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Linking MRI Postprocessing with Magnetic Source Imaging in MRI-negative Epilepsy

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Abstract

Objective—MRI-negative (MRI–) pharmacoresistant focal epilepsy (PFE) patients are most challenging for epilepsy surgical management. This study utilizes a voxel-based MRI postprocessing technique, implemented using a morphometric analysis program (MAP), aiming to facilitate detection of subtle focal cortical dysplasia (FCD) in MRI– patients. Furthermore, the study examines the concordance between MAP-identified regions and localization from magnetic source imaging (MSI).

Methods—Included in this retrospective study were 25 MRI– surgical patients. MAP was performed on T1-weighted MRI, with comparison to a normal database. The pertinence of MAP+ areas was confirmed by MSI, surgical outcome and pathology. Analyses of MAP and MSI were performed blindly from patients' clinical information and independently from each other.

Results—The detection rate of subtle changes by MAP was 48% (12/25). Once MAP+ areas were resected, patients were more likely to be seizure-free ($p = 0.02$). There were no false positives in the 25 age-matched normal controls. Seven patients had a concordant MSI correlate. Patients in whom a concordant area was identified by both MAP and MSI had a significantly higher chance of achieving a seizure-free outcome following complete resection of this area ($p = 0.008$). In the 9 resected MAP+ areas, pathology revealed FCD type IA in 7 and type IIB in 2.

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Interpretation—MAP shows promise in identifying subtle FCD abnormalities and increasing the diagnostic yield of conventional MRI visual analysis in presurgical evaluation of PFE. Concordant MRI postprocessing and MSI analyses may lead to the noninvasive identification of a structurally and electrically abnormal subtle lesion that can be surgically targeted.

Keywords

epilepsy; MRI; presurgical evaluation; image processing; MRI-negative epilepsy; voxel-based morphometric MRI postprocessing; magnetoencephalography; MEG; MSI; focal cortical dysplasia

Introduction

MRI-negative (MRI–) pharmacoresistant focal epilepsy (PFE) patients constitute one of the most challenging and cost-intensive groups for epilepsy surgical management.¹⁻³ Lack of an MRI-visible lesion is an important determinant of surgical failure.^{4, 5} Focal cortical dysplasias (FCD) represent the most common pathological substrate of neocortical PFE^{6, 7} and are often difficult to delineate by conventional MR imaging. Up to 25%-30% of pathologically verified FCD is not visible on preoperative MRI, even with high-resolution dedicated epilepsy MRI protocols reviewed by expert neuroradiologists.⁸⁻¹⁰

Many advanced image processing strategies have been investigated to improve the detection of subtle cortical abnormalities in the epileptogenic zone that might escape conventional visual analysis.¹¹ These strategies include curvilinear reformatting of 3D MRI,¹²⁻¹⁴ texture analysis,¹⁵⁻¹⁷ quantitative voxel-based intensity analysis,¹⁸⁻²⁰ cortical thickness analysis,²¹ sulcal morphometric analysis²² and quantification of gray and white matter distribution by voxel-based morphometry.²³⁻²⁹ Among them, a voxel-based MRI morphometric analysis program (MAP), implemented using parametric mapping software (SPM), has been used to detect subtle cortical malformations with a high degree of sensitivity.³⁰⁻³² In practice, MAP directs the reader's attention to suspicious brain regions, on the basis of abnormal gray-white junction blurring, abnormal cortical gyration, or abnormal cortical thickness. These features, particularly the blurred gray-white matter junction, are common accompaniments of FCD.³³ As a first step, our study aims to investigate the ability of MAP to identify subtle FCD in a well-defined group of MRI– PFE patients.

MAP relies purely on analysis of structural images; therefore subtle changes highlighted by MAP are in principle nonspecific in terms of their epileptogenicity. Hence, it is essential to confirm the epileptogenicity of MAP+ changes by electrophysiological means. Magnetic Source Imaging (MSI) is a noninvasive modality that not only has temporal and spatial resolution approaching that of intracranial EEG, but also provides a “broad” view of whole-head activities.^{34, 35} In this study, we elected to investigate, as a second step, the concordance of MAP+ changes with MSI localization to improve noninvasive identification of subtle FCDs. We hypothesize that the co-localization of concordant MAP and MSI abnormalities will lead to better identification of the epileptogenic focus, which is most likely associated with an underlying FCD. We further hypothesize that complete resection of such MSI/MAP+ area associates positively with seizure-free outcome.

Patients and Methods

Study Design and Presurgical Evaluation

This study was designed to be retrospective. MAP was not previously available and therefore did not influence the preoperative hypothesis or surgical decision-making. Analysis of MAP and MSI was performed blindly from patients' clinical information and independently from each other. The strategies for intracranial EEG (ICEEG) implantation were discussed during a multidisciplinary patient management conference (PMC) based on a variety of clinical diagnostic modalities including MRI, video scalp-EEG, FDG-PET, subtraction ictal SPECT coregistered with MRI (SISCOM), and MSI. MRI scans were performed with Siemens scanners (Erlangen, Germany) and interpreted by a dedicated neuro-radiologist as well as the epilepsy team at PMC. Scalp-EEG monitoring was performed using the international 10-20 system of electrode placement including anterior temporal electrodes and sphenoidal electrodes if appropriate. FDG-PET scans were performed on Siemens Biograph PET CT (Munich, Germany). Scans were coregistered to the volumetric MRI and visual analysis was performed by a nuclear medicine physician. SPECT images were acquired on a Siemens (Erlangen, Germany) Symbia dual-head camera. The interictal image was subtracted from the ictal image and analyzed following methodology of SISCOM.³⁶ According to the consensus hypothesis of epilepsy localization at PMC, intracranial EEG studies were performed using a combination of subdural grid arrays and strip electrodes, or stereotactic-EEG depth electrodes. In all our patients, the type and extent of resection was recommended during a second PMC, after reviewing results of the invasive evaluation and functional mapping. Detailed methodologies can be found elsewhere.³⁷⁻³⁹

Patient Selection

We identified patients by reviewing electronic medical records over a 3-year period (2008-2011) since MSI became available at our center. Institutional review board approval was obtained. Patients were included if they: (1) underwent preoperative magnetoencephalography (MEG); (2) had a pre-operative 1.5 or 3-Tesla MRI with T1-weighted Magnetization Prepared Rapid Acquisition with Gradient Echo (MPRAGE) sequence; (3) were considered MRI- prior to surgery, and (4) underwent a postoperative MRI and had more than 12 months of postsurgical follow-up. All preoperative MRI scans had been evaluated prospectively by dedicated epilepsy neuroradiologists for possible epileptogenic abnormalities, and were re-reviewed by neuroradiologists and epilepsy neurosurgeons during PMC, paying special attention to the areas indicated by results of noninvasive testing. For a strictly defined MRI- cohort, we only selected patients who were still considered MRI- after the two-step reviewing process. Patients were excluded if they were less than 5 years old and/or had poor image quality.

MRI Postprocessing

MAP was carried out in SPM (Wellcome Department of Cognitive Neurology, London, UK) in MATLAB 2007a (MathWorks, Natick, Massachusetts) following previously published methods.^{30, 31} MAP was performed on T1-weighted MPRAGE images. The majority of patients (22 of 25) underwent MRI acquisition using a 3T Siemens Trio scanner (Erlangen,

Germany); the remaining 3 patients (P15, P18, and P24) had MRI acquired using 1.5T Siemens Avanto scanner (Erlangen, Germany). Sequence parameters at 3T were repetition time = 1,860 milliseconds, echo time = 3.4 milliseconds, inversion time = 1,100 milliseconds, flip angle = 10 degrees, band width = 130kHz, slice thickness = 0.94mm, no gap, and a 256×256 matrix providing isotropic voxels of 0.94mm. Sequence parameters at 1.5T were repetition time = 11 milliseconds, echo time = 4.6 milliseconds, no inversion, flip angle = 20 degrees, band width = 130kHz, slice thickness = 1.25 mm, no gap, and a 256×256 matrix providing 0.9mm in-plane resolution. For patients with 3T MRI, we used a database comprised of 90 normal controls (41 females, 49 males, mean age 42.0 years, range 22–80 years), whose MRIs were acquired on the same 3T Siemens Trio scanner using the same MPRAGE sequence as the patients. For patients with 1.5T MRI, we used an average normal database of 150 controls, 70 females, 80 males, mean age 30.9 years, range 15–77 years, with MRIs acquired on five different MRI scanners (1.5T and 3T), which was kindly provided to us along with the MAP program.³¹ The computed output consists of three volumetric statistical maps, namely the junction, extension, and thickness z-score images. All three images highlight in each individual patient brain structures deviating from the average normal brain, and may therefore correlate with the presence of subtle features of FCD on the corresponding MRI. The junction image is sensitive to blurring of the gray-white matter junction; the extension image is sensitive to abnormal gyration and extension of gray matter into white matter; the thickness image is sensitive to abnormal cortical thickness.³¹

MAP was performed by ZIW who was blinded to the patient's clinical and imaging information. Candidate MAP+ regions are those with significant deviation from the standard brain on the junction image (z-score >4), the extension image (z-score >6), or the thickness image (z-score >4). With guidance from MAP findings, a board-certified neuroradiologist (SEJ) conducted a focused re-review of the pre-surgical clinical MRI, blinded to the patient's clinical and surgical information, to assess for the presence or absence of a subtle but visually-identifiable structural change concordant with each candidate MAP+ region. In addition to the T1-weighted MPRAGE data, the neuroradiologist also reviewed images from T2-weighted fluid-attenuated inversion recovery (FLAIR) and T2-weighted turbo spin-echo (TSE) sequences. Image parameters at 3T were: coronal FLAIR, slice thickness = 3mm, gap = 0.6mm, 0.82mm in-plane resolution; axial FLAIR, slice thickness = 3mm, no gap, 0.66mm in-plane resolution; coronal TSE, slice thickness = 3mm, gap = 0.6mm, 0.28mm in-plane resolution. Image parameters at 1.5T were: coronal FLAIR, slice thickness = 4mm, gap = 0.8mm, 0.88×0.70 mm in-plane resolution; axial FLAIR, slice thickness = 4mm, gap = 0.8mm, 0.94×0.70 mm in-plane resolution; coronal TSE, slice thickness = 4mm, gap = 0.8mm, 0.70×0.56 mm in-plane resolution. A candidate MAP+ region was considered positive if the location correlated with a visible abnormality on the original MRI. Such abnormalities include the standard findings of FCD, such as indistinction of gray-white junction, T2/FLAIR signal abnormality, T1 signal abnormality, abnormally thickened cortex, or subcortical T2/FLAIR abnormality extending along a migrational line. To minimize subjectivity, SEJ applied a consistent 5 point scale to rate the abnormality in each patient: 1: nothing; 2: unlikely; 3: ambiguous; 4: possible; 5: most likely. Only abnormalities with ratings ≥ 3 were regarded as MAP+. Examination of the MAP and MRI studies was

based on visual inspection alone without using automated detection algorithms. MAP+ regions caused by signal inhomogeneities due to technical reasons and nonspecific white matter lesions were not reviewed.

False Positive Analysis with Normal Controls

To perform false positive analysis, 25 normal controls were chosen that were age and gender matched to the 25 patients in this study. The control subjects were free of any neurological diseases, with mean age of 30.5 years (range 22 to 58 years). Control studies were intermixed with patients, i.e., the reviewers were blinded to the study group (patient or control). Controls were reviewed with the same methodology as described in the previous section.

Magnetic Source Imaging (MSI)

MSI analysis was performed without prior knowledge of the clinical history, EEG or imaging findings. MEG data was recorded from a 306-channel whole-head MEG system (Elekta, Helsinki, Finland; sampling frequency = 1000Hz; band-pass filtered between 0.03 Hz and 330 Hz), and source localization analysis was performed using vendor software. Individual spike analysis was performed on data segments containing visually identified epileptiform discharges.⁴⁰ The location, orientation, and strength of dipole sources that best fit the measured magnetic fields were calculated using single equivalent current dipole model at the peak of the global field power of each interictal activity.^{41, 42} The final output is represented by one or several clusters of dipoles superimposed on the patient's coregistered MRI.

Surgical Outcome and Pathology

Surgical outcome at 12 months was classified into two groups with modified Engel's classification: completely seizure-free (Engel's class Ia) and not seizure-free (Engel's class Ib – IV).⁴³ Histopathological specimens were retrospectively reviewed by a pathologist (RAP) and FCD was classified according to the Palmini et al. classification.⁴⁴ Positive pathology is defined by finding of FCD, heterotopia, or hippocampal sclerosis.

Concordance Analysis and Statistics

Concordance of MAP and MSI localization, as well as completeness of resection, was determined on a sublobar level. Sublobar regions of the neocortex were defined using a common classification scheme,⁴⁵ specifically including the following regions: frontopolar, dorsolateral frontal (superior), dorsolateral frontal (inferior), mesial frontal, anteroparietal, posteroparietal (superior), posteroparietal (inferior), mesial parietal, lateral occipital, mesial occipital, temporopolar, lateral temporal, mesial (neocortical) temporal, anterior insular, posterior insular, anterior cingulate, posterior cingulate and central. MAP+ and MSI were considered as concordant if both modalities implicated the same sublobar region. In cases where MAP+ and MSI involved > one sublobar location, we considered the overlapping region as the concordant region. We considered results as congruent with the surgical resection if the sublobar regions identified by MSI or MAP were contained within the area of resection determined by postoperative MRI. For each test (MAP, MSI, MAP+MSI),

association with seizure outcome was performed for the complete or incomplete resection of the identified areas. The data was considered to have a binomial distribution. Statistical significance was assessed using the Fisher's exact test, with significance defined as p value 0.05.

Results

Patient Demographics

A total of 227 consecutive patients were screened from the MEG database; 77 (34%) had negative MRI. Forty-eight (62%) of these patients underwent surgical resections. Twenty-five patients fulfilled all the inclusion requirements. Mean age at time of surgery was 29 years ($SD \pm 14$, range 10–59), and mean duration of epilepsy 16 years ($SD \pm 12$ years, range 2–46 years). There were 10 temporal lobe resections (40%), 5 frontal lobe resections (20%), 3 parietal lobe resections (12%) and 7 multi-lobar resections (28%). Fourteen patients (56%) were seizure-free at 12 months follow-up. Relatively early recurrence of seizures was seen in the remaining 11 patients (within 3 months in 8 and within 6 months in 3 patients). Detailed demographics and pre-surgical evaluation information can be found in Supplementary Table 1.

Twenty-four out of the 25 patients underwent ICEEG monitoring. In this cohort there was no significant correlation between complete removal of ICEEG onset zone and surgical outcome ($p > 0.9$). Positive pathology (included in Supplementary Table 2) and surgical outcome were not significantly correlated ($p = 0.24$).

MAP Detection Rate

Detailed localization information of MAP and MSI for each patient is included in Supplementary Table 2. MAP was positive in 12 patients, for a detection rate of 48%. All 12 MAP+ patients are presented in Figures 1 through 4. Three patients (12%) exhibited MAP+ changes in two non-adjacent locations. All MAP+ regions were detected by visual analysis of the junction file; only 3 patients exhibited associated changes on the corresponding extension file (P8, P12, and P21). No MAP+ region was identified by isolated review of the extension or thickness file. All MAP+ regions were found in retrospect to have subtle blurring of gray-white matter junction in the original T1 image; only 5 had accompanying minimal FLAIR signal changes (P8, P14, P15 region 1, P21 region 2, and P25 region 1).

Supplementary Table 3 shows the number of candidate MAP+ areas (junction file z-score > 4) reviewed and the number of areas judged to be MAP+. Overall, 11 patients had only one area reviewed and 7 were determined MAP+. Ten patients had > 1 region reviewed: in 2 patients, one region was judged to be MAP+; in 3 patients, two regions were determined MAP+; in the remaining 5 patients, all regions were deemed non-significant.

False Positive Rate in Normal Controls

All 25 subjects in the control group were correctly classified as MAP-. Only 2 subjects had z-score > 4 areas on the junction image. In one subject, the area was deemed non-significant;

in the other subject, the areas highlighted by the junction image were at the posterior horns of the lateral ventricles bilaterally, and were felt to represent normal myelination.

Correlation of MAP, Resection and Outcome

Nine out of the 12 MAP+ (75%) were seizure-free at 12 months, whereas 5 out of the 13 MAP- patients (38%) became seizure-free. Although MAP+ patients tended to have better seizure outcome compared with MAP- patients, the difference was not significant ($p = 0.11$).

Six out of 11 MAP+ patients had the MAP+ region completely resected; all 6 patients became seizure-free (P1, P4, P8, P14, P19, P24, Figures 1 and 2). Three patients (P15, P21, P25, Figure 3) exhibited two nonadjacent MAP+ areas; with only one of the two areas completely resected, these three patients remained seizure-free. In P12, P18 (Figure 2) and P9 (Figure 4), MAP+ regions were not resected; these patients had immediate seizure recurrence. Comparing the group of patients who had the MAP+ region completely resected versus the rest of the cohort, we found a significant correlation between complete resection of MAP+ region and seizure-free outcome ($p = 0.02$). MAP by itself had positive predictive value (PPV) of 100% and negative predictive value (NPV) of 58%.

Correlation of MSI, Resection and Outcome

Fifteen out of 25 patients had one dipole cluster; 8 patients had multiple (2 or more) dipole clusters; two patients had negative studies (no interictal abnormalities recorded). Ictal events were recorded and localized in 3 patients (P2, P12 and P17). Details of the MEG results and example patients are shown in Supplementary Table 2 and Figure 5.

The area localized by MSI was completely resected in 11 patients, 9 of whom became seizure-free. Of the 14 patients who had incomplete or no resection of the MSI localized area, or had negative MSI, only 5 remained seizure-free. Comparing the group in which the MSI localized region was completely resected versus the rest of the cohort, we found a significant ($p = 0.04$) correlation with seizure-free outcome. MSI by itself had PPV of 82% and NPV of 64%. When compared with MSI, interictal and/or ictal scalp EEG provided localizing information in 9/25 patients, only at the lobar level, which was inferior to MSI (15 sublobar localization).

Correlation of MAP, MSI, Resection and Outcome

A concordant MSI correlate was found in 8 out of 11 MAP+ patients (P1, P4, P8, P14, Figure 1; P15, P21, P25, Figure 3; P9, Figure 4). Detailed information on the concordant sublobar areas can be found in Supplementary Table 2. The areas localized by MSI always encompassed the region of concordant MAP+ areas. In patients with two nonadjacent areas of MAP+ change, only the MAP+ area with an MSI correlate was resected. The concordant MSI/MAP+ region was completely resected in 7 patients, all of whom became seizure-free. Of the 18 patients who had incomplete or no resection of the MSI/MAP+ co-localized area, or had negative studies, only 7 were seizure-free. Comparing the group in which the concordant MSI and MAP+ region was completely resected versus the rest of the cohort, we found a significant ($p = 0.008$) correlation with seizure-free outcome. MSI/MAP+

conjunctively had PPV of 100% and NPV of 61%. Compared with MSI, scalp-EEG was concordant with MAP in far fewer patients (only 2). Supplementary Table 4 summarizes true positive / true negative / false positive / false negative rates for MAP and MSI, alone and combined.

MAP and Pathology

Examples of pathological findings are shown in Figure 6. Assisted by MAP, we were able to correctly recognize 7 out of the 13 pathologically-confirmed FCD type I lesions, plus 2 subtle FCD type IIB lesions. Surgical pathology was negative in the 3 MAP+ patients in whom the MAP+ area had not been resected. Of the 13 MAP- patients, 4 had FCD IA (one was seizure-free), 2 had FCD IB (none of them became seizure-free), 6 showed gliosis (3 were seizure-free), and one had no identifiable histopathological abnormalities (seizure-free).

Discussion

Our study aims to investigate the usefulness of combining an image processing method (MAP) with an electrophysiological measure (MSI) to identify subtle cortical dysplasia in patients with negative pre-surgical MRI. The clinical impetus for this work comes from a pressing need to enhance and improve the yield of the presurgical *noninvasive* evaluation in the most challenging group of patients with MRI- PFE.

The most important finding from our study is that complete resection of the MAP+ region was significantly associated with a seizure-free outcome, and a high PPV. When multiple MAP+ regions were present, an MSI correlate provides excellent electrophysiological confirmation of the epileptogenic relevance. Patients whose resections did not include the MAP/MSI+ region had seizures recurring immediately post-operatively, possibly indicating a missed epileptogenic zone.^{46, 47} Consistent with our hypothesis, these observations suggest that the approach of linking MAP and MSI findings provides strong anatomo-electrical indication of an underlying “MRI-occult” epileptogenic focus which could be targeted more confidently, and therefore this strategy may contribute to improved surgical outcomes.

Sensitivity of MAP

It is not surprising that MAP, especially its gray-white junction output, is sensitive to subtle FCD lesions that can escape conventional MRI visual analysis. FCD has been demonstrated as the most common pathology underlying MR- epilepsies,⁴⁸ and among common imaging characteristics of FCD, gray-white matter junction blurring occurs most frequently.^{33, 49} Consistent with the published literature,^{30, 32} we found the gray-white junction file to be the most helpful feature map. Others have reported that the extension file by itself can also uniquely identify some subtle lesions,³² but our analysis of this cohort did not support this observation. We emphasize that it is important to reformat in different planes and perform a focused re-examination of the original MRI for the presence or absence of a subtle plausible lesion. This practice may substantially help reduce the number of false positive findings. Although the detection rate and diagnostic yield of MAP have been reported to be higher for

3T MRI studies than 1.5T,³² all three patients with 1.5T MRI included in our study happened to be MAP+.

Our findings are in-line with previous studies, although most investigated mainly patients with MRI-visible (MRI+) lesions and pathologically confirmed FCD. In a 2005 retrospective study of 25 patients with histologically confirmed FCD, MAP was able to detect all MRI-identifiable lesions as well as 4 MRI- lesions.³⁰ In a 2011 retrospective study of 91 patients with confirmed FCD type II, MAP increased the detection rate of MRI visual analysis from 65% to 82% in FCD type IIa. When combined with conventional visual analysis, MAP identified 98% of all pathologically-confirmed FCD type II lesions.³² Our choice of z-score threshold is also consistent with the literature,⁵⁰ although optimization of z-score for lesion detection and delineation should be provided by further studies.

Epileptogenicity of MAP+ Areas

MAP is purely a structural image processing technique which does not provide any electrical or functional information. High-z-score areas on the gray-white feature map may be spurious/artifactual or electrographically silent and/or completely unrelated to the epilepsy.⁵¹ To advance the field of noninvasive investigations in patients with MRI- epilepsies, MAP and other MRI postprocessing techniques will need to be combined with noninvasive modalities that can characterize the pathophysiological features of suspicious imaging findings. At present, noninvasive neurophysiological techniques, including EEG and MEG, remain the cornerstone of presurgical evaluation. The shortcomings of scalp EEG in the presurgical investigations of MRI- epilepsy patients have been well recognized in the literature.^{52, 53} Despite its own shortcomings related to cost, and brevity of recording, MEG has better localization abilities as compared to scalp EEG, in part due to a combination of simpler source modeling parameters⁵⁴ and more sensor coverage. For these reasons, in this study we utilized MSI to provide noninvasive electrophysiological confirmation of epileptogenicity at the sublobar level when MAP indicates a possible region of concern.

Only a small number of previously published studies reported on correlation of MAP and MSI in epilepsy patients. A recent case series reported on 3 peri-insular epilepsy patients; two were MAP+ and had concordant MSI localization. Both patients were rendered seizure-free after removal of the MSI/MAP+ concordant area.⁵⁵ A 2011 study reported on 51 patients with MRI- epilepsy and a suspected unilobar focus.⁵⁶ The authors compared the sensitivity of MAP, MSI, SPECT and PET based on the unilobar focus hypothesis. MAP was reported to show 24% sensitivity and 96% specificity. MSI was found to have a sensitivity of 62%. Unfortunately, not all patients underwent surgery; therefore pathology and outcome information was not available. A limitation of this and some previous studies is that semiology and scalp-EEG monitoring results, rather than surgical outcome, were used to define the “true” ictal onset zone,^{19, 56} which may be a justifiable approach for more “straightforward” cases, but has significant limitations when applied to the more complex MRI- patients.

Other noninvasive, indirect measures of focal epileptogenicity, such as FDG-PET or ictal SPECT, may also be useful to confirm the potential epileptogenicity of subtle structural abnormalities.⁵⁷⁻⁵⁹ Additional diagnostic gain may be achieved with addition of either PET

or ictal SPECT to MSI.^{60, 61} In this cohort, the yield of these nuclear imaging modalities appeared to be lower compared to MSI. However, one should note that expertise in noninvasive approaches varies from center-to-center. Therefore, further studies combining MAP with advanced analysis of PET and SISCOM are warranted.

Intracranial EEG evaluation is intuitively the most direct approach to confirm the relevance of MAP+ changes.^{30, 31, 51} However, it is not always possible to record from the vicinity of MAP+ regions, unless implantation is planned prospectively to explicitly target these changes. As our study shows, when sampled by the implanted invasive electrode, the majority of the MAP+ areas correlated with the epileptogenic region; however in some patients the electrophysiological significance and histopathology of the MAP+ region could not be confirmed as it had not been sampled. In retrospect, in P9, 12 and 18 (patients in whom seizures recurred), the MAP+ areas might have led to placement of additional intracranial electrode, and as a result could have increased the patients' chances to become seizure-free.

Multiple MAP+ regions

The presence of multiple MAP+ regions in some patients is an uncommon but intriguing finding, and our results are consistent with literature.^{15, 19, 51} In the absence of a noninvasive electro-functional correlate such as MSI, direct invasive targeting of any MAP+ regions would be necessary to look for evidence of current epileptogenicity. Whether these additional MAP+ regions represent non-specific changes, or perhaps a dormant epileptogenic focus is a question that can only be answered by long-term follow-up of such patients, as well as future prospective studies in which MAP results are included in the pre-implantation discussion.

MAP-negative Patients

The MAP- cases may indicate a need for higher resolution analysis, or more likely, illustrate that MAP cannot uncover all pathologies underlying MRI- epilepsies. MAP- patients can still be rendered seizure-free (patients 2, 10 and 23). Some MAP- patients did have type I FCD in their surgically resected specimens (patients 2, 3, 5, 7, 20 and 22). Type I FCD lesions have highly idiosyncratic presentations, show more diffuse epileptogenicity and exhibit worse surgical outcomes (as compared to type II lesions), making them the most challenging to presurgical evaluation.^{33, 49, 62, 63} Our findings imply that our current MAP analyses only uncovers those type I FCDs associated with T1-weighted changes caused by blurring of gray-white-matter junction, and to a lesser degree alteration of gyration pattern, or cortical thickness. Morphometric analysis of T2-weighted MRI volume data may provide additional information for visualizing subtle FCD.⁶⁴

Using MAP and MSI to Assist Epilepsy Surgery

At present, confirmation of seizure onset zone in MRI- PFE patients relies mainly on ICEEG. Inherent limitations of ICEEG include the fact that it must be hypothesis-driven, and suffers from major spatial limitations, as the “optimal” placement of the relatively small number of implanted electrodes can not provide complete and comprehensive coverage of the brain for obvious practical reasons. Our study suggests that when a suspicious MAP+

area exists, it would lead to a stronger pre-implantation hypothesis, and subsequently the implantation and surgical strategy can be significantly optimized. Outcomes are also likely to be improved since it is already known that the unequivocally lesional (MRI+) surgical candidates do have a two times higher probability of attaining seizure-free outcomes.¹⁰ For these reasons the finding of a concordant MSI/MAP+ area can become an important determinant of accurate ICEEG/epilepsy localization and seizure-free outcome in the challenging cohort of MRI- PFE.⁵⁰

The observed high PPV of MSI/MAP, if replicated in future prospective studies, may be useful in predicting outcome in MRI- surgical candidates. In addition, accurate identification of a small FCD by MSI/MAP or MAP alone may lead to more limited resection and less invasive testing. Patient 15, for example, would have gone through invasive monitoring because it was not clear from her scalp EEG whether her seizures originated from the frontal or temporal lobe. With concordant MSI and FDG-PET, resection of the non-dominant temporal lobe was performed without invasive monitoring. In retrospect, MAP results could have provided an additional structural correlate, thus strengthening clinical confidence and perhaps allowing for a more tailored resection in this patient.

In general, patients with MRI- PFE are not considered favorable surgical candidates, and may not even be referred for presurgical evaluation. Moreover, their preoperative testing is usually reserved for quaternary epilepsy centers. This existing gap in offering surgical therapy to MRI- PFE cannot be overstated.⁶⁵⁻⁶⁷ Enhancing the yield of noninvasive testing is paramount given that some MRI- patients, who are found to have concordant MSI/MAP+ results, may eventually be regarded as more favorable candidates and be offered potentially curative epilepsy surgery.

Limitations

1. Our study is inherently limited by its retrospective nature. Although this is the largest consecutive series to date to evaluate the usefulness of MAP and MSI in a MRI- cohort, the included patients were still highly selected and one should be cautious about generalizing the study findings to all pre-surgical candidates.
2. One should note that MSI was used clinically during the surgical decision making process, while MAP data was generated and analyzed retrospectively; therefore comparison of the independent localizing significance of MSI and MAP results should be interpreted with caution.
3. Most of the MSI studies were performed during the interictal periods, an inherent limitation of MEG. It is possible that some of the MSI- MAP+ areas would have had MSI correlates, if we had recorded MEG long enough, or ICEEG correlates if these areas were targeted.
4. Five patients were of ages younger than those included in the control databases (P8, 9, 22, 23 and 24, 10-14 years old). Although in 3 of these patients, MAP+ regions were still uncovered, one should note that there can be structural differences in younger brains (especially in cortical thickness) as compared to mature brains.

Currently, we are in the process of acquiring additional younger normal brain controls to incorporate into the normal database.

5. With the current methodology, confirmation of the MAP+ area still relies on the review of an experienced neuroradiologist; therefore there is a need for an automated statistical thresholding method using which the sensitivity/specificity of MAP can be better controlled across multiple sites.
6. Lastly, it should always be remembered that surgical resection is based on a number of factors that cannot be standardized, and the seizure onset zone cannot always be resected in its entirety for practical reasons, such as overlap with eloquent cortex.⁶⁸ Therefore, for those patients who were not completely seizure-free, imaging localization may not necessarily be incorrect.

Conclusions

Improving noninvasive localization is paramount in MRI-negative pharmacoresistant focal epilepsies. As a low-cost and noninvasive MRI postprocessing approach, MAP shows promise in identifying subtle FCD abnormalities, and thus increasing the diagnostic yield of conventional MRI reading in any epilepsy center utilizing a standardized epilepsy protocol on a 1.5T or 3T scanner. Concordant MRI postprocessing and MSI analyses may lead to the noninvasive identification of a structurally and electrically abnormal subtle lesion that can be surgically targeted. Complete resection of the MSI/MAP+ area likely leads to a favorable seizure outcome. It is our hope that retrospective studies like ours will pave the way for more definitive prospective investigation on a large number of patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

FLAIR	fluid-attenuated inversion recovery
FCD	focal cortical dysplasia
MAP	morphometric analysis program
MRI	magnetic resonance imaging
PFE	pharmacoresistant focal epilepsy
ICEEG	intracranial EEG
MSI	magnetic source imaging
MEG	magnetoencephalography

Figure 1.

Four MRI- patients with concordant MAP and MSI findings. In Figures 1-4, the crosshairs pinpoint the location of MAP+ regions. First and second columns: patient's conventional high-resolution T1-weighted and FLAIR images used during pre-surgical evaluation. Third column: gray-white matter junction z-score file as output of MAP, coregistered with the patient's T1-weighted MRI. Fourth column: composite image of MSI single-dipole source localization results, with each dipole representing a single epileptiform spike captured during MEG recording. Fifth column: post-surgical MRI coregistered with pre-surgical MRI, indicating site and extent of resection. All four cases demonstrate complete resection of the MAP/MSI concordant abnormalities. All four patients remained seizure-free.

Figure 2.

Four MRI- patients with discordant MAP and MSI findings. In P19 and P24, surgical resection (based on ICEEG evaluation) included the MAP+ area and patients became seizure-free. The MSI localized areas were not included in the resection. In P18 and P12, the area implicated by MSI was resected. The discordant MAP+ area was not included in the resection. Both patients had recurring seizures. Note that P12 did not have preoperative FLAIR sequences available, and therefore FLAIR image is not shown in this Figure.

Figure 3.

Three MRI- patients with dual nonadjacent MAP+ changes. MSI localization is concordant with only one of the two MAP+ areas in each patient. The concordant MAP+ area had been resected in its entirety. The other nonadjacent MAP+ area was not included in the resection. All patients became seizure-free.

Figure 4.

One MRI- patient with concordant MAP and MSI findings in whom seizures recurred immediately after surgical resection. Lobar concordance of MAP and MSI was observed in this patient. Surgery was directed to the parietal lobe based on results of ICEEG, and did not include the frontal lobe regions implicated by MAP and MSI.

Figure 5.

Example of MAP- but MSI+ patients and their corresponding surgical resection. In P2, surgical resection completely included the MSI localized sublobar area, and this patient was seizure-free. P22 exemplifies a patient whose surgical resection did not include all the MSI localized areas, and this patient had recurring seizures.

Figure 6. Surgical pathology in resected MAP+ areas (hematoxylin and eosin staining; 200× magnification). A: FCD type IA (P15); B: FCD type IIB with balloon cells (P14); C: gliosis (P9). Scale bar in the lower left corner of panel C corresponds to 50 microns in length.