Clinical Neurophysiology 129 (2018) 1651–1657

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

# Magnetoencephalography and ictal SPECT in patients with failed epilepsy surgery

Riëm El Tahry [a,e], Z. Irene Wang [b,*], Aung Thandar [b], Irina Podkorytova [c], Balu Krishnan [b], Simon Tousseyn [d], Wu Guiyun [b], Richard C. Burgess [b], Andreas V. Alexopoulos [b]

[a] Cliniques Universitaires Saint Luc, Av Hippocrate 10, 1200 Brussels, Belgium
[b] Cleveland Clinic, Epilepsy Center, Cleveland, OH 44195, USA
[c] UTSW, Department of Neurology and Neurotherapeutics, TX 75390, USA
[d] Academic Center for Epileptology, Kempenhaeghe and Maastricht UMC+, Heeze, The Netherlands
[e] Institute of Neuroscience, Université Catholique de Louvain, Av Mounier 53 & 73, 1200 Brussels, Belgium

ARTICLE INFO

*Article history:*
Accepted 3 May 2018
Available online 6 June 2018

*Keywords:*
Epilepsy
Failed surgery
MEG
SPECT

HIGHLIGHTS

- Patients with failed epilepsy surgery should be considered for re-evaluation for new surgery.
- Resection of the MEG localization positively associated with favorable outcomes.
- Resection of SPECT localization with injection ≤20 s positively associated with favorable outcomes.

ABSTRACT

*Objective:* Selected patients with intractable focal epilepsy who have failed a previous epilepsy surgery can become seizure-free with reoperation. Preoperative evaluation is exceedingly challenging in this cohort. We aim to investigate the diagnostic value of two noninvasive approaches, magnetoencephalography (MEG) and ictal single-photon emission computed tomography (SPECT), in patients with failed epilepsy surgery.
*Methods:* We retrospectively included a consecutive cohort of patients who failed prior resective epilepsy surgery, underwent re-evaluation including MEG and ictal SPECT, and had another surgery after the re-evaluation. The relationship between resection and localization from each test was determined, and their association with seizure outcomes was analyzed.
*Results:* A total of 46 patients were included; 21 (46%) were seizure-free at 1-year followup after reoperation. Twenty-seven (58%) had a positive MEG and 31 (67%) had a positive ictal SPECT. The resection of MEG foci was significantly associated with seizure-free outcome ($p = 0.002$). Overlap of ictal SPECT hyperperfusion zones with resection was significantly associated with seizure-free outcome in the subgroup of patients with injection time ≤20 seconds ($p = 0.03$), but did not show significant association in the overall cohort ($p = 0.46$) although all injections were ictal. Patients whose MEG and ictal SPECT were concordant on a sublobar level had a significantly higher chance of seizure freedom ($p = 0.05$).
*Conclusions:* MEG alone achieved successful localization in patients with failed epilepsy surgery with a statistical significance. Only ictal SPECT with early injection (≤20 seconds) had good localization value. Sublobar concordance between both tests was significantly associated with seizure freedom. SPECT can provide essential information in MEG-negative cases and vice versa.
*Significance:* Our results emphasize the importance of considering a multimodal presurgical evaluation including MEG and SPECT in all patients with a previous failed epilepsy surgery.


## 1. Introduction

Approximately 30% of patients with intractable focal epilepsy still have recurring seizures after the first resective surgery (Spencer and Huh, 2008). In these patients, re-evaluation for a

* Corresponding author at: Cleveland Clinic, Epilepsy Center, Desk S-51, 9500 Euclid Avenue, Cleveland, OH 44195, USA.
*E-mail address:* wangi2@ccf.org (Z.I. Wang).

https://doi.org/10.1016/j.clinph.2018.05.010
1388-2457/

potential reoperation can be a worthwhile attempt. Previous studies reported reoperation rates to be between 35.9% and 65.2% in patients with unfavorable outcome after initial surgery; seizure-free rate vary considerably among studies and ranged from 9.5 to 57.1%, and was estimated at 36.6% across all the studies (Surges and Elger, 2013).

As noninvasive procedures commonly used in presurgical evaluation, magnetoencephalography (MEG) and ictal single-photon emission computed tomography (SPECT) provide interictal and ictal localization and can yield essential localization information (Knowlton et al., 2006; Schneider et al., 2013, 2012). No previous studies specifically address the utility of MEG and SPECT on patients with previously *failed* surgery. In this study, we aim to investigate whether the noninvasive multimodal approach with MEG and ictal SPECT contributes to better post-operative seizure outcome in patients with previously failed epilepsy surgery.

## 2. Materials and Methods

### 2.1. Patient population

The study was approved by the Institutional Review Board of the Cleveland Clinic. We reviewed all medical records from the epilepsy surgical database between January 2009 and September 2014. The following inclusion criteria were used: (1) intractable epilepsy as defined by ILAE classification (Kwan and Brodie, 2001); (2) prior resective epilepsy surgery (single or multiple); (3) re-evaluation including MEG and ictal SPECT; (4) resective epilepsy surgery following the re-evaluation as mentioned in (3); and (5) follow-up of 12 months after the surgery mentioned in (4). We excluded patients whose prior brain surgery was non-resective, e.g., vagus nerve stimulation, intracranial EEG (ICEEG), brain biopsy, craniotomy and drainage for intracranial hemorrhage, placement of shunts and aneurysm clipping (however, if there was a subsequent resective surgery following these non-resective procedures, patients can be included). We also excluded patients who had functional hemispherectomy as the reoperation, and patients whose postoperative MRI or CT scans were unavailable or of unsatisfactory quality for delineation of resection extent.

### 2.2. Non-invasive and invasive video-EEG monitoring

Scalp video-EEG monitoring was performed using international 10–20 system of electrode placement. ICEEG with placement of subdural grids and depth electrodes or stereo-EEG were performed per consensus of panel discussion at patient management conferences. Ictal scalp EEG localization results were obtained from clinical report and classified as lobar, multilobar, hemispheric, generalized or normal (no EEG change). Lobar and multilobar patterns were considered localizing and the remaining patterns were considered nonlocalizing. The ictal onset zone was used as the localization result of ICEEG, which was determined based on the final clinical report used to guide surgical resection.

### 2.3. MEG

A 60-minute spontaneous MEG recording was performed using a whole-head, 306-channel Neuromag system (Elekta, Helsinki, Finland). Acquisition parameters can be found elsewhere (Kakisaka et al., 2013; Murakami et al., 2016). MEG spike localizations were calculated based on a single equivalent current dipole model (Bagic et al., 2011). Dipole sources were co-registered to the patient's MRI. A negative MEG was defined as a study with no epileptiform discharges, slowing only, or if the number of spikes in the entire study is <5 (Bagic et al., 2011). A localizable MEG was defined as a study with more than 5 dipoles with acceptable statistics (Bagic et al., 2011). If the interictal MEG was negative and only ictal events were captured, ictal dipoles were used for analysis if they were localizable. A tight cluster was defined by 5 or more dipoles located in one sulcus and/or adjacent 2 gyri; a loose cluster was defined by 5 or more dipoles located in one sublobar region (details in "concordance analysis" section) (Murakami et al., 2016). When there were interictal/ictal epileptiform activities within the MEG study but they were not localizable by the single equivalent current dipole modeling, the study was defined as nonlocalizable.

### 2.4. Ictal SPECT

The ictal SPECT images were acquired on a SPECT CT camera (Siemens, Symbia T16) within 2 h after injection of 20–40 mCi of 99mTc-ECD (ethyl-cysteinate dimer). Interictal SPECT studies were accomplished after a minimum of 24 h of no seizures. The SPECT data were processed using computerized imaging analysis tool SISCOM (Subtraction Ictal SPECT Co-registered to MRI) (O'Brien et al., 2000). For clinical interpretation, a z-score threshold of 2 was used. The hyperperfusion zones considered for analysis were those described in the official clinical report by a nuclear medicine physician and the patient management team; if there were no dominant area of hyperperfusion, the study was concluded as nonlocalizable. A "not-obtained" SPECT study was defined by the scenario when SPECT was ordered, but no seizures were recorded during the video-EEG monitoring. Injection time of SPECT was calculated as the time lapse between the start of the seizure based on video-EEG recording and tracer injection. If several SPECT seizures were recorded, the shortest injection time was used. Although there might have been ictal SPECTs obtained on multiple seizure types on the same patient, the one included in the analyses was on the main seizure type.

### 2.5. Resection analysis

Image coregistration was performed using CURRY 6 (Compumedics Neuroscan, Hamburg, Germany). Consistently for each patient, we coregistered three sets of images: pre-surgical MRI (which contained resection from the previous surgery), MEG results (pre-surgical MRI with dipole locations imprinted), hyperperfused z-score maps from SISCOM analysis, and post-operative MRI (which contained resection of the previous surgery and the re-surgery). Blinded to outcome data and other clinical data used for the current and previous evaluations, we used the coregistered images to determine: (1) the location of re-surgery (especially helpful when the re-surgery was an extension of the previous resection); (2) whether resection overlapped with MEG dipoles; and (3) whether resection overlapped with SISCOM hyperperfusion (z-score = 2 to be consistent with what was used for the clinical report). We considered MEG cluster resection complete if the surgically resected area contained more than 90% of the MEG dipoles. For SISCOM, as in most cases the hyperperfusion was more extended than the resection, we regarded SISCOM to be included in resection, if one of the hyperperfusion zones overlapped with the resection cavity, consistent with previous studies (O'Brien et al., 2000; Sulc et al., 2014). Considering post-operative movement of tissue around the resection cavity, MRI distortion and coregistration error, the dipoles/hyperperfusion areas were considered as inside the resection if they were within 5 mm from the resection margin. We then assessed the association between seizure outcomes and whether the MEG/SISCOM localization was contained in the resection.

**Table 1**
Concordance patterns between MEG and SPECT, independent of epilepsy surgery resection.

| | |
|---|---|
| A | Sublobar concordance |
| B | Sublobar plus[a] |
| C | Lobar concordance[a] |
| D | Not overlapping but localized ipsilateral |
| E | Not overlapping and bilateral |

[a] Overlapping but one or both test can be more widespread.

### 2.6. Concordance analysis

As shown in Table 1, concordance between MEG and SPECT was defined as "sublobar" (A), "sublobar plus" (B), "lobar" (C), "multilobar ipsilateral" (D) and "multilobar bilateral" (E). Sublobar regions were defined with modifications form literature as follows: frontopolar, frontal superior mesial, dorsolateral frontal superior, dorsolateral frontal inferior, orbitofrontal, parietal superior mesial, parietal inferior mesial, parietal superior lateral, parietal inferior lateral, temporomesial, temporolateral, temporopolar, temporobasal, occipital mesial, occipital lateral, frontal opercular, temporal opercular, parietal opercular, anterior insular, posterior insular, temporo-occipital junction, temporo-parietal junction, anterior cingular, middle cingular and posterior cingular (Schneider et al., 2013). On the lobar level, the operculum, the insula and temporal junctions were classified as separate regions. The concordance between scalp EEG and MEG was performed at the lobar level (frontal, temporal, parietal and occipital). The concordance patterns were assessed in terms of their association with seizure outcomes.

### 2.7. Seizure outcome and pathology

Outcome was assessed at 1 year after surgery and classified into completely seizure-free and not seizure-free. Histopathological specimens were reviewed by a dedicated neuropathologist and focal cortical dysplasia (FCD) was classified according to the Palmini classification (Palmini et al., 2004).

### 2.8. Statistics

SPSS 19 (IBM Co., Armonk, NY, U.S.A.) was used for statistical processing of the data. The statistical methods were descriptive statistics with frequency analysis and cross tab analysis, as well as mean and standard deviation (SD) calculation in parametric data. Statistical significance was assessed using a Fisher exact (when $N < 5$) or Chi Square test, with a significance defined as a probability ($p$) value $\leq 0.05$.

## 3. Results

### 3.1. Demographics and clinical profiles

From the 1512 patients screened, 158 patients had previous epilepsy surgery. Among these patients, 54 had both MEG and SPECT performed. Seven patients underwent functional hemispherectomy and were excluded. One patient had a postoperative CT scan with unsatisfactory quality for analysis and was also excluded. Therefore, a total of 46 patients were included. Demographics and clinical profile can be found in Table 2. Seizures recurred within 6 months after the first surgery in the majority of these patients (30/46, 65%). At one-year follow-up after reoperation, 21 patients (46%) remained seizure-free. In most but not all patients (65%), reoperation aimed at extending the area of the previous resection. Type of resection, type of epilepsy and type of pathology did not significantly associate with seizure outcome after the reoperation. Thirty-three patients had the same seizure semiology and 13 had altered semiology before and after the previous (failed) surgery.

**Table 2**
Demographics and clinical data of included patients (N = 46).

| | |
|---|---|
| Mean age | 30y (range 2–54, SD ± 14) |
| Sex | 21F/25M |
| Duration of epilepsy | 20y (range 1–53, SD ± 13) |
| Handedness | 38R/8L |
| Seizure free | 21 (46%) |
| Non-contributive MRI | 31 (67%) |
| More than one previous surgery | 10 (22%) |
| Time of seizure reoccurrence after previous surgery | 11.7 months (range 0–148, SD ± 26 months)<br>30 patients < 6 months<br>6 patients 6–12 months<br>10 patients > 12 months |
| Time between surgeries | 6 years 6 months (range 1–23 years) |
| Epilepsy Type | 3/46 mTLE, 11/46 TLE, 32/46 ETLE |
| Surgery | 29 lobar, 17 multilobar |
| Localization of the new surgery | Extension of previous surgery: 30/46<br>New localization: 16/46 |
| Pathology | 25 FCDs (21 FCD type I, 4 FCD type II)<br>15 non-specific<br>1 dysplasia + hippocampal sclerosis<br>1 hippocampal sclerosis<br>2 tumors<br>1 cavernous angioma<br>1 unknown |
| Scalp EEG Interictal | 10 (22%) lobar<br>27 (59%) multilobar<br>9 (20%) nonlocalizable |
| Scalp EEG Ictal | 16 (35%) lobar<br>18 (39%) multilobar<br>11 (24%) nonlocalizable<br>1 (2%) no seizures |
| MEG | 27 58%) localizable<br>• 11 single tight cluster, 7 single loose cluster, 9 multiple clusters<br>• 14 had at least 1 cluster at previous resection margin<br>18 (39%) negative<br>1 (2%) nonlocalizable |
| SPECT | 31 (67%) localizable<br>• 8 single, 23 multiple hyperperfusion regions<br>• 17 had at least 1 hyperperfusion region at previous resection margin<br>12 (26%) not obtained<br>3 (6%) nonlocalizable |
| Mean duration of ictal SPECT seizures | 105 sec (range 16–660 s, SD ± 122 s) |
| Mean injection time | 20 sec (range 4–185 s, SD ± 29 s) |
| ICEEG | 25 (54%) |

Out of the 46 selected patients, 24 had the previous surgery at the Cleveland Clinic. Only one patient had a preoperative MEG, which was localizable. Five patients (21%) had SPECT which was localizable in all cases. The majority (13/24, 54%) had ICEEG.

The remaining 22 patients had their previous surgery at another institution. Therefore, details of their original preoperative investigations were not always available. One patient had a preoperative MEG which was negative. Three patients (14%) had SPECT which was localizable in all cases. Nine patients (41%) had ICEEG.

### 3.2. Positive rates

As detailed in Table 2, of the 46 patients included in this study, 27 (58%) had a localizable MEG, of which 2 patients had exclusively ictal MEG findings. A total of 34 patients (74%) had a successful ictal SPECT injection performed during a typical seizure. Secondary generalization occurred in 8/34 (24%) of ictal SPECT seizures. SPECT studies were nonlocalizable (i.e. had no dominant areas of hyperperfusion) in three patients: one with a late injection (38 s, after clinical onset during a 131-second seizure), one with a postictal injection (8 s after the end of a brief 19-second seizure) and one with early injection (12 s into a seizure that lasted for 83 s). The remaining 31 patients with localizable SPECT had ictal injections with a mean injection time of 20 s (range 4–185 s; median 16 s) after EEG onset (29 patients) or after clinical seizure onset when the earliest clinical change preceded the EEG onset (3 patients). All injections occurred within less than 35 s, with the exception of one case with a long injection time of 185 s during an exceptionally long seizure that lasted for 660 s.

### 3.3. Resection analysis

Table 3 describes the resection analysis. Figs. 1 and 2 show two illustrative cases.

#### 3.3.1. MEG, resection and seizure outcomes

Eleven patients had complete resection of the MEG cluster, of which 9 became seizure-free (82%); 16 patients had the MEG cluster partially removed or not removed, of which 3 were seizure-free (19%); 19 patients had a negative or non-localizable MEG study, of which 9 were seizure-free (47%). Patients with complete MEG cluster resection were more likely seizure-free than patients who did not have the MEG cluster removed ($p = 0.002$).

In the 27 patients who had a localizable MEG, 11 had a single tight cluster, 7 had a single loose cluster and 9 had multiple clusters (4 patients had two tight clusters; 4 patients had one loose and one tight cluster; 1 patient had two loose clusters). Seven of the 11 (63%) patients with a tight cluster became seizure-free, and 4 of the 16 (25%) patients who had a loose cluster or multiple clusters became seizure-free. The presence of a single tight cluster was not significantly associated with seizure freedom ($p = 0.06$). In 14 (15/27, 55%) patients, at least one of the MEG clusters were at the margins of the previous resection.

#### 3.3.2. Ictal SPECT, resection and seizure outcomes

Nineteen patients had at least one of the hyperperfusion areas overlapping with resection, and 10 became seizure-free (53%); 12 patients did not have any hyperperfusion areas overlapping with resection, and 4 were seizure-free (33%); the 3 patients who had a nonlocalizable SPECT all had recurring seizures. In the 12 patients who had a negative SPECT study, 7 were seizure-free (58%). The overlapping of a SPECT hyperperfusion area with resection did not associate with better seizure outcomes when compared with the group of patients with no overlapping ($p = 0.46$).

**Table 3**
Association between MEG localization/SPECT hyperperfusion, resection and outcome.

| Group (N = 46) | Total | Seizure-free (12 m) | Not seizure-free (12 m) | P value |
|---|---|---|---|---|
| MEG resected? | | | | 0.002 |
| Yes | 11 | 9 | 2 | |
| No | 16 | 3 | 13 | |
| SPECT resected? | | | | 0.46 |
| Yes | 19 | 10 | 9 | |
| No | 12 | 4 | 8 | |
| SPECT resected? (injection ≤20 sec, N = 23) | | | | 0.03 |
| Yes | 14 | 9 | 5 | |
| No | 9 | 1 | 8 | |
| SPECT resected? (injection >20 sec, N = 8) | | | | 0.63 |
| Yes | 5 | 1 | 4 | |
| No | 3 | 3 | 0 | |

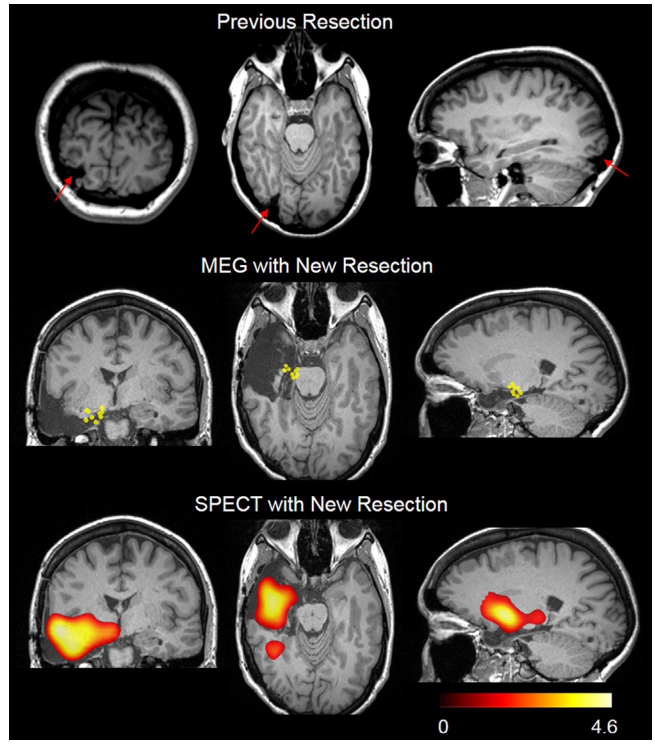


**Fig. 1.** Example of a patient with right temporal lobe epilepsy, whose MEG and ictal SPECT showed sublobar plus concordance (right mesial temporal for MEG and right temporal for SPECT). ICEEG confirmed a right mesial temporal seizure onset. The previous resection was a right occipital resection. The MEG focus and the temporal SPECT hyperperfusion zone were both resected with re-surgery, and the patient became seizure-free. Surgical pathology showed FCD type I. Ictal SPECT injection time was 20 s. In Figs. 1 and 2, first row indicates previous resection; second row shows MEG superimposed on the new resection; third row shows SPECT superimposed on the new resection. The yellow dots indicate the location of the MEG dipoles, superimposed on the MRI with a slice persistence of 10 mm. Ictal SPECT was processed with the SISCOM methodology and displayed with a z-score of 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

We further performed subgroup analyses based on injection time. Twenty-three patients had an injection time of ≤20 s; 14 of them had at least one of the hyperperfusion areas overlapping with resection, and 9 became seizure-free (64%); 9 patients did not have any hyperperfusion areas overlapping with resection, and only 1 became seizure-free (11%). In this subgroup, the overlapping of SPECT hyperperfusion area with resection did associate with better seizure outcomes ($p = 0.03$). This significance was not found in the subgroup of patients whose injection time exceeded 20 s ($p = 0.63$).

In the 10 patients who had at least one of the hyperperfusion areas overlapping with resection and became seizure-free, 4 had single hyperperfusion area, 6 had multiple hyperperfusion areas, 50% of whom (3/6) had the hyperperfusion with the highest z-score resected.

### 3.4. Concordance between MEG and ictal SPECT

Concordance analysis (Table 4) was performed on all patients with localizable MEG and localizable SPECT. Sublobar concordance (A + B) of MEG and ictal SPECT was found in 6 patients, and 5 of them were seizure-free (83%). Five patients showed concordance pattern C; 3 patients showed pattern D; and 6 showed pattern E. The seizure-free percentage was 20% (1/5), 33% (1/3) and 33% (2/6) for the C, D and E subgroups. Patients with a MEG and ictal SPECT that were sublobarly concordant had significantly higher

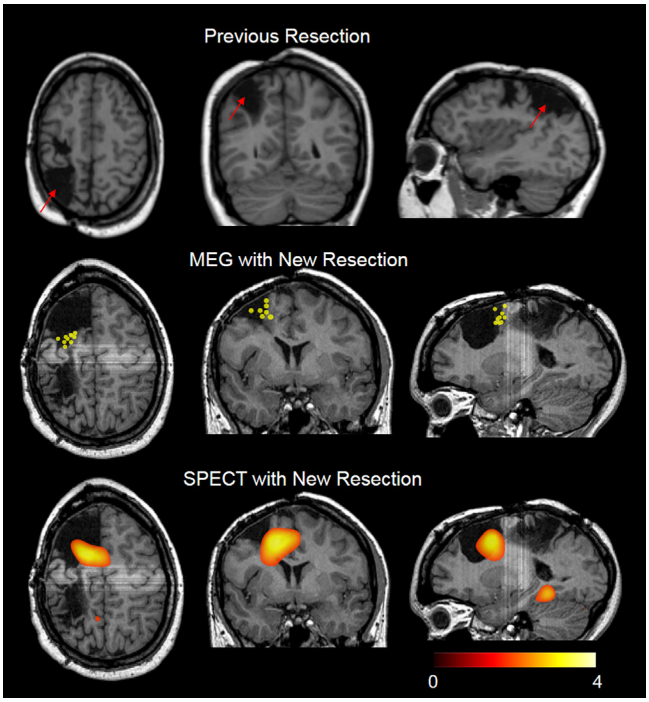


**Fig. 2.** Example of a patient with right frontal lobe epilepsy, whose *ictal* MEG and ictal SPECT showed sublobar concordance (right superior frontal mesial). Interictal MEG was negative in this patient. The previous resection was multilobar involving right *peri*-rolandic and parietal areas. The MEG focus and the right frontal SPECT hyperperfusion zone were both resected with the new surgery, and the patient became seizure-free. Surgical pathology showed FCD type I. Injection time of the ictal SPECT was 9 s.

chance of seizure freedom as compared to the rest of the group ($p = 0.05$).

### 3.5. Negative or nonlocalizable MEG/SPECT

Of the 19 patients with a negative or nonlocalizable MEG, 11 had a localizable SPECT. Four of the 11 patients had at least one of the hyperperfusion areas overlapping with resection and became seizure-free. Of the 15 patients with a negative or nonlocalizable SPECT, 7 had a localizable MEG. Three of the 7 patients had complete resection of the MEG cluster and became seizure-free.

### 3.6. Scalp EEG

Ictal scalp EEG had localizing results in 34 patients (16 lobar, 18 multilobar). In 13 patients the localization from ictal scalp EEG was contained within resection, and 7 patients became seizure-free (53%). In 21 patients, the ictal EEG localization was partially included or not included in the resection, and 10 were seizure-free (48%). Resection of ictal scalp EEG localization did not associate with better seizure outcomes when compared with the partial/no resection group ($p = 0.5$).

### 3.7. ICEEG

Twenty-five patients in our cohort (25/46, 54%) had ICEEG, in whom 10 were seizure-free (10/25, 40%); in 21 (21/46, 46%), no ICEEG was performed and 11 became seizure-free (11/21, 52%). Patients with ICEEG performed did not have a significantly higher chance of becoming seizure-free ($p = 0.5$). Localization from the ICEEG showed sublobar concordance with MEG in 28% (7/25) and lobar concordance in 16% (4/25). ICEEG showed sublobar concordance with ictal SPECT in 20% (5/25), lobar concordance in 24% (6/25). ICEEG, MEG and ictal SPECT were all concordant on a sublobar level in 4 patients (4/25, 16%). No significant association between ICEEG/MEG/SPECT concordance pattern and seizure outcomes can be observed, likely due to small sample size.

### 3.8. Surgical pathology

Surgical pathology results consisted of 21 FCD type I (48%, 9/21 seizure-free), 4 FCD type II (9%, 3/4 seizure-free), and 2 tumors (4%, both seizure-free). One patient (2%) had a cavernous angioma (seizure-free), one had hippocampal sclerosis (not seizure-free) and another one had hippocampal sclerosis together with dysplasia (seizure-free). In 15 patients, findings of surgical pathology were nonspecific, such as gliosis or negative (32%, 1/15 seizure-free). One patient did not have tissue submitted for pathological examination.

## 4. Discussion

We present the first study that specifically examines the value of two noninvasive tests, MEG and ictal SPECT, in a large group of patients with *failed* epilepsy surgery, who were referred for and underwent subsequent reoperation. Appropriate patient selection and interpretation of repeat preoperative evaluation are exceedingly challenging in this cohort. Our findings suggest that MEG and ictal SPECT provide unique and complementary information, which can be used to guide electrode implantation and surgical strategy.

### 4.1. Characteristics of study cohort

In our challenging cohort, 67% of patients had a noncontributory MRI prior to any surgical intervention, and 22% had previously undergone more than one surgical resection. Importantly, almost half (46%) of these patients were seizure-free one year after reoperation. This result in itself is encouraging and indicates that a repeat presurgical evaluation can lead to promising seizure outcomes despite the various complexities. Previous studies of cohort similar to ours (mixed cohort with heterogeneous pathology and epilepsy type) showed variable seizure-free rates between 19% and 43% (González-Martínez et al., 2007; Holmes et al., 1999; Schwartz and Spencer, 2001; Siegel, 2004), consistent with our findings. Comparing seizure-free rates between different epilepsy centers remains challenging given that selection of patients and utilization of tools for preoperative investigations are highly heterogeneous.

**Table 4**
Concordance between MEG localization/SPECT hyperperfusion and outcome.

| Group (N = 46) | Total | Seizure-free (12 m) | Not seizure-free (12 m) | *P* value |
|---|---|---|---|---|
| MEG and SPECT had sublobar concordance (A + B)? | | | | 0.05 |
| Yes | 6 (2A, 4B) | 5 (2A, 3B) | 1 (0A, 1B) | |
| No | 14 (5C, 3D, 6E) | 4 (1C, 1D, 2E) | 10 (4C, 2D, 4E) | |

Comparing the differences between the previous (failed) evaluation and the re-evaluation, neither MEG nor SPECT had been obtained prior to the initial "failed" epilepsy surgery in the vast majority of patients in our cohort, regardless of whether the evaluation was performed at our center or elsewhere, probably due to their unavailability or infrequent use in the earlier years. Interestingly, the percentages of patients who underwent ICEEG (approximately half) were similar from the previous evaluation and the re-evaluation. This data perhaps corroborate the notion that noninvasive imaging techniques provide crucial information in improving the accuracy of invasive evaluation (Murakami et al., 2016).

### 4.2. Diagnostic values of MEG and SPECT

Our analysis of the patient cohort in its entirety shows that complete resection of MEG foci was significantly associated with seizure-free outcome, whereas resection of the SPECT hyperperfusion zone was not. Importantly, further subgroup analysis indicates that resection of the region of SPECT hyperperfusion did associate significantly with seizure-free outcome in the subset of patients who had a relatively early SPECT injection ($\leq$20 s). Notably, all patients included in this cohort had truly ictal injections with a mean injection time of 20 s and a median of 16 s. The importance of early injections was previously highlighted by Lee et al., who noted that injection times of less than 20 s were critical in obtaining accurate SPECT localization (Lee et al., 2006).

It is worth pointing out that a large proportion of patients with MEG-negative studies did have a localizable SPECT result – an observation that highlights the value of SPECT in this situation, especially when early injections are feasible. Similarly, a localizable MEG provided unique/complementary information, when ictal SPECT injection was unsuccessful or delayed beyond 20 s in the course of the patient's seizure.

Our results are consistent with other studies, which showed that resection of MEG foci was significantly associated with better seizure outcomes in patients without (Almubarak et al., 2014; Fischer et al., 2005; Otsubo et al., 2001; RamachandranNair et al., 2007) or with prior surgery (Kirchberger et al., 1998; Mohamed et al., 2007). The advantage of MEG could be attributed to the fact that MEG signals (unlike scalp EEG) are not significantly distorted by postoperative skull defects, underlying lesions or surgical cavities (Okada et al., 1999). In fact, our data showed that resection of the ictal onset zone determined by scalp EEG did not associate with a favorable postoperative seizure outcome in this patient cohort. Taken together, the previous literature and our current study indicate that MEG is a uniquely suited tool for the localization of residual epileptogenic foci in patients who have failed epilepsy surgery.

O'Brien et al. reported that resection of the SPECT hyperperfusion zone was significantly associated with seizure freedom in a group of 36 patients with extratemporal lobe epilepsy (O'Brien et al., 2000). There are differences between their study and ours in patient selection (our cohort failed previous surgery and theirs did not) and approaches to estimate completeness of resection. In their study, a complete resection had to include all areas of hyperperfusion identified by SISCOM analysis. Had the same criteria been applied to our cohort, only few resections (8 in total) would have been deemed as complete, given that the areas of hyperperfusion in our patient population often had a multilobar or relatively diffuse appearance. This more diffuse pattern cannot be attributed to later injections given that that the mean injection time was 20 s in this study, as compared to 43 s in the study of O'Brien et al (O'Brien et al., 2000). Wetjen et al. examined SISCOM in a cohort of 58 patients who had failed previous epilepsy surgery (Wetjen et al., 2006). In 70% of the included patients, SISCOM localization was consistent with the putative epileptogenic zone. About half the patients underwent reoperation in the study; 10 of 20 patients (50%) with a concordant SISCOM focus compared with none of 3 patients with a discordant focus had a favorable seizure outcome ($p = 0.23$). The non-significance is consistent with our findings, although it could also be due to small sample size. Injection time was not specifically reported in the study, so no comparison can be performed with our subgroup analysis. Lastly, Dupont et al. examined patients with visible FCD lesions and their SISCOM analysis, and reported that full resection of the SISCOM hyperperfusion was *not* always required to render a patient seizure-free; as long as the lesion and the hyperperfusion within and immediately surrounding the lesion was resected, patients tended to do well (Dupont et al., 2006). This study highlights the nature of ictal SPECT, which should be viewed as a dynamic study that reflects not only the site of generation, but also areas of seizure propagation (Newey et al., 2013). Our methodology was consistent with the concept of the study by Dupont et al., in that we evaluated in this cohort (which had FCD as the main pathology) overlap of resection with at least one area of SPECT hyperperfusion, rather than requiring completeness of resection of all the hyperperfusion regions.

### 4.3. Concordance between MEG and ictal SPECT

Our findings indicate patients are more likely to become seizure-free when their MEG and SPECT studies show concordance on a sublobar or sublobar plus level. Test concordance is an important predictive factor in epilepsy surgery as a whole (Lee et al., 2005). Knowlton et al. performed a controlled, prospective, observational study to determine the predictive value of functional imaging tests for seizure outcome after surgery (Knowlton et al., 2008). In this important study, localization concordance with ICEEG was shown to be the greatest with MEG, and additional diagnostic gain was achieved with the combination of SPECT with MEG. Schneider et al. retrospectively studied a group of 14 patients with nonlesional MRI, and reported that the combined use of MEG and ictal SPECT increases the accuracy of localizing the epileptogenic zone compared to each single test alone (Schneider et al., 2013). Our study finding is consistent with the previous two studies (which used cohorts primarily of patients without prior surgery), suggesting that test concordance is similarly important for patients with previously failed surgery. The presence of concordance could indicate convergence of the underlying mechanisms of the epileptogenic substrate, and thus be attributable to (or predictive of) a more focal epileptogenic process, which in turn provides for a more confident preoperative localization. Test concordance between MEG and SPECT is also of practical importance when ictal SPECT shows multiple regions of hyperperfusion. These regions of hyperperfusion can provide valuable information on how epileptic activities propagate and should not be overlooked. However, the hyperperfusion region most relevant to the initiation of seizures can sometimes be most effectively localized by examining concordance with other tests such as MEG.

### 4.4. Negative MEG

One should note the relative high proportion (39%) of negative MEG cases in the current study. These same patients typically had a low incidence or complete absence of discernible interictal spikes on prolonged scalp EEG recordings – a fact that can explain the lack of interictal activities during the brief sampling window afforded by a single MEG study. In a study that was previously published by our group, MEG was found to be negative in 12 of the 197 patients, i.e. 6% (Almubarak et al., 2014). The vast majority of these 197 patients did not have previous surgical resection. The significantly higher rate of MEG-negative cases in the current study (39%, compared to 6% in all comers with intractable epilepsies in the study of Almubarak et al., $p < 0.001$) could be attributable to a cohort selection bias. It is possible that patients with a negative MEG have epilepsies that are more difficult to localize and are therefore more likely to fail epilepsy surgery.

### 4.5. Limitations

1. MEG and SPECT are inherently difficult to compare, given that they rely on different pathophysiological processes. MEG captures the direct electromagnetic expression of primarily interictal epileptic discharges, whereas SPECT identifies the resulting signature of brain hyperperfusion in the course of a seizure and thus depicts a complicated network of generated and propagated activities. Taking into account the fundamental differences of the two modalities and previously published methodology in related studies, we opted to use a stricter definition for completeness of resection when examining MEG results, i.e. resection of >90% of MEG dipoles, as compared to SPECT findings, i.e. overlap of resection with at least one area of SPECT hyperperfusion. Note that by adopting this methodology on SPECT, we are not implying the hyperperfusion regions other than the ones overlapping with resection can be totally neglected. These regions of hyperperfusion may reveal the propagation of epileptic activities and should always be taken into consideration with the patient's electroclinical profile.
2. We only included patients who had both MEG and SPECT performed as part of their re-evaluation, while a substantial number of patients might have MEG alone, or SPECT alone, or neither of the two tests. Hence caution should be used to avoid generalizing these results to all patients failing initial resective surgery.

## 5. Conclusions

Our study emphasizes the importance of considering a multimodal presurgical evaluation including MEG and SPECT for patients with a previously failed epilepsy surgery. MEG alone achieved successful localization in patients with failed epilepsy surgery with a statistical significance. Only ictal SPECT with early injection ($\leq$20 s) had good localization value. Sublobar concordance between both tests was significantly associated with seizure freedom. SPECT can provide essential information in MEG-negative cases and vice versa.

## Acknowledgement and funding

Dr. Riëm El Tahry was funded by the Horlait Dapsens Foundation and La Foundation Saint Luc.

## Disclosure of interest

None of the authors have potential conflicts of interest to be disclosed. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## Authorship statement

All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

## References

Almubarak S, Alexopoulos A, Von-Podewils F, Wang ZI, Kakisaka Y, Mosher JC, et al. The correlation of magnetoencephalography to intracranial EEG in localizing the epileptogenic zone: a study of the surgical resection outcome. Epilepsy Res 2014;108:1581–90.
Bagic AI, Knowlton RC, Rose DF, Ebersole JS. American clinical magnetoencephalography society clinical practice guideline 3: MEG-EEG reporting. J Clin Neurophysiol 2011;28:362–3.
Dupont P, Van Paesschen W, Palmini A, Ambayi R, Van Loon J, Goffin J, et al. Ictal perfusion patterns associated with single MRI-visible focal dysplastic lesions: implications for the noninvasive delineation of the epileptogenic zone. Epilepsia 2006;47:1550–7.
Fischer MJM, Scheler G, Stefan H. Utilization of magnetoencephalography results to obtain favourable outcomes in epilepsy surgery. Brain 2005;128:153–7.
González-Martínez JA, Srikijvilaikul T, Nair D, Bingaman WE. Long-term seizure outcome in reoperation after failure of epilepsy surgery. Neurosurgery 2007;60:873–9.
Holmes MD, Wilensky AJ, Ojemann LM, Ojemann GA. Predicting outcome following reoperation for medically intractable epilepsy. Seizure 1999;8:103–6.
Kakisaka Y, Mosher JC, Wang ZI, Jin K, Dubarry AS, Alexopoulos AV, et al. Utility of temporally-extended signal space separation algorithm for magnetic noise from vagal nerve stimulators. Clin Neurophysiol 2013;124:1277–82.
Kirchberger K, Hummel C, Stefan H. Postoperative multichannel magnetoencephalography in patients with recurrent seizures after epilepsy surgery. Acta NeurolScand 1998;98:1–7.
Knowlton RC, Elgavish RA, Bartolucci A, Ojha B, Limdi N, Blount J, et al. Functional imaging: II. Prediction of epilepsy surgery outcome. Ann Neurol 2008;64:35–41.
Knowlton RC, Elgavish R, Howell J, Blount J, Burneo JG, Faught E, et al. Magnetic source imaging versus intracranial electroencephalogram in epilepsy surgery: a prospective study. Ann Neurol 2006;59:835–42.
Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. Epilepsia 2001;42:1255–60.
Lee SK, Lee SY, Kim KK, Hong KS, Lee DS, Chung CK. Surgical outcome and prognostic factors of cryptogenic neocortical epilepsy. Ann Neurol 2005;58:525–32.
Lee SK, Lee SY, Yun CH, Lee HY, Lee JS, Lee DS. Ictal SPECT in neocortical epilepsies: clinical usefulness and factors affecting the pattern of hyperperfusion. Neuroradiology 2006;48:678–84.
Mohamed IS, Otsubo H, Ochi A, Elliott I, Donner E, Chuang S, et al. Utility of magnetoencephalography in the evaluation of recurrent seizures after epilepsy surgery. Epilepsia 2007;48:2150–9.
Murakami H, Wang ZI, Marashly A, Krishnan B, Prayson RA, Kakisaka Y, et al. Correlating magnetoencephalography to stereo-electroencephalography in patients undergoing epilepsy surgery. Brain 2016;139:2935–47.
Newey CR, Wong C, Wang ZI, Chen X, Wu G, Alexopoulos AV, et al. Optimizing SPECT SISCOM analysis to localize seizure-onset zone by using varying z scores. Epilepsia 2013;54:793–800.
O'Brien TJ, So EL, Mullan BP, Cascino GD, Hauser MF, Brinkmann BH, et al. Subtraction peri-ictal SPECT is predictive of extratemporal epilepsy surgery outcome. Neurology 2000;55:1668–77.
Okada YC, Lahteenmaki A, Xu C. Experimental analysis of distortion of magnetoencephalography signals by the skull. Clin Neurophysiol 1999;110:230–8.
Otsubo H, Ochi Ayako, Elliott I, Chuang SH, Rutka JT, Jay V, et al. MEG predicts epileptic zone in lesional extrahippocampal epilepsy: 12 pediatric surgery cases. Epilepsia 2001;42:1523–30.
Palmini A, Najm I, Avanzini G, Babb T, Guerrini R, Foldvary-Schaefer N, et al. Terminology and classification of the cortical dysplasias. Neurology 2004;62:S2–8.
RamachandranNair R, Otsubo H, Shroff MM, Ochi A, Weiss SK, Rutka JT, et al. MEG predicts outcome following surgery for intractable epilepsy in children with normal or nonfocal MRI findings. Epilepsia 2007;48:149–57.
Schneider F, Alexopoulos AV, Wang Z, Almubarak S, Kakisaka Y, Jin K, et al. Magnetic source imaging in non-lesional neocortical epilepsy: additional value and comparison with ICEEG. Epilepsy Behav 2012;24:234–40.
Schneider F, Wang ZI, Alexopoulos AV, Almubarak S, Kakisaka Y, Jin K, et al. Magnetic source imaging and ictal SPECT in MRI-negative neocortical epilepsies: additional value and comparison with intracranial EEG. Epilepsia 2013;54(2):359–69.
Schwartz TH, Spencer DD. Strategies for reoperation after comprehensive epilepsy surgery. J Neurosurg 2001;95:615–23.
Siegel AM. Presurgical evaluation and surgical treatment of medically refractory epilepsy. Neurosurg Rev 2004;27:1–21.
Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol 2008;7:525–37.
Sulc V, Stykel S, Hanson DP, Brinkmann BH, Jones DT, Holmes DR, et al. Statistical SPECT processing in MRI-negative epilepsy surgery. Neurology 2014;82:932–9.
Surges R, Elger CE. Reoperation after failed resective epilepsy surgery. Seizure 2013;22:493–501.
Wetjen NM, Cascino GD, Fessler AJ, So EL, Buchhalter JR, Mullan BP, et al. Subtraction ictal single-photon emission computed tomography coregistered to magnetic resonance imaging in evaluating the need for repeated epilepsy surgery. J Neurosurg 2006;105:71–6.