly evolved since the first MEG recordings almost 50 years ago (Cohen, 1968, 1970). While technical and methodological developments dominated initially, the technique was introduced early to clinical neurophysiology. Evaluation of the clinical value followed in the late eighties and early nineties (Sutherling *et al.*, 1987, 1991; Stefan *et al.*, 1990). The high temporal and good spatial resolution, as well as the relative insensitivity of MEG localization to conductivity differences e.g. of the skull or brain tissues (Scheler *et al.*, 2007; Güllmar *et al.*, 2010; Vorwerk *et al.*, 2014) provided incentives especially for utilization for epileptic focus localization as well as functional mapping (Coolen *et al.*, 2018).

An extensive and growing number of studies have evaluated MEG-based source analysis (or "magnetic source imaging" – MSI) in patients with focal epilepsies. MSI allows early identification of surgery candidates (Ossenblok *et al.*, 2007). It improves planning and results of invasive recordings (Sutherling *et al.*, 2008; Murakami *et al.*, 2016). MEG yields non-redundant information in up to about 30% of cases and is confirmatory in an additional 50% (Stefan *et al.*, 2003). It yields valuable information also in complex cases (Nissen *et al.*, 2016). Application is viable also in young and very young children (Garcia-Tarodo *et al.*, 2018). Seizure-freedom rates after epilepsy surgery are higher if MEG findings are taken into account (Vadera *et al.*, 2013; Mu *et al.*, 2014; Englot *et al.*, 2015; Kasper *et al.*, 2018). Furthermore, reevaluation of patients with recurrent seizures after surgery, up to 40% (de Tisi *et al.*, 2011), is facilitated and enables successful second surgery (Muthaffar *et al.*, 2017).

The emergence of clinical MEG-focused associations, as well as the endorsement by existing societies, now also provide a professional framework and has led to the definition of guidelines for clinical MEG applications (Hashimoto *et al.*, 2005; Bagic *et al.*, 2009; De Tiège *et al.*, 2017; Hari *et al.*, 2018). The recommended methods are based on many studies and decades of experience, yielding reliable and valid results.

In the present study, we investigate the role of such clinical application of MEG in presurgical workup for epilepsy surgery. In the largest series to date of 1000 patients and more than 400 surgical procedures over the time span of 28 years, we evaluate the hypothesis that MEG supports patient selection, contributes to identification of the epileptogenic zone in presurgical evaluation and impacts long-term seizure outcomes after epilepsy surgery.

MATERIALS AND METHODS

PATIENTS

This retrospective observational cohort study evaluates consecutive patients with focal epilepsies who underwent MEG recordings for focus localization from the installation of the first clinical MEG system at the University Hospital Erlangen in 1990 to the time of writing in 2018.

Decision for an MEG recording was based on individual clinical considerations. While there was no canonical set of indications, patients with clear and concordant structural, semiological and electrophysiological findings tended not to be referred to MEG. Exclusion criteria were MEG incompatibility (metal implants, pacemaker, etc.).

All recordings, source imaging and interpretation were performed prospectively before surgery. Findings were available to the medical and surgical team and were presented and discussed in patient management conferences. Localizations were also provided for neuronavigation for epilepsy surgery and implantation of invasive electrodes if requested.

All patients, respectively their parents in case of children or juveniles, gave their written informed consent according to the Declaration of Helsinik to participate in the MEG/EEG recordings as part of the clinical workup and to use their anonymized data for scientific purposes and publication.

MEG RECORDINGS

Three different MEG systems were used: from 1990-1994, a 37 channel gradiometer system (Krenikon, Siemens AG, Erlangen, Germany), from 1995-2010 a 2x37 channel axial gradiometer Magnes II system (Biomagnetic Technologies, Inc. (BTI), San Diego, CA, USA) and from 2010 a 248 channel whole-head magnetometer 3600WH system (BTI, San Diego, CA, USA). During the time period from 1995-2010, individual patients with complex epilepsies were measured at the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig, Germany, using a 148 channel axial gradiometer 2800WH system ((BTI, San Diego, CA, USA). During the transition time from the Magnes II to the 3600WH system, individual patients were also recorded at the Department of Neurology, University Hospital Magdeburg, Germany.

Patients were recorded in supine and/or seated position, with their eyes closed for 40-60 minutes. The Krenikon system only allowed measurement from a limited region of interest (ROI) with a diameter of approximately 20cm. The Magnes II system consisted of two sensors in separate dewars, which allowed recording from two ROIs simultaneously. For complete coverage of the brain, sensor positions were varied in subsequent runs. Clinical information was utilized to optimize positioning and recording time per position.

Recordings usually included simultaneous EEG. However, the number of channels was initially limited to 20-33 electrodes. With the 3600WH system, EEG was recorded with 64 electrodes.

EEG data were utilized to identify artifacts and normal variants, as well as epileptic activity for separate source analysis and detection of MEG correlates. Due to the scope of the presented study, as well as the limitations of only low resolution EEG (Brodbeck *et al.*, 2011) in a substantial percentage of patients, we did not perform a comparison with the results of ESI (electric source imaging). However, we have reported previously on such comparisons in patient subgroups (A. Paulini *et al.*, 2007; Scheler *et al.*, 2007; Heers *et al.*, 2010a,b).

INTERICTAL EPILEPTIC DISCHARGES (IED)

Findings used for the presented study were interictal epileptic discharges (IED), i.e. spikes and sharp waves. IED detection was performed visually by experienced interpreters routinely involved in presurgical evaluation. In general, at least 5 IEDs with similar morphology and topography were necessary for further analysis and reporting. Only in cases of highly specific signals and robust localizations were fewer IEDs considered sufficient.

SOURCE LOCALIZATION

All IEDs were localized using dipole analysis. Software included the manufacturer's software, as well as Curry (versions 4.6 to 7, Compumedics Neuroscan, Hamburg, Germany) and BESA (versions 5.3 to 6.1, BESA GmbH, Gräfeling, Germany). Two main localization approaches were utilized: Single and averaged IED analysis. Single IED analysis fitted single dipoles to the rising flank of the IED pattern. Averaged spike analysis fitted regional dipoles at the onset and at the peak of the pattern. Both approaches stressed robust results in early time segments.

Dipoles were selected according to statistical criteria, such as correlation of measured and estimated signal, confidence volume and source amplitude. Plausibility was evaluated subjectively (e.g. no erratic propagation, exclusion of deep dipoles in the center of the head, etc.).

Localizations utilized single or multiple spheres, a single shell adapted to the shape of the inner skull surface or individual BEM (boundary element model) for volume conductor models. In a study comparing some of these approaches, differences were found to be minimal for MEG (Scheler *et al.*, 2007). The choice of volume conductor model was therefore secondary to other considerations, i.e. technical details and usability of the respective software.

Starting in 2001, additional inverse solutions were calculated using Curry and BESA software. This was added to ensure that the results were not significantly affected by erroneous assumptions, e.g. the use of single dipoles, etc.

All results were superimposed on MRIs of the individual patient, presented as part of patient management conferences and/or provided as written reports, including clinical discussion and interpretation.

LOCALIZATIONS

For statistical evaluation in the presented study, localizations were classified according to side and region (frontal, parietal, temporal, occipital and insular). Localizations reported as central were distinguished into frontal and parietal.

Localizations were classified regarding their spatial distribution. Focal localizations show one single cluster of activity. Multifocal findings consist of several distinct groups of localizations, based on different pattern morphology and field topography. Finally, diffuse localizations are scattered over one or several regions without clear clustering.

REFERENCE STANDARD

MEG results were related to findings of presurgical evaluation and results of epilepsy surgery. Diagnostic accuracy was compared to lesionectomy in patients with lesional epilepsies. In case of missing data, the respective cases were excluded from the specific statistical analysis. Operated cases were only excluded from Kaplan-Meier survival statistics if no follow-up data were available, e.g. due to surgery at another institution.

PRESURGICAL WORKUP

MEG results were compared presurgical evaluation, including MRI, long-term Video-EEG, as well as SPECT in most cases, as well as ictal SPECT, PET and invasive EEG recordings. Specifics of the different modality depended on availability and standards at the time of investigation. For example, MRI field strength was initially 1.5T, whereas patients since 2008 had 3T MRI. Results were classified into regions as described above for MEG localizations. Concordance of MEG results and presurgical consensus were evaluated on a lobar level using chi-square tests. The degree of concordance was classified into the categories concordant, consistent and discordant findings. Concordant MEG findings exactly reproduce the presurgical synopsis. Consistent findings have an overlap of at least one lobe, but also show differences. Concordant findings were not included in the group of consistent findings. Finally, discordant findings do not show an overlap.

EPILEPSY SURGERY

Association of seizure outcome after surgery with MEG/focus hypothesis concordance, as well as MEG resection, was evaluated using chi-square tests. Outcomes were graded according to the Engel classification (Engel *et al.*, 1993). Outcomes were compared using non-parametric Mann-Whitney-U-tests.

A detailed analysis of the relation of MEG findings to surgery and outcome was performed by visually evaluating whether the respective MEG localizations had been resected completely (except spurious localizations), partially or not at all, similar to previous studies (Vadera *et al.*, 2013; Mu *et al.*, 2014). In case of averaged spike analysis, which yields only a single localization, complete resection was assumed if the results were contained in the resection or within 1cm of the border, to account for e.g. coregistration inaccuracies. Partial resection was assumed when the respective dipole was located outside the resection but within 2-3cm of the border. This analysis was only possible when adequate postoperative imaging or a detailed description by the surgeon was available.

Parameters of diagnostic accuracy (sensitivity, specificity, positive and negative predictive value (PPV, NPV), diagnostic odds ratio (DOR), positive and negative likelihood ratio (PLR, NLR)) were calculated for the association of complete MEG resection with the reference standard of: a) postoperative Engel 1 and b) postoperative Engel 1A outcomes at last follow-up after at least 1 year. Additionally, a second analysis focused on long-term outcomes after at least 5 years after surgery.

Kaplan-Meier survival analysis was calculated to evaluate the influence of MEG resection on persistence of an Engel 1 outcome after surgery. Recurring seizures classified as Engel ≥ 2 were considered as events in terms of Kaplan-Meier analysis. Differences between degrees of MEG resection were evaluated using a Tarone-Ware test.

LESIONECTOMY

Resection size could potentially confound the influence of MEG resection on postsurgical seizure freedom, i.e. any benefit of complete MEG resection may be caused only by increasing the resection size and only secondarily result in a higher percentage of seizure-free cases. Seizure freedom in this group would then mainly rely on complete or extended lesionectomy. We therefore compared resection extent in lesional cases with seizure outcome. Reports and/or postoperative MRI were evaluated to classify lesionectomies into categories: no, partial, complete or extended resection of the suspected epileptogenic lesion. Multiple subpial transections (MST) and callosotomy in lesional cases were categorized as operative procedures without lesionectomy (category "no resection"). Extension of a previous resection was counted as extended lesionectomy. In case of temporal lobe surgeries, selective amygdala-hippocampectomy (SAH) and tailored resection were classified as complete resection, standard anterior 2/3-lobectomies as extended. If MST was performed in addition to resection, the extent of the resection was used.

Extent was compared to the last available seizure outcome using chi-square tests, with follow-ups after at least 1 and 5 years. The analysis was performed a) in all lesional surgeries and b) limited to cases with IEDs on MEG findings, to enable a comparison with MEG resection in the same patient group. Additionally, parameters of diagnostic accuracy were calculated.

DATA AVAILABILITY

Anonymized evaluation data are available upon request.

RESULTS

PATIENTS

Of the 1000 patients, 475 were female. Mean age on the day of MEG recording was 32.4 years (± 12.5, 3-70years). A total of 114 patients were below the age of 18. Mean age at epilepsy onset was 13.9 years (±11.7 years, range 0-60 years). Mean duration of epilepsy at the time of first MEG recordings was 18.0 years (± 12.0 years, range 0-66 years).

A total of 375 patients had a normal MRI, i.e. without any lesion or epilepsy-related structural alteration. In 17 patients, information on the presence of a lesion on MRI was not available. Table 1 summarizes etiologies and lesions.

Putative location of the epileptic focus was determined from the consensus of available clinical information, which is referred to in the following as "focus hypothesis". The focus hypothesis included one lobe in 678 patients (885 recordings), two lobes in 173 cases (210 recordings) and three or more in 41 patients (49 recordings). It included the frontal lobe in 425 patients, the temporal lobe in 645, the parietal lobe in 179, the occipital lobe in 105, the insula in 11 and was unclear in 85. Lateralization was left in 418 patients, right in 407, bilateral in 87 and unclear in 88 patients. MEG was performed after previous surgery in 117 patients, corresponding to 165 recordings. A total of 405 patients underwent epilepsy surgery after MEG; however outcome data were not available for 19 procedures.

MEG RECORDINGS

A total of 1274 MEG recordings in 1000 patients were evaluated. Of these, 184 patients had repeated MEG due to different reasons, e.g. no spikes in the first recordings or due to technical factors. This also included measurements after epilepsy surgery in case of persisting seizures. Before 2000, 283 patients were investigated with 371 recordings (24% repeated recordings). Between 2000 and 2009, 470 patients were evaluated with 616 recordings (24% repeated recordings) and after 2009, 247 patients with 287 recordings (14%). The difference in repeated measurements was statistically significant ($p = 0.002$, $chi^2 = 12.6$, Chi-square test, $p < 0.001$, $chi^2 = 12.6$, comparing before and after 2009).

SPIKE DETECTION

A total of 1231 recordings could be evaluated for IEDs; the remaining 43 (3%) were unusable due to strong artifacts, 35 of these were first recordings, while 8 were repeated.

MEG detected IEDs in 883 of 1231 recordings (72%), in 692 of 965 first (71%) and 191 of 266 repeated recordings (72%). Recordings before 2000 yielded spikes in 74.4%, between 2000 and 2009 in 64% and after 2009 in 73.2% ($p = 0.001$, $chi^2=13.4$, Chi square test).

In patients with suspected involvement of the frontal lobe, MEG detected IEDs in 325 of 413 recordings (79%), in 132 of 171 recordings (77%) with parietal involvement, 76 of 100 (76%) with occipital and 8 of 11 recordings (73%) with putative insular involvement. This results in IED detections in 458 of 592 recordings (77%) with suspected extra-temporal lobe epilepsy (ETLE). In patients with suspected temporal lobe epilepsy (TLE), IEDs were identified in 423 of 625 recordings (68%). The difference between TLE and ETLE was statistically significant ($p < 0.001$, $chi^2 = 17.9$, Chi-square test).

Earlier onsets of epilepsy were related to an increased likeliness to detect spikes in the first recordings, also when duration of epilepsy, as well as TLE vs. ETLE, was taken into account (logistic regression, $p < 0.001$ for onset). Patients with ETLE showed significantly earlier onsets (11.0 ± 11.0 vs. 14.6 ± 12.4 years, $p = 0.002$, $t = 5.7$, two-sided t-test). In contrast, duration of epilepsy did not show a significant influence or differences between TLE and ETLE groups.

MEG LOCALIZATIONS

MEG localizations included the frontal lobe in 379 recordings (figure 1 shows an example), the temporal lobe in 480, the parietal lobe in 189, the occipital lobe in 50 and the insula in 8 recordings. Information about focality of spike localizations was available in 876 recordings. Localizations were monofocal in 619 recordings with spikes (70.7%), multifocal in 185 (21%) and diffuse in 74 (8.4%).

COMPARISON TO PRESURGICAL WORKUP

In 115 of 802 recordings (14%), MEG findings involved fewer lobes than the clinical focus hypothesis. In a total of 635 recordings (79%), MEG and focus hypothesis involved an equal number of lobes. In the remaining 167 recordings, MEG yielded more extended results (20%), which showed differences when comparing the time before (and including) 2009 and thereafter, corresponding to the use of a whole-head MEG in our lab. Before 2009, 461 recordings yielded MEG results which involved less or an equal number of lobes compared to the focus hypothesis and 145 recordings involved more lobes. After 2009, 174 versus 22 recordings were more focal ($p < 0.001$, $chi^2 = 14.5$, $df = 3$, Chi-Square test). Similarly, confirmatory MEG and focus hypothesis findings were slightly more frequent after 2009 (49% vs. 57%, $p = 0.058$, $chi2 = 3.6$, $df = 3$),

however no significant difference was shown in the number of overlapping results (81% vs. 86%, $p > 0.1$, $chi^2 = 2.2$, df = 3, Chi-Square test). Consistent findings were slightly more frequent when a lesion was present (78% vs. 71%, $p = 0.024$, $chi^2 = 5.1$, df = 3, Chi-Square test).

MEG findings were concordant with the consensus of presurgical evaluation in 405 of 802 cases with IEDs and known focus hypothesis (50.5%). They were consistent in an additional 254 patients (32%) and discordant in 143 (18%).

Concordant findings were less frequent in ETLE vs. TLE (44% vs. 59%, $p < 0.001$ Chi-square test); whereas consistent findings were more frequent (36% vs. 26%, $p < 0.001$ Chi-square test). A total of 254 patients with spikes presented with multilobar findings in presurgical evaluation. MEG provided monofocal localizations in 93 (37%). Of these, 13 patients underwent surgery with a median last available outcome of Engel 1 (range 1-3). The monofocal MEG result was located in the operated lobe in 11 (85%).

MEG AND EPILEPSY SURGERY

A total of 405 surgeries after MEG were performed. Outcome data were available in 386, MEG data were usable in 371 cases (92%). Last available outcome was Engel 1 in 215 patients (Engel 1a in 152), Engel 2 in 69, Engel 3 in 59 and Engel 4 in 43 patients. Median follow-up after surgery was 4.0 years (1^{st} quartile 1.0 years, 3^{rd} quartile 6.0 years). In 325 patients, outcome after at least one year was available. Long-term outcomes after at least 2 years were available in 278, after at least 5 years in 188 and after 10 years or more (20 years maximum) in 61. IEDs were detected in 256 of 371 recordings (69%). Localizations were monofocal in 203 recordings (79%), multifocal in 39 (15%) and diffuse in 14 (6%). Two patients underwent callosotomy and were excluded from comparisons with the area of surgery.

Patients undergoing epilepsy surgery had a significantly higher percentage of monofocal MEG localizations than patients who did not proceed to surgery (79% vs. 67%, $p < 0.001$, Chi-square, 876 patients with spikes). This was reflected by more focal presurgical evaluation results ($p<0.001$, $chi^2 = 12.7$, df = 3, Chi-square, 895 patients with focus hypothesis).

In the subgroup of operated patients with IEDs in MEG, MEG localization and presurgical focus hypothesis were concordant or consistent in 219 of 254 cases (86.2%). Such findings were favorable regarding seizure outcome when Engel 1 or 2 outcomes were evaluated (Chi squared, $p=0.014$, $chi^2=6.0$, last available outcomes, $p=0.11$, $chi^2=2.6$, after at least 1 year, $p=0.019$, $chi^2=5.5$, after at least two years, df=3, not significant thereafter). Comparison to Engel 1 outcomes did not reveal a significant association. MEG findings and focus hypothesis were concordant in 160 (63%), without clear association with postoperative seizure outcomes.

Resection extent of MEG localizations could be evaluated in 174 operated patients with IEDs, limited by the availability of adequate MRIs and documentation. Follow-up data after at least 1 year were available in 149 patients, after at least 5 years in 78.

MEG resection extent was significantly related to seizure freedom at the last available follow-up after at least 1 year (Engel 1 $p<0.001$, $chi^2=35.1$, Engel 1a $p < 0.004$, $chi^2=10.9$, df=3, Chi-Square, supplementary table 1a) and after at least 5 years (Engel 1 $p<0.001$, chi2=22.7, Engel 1a $p<0.005$, chi2=10.6, df=3, Chi-Square, supplementary table 1b).

Sensitivity of complete MEG resection for an Engel 1 outcome (≥1y) was 66% (57% - 73%); specificity was 83% (76% - 89%). PPV amounted to 83% (76% - 89%) and NPV to 65% (57% -

73%) (table 2, supplementary table 2). Long-term outcomes showed similar results (table 2). Diagnostic accuracy was considerably better for ETLE vs. TLE cases. In ETLE cases, complete MEG resection reached a PLR of 7.55 (6.25 – 9.12) (table 3).

Stability of Engel 1 outcome over time was evaluated using Kaplan-Meier survival analysis (figure 2). The results show that seizure freedom rates are significantly higher and more stable over the course of up to 10 years after surgery if MEG localizations are completely resected in comparison to both partial and no resection ($p < 0.001$, Tarone-Ware test).

COMPARISON WITH LESIONECTOMY

Information about the extent of lesionectomy was available for 284 surgical procedures for lesional epilepsy, 134 of which with IEDs on MEG and information about MEG resection.

All lesionectomies

Extended resections were performed in 130 of the 284 cases (46%). Complete lesionectomies were constrained to the lesion in 124 (44%). Only partial resections were performed in 13 (5%). The lesion was not resected in 17 cases (6%). Median follow-up in this group was 4 years (1st quartile 1.0 year, 3rd quartile 5.0 years).

Complete or extended resection was significantly related to Engel 1 outcome ($p<0.001$, $chi^2=20.8$, last follow up and $chi^2=15.0$, after at least 1 year, Chi-Square test, df=3). Outcome differences between complete and extended resections were not significant ($p = 0.10$, Mann-Whitney-U-test).

Sensitivity of complete or extended resection for an Engel 1 outcome (≥1y) was 96% (93% - 98%); specificity was 19% (14% - 25%). PPV amounted to 64% (57% - 70%) and NPV to 78% (72% - 83%). Diagnostic performance was similar for long-term outcomes (≥5y) (supplementary table 3).

Lesionectomies in patients with MEG resection data

In the group with operated patients with IEDs on MEG, extended resections were performed in 75 (56%). Lesions were completely resected without extension in 52 (39%), only partially in 6 (5%) and not at all in 1 case (1%). Median follow-up in this group was 3.8 years (1st quartile 1.0 year, 3rd quartile 5.0 years).

There was no clear relation of Engel 1 outcome to complete or extended resection ($p = 0.27$, $chi^2=1.2$, last outcome, $p = 0.63$, $chi^2=0.2$, after at least 1 year, df=3, Chi-Square test) or extended resection only ($p = 0.15$, $chi^2=2.1$, last outcome, $p = 0.06$, $chi^2=3.6$, after at least 1 year, df=3). However, association of complete MEG resection with Engel 1 outcome in this group remained significant ($p < 0.001$, $chi^2=22.6$, last outcome and $chi^2=18.7$, after at least 1 year).

Sensitivity of complete or extended resection for an Engel 1 outcome (≥1y) was 97% (92% - 100%); specificity was 5% (2% - 11%). PPV amounted to 62.04% (52% - 71%) and NPV to 50% (41% - 60%) (table 4, supplementary table 4). Diagnostic parameters were comparable or worse for long-term outcomes (≥5y) (table 4).

DISCUSSION

In this study, we evaluate application of MEG for presurgical epileptic focus localization in 1000 patients over the course of 28 years. The results show that MEG provides non-redundant information, which significantly contributes to long-term seizure freedom after epilepsy surgery.

SENSITIVITY FOR SPIKES

MEG detected IEDs in 72% of recordings. Detection rates in cases with suspected ETLE were higher in comparison to TLE (77% vs. 68%) and were comparable between first and repeated recordings. These findings are compatible with previous reports on subgroups from the evaluated population (Stefan *et al.*, 2003; Andrea Paulini *et al.*, 2007), as well as other groups (Knake *et al.*, 2006; Englot *et al.*, 2015), which range between 70-78%. No systematic difference was seen comparing the different extratemporal compartments.

Earlier onset of epilepsy was significantly related to higher detection rates. Onsets were also earlier in patients with ETLE, suggesting that the difference in spike detection may be related to the different etiologies in predominantly extra-temporal vs. temporal localizations.

Detection rates varied over the years, probably due to usage of a whole-head system after 2009, evaluator experience and methodology. Between 1990 and 2000, more recordings presented with IEDs in comparison to 2001-2009, although the Krenikon system had more restrictions than later systems. This apparent higher sensitivity may be a result of overinterpretation of e.g. benign epileptiform variants when the technique was still new and evaluators had limited experience. This is supported by the lower number of focal findings in the first decades, as e.g. normal variants or unspecific patterns show more distributed generators (Rampp *et al.*, 2018) and thus result in diffuse localizations.

COMPARISON WITH PRESURGICAL DIAGNOSTICS

Concordant presurgical findings are predictors of good postsurgical outcome (West *et al.*, 2015). We therefore evaluated overlap of MEG and focus hypothesis, the consensus of presurgical diagnostics. MEG and focus hypothesis were consistent in 82%. The percentage was higher in TLE compared to ETLE cases (86% vs. 80%, $p = 0.014$). Findings were completely concordant in 50%, with also a higher percentage in patients with putative TLE vs. ETLE (49% vs. 44%); however, the difference did not achieve statistical significance.

In cases in which MEG and presurgical evaluation were not completely concordant, MEG may suggest involvement of additional areas, which were not indicated by other methods. This interpretation is supported by studies comparing MEG and invasive EEG (Sutherling *et al.*, 2008; Knowlton *et al.*, 2009; Murakami *et al.*, 2016). In a prospective study (Sutherling *et al.*, 2008), MEG indicated additional areas in 13% and changed invasive EEG coverage in 23% of 69 patients. MEG changed the surgical decision in 20%. Murakami et al. (Murakami *et al.*, 2016) similarly report that patients were more likely to become seizure free when MEG findings were resected completely and when stereo-EEG completely sampled the area suggested by MEG. In this light, our results suggest that the degree of added information is greater in ETLE cases, reflecting the known role of MEG in this subgroup (Knowlton, 2007).

Lower degrees of MEG concordance may be interpreted as lower redundancy, and thus the information added by MEG would be higher in cases with ETLE. This interpretation is supported by better outcomes after resection of focal localizations. However, the higher number of lobes

included in the definition of ETLE may confound these results. Taken together, the available evidence suggests that MEG provides highly relevant information especially in ETLE.

MEG AND EPILEPSY SURGERY

SELECTION OF CANDIDATES FOR EPILEPSY SURGERY

Operated patients presented with more focal presurgical findings. As a circumscribed focus in an accessible region is a prerequisite for successful epilepsy surgery, this difference is not surprising. However, the aspect that the MEG results could be used as a surrogate for selection of surgical candidates may have practical consequences. MEG and source localization can be performed early in the diagnostic process to evaluate eligibility for epilepsy surgery (Ossenblok *et al.*, 2007; Colon *et al.*, 2009; Heers *et al.*, 2010a,b) and is also viable in complex cases (Nissen *et al.*, 2016). A focal finding at an early time point may inform the further diagnostic evaluation, enable more effective workflows and shorter delays to surgery, e.g. as implied by Knowlton et al. (Knowlton, 2006). MEG findings consistent with the consensus of presurgical evaluation indicated patients with sustained good surgical outcome, as also demonstrated e.g. by Englot et al. (Englot *et al.*, 2015).

SURGICAL OUTCOME

The relation of complete MEG resection and an Engel 1 outcome could be evaluated in a subgroup of 174 patients. The data shows that complete resections of focal MEG localizations are significantly related to Engel 1 (freedom of disabling seizures, $p<0.001$, table 1). This holds true even when Engel 1a outcomes are considered (complete seizure freedom, $p=0.004$ and $p=0.005$, table 1). Only partial resections do not show this association. This finding is supported by a recent study (Murakami *et al.*, 2016). The authors compared MEG localizations with stereo-EEG (sEEG) and surgical outcome. They similarly showed that complete resection of densely clustered spikes, adequately sampled by sEEG, was significantly related to seizure freedom in comparison to partial or no resection. Seizure outcome was restricted to a 12 month follow-up. The long follow-ups of our data now suggest that results may also be indicative of long-term outcomes. Comparison of MEG findings and the consensus of presurgical evaluation on a lobar level provided a less clear contrast, possibly due to the coarser comparison. Although MEG and the focus hypothesis may indicate the same lobe, a resection may not necessarily include the MEG findings.

LESIONECTOMY

Complete resection of an epileptogenic lesion was also related to a better outcome, compared to cases with partial or no resection. Extension to include neighboring tissue did not result in different seizure outcomes. In the subgroup of operated patients with MEG findings, however, degree of lesionectomy was only weakly related to outcome. Only extended resections showed a (non-significant) tendency towards more frequent Engel 1 outcomes. This lack of influence is explained by almost all patients in this group having complete or extended lesionectomy. Only 5% presented with no or partial resection. Evaluating all operated lesional cases, differences of partial vs. complete resection are responsible for the impact on seizure outcome. MEG, however, still showed a significant relation to Engel 1 outcome.

These data correlate well with the concept of epileptogenic lesions (Jehi, 2018): While the lesion plays a significant role in the generation of seizures and thus removal is necessary for seizure control, the epileptogenic zone itself may not be constrained to the lesion. At least in our data, this seems to be the rule, rather than the exception. By definition, the non-lesional part of the

epileptogenic zone cannot be identified by structural features but only by its pathological function. MEG seems to be well suited to provide this functional information, at least when robust, focal results are available.

METHODOLOGICAL CONSIDERATIONS

The spread of MEG dipoles significantly impacts how these can be taken into account for resection. Scattered localizations may not be amenable to complete resection and may be a sign of extended and potentially multifocal generation (Fischer *et al.*, 2005). However, while truly extended epileptic areas may generate scattered activity, noise and subsequent low SNR fabricate the false impression of extent (Bast *et al.*, 2006). This may explain why partial resection of MEG also did not necessarily imply persisting seizures after surgery. Noise may have led to scattered localizations, which could not be resected completely. However, if the true epileptogenic zone was in fact focal, epilepsy surgery may of course nevertheless be successful. Due to this reasoning, robust, focal findings are most informative, as tight clusters of localizations or high quality averaged results are indirect evidence of both focal generation and low noise.

Averaging may reduce the influence of noise and thus provide more focal results in case of truly focal generation. In addition, averaging provides higher SNR especially at the spike onset, which has been shown to more closely reflect the epileptogenic zone due to limited propagation at early time points (Bast *et al.*, 2006; Mălîia *et al.*, 2016; Kasper *et al.*, 2018). However, averaging relies on the subjective classification of spikes into morphologically similar groups. Investigators in our study using averaging techniques were experienced and compared morphology and topography of individual IEDs with the respective average patterns.

ETLE VS. TLE

Brodbeck et al. (Brodbeck *et al.*, 2011) evaluated the use of EEG based-source imaging for epilepsy surgery in 152 patients, 52 of which had high-density EEG (hdEEG). hdEEG showed better diagnostic accuracy in comparison to low-density EEG, as well as PET, SPECT and MRI. Mean follow-up of 4 years captured seizure recurrence in the 2-5 years after surgery (de Tisi *et al.*, 2011). Sensitivity and specificity were 80% and 88%, when Engel 1 and 2 outcomes after surgery were considered as reference standard. In ETLE patients, these results were considerably lower, e.g. sensitivity amounted to 75%. In contrast, TLE results were respectively better, with a sensitivity of 92%. This represents the complement to our MEG results, which provide higher diagnostic accuracy in ETLE (84% sensitivity, 89% specificity) and lower in TLE (56% and 77%), although more strictly evaluated for Engel 1 outcomes. These results underline the frequent suggestion to combine EEG and MEG to cover the complete spectrum of focal epilepsies.

Our results are based solely on interictal epileptic activity, reflecting the irritative zone. Beniczky et al. (Beniczky *et al.*, 2013) have rigorously evaluated source imaging of ictal EEG using presurgical evaluation as reference standard. They report a PPV of 92% and a NPV of 43% in 20 operated patients with mostly TLE. The likelihood ratio for matching source imaging and presurgical evaluation was nine times higher than non-matching results. This compares to a factor of 4.45 (PLR / NLR) in TLE cases in our data (PPV 82%, NPV 50%). Source imaging of ictal EEG seems superior to interictal MEG localization. However, in ETLE, this factor amounts to 41.9 (PPV 87%, NPV 86%), which clearly exceeds ictal EEG imaging.

LIMITATIONS

While MEG analysis was performed before surgery, evaluations regarding outcome, resection volumes and presurgical diagnostics were performed retrospectively, implicating the limitations of a retrospective study. Specifically, patient selection was not based on considerations regarding the study to ensure comparability, avoid bias, etc. Furthermore, due to the span of almost three decades, evaluation procedures and integration into clinical routine varied over the years.

While complete removal of an epileptogenic lesion was associated with better postsurgical outcomes, extending the resection did not show better results. However, the group of extended lesionectomies includes rather different surgical strategies, depending on the operated lobe and lesion. For example, removal of a hemosiderin ring around a cavernoma was considered as extended lesionectomy, just like a standard temporal lobe resection. This may have led to less clear results in regard to seizure outcome.

It is also expected that the type of pathology influences surgical outcome (Blumcke *et al.*, 2017). We did not investigate this in detail due to the long time span covered by the study, during which imaging and classifications of epileptogenic lesions have changed considerably.

CONCLUSIONS

Evaluation of the largest cohort with the longest follow-up to date revealed that MEG provides non-redundant information, which may be utilized for selection of epilepsy surgery candidates, adds to presurgical focus localization and significantly contributes to long-term seizure freedom after epilepsy surgery. In ETLE, MEG provides optimal accuracy when compared to interictal or ictal scalp EEG.

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COMPETING INTERESTS

The authors report no competing interests.

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FIGURES

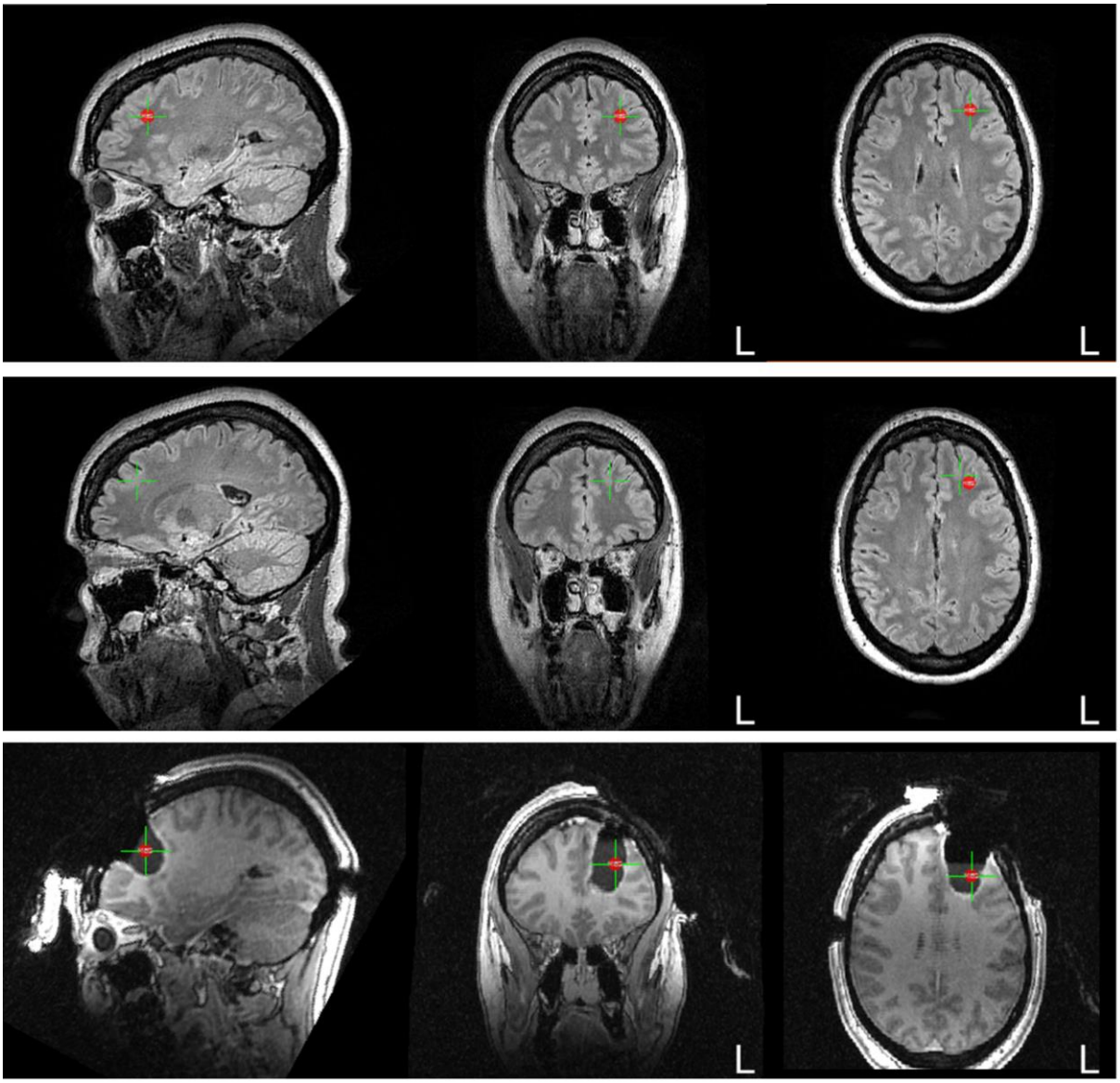

Figure 1: Patient example. MEG localized (average of 33 spikes) to the left frontal lobe (top row), slightly lateral to the FCD IIb (middle row, intraoperative MRI immediately after resection). Resection included the lesion, as well as the MEG result. Postsurgical outcome was Engel 1a, one year follow-up.

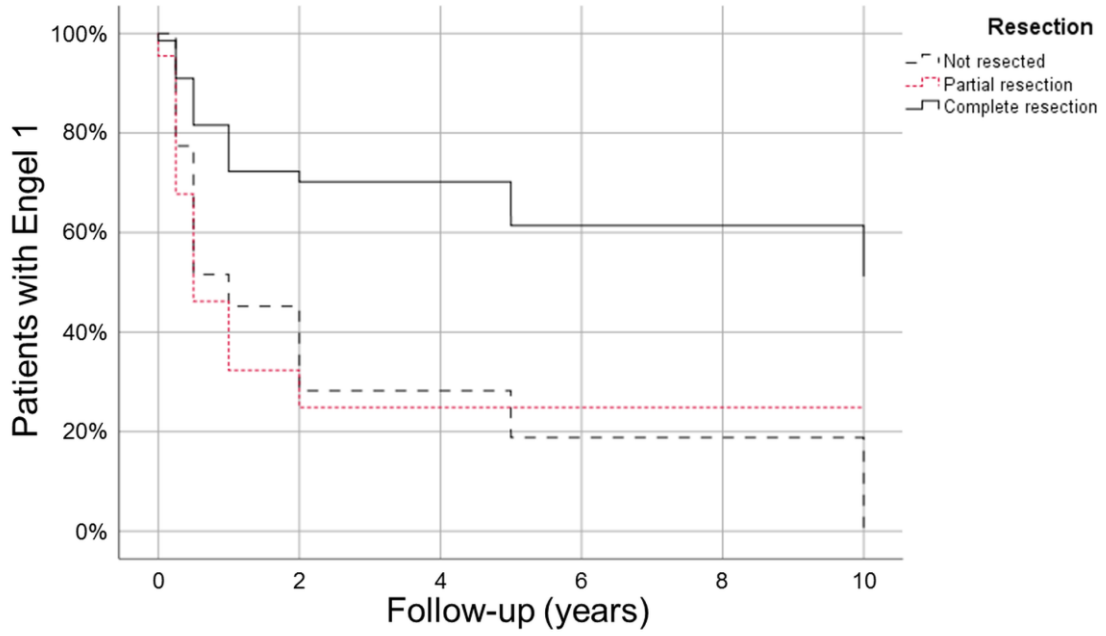

Figure 2: Kaplan-Meier survival analysis of postoperative seizure freedom (Engel 1) over time in relation to extent of MEG resection. Differences are statistically significant ($p < 0.001$, Tarone-Ware test).

TABLES

Etiology	Cases	Percentage of cases with MRI findings
No lesion	375	
Lesional/MRI finding	625	
Hippocampal sclerosis	86	14%
FCD 2	25	4%
Other dysplasia	89	14%
Malformations (incl. polymicrogyria, paychygyria, heterotopia, tuberous sclerosis and double cortex)	80	13%
Tumor	112	18%
Cystic lesions (except tumors)	11	2%
Inflammatory	52	8%
Traumatic brain injury	45	7%
Intracranial bleeding or ischemia (incl. perinatal)	38	6%
Vascular malformations	71	11%
Other	18	3%
Unclear lesions	16	3%
Cases with multiple lesions/etiologies	59	9%
Missing data	17	3%

Table 1: Overview of etiologies and lesions

Complete MEG resection		
Follow-up	**>= 1y**	**>=5y**
n	149	78
Engel 1	84	47
Sensitivity	65% (57% - 73%)	75% (63% - 84%)
Specificity	83% (76% - 89%)	74% (63% - 83%)
PPV	83% (76% - 89%)	81% (71% - 89%)
NPV	65% (57% - 73%)	66% (54% - 76%)
DOR	9.3 (4.2 - 20.5)	8.4 (3.0 - 23.7)
PLR	3.9 (3.2 - 4.7)	2.9 (2.2 - 3.8)
NLR	0.4 (0.3 - 0.5)	0.3 (0.3 - 0.5)
Engel 1a	55	27
Sensitivity	62% (54% - 70%)	74% (63% - 83%)
Specificity	66% (58% - 73%)	55% (43% - 66%)
PPV	52% (43% - 60%)	47% (35% - 58%)
NPV	75% (67% - 81%)	80% (69% - 88%)
DOR	3.1 (1.6 - 6.3)	3.5 (1.3 - 9.7)
PLR	1.8 (1.4 - 2.4)	1.6 (1.2 - 2.4)
NLR	0.6 (0.4 - 0.8)	0.5 (0.3 - 0.7)

Table 2: Parameters of diagnostic accuracy of complete MEG resection for a seizure free outcome (Engel 1 and Engel 1A). PPV, NPV – positive, negative predictive value; DOR – diagnostic odds ratio; PLR, NLR – positive, negative likelihood ratio.

Complete MEG resection, follow-up ≥1y		
	TLE	**ETLE**
n	86	67
Engel 1	55	31
Sensitivity	56% (45% - 67%)	84% (72% - 92%)
Specificity	77% (67% - 86%)	89% (78% - 95%)
PPV	82% (71% - 89%)	87% (76% - 94%)
NPV	50% (39% - 61%)	87% (75% - 94%)
DOR	4.4 (1.6 – 12.0)	41.60 (10.1 - 170.9)
PLR	2.5 (1.8 - 3.4)	7.6 (6.3 - 9.1)
NLR	0.6 (0.4 - 0.8)	0.2 (0.2 - 0.2)

Table 3: Parameters of diagnostic accuracy of complete MEG resection for an Engel 1A outcome after at least one year for temporal (TLE) and extratemporal lobe epilepsy (ETLE). PPV, NPV – positive, negative predictive value; DOR – diagnostic odds ratio; PLR, NLR – positive, negative likelihood ratio.

Lesionectomies in cases with MEG resection data		
Follow-up	**>= 1y**	**>=5y**
n	112	58
Engel 1	69	37
Sensitivity	97% (91% - 100%)	97% (88% - 100%)
Specificity	5% (2% - 11%)	0% (0.2% - 6%)
PPV	62% (52% - 71%)	63% (49% - 75%)
NPV	50% (40% - 60%)	0.00% (0.2% - 6%)
DOR	1.6 (0.2 - 12.0)	0.0 (nc)
PLR	1.0 (0.4 - 2.7)	1.0 (nc)
NLR	0.6 (0.2 - 1.7)	nc
Engel 1a	44	20
Sensitivity	100% (96% - 100%)	100% (92% - 100%)
Specificity	6% (3% - 12%)	3% (0.3% - 11%)
PPV	41% (32% - 50%)	35% (23% - 49%)
NPV	100% (96% - 100%)	100% (92% - 100%)
DOR	nc	nc
PLR	1.1 (0.9 - 1.3)	1.0 (0.7 - 1.5)
NLR	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)

Table 4: Parameters of diagnostic accuracy of complete or extended lesionectomy for a seizure free outcome (Engel 1 and Engel 1A). Only cases with IEDs on MEG and information on MEG resection were considered, corresponding to table 2. Nc – not computable due to zeros in the denominator, etc. PPV, NPV – positive, negative predictive value; DOR – diagnostic odds ratio; PLR, NLR – positive, negative likelihood ratio.

SUPPLEMENTARY TABLES

Resection	Outcome (≥1 year)		p (Chi-Square test)
	Engel 1	**>Engel 1**	**< 0.001**
Complete	55	11	
Partial	19	34	
No	10	20	
	Engel 1a	**>Engel 1a**	**0.004**
Complete	34	32	
Partial	13	40	
No	8	22	

Supplementary table 1a: Resection extent of MEG localizations vs. last available postsurgical outcome after at least 1 year (median 5.0y follow-up, 1st quartile 2.0y, 3rd quartile 7.0y).

Resection	Outcome (≥5 year)		p (Chi-Square test)
	Engel 1	**>Engel 1**	**< 0.001**
Complete	35	8	
Partial	10	10	
No	2	13	
	Engel 1a	**>Engel 1a**	**0.005**
Complete	20	23	
Partial	7	13	
No	0	15	

Supplementary table 1b: Resection extent of MEG localizations vs. long-term outcome after at least 5 years (median 7.0y follow-up, 1st quartile 5.0y, 3rd quartile 11.0y).

Complete MEG resection	
Follow-up	**All (including <1y)**
n	174
Engel 1	100
Sensitivity	63% (55% - 70%)
Specificity	85% (79% - 90%)
PPV	85% (79% - 90%)
NPV	63% (55% - 70%)
DOR	9.8 (4.6 - 20.8)
PLR	4.2 (3.6 - 5.1)
NLR	0.4 (0.4 - 0.5)
Engel 1a	69
Sensitivity	59% (52% - 67%)
Specificity	69% (61% - 75%)
PPV	55% (48% - 63%)
NPV	72% (65% - 78%)
DOR	3.2 (1.7 - 6.0)
PLR	1.9 (1.5 - 2.4)
NLR	0.6 (0.5 - 0.8)

Supplementary table 2: Parameters of diagnostic accuracy of complete MEG resection for a seizure free outcome (Engel 1 and Engel 1A) at the last available outcome, including early outcomes <1 year. PPV, NPV – positive, negative predictive value; DOR – diagnostic odds ratio; PLR, NLR – positive, negative likelihood ratio.

All lesionectomies			
Follow-up	**>= 1y**	**>=5y**	**Including <1y**
n	234	129	284
Engel 1	139	82	167
Sensitivity	96% (93% - 98%)	96% (91% - 99%)	96% (93% - 98%)
Specificity	19% (14% - 25%)	19% (13% - 27%)	21% (16% - 26%)
PPV	64% (57% - 70%)	68% (59% - 75%)	63.39% (57.46% - 68.95%)
NPV	78% (72% - 83%)	75% (66% - 82%)	80.00% (74.77% - 84.43%)
DOR	6.3 (2.2 - 17.5)	6.2 (1.6 - 24.4)	6.9 (2.7 - 17.6)
PLR	1.2 (0.9 - 1.5)	1.2 (0.8 - 1.7)	1.2 (1.0 - 1.5)
NLR	0.2 (0.2 - 0.2)	0.2 (0.1 - 0.3)	0.2 (0.1 - 0.2)
Engel 1a	97	51	122
Sensitivity	98% (95% - 99%)	98% (93% - 100%)	98% (95% - 99%)
Specificity	15% (11% - 21%)	14% (89% - 21%)	17% (13% - 22%)
PPV	45% (39% - 52%)	43% (34% - 52%)	47% (41% - 53%)
NPV	91% (87% - 95%)	92% (85% - 96%)	90% (86% - 93%)
DOR	8.6 (2.0 - 37.6)	8.2 (1.0 - 65.7)	7.9 (2.4 - 26.8)
PLR	1.2 (1.0 - 1.4)	1.1 (0.9 - 1.5)	1.2 (1.0 - 1.4)
NLR	0.1 (0.1 - 0.2)	0.1 (0.1 - 0.2)	0.2 (0.1 - 0.2)

Supplementary table 3: Parameters of diagnostic accuracy of complete or extended lesionectomy for a seizure free outcome (Engel 1 and Engel 1A). All lesional cases were considered, irrespective of IEDs on MEG. PPV, NPV – positive, negative predictive value; DOR – diagnostic odds ratio; PLR, NLR – positive, negative likelihood ratio.

Lesionectomies in cases with MEG resection data	
Follow-up	**All (Including <1y)**
n	134
Engel 1	84
Sensitivity	96% (91% - 99%)
Specificity	8% (4% - 14%)
PPV	64% (55% - 72%)
NPV	57% (48% - 66%)
DOR	2.4 (0.5 – 11.0)
PLR	1.1 (0.5 - 2.0)
NLR	0.5 (0.2 - 0.9)
Engel 1a	57
Sensitivity	98% (94% - 100%)
Specificity	8% (4% - 14%)
PPV	44% (36% - 53%)
NPV	86% (78% - 91%)
DOR	4.7 (0.6 - 40.5)
PLR	1.1 (0.7 - 1.5)
NLR	0.2 (0.2 - 0.3)

Supplementary table 4: Parameters of diagnostic accuracy of complete or extended lesionectomy for a seizure free outcome (Engel 1 and Engel 1A) at the last available outcome, including early outcomes <1 year. Only cases with IEDs on MEG and information on MEG resection were considered, corresponding to table 2. Nc – not computable due to zeros in the denominator, etc. PPV, NPV – positive, negative predictive value; DOR – diagnostic odds ratio; PLR, NLR – positive, negative likelihood ratio.