

Source localization of rhythmic ictal EEG activity: A study of diagnostic accuracy following STARD criteria

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SUMMARY

Purpose: Although precise identification of the seizure-onset zone is an essential element of presurgical evaluation, source localization of ictal electroencephalography (EEG) signals has received little attention. The aim of our study was to estimate the accuracy of source localization of rhythmic ictal EEG activity using a distributed source model.

Methods: Source localization of rhythmic ictal scalp EEG activity was performed in 42 consecutive cases fulfilling inclusion criteria. The study was designed according to recommendations for studies on diagnostic accuracy (STARD). The initial ictal EEG signals were selected using a standardized method, based on frequency analysis and voltage distribution of the ictal activity. A distributed source model—local autoregressive average (LAURA)—was used for the source localization. Sensitivity, specificity, and measurement of agreement (κ) were determined based on the reference standard—the consensus conclusion of the multidisciplinary epilepsy surgery team. Predictive values were calculated from the surgical outcome of the operated patients. To estimate the clinical value of the ictal source analysis, we compared the likelihood ratios of concordant and discordant results. Source localization was performed blinded to the clinical data, and before the surgical decision.

Key Findings: Reference standard was available for 33 patients. The ictal source localization had a sensitivity of 70% and a specificity of 76%. The mean measurement of agreement (κ) was 0.61, corresponding to substantial agreement (95% confidence interval (CI) 0.38–0.84). Twenty patients underwent resective surgery. The positive predictive value (PPV) for seizure freedom was 92% and the negative predictive value (NPV) was 43%. The likelihood ratio was nine times higher for the concordant results, as compared with the discordant ones.

Significance: Source localization of rhythmic ictal activity using a distributed source model (LAURA) for the ictal EEG signals selected with a standardized method is feasible in clinical practice and has a good diagnostic accuracy. Our findings encourage clinical neurophysiologists assessing ictal EEGs to include this method in their armamentarium.

KEY WORDS: EEG, Epilepsy, Seizure, Sensitivity, Specificity, Predictive value.

The epileptogenic zone (cortical area indispensable for the generation of clinical seizures) cannot be localized by a single method (Rosenow & Lüders, 2001). Therefore the

presurgical investigation relies on a multimodal approach, in which an important part is the localization of the seizure-onset zone, defined as the area of the cortex from which clinical seizures are actually generated, as demonstrated by electroencephalography (EEG) techniques (Rosenow & Lüders, 2001).

Most studies on the accuracy of EEG source localization techniques focused on the interictal epileptiform discharges (the irritative zone) (Michel et al., 2004; Leijten & Huiskamp, 2008; Plummer et al., 2008; Brodbeck et al., 2011). However, several studies suggested that the source of interictal epileptiform activity does not necessarily coincide with the seizure-onset area (So et al., 1989; Hirsch et al., 1991; Alarcon et al., 1994). Despite the high clinical relevance, there are relatively few clinical studies on the source localization of the ictal epileptiform activity. None of the previously published studies included blinded analysis and interpretation of the source localization, and only

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one study was prospective (Boon et al., 2002). Similarly, only one study determined the specificity (Assaf & Ebersole, 1997), whereas the majority of studies were done on relatively few (5–15) patients (Boon & DHavé, 1995; Lantz et al., 1999; Blanke et al., 2000; Worrell et al., 2000; Lantz et al., 2001; Merlet & Gotman, 2001; Beniczky et al., 2006; Ding et al., 2007; Stern et al., 2009; Holmes et al., 2010; Koessler et al., 2010; Yang et al., 2011; Lu et al., 2012a,b). The only prospective study in the literature, which also included a larger patient population (Boon et al., 2002) addressed the clinical usefulness of EEG source localization techniques as defined by their influence on decision-making. However, the accuracy (sensitivity and specificity) of the ictal source localization was not determined in this study.

The major difficulties with analyzing the source localization of ictal EEG activity consist in artifacts often occurring during the seizures, low signal-to-noise ratio, absence of ictal EEG correlate in scalp recordings, short duration of some seizures, and the rapid propagation of ictal activity (Pacia & Ebersole, 1997; Foldvary et al., 2001; Rosenow & Lüders, 2001; Boon et al., 2002). Although a standardized algorithm for the analysis of interictal epileptiform discharges has been proposed (Leijten & Huiskamp, 2008), there is no consensus on the strategy of localizing the source of the rhythmic ictal activity (Foldvary et al., 2001).

To improve the accuracy and completeness of reporting of studies of diagnostic accuracy, and to improve the design of these studies, the STARD (Standards for Reporting of Diagnostic Accuracy) initiative was published simultaneously in six journals (Bossuyt et al., 2003).

Our objective was to assess the clinical feasibility and to estimate the accuracy of source localization of rhythmic ictal activity, using a distributed source model (local autoregressive average [LAURA]) for the ictal EEG signals selected with a standardized method. The aim of the standardized method was to shortcut the intrinsic problems of the ictal EEG signals—the low signal-to-noise ratio and the rapid propagation—using an approach that is not time-consuming and that is feasible in the clinical practice. We designed the study and we report it according to the STARD criteria. We determined the sensitivity, specificity, predictive values, and likelihood ratios of the ictal source localization.

METHODS

EEG data

Long term video-EEG recordings were done as part of the presurgical workup at the epilepsy monitoring unit (EMU), Department of Clinical Neurophysiology, Danish Epilepsy Center, Dianalund, Denmark, between 2008 and 2011. Prior to being admitted to the EMU, patients gave their informed consent. The regional ethics committee and the national data protection agency approved the study.

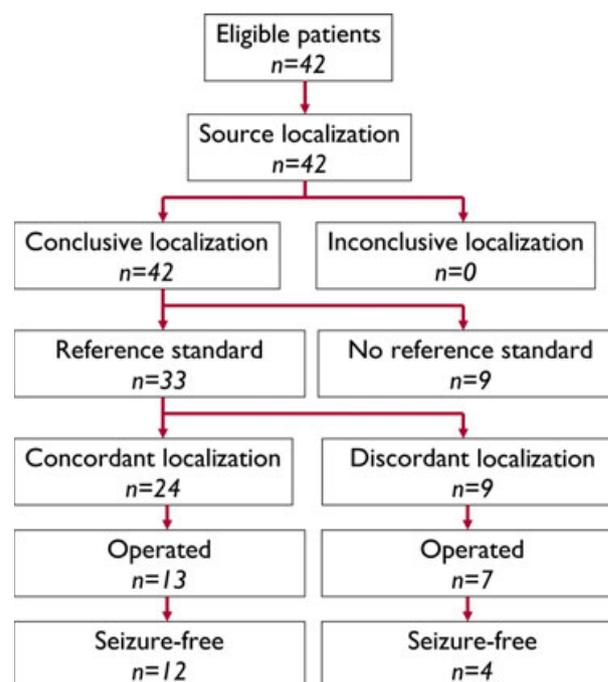


Figure 1.

Flowchart of the study. Concordant localization: match between the ictal source localization and the reference standard (at sublobar level). Discordant localization: no match between the ictal source localization and the reference standard (at sublobar level). *Epilepsia* © ILAE

Ictal EEG data from 42 consecutive patients (23 female), aged between 9 and 69 years (mean 35.9, median 38 years) fulfilling the inclusion criteria were analyzed (Fig. 1 – STARD flow diagram). Inclusion criteria were the following: (1) patients with therapy-resistant focal epilepsy; (2) seizures affecting the social life of the patients and causing significant decrease in the quality of life (determined by the multidisciplinary team); and (3) at least one habitual seizure with rhythmic ictal activity recorded in the EMU. Patients with previous cranial surgery were excluded.

Eighteen patients referred to the EMU for presurgical evaluation did not meet the inclusion criteria. Two patients did not have epileptic seizures. In five patients, ictal EEG activity could not be identified at all. Two patients were excluded because of previous cranial surgery. In three patients the ictal EEG was obscured by artifacts. In six patients, ictal patterns other than rhythmic activity were identified: irregular, arrhythmic burst of spikes (three patients), sharp-waves (one patient), sharp-and-slow-wave complexes (one patient), and electrodecremental response not followed by other ictal EEG pattern (one patient).

All patients had MRI of the brain (3 Tesla) according to the epilepsy surgery protocol. MRI showed a potentially epileptogenic lesion in 25 patients. Patients with normal magnetic resonance imaging (MRI) and those with discordant data (EEG, semiology, MRI) underwent functional

neuroimaging studies too. Eleven patients had only single photon emission computed tomography (SPECT) scans (ictal and interictal; eight patients had subtraction ictal SPECT coregistered with MRI = SISCOM); seven patients had only fluorodeoxyglucose–positron emission tomography (FDG-PET) scans; two patients had both SPECT and PET scans. Altogether 20 patients had functional neuroimaging studies. Demographic and clinical data of the 42 patients are summarized in Data S1.

EEG was recorded using a standard 25 electrode array (19 electrodes of the international 10–20 system, extended with six electrodes in the inferior temporal chain: F9/10, T9/10, P9/10) (Scherg et al., 2002) and a sampling rate of 256 samples/s. Recordings were digitally filtered off-line (1–70 Hz). To lessen any extra burden on the standard clinical procedures, we used for analysis the lowest possible amount of electrodes (but covering also the inferior part of the temporal lobes), standard electrode positions, and template MRI.

Ictal source localization

The steps of the standardized method for the ictal source localization are illustrated in Figure 2. Seizures were visually identified by a board-certified clinical neurophysiologist (SB) with experience in assessing long-term video-EEG recordings. For patients with several recorded seizures, only one seizure was analyzed (the least affected by artifacts), provided all seizures were considered stereotypical, and showing the same rhythmic ictal activity. When the seizures were considered as having different semiology or showing different EEG patterns at onset, each seizure was analyzed separately and included into further evaluation.

The ictal rhythmic activity had to be the earliest (first) EEG pattern (except for electrodecremental response), but it could occur at any time throughout the seizure. The next step was the preparation of the ictal EEG signals for the source localization. The electrographic start was marked at

the time point where the earliest rhythmic ictal activity was identified. To limit the source localization to the initial scalp EEG activity, we combined two strategies based on the results of previous publications (Assaf & Ebersole, 1997; Lantz et al., 1999, 2001; Merlet & Gotman, 2001; Beniczky et al., 2006). First we marked the end point of the analyzed EEG epoch as follows. The frequency of the EEG activity was analyzed using fast Fourier transform (FFT) in successive segments of 1 s, with a 50% sliding window (Fig. 3). The end point was identified where the peak frequency of the segment deviated by 1 Hz from the frequency in the first segment. Therefore, the epochs used for the analysis consisted of the period from ictal onset to the time point where the frequency of the ictal activity deviated more than 1 Hz from the initial frequency. The duration of these epochs ranged between 1 and 11 s (median 3 s). Then, within these epochs, voltage maps were drawn at the time points corresponding to the negative peaks in the channel with the highest amplitude of the ictal signal, in common average montage. Ictal waves showing similar voltage map distributions were averaged aligned to the negative peak (Fig. 3). Voltage distributions were considered similar, when the negative peaks were in the same location in the voltage maps and the positive peaks were in the same quadrant of the two-dimensional (2D) map. When artifacts affected the whole ictal epoch, the signals were digitally filtered, focusing on the peak frequency of the rhythmic activity. Ictal waves considered outliers were discarded; these waves were typically contaminated by artifacts, resulting in a voltage distribution different from the majority of the ictal waves in the epoch selected as described earlier. After averaging the selected ictal waves, successive voltage maps were displayed that corresponded to the ascending part of the averaged waveform (Fig. 4), from the start of the ascending (negative) slope (time zero) to the negative peak of the wave. On the sequential voltage maps, the negative and positive peaks were automatically marked (Fig. 4) and the emerging topographies were easily visualized. The lines connecting these points reflected well the changes in voltage distribution. Topographies were considered to resemble each other when the negative peaks were in the same location in the voltage maps, and the positive peaks were in the same quadrant of the 2D map. When the topography did not change throughout the ascending phase, the time point corresponding to the largest amplitude (negative peak) was forwarded for further analysis. When the voltage map distribution changed during the ascending slope of the averaged waveform, the last time point of the topography closest to time zero (initial voltage distribution) was marked and forwarded for further analysis. In practice this meant the time point with the largest global field power (GFP) within the initial voltage distribution, as defined earlier.

This method of selecting and preparing ictal EEG signals was feasible in the clinical practice, and it only took 5–10 min of extra work in the clinical setting. The EEG

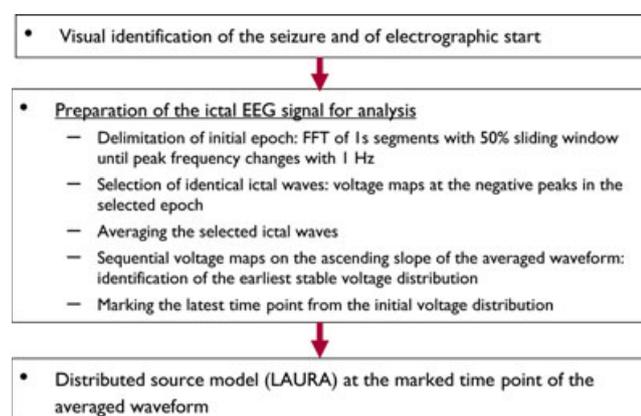


Figure 2. Steps of the standardized method for ictal source localization. *Epilepsia* © ILAE

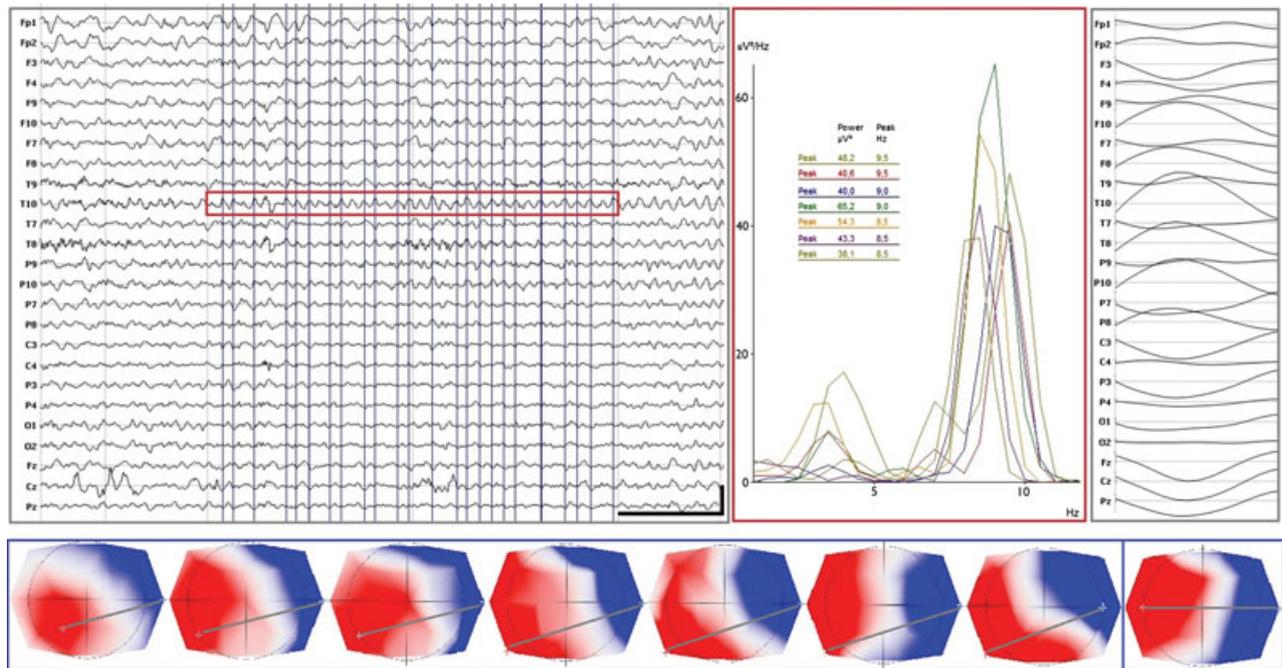


Figure 3.

Selection and preparation of ictal EEG signals for the source analysis. Upper row, to left: EEG recording at the electrographic seizure start (patient 12). Scale: $1 \text{ s} \times 100 \mu\text{V}$. FFT analysis is performed on successive segments of 1 s, with a 50% sliding window (upper row, in the middle) until the decrease in peak frequency changes by 1 Hz (from 9.5 to 8.5 Hz). This way, the EEG epoch to be analyzed further is delimited (red box within the EEG recording). Voltage maps are drawn at the negative peaks (lower row). Signals with similar voltage distribution are averaged; in this figure the last voltage distribution (lower row, to the right) is different; therefore, it is not included into the averaging. The averaged waveform is shown in the upper row to the right.

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signals prepared as described earlier were fed into a freely available source analysis software (Cartool) by one of the authors (IR), a neuropsychiatrist who was blinded to all clinical data.

The source reconstruction algorithm that was used in this study (LAURA) belongs to the class of distributed source models. For details see (Grave de Peralta Menendez et al., 2004). The source reconstructions space was built using an anatomically constrained head model (Spinelli et al., 2000), with 3005 solution points that were restricted to the gray matter of the MRI. A template MRI, the so-called Montreal Neurological Institute (MNI) brain, was used. This standard brain has been constructed by the Montreal Neurological

Institute by using a large series of MRI scans on normal controls.

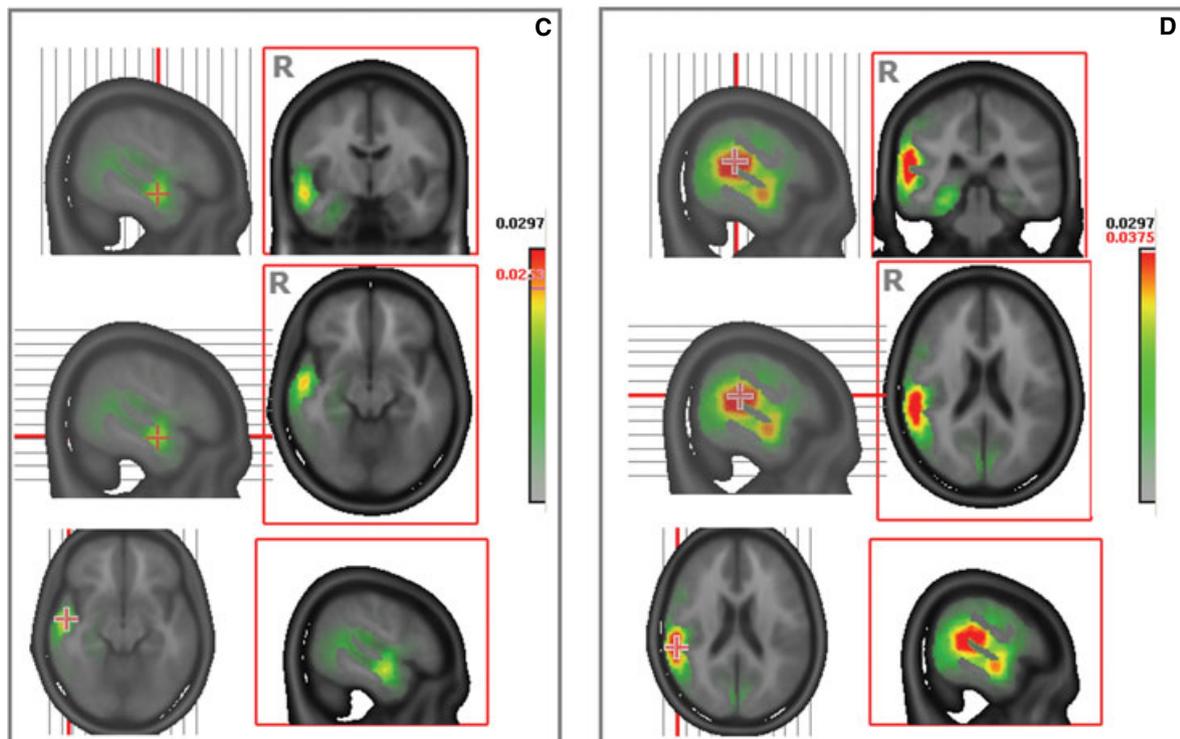
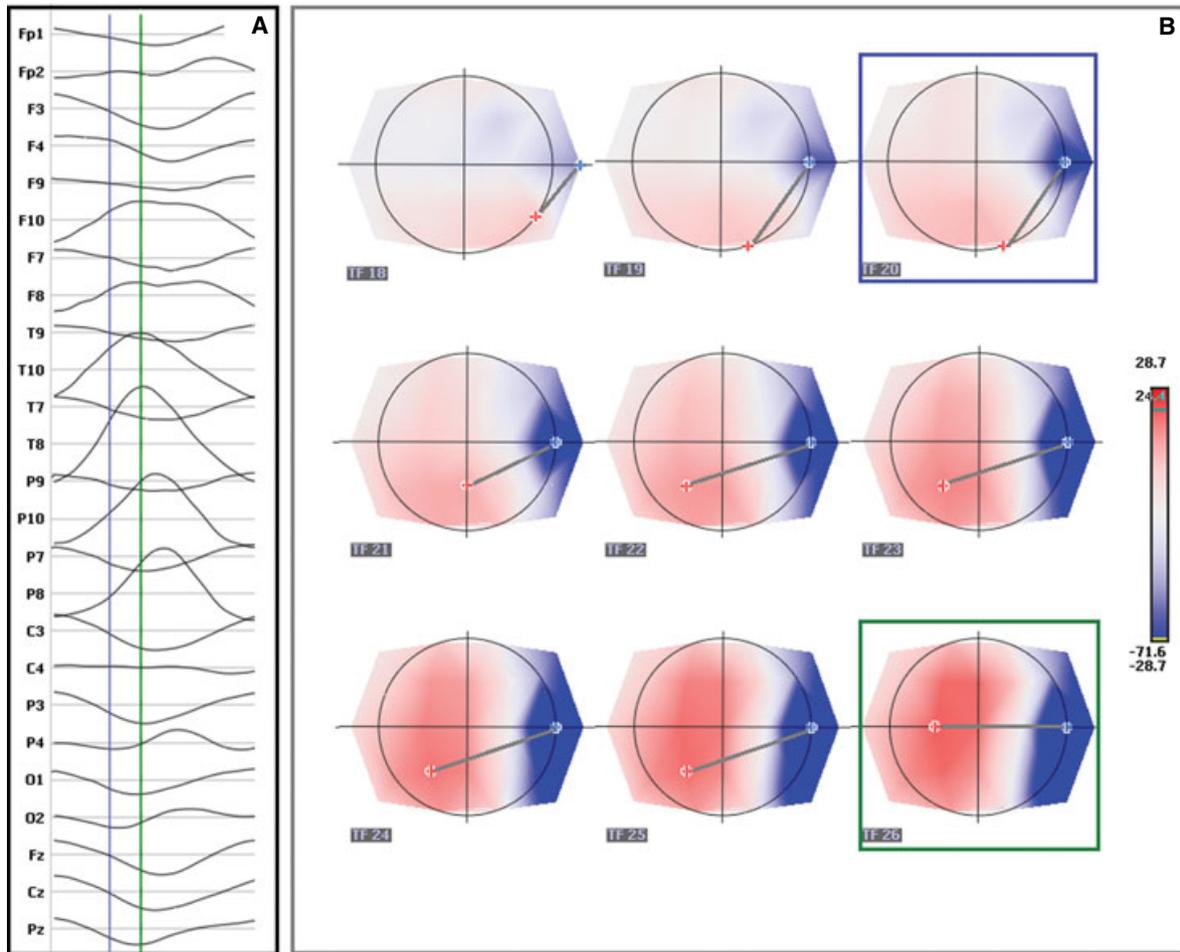
The source localization was done at the marked time point of the averaged waveform (as detailed above). Neither regularization constant nor automatically set intensity scales were changed. Postprocessing was not done, and each signal was analyzed only once (iteration was not allowed).

The anonymized axial, coronal and sagittal images were inspected by a board-certified neuroradiologist (PA) with experience in the presurgical evaluation, who was blinded to all other data. The maxima were automatically marked (Fig. 4), but the rest of the activity was also visualized and the neuroradiologist inspected the whole distributed source

Figure 4.

Ictal source localization in a patient with right mesial temporal focus (patient 15). (A) The averaged waveform. (B) Sequential voltage maps on the ascending slope of the averaged waveform (timeframes: 18–26; duration of a timeframe: 4 msec). In each voltage map the negative and positive peaks are marked automatically. A change in the voltage distribution along the ascending slope is observed. Source localization is performed at timeframe 20 (blue box in Fig. 4B corresponding to the blue cursor line in Fig. 4A) and at timeframe 26 (green box in Fig. 4B corresponding to the green vertical cursor in Fig. 4A). (C) The source localization corresponding to the initial voltage distribution (timeframe 20) shows activation at the anterior part of the right temporal lobe/pole. (D) At the peak of the averaged waveform (timeframe 26) the activation propagates to the posterior-lateral part of the temporal lobe and to the parietal lobe. The original ictal EEG is shown in Data S5.

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model. The localization of the ictal source as showed by the distributed source model (LAURA) was logged.

Reference standard

For determining the diagnostic accuracy of ictal source localization, the reference standard for localizing the seizure-onset zone was the consensus conclusion of the local multidisciplinary epilepsy surgery team (Rosenow & Lüders, 2001; Burch et al., 2012a,b). The team included experienced, board-certified clinical neurophysiologists, epileptologists, and neuropsychologists who evaluated the video-EEG recordings, able to change between different montages, and who had access to all clinical and neuroimaging data interpreted by an experienced neuroradiologist. Ictal source localization data were not included in the decision process. Because no single or fixed reference method is available for the localization of the seizure-onset zone (Stefan, 2011; Burch et al., 2012a,b), a consensus decision is necessary for the reference standard (Weller & Mann, 1997; Bossuyt et al., 2003). We calculated the predictive values based on the surgical outcome, as evaluated 1 year after the operation.

Evaluation of the localization results

The results of the ictal source localization and the conclusion on the seizure-onset zone of the multidisciplinary team were logged at a sublobar level (side + lobe + sublobar region). The source localization was considered concordant with the reference standard when there was a match at the sublobar level.

When several seizure types were recorded, the ictal localization results were logged as independent foci. The other scenario resulting in multiple localizations was the simultaneous activity at the analyzed seizure-onset time point. If the reference standard matched all of these localizations, the ictal source localization was considered concordant with the reference standard. If these localizations only partially matched the reference standard (only one focus identified correctly), the source localization was considered discordant.

Because of the relatively low number of electrodes, we did not attempt to evaluate the results at a higher spatial resolution. Although a higher spatial resolution would be desirable, in our experience the sublobar precision of localizing the seizure-onset zone is reasonably accurate for clinical decision making.

Sensitivity (Fisher & van Belle, 1993) was calculated as the percentage of true positive patients (i.e., patients who had source localization concordant with the reference standard). Specificity was calculated according to the formula: number of true negatives / (number of true negatives + number of false positives). Because the number of patients with focus outside the temporal lobe was low, we have grouped them together. In each subgroup, true negative was considered a localization outside the region of interest, this being

confirmed by the reference standard; false positive was considered a localization in the region of interest, this being contradicted by the reference standard.

The measurement of agreement between the source localization and the reference standard, and 95% confidence intervals (CIs) was determined by weighted Cohens kappa (Fleiss, 1981; Altman, 1991). Because most of the patients in our series had temporal lobe epilepsy, for kappa statistics we defined the following categories: left temporal mesial, right temporal mesial, bilateral temporal mesial, left temporal lateral-neocortical, right temporal lateral-neocortical, bilateral temporal lateral-neocortical, left temporal mesial-and-lateral, right temporal mesial-and-lateral, bilateral temporal mesial-and-lateral, and extratemporal.

Based on studies using simultaneous recording of scalp EEG and intracranial electrodes, we categorized a temporal ictal source as mesial when it was localized in the mesial structures, basal part of the temporal lobe, and/or the anterior part of the temporal lobe (pole); other localizations were categorized as lateral-neocortical (Alarcon et al., 1994; Assaf & Ebersole, 1997; Pacia & Ebersole, 1997; Merlet & Gotman, 2001; Wennberg et al., 2011).

Kappa values were interpreted according to the conventional groups: no agreement ($k < 0$), slight (0.01–0.2), fair (0.21–0.4), moderate (0.41–0.6), substantial (0.61–0.8), and almost perfect agreement (>0.8) (Landis & Koch, 1977).

Predictive values were determined based on the outcome of the surgery. Positive predictive value (PPV) was calculated as the percentage of patients with Engel class I postoperative outcome (Engel et al., 1993) when the focus showed by source localization was resected. Negative predictive value (NPV) was calculated as the percentage of patients not becoming seizure free when the focus showed by the source localization was not resected.

To estimate the clinical value of the ictal source analysis, we calculated likelihood ratios based on contingency tables (Burch et al., 2012a,b). In this study only complete match between the index test (LAURA) and reference standard was considered concordant. Therefore, partial concordant and discordant results (Burch et al., 2012a,b) were combined into the same category. Because all included data yielded a localization solution, we did not have patients in the nonlocalizing category. From the 2×2 table (concordant/nonconcordant vs. seizure-free/non-seizure-free outcome) (Table 1), likelihood ratios were calculated for the concordant results: (number of concordant seizure-free / total seizure-free) / (number of concordant non-seizure-free / total non-seizure-free), and for the discordant results: (num-

Table 1. Likelihood ratios for the concordant and discordant cases

	Seizure-free	Not seizure-free	Likelihood ratio
Concordant	12	1	3
Discordant	4	3	0.33

ber of discordant seizure-free/total seizure-free)/(number of discordant non-seizure-free/total non-seizure-free). Is the likelihood ratio for the concordant and discordant categories the same, the index test is of no value as the likelihood of becoming seizure-free is the same regardless of the result of the index test. The higher the likelihood ratio of the concordant results compared to the likelihood ratio of the discordant result, the higher the clinical value of the index test.

Timing and execution of the tests

According to the recommendation of the STARD initiative, we included a flow diagram of the study (Fig. 1). The index test (ictal source localization) was done after recording the EEG studies and before the reference standard.

The time interval between the index test and the reference standard varied between 1 week and 6 months. Antiepileptic drug (AED) treatment was typically restarted in this period (in most cases AEDs were withdrawn before the long-term video-EEG). However, it is unlikely that AEDs changed the localization of the epileptic focus. A detailed account for the 25 items in the STARD checklist is summarized in Data S2.

RESULTS

Ictal source localization was completed and yielded interpretable results in all included patients with visually identifiable rhythmic ictal activity ($n = 42$). The average time from the first clinical sign to the start of the analyzed rhythmic ictal activity was 7.7 s (range: 16 s before – 38 s after the first sign). In one case the analyzed rhythmic ictal activity started 37 s after the electrodecremental response (flattening); in all other cases, the analyzed rhythmic ictal activity was the first identifiable ictal EEG pattern.

Figures 4 and 5 and Data S3 and S4 show the results of the ictal source localization for patients with mesial temporal lobe epilepsy, lateral-neocortical temporal lobe epilepsy, and frontal lobe epilepsy. The results of the ictal source localization for the 42 patients are summarized in Data S1.

None of the included patients with visually identifiable rhythmic ictal activity was excluded because of artifacts. Examples of analyzed ictal recordings contaminated by artifacts are in Data S4 (page 2) and Data S7.

Using the standardized method, the analyses took <30 min for a seizure. All patients had been discussed at the meetings of the multidisciplinary epilepsy surgery team. However, consensus conclusion on the seizure-onset zone (reference standard) could not be achieved in nine cases (Fig. 1; Data S1).

Reference standard was thus available in 33 patients. The ictal source localization showed identical results with the reference standard in 23 patients. The sensitivity of the ictal source localization was 69.7% and the specificity was

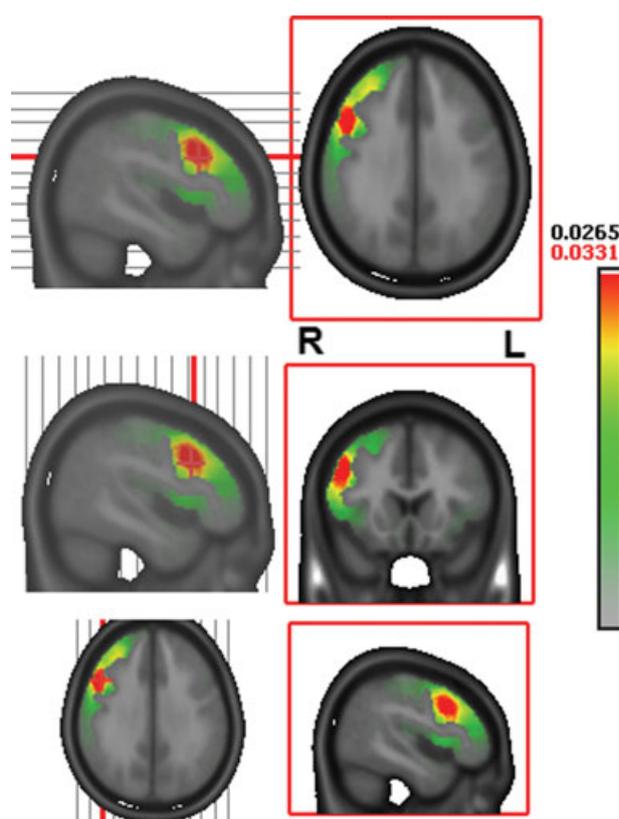


Figure 5.

Ictal source localization in a patient with right lateral frontal focus (patient 10). The original ictal EEG is showed in Data S6. *Epilepsia* © ILAE

75.7%. The mean measurement of agreement (kappa) was 0.61 (95% CI for k : 0.38–0.84) corresponding to substantial agreement. Of the 25 patients with potentially epileptogenic lesion on the MRI, 18 patients (72%) had ictal source localization concordant with the lesion location.

Twenty patients underwent surgery and 16 patients (80%) became seizure-free (see the flow diagram in Fig. 1). In 13 cases, the resection included the cortical area showed by the ictal source localization; 12 of them became seizure-free. The PPV of the ictal source localization was 92%. Seven patients underwent resection not including the cortical area showed by the ictal source localization; three of them did not become seizure-free. The NPV was 42.8%.

Of the 20 operated patients, 10 had selective amygdalo-hippocampectomy or tailored resections. Two patients with the epileptogenic zone involving both mesial and neocortical temporal structures underwent anteromedial temporal resection. Eight patients with mesial temporal focus underwent anteromedial temporal resection. Therefore, in these eight patients the resection exceeded the ictal sublobar localization. A subgroup analysis for the 12 patients in which the localization at sublobar level had therapeutic consequences, yielded results similar to the whole group of operated patients (PPV 86%; NPV 60%).

The likelihood ratio for the concordant results (ictal source localization matching the reference standard) was nine times higher than the likelihood ratio of the discordant results (mismatch between ictal source localization and the reference standard) (Table 1).

In 17 patients, the basic modalities (MRI, semiology, visually analyzed EEG) did not localize well the focus (normal MRI and/or discordant data). In these patients, additional investigations (functional neuroimaging, invasive recordings) were done. In this subgroup of patients with difficult temporal lobe epilepsy, the ictal source localization matched the reference standard in 13 cases (76%). In nine of these patients, the resection included the cortical area showed by the ictal source localization; all of them became seizure-free (PPV = 100%). Four patients in this subgroup underwent resection not including the cortical area showed by the ictal source localization; two of them did not become seizure free (NPV = 50%).

Most of the patients fulfilling the inclusion criteria turned out to have temporal lobe epilepsy (91%). Reference standard was available for three patients with extratemporal focus. The result of the ictal source analysis matched the reference standard in two of these patients. The third (no-match) patient underwent surgery in a location outside the area indicated by the ictal source localization; this patient did not become seizure-free. Two patients had several foci. The ictal source localization correctly localized them in both patients.

DISCUSSION

Source localization of the rhythmic ictal activity, using a standardized method for selection and preparation of the ictal signals, and a distributed source model (LAURA), proved to be feasible in clinical practice: it yielded localization solutions in all patients who fulfilled inclusion criteria, and the total extra time consumption was <30 min for a patient.

Sixteen patients referred to the EMU for presurgical evaluation and who had at least one seizure, did not meet the inclusion criteria. Therefore, our method could be applied in 72% (n = 42) of the patients who had at least one epileptic seizure in the EMU (n = 58). The relatively low number of electrodes allowed only a subobar precision level. However, this level can be helpful for making clinical decisions.

The proposed method evades the two major difficulties with source analysis of the ictal signals: low signal-to-noise ratio and propagation of the ictal activity. As suggested previously, to increase the signal-to-noise ratio we averaged the selected ictal wave-forms with similar topography (Assaf & Ebersole, 1997; Merlet & Gotman, 2001; Beniczky et al., 2006). We aimed at confining the analysis to the earliest detectable ictal signals, using two steps. First, we selected the EEG epoch with the initial frequency (Lantz et al., 1999, 2001) (Fig. 3). Then, on the ascending slope

of the averaged waveform we marked the last timeframe showing the initial voltage distribution (Fig. 4).

One of the impediments of implementing source analysis of the ictal EEG signals in the clinical practice is the high extra workload imposed by time-consuming methods. Only two of the previous publications addressed this issue, and the authors reported that ictal source localization was highly time-consuming, often requiring several times the length of time compared with standard visual assessment, approximately 10 h per patient (Boon et al., 2002; Holmes et al., 2010). In stark contrast, our standardized method took <30 min per patient. Furthermore it provided localization results with high accuracy (sensitivity: 70%; specificity 76%) and high PPV (92%). Of other used neuroimaging methods, ictal SPECT also aims at localizing the seizure-onset zone (Rosenow & Lüders, 2001) but unlike our method, its logistic aspects and the timing are recognized as technically more demanding.

A previous, large-scale study (40 patients with temporal lobe epilepsy) using multiple fixed dipoles gave sensitivity between 36% and 66% and specificity between 92% and 96% (Assaf & Ebersole, 1997). Another study on a larger population (22 patients) used a distributed source model (low resolution electromagnetic tomography [LORETA]) and demonstrated preferential propagation patterns of the ictal activity originating in mesial temporal epileptic foci (Lee et al., 2009). The only prospective study published previously on the source localization of the ictal EEG activity comprised a large patient population (100 patients) (Boon et al., 2002). Due to movement or other artifacts, ictal source localization was possible in only 31 patients; in 14 patients it proved to be a key element in the surgical decision process. Sensitivity and specificity were not determined in this study as the results of the source analysis contributed to the decision process. All other studies were done on relatively few patients (5–15) and gave results with sensitivity between 40% and 100%. Finally, none of the previous studies were blinded.

Our study was designed and reported in accordance with the STARD recommendations (Bossuyt et al., 2003). Recently, International League Against Epilepsy (ILAE) guideline criteria for imaging and neurophysiology studies in epilepsy have been published (Gaillard et al., 2011). Although these criteria were published after we started the study, application of the STARD criteria for ictal source localization resulted in a study design that fulfils the criteria suggested by the ILAE task force of the Commission for Diagnostics (Gaillard et al., 2011).

Recently published critical reviews emphasized the difficulties in the interpretation of diagnostic accuracy studies on presurgical workup for epilepsy surgery, and it was suggested to supplement the currently available imperfect reference standard (consensus decision from a combination of tests) with the outcome following surgery (Burch et al., 2012a,b). The likelihood ratios calculated from these

tables reflect the clinical usefulness of the index test. In our study the likelihood ratio for the concordant results was much (nine times) higher than the likelihood ratio of the discordant results, proving the clinical value of ictal source localization.

Seizure identification, selection, and preparation of the ictal EEG signals for analysis were integrated into the clinical setting. The source analysis was done with blinding to the clinical data, and no iteration was allowed. The MRI pictures visualizing the estimated source of the ictal EEG activity are easy to understand also for those physicians who are less familiar with EEG, and thus help communicating the results at the multidisciplinary conferences. The main goal of our approach was to equip the clinical neurophysiologist with an additional reliable tool and not to advocate the replacement of the clinical expertise with an automated method.

Pacia & Ebersole (1997), using simultaneous intracranial and surface recordings, elegantly showed that ictal activity confined to the hippocampus did not result in scalp EEG rhythms. This was explained by (1) the small volume of the hippocampus; (2) its curved geometry which causes field cancellation; and (3) the usual shielding effect of the skull and scalp. Nevertheless, scalp EEG rhythms appeared when the adjacent temporal cortex became involved. On the mesial part of the temporal lobe, the cortical structures adjacent to hippocampus are the parahippocampal gyrus and the mesial part of the fusiform gyrus. The distributed source model in our study did not show ictal activity confined to hippocampus in any of the patients with hippocampal sclerosis. In these patients the ictal activation typically appeared in the adjacent temporal cortical structures: parahippocampal gyrus, fusiform gyrus, temporal pole, and inferior temporal gyrus (Fig. 4; Data S3). This pattern was consistent with the results of the studies using simultaneous scalp and intracranial recordings.

Our study focused solely on the rhythmic ictal activity and as such does not allow for the extrapolation of its results to the other ictal EEG patterns, for example, suppression, repetitive epileptiform activity, and arrhythmic activity (Foldvary et al., 2001). Further prospective studies are needed to assess the diagnostic accuracy of source localization of these patterns. Moreover, as most of the seizures (67%) with rhythmic ictal activity originate in the temporal lobe (Foldvary et al., 2001), this constituted a selection bias in our study.

Our results can apply only to the group of patients in which a reference standard could be obtained. Ictal source analysis yielded localization results in the other patients too; however, due to lack of reference standard, the accuracy of these results could not be determined.

In all operated patients, the surgical intervention was planned based on the consensus conclusion of the multidisciplinary team. Sixteen of the 20 patients became seizure free. Therefore, the multimodal, consensus conclusion gave a PPV of 80%. The index test based on a single modality (ictal source imaging) gave a PPV of 92%.

Despite the high sensitivity and PPV, the ictal source localization gave relatively low NPV (43%) in our study. This could be partially due to the relatively low number of patients who underwent resection not including the cortical area showed by the ictal source localization. The NPV of source imaging of interictal epileptiform discharges increased significantly (from 15% to 50%) when using a high-density electrode array and individual MRI (Brodebeck et al., 2011). Therefore it is reasonable to assume that long-term EEG recordings with high-density EEG array would improve the overall performance of the ictal source localization. Further prospective studies on large patient populations are needed to elucidate whether this is feasible in a clinical setting and whether it provides an added value that is cost-effective. At the time we designed this study, the high-density EEG caps were not suitable for long-term recordings. Today, however, high-density EEG nets specially designed for long-term monitoring are available.

In conclusion, our results suggest that source localization of the rhythmic ictal activity, using a standardized method for selection and preparation of the ictal EEG signals, provides reliable solutions at sublobar resolution and that as such it should be included into the key armamentarium of the clinical neurophysiologist interpreting ictal EEG recordings.

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DISCLOSURE

Göran Lantz is an employee of Electrical Geodesics Inc., a manufacturer of EEG systems. The remaining authors have no potential conflicts of interest to disclose. We confirm that we have read the Journals position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Demographic and clinical data, results of the ictal source localization (LAURA), reference standard, and surgical outcome for the 42 patients included in the study.

Data S2. STARD checklist for reporting diagnostic accuracy studies.

Data S3. Ictal source localization in a patient with right mesial temporal focus (patient 12—the same patient as in Fig. 3).

Data S4. Ictal source localization in a patient with left lateral temporal focus (patient 39).

Data S5. The original EEG signal corresponding to the ictal epoch presented in Figure 4.

Data S6. The original EEG signal corresponding to the ictal epoch presented in Figure 5.

Data S7. Examples of analyzed ictal epochs contaminated by artifacts.