Ictal EEG source localization in focal epilepsy: Review and future perspectives

Pieter van Mierlo a,1, Bernd J. Vorderwülbecke b,c,1, Willeke Staljanssens a, Margitta Seeck b, Serge Vulliémoz b,*

a Medical Image and Signal Processing Group, Department of Electronics and Information Systems, Ghent University, Corneel Heymanslaan 10, 9000 Ghent, Belgium
b EEG and Epilepsy Unit, University Hospitals and Faculty of Medicine Geneva, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland
c Department of Neurology, Epilepsy-Center Berlin-Brandenburg, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

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Abstract
Electroencephalographic (EEG) source imaging localizes the generators of neural activity in the brain. During presurgical epilepsy evaluation, EEG source imaging of interictal epileptiform discharges is an established tool to estimate the irritative zone. However, the origin of interictal activity can be partly or fully discordant with the origin of seizures. Therefore, source imaging based on ictal EEG data to determine the seizure onset zone can provide precious clinical information. In this descriptive review, we address the importance of localizing the seizure onset zone based on noninvasive EEG recordings as a complementary analysis that might reduce the burden of the presurgical evaluation. We identify three major challenges (low signal-to-noise ratio of the ictal EEG data, spread of ictal activity in the brain, and validation of the developed methods) and discuss practical solutions. We provide an extensive overview of the existing clinical studies to illustrate the potential clinical utility of EEG-based localization of the seizure onset zone. Finally, we conclude with future perspectives and the needs for translating ictal EEG source imaging into clinical practice.

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* Corresponding author at: EEG and Epilepsy Unit, University Hospitals and Faculty of Medicine Geneva, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland.
E-mail addresses: pieter.vanmierlo@ugent.be (P. van Mierlo), bernd.vorderwuelbecke@charite.de (B.J. Vorderwülbecke), margitta.seeck@hcuge.ch (M. Seeck), serge.vulliemoz@hcuge.ch (S. Vulliémoz).
1 Contributing equally.

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1. The importance of seizure onset zone localization in the presurgical evaluation

The ultimate goal of epilepsy treatment is to render a patient seizure-free without causing side-effects. In pharmaco-resistant focal epilepsy, resective brain surgery is the treatment with highest efficacy. The multimodal presurgical evaluation aims to answer the question as to whether a patient can benefit from epilepsy surgery by delineating the so-called epileptogenic zone (EZ), i.e. the minimal brain region that needs to be removed to stop the seizures, and at distinguishing it from eloquent brain areas which must remain untouched (Ryvlin et al., 2014).

1.1. First-line diagnostic methods: Noninvasive video-EEG, structural MRI, and neuropsychology

During the presurgical evaluation process, a multitude of techniques is used to approach the EZ. Long-term videographic recording identifies seizure semiology, which, together with the patient’s subjective experience, already gives important hints for seizure onset localization. Simultaneously, non-invasive (scalp) electroencephalogram (EEG) is recorded in the form of long-term combined video-EEG monitoring. The EEG is generated by potential differences across EEG electrodes over time, and conventional EEG analysis is based on visual inspection of waveform patterns. The EEG signature of seizures and interictal epileptiform discharges (IEDs) allow for a crude estimation of the seizure onset zone (SOZ) and the onset zone of IEDs, which is termed the irritative zone (IZ). Both the SOZ and, to a lesser extent, the IZ are taken as a surrogate for the conceptual EZ (Zijlmans et al., 2019).

High-resolution structural magnetic resonance imaging (MRI) visualizes potential structural abnormalities in a patient’s brain. The identification of a resectable brain lesion via MRI doubles the chance of postsurgical seizure-freedom (Tellez-Zenteno et al., 2010). In addition, neuropsychological testing aims at revealing localization-related brain dysfunctions. If seizure semiology, EEG, structural MRI and neuropsychology yield concordant results, and if the presumed EZ does not include eloquent cortex, the patient can directly proceed to surgery (Ryvlin et al., 2014).

1.2. Second-line methods: Additional noninvasive diagnostic tools

In case the basic workup leads to inconclusive or insufficient results, further non-invasive techniques can be added, and some of them are performed routinely in specific centers. First, the sensitivity of MRI can be increased by morphometric postprocessing. Second, nuclear imaging techniques are widely used to visualize metabolic correlates of epilepsy. While interictal positron emission tomography (PET) using fluorodeoxyglucose or other radioactive tracers visualizes chronic changes in brain metabolism, single photon emission computed tomography (SPECT) is performed ic tally to visualize regionally altered brain perfusion during seizures. The SPECT tracer is administered as early as possible during a seizure, followed by postictal image acquisition (von Oertzen, 2018). Contrast and accuracy increase when images are subtracted from an interictal baseline and coregistered to MRI (Subtraction of Ictal SPECT Co-registered with MRI, SISCOM). Magnetencephalography (MEG) records magnetic fields over the scalp using magnetometers, and MEG data can be processed similarly to EEG data (Ryvlin et al., 2014; Zijlmans et al., 2019).

A further diagnostic option is expanding the diagnostic yield of scalp EEG beyond the limits of conventional analysis (see below). While the EEG has a high temporal resolution in the order of milliseconds, its spatial resolution at the sensor level is low with only lobar or sub-lobar precision (Burle et al., 2015). It can be increased by using high-density (hd-) EEG recording systems with 64 or more electrodes. Although hd-EEG systems became more available worldwide, keeping hd-EEG caps in place for more than 24 hours can cause a patient discomfort, and it may be difficult to achieve good signal quality across all electrodes for a long time.

Furthermore, EEG suffers from the volume conduction problem: Potentials at a certain brain region are recorded by all electrodes simultaneously. Given the orientation of the gray matter generating the potential, the brain activity can be seen at distant electrodes. EEG source imaging (ESI) helps to overcome this problem. Based on mathematical models, ESI estimates the localization of scalp-recorded potentials and plots the sources of cerebral activity within a 3D model of the brain (see Section 3.3). Although not widely used yet, ESI of interictal epileptic activity (“spikes”) has started to find its way into presurgical epilepsy evaluation (Mouthean et al., 2016).

The reported sensitivities to successfully localize the EZ in the presurgical evaluation range from 30% to 90% for interictal PET (70–90% in temporal lobe epilepsy (TLE), 30–60% in extratemporal lobe epilepsy (ETLE)) and from 66% to 97% for ictal SPECT (Knowlton, 2006; la Fougère et al., 2009). A study based on 152 patients (102 TLE, 50 ETLE) accounted for a sensitivity of 69% and a specificity of 44% for PET, 58% and 47% for SPECT, and 76% and 53% for structural MRI (Brodbeck et al., 2011). By comparison, interictal ESI had a sensitivity and specificity of 84% and 88% in.
case of hd-EEG. These numbers dropped to 66% and 54%, respectively, when using low-density EEG with no more than 32 electrodes. MEG source imaging (MSI) of IEDs achieves sensitivity values between 55 and 90% (Knowlton et al., 2008; Stefan et al., 2011; Kasper et al., 2018; Ramp et al., 2019). Recently, a sensitivity and specificity of 75% and 75% were reported for ESI of automatically detected spikes in long-term low-density EEG (van Mierlo et al., 2017). Clinical interpretation of automatically generated source localization reports from long-term EEG increased the sensitivity to localize the EZ to 88% (Baroumand et al., 2018). In addition, interictal ESI and MSI have recently been shown to provide valuable information for tailoring individual invasive EEG monitoring (Duez et al., 2019).

1.3. Third-line investigations: Intracranial EEG recordings

Even additional non-invasive methods might not be sufficient to reliably delineate the SOZ. In such cases, invasive EEG (IEEG) becomes necessary. Subdural electrodes are placed onto the cortex (electrocorticography), while depth electrodes are inserted into the brain tissue itself (stereo-EEG). Other than scalp EEG, IEEG allows recording seizure activity directly from its origin, as long as the electrodes have been placed correctly. On the other hand, the spatial sampling of IEEG is comparably low, since only well-chosen parts of the brain can be assessed. Due to its invasive nature, IEEG bears a 0.5% risk of major complications (Jayakar et al., 2016). Therefore, ideally, results from the non-invasive diagnostic methods help avoiding intracranial EEG or at least aid in selecting candidate regions for IEEG as accurately as possible.

1.4. Why ictal ESI?

Overall, despite the widely available ictal EEG recordings in most patients, neuroimaging during presurgical evaluation (except for ictal SPECT) relies on interictal epileptic activity. However, epilepsy surgery aims at eliminating the origin of seizures and not of IEDs, and SOZ and IZ are not necessarily concordant (Hamer et al., 1999; Bartolomei et al., 2016). Therefore, it is of high clinical value to localize the sources of seizures complementary to those of interictal epileptic activity. Ictal ESI promises to provide more accurate and/or objective interpretation of scalp EEG compared to visual inspection, and to add useful localization information that can guide resection or placement of intracranial EEG electrodes. In this review, we focus on what are the challenges of ictal ESI, how they can be overcome, what the performance is to estimate the EZ, and what is needed to bring ictal ESI into the clinical practice.

2. How to tackle issues and challenges in ictal EEG source imaging

There are several challenges to localize the SOZ from scalp EEG during presurgical workup. The quality of ictal EEG data is often impaired by movement, muscle, and eye artifacts, and the ictal activity can propagate during a seizure. Furthermore, choosing a suitable validation strategy for ictal ESI is not trivial. Below, we address established ways to tackle these problems.

2.1. Dealing with artifacts in ictal EEG

EEG recorded during a seizure is often of low quality due to clinical manifestations of the seizure. Muscle, movement and/or eye artifacts can significantly reduce the EEG’s signal-to-noise ratio (SNR). Since it is not possible to prevent the occurrence of these artifacts, strategies have been developed to cope with or to enhance the low SNR. As a first step in most analyses, data are pre-processed, usually involving a band-pass filter to reduce baseline drift (low frequencies) and muscle artifacts (high frequencies), and a notch filter at 50 or 60 Hz to reduce the power line noise. Additional techniques such as principal or independent component analysis (PCA or ICA) can remove eye blinks or cardiac artifacts from the EEG.

Once the EEG is preprocessed, one strategy is to manually select ictal time points with high SNR for EEG source localization. For instance, a single time-point or a short EEG epoch close to the seizure onset may be chosen that contains as little artifact as possible. Repetitive ictal EEG events such as spikes or rhythmic waveforms during seizure onset can be averaged to further increase the SNR. Unfortunately, ictal events may be non-uniform and seizures may spread rapidly. Therefore, the average is often restricted to a small number of events which sets limits to SNR enhancement (Boon et al., 1997a).

Another strategy is scalp voltage map analysis, also called topographic analysis, of the ictal EEG. A specific scalp EEG topography that reflects the ictal EEG activity is extracted and used as input for source localization. One way to extract the ictal EEG topography is spectral analysis. The frequency band of interest can be chosen manually so that it includes the rhythmic seizure activity of choice and, at the same time, excludes physiological activity at other frequencies. Then, the power at each electrode in this frequency band is computed. Defining the frequency band upfront can be tricky since seizure activity can arise at multiple frequencies simultaneously, and the choice is, to a certain extent, subjective. Recently, an automated technique has been proposed to determine the most dominant rhythmic EEG pattern within the earliest ictal activity and its corresponding topography (Koren et al., 2018).

An alternative way for ictal scalp topography extraction is using decomposition techniques such as PCA, ICA or tensor decomposition. The EEG is divided into components with specific spatial and temporal signatures, and in case of tensor decomposition also with a spectral signature. From these components, the one which represents best the seizure activity is selected for source localization. As a potential limitation, decomposition methods depend on assumptions. For example, PCA assumes orthogonality between neural activities and artifacts, while ICA assumes that the components are mutually statistically independent. Although this sounds logical in theory, in practice the story is more complicated. Ictal activity may be smeared into multiple components, or other unwanted activity, such as muscular artifacts, can remain in the ictal component. This can make the selection of single components for source localization cumbersome and sometimes even impossible.

2.2. Visualizing the spread of ictal activity

Ictal activity can rapidly spread through the brain and several cortical regions can become active during a seizure as part of the patient’s individual epileptic network. Therefore, in addition to ESI that estimates the brain region that is most active during a seizure, connectivity analyses study interactions of brain regions within the network. Functional connectivity assesses activations within the network which are correlated, for example via functional MRI. In addition, effective connectivity also estimates causality, in order to distinguish the main driver(s) of the epileptic network from regions which are secondarily activated (Spencer, 2002; Richardson, 2012). The main epileptic drivers are thought to represent the seizure onset zone more accurately than brain sources of maximum ictal activity.

2.3. Choosing the best validation strategy

Once an innovative diagnostic technique such as ictal ESI is developed, the final challenge is to find a validation strategy to...
optimally quantify the method’s performance. Basically, ESI can be validated via concordance with a ‘ground truth’. One obvious ground truth for ictal ESI could be the SOZ defined by IEEG (Megevand et al., 2014). Ideally, ictal ESI results could be compared to simultaneously recorded IEEG. However, only very few centers perform simultaneous scalp and intracranial recordings for research purposes, and application of ESI on simultaneously recorded seizures comes with additional challenges. Intracranial electrodes, burr holes and bone flaps can influence the propagation of the electric field and distort scalp voltage topography and ESI. Indeed, the non-conductive part of subdural grids has been shown to attenuate scalp potentials of generators located beneath (van Mierlo et al., 2014). If instead scalp EEG and IEEG are recorded separately, one cannot guarantee that seizures originated from the same localization and extent.

Even more, IEEG does not necessarily sample the true or full SOZ. If invasive electrodes were placed close to the SOZ but not inside it, the tissue beneath the electrodes closest to the real SOZ would be incorrectly considered to harbor the SOZ. Thus, as an alternative, the ground truth can be based on the outcome of the complete presurgical evaluation or, which appears to be the best solution, on the resected brain area combined with the patient’s postsurgical seizure outcome (Staaljans et al., 2017a, 2017b; Koren et al., 2018). If a patient is seizure-free after surgery, the EZ must have been harbored in the resected tissue. Still, since the extent of the resected brain area is a compromise between the risk of functional loss for larger resections and the risk of not being seizure-free for smaller resections, the area that was delineated during presurgical evaluation or that was eventually resected is often larger than the SOZ. Another way to investigate clinical usefulness is estimating the added value of ictal ESI for the presurgical evaluation process (Boon et al., 2002; Koren et al., 2018), to see if changes are made to diagnostic and therapeutic management. Other studies validated their ESI results by comparison to ictal SPECT (Hallez et al., 2009; Yang et al., 2011; Habib et al., 2016) or structural MRI results (Ding et al., 2007; Kovac et al., 2014) which has limitations when the SPECT shows ictal spread or when the MRI-identified lesion is not the cause of epilepsy.

When reviewing the concordance of a specific analysis, spatial accuracy criteria are critical. Some studies report absolute distances, with the limitation that short distances cannot rule out lateralization in the wrong hemisphere. Sub-lobar and lobar concordance (with or without an atlas-based parcellation) or a margin of tolerance around the reference standard, or variable distinction between full/partial concordance are also frequently mentioned. Some studies report absolute distances to the lesion, to IEEG-defined SOZ. Consistently across these early works, most stable dipoles were found in cases of mesial TLE, and most examined patients had this type of epilepsy.

Other authors focused on the temporal lobe specifically. In 40 TLE patients who later underwent successful temporal epilepsy surgery, Assaf and Ebersole projected ictal EEG into 19 predefined cortical regions, 4 of those in each temporal lobe (Assaf and Ebersole, 1997). By comparing the most prominent source at the earliest recognizable ictal rhythm to the SOZ identified by IEEG, they could reliably differentiate temporal lobe seizures of mesial origin from those of lateral neocortical origin. Using the same approach, the authors successfully correlated ictal source localization to surgical outcome in 75 patients with anteromesial temporal lobectomy (Assaf and Ebersole, 1999). Around the same time, Mine et al. applied ESI to a 10–ms window around the peak of an early ictal discharge in one TLE and one ETLE patient (Mine et al., 1998). In an extension study, the authors were able to discriminate mesial from lateral temporal sources, other than by visual interpretation of the scalp EEG (Mine et al., 2005). Spatial resolutions were limited to large sub-lobar regions, and comparison with interictal ESI was not performed.

These early studies showed that ictal ESI is feasible and can have an added value in the presurgical evaluation of epilepsy. The methods used were straightforward, the spatial resolution limited, and the validation often solely qualitative or descriptive, meaning that no quantitative distances to the lesion, to IEEG...
| Reference                          | # pat (TLE/ETLE) | # elec | Head model | Inverse solution                  | Connectivity analysis | SOZ localization approach                                                                 | Validation approach                   |
|-----------------------------------|------------------|--------|------------|-----------------------------------|-----------------------|-------------------------------------------------------------------------------------------|---------------------------------------|
| Aldenhoven et al., 2016           | 15 (11/4)        | 64     | ind. 3-layer BEM | LORETA, discrete multiple dipoles fitting, cortical CLARA | Source map maximum at seizure onset | Dipole location or source map maximum of averaged seizure onset waveforms following ICA | Concordance with RZ                    |
| Alving et al., 2017               | 3 (0/3)          | 33     | Template FEM | FOCUS                             | Most prominent source component at earliest recognizable ictal rhythm | Most prominent source component at earliest recognizable ictal rhythm | Qualitative agreement with IEEG and RZ |
| Assaf and Ebersole, 1997          | 40 (40/0)        | 23–27  | 3-shell spherical | FOCUS                             | Most prominent source component at earliest recognizable ictal rhythm | Sublobar concordance with RZ          |                                     |
| Assaf and Ebersole, 1999          | 75 (75/0)        | 21–27  | 3-shell spherical | FOCUS                             | Most prominent source component at earliest recognizable ictal rhythm | Sublobar concordance with RZ          |                                     |
| Batista Garcia-Ramo et al., 2019  | 5 (2/3)          | 7      | ind. 3-layer BEM | MSP                               | ESI with or without ictal SPECT results as a spatial constraint for source localization | Sublobar concordance with RZ          |                                     |
| Beniczky et al., 2006             | 10 (10/0)        | 23     | template 3-layer BEM template SMAC | eLORETA | Source maximum during injection of SPECT tracer at seizure onset | Sublobar concordance with clinically defined SOZ | Qualitative agreement with RZ          |
| Beniczky et al., 2013             | 42 (30/3)*       | 25     |             | LAURA                             | Source maximum at predefined time-point of averaged ictal waveform | Sublobar concordance with decision of epilepsy team | Qualitative agreement with RZ          |
| Beniczky et al., 2016             | 22 (14/8)        | 64     | template FEM | ECD, CLARA, cortical-CLARA, MNE    | Dipole location or source map maximum of averaged seizure onset waveforms | Qualitative agreement with RZ          |                                     |
| Bersaglieri et al., 2013          | 4 (0/4)          | 19     |             | eLORETA                           | Source maximum of sigma activity (12–16 Hz) during 5 s before clinical seizure onset | Qualitative agreement with RZ          |                                     |
| Blanke et al., 2000               | 10 (10/0)        | 21     | 3-shell spherical | rwMNE                             | Source localization of dominant ictal frequency | Qualitative agreement with RZ          |                                     |
| Boon and D’Havé, 1995            | 15 (11/4)        | 27     | 3-shell spherical | ECD                               | Orientation and location of the dipole of single ictal discharges | Qualitative agreement with interictal ESI and MRI |                                     |
| Boon et al., 1997a                | 33 (28/5)        | 21–27  | 3-shell spherical | ECD                               | Orientation and location of the dipole of single ictal discharges | Qualitative agreement with interictal ESI and MRI |                                     |
| Boon et al., 1997b                | 11 (9/2)         | ≤32    | 3-shell spherical | ECD                               | Orientation and location of the dipole of single ictal discharges | Qualitative agreement with interictal ESI and MRI |                                     |
| Boon et al., 1999                 | 41 (35/6)        | 27     | 3-shell spherical | ECD                               | Orientation and location of the dipole of single ictal discharges | Qualitative agreement with interictal ESI and MRI |                                     |
| Boon et al., 2002                 | 31 (26/5)        | 27     | 3-shell spherical | ECD                               | Orientation and location of the dipole of single ictal discharges | Qualitative agreement with interictal ESI and MRI |                                     |
| Breedlove et al., 2014            | 20 (20/0)        | 21     | BEM         | empirical Bayesian                | Voxel-based analysis of early ictal 30 s-epochs | Influence on presurgical decision process | Hemispherical concordance to clinically defined SOZ / RZ |
| Catarino et al., 2012             | 2 (0/2)          | 32–64  |            | average FEM                       | Dipole analysis of visually determined seizure onset | (Solutions were restricted to the temporal lobes) | Qualitative agreement with RZ          |
| Despotovic et al., 2012           | 10 (0/10)        | 17     | ind. 4-tissue FDM | ECD                               | Dipole location of topography after PARAFAC of ictal spikes | Distance to nearest lesion border |                                     |
| Ding et al., 2007                 | 5 (3/2)          | 31     | ind. 3-layer BEM | FINE                              | Identify primary driver with significant DTF value of 3 s EEG epoch at seizure onset | Concordance with MRI lesions |                                     |
| Ebersole 1994                     | 17 (13/4)        | 27     | 3-shell spherical | spatiotemporal 2-dipole model      | Dipole orientation and location at earliest recognizable ictal rhythm | Sublobar concordance with RZ          |                                     |
| Elshoff et al., 2013              | 11 (6/5)         | 38–50  | 5-shell spherical | DICS                              | First and second source found by DICS of 1–10 s around seizure onset | Sublobar concordance with RZ          |                                     |
| Elwan et al., 2013                | 33 (23/10)       | 7      | 3-shell spherical | FOCUS                             | First 5–10 s of seizure, narrowly band pass filtered from 2-20 Hz | Sublobar concordance with RZ          |                                     |
| Erem et al., 2017                 | 4 (3/0)*         | 21–128 | ind. 5-tissue FDM | LORETA, DSI                       | DSI of collections of 50–100 ms epochs following an autoregressive linear time-invariant model | Sublobar concordance with RZ          |                                     |
| Foged et al., 2020                | 82 (38/25)       | 25     | template 4-layer FEM | ECD, cortical CLARA              | Dipole location or source map maximum of averaged seizure onset waveforms | Change in clinical management during presurgical evaluation | Qualitative agreement with clinically defined SOZ |
| Gonzalez Andino et al., 2001      | 1 (0/1)          | 28     | (not explained) | ELECTRA                          | Maximum source of early ictal short-time Fourier-transformed epochs | Qualitative agreement with clinically defined SOZ |                                     |
| Habib et al., 2016                | 8 (3/5)          | 21     | ind. 3-layer BEM | wMNE, dSPM, sLORETA              | Source map maximum at peak of averaged ictal rhythms | Sublobar and hemispherical concordance with ictal SPECT foci | Qualitative agreement with RZ          |
| Habib et al., 2020                | 8 (7/1)          | 21     | 4-shell spherical | ECD                               | Dipole of ictal independent component identified by ICA | Sublobar and hemispherical concordance with ictal SPECT foci | Qualitative agreement with RZ          |
| Reference          | # pat | Head model | Inverse solution | Connectivity analysis | SOZ localization approach | Validation approach                  |
|--------------------|-------|------------|------------------|----------------------|--------------------------|--------------------------------------|
| (Hallez et al., 2009) | 8     | template   | 4-shell spherical | ECD                  | Dominant sources in moving windows of 0.25 s | Distance to ictal SPECT foci |
| (Herrendorf et al., 2000) | 1     | template   | 4-shell spherical | ECD                  | Largest magnitude in source map at seizure onset time-point | Distance to interictal source, sublobar concordance with RZ |
| (Holmes et al., 2010) | 10    | template   | 4-shell spherical | ECD                  | Dipole sources of ictal components identified by ICA | Qualitative agreement with RZ |
| (Jung et al., 2009) | 12    | template   | 4-shell spherical | ECD                  | 2 ROIs after ESI, DCM of averaged seizure initiating spikes, from onset until peak | Concordance with IEEG |
| (Klamer et al., 2015) | 1     | template   | 4-shell spherical | ECD                  | Largest magnitude in source map in 2.56 s epochs from the initial part of the seizure, dipole location of averaged definite ictal rhythms | Qualitative agreement with IEEG |
| (Kobayashi et al., 2000) | 3     | template   | 4-shell spherical | ECD                  | Analysis of ictal activities (few ms – 1 s); ECD: dipole with max. goodness of fit; MUSIC: max. music metric; sLORETA: source with highest amplitude over space and time | Sublobar concordance with IEEG |
| (Koessler et al., 2010) | 10    | template   | 4-shell spherical | ECD                  | Automatically determine the most dominant rhythmic EEG pattern within the earliest ictal activity and extract spatial topography | Sublobar concordance with RZ |
| (Koren et al., 2018) | 28    | template   | 4-shell spherical | ECD                  | ROIs with highest outdegree during ictal epoch | Qualitative agreement with IEEG / RZ |
| (Kouti et al., 2019) | 3     | template   | 4-shell spherical | ECD                  | Dipole location or source map maximum of averaged seizure cycles | Convergence to lateralization of lesion on MRI |
| (Kuo et al., 2018) | 12    | template   | 4-shell spherical | ECD                  | Source maxima over multiple seizures following joint time–frequency analysis | Sublobar concordance with MRI lesion, IEEG and RZ |
| (Lantz et al., 1999) | 7     | template   | 4-shell spherical | ECD                  | Dipole reconstruction based on frequency power spectra | Lobar concordance with RZ |
| (Lantz et al., 2001) | 9     | template   | 4-shell spherical | ECD                  | New data matrix based on GFP peaks segmented into limited amount of topographies, most important topographies inverted | Correspondence with IEEG |
| (Lee et al., 2006) | 3     | template   | 4-shell spherical | ECD                  | Best fit dipoles for spatial components of ictal rhythmic activity following ICA | Qualitative agreement with clinically defined SOZ |
| (Leal et al., 2008) | 4     | template   | 4-shell spherical | ECD                  | Source maximum for spatial components of ictal rhythmic activity following ICA | Proximity to RZ / MRI-visible lesion |
| (Lee et al., 2009) | 22    | template   | 4-shell spherical | ECD                  | Group analysis of two distinct initial ictal discharge patterns | Qualitative agreement with RZ |
| (Li et al., 2016) | 10    | template   | 4-shell spherical | ECD                  | Cross-frequency coupled potential signals vs. raw EEG data | Qualitative agreement with IEEG and RZ |
| (Lopes et al., 2020) | 15    | template   | 4-shell spherical | ECD                  | ROI with highest ictogenicity, i.e. importance for the network’s ability to generate seizures | Convergence to lateralization of surgery |
| (Lu et al., 2012a) | 9     | template   | 4-shell spherical | ECD                  | ROI with highest ictogenicity, i.e. importance for the network’s ability to generate seizures | Distance to border of RZ, concordance with IEEG |
| (Lu et al., 2012b) | 10    | template   | 4-shell spherical | ECD                  | Identify primary driver with significant DTF value of 2–3 s EEG epoch at seizure onset | Distance to boundary of RZ |
| (Martinez-Vargas et al., 2017) | 3     | template   | 4-shell spherical | ECD                  | Localization of most active dipole (of 2) fitted to the ascending phase and the complete wave of averaged ictal waveform | Distance to most active IEEG contacts |
| (Merlet and Gotman, 2001) | 9     | template   | 4-shell spherical | ECD                  | ESI based on different frequency spectra, with and without PCA | Lobar concordance with clinically determined SOZ / RZ |
| (Miller et al., 2007) | 11    | template   | 4-shell spherical | ECD                  | | |

(continued on next page)
| Reference          | # pat (TLE/ETLE) | # elec | Head model     | Inverse solution | Connectivity analysis | SOZ localization approach       | Validation approach               |
|--------------------|------------------|--------|----------------|------------------|-----------------------|---------------------------------|----------------------------------|
| (Mine et al., 1998) | 2 (1/1)          | 21     | ind. 3-layer   | ECD              | /                     | Location of the dipole at the peak of a single ictal spike | Qualitative agreement with IEEG   |
| (Mine et al., 2005) | 8 (8/0)          | 21     | ind. 3-layer   | ECD              | /                     | Location of the dipole at the peak of a single ictal spike | Qualitative agreement with IEEG   |
| (Neal et al., 2018) | 2 (2/0)          | 24     | ind. 3-layer BEM | empirical Bayesian | /                     | ROIs defined by ESI as controls for resting-state fMRI networks | Qualitative agreement with clinically defined SOZ / RZ |
| (Nentsas et al., 2017) | 14 (9/5)        | 128–204 | ind. LSMAC     | LORETA           | /                     | ESI was performed at every time-point of the first 2 s of seizure; maximum of averaged source maps was selected | Concordance with RZ               |
| (Pellegrino et al., 2016) | 15 (0/12)*     | 54     | ind. 3-layer BEM | wMEM             | /                     | First component of PCA decomposition of spatiotemporal source maps of narrow time window around seizure onset | Sublobar concordance with and distance to border of clinically defined SOZ |
| (Peters et al., 2019) | 5 (1/4)          | 23     | ind. 5-tissue FDM | LORETA           | /                     | Epileptogenics scores for multiple lesions based on ability to approximate source maxima | Concordance with RZ               |
| (Plummer et al., 2019) | 13 (5/8)        | 72–94  | ind. 3-layer BEM | sLORETA          | /                     | Source maximum of averaged monomorphic ictal discharges | Concordance with RZ / IEEG        |
| (Rullmann et al., 2009) | 1 (0/1)         | 24     | ind. anisotr. 6-tissue FEM | dipole scanning, rotating ECD, fixed ECD, MNE, sLORETA | /                     | Dipole location or largest magnitude in source map at the peak of averaged delta bursts | Qualitative agreement with lesion border and IEEG |
| (Sharma et al., 2018) | 84 (38/16)*     | 25     | ind. template FEM | ECD, CLARA       | /                     | Dipole location or source map maximum of averaged seizure onset waveforms | Sublobar concordance with IEEG and RZ |
| (Sohrabpour et al., 2016) | 1 (0/1)         | 76     | ind. 3-layer BEM | sLORETA          | ADTF                  | Driver by ADTF analysis of sources identified by DSI | Concordance with IEEG and RZ |
| (Staljanssens et al., 2017a) | 5 (4/1)         | 32–204 | ind. 6-tissue FDM | LORETA           | swADTF                | Source point with highest power or outdegree | Distance to boundary of RZ |
| (Staljanssens et al., 2017b) | 27 (24/3)       | 27–32  | ind. 6-tissue FDM | LORETA           | swADTF                | Source point with highest power or outdegree | Distance to boundary of RZ |
| (Stern et al., 2009) | 5 (5/0)          | 20     | 3-shell spherical | LORETA           | /                     | Most robust local maximum of ictal 5 s-epoch decomposed by PCA | Qualitative agreement with RZ |
| (Vespa et al., 2020) | 24 (0/24)        | 19–23  | ind. 6-tissue FDM | LORETA           | swADTF                | Source point with highest power or outdegree | Sublobar concordance with RZ |
| (Waberski et al., 2000) | 1 (1/0)          | 64     | 3-shell spherical, ind. 3-layer BEM | ECD, MUSIC, FOCUS, CDR | /                     | Averaged dipole of ictal rhythmic activity | Lobar / sublobar concordance with RZ |
| (Worrell et al., 2000) | 10 (8/2)         | 31     | 3-shell spherical | LORETA           | /                     | Source maximum of phase-encoded scalp map for ictal frequencies (PEFSA), at seizure onset DSI (see text) | Lobar concordance with MRI-visible lesion |
| (Yang et al., 2011) | 8 (7/1)*         | 76     | ind. 3-layer BEM | LORETA           | /                     | Overlap with/ distance to border of RZ or ictal SPECT foci or IEEG |                               |

**Abbreviations.** 3-shell/layer = scalp, skull, brain; 4-tissue/layer = scalp, skull, brain, cerebrospinal fluid (CSF); 5-tissue = scalp, skull, CSF, grey matter, white matter; 6-tissue = scalp, skull, CSF, grey matter, white matter, air; 7-tissue = scalp, skull, CSF, grey matter, white matter, air, eyeball; BEM = Boundary Element Method; CDR = Current Density Reconstruction; CLARA = Classical LORETA Analysis Recursively Applied; DCM = Dynamic Causal Modeling; DICS = Dynamic Imaging of Coherent Sources; (sw)(A)DTF = (spectrum-weighted)(Adaptive) Directed Transfer Function; DSI = Dynamic Seizure Imaging; ECD = Equivalent Current Dipole modeling; ELECTRA = Electrical Analysis; ESI = Electric Source Imaging; FDM = Finite Difference Method; FEM = Finite Element Method; FOCUS = Deconvolution with fixed locations and orientations; GFP = Global Field Potential; ICA = Independent Component Analysis; IEEG = Intracranial EEG; LAURA = Local Autoregressive Average; (e)/(s)LORETA = (exact)/(standardized) Low-Resolution Electromagnetic Tomography; (r)(w)MNE = (radially)(weighted) Minimum Norm Estimation; (f)MRI = (functional) Magnetic Resonance Imaging; (ta)MSP = (temporally adaptive) Multiple Sparse Priors; (RAP-)MUSIC = (Recursively Applied and Projected) Multiple Signal Classification; PARAFAC = Parallel Factor Analysis; PCA = Principal Component Analysis; PEFSA = Phase-Encoded Frequency Spectral Analysis; PLV = Phase-Locking Value; ROI = Region of Interest; RPDC = Renormalized Partial Directed Coherence; SOZ = Seizure Onset Zone; (L)SMAC = (Locally) Spherical Model with Anatomical Constraints; (E)TLE = (Extra-) Temporal Lobe Epilepsy. * The ground truth (TLE vs. ETLE) was unclear or not detailed in the remaining cases.
more sophisticated methodological approaches like frequency- 
given. Around the year 2000, the first papers were published using 
electrodes with highest ictal activity, or to the resection were 
lobe. Modified from (Beniczky et al., 2013).

D: Source localization during the later time frame (** shows 
waveform’s ascending slope. Timeframes * and ** correspond to the cursor lines in 
Sequential scalp voltage maps during subsequent 4-ms timeframes along the 
source model in right mesial temporal lobe epilepsy. A: Averaged ictal waveform. B: 
Electric source imaging of averaged ictal waveforms using a distributed 
epoch of interest. Modified from (Boon and D’Havé, 1995).

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Ictal ESI was possible in 6 of 15 patients only. In 4 of these, the distance to the most active IEEG contact was 
smaller than 15 mm. The authors found that mesial temporal ictal 
discharges were depictable for ESI but invisible for conventional 
EEG inspection, other than seizure spread to lateral temporal or 
frontal areas. Although the study showed that at that time, ictal 
dipole modelling was feasible for a minority of seizures only, it 
proved that quantitative validation of ictal ESI is possible.

3.3. Influence of different head models and source imaging techniques

ESI algorithms must solve two bioelectrical problems, the 
forward and the inverse problem. The forward problem is, which 
scaler voltage distribution results from a given cerebral source activity? To solve it, the anatomy and the different volume conduc-
activity? To solve it, the anatomy and the different volume conduc-
properties of the head’s tissues and compartments need to be 
modelled as realistically as possible. Early forward models (or: 
head models) consisted of 3 concentric spheres representing brain, 
skull, and scalp, while nowadays, realistic head models with up to 
7 compartments modelling the individual anatomy are in use.

The inverse problem is, which cerebral source activity results 
from a given scalp voltage distribution? The number of solutions 
for the inverse problem is infinite. Thus, inverse models include 
various assumptions and constraints to lead to meaningful ESI 
results. There are two main types of inverse solutions: equiva-
lent/single dipole models and distributed source models. Single 
dipole models aim at defining location and/or orientation of single 
dipoles that best explain the EEG signal. Such dipoles represent a 
“center of mass” in a patch of activated cortex; however, such a 
center of mass is often localized in the white matter if the solution 
space is not restricted to the cortex. Single dipoles have no spatial 
extent; thus, the size of a source cannot be estimated. As an advan-
tage, the orientation of the dipole carries important information 
(see Fig. 1). Instead, distributed inverse solutions are based on reg-
ular 3D grids of up to thousands of solution points throughout the 
brain or gray matter. Patches of gradually activated sources are dis-
played; therefore, the maximum of activation is usually taken for 
validation (see Fig. 2). Localization accuracy of distributed inverse 
solutions is intrinsically limited by the distance between solution 
points (usually around 5 mm) so that concordances can be formally 
expressed as multiples of inter-point distances only.

Until the 1990s, ictal ESI studies relied on source models of sin-
gle or very few dipoles. Later, distributed inverse solution tech-
niques like multiple signal classification (MUSIC) or low-
resolution electromagnetic tomography (LORETA) were increas-
ingly used. Around the year 2000, Herrendorf, Waberski and 
colleagues aimed at comparing different head models and inverse 
solutions for ESI of interictal epileptic discharges. By chance, they 
recorded a seizure in one patient with mesial TLE during a short-
duration standard EEG. Following ESI with their realistic individual 
head model, this patient’s ictal source located 12 mm remote from the 
interictal source (Herrendorf et al., 2000). When they com-
pared six different combinations of forward and inverse models 
including MUSIC and a current density reconstruction approach, 
ictal and interictal findings of the same patient were highly similar 
and concorded with the area of successful resection on a lobar level 
(Waberski et al., 2000).
A couple of years later, Beniczky et al. systematically tested MUSIC to localize ictal EEG activity across 10 patients with TLE (Beniczky et al., 2006). In 8 patients, ictal source maxima were in the same area as SPECT-detected hyperperfusion during the same seizure. As a limitation, ictal SPECT hyperperfusion clusters have low temporal resolutions and often display not only the ictal onset zone but also regions of ictal propagation (Van Paesschen et al., 2007). In 2009, Lee et al. were the first to use the LORERA algorithm for ictal ESI (Lee et al., 2009). Initial ictal discharges of 22 patients with subsequent successful temporal resections were divided into three different frequency bands and compared to baseline EEG recordings. Different scalp EEG patterns led to distinct patterns of source activation, with solutions of the 5–9 Hz frequency band corresponding best to the resected areas.

Ten years later, Rullmann et al. showed that different ESI techniques applied on a single patient's averaged ictal peak led to similar localizations close to a MRI lesion (Rullmann et al., 2009). They found it crucial that the forward model correctly modelled CSF and skull. Of note, segmentation of the different tissues in patients with large brain lesions may be prone to mistakes (Briot et al., 2014). Another study in 10 patients found more pronounced differences between the applied inverse techniques (Koessler et al., 2010). The authors reported sub-lobar concordance with IEEG in 9/10 patients using single dipolar methods and in 5–7/10 patients using distributed inverse techniques. Later, Habib et al. found ictal SPECT foci to correspond well to results of several distributed inverse techniques, namely weighted minimum norm estimates (WMNE), dynamic statistical parametric mapping (dSPM) and standardized low resolution tomography (sLORETA) in 8 patients (Habib et al., 2016). Kovac et al. tested different inverse solutions on ictal EEG patterns that were non-lateralizing during visual inspection (Kovac et al., 2014). ESI of 17 seizures of 8 patients was compared to frontal MRI lesions. Ictal ESI clearly lateralized the ictal EEG patterns in 47% of patients using a single dipole approach (75% correct) and in 29% of patients using distributed solutions (60–80% correct). This emphasized the usefulness of ictal ESI in case of non-lateralizing visual EEG interpretation. Nevertheless, all these studies were certainly underpowered to detect statistically significant and meaningful differences in the performance of various forward and inverse models.

Beniczky et al. applied five different inverse solutions on averaged ictal onset waveforms of 38 seizures in 22 patients obtained with 64-channel EEG (Beniczky et al., 2016). In 13 of their patients, all inverse methods agreed on the localization on a sublobar level, and in another 6 patients, all but one technique agreed. A distributed technique called Cortical Classical LORETA Analysis Recursively Applied (CLARA) and dipole fitting yielded the highest accuracy. These concorded with the resected zone (RZ) in 13 of those 14 patients who became seizure-free after surgery. This study confirmed that different techniques lead to similar source localization in most patients, but patient-specific differences may occur. Thus, the use of different approaches and assessment of their concordance can lead to more robust results.

Lately, Sharma et al. compared ictal and interictal ESI using a single dipole and a distributed source model in 87 consecutive patients (Sharma et al., 2018). Of these, 84 had seizures during long-term low-density EEG. Ictal ESI using the single-dipole method yielded meaningful results in 79 cases, significantly more than the distributed source model (n = 69). In 47 patients with surgery and 12-month follow-up, localization accuracies across all types of ESI were similarly high (51–62%) and not significantly different from that of other methods (e.g., MRI, 55%). These results, obtained in a large patient cohort, underline that modern state-of-the-art ialt ESI is feasible and accurate in most patients undergoing presurgical epilepsy evaluation.

3.4. Added value of high-density EEG

In interictal ESI, accuracy was shown to improve when the spatial sampling of scalp EEG was increased through the use ofhd-EEG setups containing 64–256 electrodes (Brodbeck et al., 2011). The first study on ictal (128–)256-channel ESI was published in 2010 (Holmes et al., 2010). The authors applied ESI on early ictal EEG epochs of 10 patients and found lobar concordance with IEEG results in 8 of them. More recently, using 64-channel EEG, Akdeniz found ictal ESI concordant with the RZ in 13/13 patients who were seizure-free after surgery, whereas for two patients with rather unfavorable surgical outcome, the SOZ estimation pointed at a region adjacent to the RZ (Akdeniz, 2016). – Nemtsas et al. evaluated 256-channel EEG recordings of 14 patients (Nemtsas et al., 2017). In 6 patients with subsequent successful surgery, the maximum of the averaged source map of each seizure was concordant with the RZ, but it was discordant in 2 patients with unfavorable seizure outcome. Furthermore, ictal ESI corresponded to interictal ESI in 5/6 non-operated patients.

Recently, Plummer et al. combined and compared hd-EEG and MEG for source imaging in epilepsy (Plummer et al., 2019). They recorded seizures in 11/13 sleep-deprived epilepsy patients using simultaneous hd-EEG/MEG. Across a total of 33 seizures, 25 were visible in both modalities, 7 were visible in EEG only, and one was visible in MEG only. Twenty-four of 33 were localizable by ESI, 14/33 by MSI, and 25/33 by combined ESI. Ictal hd-ESI had higher agreements with subsequent surgical RZs than ictal MSI; both for ictal and interictal discharges, most accurate results came from very early time points. Other than previously expected by the authors, the combination of independent hd-ESI and MSI analyses outperformed spatially combined ESI. The superior accuracy of ictal hd-ESI results, on top of the difficulty of MEG to record ictal events, strengthen the potential clinical usefulness of hd-EEG for SOZ localization.

To date, there are three studies formally comparing high and low electrode sampling. Kuo et al. assessed accuracy of ictal vs. interictal ESI based on 256-channel EEG vs. routine EEG (10–20 system) (Kuo et al., 2018). Out of 10 patients who had epilepsy brains with MRI lesions (n = 7), IEEG (n = 6) and/or resective surgery (n = 6), hd-EEG yielded sublobar concordance with the clinical findings in 9/10 cases for ictal ESI and in 6/10 for interictal ESI. For comparison, low-density ESI of interictal discharges was concordant in 4/10 and of ictal discharges in another 4/10 cases. These results indicate that the use of hd-EEG might be of additional value if recordings can be sufficiently long to capture seizures. – Staljanssens et al. (Staljanssens et al., 2017a) and Lu et al. (Lu et al., 2012b) both applied ESI and subsequent connectivity analyses on ictal hd-EEG (see Section 3.9). Both groups consistently found that spatial down-sampling of EEG to fewer electrodes increased the localization error of the respective connectivity approach.

Further studies based on hd-EEG will be reviewed in the following sections (see also Table 1). As a limitation of hd-EEG, duration of recordings is limited to about 24 hours due to technical aspects and potential discomfort to the patient. Therefore, ictal hd-EEG can usually be recorded in patients with very frequent seizures only or by pure chanc.

3.5. Constraining the solution space based on previous assumptions

The source space for ESI is normally constrained to the whole brain, the cerebrum, the gray matter, or the cerebral cortex only. Still, it can be restricted further. To compare sources of ictal activity in favorable vs. unfavorable surgical outcome in mesial TLE, Breedlove et al. restricted the solution space to the temporal lobe (Breedlove et al., 2014). In 10 patients per group, one representative seizure per patient was analyzed with a voxel-based inverse solution. Patients with poor surgical outcome had a broader distr-
bution of ictal sources, beyond the limits of the anterior temporal lobe resections, in comparison to those who became seizure-free. The authors concluded that unfavorable surgical outcome in mesial TLE seems correlated with a more widespread epileptogenic network. Nevertheless, they admitted that by restricting the sources to the temporal lobes, extratemporal activation may have been missed.

Two retrospective pilot studies constrained the source space further to areas pre-defined by other imaging methods. Peters et al. restricted the source solution to MRI-identified multiple tubers in 6 children with tuberous sclerosis complex (Peters et al., 2019). This increased the sensitivity of ictal ESI from 30% to 100%, with specificities of 100%. Using SPECT in 5 cases of MRI-negative epilepsy, Batista García-Ramó et al. constrained the source space to areas of ictal hyperperfusion (Batista García-Ramo et al., 2019). Such SPECT-informed ESI concorded better with the RZ than ESI alone in two TLE patients with favorable surgical outcome, but not in 1 ETLE patient with unfavorable outcome; two more patients had multifocal results and did not proceed to surgery. Unfortunately, numbers of EEG electrodes and criteria for epoch selection were not detailed, and the solution constrained by non-gold-standard techniques may bias the results towards inaccurate solutions.

3.6. Ictal ESI in special constellations

Some authors investigated the value of ESI in case of misleading ictal EEG waveform patterns. For example, Catarino et al. studied paradoxical lateralization of ictal EEG (Catarino et al., 2012). In 4 patients with ETLE, visual EEG analysis showed maxima contralateral to the clinically defined epileptogenic focus. In two of them, the ictal EEG could be analyzed with ESI, and in one of those, the source located in the correct hemisphere. In the other case, the source was apparently in the wrong hemisphere as well, and for the two remaining patients, ictal ESI was not possible for reasons not explained. In sum, ictal ESI was able to “correct” the paradoxical EEG lateralization in one out of four patients only.

Around the same time, Elwan et al. applied ESI on ictal EEG patterns with “pseudo-temporal” maxima in 10 patients with confirmed ETLE (Elwan et al., 2013). One seizure per patient was analyzed, selection criteria were not detailed. The ictal source located falsely inside the temporal lobe in 7 patients and was not localizable in the 3 remaining patients. As control patients, 9 out of 12 subjects with mesial TLE had ictal sources within the temporal lobe, and only 2 out of 11 with neocortical TLE. All patients later underwent successful epilepsy surgery. The authors concluded that ESI failed to differentiate pseudo-temporal ictal EEG patterns from “truly” temporal discharges.

In order to integrate non-invasive multimodal data for presurgical epilepsy evaluation, Neal et al. developed an algorithm to co-register non-concurrent scalp EEG, resting-state fMRI, and diffusion tensor MRI to create individual 3D brain network maps (Neal et al., 2018). In a preliminary validation study, resting-state fMRI findings were co-registered to ictal ESI results in one patient with unilateral TLE and another with bilateral TLE, and compared to the fMRI resting network of a healthy control subject. The authors found symmetric network representations in the healthy control person and the person with bilateral TLE, and an asymmetric network in the patient with unilateral TLE. Further validation studies with larger patient numbers and longitudinal follow-ups of individual patients were announced.

3.7. Spectral analysis of EEG data

In the studies presented above, ictal discharges or epochs were chosen manually and, thus, at least to a certain extent, arbitrarily. In what follows, more advanced analysis techniques were used to extract scalp voltage maps (voltage topography) from the ictal EEG prior to source localization. These analyses are based on spectral analysis (time–frequency data) or mathematical decomposition methods of the signal across time (independent components, principal components) to identify meaningful ictal components and to limit the contamination by artifacts.

Time-frequency plots of ictal data using spectral analysis allows isolating the ictal generator from other EEG signals such as biological and technical artifacts and non-epileptic brain activity. Already in the late 1990s, Lantz et al. transformed 2-seconds epochs at seizure onset into the frequency domain using fast Fourier transformation (FFT), and the dipoles were modeled for the dominant seizure frequencies (Lantz et al., 1999). The obtained dipoles were found homogeneous across 7 patients with mesial TLE. Using a modification of this approach, the source of the dominant ictal rhythm was correctly lateralized in 9 out of 10 patients with successful partial temporal lobectomy (Blanke et al., 2000). As an alternative to FFT dipole approximations, authors from the same group proposed a non-stationary distributed source approximation and applied it on frontal lobe seizures of one patient (Gonzalez Andino et al., 2001). Worrell et al. used spectral analysis to determine a scalp voltage map that best described the measured scalp potentials at the seizure frequency during a 3-seconds epoch at seizure onset (Waberski et al., 2000). Source localization of the extracted scalp voltage map concorded with the symptomatic brain lesion in 9/10 patients on a lobar level.

Twelve years later, Bersagliere et al. applied ESI on EEG of sleep-related frontal lobe seizures (Bersagliere et al., 2013). To avoid the heavy movement artifacts associated with these hyperkinetic seizures, the authors defined the 5 seconds before clinical seizure onset as the early ictal period and compared it to a pre-ictal epoch which was at least 13 seconds before clinical seizure onset. Following spectral analysis, they located the sources of delta (1–4 Hz) and sigma activity (12–16 Hz spindles). While interictal and ictal EEG patterns per se were of no lateralizing value, the average source maximum of sigma activity lateralized correctly in all four patients who subsequently underwent successful surgical resections, while the source of delta activity lateralized correctly in one patient only. However, in two of the patients, left–right differences for sources of sigma activity were only marginal.

At the same time, Beniczky et al. validated the diagnostic accuracy of ictal ESI in a blinded study design according to the STARD criteria (Beniczky et al., 2013). STARD, “standards for the reporting of diagnostic accuracy studies”, is a rigorous approach to compare the accuracy of an index test to a reference test (Bossuyt et al., 2015). Forty-two consecutive patients fulfilled the inclusion criteria, and for 33 of them, the epilepsy team agreed on a clinical reference standard. For each patient and each seizure type, a time-window was defined using time–frequency plots and a voltage map was created for every time-point of an averaged ictal waveform. ESI was performed for the voltage map distributions at onset of discharge (Fig. 2). Estimated by sub-lobar concordance with the reference standard, ictal ESI achieved a sensitivity and specificity of 70% and 76%, respectively. Twenty patients underwent surgery and 16 patients became seizure free, resulting in a positive predictive value (PPV) of 92% and a negative predictive value (NPV) of 43%. A couple of years later, using a similar approach but including ICA, authors from the same group localized the seizure onset zone of self-limiting epilepsy with centro-temporal spikes to the operculo-insular region in three patients (Alving et al., 2017).

In 2018, also in concordance with STARD, Koren et al. investigated the performance of an automatic algorithm for ictal onset source localization in 28 consecutive patients (Koren et al., 2018). The algorithm detected the most dominant rhythmic EEG pattern within the earliest ictal activity, its corresponding spatial
3.8. Decomposition analyses

The first study using decomposition analysis on ictal EEG was published in 2000 by Kobayashi et al. (Kobayashi et al., 2000). Ten seizures of 3 patients with TLE were investigated, and in every case, a source corresponding to iEEG seizure activity was found, even when seizure activity was not visually identifiable in the scalp EEG nor by spectral analysis. This indicated that decomposition techniques can extract ictal EEG information that is not apparent by visual or spectral analysis. – Lantz et al. decomposed ictal EEG based on peaks of seizure activity identified by the EEG global field power (Lantz et al., 2001). They found a dominant topography in 7/9 patients, and in 6 of these 7, source localization of this topography qualitatively corresponded to iEEG results.

In 2006, Leal et al. applied ESI on EEG recordings of gelastic seizures (Leal et al., 2006). Gelastic seizures are typically caused by hamartomas in the hypothalamus, a deep brain region far from the scalp, and visual analysis of ictal EEG is usually of little diagnostic value. Following ICA, the authors found a rhythmical component that indicated a hypothalamic source in 3 out of 3 patients. Interestingly, two of the patients had additional components that occurred later and were compatible with more superficial sources (Fig. 3). – Two years later, the same team of authors applied the same method to ictal EEG of 4 patients with tuberous sclerosis (Leal et al., 2008). Sources of the identified rhythmical components were nearer to the epileptogenic tuber than sources of interictal discharges.

Jung et al. used an ICA-based approach to study propagation of ictal onset patterns in 12 patients with TLE (Jung et al., 2009). During the first 10 s of averaged seizures, dipole sources located primarily in the mesial temporal and the medial frontal lobe, while at 20–40 s, the lateral anterior temporal lobe and the basal ganglia were involved as well. On a group level, two different ictal onset EEG waveform patterns, regular theta activity vs. irregular delta activity, had distinct propagation patterns. These findings are of pathophysiological relevance, but patients with prototypical ictal onset patterns only were included into the study.

Stern et al. decomposed early ictal 5-second epochs with principal component analysis (PCA) to perform ESI with the distributed inverse solution LORETA (Stern et al., 2009). Among the principal components, they visually identified the ictal component and chose the most robust local maximum following LORETA. For each of 5 successfully operated patients with TLE, the identified source was consistent across up to 3 seizures, indicating a high reliability of the findings. However, only in 2 of the 5 patients, the located source was actually inside the temporal lobe. – Miller et al. studied infraslow (<0.5 Hz) ictal EEG activity recorded with direct current-coupled electrode setups (Miller et al., 2007). Five of their 11 patients had successful epilepsy surgery and the sources of infraslow activity concorded to the resection sites on a lobar level. PCA was performed in specific seizures with a clear low-frequency signal; however, the authors found ESI of the identified dominant components of little value to study infraslow ictal shifts.

Still, decomposition techniques may help to clean artifactual EEG data. When Hallez et al. identified muscle and eye artifacts via blind source separation or ICA and removed them from ictal EEG, ESI improved in 5 of 8 patients, meaning that distances to a region of ictal SPECT activation became smaller than in ESI based on the raw EEG (Hallez et al., 2009). Nevertheless, median distances between the source estimations and ictal SPECT were larger than 20 mm in 7/8 patients. Seven years later, Li et al. based ictal ESI on raw EEG vs. cross-frequency coupled potentials (Li et al., 2016). The latter were calculated from the phase feature of low frequency rhythms and the amplitude feature of high frequency rhythms. Across 7 patients with favorable surgical outcome, 14 of 17 seizures were localized correctly, compared to 0 out of 17 based on raw EEG. As a limitation, the authors did not describe durations of postsurgical follow-up, and one of the patients with presumably favorable outcome died a few weeks after the surgery. Still, the approach seemed effective to extract brain signals from artifactual EEG data.

Another interesting approach for SOZ localization is to first decompose the ictal EEG data to isolate seizure components, perform ESI on each component and then integrate the ESI results.
Using such a dynamic seizure imaging (DSI) technique on 76-electrode EEG, Yang et al. identified the SOZ in good correlation with the successfully resected zone or the SOZ as defined by IEEG/SPect imaging methods in 17 seizures of 8 patients (Yang et al., 2011). The DSI method colocaled with the ground truth in 14 seizures and had a mean localization error of 10 mm in the remaining 3 seizures. For comparison, direct source imaging of the raw EEG data had a mean localization error of 28 mm. In a follow-up study, Lu et al. applied the same approach on 32-channel EEG (Lu et al., 2012a). In 7 out of 9 pediatric patients, the SOZ was estimated within the resected brain area, and in the remaining two patients, it was at least close. However, 4 patients had an unfavorable postsurgical outcome, so the RZ did not include the “true” EZ in these cases. Still, DSI corresponded well with IEEG that was recorded in 7 patients, also for localizing multiple foci during later seizure propagation.

Despotovic et al. applied decomposition methods on seizure EEG of neonates with perinatal hypoxic brain lesions (Despotovic et al., 2012). They proposed a technique based on atlas-free segmentation and a brain extraction algorithm to construct neonatal head models including scalp, skull (with modelling of the fontanelle), CSF, and brain. Forty-five focal seizures of 10 neonates were studied. In 9/10 patients, all seizures localized within 15 mm to a border of the MRI lesion, most of those even within 5 mm.

Instead of decomposing EEG data in the sensor space, Pellegrino et al. applied decomposition analysis on spatiotemporal source maps (source space) obtained from simultaneous MEG/EEG recordings in a heterogeneous population including TLE and ETLE patients (Pellegrino et al., 2016). On a sub-lobar level, the most active source component was concordant in 9/14 seizures or 6/8 patients. The median distance of the source map maximum to the clinically defined SOZ based on IEEG was 11 mm. Ictal MEG was more accurate than ictal ESI which can be partly due to the difference in spatial sampling, given that MEG used 275 MEG gradiometers while ESI only used 54 EEG electrodes. Usually, ictal MEG data are rare because of limited MEG recording times.

In order to entirely avoid the averaging of ictal EEG epochs which may lead to loss of information, Erem et al. proposed a dynamic ESI approach that explicitly models inter-epoch variation (Erem et al., 2017). Ictal EEG data are divided into series of consecutive short epochs which do not need to contain rhythmic activity, and dynamic ESI is applied on the epoch collections. The feasibility of the approach was tested in simulated data as well as in real data of four patients. Two of these had a second epilepsy surgery to extend a first, unsuccessful anterior temporal resection, and dynamic ESI localized the SOZ in the area resected during the second surgery. However, regarding the defects of brain and skull caused by the first surgery, these patients may not have been ideal candidates for ESI.

To reduce the impact of human judgement on ictal component selection, Habib et al. proposed a recursive ICA approach to eliminate unwanted components from ictal ESI (Habib et al., 2020). Noise was eliminated in each recursive cycle to obtain a single independent component containing the ictal EEG signal. In 24 seizures of 8 epilepsy patients (7 TLE) who subsequently underwent successful surgical resections, the approach was able to identify such a “best ictal component”, and the source concorded with the resection in 20 of these. When applied on simulated datasets, the recursive ICA approach led to more accurate ESI results than ESI based on visual inspection of the EEG. The average time to compute the recursive ICA on a laptop computer was 13 minutes which seems acceptable for clinical practice.

3.9. Additional connectivity analysis

All studies presented until here focused on the sources with maximum power as the estimate of ictal onset. This means, they did not take into account that epilepsy is a network disease and that connectivity between regions is likely to play an important role at seizure onset. In the following, we will give an overview on ictal ESI studies with additional functional connectivity analyses. Functional connectivity describes the temporal correlation of neuronal activity in different brain regions. It allows studying the communication between brain regions during a seizure to see how the ictal neuronal activity propagates. In epilepsy, Granger causality, a statistical concept of causality based on how well one signal can predict another one, has frequently been used to localize the SOZ from ictal IEEG (van Mierlo et al., 2014). The preferred techniques to extract the ictal connectivity pattern are the Partial Directed Coherence (PDC) and the Directed Transfer Function (DTF). PDC models direct connections only, while DTF also considers indirect and cascade connections. Since indirect connections tell us much about where the information originally spread from, DTF is very suitable to localize the SOZ (van Mierlo et al., 2018).

Ding et al. were the first to combine ESI and subsequent connectivity analysis to estimate the SOZ in two studies (Ding et al., 2007; Lu et al., 2012b). Ictal 3-seconds epochs at seizure onset were selected and reconstructed in the source space via ESI. Via DTF, connectivity between the sources’ estimated time-series was assessed, and those sources with most outgoing connections were considered to represent the SOZ. In the first study, 32-electrodes EEG recordings of 20 seizures in 5 patients were analyzed. The estimated SOZ were within 15 mm of the presumed EZ, confirmed by MRI visible lesions or SPECT images. However, intracranial recordings were not performed, and no details on surgery or outcome were given (Ding et al., 2007). In the follow-up study, the authors used the same method to compare 76-, 64-, 48-, 32-, and 21-electrode setups (Lu et al., 2012b). In 23 seizures of 10 patients with subsequent successful resections, higher numbers of electrodes led to better localizing results.

In another study from the same group, Sohrabpour et al. used DSI (see above, decomposition analysis) in combination with connectivity analysis (DTF) to study a patient who had 3 seizures during 76-channel EEG recording (Sohrabpour et al., 2016). The source with the highest out-going connections concorded well with the SOZ defined by IEEG recordings and with the EZ. Although confirming the usefulness of the approach, this was only a single-case study. – Elshoff et al. studied ictal sources and networks in 11 patients who later underwent epilepsy surgery (Elshoff et al., 2013). Other than in the 3 patients with unfavorable surgical outcome, in those 8 patients who were rendered seizure-free, the first two sources identified by ictal ESI were concordant with the RZ on a sub-lobar level. When the authors applied connectivity analysis (renormalized PDC), they found that the network at the onset of the seizure had a star-like topography with the SOZ as the main hub, whereas in the middle of the seizure, it had a circular pattern without a central hub. This provided the first supporting evidence that an epileptic network can dynamically change over the course of a seizure. As a limitation of the study, only one seizure per patient was analyzed.

In 2015, Klamr et al. were the first to use Dynamic Causal Modeling (DCM), a technique estimating directed connections based on a set of underlying neural mass models using inference of hidden neuronal states from measurements of brain activity (Klamr et al., 2015). In a patient with musicogenic epilepsy, they localized the onset zone of seizures recorded with simultaneous hd-EEG/MEG. Functional MRI analysis revealed two competing regions of interest (ROI), one frontal and one right mesiotemporal, as the possible SOZ. Two models, each with one ROI acting as autonomous input over the other one, were compared to each other using a Bayesian framework. The model of the right mesiotemporal region driving the frontal ROI explained the ictal EEG better than the other one, and IEEG confirmed the SOZ in...
was down sampled to 32 electrodes, the combination of ESI and analysis led to decreased concordance with the resection. If the EEG power alone (ESI without connectivity) resulted in estimation inside the resected area in 4/5 patients and within 10 mm in 5/5. Fig. 4 illustrates the two approaches, ESI power alone vs. ESI followed by connectivity analysis. In 3 patients the right hippocampus. Although this study focused on two ROIs only, it proved that advanced connectivity modeling of hidden neuronal states is possible and can provide valuable information. Kouti et al. proposed a data-driven approach to define a variable number of ROIs for time-varying source connectivity analysis (Kouti et al., 2019). Spatially compact ROIs were identified based on power of dipoles within a distributed inverse solution, followed by extraction of single time courses from each ROI, and connectivity analysis via adaptive directed transfer function. In 3 patients with pharmacoresistant focal epilepsy, 3–4 ROIs per patient were identified among at least one was inside the clinically determined seizure onset zone. Still, only 3 out of 23 available patient datasets were examined, and comparative results of other methods were not shown.

Most recently, Lopes et al. used a total of 15 ROIs for lateralizing the SOZ based on low-density EEG data of 62 seizures in 15 patients (Lopes et al., 2020). Functional networks were computed using the phase locking value, and a model of ictogenicity was applied to predict the relative importance of each ROI to the network’s ability to generate seizures. The model predicted the hemisphere of surgery correctly in 6 out of 10 patients with favorable surgical outcome but only in 1 out of 5 patients with unfavorable outcome. In 4 out of all 15 patients, predicted ROIs were found in both hemispheres which was rated as inconclusive.

Staljanssens et al. applied ESI and connectivity analysis (DTF) on the first 3 s of a seizure recorded with 256-channels EEG in 5 patients (Staljanssens et al., 2017a). Considering the source with highest outgoing connections as the SOZ, this estimation was inside the resected area in 4/5 patients and within 10 mm in 5/5 patients. For comparison, selecting the source map maximum alone (ESI without connectivity) resulted in estimation inside the RZ only in 1/5 patients and within 10 mm in 2/5. Fig. 4 illustrates the two approaches, ESI power alone vs. ESI followed by connectivity analysis. Reducing the number of electrodes used for the analysis led to decreased concordance with the resection. If the EEG was down sampled to 32 electrodes, the combination of ESI and connectivity analysis was capable of estimating the SOZ within 10 mm of the RZ in 1 patient only, while ESI alone estimated the SOZ within 10 mm in 2/5 patients. Using a similar methodology in 6 seizures of 3 patients who later were rendered seizure-free by surgery, Martinez-Vargas et al. showed that ESI followed by connectivity analysis can localize the SOZ from clinical 27-channels EEG (Martinez-Vargas et al., 2017). The approach localized the RZ in 5/6 seizures while in the remaining seizure, localization was within 10 mm of the resection.

In a follow-up study, Staljanssens et al. adapted the hd-EEG approach to clinical long-term EEG (Staljanssens et al., 2017b). In 111 seizures of 27 patients with favorable surgical outcome, an artifact-free EEG epoch was studied with connectivity analysis restricted to the seizure’s frequency band. The SOZ was within 10 mm of the RZ’s border in 94% of the seizures. Here again, ESI followed by connectivity analysis performed significantly better than the ESI source map maximum alone. This study was the first to obtain high accuracy for SOZ localization using ESI and functional connectivity analysis in a larger patient cohort, based on widely available clinical recordings with standard electrode numbers. However, the study cohort included almost exclusively patients with TLE, and the method’s specificity was not assessed.

Most recently, the authors validated the same approach in 24 patients with various forms of ETLE (Vespa et al., 2020). Following visual identification of ictal EEG epochs, a spectrogram-based algorithm selected the optimal time window and frequency of interest for ESI and connectivity analysis. In a total of 94 seizures, additional functional connectivity analysis raised the specificity of ESI from 36% to 52% and the specificity from 62% to 84%. Connectivity analysis also helped to substantially increase the inter-rater agreement for the interpretation of the results. As a limitation of the method, it was not applicable to 10 patients who had no rhythmic EEG activity during their seizures.

3.10. Helpfulness in clinical decision-making

For clinical ESI, not only feasibility and accuracy are important, but also the yield of non-redundant information and the influence on the process of clinical decision-making. Already in 2002, Boon et al. prospectively assessed the added diagnostic value of ESI to clinical decision making in presurgical epilepsy evaluation (Boon et al., 2002). In 14% of 100 patients, ictal ESI influenced the presurgical decision-making process. The consequence of ictal ESI was mainly to avoid IEEG because the candidates appeared unsuitable for resection, as ESI supported initial incongruences between MRI and conventional ictal EEG results. Here, using ictal ESI for the decision process limited interpretation of its contribution to predict surgical outcome because it is unknown whether the respective patients truly could not have benefited from epilepsy surgery.

More recently, Foged et al. compared the added diagnostic value of low-density ictal and interictal ESI (25 EEG electrodes) to high-density interictal ESI (256 electrodes) in 82 patients (Foged et al., 2020). Information obtained from low-density ESI (ictal and interictal) changed the presurgical management plan in 20% of the patients while hd-ESI (interictal only) changed it in 28%. In 80% of cases, both ESI methods yielded congruent results. Congruencies of ictal vs. interictal low-density ESI results were not detailed. Nevertheless, the results indicate that a relevant proportion of patients evaluated for epilepsy surgery can benefit from ictal ESI.

4. Discussion and future perspectives

We reviewed the literature about ictal EEG source localization in detail. Overall, the 67 studies on a total of almost 1,000 patients with epilepsy show that ictal ESI is feasible and informative. Nev-
ertheless, there are several limitations that we will discuss in the sections below. We will also comment on further steps towards bringing ictal ESI into clinical practice.

4.1. Where are we now?

Thanks to research that started two and a half decades ago, current state-of-the-art ictal ESI can provide a more accurate and a more objective interpretation than visual inspection of ictal EEG alone. Contrary to other second-line presurgical diagnostic methods like MEG, fMRI and ictal SPECT, ictal EEG data are already available for almost every patient undergoing presurgical evaluation worldwide. Ictal ESI achieves similar sensitivities and specificities as ictal SPECT and MEG, but tracers or additional scanning facilities are not required, and it is highly cost-effective.

Therefore, in theory, ictal ESI based on clinical video-EEG monitoring can easily be included in the non-invasive phase of the evaluation process. Its results can have an impact on if and which additional investigations might be needed depending on other clinical parameters. In certain situations, patients may benefit from less diagnostic procedures, financial costs can decrease, and patient throughput can be increased. Nevertheless, and despite many promising results, the method has not yet found its way into clinical practice because of several reasons.

Since the first ictal ESI studies in the 1990s, a plethora of different methodological approaches have been proposed to localize the SOZ from ictal scalp EEG. As detailed above, these include various spherical or realistic head models with 3–7 compartments, different single-dipole or distributed inverse solutions, spectral analyses or decomposition methods for EEG data preprocessing, and subsequent functional connectivity analyses. Unfortunately, the wide spectrum of strategies hampers detailed comparisons. Additionally, the methodological complexity of ictal ESI currently renders it a tool for researchers and expert users only. Although ictal EEG data are obtained in every surgical epilepsy center, and both commercial and free ESI software packages are available, the knowledge of how to use them is narrowly distributed. Even though most recent methods are fairly objective, a minimum of human intervention is needed to start the analysis, e.g. epoch selection, ictal spike definition for averaging, or definition of the frequency band of interest. This increases the manpower needed and potentially decreases the reproducibility of results and the spread of the technique.

By comparison, ESI of interictal epileptic discharges is rather straightforward, and best practice is better documented. IEDs are usually more frequent than seizures and less often corrupted by artifacts, they display relatively simple spatio-temporal dynamics and are easy to average. Nevertheless, presurgical decision-making aims at localizing the seizure onset and not necessarily the origin of interictal spikes. Therefore, theoretically, ESI to localize the SOZ should be more informative than ESI of the EZ. Several authors validated their ictal ESI results based on interictal ESI (see Table 1). However, until now, there are no large studies that show a superiority of ictal ESI compared to interictal ESI. In a recent meta-analysis of 6 studies on 159 patients validated by surgical outcome, ictal ESI had a sensitivity of 90%, a specificity of 47%, and an overall accuracy of 75%. The diagnostic odds ratio of favorable seizure outcome if the ESI-SOZ was resected was 7.9. For comparison, interictal ESI had a sensitivity of 80% and a diagnostic odds ratio of 4.0 while specificity and overall accuracy were the same as in ictal ESI (Sharma et al., 2019). One can conclude that there is at least a trend towards more accuracy in ictal vs. interictal ESI.

As described in the introduction of this article, the biggest need for additional diagnostic methods exists in cases with incongruent or insufficient information from the first-line diagnostic workup. Most often, this relates to patients with normal structural MRI (“MR-negative” or “non-lesional” cases) and/or ETLE. However, very few studies included more than a fistful of ELTE cases (see Table 1), and only five of these focused on ETLE specifically (Despotovic et al., 2012; Elwan et al., 2013; Kovac et al., 2014; Pellegrino et al., 2016; Vespa et al., 2020). The most recent one was also the largest: Vespa et al. demonstrated the usefulness of low-density ESI and subsequent connectivity analysis in 24 patients with ETLE. Regarding MRI-negative epilepsy, one single study focused on non-lesional epilepsy, and this included 5 patients (Batista Garcia-Ramo et al., 2019). Hence, the clinical value of ictal ESI in these important conditions has not yet been assessed systematically enough.

4.2. What is needed to bring the technique into clinical practice?

Further advances in the various methodologies of ictal ESI can be expected which will further increase its accuracy. For example, until now, there are different techniques to deal with the low SNR of ictal EEG signals. While some studies found optimal localization results at the seizure’s very beginning, other studies show that data quality appears more important. The best compromise may vary depending on individual early ictal signal changes and on biological or technical artifacts, and a systematic approach remains to be found. In addition, it is likely that EEG data decomposition techniques and connectivity analyses will be refined and that best practice guidelines will evolve with future validation studies (He et al., 2019; Babiloni et al., 2020).

During the evolution of EEG-based SOZ localization from a rather experimental technique to a widely established clinical tool, it is likely that a handful of specific approaches emerge on which the community can agree on as a standard. These need to provide a fair cost-benefit ratio in terms of accuracy, reproducibility and reliability of the results on the one hand, and manpower and skills needed on the other hand. A possible solution that can help bringing ictal ESI to clinical practice is automated analysis. For interictal ESI, there are already automated methods that detect interictal spikes and localize them with sensitivities of 79–88% (van Mierlo et al., 2017; Baroumand et al., 2018). Automated ictal ESI as proposed in (Koren et al., 2018) has the potential to be rapidly included in the presurgical evaluation.

High spatial sampling via use of hd-EEG setups seems to increase the accuracy of ictal ESI and subsequent connectivity analyses substantially. Unfortunately, such setups are not available in all presurgical centers, and the cost of EEG amplifiers strongly depend on the number of channels. On the other hand, the most substantial increase in accuracy was shown for 64- to 128-channel EEG in comparison to 32 electrodes or less. Therefore, it may not be necessary to acquire full 256-channel EEG hardware.

Finally, since ictal ESI is much more difficult to perform than interictal ESI, we need an answer to the question: In which patients does interictal ESI provide sufficiently accurate information, and who needs additional ictal ESI? Given that interictal ESI already has a sensitivity of 70–80% to localize the EZ (Sharma et al., 2019), ictal ESI could confirm results of interictal ESI and other localization techniques or provide an additional localizing hypothesis in patients with discordant non-invasive results who are candidates for IEEG. Like (Foged et al., 2020), future studies should target the added value of ictal ESI in comparison to interictal ESI that is already taking an increasingly prominent role in the presurgical evaluation in epilepsy centers worldwide. Ideally, these studies should be prospective and multicenter-based, and they need to put an emphasis on ETLE and MRI-negative cases, since these are usually the most difficult cases to evaluate for epilepsy surgery, and ictal ESI could be particularly helpful here.
5. Conclusion

Ictal ESI is a promising neurophysiological tool to approach the epileptogenic zone in pharmaco-resistant focal epilepsy, especially in ETLE and MR-negative cases. Connectivity analyses have been shown to add substantial information to pure ESI, while automated approaches promise to lower the required efforts. Still, more research is needed to replicate, compare, and extend prior findings with validation in large and heterogeneous patient groups. In this way, the algorithms' performance can be compared across patient characteristics (EEG ictal pattern, focus localization, MRI lesions, and surgical outcomes), and the added value of ictal ESI can be compared to interictal ESI and current state-of-the-art presurgical tools.

Declaration of Competing Interest

Pieter van Mierlo, Margitta Seeck and Serge Vulliémoz are shareholders of Epilog NV, Ghent, Belgium. Margitta Seeck received a travel grant to attend the 16th ICA World Congress. The funders were not involved in the study design, data collection, analysis and interpretation of data, in the writing and publication of the report, and in the decision to submit the article for publication.

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