Epilepsy is one of the most common neurological disorders, affecting approximately 50 million people worldwide. About 30% of the epilepsies are refractory to medical treatment and are associated with devastating socioeconomic consequences, diminished quality of life, and higher morbidity and mortality rates. Resective surgery is recognized as an effective treatment option for temporal lobe epilepsy (TLE) with proven results better than medical treatment. However, in approximately 30% of the patients with refractory focal epilepsy, seizures arise extratemporally (extratemporal lobe epilepsy [ETLE]). The surgical treatment of ETLE often presents a challenge for neurosurgeons and epileptologists that is reflected by moderate seizure-free rates, which are rarely higher than 50%. The accurate localization of the epileptogenic zone represents one of the greatest difficulties during the presurgical evaluation of ETLE. Although the routine establishment of high-resolution MRI has revolutionized epilepsy treatment by proper detection of the epileptogenic zone, in approximately 20%–40% of the patients with ETLE no surgical target can be identified. Patients with MRI-
negative epilepsy have the poorest seizure outcome and represent one of the greatest treatment challenges in tertiary epilepsy centers.21

Different technical tools, imaging modalities, and improvements have been developed in the hope of facilitating the treatment of MRI-negative epilepsy.28 One of those image modalities is the computational postprocessing of structural MR images by voxel-based comparison of morphometric changes in the gray/white delineation between patients and healthy individuals (morphometric analysis program [MAP] analysis).8,9,23 Recent studies have shown that MAP analysis can facilitate and increase the detection rate of focal cortical dysplasia (FCD) in patients with previously diagnosed MRI-negative epilepsy.23,24 Especially in cases with very small FCDs, the postprocessing results can be transferred to the structural MR image for a “second look” and can eventually lead to recognition of subtle lesions.25 However, MAP analyses are commonly performed separately from routine diagnostic tests, often limiting their availability during surgical procedures such as invasive electroencephalography (EEG) or resective surgery.19

As recently reported, a multimodal concept is commonly required during epilepsy diagnostic tests to create a precise working hypothesis about the localization of the epileptogenic zone.6,19 Such a multimodal concept should be robust, “straightforward,” and time efficient to be routinely applicable. Such practicable workflow has already been reported in 1 patient with previously nonlesional epilepsy, in whom electrode implantation was based on the integration of MAP results into the neuronavigation.26 During the past few years, an optimized and extended workflow was routinely integrated into the presurgical evaluation of patients with apparently nonlesional epilepsy at our center. Even more important, the neuronavigation-integrated data were used to designate a precise resection target, thus facilitating the surgical process.

In this study we report on 14 consecutive cases with apparently nonlesional epilepsy who underwent this algorithm and highlight some of the main aspects of the workflow. First, we have improved the integration of MAP (and other functional data) into the neuronavigation by creating regions of interest (ROIs), which were then transferred into the navigation software. Second, those ROIs were confirmed to match the epileptogenic zone by implanting a low number of depth electrodes, thus keeping the complication rate to a minimum. Finally, the ROIs were directly used for resection planning in those patients, who were referred for surgery. The final aim was to validate the use of the algorithm in clinical practice by reporting the detection rate of epileptic EEG activity and histological findings after ROI-navigated surgery for patients with apparently nonlesional epilepsy.

**Methods**

**Patient Characteristics and Noninvasive Presurgical Evaluation**

This was a single-center retrospective study. A total of 14 consecutive patients with apparently cryptogenic ETLE, treated from 2012 until 2015, were included and evaluated, which represents about 10% of the patients undergoing presurgical assessment during this time period. All patients underwent comprehensive presurgical workup at the Department of Epileptology and surgical treatment at the Department of Neurosurgery, both at the University Hospital in Bonn. Further patient characteristics are presented in Table 1. This retrospective audit was approved as such by the ethics committee of the University of Bonn Medical Center.

For each patient, 3.0-T MRI, ictal and interictal scalp video-EEG, and neuropsychological testing were performed. The epilepsy was defined as cryptogenic if no definitive epileptogenic lesion could be found after conventional visual analysis by an experienced neuroradiologist.

Postprocessing was performed using the MAP07 toolboxes for statistical parametric mapping (SPM; Wellcome Department of Cognitive Neurology) and MATLAB (The MathWorks, Inc.). The MAP analysis rationale and methods have been previously described.8,10 Postprocessing was performed on both 3D isotropic T1- and FLAIR-weighted images acquired at 3 T using the commercially available tool from the original developers. The resulting feature z-score maps were visually inspected in search of focal deviations from the norm. Abnormalities that were observed on more than 1 feature map were given more consideration. Back and forth comparison of these results with the structural images and the data collected from the EEG were used for completing the final report as well.

In some of the patients, additional ictal subtraction SPECT imaging (interictal SPECT subtracted from ictal SPECT) was performed using the ictal-interictal SPECT analysis by SPM (ISAS) implementation44 of the usual subtraction ictal SPECT coregistered to MRI (SISC0M) analysis.

**ROI Creation and Further Image Processing**

MRlcrco (http://www.mccauslandcenter.sc.edu/crnl/mrcro) and the FSL Suite (FMRIB Analysis Group) were used for evaluation of the results and creation of the ROIs. The ROIs were manually drawn on the T1-weighted images using the MAP feature maps (in most cases the extension map) as a guide. In some cases with highly significant single clusters, a simple threshold of the feature map was enough to obtain the ROI. After the ROIs were superimposed on the original T1-weighted image, the resulting Analyze image was converted to DICOM using the opensource tool kit XMedCon (http://xmedcon.sourceforge.net/).

**Stereotactic Implantation of Depth Electrodes**

All cases were discussed in regular multidisciplinary conferences. The feasibility of the MAP lesion being the probable epileptogenic zone was considered by cross-checking the semiological and neurophysiological information, other image modalities, as well as a “second look” at the structural MRI. In some cases the putative structural abnormalities were identified only after automatic postprocessing analysis that guided the neuroradiologists (“second look”). These MRI abnormalities were considered subtle lesions. After a consensus was reached, patients were pro-
posed to undergo invasive surgical evaluation to confirm the putative epileptogenic focus by video-EEG recordings.

The created ROIs were used as targets for the depth electrodes. Subdural strip or grid electrodes were not used in this series. The T1-weighted DICOM images with the superimposed ROI were easily imported into the neuronavigation system. For the implantation of all depth electrodes, a Leksell stereotactic frame was used, which was placed on patients’ heads under general anesthesia. A CT scan was then obtained, the images were exported to iPlan Net Stereotaxy version 2.3 (BrainLAB), and an image fusion between the CT scan and the MR image with designated ROIs and trajectories was performed to obtain the coordinates of the electrodes. A CT scan was performed immediately after surgery to check the position of the electrodes and rule out bleedings and further complications. The correct localization of the depth electrodes was also confirmed on MRI, usually after a sufficient number of seizures were registered and before the removal of the electrodes. The mean (± SD) duration of the invasive diagnostic was 7.8 ± 2.9 days (range 3–15 days).

Invasive EEG Recordings and Video Monitoring

One day after electrode implantation, continuous video-EEG recordings were started at the Department of Epileptology. EEG data acquisition was performed with a Micromed System Plus Evolution System (Micromed) using up to 128 channels, a sampling rate of 200 Hz, and a 16-bit analog to digital converter. Data were band-pass filtered between 0.53 and 70. If necessary, antiepileptic drugs were reduced or withdrawn so that occurrence of habitual seizures was facilitated.

Resection Planning

If the depth electrodes confirmed the hypothesis of the epileptogenic focus, the ROIs were further processed to match an extended lesionectomy (resection ROIs, [rROIs]) and transferred again into the neuronavigation. The rROI included the ROI plus a small amount of adjacent healthy cortex to make the resection anatomically coherent (see Figs. 3C and 4C) with the ultimate goal of completely resecting the cortical abnormality. The complete algorithm is shown in Fig. 1.

Results

Noninvasive Diagnostics, MAP and SISCOM Analysis

In 11 (79%) of the 14 apparently MRI-negative patients, a clinically plausible MAP abnormality was found (Fig. 2, Table 1). In 8 of those patients a very subtle MRI lesion was retrospectively identified when refocusing on the MAP abnormality, usually a possible FCD with almost no cortical thickening and very mild transmantle sign (Fig. 3B).

SPECT and SISCOM were performed in 8 patients. In 6 (75%) of the 8 patients, a single informative hyperperfusion cluster was found. In 4 patients SISCOM analysis confirmed the MAP findings and additionally helped identify 2 MAP-negative lesions after reevaluation of the hyperperfusion cluster on the structural images (Fig. 2, Table 1).

One patient (Case 7, Table 1) ultimately received electrode implantation after a very mild fluid-attenuated inversion recovery (FLAIR) abnormality in the right cingulum was identified. In this particular patient, MAP and SISCOM analysis were negative, but the seizure semiology during video-EEG monitoring with surface EEG was consistent with this hypothesis. This patient was included in the study because both electrode implantation and guided resection were performed according to the algorithm (Fig. 1).

Electrode Implantation, Invasive EEG, and Focus Detection Rate

All 14 patients underwent implantation of depth elec-

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>MAP ISAS</th>
<th>Localization of the Lesion</th>
<th>Depth Electrodes</th>
<th>Invasive EEG</th>
<th>Histology</th>
<th>Treatment</th>
<th>Follow-Up (mos)</th>
<th>Engel Class</th>
<th>ILAE (1–6)</th>
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<tr>
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<td>Frontal</td>
<td>4</td>
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<td>Lesionectomy</td>
<td>12</td>
<td>IA</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>18</td>
<td>6 -</td>
<td>+</td>
<td>Frontal</td>
<td>2</td>
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<td>IA</td>
</tr>
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<td>3</td>
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<td>2 +</td>
<td>NP</td>
<td>Frontal</td>
<td>2</td>
<td>Seizure &amp; ID</td>
<td>FCD IIA</td>
<td>Lesionectomy</td>
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<td>IA</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>22</td>
<td>34 +</td>
<td>+</td>
<td>Frontal</td>
<td>2</td>
<td>Seizure &amp; ID</td>
<td>FCD IIA</td>
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<td>16</td>
<td>IA</td>
</tr>
<tr>
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<td>F</td>
<td>44</td>
<td>6 +</td>
<td>+</td>
<td>Frontal</td>
<td>1</td>
<td>Seizure &amp; ID</td>
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<tr>
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<td>16</td>
<td>14 −</td>
<td>+</td>
<td>Frontal</td>
<td>2</td>
<td>Seizure &amp; ID</td>
<td>FCD IIB</td>
<td>Lesionectomy</td>
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<td>IA</td>
</tr>
<tr>
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<td>M</td>
<td>34</td>
<td>6 −</td>
<td>−</td>
<td>Frontal</td>
<td>2</td>
<td>Seizure &amp; ID</td>
<td>Gliosis</td>
<td>Lesionectomy</td>
<td>16</td>
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</tr>
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<td>29</td>
<td>19 +</td>
<td>−</td>
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<td>Seizure &amp; ID</td>
<td>Unspecific</td>
<td>Lesionectomy</td>
<td>16</td>
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<tr>
<td>11</td>
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<td>46</td>
<td>7 +</td>
<td>+</td>
<td>Frontal</td>
<td>2</td>
<td>Seizure &amp; ID</td>
<td>FCD IIB</td>
<td>Lesionectomy</td>
<td>16</td>
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</tr>
<tr>
<td>12</td>
<td>F</td>
<td>19</td>
<td>20 +</td>
<td>+</td>
<td>Frontal</td>
<td>4</td>
<td>Seizure &amp; ID</td>
<td>FCD IA</td>
<td>Lesionectomy</td>
<td>17</td>
<td>IIIA</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>22</td>
<td>8 +</td>
<td>NP</td>
<td>Frontal</td>
<td>2</td>
<td>Seizure &amp; ID</td>
<td>FCD IIB</td>
<td>Lesionectomy</td>
<td>5</td>
<td>IA</td>
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<tr>
<td>14</td>
<td>M</td>
<td>47</td>
<td>9 +</td>
<td>NP</td>
<td>Frontal</td>
<td>2</td>
<td>Seizure &amp; ID</td>
<td>FCD IIB</td>
<td>Lesionectomy</td>
<td>6</td>
<td>IA</td>
</tr>
</tbody>
</table>

+ = positive; − = negative; ID = interictal discharges; NP = not performed.
trodes as part of the invasive presurgical diagnostics. A total of 33 ROI-guided depth electrodes were stereotactically implanted. No complications, hemorrhages, or neurological deficits occurred during or after the invasive diagnostics. Postoperative MRI confirmed the correct localization of the depth electrodes in 12 patients. In 1 patient (Case 9), the depth electrodes were not exactly in the ROI but hit its border and showed epileptogenic activity, making it suitable for further diagnostics. The ROI was missed in 1 patient (Case 4, Table 1), which was corrected after...
performing a second implantation procedure (2 additional depth electrodes).

The invasive EEG (iEEG) registered interictal and ictal epileptiform discharges in 12 patients. One patient (Case 8, Table 1) presented only interictal discharges and another (Case 9, Table 1) displayed only ictal discharges without interictal activity.

**Surgery, Histology, and Outcome**

A total of 13 patients underwent resective surgery after the invasive diagnostics, leading to 12 frontal and 1 insular lesionectomies. The extension of the resection volume (rROI) was discussed and designated in a multidisciplinary conference (Fig. 3C and D; Fig. 4C and D). One patient underwent radiosurgery, as the rROI would have included the precentral gyrus, thus bearing a high risk for postoperative neurological deficit.

The histological analysis findings were distributed as follows: 9 patients with FCD (FCD IA = 1, FCD IB = 1, FCD IIA = 3, FCD IIB = 4), 3 patients with gliosis and 1 patient with unspecfific findings. Surgical complications after resective surgery occurred in 3 patients; 1 of them suffered from minor permanent neurological deficit.

Mean postoperative follow-up was 17 ± 6.9 months.
Multimodal concept for surgical treatment of nonlesional epilepsy

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Postoperative seizure outcome was rated according to both the Engel and the International League Against Epilepsy (ILAE) classifications (Table 1). At the last available follow-up, 57% of the patients (n = 8) were completely seizure free (ILAE Class I or Engel Class IA). The remaining 6 patients continued having seizures. Subsequent analysis to explain surgical failure revealed incomplete (or not extended) resection, unspecific histology, and lack of ictal discharges during the iEEG (Table 2). One patient with Engel Class IV/ILAE Class 5 (Case 9) underwent radiosurgery because of the eloquently localized epileptogenic lesion. Another patient (Case 8) was seizure free for 1 year but presented with relapse of seizures after discontinuing the antiepileptic drugs.

Discussion

In this retrospective case series, an algorithm for ROI-guided stereotactic implantation of depth electrodes followed by neuronavigated resective surgery was rigorously applied to 14 consecutive patients with previously nonlesional epilepsy, achieving full seizure control in 57% of the cases. The results support the feasibility and usefulness of a technical method for implementation of ROI-based targets into the neuronavigation. The very selective ROI-guided stereotactic implantation of a low number of depth electrodes was able to confirm the seizure-onset hypothesis and lead to surgery in 13 of 14 patients. In our opinion, one of the greatest challenges of daily practice during the preparation of complex epilepsy cases for surgery is

FIG. 4. Case 2. Visualization of important algorithm steps, starting with ISAS analysis and ending with resection. A: Identification of a lesion based on hyperperfusion during the ISAS analysis. B: Second look on the normal MRI leading to identification of a very subtle lesion (putative FCD). C: Creation of the ROI (green area) based on data from the ISAS analysis followed by ROI-guided implantation of the depth electrodes, confirming the epileptogenicity of the lesion. Creation of the rROI (blue area). D: Postoperative MRI showing extent of the resection. Figure is available in color online only.
to find an appropriate and efficient way of communication and logistics between epileptologists and neurosurgeons. In our case series, we illustrated how such difficulties can easily be overcome: the epileptologist creates an ROI that summarizes all the information required to confirm the seizure-onset hypothesis. By simply implementing the ROI into the neuronavigation system, the neurosurgeon is able to plan independently the implantation procedure and the following resection. Because the ROI implementation into the neuronavigation has made the neurosurgical planning more practical and straightforward, this simple algorithm is currently used on a routine daily basis in our department. Finally, the multimodal concept has been further developed to plan an ROI-navigated lesionectomy, facilitating surgery in a rather challenging subgroup of patients with MRI-negative ETLE.

**Importance of Stereotactic ROI-Guided Invasive Diagnostic**

Invasive diagnostics with depth electrodes involves hazards but can hardly be skipped in formerly nonlesional cases. The ROI-guided invasive diagnostics allowed selective targeting, leading to implantation of a very low number of electrodes (mostly 1 or 2). There were no complications related to the electrode implantation. The epileptogenicity of the presumed lesion could be confirmed not only in the 11 cases that were MAP-positive, but also in those with just presumed abnormalities based on SPECT findings or suspected subtle MRI lesions (and consistent electroclinical findings on video-EEG recordings with surface electrodes). Thus, the implantation of a minimal number of depth electrodes facilitated the invasive diagnostic without leading to any obvious disadvantages for the patient.

**Histological Findings, Seizure Outcome, and Failure Analysis**

Unspecific histological results or gliosis were found in only 4 patients. These findings are similar to the results recently reported by Wang et al., who described approximately 30% pathologically negative results (gliosis, hamartia, or normal).14

Eight patients (57%) were seizure free at the last available outcome, which is similar to other case series with ETLE.5 If compared with series describing MRI-negative extratemporal epilepsies, the seizure-free rate among our cohort was higher,15,16 thus supporting the role of the presented algorithm in creating a constrained focus hypothesis and facilitating the resection. However, this could be also due to the fact that the series of MRI-negative patients with ETLE included very different epilepsy syndromes and histological findings and were not focused on a small and homogeneous group of epilepsy syndromes, mostly caused by FCD, as was the case in our series.

Failure analysis of the patients who did not become seizure free suggests that incomplete or narrow resection and unspecific histology may predict unfavorable outcome following resective surgery. Additionally, patients without completely coherent iEEG findings (i.e., lack of ictal activity during iEEG) appear to be at greater risk of not becoming seizure free.

**Comparison With Previous Studies**

In their recent studies, Rodionov et al.19 and Nowell et al.17 reported a workflow describing the feasibility of 3D neuroimaging during the implantation of intracranial electrodes. There are, however, some differences to our approach. First, the surgical procedures of this study were mainly based on the data delivered from MAP analysis in nonlesional epilepsy. Second, these 2 studies used a standalone software platform (Amira) to integrate the multimodal data, whereas we created a MAP/SISCOM-based ROI, which was then transferred into DICOM format. This allowed the import and coregistration of the ROIs more easily to the structural MR images of the patients, followed by the direct planning of the trajectories for the depth electrodes. A further advantage of the direct ROI integration into the neuronavigation was its availability during the planning and performing of the resection. This last step of the algorithm has been described here for the first time. Two other studies15,31 have investigated the role of multimodal imaging for apparently nonlesional epilepsy. However, these works predominantly addressed presurgical evaluation and focus localization and not the intraoperative usage of the data. The importance of the intraoperative usage of multimodal data during epilepsy surgery has been described in previous studies by Wellmer et al.27 and Murphy et al.,28 but these case series did not include any postprocessing data.

In contrast to previous works,15 only a small number of depths electrodes were implanted in our patients, and almost all patients underwent resective surgery after the invasive diagnostic. This fact probably reflects the “go-no-go” mentality of our approach. That is, our approach

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**TABLE 2. Failure analysis of the patients who did not become seizure free due to surgical and/or epileptological reasons**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Surgical Reasons</th>
<th>Histology</th>
<th>Invasive EEG</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Complete and extended resection</td>
<td>Unspecific*</td>
<td>Seizure &amp; ID</td>
</tr>
<tr>
<td>8</td>
<td>Incomplete resection*</td>
<td>Unspecific*</td>
<td>ID*</td>
</tr>
<tr>
<td>9</td>
<td>No resection, only radiotherapy*</td>
<td>No histology*</td>
<td>Seizure &amp; ID</td>
</tr>
<tr>
<td>10</td>
<td>Complete and extended resection</td>
<td>Unspecific*</td>
<td>Seizure &amp; ID</td>
</tr>
<tr>
<td>11</td>
<td>Complete, but not extended resection*</td>
<td>Specific (FCD IIb)</td>
<td>Seizure &amp; ID</td>
</tr>
<tr>
<td>12</td>
<td>Complete, but not extended resection*</td>
<td>Specific (FCD IA)</td>
<td>Seizure &amp; ID</td>
</tr>
</tbody>
</table>

* Characteristics considered to negatively influence the final seizure outcome.
aimed at confirming a subtle suspected lesion as being the epileptogenic focus, to proceed with further resection. We intentionally avoided a more extensive exploratory approach, requiring numerous intracranial electrodes. Thus, the risk related to the multiple depth electrode implantations was decreased by simultaneously increasing the rate of successful resective surgery. Our algorithm is somewhat more conservative, as we prefer to use only a small number of electrodes based on MRI or other modalities, thus increasing the number of confirmed hypotheses for resection. Nevertheless, the aim of this study was not to assess the efficacy of this proposed algorithm and to compare it to other approaches, but rather to describe the procedure and to report its feasibility.

Limitations of the Study

The present study was not designed to evaluate the effectiveness of the MAP analysis for detecting FCDs or to compare the efficacy of resection techniques. Due to the low number of implanted electrodes, the true extent of the seizure generator could have been underestimated due to spatial sampling error. This would also be true if extensive mapping of eloquent cortex would be needed. In such cases, either the implantation of more depth electrodes or the combination of depth and subdural grid electrodes can be taken into consideration. The postoperative seizure outcome, however, was excellent in 57% of our patients, strengthening the validity of our approach. The relatively small number of patients and the retrospective nature of our case series do not allow the identification of selection criteria for suitable candidates and predictors of favorable postsurgical outcome. This is also the reason why the reported seizure-free rate, which was higher than other ETLE studies, should be carefully interpreted and needs validation in a larger cohort. Further development of MRI (greater field strengths, novel technical sequences) and improved postprocessing techniques will hopefully increase the surgical options for patients without lesions. A further potential technical limitation of our approach is the usual shift of the brain caused by the implantation of the depth electrodes, which may impair the accuracy of the overlay of the images before and after the implantation. In view of the low number of implanted electrodes, this shift is likely to be less important than in cases of extended implantations.

Conclusions

We present an algorithm for invasive diagnostics followed by resective surgery in previously nonlesional epilepsy based on the neuronavigated ROIs obtained after postprocessing of MRI data. Our results support the role of the postprocessing analysis in localizing the epileptogenic zone and suggest that its confirmation can be achieved with a restricted number of depth electrodes. Furthermore, the integration of the ROIs into the neuronavigation facilitated the surgical procedure, which can be a challenging obstacle in cases of apparently nonlesional epilepsy. Finally, all steps were incorporated in a robust and straightforward algorithm, allowing its use in daily clinical practice.

References

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Disclosures
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Author Contributions
Conception and design: Delev, Quesada, Surges. Acquisition of data: Delev, Quesada, Grote, Boström. Analysis and interpretation of data: Delev, Quesada, Surges. Critically revising the article: Grote, Boström, Elger, Vatter, Surges.

Supplemental Information
Previous Presentations
Part of this work was presented in abstract form at the 67th annual meeting of the German Society of Neurosurgery (DGNC), Frankfurt, Germany, in June 2016.

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