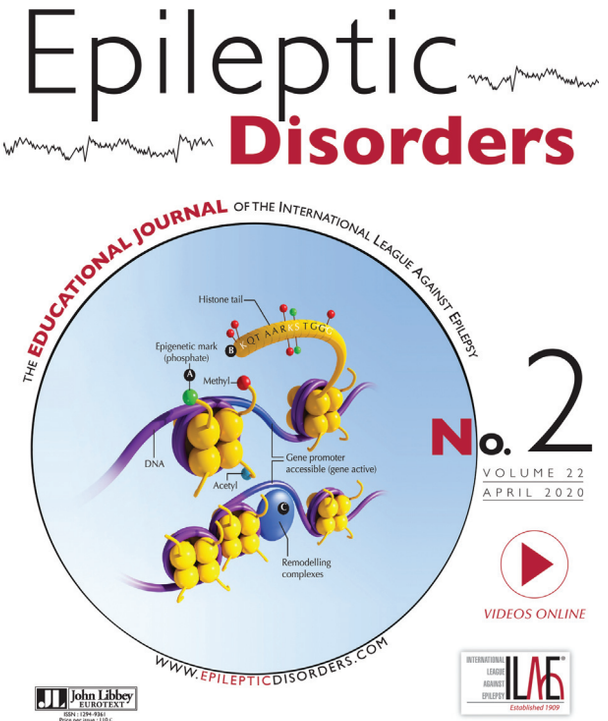

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Additional clinical value of voxel-based morphometric MRI post-processing for MRI-negative epilepsies: a prospective study

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ABSTRACT – *Aims*. Magnetic resonance imaging is of paramount importance in the presurgical evaluation of drug resistant epilepsy. Detection of a potentially epileptogenic lesion significantly improves seizure outcome after surgery. To optimize the detection of subtle lesions, MRI post-processing techniques may be of essential help.
Methods. In this study, we aimed to evaluate the detection rate of the voxel-based morphometric analysis program (MAP) in a prospective trial. We aimed to study the MAP+ findings in terms of their clinical value in the decision-making process of the presurgical evaluation.
Results. We included, prospectively, 21 patients who had negative MRI by visual analysis. In a first step, results of the conventional non-invasive presurgical evaluation were discussed, blinded to the MAP results, in multidisciplinary patient management conferences to determine the possible seizure onset zone and to set surgical or invasive evaluation plans. Thereafter, MAP results were presented, and the change of initial clinical plan was recorded. All MAP detections were reaffirmed by a neuroradiologist with epilepsy expertise. For the 21 patients included, mean age at the time of patient management conference was 26 years (SD 15 +/- years, range: 5-54 years). In total, 4/21 had temporal lobe epilepsy and 17/21 had extra-temporal lobe epilepsy. MAP was positive in 10/21 (47%) patients and in 6/10 (60%) a diagnosis of focal cortical dysplasia was confirmed after neuroradiologist review, corresponding to a 28% detection rate. MAP+ findings had a clear impact on the initial management in 7/10 patients (7/21, 33% of

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all patients), which included an adaptation of the intracranial EEG plan (6/7 patients), or the decision to proceed directly to surgery (1/7 patients).
Conclusion. MRI post-processing using the MAP method yielded an increased detection rate of 28% for subtle dysplastic lesions in a prospective cohort of MRI-negative patients, indicating its potential value in epilepsy presurgical evaluation.

Key words: voxel-based morphometry, morphometric analysis program, refractory epilepsy, epilepsy surgery, non-lesional MRI, pre-surgical evaluation

Magnetic resonance imaging is of paramount importance in the presurgical evaluation of pharmacoresistant epilepsy. Detection of a potential epileptogenic lesion significantly improves outcome after surgery (Bien *et al.,* 2009). Subtle lesions such as focal cortical dysplasia (FCD) type I are missed in up to 30% cases (Bernasconi *et al.,* 2011), which may lead to the mistaken assumption that these patients are not good surgery candidates and consequently might potentially not be referred for epilepsy surgery, especially when the other non-invasive investigations such as scalp electroencephalogram (EEG) and semiology fail to localize. To optimize the presurgical evaluation in non-lesional patients with refractory epilepsy, MRI post-processing techniques are increasingly used to complement visual analysis of MRI in order to reveal structural epileptogenic lesions that were invisible at first visual inspection (Wang *et al.,* 2015; Wang *et al.,* 2016). Voxel-based morphometry (VBM) is an automated technique that extracts grey and white matter maps from individuals to make comparisons with normal control data. The voxel-based morphometric analysis program (MAP) uses the statistical parametric mapping (SPM) platform to detect subtle cortical malformations on the basis of abnormal grey-white junction blurring, abnormal cortical gyration and abnormal cortical thickness, which are common features of FCD (Barkovich *et al.,* 1996; Lee *et al.,* 1998; Besson *et al.,* 2008). MAP is a post-processing method that can be applied to standard MRIs without incurring additional cost or risk for the patient. Based on previous results (Huppertz *et al.,* 2005; Wagner *et al.,* 2011), it has been proposed to integrate MAP analysis into the standard presurgical evaluation to increase the yield of detection of lesions; additionally, MAP has also shown value in confirming subtle lesions that were suspected at multimodal patient management conferences (PMCs) (Wang *et al.,* 2015). However, a prospective study assessing the overall clinical value of MAP in non-invasive presurgical evaluation, examining its interpretation and added value by epileptologists in a real clinical setting, is currently lacking. This is the goal of the current study. We used a blinded intention-to-treat design to prospectively assess 21 patients with refractory focal epilepsy referred for surgery at Cliniques Universitaires Saint Luc to study the impact of MAP results on surgery decision making.

Materials and methods

Study group and study design

Between March 2016 and August 2017, all patients undergoing presurgical evaluation of refractory focal epilepsy with negative MRI were prospectively included in the study after clearance by the local Ethical committee. Inclusion criteria were:
– preoperative 3T MRI with 3D volumetric T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence (TE = 2.98 ms, TR = 2300 ms, TI = 900 ms, resolution = 1.0 x 1.0 x 1.1 mm^3, scan time = 5 min 12 sec) and 3D volumetric T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence (TE = 387 ms, TR = 5000 ms, TI = 1800 ms, resolution = 0.4 x 0.4 x 0.9 mm^3, scan time = 5 min 42 sec);
– and initial MRI read as negative according to the official radiology report before PMC discussion.
Patients were excluded if they:
– presented with an epileptic lesion visible on MRI;
– had poor MR image quality;
– or if they had already undergone intracranial EEG (ICEEG) before the MAP results were discussed.
Surgical outcome was classified according to ILAE classification at six months of follow-up (Wieser *et al.,* 2001). All patients underwent presurgical evaluation that comprised clinical and neurological evaluations, neuropsychological assessment, video-EEG monitoring, structural 3T MRI and positron emission tomography with [18F]-fluorodeoxyglucose. In a first step, evaluation results were discussed, blinded to the MAP results at PMC, to determine the possible seizure onset zone and to set surgical or additional presurgical plans (A. focal resective surgery; B. intracranial EEG [ICEEG]; C. rejected for surgery; D. other additional investigation needed [MEG, ictal SPECT, repetition of scalp video-EEG monitoring, further neuropsychological testing or WADA test]). When ICEEG was planned, anatomical locations of the depth electrodes were determined during the meeting. The MAP analysis

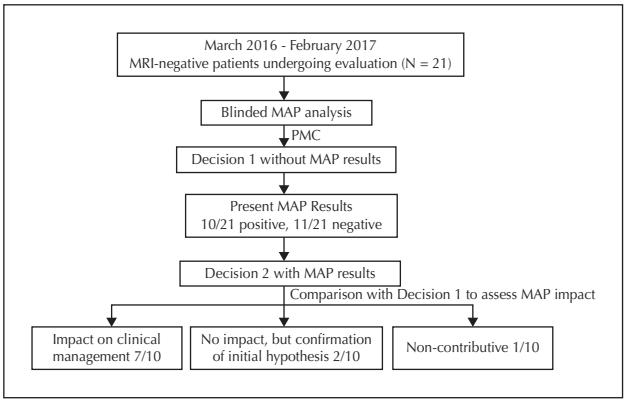

Figure 1. Twenty-one consecutive MRI negative patients were prospectively enrolled in this study. In a first step, results of the conventional non-invasive presurgical evaluation were first discussed blind to the MAP results. In a second step, adding MAP results to the clinical discussion changed the initial management plan in 7 patients.
MAP: morphometric analysis program; PMC: patient management conference.

was blinded to intention-to-treat and performed by ZIW at the Cleveland Clinic Foundation (CCF), who did not participate in any decision-making process for the patients. In a second step, MAP results were presented at PMC, where the surgical/additional presurgical plans, before and after integrating MAP information, were noted and then compared. Changes from the initial management plans were considered relevant when MAP results led to:
– a change in the initial plan (A, B, C or D);
– or a change in the ICEEG planning (*e.g.* additional electrodes).
In a third step, patients were followed to determine the clinical relevance of MAP-based changes in the management plan. The study workflow is shown in *figure 1*.

MRI post-processing

MAP07 was carried out using SPM toolbox (Wellcome Department of Cognitive Neurology, London, UK) in MATLAB 2007a (MathWorks, Natick, MA, USA) following previously established methods (Huppertz *et al.*, 2005; Huppertz *et al.*, 2008). MAP was performed on T1-weighted MPRAGE images. All patients were scanned at Cliniques Universitaires Saint Luc (St Luc) using a standardized epilepsy protocol. The blinded MAP analysis was performed by ZIW at CCF, who did not participate in any clinical decision-making process. The normative database consisted of a 1.5T and 3T average of 150 subjects (70 females, 80 males; mean age at MRI: 30.9 years, range: 15-77 years old), with MRIs acquired on five different MRI scanners, which were provided along with the MAP07 program. The computed output consists of three volumetric statistical maps, called the junction, extension and thickness maps. From previous studies, the junction map seemed to be the most useful to screen negative MRI for eventual lesions (Wang *et al.*, 2015) and was used in the current study. A z score threshold of 4 was used to identify candidate MAP+ regions on the junction file. The reviewer also examined whether there was an accompanying region on the extension file ($z > 6$) and the thickness file ($z > 4$). The choice of z score threshold was consistent with those reported in the literature (Wang *et al.*, 2014; Wellmer *et al.*, 2010). The final MAP result transmitted from CCF to St Luc consisted of a junction file with one or more potential lesions. All candidate MAP+ regions were then addressed by an experienced neuroradiologist (TD) at St Luc, who conducted a corresponding focused re-review of the presurgical clinical MRI. The neuroradiologist was also blinded to the patient's clinical and surgical information. If TD agreed that the conventional MRI showed subtle abnormalities at these sites, the patient was labelled as cMAP+ (confirmed MAP+). TD applied a consistent 5-point scale to rate the abnormality in each patient: 1=nothing; 2=unlikely; 3=ambiguous; 4=possible; and 5=most likely. Features suggesting non-significance were the presence and amount of image noise, such as poor signal, excess motion, and pulsation artefacts. Only abnormalities with ratings > 3 were regarded as cMAP+, while those rejected by the neuroradiologist (*i.e.* ratings < 3) were labelled ncMAP+ (non-confirmed MAP+). MAP- patients included those who had no regions exceeding the z score threshold.

Surgical pathology

FCD was classified according to the International League Against Epilepsy classification (Blumcke *et al.*, 2011). Negative pathology was defined by a finding of gliosis or the absence of any identifiable microscopic/histological abnormalities.

Statistical analysis

When applicable, we used the Fisher exact test to assess the relationship between parameters and seizure outcomes (if $n < 5$).

Results

Demographics and clinical data

A total of 93 patients were presented at PMC between March 2016 and February 2017. From these 93 patients, 22 patients were considered to have initial negative MRI and potentially eligible for surgery and prospectively included in the study. One patient was excluded

Table 1. Summary of non-invasive presurgical evaluation in all patients included in this study.

Pt #	Age (y)	Gender	H	EEG interictal	EEG ictal	MRI	FDG-PET	PLEZ
1	5	M	R	L Fcen, Bil P	L F	N	Hypo L F	L Pre F
2	25	F	R	R F	R T, R P	N	Hypo L T, R O	Non Loc
3	24	M	L	Gen L T	L F	N	N	L Fmes
4	33	M	R	L T	Non Loc	N	Hypo R T	L ParIns
5	6	F	R	Bil P	Non Loc	N	Hypo LT, L P, LF	Non Loc
6	19	M	R	R O	Non Loc	N	N	R PO
7	5	M	R	R Fcen	R Fcen	N	Hypo L Ins	R InsOp
8	31	M	L	R T, L T	R T, R Pmes, R Fmes	N	N	R T
9	54	M	R	R T	Non Loc	N	N	R Fmes, R TPol
10	16	M		Gen, max R F	Gen, max R Fcen	N	N	Cing, Fmes
11	25	M	R	L T	L FT	N	N	LTPol
12	39	M	U	LT	L T	N	Hypo L T, L F	L Fmes, L OF, L TPol
13	5	F	R	N	Non Loc	N	N	R FrontOpIns
14	10	F	R	R P, R F	Gen	N	Hyper R F, R P	R F, R CenPar
15	41	M	R	Bil F	Non Loc	N	N	F
16	14	M	R	Cen	Non Loc	N	N	R Pmes, R Fmes
17	44	F	R	Bil Fmes, LT, Pcen	Bil FOp, POp	N	Hypo L T	L Fmes
18	39	M	R	N	L FCen	N	N	L Cen
19	51	M	R	RT	R T	N	N	R T
20	34	F	R	Bil T	R T, L T	N	N	R T > L T
21	36	M	R	R FT	R FT	N	Hypo R T	R F

Pt: patient; Bil: bilateral; Cen: central; CenPar: centro parietal; Cing: cingular; F: Frontal; Fcen: fronto central; Fmes: frontomesial; FOp: fronto opercular; FrontOpIns: fronto-opercular-insular; FT: frontotemporal; Gen: generalized; Ins: insular; L: left; Non Loc : non localizable; O: occipital; OF: orbitofrontal; P: parietal; Pcen: centro parietal; Pmes: mesial parietal; ParIns: parietal-insular; PLEZ: presumed localization of epileptogenic zone; PO: parieto occipital; POp: parieto-opercular; R: Right; T: temporal; TPol: temporopolar; N: MRI negative.

as she already underwent ICEEG at the beginning of the study. For the 21 patients included, mean age at time of PMC was 26 years (SD 15 +/- years, range 5-54 years). Overall, 4/21 had temporal lobe epilepsy and 17/21 had extratemporal lobe epilepsy. A small percentage of patients underwent resective surgery at the conclusion of our study (5/21). Six of 21 patients were considered ineligible for surgery and a treatment with vagus nerve stimulation (VNS) or deep brain stimulation (DBS) was proposed; these included patients with multifocal seizure onset or inconclusive results from ICEEG evaluation. Several patients had a positive reduction of their seizures after adapting the antiepileptic drug regimen (5/21); one patient remained seizure-fee after ICEEG, likely due to lesional effect of the electrodes (1/21) (Morrell and Halpern, 2016); one (1/21) patient became seizure-free after the resection of a cerebral metastasis which was originally not suspected to be seizure-related. Two patients declined the next steps of further surgical evaluation (*i.e.* ICEEG or ictal SPECT) and one patient was awaiting ICEEG. A summary of presurgical evaluation data can be found in *table 1*.

MAP findings

Candidate MAP+ regions were reported in 10/21 (47%) of patients; 6/10 patients had a single region and 4/10 had two regions, from which two were adjacent and two were in non-adjacent locations. All candidate

Table 2. Summary of MAP results and clinical impact on the study cohort (total *n*=21).

MAP yield (total cohort=21)		
Candidate MAP+	10	
cMAP+	6	P3, P7, P8, P9, P18, P21
ncMAP+	4	P6, P10, P11, P13
Resection, outcome and pathology for cMAP+ findings (*n*=4)		
cMAP+ lesion completely resected	3	2 ILAE 1 (P9, P21), 1 ILAE 3 (P3)
cMAP+ lesion partially resected	1	ILAE 4 (P7)
Pathology	1 FCD type 1B, 2 nonspecific, 1 not available	
Clinical impact of cMAP+ and ncMAP+ findings (*n*=10)		
Directly lead to surgery	1	P21
Change of ICEEG plan and proceed with surgery	2	P3, P9
Change of ICEEG plan but no further surgery	3	P8, P10, P11
Change of ICEEG plan but patient declined ICEEG	1	P18
Unchanged but confirmed initial hypothesis	2	P7, P13
Non-contributory	1	P6

ncMAP+: non-confirmed MAP+; cMAP+: confirmed MAP+. Seizure outcome was based on the ILAE classification at six months post-op. Further follow-up data showed the same seizure outcome (Patient 3 at one year and eight months, Patient 7 at two years, Patient 9 at eight months, Patient 21 at one year).

MAP+ regions were detected by visual analysis of the junction map; 50% of the candidate MAP+ regions had associated changes in the extension map and none in the thickness map. From the 10 patients with candidate MAP+ regions, 6/10 were confirmed to indicate subtle FCDs after reviewing by the neuroradiologist (cMAP+). Four of six cMAP+ were found to have subtle blurring of the grey-white matter junction on the T2w FLAIR and T1w sequences, while in two patients, the lesion was only visible in one sequence (T2w FLAIR or T1w). For patients with multiple candidate MAP+ regions, only one patient was considered cMAP+ for one of the two locations. All cMAP+ were located outside the temporal lobe. In 4/6 cMAP+ cases, the patients underwent resective surgery. From these four patients, three had a resection that included the cMAP+ region (Patients 3, 9 and 21; seizure outcomes were ILAE 1 for 2/3 and ILAE 3 in 1/3). For Patient 7, the initial resection was planned to remove the cMAP+, but review of the post-operative MRI showed that the cMAP+ region was not completely removed, likely due to surgical difficulties (seizure outcome for this patient was ILAE 4).

Impact on clinical management

Candidate MAP+ regions had a clear impact on the initial management in 7/21 patients (33%, Patients 3, 8-11, 18 and 21) (*table 2, figure 1*), which are specifically described below.

In Patient 21, the cMAP+ region confirmed the initial hypothesis of a left mesial frontal seizure onset zone. Therefore, the patient did not undergo ICEEG and a resection was proposed after repeating the MRI, which confirmed the presence of the lesion. The patient became seizure-free (ILAE 1) and pathology showed FCD type 1B (*figure 2*).

In Patient 3, interictal scalp EEG showed generalized spike waves maximally in the left frontal and independently in the left temporal regions. Ictal scalp EEG was non-localizable. The cMAP+ region was in the left mesial frontal region, and led to an ICEEG specifically covering that region (which would not have been covered otherwise). The results of the ICEEG showed two distinct seizure onset zones, *i.e*. left mesial frontal and left mesial temporal. As the frontal onset appeared to be the dominant focus, a left frontal mesial resection was performed. Patient 3 had significant seizure reduction (ILAE 3). In Patient 9, initial scalp EEG was compatible with a temporopolar or mesial frontal seizure onset. The interictal ICEEG showed a quasi-constant rhythmic delta activity with spike waves in the contacts targeting the cMAP+ lesion, but due to an infection, the ICEEG was interrupted and no seizures were recorded. Thereafter, the patient was seizure-free for four months probably due to micro- and macro-lesional effects of the implanted electrodes. A new scalp monitoring was performed after the seizures had reoccurred and a left frontal mesial start was suspected which led to a prefrontal disconnective surgery. The patient's outcome was classified as ILAE 1.

In Patient 8, the interictal scalp EEG showed bilateral temporal spike waves, but ictal scalp EEG showed

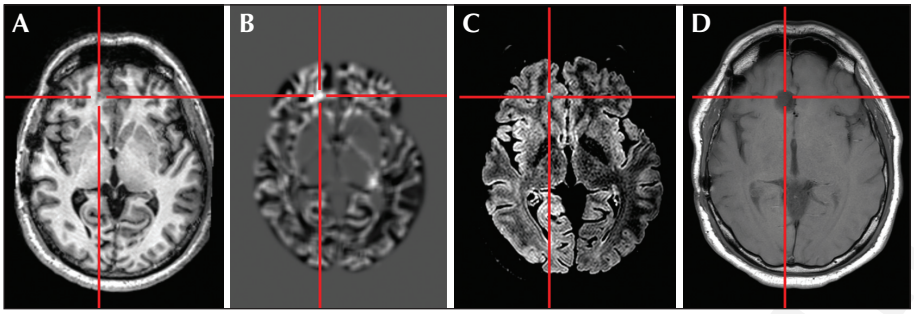

Figure 2. In patient 21, the cMAP+ region confirmed the initial hypothesis of a left mesial frontal seizure onset zone. Therefore, the patient did not go through ICEEG and a resection was proposed after repeating the MRI, which confirmed the lesion. The patient became seizure free (ILAE 1) and pathology showed FCD type 1B.

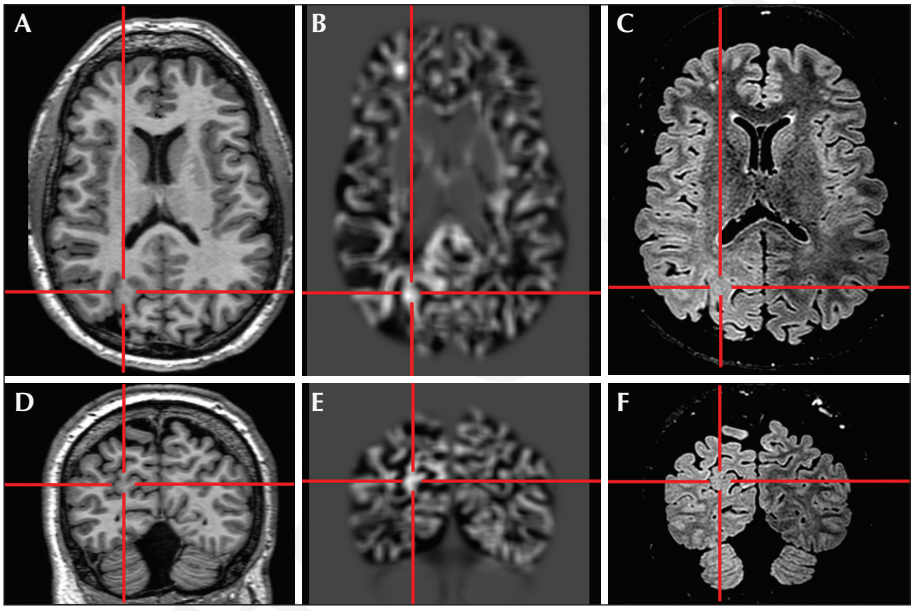

Figure 3. In patient 8, the interictal scalp EEG showed bilateral temporal spike waves, but ictal scalp EEG showed a right temporal start with a rapid diffusion to the midline. The initial ICEEG planning was adapted from a temporal and mesial frontal exploration to a temporal and mesial parietal investigation with additional electrodes covering the cMAP+ in the parietal lobe. The ICEEG showed a synchronous seizure onset between the R mesial parietal and temporal regions. In addition, the contralateral scalp EEG also showed left temporal seizures in addition to the right seizures recorded with the ICEEG, therefore patient was deemed to be not a suitable candidate for resective surgery.

a right temporal start with a rapid diffusion to the midline. The initial ICEEG planning was revised from a temporal and mesial frontal exploration to a temporal and mesial parietal investigation with additional electrodes covering the cMAP+ in the parietal lobe (*figure 3*). The ICEEG findings showed a synchronous seizure onset between the right mesial parietal and temporal regions. In addition, the contralateral scalp EEG (simultaneously recorded with ICEEG), also showed left temporal seizures in addition to the right seizures recorded with the ICEEG. Therefore, the patient was deemed to be not a suitable candidate for resective surgery.

In Patient 10, ICEEG additionally covered the right anterior insula where the ncMAP+ was found, as it was consistent with the original right frontal mesial and right orbito-frontal hypothesis. The ICEEG showed multifocal onset with right mesial frontal, right insular and left frontal seizures. Moreover, the scalp EEG simultaneously recorded with ICEEG also showed left-sided seizures. Therefore, this was not judged to be a good surgical case and no further resection was pursued. In Patient 11, the ncMAP+ result led to a bilateral mesial temporal implantation instead of a unilateral left temporal implantation as initially planned. ICEEG indeed showed bilateral independent seizures

and the patient was not considered a good surgical candidate.

In Patient 18, the ICEEG plan was adapted by adding an electrode in the left anterior insular region to cover the cMAP+ finding, in addition to the originally planned left frontal and paracentral region, but the patient declined ICEEG.

In Patient 7 and 13, the MAP findings did not change the management plan, however, the MAP finding helped confirm the initial proposed seizure onset zone (SOZ) hypothesis. Patient 7 was considered to be a good surgery candidate, but the very focal resection only partially included the lesion, explaining the ILAE 4 outcome. In Patient 6, the ncMAP+ finding was considered non-contributory to the epilepsy and was not further pursued by ICEEG/surgery.

Discussion

In this study, 21 potential surgical candidates with visually negative 3T MRI were prospectively included for evaluating the added clinical value of MRI post-processing with the MAP method. MAP results led to the discovery of six subtle FCDs (29%, 6/21), after re-review of the MRI by an experienced neuroradiologist. To date, the value of MAP has only been studied in retrospective studies, in which the sensitivity and specificity are based on correlation of MAP+ findings with histopathological proven FCD in patients who had resective surgery. Huppertz *et al.,* performed a retrospective study in 2005 in 25 patients with histologically confirmed FCD, and MAP successfully detected the lesions in all MRI+ cases and 50% of the MRI-negative cases (Huppertz *et al.,* 2005). In 2011, Wagner *et al.,* performed a retrospective study in 91 patients with confirmed FCD type II. The combination of visual analysis with MAP led to a detection rate of 85% in the MRI-negative patients (11/13) (Wagner *et al.,* 2011). In 2015, Wang *et al*. reported that MAP+ areas were detectable in 65 of 150 (43%) MRI-negative patients (Wang *et al.,* 2016); in another study, the same group reported a MAP+ rate of 44/78 (56%) in a cohort of MRI-negative paediatric patients (Wang *et al.,* 2019). Our 28% detection rate (6/21) is lower compared to the different retrospective studies using MAP (Kassubek *et al.,* 2002; Huppertz *et al.,* 2005; House *et al.,* 2013; Wang *et al.,* 2015); this discrepancy may be explained by the fact that all patients included in the cited studies underwent surgery, which might indicate a more focal epilepsy and thus a higher success rate for MAP to detect FCD lesions. In addition, rates may vary according to the initial labelling of MRI-negative across centres which highly depends on the experience of the neuroradiologists. In any case, the 28% detection rate in our study suggests a substantial diagnostic benefit for day to day practice, as MAP is only a post-processing method of standard MRI without any additional cost or risk for patients.

In addition, MAP results changed the management plan in 33% (7/21), which was considered to be clinically relevant in all the patients. The most representative example in our study is Patient 21, in whom the MAP lesion was confirmed by the neuroradiologist as a FCD in the right inferior mesial frontal lobe which was concordant with all the other investigations, leading to a successful surgery. For this patient, the MAP analysis helped omit an ICEEG, with an obvious benefit. In the other six patients, the altered management plan consisted of an adapted ICEEG scheme with extra electrodes targeting the suspected lesions, increasing the accuracy of the ICEEG planning. In 2/6, the targeted lesions were shown to participate in the SOZ leading to surgery thereafter, while in 3/6, the ICEEG findings of the targeted lesions significantly contributed to the diagnosis of multifocal epilepsy and consequently patients were considered to be not eligible for surgery. Moreover, when the MAP results did not change the management of the patient, they could help confirm the electroclinical hypothesis, as seen in Patients 7 and 13.

The potential utility of MAP as a confirmation tool was also shown in a previous retrospective study by Wang *et al*. (Wang *et al.,* 2015). In this study, 80/150 patients were considered to have subtle lesions on MRI per re-review at the PMC guided by multimodal data, and a subgroup analysis suggested that visually identified subtle MRI findings were more likely to be relevant if they were MAP+, indicating that MAP may increase the level of confidence in the process of determining the hypothesis of SOZ. Even though, in seven patients in the current study, MAP resulted in a clinical relevant change of management plan, the absence of a reliable reference standard in all patients (ICEEG, resection cavity, seizure outcome) to assess the clinical relevance remains an issue. Indeed, the clinical utility of diagnostic tests is typically assessed with measures of accuracy such as sensitivity and specificity which require comparison of test results with a reference (or "gold") standard. In similar studies studying the clinical utility of magnetic source imaging (MSI) in the presurgical evaluation (De Tiège *et al.,* 2012), the same issue of valid reference has been discussed. In addition to the lack of a reference, surgical management and procedures are considered to be highly variable across centres depending on experience and expertise, which complicates relevant comparisons or generalizations. Moreover, it is usually difficult to independently quantify the real clinical added value of a single test due to the involvement of multiple factors in the multidisciplinary decision process.

Despite the significant detection rate of 28%, only a few patients underwent surgery. The low surgery rate is not surprising, as the included patients were all MRI-negative and no inclusion restriction was made with respect to the potential presence of a unilobar seizure hypothesis or the results of the Phase I presurgical evaluation being concordant or not. Even though the absolute number of patients going through surgery was small (5/21, 24%, all extratemporal resections), the surgery rate is quite comparable to other studies (Noe *et al.,* 2013; Martin *et al.,* 2017; Hu *et al.,* 2018). In a retrospective study analysing the long-term outcomes after non-lesional extratemporal lobe epilepsy surgery, 47 of the 85 patients (55%) had sufficiently localizing non-invasive findings to justify implantation of intracranial electrodes. Of these 47 patients, 31 (66%) proceeded to long-term intracranial EEG, and in 24 of these 31 patients, a seizure focus was identified and surgically resected, corresponding to a final surgery rate of 24/85 (28%) (Noe *et al.,* 2013). In a recent study comparing MAP, PET/MRI co-registration and statistical parametric mapping (SPM) analysis of PET, 66/221 (31%) MRI-negative patients underwent surgery consisting of temporal and extra-temporal resections. This study showed a higher surgery rate compared to our study, but this might be explained by the fact that proportionally a higher number of temporal lobe epilepsy patients were included compared to our study (Hu *et al.,* 2018). In a study by Martin *et al*. analysing specificity and sensitivity of different VBM techniques (Martin *et al.,* 2017), 129/144 patients included were non-lesional of whom 27 had surgery (20.9%) which was also quite comparable with our study.

It is important to point out that MAP results need to be interpreted in the context of the patient's anatomo-electro-clinical presentation. In addition to the need for interpretation by a trained neuroradiologist in the field of epilepsy, several studies show the efficacy of combining different modalities. For example, in a retrospective study, it was shown that when both MAP and magnetic source imaging were concordant, patients had a significantly higher chance to be seizure-free following complete resection of this area (Wang *et al.,* 2014). In a study comparing the complementary value of MAP, SPM-PET, and PET/MRI co-registration in 33 extratemporal MRI-negative patients who underwent surgery and had proven FCD, PET/MRI co-registration was the most effective in FCD detection (91%), but the combination of three modalities increased the detection rate to 97% (Hu *et al.,* 2018). In contrast, in a cohort of 39 histologically proven FCD cases, the sensitivity and specificity of MAP was shown to be higher than qualitative MRI review, SISCOM and FDG-PET (Wong-Kisiel *et al.,* 2018). Implantation of a depth electrode into a patient's MAP lesion, located within a neocortical compartment suggested by semiology, led to good localizing data and successful surgery (Wellmer *et al.,* 2010).

Although our study utilized the MAP technique, many other morphometric post-processing techniques exist. For example, Martin *et al*. compared different types of VBM techniques, three based on T1 weighted images (grey matter volume, grey matter concentration, junction map and one based on normalized fluid-attenuated inversion recovery) in a retrospective study including lesional and non-lesional cases. They demonstrated that VBM based on T2-weighted FLAIR images had the best specificity and junction maps based on T1-weighted images had the best sensitivity in a mixed patient population. In addition, spatial co-localization of different maps can improve the confidence of a finding (Martin *et al.,* 2017). In our study, only the 3D T1-weighted volumetric MRI was used as input to MAP in this study due to its availability as part of our routine epilepsy MRI protocol.

Limitations

Our study was underpowered to show any effect of MAP on the final endpoint of surgery as only a small percentage of patients underwent surgery. A multicentre approach could increase the number of included patients leading to potential prospective specificity and sensitivity values, which are lacking in this study. On the same note, the detection rate of 28% should be interpreted with caution and further studies with more patients may be necessary to confirm this yield.

It is usually difficult to independently quantify the real clinical added value of a single test due to the involvement of multiple factors in the multidisciplinary decision-making process. The absence of a reliable reference standard to assess the clinical relevance of the test under consideration remains an inherent limitation.

The VBM technique in our study was performed based on the MAP which uses a normative database consisting of a mix of 1.5T and 3T average of 150 subjects acquired on different types of scanners. Ideally, the MAP analysis should have been compared with an in-house normative database, which was not available at the time of our study.

Conclusion

We present here the first prospective trial that included MAP in the presurgical evaluation of 3T-MRI-negative refractory epilepsy patients. Our study confirms the diagnostic benefit of MAP in a particularly challenging patient population, as MAP led to detection of subtle FCD lesions in 28% cases. In addition, MAP findings led to an adapted ICEEG plan in 70% of patients

who had positive MAP findings and much of the additional coverage played an instrumental role in mapping the epileptogenic zone. Our results indicate the usefulness of MAP in clinical decision-making during epilepsy presurgical evaluation. □

Disclosures.
None of the authors have any conflict of interest to declare.

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