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The “Connectivity Epileptogenicity Index” (cEI), a method for mapping the different seizure onset patterns in Stereoelectroencephalography recorded seizures

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Abstract

Objective

Localization of epileptogenic brain regions is a crucial aim of pre-surgical evaluation of patients with drug-resistant epilepsy. Several methods have been proposed to identify the seizure onset zone, particularly based on the detection of fast activity. Most of these methods are inefficient to detect slower patterns of onset that account for 20-30% of commonly observed Stereo-Electro-Encephalography (SEEG) patterns. We seek to evaluate the performance of a new quantified measure called the connectivity epileptogenicity index (cEI) in various types of seizure onset patterns.

Methods

We studied SEEG recorded seizures from 51 patients, suffering from focal drug-resistant epilepsy. The cEI combines a directed connectivity measure (“out-degrees”) and the original epileptogenicity index (EI). Quantified results (Out-degrees, cEI and EI) were compared to visually defined seizure onset zone (vSOZ). We computed recall (sensitivity) and precision (proportion of correct detections within all detections) with vSOZ as a reference. The quality of the detector was quantified by the area under the precision-recall curve.

Results

Best results (in terms of match with vSOZ) were obtained for cEI. For seizures with fast onset patterns, cEI and EI gave comparable results. For seizures with slow onset patterns, cEI gave a better estimation of the vSOZ than EI.

Conclusions

We observed that cEI discloses better performance than EI when seizures starts with slower patterns and equal to EI in seizures with fast onset patterns.

Significance

The cEI is a promising new tool for epileptologists, that helps characterizing the seizure onset zone in sEEG, in a robust way despite variations in seizure onset patterns.

Key Words : StereoElectroEncephalography, Focal epilepsy, Epilepsy surgery, Connectivity, Epileptogenicity Index

List of Abbreviations:

SEEG: StereoElectroEncephalography

EI: Epileptogenicity Index

cEI: connectivity-Epileptogenicity Index

h^2 : non-linear correlation coefficient

SOP: seizure onset pattern

SOZ: seizure onset zone

vSOZ: visual seizure onset zone

AUC : Area under the curve

SSO: slow seizure onset patterns

FSO: fast seizure onset patterns.

Highlights

1. A new quantified measure called the connectivity epileptogenicity index(cEI) is introduced in order to quantify the Seizure Onset Zone (SOZ).
2. cEI combines a directed connectivity measure (“out-degrees”) and the original epileptogenicity index (EI).
3. For seizures with slow onset patterns, cEI gave a better estimation of the visual SOZ than EI.

INTRODUCTION

Epilepsy surgery can significantly improve the quality of life of patients with drug-resistant epilepsy. It consists in the removal of the brain regions generating seizures. These regions, (called the “Epileptogenic zone ” (Bancaud, 1980)) must be thus precisely defined from anatomico-electro-clinical observations obtained during pre-surgical evaluation. In a large number of cases, this evaluation involves invasive EEG recordings, in particular stereo-electroencephalography (SEEG)(Bancaud et al. , 1965, Cardinale et al. , 2016, Isnard et al. , 2018).

Defining the epileptogenic zone from SEEG can be challenging (Bartolomei et al. , 2017, Bartolomei et al. , 2018). The epileptogenic zone is increasingly recognized as a network of hyperexcitable connected regions generating seizures and secondary leading to ictal spreading in propagation networks (Bartolomei et al. , 2017). The electrical onset of seizures may appear quite complex in its aspect, both in term of involved frequencies and in term of spatial extension. In 75% of cases, the seizure onset patterns involve high frequencies, most often in the high beta or gamma band (Perucca et al. , 2014, Lagarde et al. , 2019).

In this context, methods for quantifying the epileptogenic zone have been developed over the past ten years in order to complement the SEEG interpretation (for review see (Andrzejak et al. , 2015, Bartolomei et al. , 2017)) . These are based on a spectral analysis of the SEEG signal obtained in each region, using energy in the high frequency (beta-gamma bands), potentially combined with other measures (low frequency deactivation, preictal activity). The first method that was developed, and the one with the largest patient population published until now, is the Epileptogenicity Index (EI)(Bartolomei et al. , 2008). EI combines the ratio of fast frequencies (beta/gamma) relative to slower frequencies and the time of involvement of each region. This method inspired a number of studies aimed at identifying the epileptogenic zone from SEEG recordings (David et al. , 2011, Gnatkovsky et al. , 2011, Gnatkovsky et al. , 2014, Grinenko, 2018). However, as most of these methods are based on the detection/mapping of high frequencies, they are inefficient to detect slower patterns of onset that account for 20-30% of commonly observed SEEG patterns (Singh et al. , 2015, Lagarde et al. , 2019). This is a clear a limitation since seizures with slow onset have worse prognosis for surgery outcome than seizures with fast activity at onset (Singh et al. , 2015, Lagarde et al. , 2019). It has been suggested that seizures with slower patterns are more

distributed and that these slow patterns are related to etiology - in particular type 1 focal cortical dysplasia (Lagarde et al. , 2019). It should be noted that the EI cannot be modified to measure low-frequency onsets because these serve as the denominator of the energy ratio from which it is calculated.

In this context, other methods based on functional connectivity have been proposed to study focal seizures onset from intracranial recordings (Brazier, 1969, Lopes da Silva et al. , 1989, Gotman, 1996, Bartolomei et al. , 2004, van Mierlo et al. , 2013, Courtens et al. , 2016). These approaches measure linear or nonlinear properties of the relationships between SEEG signals, during the seizure onset period or the transition from interictal to ictal periods. Thus, the functional connectivity between SEEG signals tends to be maximal before the emergence of the fast discharges and to decrease just after, followed by later increase during the seizure course (Courtens et al. , 2016). Some studies have used measure of causality (or directed or effective connectivity) and have shown that the definition of "leader/driver" regions may add important clues into the definition of the network generating seizures (Bartolomei et al. , 2004, Varotto et al. , 2012, van Mierlo et al. , 2013, Courtens et al. , 2016).

The epileptogenicity of a brain network (i.e. its ability to generate seizures) is related to the level of excitability and the level of connectivity (Proix et al. , 2014, Hebbink et al. , 2017). In the present study we therefore propose an approach which combines two types of measures in the same quantity. A measure of connectivity and a measure of the capacity of regions to generate seizures with a short delay (EI). The objective is to improve sensitivity while better accounting for the diversity of seizure onset patterns, including slower ones. The connectivity measure was based on the nonlinear correlation coefficient (h^2) and on graph theory measures (out-degrees) (Courtens et al. , 2016). We focused our study on a cohort of patients in whom the seizure onset patterns (SOP) have been previously defined (Lagarde et al. , 2016), relatively homogeneous in terms of etiology (malformation of cortical development) and included a proportion of slow onset patterns (20%).

MATERIAL AND METHODS

Patient selection and data collection

We retrospectively analyzed data from 51 patients with pharmacoresistant focal epilepsy, who underwent SEEG in the context of their presurgical evaluation in the Epilepsy Unit of the Clinical Neurophysiology Department in Timone Hospital, Marseille, France from 2000 to 2016. The 51 patients are extracted from a cohort of 53 patients with a malformation of

cortical development (focal cortical dysplasia type 1 or 2 (FDC1 or 2), Neurodevelopmental tumour, NDT), already studied in terms of seizure onset pattern (SOP) (Lagarde et al. , 2016). Seizures in 2 patients were too short to be analyzed by the methods described here (seizures lasting less than 3 seconds and associated with brief tonic contraction). All patients had detailed non-invasive presurgical evaluation: medical history, neurological examination, neuropsychological testing, magnetic resonance imaging, positron emission tomography and scalp video-EEG recordings. SEEG implantation was planned according to anatomo-electro-clinical hypothesis about the localization of the epileptogenic zone, that was formulated individually for each patient, based on non-invasive data. Follow-up information was collected from a review of the medical records and database. The Institutional Review Board of the French Institute of Health (IRB15226) approved this study

SEEG recordings

Recordings were performed using intracerebral multiple contact electrodes (10-15 contacts with length = 2 mm, diameter = 0.8 mm, 1.5 mm apart). The electrodes were implanted according to the Talairach stereotactic method using orthogonal or oblique trajectories until 2017. After this date, implantation used a robot procedure (ROSA apparatus) or frameless neuronavigation method (Scavarda et al. , 2018). Signals were recorded on a 128- or 256-channel Natus system, sampled at 256, 512, or 1024 Hz, depending on the year of recording, and saved on a hard disk (16 bits/sample) using no digital filter. Two hardware filters were present in the acquisition procedure: a high pass filter (cutoff frequency equal to 1 Hz at -3 dB) and an antialiasing low-pass filter (cutoff frequency equal to 97 Hz at 256 Hz, 170 Hz at 512 Hz, or 340 Hz at 1024 Hz).

SEEG signal analysis

Definition of period of interest

Signals were reviewed with the AnyWave software (Colombet et al. , 2015) available at <http://meg.univ-amu.fr/wiki/AnyWave>. For each seizure, we selected a 20-30 sec analysis window (depending on the duration of SOP). The window start was marked 3 sec before the seizure onset. All analyses were performed with a bipolar derivation (difference of adjacent contacts) to avoid bias linked to a common reference in connectivity estimation. An average of 40 bipolar channels (range 27–55) were selected per patient, representative of the main explored brain regions. The seizure onset zone (SOZ) was delimited by an experienced neurologist (F.B.) through visual inspection (visual SOZ, vSOZ). SOP were defined according

to previous classification (Lagarde et al. , 2016) in six patterns and then divided into two groups: slow seizure onset (SSO) and fast seizure onset (FSO) patterns. FSO group included patterns in which seizure onset presented a fast discharge (beta/gamma). SSO corresponded to seizure onset patterns that did not include fast activity and that could be characterized by rhythmic spikes or spike-waves pattern or theta/alpha sharp activity pattern.

Three measures were computed: i) the Epileptogenicity Index (EI)(Bartolomei et al. , 2008), ii) out-degrees (Courstens et al. , 2016) estimated from non-linear regression graph analysis and iii) a newly proposed “connectivity Epileptogenicity Index” (cEI) that combines the two previous measures.

Epileptogenicity index (EI).

For each seizure, we computed the EI, a semi- automatic procedure that quantifies the SOZ (Bartolomei et al. , 2008). The EI ranks brain structures according to the “tonicity” of the fast discharge (ratio of high frequency content over low frequency) and the delay of involvement at seizure onset. It combines (i) the change of signal energy from lower frequency bands [delta (0.4-4 Hz) theta (4–7.4 Hz) and alpha (7.4–12 Hz)] towards higher frequency bands [beta (12–24 Hz), gamma (24–127 Hz)] at the transition from preictal to ictal activity and (ii) the delay of change in a given electrode contacts (brain structures) with respect to the first ones. Its normalized values range from 0 to 1, with 1 corresponding to the most epileptogenic region (for details see (Bartolomei et al. , 2008). To compute the EI, we used the plugin designed for the open-source AnyWave software (Colombet et al. , 2015). Channels exhibiting EI values above 0.2 to 0.4 were considered to denote epileptogenic areas in previous studies (Roehri et al. , 2018).

Connectivity. Signals were processed with the AnyWave software (Colombet et al. , 2015). They were filtered in beta-gamma range (12–45 Hz) according to a previous study(Courstens et al. , 2016). A nonlinear regression analysis was computed between all pairs of channels based on the h2 index (Wendling et al. , 2001). The h2 is an asymmetric measure - the directionality of the link was determined based on the delay of the higher h2 across directions. For h2 analysis we used a 3s sliding window with a step of 0.5s, a maximum lag of 0.1s. A threshold of 0.2 was applied to the connectivity matrix at each time window, yielding a binary connectivity matrix for each step.

The out-degree value for each time window was calculated by computing the number of outgoing connections (out- degrees). The median values of out-degrees were computed across

all time windows for each SEEG channel and used for further analysis. This allowed us to define the leading regions as those having the higher out-degree values (van Mierlo et al. , 2013, Courtens et al. , 2016)

Definition and computation of the cEI.

In each patient, and for each channel, we summed the normalized values of the h^2 out-degrees and the normalized EI. Normalization was performed by dividing all measures by the maximum value of the sum across all channels. This resulted in a combined index called connectivity epileptogenicity index (cEI) defined as follows:

$$cEI_{i,p} = \frac{nEI_{i,p} + nOut\ degree_{i,p}}{\max_i(nEI_{i,p} + nOut\ degree_{i,p})},$$

where i stands for the channel number, p is a patient number, n means normalized, and \max is a highest value among all channels.

Finally, the three measures (cEI, EI and out-degrees) were estimated in a period including the immediate pre-ictal period and the beginning of the seizure (fast activity when present, or the beginning of the discharge in slow patterns). Three to 6 seconds in the preictal period were included in the analysis.

Visualization of results on the MRI

The position of SEEG contacts was performed with in-house GARDEL software (Medina Villalon et al. , 2018). In short, a CT image with SEEG electrodes is registered to the anatomical MRI of each patient. Then image segmentation is performed to extract the position of each contact, and aligned contacts are group as belonging to the same electrode.

Verification and labelling of each electrode are performed visually. Then, a separate software (3D viewer, available here: <http://meg.univ-amu.fr/wiki/3DViewer>) permits to visualize color-coded the results of different markers (EI, Out-degrees, cEI) in the patient's anatomy.

Statistical analysis

A statistical analysis was performed to assess potential links between measures (cEI, EI, out-degree) and clinical data (histopathological parameters, surgery outcome). We computed for each patient and each threshold the recall (proportion of correctly detected vSOZ contacts, i.e.,

sensitivity) and the precision (proportion of correct detections within all detections). Then, the harmonic mean F1 of precision and recall were computed to find the optimal threshold range for cEI. The quality of the detector was quantified by the area under the precision-recall curve (area under the curve, AUC). An AUC of 1 means perfect classification.

To test for differences between thresholds we used the Friedman test (the non-parametric alternative to the one-way ANOVA with repeated measures). The factor is the F1 test, the number of levels is the number of thresholds, and the replication per block is 1 (one seizure per patient). The Friedman test computes the mean rank for each block (that ranges between 1 and 10) and assesses whether mean ranks are similar across levels (thresholds). In a second step, we computed a post-hoc analysis by comparing levels two at a time, and corrected significance for multiple comparisons using Bonferroni correction (for 3 comparisons).

RESULTS

Data from 51 patients (27 female) were analyzed. Since the objective was not to measure intra-patient reproducibility but to compare two measures estimating SOZ in relation to visual analysis, we chose a single representative seizure per patient. We took the first recorded seizures with well-defined seizure onset pattern category. Table 1 summarizes clinical data. The mean age at epilepsy onset was 7.3 years (range 0–28); the mean age at SEEG acquisition was 23.5 years (range 2.75–56) and the mean epilepsy duration before SEEG was 16.4 years (range 2–45). Thirty-nine patients had a visible lesion on MRI and twelve were considered as MRI negative.

A median of 10 electrodes were implanted per patient (range 5–15, 10-15 contacts per electrode), including 25 patients with bilateral electrodes. The total number of electrodes was 214 in frontal lobes (median per patient 3, range 0–11); 160 in temporal lobes (median per patient 3, range 0–7); 83 electrodes in parietal lobes (median per patient 1, range 0–5); 35 electrodes in occipital lobes (median per patient 0, range 0–5); and 10 electrodes in the insula (median per patient 0, range 0–2). Among the 39 patients with an MRI lesion, at least one electrode was in the core of the lesion or in the immediate surrounding cortex.

The localization of the epileptogenic zone was frontal in 19 patients, temporal in 15, parietal in 7, occipital in 1, fronto-temporal in 1, occipito-temporal in 3. Five patients had also insular involvement (two- fronto-insular, one- parieto-insular, one- frontal operculum and one parieto-

fronto-insular). A total of 29 patients became seizure free after surgery (Engel 1), five patients were Engel II, six patients Engel III and nine patients Engel IV. Two patients have not been operated. The mean follow-up duration after surgery was seven years (range 0.5–18.5y).

Estimation of the SOZ by cEI and EI using AUC analysis

Fifty one seizures (1 seizure per patient) were analyzed. For each seizure we computed three measures (EI, out-degree, cEI), with out-degree measure computed in the beta-gamma band (12-25 Hz) (see Methods section). The performance of each measure compared to a reference set (vSOZ) was calculated using AUC of the precision-recall graph.

Figure 1 presents the performance of each AUC (precision-recall) measure for all seizures (fig. 1A) and for the two onset patterns separately (fig.1B,C) in comparison with vSOZ. Slow patterns were observed in 20 seizures and fast patterns in 31. The best results in the whole population were obtained for cEI in both type of seizure onsets (median AUC whatever seizure onset type 0.73; range 0.4- 1) (Fig 1A). For seizures with fast onset (Fig 1B) EI and cEI disclosed comparable results (cEI median AUC - 0.74; range 0.39- 1; EI median AUC - 0.71; range 0.2- 1), better than out-degree alone (median AUC – 0.6; range 0.16-0.86), ($p < 0.05$).

For seizures with slow onset pattern (Fig 1C) cEI perform better than EI (cEI median AUC- 0.72, range 0.4- 1; EI median AUC- 0.6, range 0.17- 0.79), ($p < 0.01$).

Figures 2, 3 and 4 illustrate three examples of SEEG recordings in patients having either fast onset (patient 21) or slow onset (patient 36, 10) patterns. In the case with fast onset pattern (fig. 2), seizure onset was recorded in contacts CC 3-6, FEF 1-4, SA 1-6, within the frontal lobe (Cingular cortex area 24, pre-motor cortex superior frontal gyrus) and associated with a fast discharge (frequency: 24-32 Hz). EI and cEI gave a good concordance with the vSOZ, contrasting with the result of out-degree measure. In a second case with slow onset (fig. 3), the seizure started by a relatively slow discharge (frequency: 10 Hz) affecting the insular cortex (contacts: LesA1-2, LesP1-4). The out-degree map shows a very good concordance with the vSOZ. In contrast, EI detected SOZ partially while cEI gave a better estimation of the SOZ. Figure 4 illustrates a seizure starting by slow waves (frequency: 2,5-3 Hz) with no detection using EI. A good concordance with vSOZ was in contrast observed with the out-degrees and the cEI.

Finally to test the best threshold for cEI, we calculated the harmonic mean F1 of precision and recall. A F1 score reaches its best value at 1 (perfect precision and recall) and worst at 0. Figure

5 shows the comparison of the F1-score of cEI obtained for different thresholds based on the Friedman non-parametric test (cf methods section). Threshold ranging from 0.2 to 0.5 better separated the SOZ from non-SOZ channels.

Table 2 presents the results of precision, recall and F1 for the different measures. All these values are computed for the threshold corresponding to the highest F1. The mean and median F1 values improve in the cEI (0.74 and 0.74) versus the EI (0.63 and 0.62 respectively).

Links between clinical data, histopathological parameters, surgery outcome

We looked for a relationship between the presence of a lesion on MRI and the AUC of each measure using the Mann-Whitney test. Significant relationship was found for cEI ($p \leq 0.001$) and out-degree ($p \leq 0.01$), with better AUC in the MRI negative group (Fig 6A) compared to MRI positive patients. We observed a trend for AUC values of cEI to be lower in NDT compared to FCD I and FCD II but without reaching differences after Bonferroni correction 5 Fig6B). The AUC value of the different measures were not significantly different between seizure free (Engel class I) and non-seizure free (Engel II, III, IV) groups.

DISCUSSION

In this study, we propose a new marker of the epileptogenic zone (cEI, Connectivity Epileptogenicity Index) based on the sum of a graph measure and a local estimate of the high frequency discharge. The cEI combines a graph connectivity measure (“out-degree”) allowing the evaluation of the leading nodes in the network (Courtens et al. , 2016), and the epileptogenicity index (Bartolomei et al. , 2008) acting as a quantified estimate of the rapid discharge at seizure onset. The main objective was to increase the performance of the EI, particularly in cases of seizure onset patterns that do not include fast activity. These slow onset patterns are observed in 20-25% of SEEG recorded seizures (Singh et al. , 2015) while most of the methods (including EI) developed for mapping SOZ have mainly focused on the high frequencies content of the discharges (Andrzejak et al. , 2015).

We observed that cEI performs equally as EI in seizures with fast onset patterns, and discloses better performance when seizures starts with slower patterns. In a large proportion of cases, the cEI results match well with the SOZ defined visually by an expert neurophysiologist, even in the case of slow onset pattern which is difficult to detect with the classical EI. Interestingly, we found that cEI (and out-degrees) was more effective than EI in normal MRI cases. This

result reinforces the idea that cEI is more efficient than EI in such difficult cases. This may be related to a slightly higher proportion of slow patterns in normal MRI forms (30% versus 19%).

The measure of connectivity (out degree) included in cEI has been used in previous works to detect seizure onset regions. Van Mierlo and colleagues (van Mierlo et al. , 2013) used this degree measure in 8 patients with intracranial EEG and showed that the “driver” contacts were in the resected nodes. In 10 patients with FCD type 2, Varotto and colleagues have used partial directed coherence and out-degree density to distinguish the epileptogenic zone from other cortical regions and showed that lesional nodes play a leading role in generating and propagating ictal EEG activity (Varotto et al. , 2012). More recently, Courtens et al (Courtens et al. , 2016) have shown that the best concordance between out-degree and EI was obtained for the high-pass filtered data in the beta-gamma band, which suggests that mid-range frequency band (beta/low gamma) is more specific to the SOZ than the large band which is sensitive to widespread slow activity. On a more conceptual point of view, cEI combines several properties that characterize the epileptogenic zone network (delay of involvement of structure; increased ictal connectivity of the nodes, hyperexcitability). Indeed, previous computational models have shown that local node excitability and strength of connectivity are two essential characteristics of a neural network to generate seizures (Proix et al. , 2014, Hebbink et al. , 2017)

A limitation of our work is that only one representative seizure was studied per patient. However, seizure patterns can vary, even within patients (Lagarde et al. , 2016). Future work will aim at analyzing more seizures in a bigger series of patients and comparing the different markers of the epileptogenic zone.

Finally, signal analysis in the field of SEEG is an important issue for improving interpretation, but its use is still unfortunately relatively uncommon in routine clinical practice. Here, we propose to use the cEI estimation in the ictal onset period for assessing the SOZ, a method that appears to be efficient in the wide repertoire of seizure onset patterns.

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DISCLOSURE OF CONFLICTS OF INTEREST

None

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LEGENDS OF TABLES AND FIGURES

Table 1. Clinical characteristics of the studied population. FCD – focal cortical dysplasia

NDT - neurodevelopmental tumor

Table 2. Precision and recall values at best threshold (corresponding to the highest F1) for the different measures.

Figure 1. AUC (precision-recall) values according to the fast (FSO) and slow (SSO)

seizure-onset patterns. A/ Results in the whole population B/ Results in FSO C/ Results in

SSO. **A.** In the whole population cEI is correlated with vSOZ significantly better than EI (*- p

≤ 0.05, Bonferroni corrected for 3 comparisons) and out-degree (** - p≤0.01, Bonferroni

corrected for 3 comparisons). **B.** For fast seizure onset difference between out-degree (beta-

gamma band) and cEI (beta-gamma band) is significant (*- $p \leq 0.05$, Bonferroni corrected for 3 comparisons). **C.** For slow seizure onset difference between EI and cEI (beta-gamma band) is very significant (**- $p \leq 0.01$). Abbreviations : EI: Epileptogenicity Index ; cEI $_{\beta\gamma}$: connectivity-Epileptogenicity Index in beta/gamma band; AUC PR : Area under the curve for precision/recall; FSO: fast seizure onset pattern, SSO: slow seizure onset pattern

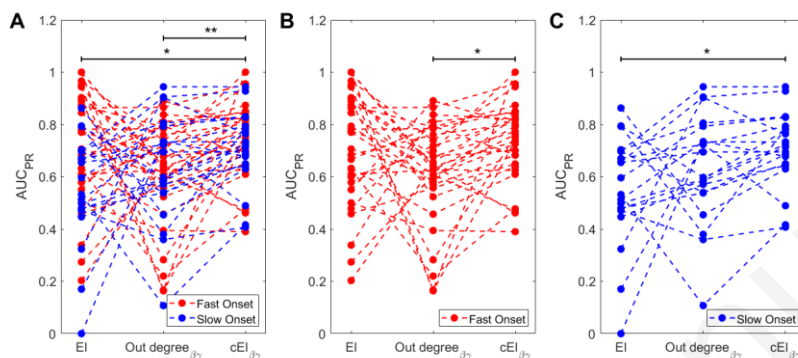


Figure 2. Example of fast seizure onset (patient 21). Comparison of EI, Out-degree, cEI

in and vSOZ. A/ SEEG time series, with a bipolar reduce montage. On the right side of SEEG time course is a bar graph with measures across channels. Orange line indicates the onset of fast activity preceded by preictal changes as defined by clinician expert B/ The measures (cEI, EI and out-degrees) are estimated in the selection shown by the figure covering the onset of the seizure including the immediate pre-ictal period and the start of the fast activity. EI energy ratio map and Out-degree (beta-gamma band) map. C/3D MRI – electrode map (right column) estimation of EI, out-degrees, cEI in beta-gamma band and vSOZ.

Abbreviations: EI: Epileptogenicity Index ; cEI: connectivity-Epileptogenicity Index vSOZ: visual seizure onset zone

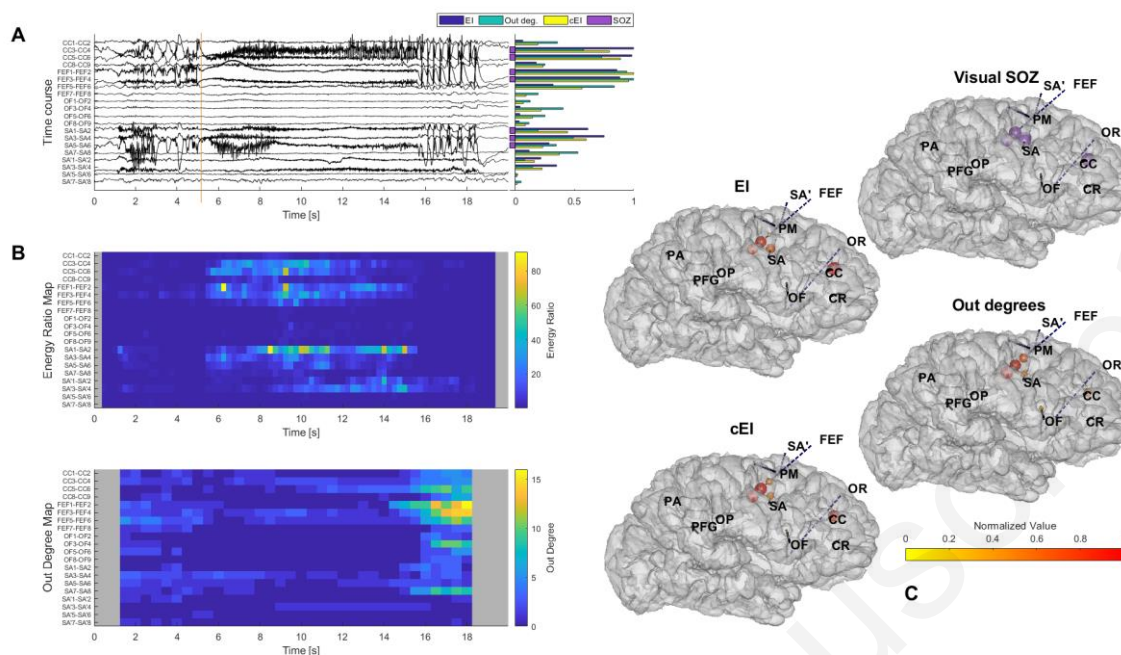


Figure 3. Example of slow seizure onset (theta/alpha sharp activity pattern) (patient 36). Comparison of EI, Out-degree in beta-gamma band, cEI in beta-gamma band and SOZ. A/SEEG time series, with a bipolar reduce montage. On the right side of SEEG time course is a bar graph with measures across channels. B/ EI energy ratio map. Out-degree (beta-gamma band) map. C/ 3D MRI –electrode map (right column) estimation of EI, out-degrees, cEI in beta-gamma band and vSOZ. OD, EI and cEI are estimated in the selection shown in the figure. Abbreviations: EI: Epileptogenicity Index ; cEI: connectivity-Epileptogenicity Index vSOZ: visual seizure onset zone

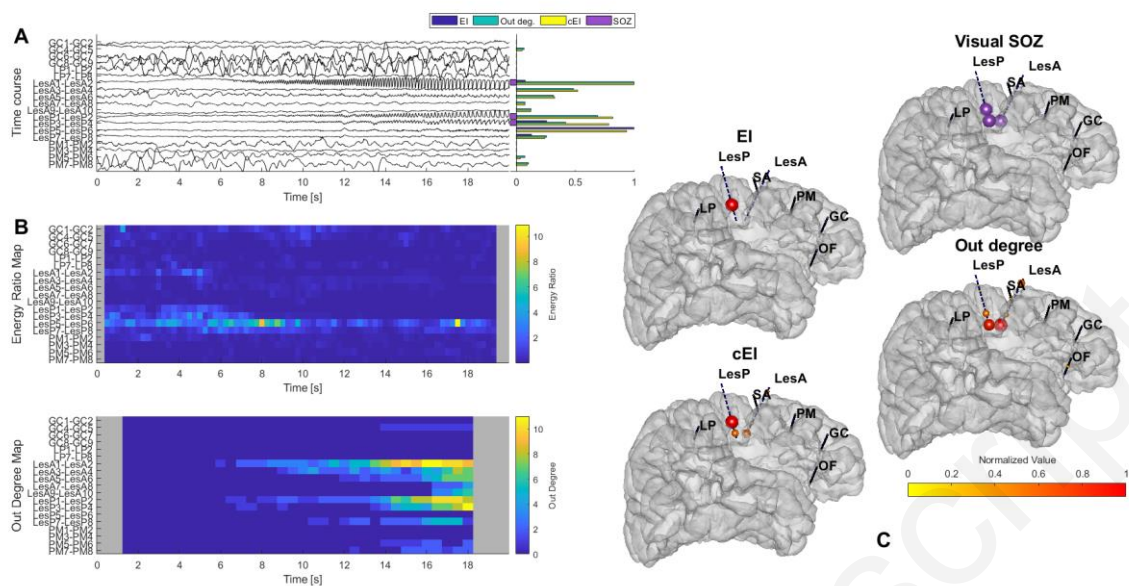


Figure 4. Example of slow seizure onset (slow waves) (patient 10). Comparison of EI, Out-degree in beta-gamma band, cEI in beta-gamma band and SOZ. A/SEEG time series, with a bipolar reduce montage. On the right side of SEEG time course is a bar graph with measures across channels (zero detection of EI). B/EI energy ratio map (zero detection). Out-degree (beta-gamma band) map. C/3D MRI –electrode map (right column) estimation of EI, out-degrees, cEI in beta-gamma band and vSOZ.

Abbreviations: EI: Epileptogenicity Index ; cEI: connectivity-Epileptogenicity Index vSOZ: visual seizure onset zone

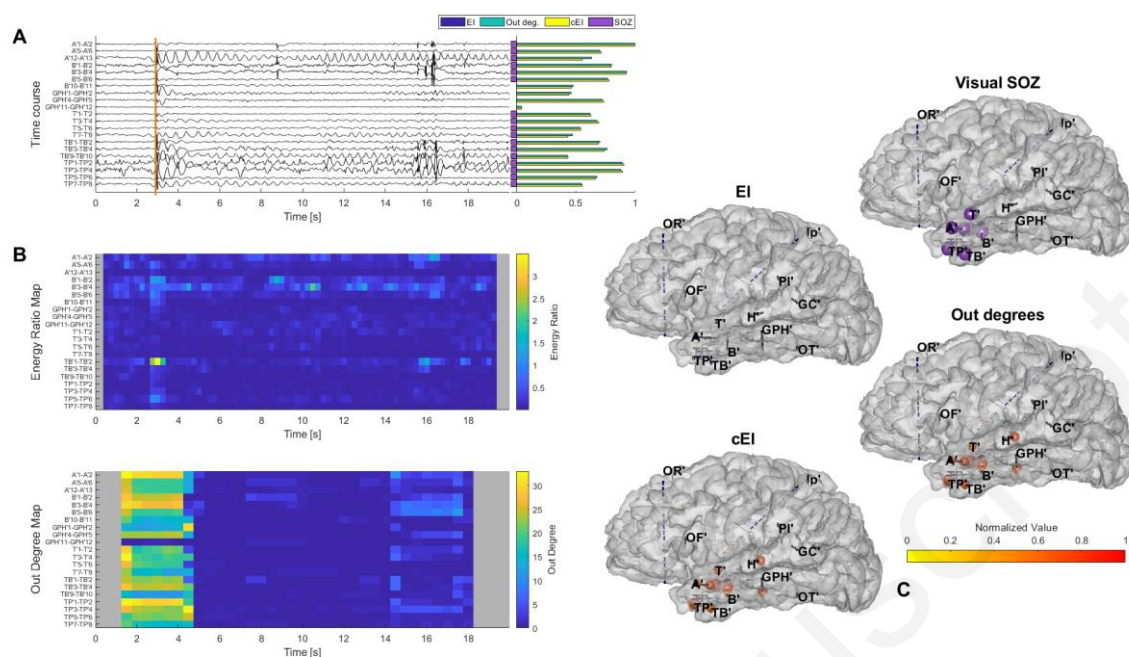
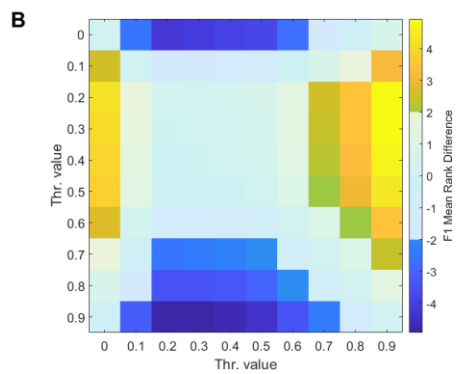
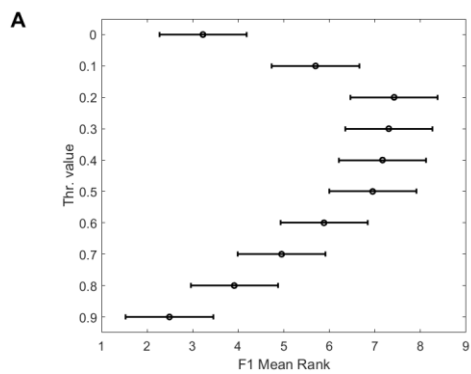


Figure 5: Comparison of the mean rank of F1-score of cEI obtained for different thresholds. **A.** Ranks of F1 are computed for each seizure across thresholds (10 possible ranks). The mean ranks across seizures are shown for each threshold together with confidence interval. **B.** Color-coded pairwise F1 mean rank differences between thresholds. The matrix can be read from line to column. Yellow shows a positive difference while blue shows a negative one. The transparent section of both the image and the color bar corresponds to non-statistically significant values after Bonferroni correction ($p > 0.05$, 45 comparisons). Thresholds ranging from 0.2 to 0.5 better separate the SOZ from non-SOZ channels.

Figure 6: A/ Correlation between lesion on MRI and Area under the curve (AUC) of all measures using Mann-Whitney test. Significant relationship was found for cEI ($p \leq 0.001$) and out-degree ($p \leq 0.009$) in MRI negative group compared to MRI positive patients.

B/ AUC values of cEI and Out-Degrees are lower in NDT compared to FCD I and FCD II, but without reaching significance after Bonferroni correction ($p > 0.016$).



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