Multimodality approach in cryptogenic epilepsy with focus on morphometric 3T MRI

Approche multimodale de l’épilepsie cryptogénique orientée sur l’IRM 3T morphométrique

M.T. Doelken a,*, A. Mennecke a, H.J. Huppertz c, S. Rampp b, E. Lukacs b, B.S. Kasper b, T. Kuwert d, P. Ritt d, A. Doerfler a, H. Stefan b, T. Hammen b

a Department of Neuroradiology, Friedrich-Alexander-University of Erlangen-Nuremberg, Schwabachanlage 6, 91054 Erlangen, Germany
b Department of Neurology, Epilepsy Center (ZEE), University of Erlangen-Nuremberg, Schwabachanlage 6, Erlangen, Germany
c Swiss Epilepsy Center, Bleulerstrasse 60, 8008 Zürich, Switzerland
d Department of Nuclear Medicine, University of Erlangen-Nuremberg, Schwabachanlage 6, 91054 Erlangen, Germany

KEYWORDS
Epilepsy; Cryptogenic; MRI; Morphometric analysis; MAP; VBM; MEG; SPECT; PET

Summary
Purpose: This study aimed to investigate the potential contribution of morphometric MRI analysis in comparison to other modalities, such as MEG, SPECT and PET, in identifying the epileptogenic focus in patients with cryptogenic epilepsy.

Patients and methods: Study inclusion was limited to epilepsy patients with a monolobar focus hypothesis, as concluded from EEG/seizure semiology and the best individual concordance rate. Feature maps, generated by the MATLAB® “morphometric analysis program” (MAP), were evaluated by a neuroradiologist blinded to conventional MRI and the focus hypothesis (MAP1). In addition, the feature maps were also interpreted by simultaneous matching conventional MRI but, again, with the reader having no knowledge of the focus hypothesis (MAP2).

Results: In 12 out of 51 patients, true-positive findings were achieved (MAP1: sensitivity 24%; specificity 96%). The sensitivity of the MAP1 results was superior extratemporally. After matching conventional MRI, FCD was traced in six of the 12 patients (MAP2: sensitivity 12%; specificity 100%). MEG sensitivity was 62%. Sensitivity of interictal and ictal SPECT was 20% and 50%, respectively. PET was not as sensitive extratemporally (19%) as temporally (82%). The greatest correspondence with the best individual concordance rate was noted with PET (14/16; 88%) and MEG (8/10; 80%), followed by interictal (5/8; 63%) and ictal (9/15; 60%) SPECT. Results for MAP1 were 53% (10/19), and 100% for MAP2 (6/6).

Conclusion: Although MAP sensitivity and specificity results are lower in comparison to other modalities, implementation of the technique should be considered first, before arranging any

* Corresponding author. Tel.: +49 9131 85 44828; fax: +49 9131 85 36179.
E-mail address: marc.doelken@uk-erlangen.de (M.T. Doelken).

0150-9861/5 - see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.neurad.2011.04.004
Introduction

In patients with cryptogenic epilepsy, localization of the epileptogenic focus remains challenging despite the extensive efforts made so far [1–5]. Nevertheless, focal epileptic activity generated by the epileptic network is located within one anatomical lobe (monolobar) in the majority of cases [6–8]. Also, recent achievements in imaging and post-processing techniques have widened the indications for the surgical treatment of patients with pharmacoresistant cryptogenic epilepsy by making anatomical localization of the underlying epileptogenic cause feasible [3,8–11].

Multimodal evaluation combining electroencephalography (EEG), high-field (3-Tesla) magnetic resonance imaging (3T MRI) with automated morphometric MRI analysis, magnetoencephalography (MEG), positron emission tomography (PET) and single-photon emission computed tomography (SPECT) contributes to accurate localization of the epileptogenic focus and optimal post-surgical outcomes [5,7,12,13]. However, even in the context of an individual focus hypothesis (as concluded from seizure semiology and EEG) and continuously improving neuroimaging techniques (such as 3T MRI), definite concordant evidence of the seizure focus is often not possible [1–3]. The question of whether epileptic activity originates in one brain lobe and whether this lobe can be reliably determined is crucial, and constitutes the basis of comparisons of neuroimaging procedures [4,7,14]. Investigations offering the maximum individual yield should be considered to reduce not only the costs but, in particular, the complexity of the workup.

Recently, a new post-processing technique for morphometric analysis using MRI was introduced that helps to highlight and detect the typical MRI features of focal cortical dysplasia (FCD) and other cortical malformations [9–11]. Yet, very little can be said as to its feasibility in clinical settings and its diagnostic yield in comparison to other neuroimaging modalities [13,15–18]. For this reason, the objective of the present study was to investigate the potential contribution of morphometric MRI analysis in determining the epileptogenic focus in patients with cryptogenic epilepsy compared to other modalities, such as MEG, SPECT and PET, with validation against an individual focus hypothesis, as concluded from EEG and seizure semiology, and the best individual concordance rate for the available modalities [6]. The present results offer guidelines for the implementation, interpretation and concordance of diagnostic procedures in this problematic patient group.

Patients and methods

This study included patients with cryptogenic epilepsy from the Epilepsy Center in Erlangen. Diagnosis of cryptogenic epilepsy was based on clinical history, seizure semiology, results of long-term EEG monitoring and negative MRI results [19]. The study complied with the Declaration of Helsinki and was approved by the local ethics committee.

Focus hypothesis

Inclusion into the study was limited to MRI-negative patients with a definite lobe focus hypothesis. The focus hypothesis was based on seizure semiology and intensive EEG monitoring, including video monitoring as described by Paulini et al. [6]. Patients with uncertain, ambiguous or a non-monolobar focus hypothesis as well as patients with suspected temporominal epilepsy were excluded. The focus hypothesis served as the “gold standard” for calculating the sensitivity and specificity of MAP, MEG, SPECT and PET, and was categorized into side and lobe, frontal, temporal and parietal hypotheses. Negative initial MRI results were confirmed by an experienced neuroradiologist. In addition, the best individual concordance rate between each modality (MEG, SPECT, PET, EEG) and seizure semiology was applied to identify and further validate the sensitivity and specificity of each technique.

MRI

MR imaging was performed, using a 3T Magnetom Trio MR scanner (Siemens Medical Solutions, Erlangen, Germany) with an 8-channel head coil, and included the following sequences: fluid-attenuated inversion recovery (3D-FLAIR; 1-mm 3D post-processing; TR 5000; TE 388; matrix 258 × 256; mm); inversion recovery (3D-IR; 1-mm 3D post-processing; TR 4000; TE 382; matrix 258 × 256); T2 turbo spin-echo (TSE; TR 6220; TE 91; slice thickness 3 mm) perpendicular to the long axis of the hippocampus; T2* fast low-angle shot (FLASH) gradient-echo (TR 875; TE 20; slice thickness 3 mm); T1 3D magnetization-prepared rapid gradient-echo (MP-RAGE; 1-mm 3D post-processing; TR 2300; TE 2.98; matrix 256 × 256); and gadolinium-enhanced T1 FLASH (TR 300; TE 2.42; 3-mm slice thickness).

MAP

Morphometric MRI analysis was performed using a technique based on algorithms used in freely available statistical parametric mapping software (SPM5; Wellcome Trust Centre for Neuroimaging, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm). These methods are described in detail elsewhere [9,10]. Briefly, a T1-weighted MRI volume dataset (MP-RAGE) was normalized to a standard brain template and segmented, using standard algorithms in SPM5. The distribution of grey and white matter was analysed on the basis of voxels, and compared with a normal database. The normal database used consisted of 50 normal adults (23 men, 27 women; age range, 20–47 years; average age 30 years) examined with the same 3T Magnetom Trio MR scanner as used for the patients with
Multimodality approach in cryptogenic epilepsy with focus on morphometric 3T MRI

Figure 1  High-resolution MP-RAGE and corresponding MAP feature images (A) of a patient with subtle focal cortical dysplasia (FCD) of the right frontobasal lobe that is primarily missed by conventional 3T MRI. Blurring of the grey–white matter junction is apparent in three orthogonal planes (white arrowhead). (B) FCD was confirmed by the enlarged coronal MP-RAGE image (black circle).

Cryptogenic epilepsy [18]. Based on this analysis, 3D feature maps — also called "extension-image", "junction-image" and "thickness-image" maps — were automatically created. These maps highlight the typical features of FCD, such as abnormal extension of grey matter into white matter (abnormal gyration), blurring of the grey–white matter junction and abnormal thickening of the cortical ribbon. The whole processing procedure was performed by the fully automated MATLAB® "morphometric analysis program" (MAP) software. By visually highlighting suspicious cortical regions, the MAP results can guide the MRI to a second look, thereby increasing the sensitivity of the MRI evaluation. The MAP images were initially evaluated by an experienced neuroradiologist blinded to both the MRI and focus hypothesis for all patients (MAP1). The most important criterion for positive MAP1 appraisal was focal blurring of the grey–white matter junction (Figs. 1a, 2 and 4). In addition, the MAP images for each patient were interpreted by the neuroradiologist by simultaneous matching of the conventional MR images, but with no awareness of the focus hypothesis (MAP2).

MEG

MEG was recorded with a 74-channel two-sensor system (Magnes II, 4-D Neuroimaging, San Diego, CA, USA) within a magnetically shielded room (Vakuumschmelze, Hanau, Germany). Each MEG sensor comprised 37 first-order gradiometers with a 5-cm baseline and an average distance between channels of 2.8 cm. On average, MEG was recorded in two to four different sensor positions lasting 20 to 30 minutes each. Measurement positions and durations were based on previous diagnostic findings. In the clinical workup, patients usually underwent video-EEG monitoring before MEG measurement. The MEG signal was processed with an analog bandpass filter (1–120 Hz), and digitised with a sampling rate of 520.8 Hz. Subsequently, M/EEG recordings were digitally bandpass-filtered (3–70 Hz; notch filter 50 Hz) using settings based on the in-house standard for clinical routine investigations.

Epileptic spikes were visually identified during inspection of the complete recording period. A minimum of five spikes was required for a localization result. A single dipole analysis assuming a spherical head model was performed using MSI software (4D-Neuroimaging). A single dipole solution was considered for localization if it had a correlation coefficient of at least 0.97 and a confidence volume less than 3 mm³. Since 2001, source localization, using CURRY software version 4.6 (Compumedics Neuroscan, El Paso, TX, USA) with three spherical shells or a boundary element method volume conductor model, has been available. Dipoles calculated with MSI or CURRY software were visualized on co-registered individual MRI data (Fig. 3).
Figure 2  Co-registration of MRI (A), MAP feature images (B, C) and SPECT (D) (SISCOM) of a patient with subtle FCD in the superior frontal gyrus (white arrows).

Figure 3  Calculated focus localizations on MEG (green mark) visualized on coregistered MRI data.
**SPECT**

SPECT examinations were performed at the Clinic of Nuclear Medicine, University of Erlangen-Nürnberg, using a previously reported protocol [12,20]: technetium-99m ethylcysteinate dimer (\(^{99m}\)Tc ECD) SPECT was carried out using the triple-headed camera MultiSPECT 3 (Siemens Medical Solutions, Hoffman Estates, IL, USA), equipped with low-energy ultra-high-resolution collimators. Data acquisition was started 30 minutes after intravenous injection of 740 MBq of \(^{99m}\)Tc ECD. A total of 120 views (3 × 40; 3.0 s/step), each registered for 40 s, were recorded in a 128 × 128 matrix with a pixel size of 2.9 × 2.9 mm\(^2\). Each view had 32,000 to 52,000 counts. Transaxial tomograms were reconstructed without prefiltering, using filtered back-projection with a Butterworth fifth-order filter and a cut-off frequency of 0.3 Nyquist. Chang’s first-order attenuation correction was applied, using a uniform coefficient of 0.12 cm\(^{-1}\). The in-plane resolution of the reconstructed images was 11 mm Full Width at Half Maximum (FWHM), and slice thickness was approximately 5.8 mm. Focus localization was based on ictal and interictal findings in all patients, and performed by a reader who had more than 20 years of experience in reading SPECT images. Coronal, sagittal and transverse planes were visually evaluated independently from the clinical, MRI and EEG data. In addition to visual analysis of the raw data, a semi-quantitative analytical approach adapted to SPECT [21] was also used. In two patients in whom SPECT had not been performed in Erlangen, equivalent protocols had been used. Subtraction SPECT co-registered to MR images (SISCOM) was constructed retrospectively in single cases as reported in the literature [22].

**Fluorodeoxyglucose (\(^{18}\)F) PET**

\(^{18}\)F-FDG PET examinations of the brain were performed with a PET/CT scanner (Biograph-64; Siemens Medical Solutions, Knoxville, TN, USA) in 27 cases, while the remaining two subjects were studied using a partial-ring PET scanner (ECAT EMERGE, Siemens); both scanners were equipped with lutetium oxyorthosilicate (LSO) detectors, the technical performance of which were recently described elsewhere [23]. Data acquisition was started 30 minutes after intravenous injection of 3 MBq/kg body weight of \(^{18}\)F-FDG in the case of measurements using the Biograph-64 and 7 MBq/kg body weight of \(^{18}\)F-FDG when the other scanner was employed. Emission data were acquired over 15 minutes and 30 minutes in 3D mode with the Biograph-64 and the EMERGE, respectively. For attenuation correction, low-dose CT (50 mAs, 100 keV) was used in the case of the Biograph-64 measurements while, in the case of the EMERGE, transmission measurements were taken using rotating line sources of cesium-137 (\(^{137}\)Cs). Emission data corrected for randoms, dead time and attenuation were reconstructed with an iterative reconstruction algorithm based on ordered-subset expectation maximization (OSEM). Matrix size was 128 × 128 in plane. Images were evaluated visually for hypometabolic foci by a reader with 24 years of experience in reading brain PET images.

**Statistical analysis**

Referring to the brain lobe focus hypothesis as the gold standard, the findings with MAP, MEG, SPECT and PET were separated into true-positive (TP), true-negative (TN), false-positive (FP) and false-negative (FN) results. Sensitivity \(t\) was calculated as \(t = TP / (TP + FN)\). Specificity was estimated as \(s = TN / (TN + FP)\); Table 1). The epileptic focus was localized to one lobe; the other five of the six lobes (both temporal, parietal and frontal lobes) were considered healthy and, thus, used to obtain TN and FP numbers. In addition, the best individual concordance rate between each available modality (MEG, SPECT, PET, EEG) and seizure semiology was applied to identify and further validate the sensitivity and specificity of each technique (Table 2). The concordance rate was determined based on more than two available modalities in each case. Figs. 2–4 present examples of congruent multimodal findings. Statistical analysis was carried out using R version 2.6.2 [24].

**Results**

A total of 51 patients (20 men, 31 women; age range 18–52 years, mean 30 years) were included in our study. Age at epilepsy manifestation ranged from 1 to 36 years. Altogether, 28 patients with a right or left frontal lobe focus hypothesis, six patients with a right or left parietal and 16 patients with a right or left neocortical temporal lobe focus hypothesis were included. In all 51 patients, morphometric post-processing analysis (MAP) was successfully performed. In 13 of the 51 patients, MEG was successfully applied. In 20 of the 51 patients, ictal SPECT was carried out and, in 16 of the 51 patients, ictal SPECT was effectively conducted. In 29 of the 51 patients, FDG-PET was performed.

A monolobar epileptogenic focus was assumed. Table 1 displays the available results (TP, TN, FP, FN, sensitivity and specificity) for the different modalities within the brain lobes, referring to the focus hypothesis based on seizure semiology and intensive EEG monitoring. Overall, the 51 patients, three lobes and two brain hemispheres yielded 306 cases. In addition, Table 2 presents the modalities matched with the focus hypothesis based on the best individual concordance rate.

**MAP\(^1\) and MAP\(^2\) results**

In 12 of the 51 patients, MAP\(^1\) TP findings were found. Thus, overall sensitivity of the MAP\(^1\) findings in the context of the individual brain lobe focus hypothesis was 24% (Table 1). In 10 of the 255 cases, FP findings were determined (specificity 96%; TN = 245, FP = 10). Sensitivity was found to be superior extratemporally in the frontal lobe (39%, TP = 11, FN = 17 vs 6%, TP = 1, FN = 16 in the temporal lobe). Given the small number of patients with a parietal focus hypothesis, the results displayed in Table 1 may be unreliable.

After comparison of the MAP\(^1\) results to the individual MR images, subtle, initially missed, FCD was traced in six of the 12 patients with TP MAP\(^1\) findings. Thus, sensitivity of the MAP\(^1\) findings decreased to 12% (TP = 6, FN = 45), while specificity of the MAP\(^1\) findings increased to 100%. Extratem-
poral sensitivity of the MAP² findings was 18% (TP = 5, FN = 23; frontal lobe only) vs 6% (TP = 1, FN = 16) in the temporal lobe.

**MEG results**

Overall, the sensitivity and specificity of MEG was 62% (TP = 8, FN = 5) and 97% (TN = 63, FP = 2), respectively (Table 1). Increased sensitivity was found extratemporally in the frontal lobe, with 83% (TP = 5, FN = 1) vs 33% (TP = 2, FN = 4) in the temporal lobe. However, specificity decreased slightly to 90% (TN = 18, FP = 2) in the frontal lobe.

**SPECT findings**

Overall, the sensitivity of interictal SPECT was 20% (TP = 4, FN = 16) vs 50% for ictal SPECT (TP = 8, FN = 8) (Table 1). Overall specificities of interictal and ictal SPECT were 96% (TN = 96, FP = 4) and 89% (TN = 71, FP = 9), respectively. Greater sensitivity with interictal and ictal SPECT was noted in the temporal lobe (interictal: 33%, TP = 2, FN = 4; ictal: 60%, TP = 3, FN = 2; excluding temporomesial findings) compared with extratemporal SPECT results (frontal lobe: interictal, 11%, TP = 1, FN = 8; ictal, 43%, TP = 3, FN = 4). However, specificity of interictal and ictal SPECT in the temporal lobe was low (88% and 81%, respectively).

**PET results**

The overall sensitivity and specificity of PET was 45% (TP = 13, FN = 16) and 97% (TN = 140, FP = 5), respectively (Table 1). Sensitivity of PET in the temporal lobe (excluding temporomesial findings) was good (82%, TP = 9, FN = 2), while extratemporal sensitivity was low (frontal lobe 19%, TP = 3, FN = 13). Specificity of PET in different lobes was good (frontal lobe 98%, temporal lobe 94%).

**Concordance of modalities based on best individual concordance rate**

To further validate the above data (Table 1), the best individual concordance rate was determined among the available modalities (Table 2). Only in one case did the best concordance rate differ from the clinical and EEG results (primary focus hypothesis) due to concordant results with SPECT and PET (Table 2; best concordance rate: 98%). The closest correspondence with the best individual concordance rate was observed with PET (14/16 cases; 88%) and MEG (8/10 cases; 80%), followed by interictal (5/8 cases; 63%) and ictal (9/15 cases; 60%) SPECT. Results of MAP¹ were 53% (10/19 cases) and 100% for MAP² (6/6 cases). Full individual concordance excluding MAP results was identified in 18/31 cases (60%), whereas full individual concordance including MAP¹ results was seen in 5/18 (28%) cases.
Multimodality approach in cryptogenic epilepsy with focus on morphometric 3T MRI

Table 1  False-positive (FP), false-negative (FN), true-positive (TP) and true-negative (TN) multimodality results in 51 patients with cryptogenic epilepsy and a focus hypothesis according to seizure semiology and EEG.

<table>
<thead>
<tr>
<th>Modality</th>
<th>n</th>
<th>FP</th>
<th>FN</th>
<th>TP</th>
<th>TN</th>
<th>Sensitivity (t) (%)</th>
<th>Specificity (s) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal lobe focus⁰</td>
<td>51</td>
<td>10</td>
<td>39</td>
<td>12</td>
<td>245</td>
<td>24</td>
<td>96</td>
</tr>
<tr>
<td>Parietal lobe focus¹</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>95</td>
<td>0</td>
<td>99</td>
</tr>
<tr>
<td>Temporal lobe focus¹</td>
<td>17</td>
<td>4</td>
<td>16</td>
<td>1</td>
<td>81</td>
<td>6</td>
<td>95</td>
</tr>
<tr>
<td>MAP²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal lobe focus⁰</td>
<td>51</td>
<td>0</td>
<td>45</td>
<td>6</td>
<td>255</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>Parietal lobe focus¹</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>96</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Temporal lobe focus¹</td>
<td>17</td>
<td>0</td>
<td>16</td>
<td>1</td>
<td>85</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>MEG</td>
<td></td>
<td>13</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal lobe focus⁰</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>18</td>
<td>83</td>
<td>90</td>
</tr>
<tr>
<td>Parietal lobe focus¹</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>25</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Temporal lobe focus¹</td>
<td>6</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>20</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Interictal SPECT</td>
<td>20</td>
<td>4</td>
<td>16</td>
<td>4</td>
<td>96</td>
<td>20</td>
<td>96</td>
</tr>
<tr>
<td>Frontal lobe focus⁰</td>
<td>9</td>
<td>0</td>
<td>8</td>
<td>1</td>
<td>31</td>
<td>11</td>
<td>100</td>
</tr>
<tr>
<td>Parietal lobe focus¹</td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>35</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>Temporal lobe focus¹</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>30</td>
<td>33</td>
<td>88</td>
</tr>
<tr>
<td>Ictal SPECT</td>
<td>16</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>71</td>
<td>50</td>
<td>89</td>
</tr>
<tr>
<td>Frontal lobe focus⁰</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>23</td>
<td>43</td>
<td>92</td>
</tr>
<tr>
<td>Parietal lobe focus¹</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>26</td>
<td>50</td>
<td>93</td>
</tr>
<tr>
<td>Temporal lobe focus¹</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>22</td>
<td>60</td>
<td>81</td>
</tr>
<tr>
<td>PET</td>
<td></td>
<td>29</td>
<td>5</td>
<td>16</td>
<td>13</td>
<td>140</td>
<td>45</td>
</tr>
<tr>
<td>Frontal lobe focus⁰</td>
<td>16</td>
<td>1</td>
<td>13</td>
<td>3</td>
<td>41</td>
<td>19</td>
<td>98</td>
</tr>
<tr>
<td>Parietal lobe focus¹</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>55</td>
<td>50</td>
<td>98</td>
</tr>
<tr>
<td>Temporal lobe focus¹</td>
<td>11</td>
<td>3</td>
<td>2</td>
<td>9</td>
<td>44</td>
<td>82</td>
<td>94</td>
</tr>
</tbody>
</table>

MAP¹: evaluation blinded to MRI and focus hypothesis; MAP²: evaluation matched with MRI, but with no awareness of focus hypothesis; MAP: morphometric analysis program; MEG: magnetoencephalography; SPECT: single-photon emission computed tomography; PET: positron emission tomography.

⁰ Focus hypothesis.

¹ Excluding temporomesial findings.

Discussion

In the present study, the individual brain lobe focus hypothesis based on seizure semiology and intensive EEG monitoring was initially used as a benchmark for lobe or focus determination and the comparison of different modalities with a focus on morphometric analysis. However, we cannot provide overall histopathological proof of the individual focus hypothesis, as only a few patients were pharmacoresistant and had to undergo curative surgery. However, in a multidisciplinary discussion of patients with epilepsy, the best concordance of all modalities applied is usually considered when making surgical decisions or proposals. For this reason, the present study also included the best individual concordance rate to identify and further validate the findings. Only in one case was the best concordance rate not

Table 2  Modalities matched with the focus hypothesis based on the best individual concordance rate.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Clinical/semiology</th>
<th>EEG</th>
<th>MEG</th>
<th>Interictal SPECT</th>
<th>Ictal SPECT</th>
<th>PET</th>
<th>MAP¹</th>
<th>MAP²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>51</td>
<td>51</td>
<td>51</td>
<td>13</td>
<td>20</td>
<td>16</td>
<td>29</td>
<td>51</td>
</tr>
<tr>
<td>Patients with positive findings (n)</td>
<td>51</td>
<td>51</td>
<td>10</td>
<td>8</td>
<td>15</td>
<td>16</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Patients with positive findings (%)</td>
<td>100</td>
<td>100</td>
<td>77</td>
<td>40</td>
<td>94</td>
<td>55</td>
<td>37</td>
<td>12</td>
</tr>
<tr>
<td>Best concordance (n)</td>
<td>50</td>
<td>50</td>
<td>8</td>
<td>5</td>
<td>9</td>
<td>14</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Best concordance (%)</td>
<td>98</td>
<td>98</td>
<td>80</td>
<td>63</td>
<td>60</td>
<td>88</td>
<td>53</td>
<td>100</td>
</tr>
</tbody>
</table>

MAP¹: evaluation blinded to MRI and focus hypothesis; MAP²: evaluation matched with MRI, but with no awareness of focus hypothesis; EEG: electroencephalography; MEG: magnetoencephalography; SPECT: single-photon emission computed tomography; PET: positron emission tomography; MAP: morphometric analysis program. Note: only in one case did the best concordance rate differ from the clinical and EEG results (see Table 1, primary focus hypothesis) due to concordant results in SPECT and PET.

⁰ Sensitivity.

¹ Specificity (Table 1).
possible to determine because of ambiguous results in EEG, seizure semiology, SPECT and PET. This finding underscores the initial individual brain lobe focus hypothesis, which was carefully determined by an experienced epileptologist based on seizure semiology and long-term EEG [6]. Thus, applying such a focus hypothesis as a benchmark is reliable to a certain extent, although histological correlation would offer the final proof.

Our present results offer an interesting multimodal imaging approach that may serve as clinical guidelines for narrowing the epileptogenic focus in cryptogenic epilepsy. Particularly in the context of the implementation of post-processing techniques such as MAP, the feasibility and clinical benefits become obvious. However, further studies including histological correlation especially in the case of suspicious MAP results are nevertheless required.

Most cryptogenic epilepsies are believed to arise from FCD [14]. Yet, subtle focal brain pathologies such as FCD are easily overlooked on conventional MRI visual examination even by experienced neuroradiologists using high-resolution 3 T MRI. Our present results demonstrate that, in patients with primarily cryptogenic epilepsy and a distinct focus hypothesis, FCD can successfully be determined by morphometric MRI analysis in up to 12% (MAP1) of patients [9,10,25—30]. In terms of the best individual concordance rate, morphometric MRI analysis (MAP) offers further data relevant to surgical decisions or proposals for therapy-refractory patients in a multidisciplinary context. However, morphometric MRI analysis is not limited to FCD. Subcortical band heterotopy (SBH) may also be detected, although it represents a relatively rare cause [11]. In our present case series, exclusively 3D-MP-RAGE datasets were used for morphometric analysis. However, additional 3D-FLAIR morphometric analysis is reported to further increase detection rates of subtle pathologies such as FCD [29,31]. Recently, 3D-FLAIR morphometric analysis has been integrated into MAP, although this was not available for our present series.

Most patients with distinctive features in the morphometric images provided by MAP fall into the category referred to as “Taylor-type FCD” [32], which can be detected visually on MRI [25,33]. Type I dysplasia or mild malformations of cortical development are not visually identifiable by the currently available diagnostic MRI, but might be detectable with MAP [9]. Also, we were not able to visualize local pathology on retrospective conventional MRI evaluation in 16 cases (Table 1: MAP1, 10 FP, 6 TP) wherein suspicious blurring of the grey−white matter (GM−WM) transition occurred. Yet, as shown in Table 2, positive findings for MAP1 corresponded with the best individual concordance rate in 53% (10/19; ~ specificity) of cases. The example in Fig. 5 displays a crucial location in the right precentral region. The conspicuous along the GM−WM transition in the junction image is “sharp-linear” without the “blurring” seen in Figs. 1, 2 and 4. To determine whether these findings represent different histopathological entities or reflect different gyral variants with no “true” correspondence, further studies involving histopathological correlation are required.

**Figure 5** Crucial location in the junction and extension images of the MAP analysis (B) in the precentral right gyrus (red lines). The conspicuous along the grey−white matter transition in the junction image delineates “sharp-linear” without the “blurring” seen in Figs. 1, 2 and 4. On retrospective 3T MRI evaluation (A), the local pathology (FCD) could not be definitively traced compared with the MAP results.
The question of why MAP sensitivity in our present study was lower in the temporal lobe remains speculative, but it could be due to the lower occurrence of FCD in that lobe. In general, the spatial resolution of the MAP method is limited by the voxel size of the original 3D datasets (1 × 1 × 1 mm^3 in the present study) and the smoothing factor used for further data processing. The lower temporal sensitivity might also be due to statistical problems resulting from interindividual cortical variability [9, 30]. Malformations in such highly variable regions could thus be more likely to escape detection (giving FN results) [34]. To minimize variation influences in our study, all scans were performed using the same 3T MRI and identical 3D-MP-RAGE sequence [18].

MEG, PET and SPECT are all used for focus localization in the epileptic brain. As shown in Tables 1 and 2, the sensitivity and specificity of MAP appears to be lower in comparison to other modalities, and notably MEG and PET. Thus, primarily matching the MAP and MRI results with findings by MEG appears to be reasonable, particularly if positive MAP findings cannot be definitively traced on conventional MRI. Despite the fact that MEG was effectively recorded in only 25% of our studied patients, the present findings support the conclusion that MEG is a valuable complementary functional modality, particularly as FCD is preferentially located extratemporally [6, 35].

PET and SPECT each have strengths, but also shortcomings, with respect to precise focus localization and spatial resolution [2]. Comparison of the techniques is difficult because they measure different aspects of the epileptic process—structure, metabolism and perfusion. MRI co-registration of PET and SPECT further improves the detection of cortical dysplasia [22, 36, 37]. Nevertheless, relatively congruent findings were obtained in our present patients with MRI-negative findings. Based on the published literature and our results, PET in adults is not as sensitive for extratemporal lobe epilepsy as it is for temporal lobe epilepsy [2, 5, 13]. As with our present findings, interictal SPECT is an insensitive method for localizing extratemporal foci [15, 38]. As for ictal SPECT, higher sensitivities have been reported, as seen in our study [13]. Yet, extratemporal seizures are often brief and it is therefore difficult to obtain an ictal recording. In addition, consistent with our findings, the specificity of ictal SPECT decreases, probably due to the propagation pathways. Limitations include some heterogeneity in the unique protocols for SPECT and PET that may possibly have obscured the results.

Conclusion

Although the sensitivity and specificity of MAP in terms of focus localization is lower in comparison to other modalities, implementation of the post-processing technique has no drawbacks for the patient and should be considered first, before arranging for further investigations. Our results here indicate that, using MAP feature maps, subtle pathologies, such as FCD, that are missed by conventional MRI can be detected in up to 12% of cases. To increase the objective diagnostic power, a primary comparison with the functional findings of MEG appears to be reasonable, especially if suspicious locations on MAP feature maps cannot be clearly traced on conventional MRI. For this reason, further studies implementing histopathological correlation with suspicious MAP results are required. Implementation of additional modalities, such as SPECT and PET, depends on the temporal and extratemporal focus hypothesis, and may offer supplemental information for the preoperative assessment of intractable epilepsy surgery candidates.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgements

This research was supported by “Erarger Leistungsbezogene Anschubfinanzierung und Nachwuchsförderung” (ELAN); grant 09.01.13.1.

References


