Seizure onset zone localization from ictal high-density EEG in refractory focal epilepsy

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Abstract

Epilepsy surgery is the most efficient treatment option for patients with refractory epilepsy. Before surgery, it is of utmost importance to accurately delineate the seizure onset zone (SOZ). Non-invasive EEG is the most used neuroimaging technique to diagnose epilepsy, but it is hard to localize the SOZ from EEG due to its low spatial resolution and because epilepsy is a network disease, with several brain regions becoming active during a seizure. In this work, we propose and validate an approach based on EEG source imaging (ESI) combined with functional connectivity analysis to overcome these problems. We considered both simulations and real data of patients. Ictal epochs of 204-channel EEG and subsets down to 32 channels were analyzed. ESI was done using realistic head models and LORETA was used as inverse technique. The connectivity pattern between the reconstructed sources was calculated, and the source with the highest number of outgoing connections was selected as SOZ. We compared this algorithm with a more straightforward approach, i.e. selecting the source with the highest power after ESI as the SOZ. We found that functional connectivity

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analysis estimated the SOZ consistently closer to the simulated EZ/RZ than localization based on maximal power. Performance, however, decreased when 128 electrodes or less were used, especially in the realistic data. The results show the added value of functional connectivity analysis for SOZ localization, when the EEG is obtained with a high-density setup. Next to this, the method can potentially be used as objective tool in clinical settings.

Keywords: high-density electroencephalogram (hd-EEG), EEG source imaging (ESI), functional connectivity, Granger causality, refractory epilepsy

1. Introduction

The electroencephalogram (EEG) is the most important clinical technique to diagnose and characterize epilepsy, because it can directly measure the aberrant electrical activity in the brain associated with this disease in a convenient, safe,
5 and inexpensive way (Smith 2005). Patients with epilepsy have a strongly abnormal ictal EEG during seizures, but also in between seizures abnormalities such as interictal epileptiform discharges (IEDs) and slow waves can be noticed.

The goal of epilepsy treatment is to suppress seizures. When antiepileptic drugs (AEDs) do not allow seizure control, surgery is an important option due
10 to its high efficacy in selected candidates (Télez-Zenteno et al. 2005; de Tisi et al. 2011). During epilepsy surgery, the brain region that causes the seizures is disconnected (disconnective surgery) or removed (resective surgery). Therefore, it is of utmost importance to accurately delineate the epileptogenic zone (EZ), that is the brain area of which surgical removal is required and sufficient to
15 render the patient seizure-free. However, the EZ is only a conceptual region since it cannot be measured directly. Only when a patient is seizure-free after surgery, we can conclude that the EZ was harbored in the resected zone (RZ) (Rosenow and Lüders 2001). Fortunately, it is possible to get an indirect estimate of the EZ by localizing the seizure onset zone (SOZ), which is the region
20 where clinical seizures originate, and/or the irritative zone (IZ), i.e. the region where interictal epileptiform discharges (IEDs) originate. In current clinical

practice, visual inspection of the EEG is combined with other investigations such as MRI, SPECT, PET, MEG, and invasive EEG (iEEG) with implanted electrodes, to localize these areas (Carrette et al. 2011). Yet, individually, none
25 of these techniques are able to localize SOZ unambiguously. On the other hand, every extra investigation is expensive, time-consuming, and potentially harmful for the patient, e.g. iEEG can lead to scarring, infection and functional loss (Sprengers et al. 2014).

Therefore, it would be of high clinical value to be able to localize the SOZ
30 based on non-invasive EEG alone, which is an inexpensive and safe technique. However, several problems are encountered when estimating the SOZ from non-invasive EEG. One of the major problems is the low spatial resolution ($\sim$ cm) of non-invasive EEG due to volume conduction. Neuronal activity propagates through different tissues (such as cerebrospinal fluid, skull and scalp) before it
35 reaches the electrodes. Because of the different conductivities of these tissues, and certainly the low conductivity of the skull, the measured activity at the electrodes is smeared and distorted. As a consequence, the potential measured at a given electrode does not necessarily represent the activity of the directly underlying brain area. The second major problem is that epilepsy is a network
40 disease, i.e. during a seizure, several brain regions become simultaneously active as part of the patient’s individual epileptic network and it is often hard to distinguish the main driver(s) of this network at seizure onset from the secondary activated regions (Spencer 2002; Richardson 2012).

One way to tackle the problem of the low spatial resolution is to reconstruct
45 the sources in the brain that are generating the EEG using EEG source imaging (ESI) techniques. In recent years, a large body of research to measure the EZ based on ESI of EEG recordings has been done. ESI can be applied on interictal or ictal EEG measurements to get information about the IZ and the SOZ, respectively. The vast majority of studies has focused on the localization
50 of the IZ (Plummer et al. 2008; Brodbeck et al. 2011; Wennberg et al. 2011; Mégevand et al. 2014; Wennberg and Cheyne 2014; Strobbe et al. 2016). Yet, it can be argued that identification of the SOZ is more indicative of the EZ

compared to the IZ, since they directly reflect the seizures (Jayakar et al. 1991; Rémi et al. 2011; Elshoff et al. 2013).

55 However, ESI of ictal activity is significantly harder to obtain due to muscle and movement artifacts during seizures. Despite these difficulties, some methods analyzing ictal EEG recordings have been proposed, suggesting that ESI of ictal activity is promising for SOZ localization (Lantz et al. 1999; Assaf and Ebersole 1997; Ebersole 2000; Boon et al. 2002; Jung et al. 2009; Koessler
60 et al. 2010; Yang et al. 2011; Habib et al. 2015).

ESI can be improved by increasing the spatial resolution of the EEG by including more electrodes. Despite the fact that increasing the number of electrodes does not solve the distortion of the brain signals, previous research has shown the benefit of high-density EEG (hd-EEG) on ESI (Lantz et al. 2003;
65 Michel and Murray 2012), with specificity and sensitivity increasing significantly with the number of electrodes used (Brodbeck et al. 2011).

The aforementioned studies did not take into account that epilepsy is a network disease and thus did not cope with the second problem mentioned above. Usually, one distinct time point was used to reconstruct the sources
70 of the averaged IED (e.g. the peak or the 50% slope of the peak of the IED) (Brodbeck et al. 2011) or, in case of ictal recordings, averaged discharges during ictal rhythms (Assaf and Ebersole 1997; Ebersole 2000; Habib et al. 2015). In other ictal cases, epochs rather than single time points were reconstructed and the source with the highest amplitude over time and space was selected
75 (Koessler et al. 2010). In another approach, ESI depended on components of the decomposed EEG associated with seizure activity, with every component corresponding to a single topography to remove the potential non-stationarity of the signals (Jung et al. 2009; Yang et al. 2011). It cannot, however, be assured that the selected time sample or epoch contains only activity of the onset and
80 no propagated activity. Moreover, there is no direct evidence to assume that the brain activity in the SOZ is stronger than the propagated activity, because a single driving neuron could trigger a larger group of neurons resulting in an area of higher power elsewhere.

The concept of functional brain connectivity can be used to investigate the
 epileptic network and its pathways. Functional brain connectivity models re-
 85 reveal how information flows are directed in the brain when applied on the re-
 constructed brain signals after ESI. Only a few studies tackling the two major
 problems stated above by combining ESI with functional connectivity analysis
 to localize the IZ/SOZ or study the epileptic networks have been performed up
 90 to date. Song et al. (2013) and Coito et al. (2015) investigated the epileptic
 network during IEDs in hd-EEG recordings. Song et al. (2013) applied ESI
 with either minimum norm or cortical surface Laplacian constraints and used
 spectral coherence for functional connectivity analysis to search for the possible
 engagement of pathological networks. They saw characteristic source coherence
 95 patterns before, during and after IEDs, but these patterns could not always
 be easily related to the EZ. Coito et al. (2015) performed source reconstruc-
 tion using Local Auto-Regressive Averages (LAURA) and used Partial Directed
 Coherence (PDC) to assess the connectivity to investigate the fast-varying be-
 havior of epileptic networks during interictal spikes and concluded that there are
 100 significantly different connectivity patterns in patients with left temporal lobe
 epilepsy, right temporal lobe epilepsy and healthy controls. [These studies had as
 main goal to map the brain networks and to investigate their properties, rather
 than localizing the IZ or SOZ.](#) Ding et al. (2007) and Lu et al. (2012) analyzed
 ictal epochs of 3 s by combining first principle vector (FINE) spatio-temporal
 105 ESI and directed transfer function (DTF) analysis to identify the ictal sources.
 While Ding et al. (2007) only used 32 electrodes, Lu et al. (2012) compared 32
 and 76 electrodes and found more localizing results for the higher number of
 electrodes. Ding et al. (2007) estimated the SOZ within 15 mm of the presumed
 EZ in five patients and Lu et al. (2012) found the SOZ in 7 out of 10 patients
 110 within 10 mm of the RZ. Elshoff et al. (2013) analyzed ictal EEG segments
 (38–50 electrodes) of max. 10 s in the beginning and in the middle of seizures
 with Dynamic Imaging of Coherent Sources (DICS) to determine the SOZ. The
 source with the highest power was identified as SOZ. Afterwards, functional con-
 nectivity analysis based on (renormalized) partial directed coherence ((R)PDC)

115 was applied on the reconstructed sources, however, not to localize the SOZ, but rather to gain insight into the characteristic underlying epileptic network. In 8 patients that were rendered seizure-free after surgery, the first two sources identified by DICS were concordant with the RZ. For three other patients, who were not seizure-free, the first two sources were not concordant with the RZ.

120 In the present study, we investigate a new combination of ESI and functional connectivity analysis to study the added value of using functional connectivity analysis compared to the more traditional method that uses power after ESI to localize the SOZ. To assess connectivity, we will use a Granger causality based measure, the spectrum-weighted Adaptive Directed Transfer Function
 125 (swADTF), as successfully applied on ictal iEEG (van Mierlo et al. 2013). Here, we extend the method to non-invasive ictal EEG. First, simulated ictal high-density EEG data is used to verify the method. Next, we validate the approach in five patients. Finally, we perform the analysis on subsets of the electrodes to mimic lower-density setups to investigate the influence of the number of
 130 electrodes on the performance of the proposed algorithm.

2. Methods

2.1. Generation of simulated data

Ictal EEG epochs of 3 s were constructed by forward projection of a simulated epileptic network in the brain. The details on the forward models used for this
 135 purpose, can be found in section 2.3.2. The epileptic network consisted of three nodes, of which the configuration can be seen in Fig. 1(a). The seizure originated in node 1 and propagated to node 3 via node 2. In node 1, the driver of the network, epileptic activity was mimicked by a sinusoid of decreasing frequency from 12 Hz at $t = 0$ s to 8 Hz at $t = 3$ s and its first two harmonics. Gaussian
 140 noise with 1/f spectral behavior was added with a signal-to-noise ratio (SNR) of 5 dB to account for background brain activity. The seizure propagated to the second node with a delay of 20 ms. Extra Gaussian 1/f noise is added with an SNR of 5dB. The resulting signal is delayed with 32 ms to node 3 and again

Gaussian 1/f noise is added. The three signals were constructed with a sample
145 frequency of 250 Hz, and an example can be seen in Fig. 1(b).

Every node corresponded with a patch in the brain, which was constructed
by growing a region in the gray matter around a randomly chosen seedpoint,
until the patch enclosed 100 gridpoints of a uniform cubic grid with spacing
4 mm (see also section 2.3.2). This resulted in a mean volume of 8.04 cm³
150 per patch. A minimal distance of 15 mm between every two patches was guar-
anteed. An example of three patches can be seen in Fig. 2(a). The activity
in the patches was smoothed towards the borders in order to obtain a three-
dimensional Gaussian-shaped power distribution to avoid abrupt power level
changes, since neighboring neurons tend to synchronize (Haalman and Vaa-
155 dia 1997), giving rise to a smooth activity distribution. The background brain
activity outside the patches was set to Gaussian 1/f noise with an SNR of 5 dB
with respect to the epileptic signal in the first node.

The brain activity in source space was projected to sensor space to obtain
hd-EEG with 204 channels, this can be seen in Fig. 2(b). Subsets of 200, 196,
160 192, 188, 184, 180, 176, 172, 168 and 164 electrodes were created by consecutive
exclusion of 4 electrodes, while keeping the electrode distribution as uniform
as possible. Additionally, subsets of 128, 64 and 32 electrodes were created to
mimic setups that are more common in clinical practice. The resulting electrode
configurations can be seen in Fig. 3.

165 2.2. Collection of patient data

Patients were selected from the database of the epilepsy unit of the Geneva
University Hospital with following inclusion criteria: (1) patients suffering from
focal refractory epilepsy; (2) they underwent hd-EEG (256 channels) monitor-
ing and had at least one seizure during recording; (3) the patients underwent
170 resective surgery of the supposed epileptogenic zone; (4) they had only one re-
section; (5) the surgical outcome of the patients was Engel Class III or higher;
(6) pre- and post-operative T1-weighted MRI of the patient was available. Five
patients (2 male) with mean age of 37.6 years fulfilled all criteria and were in-

cluded. Table 1 gives an overview of the patients’ age and sex, clinical and MRI
175 findings, the result of visual analysis of the scalp EEG, the performed resective
surgery, and the outcome of the surgery. The local ethical committee approved
the study and all patients gave written informed consent.

Long term hd-EEG was recorded for approximately 24 hours in each patient
(EGI, Geodesic Sensor Net with 256 electrodes). From the 256 electrodes, the
180 facial electrodes and the bottom line of the cap were removed due to major
muscle artifacts, resulting in a setup of 204 electrodes. Electrode positions were
estimated for every patient by manually fitting a template cap on the individual
MRI. Also for the patient data, subsets of 200, 196, 192, 188, 184, 180, 176, 172,
168, 164, 128, 64 and 32 electrodes were created, with the configurations shown
185 in Fig. 3. The sample frequency was either 250 Hz or 1000 Hz. In the latter
case, the EEG was downsampled offline to 250 Hz for consistency and to reduce
computation time.

For every patient, an epoch of 3 s was selected that started at the seizure
onset time marked by an EEG expert (MG).

190 2.3. From EEG to SOZ

An overview of the presented approach to get from the EEG to SOZ estima-
tion is shown in Fig. 4. The data of patient 1 is used for illustration purpose.
To summarize, we selected 3 seconds of ictal hd-EEG beginning at the marked
seizure onset and reconstructed the sources generating the ictal brain activity
195 with ESI. In the inverse solution, we selected local hotspots of higher activity.
This resulted in 8 sources. As no constraints on the orientation of the sources
were applied in the reconstruction, each of these 8 sources is represented by
three time series, for the x, y and z direction. We used singular value de-
composition (SVD) to represent each source with one time series (Golub and
200 Reinsch 1970). Using these time series, functional connectivity analysis was
applied with the spectrum-weighted adaptive transfer function (swADTF) (van
Mierlo et al. 2013). Next, the swADTF values were summed to get the out-
degree of every source as a measure for the total outgoing information flow

from a source. The source with the highest outdegree, source 2 in the example
 205 (Fig. 4(g)), was selected as SOZ. This estimated SOZ was compared to the RZ
 of the patient and also to the source with highest power after ESI, i.e. source
 3. In the following sections, we present every step of this method in detail.

2.3.1. EEG preprocessing

The patient data was common average referenced and band-pass filtered
 210 between 1 and 30 Hz, to remove baseline drift and to reduce high frequency
 noise resulting from movement artifacts. An extra notch filter at 50 Hz was
 applied to filter out remaining power line noise. In patient 4 and 5, ICA was
 applied to remove remaining artifact (Makeig et al. 1996)..

2.3.2. EEG source imaging

215 To reconstruct the sources generating the ictal epochs, EEG source imaging
 (ESI) was done. For the forward model, patient-specific head models were con-
 structed based on the finite difference method (FDM) (Hallez et al. 2005). Air,
 scalp, skull, cerebrospinal fluid (CSF), gray and white matter were segmented
 from the individual pre-operative T1-weighted MRI of the patient (resliced to
 220 voxels of $1 \times 1 \times 1 \text{ mm}^3$) using the Statistical Parametric Mapping (SPM12)
 toolbox (<http://www.fil.ion.ucl.ac.uk/spm>). The segmented volumes were
 combined into a single head model with 6 tissue classes, and following con-
 ductivity values were assigned to the different tissues: 0.33 S/m for gray mat-
 ter, 0.14 S/m for white matter, 1.79 S/m for CSF (Baumann et al. 1997),
 225 $0.33/25 \text{ S/m} = 0.0132 \text{ S/m}$ for the skull and 0.33 S/m for scalp (Montes-
 Restrepo et al. 2014; Vorwerk et al. 2014), and 0 S/m for air. The solution
 space was created based on the segmented gray matter. Solution points (SP)
 were uniformly distributed in the gray matter of the patient with a grid spacing
 of 4 mm, which resulted in approximately 8000 SP for every patient. These
 230 SPs formed the central nodes of the dipole model, so we ensured that at least 2
 voxels of gray matter were left open between the SPs and the boundaries with
 other tissues in all directions, in order to keep the dipoles restricted to the gray

matter.

An in-house implementation of the LOw Resolution Electromagnetic Tomog-
rAphy (LORETA) algorithm (Pascual-Marqui et al. 1994) was used to solve
the inverse problem. This is a distributed linear method that is based on the
physiological assumption that neighboring neurons are simultaneously and syn-
chronously activated, which practically means that the solution should be as
smooth as possible. There are no constraints on dipole orientation, so after
solving the inverse problem, every SP is represented by 3 time series, one for
each orthogonal spatial direction (x, y, z).

2.3.3. Source selection and time series

In a typical LORETA solution, the brain activity is smooth throughout the
volume of the brain with one or more hotspots of higher activity that vary in
intensity and that may overlap partially. During an epileptic seizure, several
brain regions become active. We assume that some of the hotspots we obtain
after ESI correspond with the active regions in the network. To determine
these hotspots, we calculated the sphere power of every SP. We defined the
sphere power of a certain SP to be the mean power of all SPs lying in a sphere
centered around that certain SP. We considered the spheres with no neighbors
with higher sphere power to be the center of a hotspot. The SP that had the
highest power in that sphere was selected and called a source. Sources in the
cerebellum were excluded. By varying the radius of the sphere, more or less
sources could be found. Two extreme cases can be distinguished: when the
radius is larger than the largest distance between two SPs, only one SP will be
selected, i.e. the one corresponding with the maximal power, and connectivity
analysis cannot be done. In the other extreme, when the radius is smaller than
the resolution of the grid (here 4 mm), all sources will be selected. This is
not only computationally unfeasible for the subsequent connectivity analysis; it
might also bias the connectivity analysis since LORETA provides a solution in
which neighboring sources are correlated, and thus possibly introducing spurious
connections. As a consequence, the radius should be chosen in a range that keeps

the number of selected sources computationally feasible and does not make the search area unnecessarily large, while not excluding possible network nodes (i.e. not excluding possibly relevant local maxima). We found good correspondence between the LORETA solution and the selected sources when a radius between 15 and 25 mm was chosen. We eventually used a radius of 20 mm as this provided overall best results and for which the number of selected sources varied between 4 and 13 for all patients during the analyzed ictal epoch.

Suppose that K sources were selected. As LORETA does not impose constraints on dipole orientation, the activity in each source k of the K selected sources can be represented by a matrix $\mathbf{F}_k \in \mathbb{R}^{3 \times N}$ for $k = 1 \dots K$, with N the number of time samples of the epoch. Each row of the matrix corresponds with an orthogonal spatial direction (x, y, z). We used singular value decomposition (SVD) to represent each source by a single time series $\mathbf{s}_k \in \mathbb{R}^N$, associated with the largest singular value of the SVD (Golub and Reinsch 1970).

2.3.4. Functional connectivity analysis

Functional connectivity analysis was used to estimate which source is the most important, i.e. the driver behind the epileptic network. We used a Granger causality based measure to investigate the network, more specifically the spectrum-weighted adaptive directed transfer function (swADTF). The general concepts of this technique have been previously described by van Mierlo et al. (2013). First, the source signals $\mathbf{s}_k$ are modeled with a time-varying multivariate autoregressive (TVAR) model in which the signals are represented as a linear combination of their own past plus additional uncorrelated white noise. This can be mathematically described as:

$$\mathbf{s}_k(t) = \sum_{p=1}^P \sum_{j=1}^J \mathbf{a}_{kj}(p, t) \mathbf{s}_j(t-p) + \mathbf{e}_k(t) \quad (1)$$

in which P is the model order, i.e. the number of past samples that are taken into account for the calculation of the current sample, $\mathbf{a}_{kj}(p, t)$ are the model coefficients, and $\mathbf{e}_k(t)$ is uncorrelated white noise at time t . In matrix represen-

tation we get:

$$\mathbf{S}(t) = \sum_{p=1}^P \mathbf{A}_p(t) \mathbf{S}(t-p) + \mathbf{E}(t) \quad (2)$$

with $\mathbf{S}(t) = [\mathbf{s}_1(t) \ \mathbf{s}_2(t) \ \dots \ \mathbf{s}_K(t)]^T$ the $K \times 1$ source matrix of the K selected sources at time t , with $\mathbf{A}_p(t)$ the $K \times K$ coefficient matrix for delay p at time t , and with $\mathbf{E}(t) = [\mathbf{e}_1(t) \ \mathbf{e}_2(t) \ \dots \ \mathbf{e}_K(t)]^T$ the $K \times 1$ matrix of the uncorrelated white noise at time t .

The model coefficients describe the directional information flow between the different signals and can change over time, making the model time-variant. In the simulation data, we set the model order to 10 ($= 40$ ms), following the ranges that are presented in literature (Astolfi et al. 2008; van Mierlo et al. 2011, 2013; Coito et al. 2015). For the patient data, we calculated the optimal model order with the Akaike Information Criterion (AIC) (Akaike 1974) and found model orders between 4 and 8. For patient 4, we found diverging results and therefore we set the model order to the maximal value found for the other patients, i.e. 8. The TVAR coefficients were estimated using the Kalman filtering algorithm (Arnold et al. 1998; Schlögl et al. 2000). The Kalman filtering algorithm is mainly influenced by the update coefficient (UC), which expresses how quickly the TVAR model coefficients will adapt to changes in the dataset. This way it provides a balance between the amount of signal and the amount of noise that is modeled. We chose a low value of 10^{-4} for the UC, as we only want to see connections that are maintained in the data and we are not interested in modeling abrupt changes.

The time-varying transfer matrix $\mathbf{H}(f, t)$ of the model can be found after Fourier transformation and inversion of the coefficient matrix:

$$\begin{aligned} \mathbf{A}(f, t) &= - \sum_{p=0}^P \mathbf{A}_p(t) e^{-i2\pi \frac{f}{f_s} p} \\ \mathbf{H}(f, t) &= \mathbf{A}^{-1}(f, t) \end{aligned} \quad (3)$$

with f_s the sample frequency and $\mathbf{A}_{p=0}(t)$ equal to the negative $K \times K$ identity matrix. The elements $\mathbf{H}_{i,j}(f, t)$ of the transfer matrix describe the information flow from signal j to signal i at frequency f at time t . From the

transfer matrix, the spectrum-weighted Adaptive Directed Transfer Function (swADTF) can be calculated to investigate the causal relation from source signal $\mathbf{s}_j$ to source signal $\mathbf{s}_i$ for a predefined frequency band at time t :

$$\text{swADTF}_{ij}(t) = \frac{\sum_{f=f_1}^{f_2} |H_{ij}(f, t)|^2 \sum_{k=1}^K |H_{jk}(f, t)|^2}{\sum_{l=1}^K \sum_{f'=f_1}^{f_2} \left(|H_{il}(f', t)|^2 \sum_{o=1}^K |H_{lo}(f', t)|^2 \right)} \quad (4)$$

Due to normalization of the swADTF, the sum of incoming information flow into a source at each time point is equal to 1:

$$\sum_{j=1}^J \text{swADTF}_{ij}(t) = 1 \quad (5)$$

2.3.5. SOZ localization

The swADTF values were calculated for every source $\mathbf{s}_j$ to every other source $\mathbf{s}_i$ at every time point of the epoch in the frequency band 3-30 Hz, as this band contained the fundamental seizure frequency noticed in the EEG. For every source $\mathbf{s}_j$, we defined the outdegree (OD) as the sum of the swADTF values to all other sources over time:

$$\text{OD}_j = \sum_{k=1}^K \sum_{t=1}^T \text{swADTF}_{kj}(t) \quad (6)$$

in which we defined $\text{swADTF}_{jj} = 0$. The outdegree is a measure for the total
300 outgoing information flow from a source to all the other sources. The source with the highest outdegree was assumed to drive the epileptic network active during the seizure and was selected as SOZ.

2.4. Evaluation of the simulated data

With the forward model of every of the 5 patients, we simulated 200 ictal
305 hd-EEG epochs of 3 seconds, resulting in a dataset of 1000 unique epochs. For all these epochs and all electrode setups, we tried to localize the driving patch of the epileptic network. The localization error (LE_{conn}) was determined as the Euclidean distance between the border of the driving patch and the estimated SOZ, i.e. the source with the highest outdegree. If the selected SOZ was in the

310 driving patch, the LE was 0 mm. LE_{conn} was then compared to the shortest distance between the driving patch and the source with the highest power (LE_{pow}), to see whether connectivity analysis can provide extra information compared to ESI alone. Also the distance LE_{min} between the driving patch and the closest source of all selected sources to the driving patch was calculated to provide a
315 measure for the quality of the combination of ESI and source selection. It offers a lower bound on the error of both the source with the highest outdegree and the source with the highest power. When $LE_{\text{conn}/\text{pow}} = LE_{\text{min}}$, the respective method achieves the best possible result, given the reconstructed sources. The different localization errors are illustrated in Fig. 5.

320 2.5. Validation in patient data

For all patients, we segmented the resected zone (RZ) from the post-operative MRI, which we coregistered to the solution space. We used the proposed approach to try to localize the SOZ for every patient and every electrode setup. Also for the patient data LE_{conn} , LE_{pow} and LE_{min} were calculated, but now
325 with the RZ as a reference.

3. Results

3.1. Simulated data

3.1.1. Overall results

The results of the SOZ localization based on 1000 simulated ictal EEG
330 epochs can be seen in Fig. 6. The data is represented in a boxplot, with the dot indicating the mean and the bar indicating the median of the errors. The data for 200, 192, 184, 176 and 168 electrodes are not shown, as they are very similar to their neighboring setups. From the figure, it is clear that connectivity analysis is better in localizing the epileptic driving patch than localization based
335 on maximal power. More precisely, the localization error based on connectivity analysis was smaller than or equal to that based on power, $LE_{\text{conn}} \leq LE_{\text{pow}}$ in 85.5% of all the cases. LE_{conn} was strictly smaller than LE_{pow} in 58.5%

and they were equal in 26.9% of all cases. Only in 14.5%, power outperformed connectivity analysis.

340 When comparing the localization errors based on connectivity and power with the minimal error that could be achieved, we found that LE_{conn} equaled LE_{min} in 66.74% of the cases. This is in contrast with LE_{pow} , which was equal to LE_{min} in only 31.64%.

3.1.2. Influence of the number of electrodes

345 From Fig. 6, it can be seen that the localization errors are not distributed normally. Therefore, we consider the median to be more useful than the mean for representing the data over the different electrode setups. An overview of the different medians can be found in Table 2. The median of the minimal localization error LE_{min} was smaller than 10 mm for all setups except for 32 electrodes, for which it was 12 mm. The upper quartile stayed below 20 mm. For all electrode setups, it was possible to find a source very close to the origin of the simulated seizure. The median of the localization error based on connectivity analysis LE_{conn} was smaller than 15 mm in all setups, except for 32 electrodes, for which it was 20.78 mm. We notice an increase in both LE_{min} and LE_{conn} 350 when we lowered the number of electrodes, especially in the upper quartile of LE_{conn} . Between 32 and 204 electrodes, the median of LE_{min} got 5.07 mm larger and the median of LE_{conn} 8.78 mm, which represented in both cases an increase of approximately 72%. In contrast, the median of the localization error based on power was much larger and varied between 40.10 and 44.72 mm over 360 all electrode setups, which reflected a fluctuation of maximal 11.5%.

3.2. Patient data

3.2.1. Overall results

In Fig. 7, an overview of the localization errors (LEs) for all patients and all electrode setups can be found. A localization error of e.g. 50 mm is consid- 365 ered to be as unfavorable as a localization error of 80 mm, therefore we used

different intervals to characterize the errors: $LE = 0$ mm, $LE \in]0, 10]$ mm, $LE \in]10, 25]$ mm, $LE \in]25, 45]$ mm, and $LE > 45$ mm.

From the figure, we can see that LE_{conn} was equal to or smaller than LE_{pow} in 91.4% of the cases, meaning that in these cases our presented method performed as well as or better than localization based on power. LE_{conn} was strictly smaller than LE_{pow} in 57.1 % of the cases. In 34.3 %, $LE_{\text{conn}} = LE_{\text{pow}}$ and, in 8.6 % of the cases, power outperformed connectivity analysis, $LE_{\text{conn}} > LE_{\text{pow}}$. These 8.6 % represent 6 cases that are mainly located in the low-density setups (3 for 32 electrodes and 1 for 64 electrodes, and two outliers for p1 for 184 and 192 electrodes).

For all setups, ESI and source selection were able to find a source inside the RZ for 4 patients, and within 10 mm of the border of the RZ or within the resection for the other patient. Connectivity analysis was able to find this optimal solution in 88.6% of the cases, whereas $LE_{\text{pow}} = LE_{\text{min}}$ in 38.6% of the cases.

3.2.2. Influence of the number of electrodes

Fig. 8 shows the result of the connectivity analysis and the source with the highest power compared to the RZ for all patients for 204 electrodes. For the 204 electrodes setup, we were able to estimate the SOZ inside the RZ ($LE_{\text{conn}} = 0$ mm in p1, p2, p4, p5) or within 10 mm of the border ($LE_{\text{conn}} < 10$ mm in p3) of the RZ. In contrast, localization based on power was only able to estimate the SOZ inside the RZ in one patient and within 10 mm of the border of the RZ in one other patient. In these cases, localization based on power and connectivity found the same source. For the three other patients, the localization error LE_{pow} was larger than 25 (1/3 patients) or 45 mm (2/3 patients). The lateralization was, however, correct. When comparing to the minimal localization error, connectivity analysis achieved the best possible result after ESI and source selection in every patient for 204 electrodes. This is also shown in Fig. 9, which displays in how many patients the minimal localization error was found, for every electrode setup and for both methods. On the contrary, localization based on power was

only able to select the optimal source in 2 patients. The same results applied when gradually lowering the number of electrodes to 128, with the exception of three cases: for 192 and 184 electrodes, localization based on connectivity analysis does not find the optimal source in p1. For 128 electrodes, power localized the optimal source only in 1 out of 5 patients. For the high-density setups we can say that the presented approach outperformed localization based on power consistently.

For 64 electrodes, the performance of the presented approach decreased. The SOZ was estimated inside the RZ (2/5 patients) or within 10 mm of the border of the RZ (1/5 patients) in only 3 patients instead of 5. Yet, this result is better than localization based on power, for which the optimal source is only found in 2 patients. Only for one patient LE_{pow} was smaller than 10 mm. This is also reflected in Fig. 9: $LE_{\text{conn}} = LE_{\text{min}}$ in 3 patients and $LE_{\text{pow}} = LE_{\text{min}}$ in one patient.

For the low-density setup of 32 electrodes, the SOZ was estimated inside the RZ in only one patient. The source with the highest power, was however inside the RZ in 2 out of 5 patients.

4. Discussion

In this paper, we proposed an approach that combines ESI and functional connectivity analysis to localize the SOZ from non-invasive EEG in patients with refractory epilepsy. We look at the connectivity instead of the power of the neuronal activity during an epileptic seizure. The presented method does not require patient-dependent parameters, which makes it suitable for use in clinical practice. We compared the localization obtained from connectivity measures with the maximal power of the electrical activity at the onset of an epileptic seizure.

We validated our method using simulated ictal EEG epochs and found that localization based on connectivity analysis had a significantly and consistently better yield than localization based on maximal power, for every electrode setup.

425 The localizing potential of the method increased with the number of electrodes,
which is in agreement with literature (Michel and Murray 2012). As a result, the
performance of connectivity analysis also increased for high-density setups. The
influence of the amount of electrodes was much smaller when localization was
based on maximal power, but the median localization error was unacceptably
430 high for all setups.

Next to simulations, we validated the method in five patients. For almost
all high-density setups with 128 electrodes or more, we found the best possible
result with the presented method: in four out of five patients the connectivity
analysis selected the best possible source to localize the SOZ in every setup.
435 For the fifth patient, the connectivity analysis was able to select the optimal
source in all but two setups. The source with the highest power coincided with
this optimal source in only two out of five patients. These results are better
than what we found with the simulations, but this can be accounted for by the
resected zones of the patients being larger than the patches of the simulated
440 network. Next, we found equally good or better results with the connectivity
method in 91.4 % of the cases compared to selecting the source with the highest
power. A possible explanation for this could be that there is some remaining
artifact in the selected epochs, and that connectivity analysis is more robust to
artifacts and noise in the EEG than the power metric. A solution would be to
445 limit the power analysis to a patient-specific seizure frequency range, to filter
out the artifact as much as possible. This is done by Elshoff et al. (2013), where
the frequency range could also change over the course of the seizure. However,
given that a patient-specific seizure range could make the method subjective
and less suitable to be directly used in a clinical setting, we opted not to do this
450 and performed wide-spectrum analysis.

In the range of 204 down to 128 electrodes, our method generally estimated
the localization of the SOZ inside (4/5 patients) or very close (< 10 mm) to the
boundary of the RZ (1/5 patients). When lowering the number of electrodes
down to 64, the performance of the method dropped, but it was still capable of
455 localizing the SOZ inside (2/5 patients) or very close to the border of the RZ

(1/5 patients). For the low-density setup with 32 electrodes, we experienced an extra drop in performance. When using only 32 electrodes, there was correct localization in only one of the patients. Setups with more electrodes are thus preferred in the current approach. We assume that the performance goes down
460 with the number of electrodes due to suboptimal estimation of the time series per source (however the goodness-of-fit did not drop significantly) and/or SVD not being able to represent the three orthogonal time series as one time series. As a consequence, these errors propagate in the connectivity analysis and the correct source cannot be selected. Nevertheless, Ding et al. (2007) used only 31
465 electrodes and they were able to localize the SOZ within 15 mm of the presumed EZ.

However, four out of the five analyzed patients showed clear large lesions on MRI that were presumed to be epileptogenic and it remains to be investigated how this influenced the results, as only one patient in this study had a small
470 lesion. Furthermore, it is not addressed whether the patients had surgery, and if so, whether surgery was successful. There were also no intracranial EEG recordings to validate the results. Lu et al. (2012) performed a similar study with 76 electrodes, and they were able to localize the SOZ within 10 mm of the border of the RZ in 7 out of 10 patients. This result is comparable with our
475 study for the 64 electrode setup.

To improve results for lower-density setups, some suggestions can be made. A possible improvement could be to use patient-specific electrode locations in the forward model. The benefit of this has been investigated and could improve the estimation of the time series corresponding to each selected source (Van Hoey
480 et al. 2000; Wang and Gotman 2001; Dalal et al. 2014). We chose LORETA, as inverse solution method as it is a simple, clear and easily controllable technique fit for the reconstruction of non-stationary signals that was ready at hand in our group. It proved itself suited for the proposed framework, however, the influence of other, more advanced inverse techniques could be investigated, such as the
485 multiple sparse volumetric priors (MSVP) algorithm (Strobbe et al. 2014), the FINE algorithm (Xu et al. 2004; Ding and He 2006; Ding et al. 2007),

dynamic imaging of coherent sources (DICS) (Groß et al. 2001, 2002), or the Maximum Entropy on the Mean (MEM) approach (Clarke and Janday 1989; Grova et al. 2006). In our analysis, the inverse solution is estimated for every
490 time sample separately, but we could take into account other time samples to improve ESI. Other connectivity measures and/or graph theory measures could be considered. Some connectivity measures related to the swADTF were tested, the integrated ADTF (iADTF) and the full-frequency ADTF (ffADTF) (van Mierlo et al. 2011), both resulting in worse results. Another interesting
495 approach for SOZ localization is to first decompose the ictal data to isolate seizure components, e.g. with ICA, and then integrate ESI with a recombination approach. This is done by Yang et al. (2011), where this dynamic source imaging technique identified ictal activity in good correlation with iEEG and surgical outcomes. It remains to be investigated how functional connectivity analysis
500 can possibly enhance this method.

ESI resulted in all cases in a source close to the resection, reflected in an overall low $LE_{\min}$. The selection of this optimal source was significantly better using connectivity analysis compared to selecting the source with the highest power, especially in high-density setups.

505 When applying functional connectivity analysis on non-invasive recordings, the volume conduction problem is a well-known phenomenon. Due to the large distance between the sources and the electrodes and the different tissues the sources have to propagate through, a single source will be seen at several electrodes. We addressed this problem by demixing the sources, i.e. with ESI, but
510 this technique does not mitigate the effects of volume conduction completely and spurious connections can still possibly exist (Schoffelen and Gross 2009). There is no technique to completely alter the mixing problem, but it would be interesting to compare the current framework with other techniques, e.g. the imaginary part of the coherency (Nolte et al. 2004), designed to undo the vol-
515 ume conduction problem in combination with functional connectivity analysis. A clear review of the volume conduction problem in functional connectivity analysis and different strategies and techniques to solve it, is given by Bastos

and Schoffelen (2015).

Considering the patient data, an important remark to make is that the
520 method was validated in a dataset limited to only 5 patients in which each
patient had one seizure. Moreover, one of the patients only had Engel Class
III. With this limited validation, we illustrated the potential of the method
and showed its possibilities. The findings were concordant with simulation re-
sults. Extensive validation in a larger and more heterogeneous (i.e. more types
525 of epilepsy) patient population is necessary to prove its clinical usefulness and
added value in SOZ localization and to investigate the interpatient variability.
This would also give a more clear view on how many electrodes are minimally
needed to achieve a certain sensitivity and specificity. Besides more patients,
more seizures per patient should be considered in order to validate the intra-
530 patient robustness. Unfortunately, no other seizures were recorded in these
patients. Not only more seizures per patient, but also more epochs per seizures
could be the subject of future research to study whether the driver of the net-
work changes during the seizure or not.

Validation was done by comparing the estimated SOZ with the RZ for all
535 patients. The RZ is, however, often an overestimation of the ground truth, the
real seizure onset zone. Therefore it could be useful to validate the method in
simultaneous hd-EEG and intracranial EEG, to see whether the networks found
with both modalities can be correlated. Even though the sampling area of iEEG
is smaller, it could provide a more precise (smaller) ground truth than the RZ,
540 provided that the SOZ is sampled.

5. Conclusion

We developed a method based on ESI and functional connectivity analysis
to localize the seizure onset zone in a non-invasive, objective way that can
potentially be used in a clinical setting. The approach consistently outperformed
545 localization based on power, and results were more accurate for high-density
EEG than for standard electrode configurations. Validation in a larger and more

diverse patient group is warranted. We conclude that our presented approach and in general ESI combined with functional connectivity analysis can serve as a useful tool for SOZ localization in the presurgical evaluation of epilepsy.

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Table 1 Overview of patient details. L = left, R = right, M = male, F = female, TPO = temporo - parieto - occipital

	p1	p2	p3	p4	p5
Age (y)	36	42	36	29	45
Sex	F	F	M	F	M
Cinical findings	complex partial seizures	complex partial seizures	epigastric aura, secondary generalisation	aura of deja vu, change of taste, non-lateralized impairment of vision	complex partial seizures, general tonic clonic seizures
MRI findings	R hippocampal sclerosis	R hippocampal sclerosis	R hippocampal sclerosis	R cortical dysplasia in amygdala and paraventricular nucleus	L TPO Gangliocytoma
Visual analysis of interictal scalp EEG	T2, F8	TP10, T8	T2, T8, P8, Tp10	T2, T8	F3, P7, CP3, P5
Surgery	R polectomy and amygdalohippo- campectomy	R temporal anterior lobectomy	R amygdalohippo- campectomy	R polectomy and temporal anterior lobectomy	L occipital lobectomy
Engel Class	I	I	I	I	III

Table 2 Overview of the medians of LE_{conn} , LE_{min} and LE_{pow} for the different setups obtained after evaluation of 1000 simulated ictal EEG epochs

(mm)	204	196	188	180	172	164	128	64	32
median LE_{conn}	12.00	12.00	12.00	12.65	12.65	12.65	13.27	14.97	20.78
median LE_{min}	6.93	6.93	6.93	8.00	8.00	8.00	8.94	9.37	12.00
median LE_{pow}	44.72	44.72	42.99	42.99	44.00	42.61	41.95	40.99	40.10

Figures

Figure 1 (a) Configuration of the simulated epileptic network. Source 1 is the overall driver.
 (b) An example of the signals that mimic epileptic activity corresponding to the three nodes of the network

Figure 2 (a) Example of three randomly located epileptic patches in the brain, corresponding to the nodes of the network. (b) Montage of the resulting EEG after projection of the epileptic brain activity to sensor space

Figure 3 The different used electrode setups: (a) original 204 electrode setup, (b) the electrodes that were subsequently removed to obtain setups of 200–168 electrodes, (c) subset with 164 electrodes (red), (d) 128 electrodes, (e) 64 electrodes and (f) 32 electrodes. L = left, R = right, A = anterior, P = posterior

Figure 4 Analysis of p1. (a) Selection and preprocessing of an ictal hd-epoch. (b) Result of EEG source imaging, (c) Source selection shown in solution space and (d) time series for x, y and z direction for these sources. (e) SVD to represent each source with one time series. (f) swADTF values over time (summed in the 3-30 Hz frequency band) for every source to every other source. (g) Summation of the swADTF values leads to the outdegree. (h) The source with the highest outdegree is selected as SOZ. The location of this source is compared with the location of the source with the highest power and with the segmented resected zone. The presented method finds the SOZ in the RZ, while the source with the highest power is not located inside the RZ

Figure 5 Illustration of the different localization errors. LE_{conn} = the Euclidean distance between the source with the highest outdegree and the driving patch in the simulated data or the RZ in the patient data, LE_{pow} = the Euclidean distance between the source with the highest power and the driving patch/RZ, and LE_{min} = the Euclidean distance between the source closest to the driving patch/RZ and the driving patch/RZ. (a) In this case $LE_{pow} > LE_{conn} > LE_{min}$. (b) The localization errors can be equal to each other. In this case $LE_{conn} = LE_{min}$, meaning that our method selected the best possible source to estimate the SOZ. A = anterior, P = posterior

Figure 6 Overview of (i) the localization errors (LE) of the SOZ estimated by connectivity analysis, (ii) the LEs of the source with the highest power, and (iii) the LEs of the closest selected source for the different electrode setups for the simulated data. The distribution of the LEs is shown as a boxplot, the dot symbolizes the mean LE, while the bar indicates the median LE

Figure 7 Overview of (a) the localization errors (LE) of the SOZ estimated by connectivity analysis, (b) the LEs of the source with the highest power, and (c) the LEs of the closest selected source for the different electrode setups for the 5 patients.

Figure 8 The selected SOZ based on the presented method (blue), the source with the highest power (red) and the resected zone (green) in the solution space for every patient, using the 204 electrode setup. L = left, R = right, A = anterior, P = posterior

Figure 9 Representation of the number of patients for who the lower limit of error is achieved for each of the methods for all electrode setups, i.e. in how many patients does the source with the highest outdegree/the source with the highest power coincides with the source closest to the RZ for each setup