STUDY PROTOCOL

Prospective Multicenter Study on Localization Accuracy and Clinical Utility of Automated Electric Source Imaging in Presurgical Evaluation(PROMAESIS)

Brief Title: Clinical Utility of Automated Electric Source Imaging in Presurgical Evaluation (PROMAESIS)

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Goal: to elucidate the accuracy and the clinical utility of automated electric source imaging (ESI) in presurgical evaluation.

Primary outcome: accuracy measures (sensitivity, specificity, positive and negative predictive values), overall accuracy (number of [TP and TN]/total patients).

Secondary outcomes: clinical utility (change in patient management decisions); inter-ESI-methods agreement (at sub-lobar level).

Patients: consecutive patients will be prospectively recruited from the EpiCare and E-pilepsy centers. Inclusion criteria: patients with drug resistant focal epilepsy, admitted to EMU for presurgical evaluation, who are afterwards discussed at the multidisciplinary epilepsy surgery team meetings. Exclusion criterion: patients who did not have a seizure during the monitoring.

Sample-size: We expect a sensitivity of 80% and specificity of 60%. We expect that 50% of the investigated patients will be operated and 66% of them will become seizure-free. Calculating with an accuracy of estimate of 10%, we need 250 patients (Hess et al., Eur J Clin Microbiol Infect Dis (2012)).

Recordings: Although there will be variations from center-to-center concerning the EEG electrode array, we will attempt to achieve as much standardization as possible. Centers will use either caps or cup-electrodes (mounted individually).

a) Caps: need to be of at least 64 electrodes (10-10 system), with even spatial distribution of the electrodes, and including the inferior electrode chain. The centers will specify how they place the cap relative to fiducials and other possible reference visible on the MRI. (For example; how far is the foremost midline electrode away from Nz and the most posterior electrode from Iz; how far is the most lateral inferior electrode away from the lateral eye corner).
b) Cup-electrodes: we need at least the standardized electrode array of 40-electrodes, described in appendix-1.

Before starting the study, we will discuss with each center the electrode array they use, and we need to validate for the study each array that will be used in the study.

In addition, the centers that have the equipment, high-density EEG (HD-EEG) will be recorded for 1-4 hours at the end of the LTM. Sampling frequency: at least 250 Hz.

The two teams (BESA and Epilog) will mark the six fiducials (T9, T10, Nz, Iz, AC, PC) in the MRI (each team marks it, the other team double-checks).

The centers will annotate in their original EEG format, the following time-points for the seizures:

- Start of the seizure (START), end of the seizure (STOP) defined as follows: Start = first semiological or EEG sign indicating seizure – whichever comes first; Stop = last semiological or EEG sign indicating seizure – whichever comes last.
- The time-limits of a (quasi) artifact-free epoch as close as possible to the electrographic onset, that they suggest being analyzed (EEG-START; EEG-STOP). The epochs should be as long as possible, with a minimum of 3 s: (EEG-start and EEG-stop)

The centers will classify seizures into “types”. A seizure type is a group of seizures that has stereotypical semiology and ictal-EEG. If there are 3 or more seizures in a group (“type”), the centers will annotate at

least 3 seizures for each type, selecting the ones with clearest EEG. All seizures per type are annotated, but maximally 3 seizures per type (in the case of more than 3 choose the best 3).

Data for source imaging: After the LTM, centers will upload two de-identified datasets for each patient: EEG (from LTM – all centers; from HD-EEG recordings: selected centers) and MRI (3D T1). For the submission the centers will use the platform developed by Epilog, which is encrypted, HIPAA/GDPR compliant and easy-to-use. BESA will get access to the data uploaded to the Epilog site, and will store data only on drives that are encrypted by Truecrypt. These drives will only be accessible by the persons participating in the study and will be password protected (long string!). One backup will be on our internal server - all encrypted.

For HD-EEG recordings, the coordinate file will also be uploaded by the centers that measure the 3D-positions of the electrodes.

Additional data provided by the participating centers: demographic and clinical data (appendix-2), results of the neuroimaging (MRI, PET, SPECT) localization at sub-lobar level (appendix-3), and screen-shots (axial, coronal and sagittal planes) and changes in patient management (appendix-4). These data will not be available for those running the automated source imaging. After the operation: information on the resection, the pathology, postoperative MRI, outcome one year after the operation.

Automated source imaging: Epilog and BESA will run the automated source imaging – both for interictal epileptiform discharges (EDs) and ictal signals. A report summarizing the results will be send to the corresponding center and the PI in a one-step procedure.

The automated source imaging consists of 2 phases:

1. Automated detection of EDs
2. Source imaging of each spike cluster and seizure onset epoch.

The complete procedure will be done using automated algorithms without subjective interactions during spike detection and source imaging. For each detected spike cluster and seizure-onset, source imaging will be done at two different time-epochs: at onset and at peak. The two analysis-teams will use two different methods for defining the onset epoch. The time-points (or epochs) for onset and peak will be specified for each spike cluster using the peak channel in the common average montage.

The analysis-teams will provide source images in axial, coronal and sagittal planes. Epilog will use SLORETA for interictal analysis and LORETA followed by functional connectivity analysis for ictal source imaging. BESA will use Multiple Dipole Analysis, Volume- and Cortical-CLARA.

Individual head models will be used for the analyses. BESA will use FEM or an approximate model if the quality of an MRI should be insufficient. Epilog will use a head model with six different tissue classes (scalp, skull, cerebrospinal fluid, gray matter, white matter and air). The finite difference method is used to calculate the lead-fields, which describe the relation between current source in the brain and measured potentials at the electrodes.

Each analysis-team will send a report to the center that submitted the data and to the PI. The report will contain the following:

- Patient code and descriptive data about the recording (duration, number of electrodes)
- Data of up to six clusters in the order of the number of spikes in each cluster
- The minimum number of spikes in a cluster must be 20 spikes

The data of each cluster should contain:

- Number of spikes in each cluster
- Waveforms of 10 examples of spikes
- Averaged waveforms and voltage maps at peak and onset.
  All waveforms (+/-500 ms around the peak) will be provided filtered with a 1 Hz forward low filter and a high filter of 70 Hz both in longitudinal bipolar and common average montages.
- Source images for the two time-points (or epochs): onset and peak (in separate images). Images should be provided in transversal, sagittal and coronal views.
- BESA will also provide source waveforms for onset and peak (only one if not substantially different) and a current vector depicting the orientation of the spike source current.
- The analyzed ictal signal for each seizure-onset epoch in common average montage with marking of the cycles/epoch that has entered the analysis.
- The source images for each seizure-onset epoch.

For the interictal EDs we will use two different definitions of the "dominant" cluster:

- Quantitative definition: the cluster with the highest number of spikes
- Qualitative definition: each center will mark a spike as dominant, in the clinical context (thus not necessarily the most prevalent cluster).

Reference standard ("gold standard"): For determining accuracy (sensitivity, specificity, PPV and NPV) and overall accuracy ((TP+TN)/total) gold standard will be the resected site and the outcome one year after the operation:

- TP: source is in the same sub-lobar region as the resection, seizure-free outcome
- FP: source is in the same sub-lobar region as the resection, not seizure-free outcome
- TN: source outside the sub-lobar region that was resected, not seizure-free outcome
- FN: source outside the sub-lobar region that was resected, seizure-free outcome.

To enable an adequate comparison between methods, each method should create an ellipsoid around each center location (maximum of SLORETA, equivalent dipole location(s), seeded center of cortical CLARA / CLARA) indicating the likely error in localization due to electrode/registration inaccuracies and unknown conductivities. The ellipsoid has a larger axis in radial direction (2.5 cm) as compared to the tangential axes (1.8 cm), because of the large effect of the unknown conductivities on source depth.

For determining clinical utility, the percentage of patients in whom ESI changed decision on patient management (appendix-4) will be calculated.

Four centers (Copenhagen, Dianalund, Freiburg and Prague) will do "manual" ESI, as part of the preoperative workup. In this sub-group, the performance of the various pipelines and analysis methods will be compared. The MDTs in these centers will first get access to the "manual" ESI, after scoring the clinical utility for the automated analysis.

Authorship:

Principal investigator, guarantor and corresponding author: Sándor Beniczky.

Co-authors:

- Epilog team: Gregor Strobbe, Pieter van Mierlo, Vincent Keereman, Amir Ghasemi Baroumand
- BESA-team: Nicole Ille, Dieter Weckesser, Patrick Berg, Michael Scherg
- From the participating centers: one author per center - provided the center submitted complete datasets for more than 10 patients, including at least 5 operated patients; two authors per center - provided the center submitted complete datasets for more than 20 patients, including 10 operated patients.

The study protocol will be registered and published at the start of the study. As the goal of the study is to assess the accuracy and clinical utility of ESI methods and not compare products of companies, the results will not be presented as a comparison between companies/products, but as comparison between different analysis methods and strategies.

Appendix-1: The standard 40-electrode array

In addition to the 25 electrode IFCN standard including the 3 inferior electrodes F9/10, T9/10, P9/10 on each side, the following 8 intermediate electrodes are added:

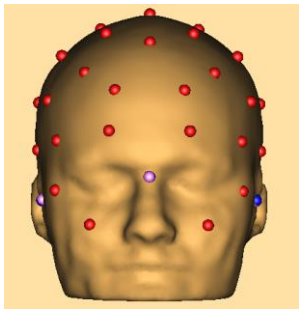
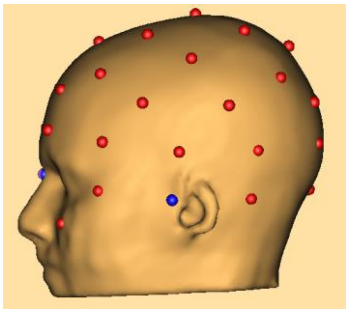
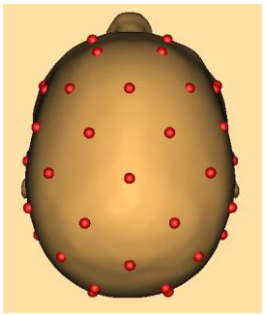
FC1, FC2, FC5, FC6, CP1, CP2, CP5, CP6

and 7 electrodes for better inferior, anterior and posterior sampling:

AF11 (IO1), AF12 (IO2), AF1, AF2, PO1, PO2, Iz

These electrode locations take into account the rules of the 10-20 placement (Jaspers 1957) as accurately as possible using a relatively good estimation of the Inion (Iz).

The measurement rules will be predefined for the placement of the 40 electrodes. We will make a video on how to place the electrodes, to make sure all centers follow a standardized method.

A**ppendix-2**: Clinical and demographic data

We intend to use the database developed by the E-pilepsy consortium (Red Cap).

The items that must be included for this study are the following:

- Patient-code: two letters for the study site code – patient number
- Age (years)
- Gender (male / female)
- Time since the start of epilepsy (years)
- MRI: normal / lesional. If lesional – specify the location using the codes in appendix-3. Add further details in free-text and image (screen-shots) in axial, coronal and sagittal planes.
- PET: normal / abnormal. If abnormal – specify the location using the codes in appendix-3. Add further details in free-text and image (screen-shots) in axial, coronal and sagittal planes.
- SPECT /SISCOM: normal / abnormal. If abnormal – specify the location using the codes in appendix-3. Add further details in free-text and image (screen-shots) in axial, coronal and sagittal planes.
- Resection: yes / no. If operated – specify the location using the codes in appendix-3. Add further details in free-text.

See the CRFs for more details on this.

Appendix-3: The sub-lobar regions

See the CRF for more details.

Side: left / right

Regions:

- Frontal
    - perisylvian-superior surface / operculum
    - lateral
    - mesial
    - polar
    - orbitofrontal
- temporal
    - mesial
    - polar
    - basal
    - lateral-anterior
    - lateral-posterior
    - perisylvian-inferior surface / operculum
- central
    - lateral convexity
    - mesial
    - central sulcus – anterior surface
    - central sulcus – posterior surface
    - perisylvian-superior surface / opercular
- parietal
    - lateral-convexity
    - mesial

    - perisylvian-superior surface / opercular
- occipital
    - lateral
    - mesial
    - basal
- insula

Appendix-4: Logging the changes in decision on clinical management of the patients:

The multidisciplinary teams take decisions in two steps:

I. Considering all data, except ESI
II. Adding ESI to all other data.

At each step, the decisions are classified into one of the following categories:

1. Stop (operation not recommended)
2. Implantation of intracranial electrodes
3. Operation

In addition, the changes are classified into one of the following categories:

1. No change – but concordant with decision.
2. No change – but discordant with decision.
3. Change from stop to implantation.
4. Change from implantation to stop.
5. Change in implantation plan: implantation of additional sites (besides the ones planned in step-1).
6. Change from implantation to operation.
7. Change from operation to implantation.
8. Other (specify in free text).

If changes are not related to all analyses results, it will be noted, which method(s) triggered the change (SLORETA-interictal / ictal; ECD-interictal/ictal; CLARA interictal/ictal).

At one-year follow-up, the changes are categorized as useful or not useful. A change is defined useful as follows: (a) change from stop to ICR: the ICR localized the source; (b) change in implantation strategy: the electrode(s) implanted based on the EMSI identified the source; (c) change from implantation to operation: the patient became seizure-free.