CIED ANALYSIS PROTOCOL

Title: Validation of Criteria for Identification of Epileptiform Discharges in EEG Recordings of Patients With Epilepsy

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Analysis of EEG samples in sensor space.

In the first round, you will assess and document the presence / absence of each of the IFCN criteria (see below) for all samples.

IFCN criteria for identifying Epileptiform Discharges

Transients distinguishable from background activity with a characteristic morphology.

Criteria:

1. Di- or tri-phasic waves with sharp or spiky morphology (i.e. pointed peak).

2. Different wave-duration than the ongoing background activity: either shorter or longer.

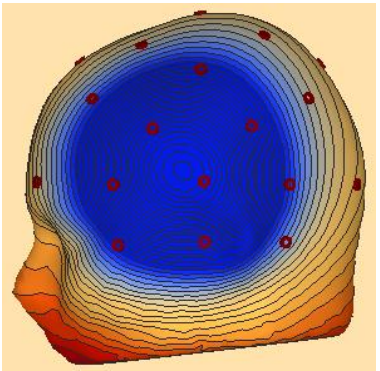
3. Asymmetry of the waveform: a sharply rising ascending phase and a more slowly decaying descending phase, or vice versa.

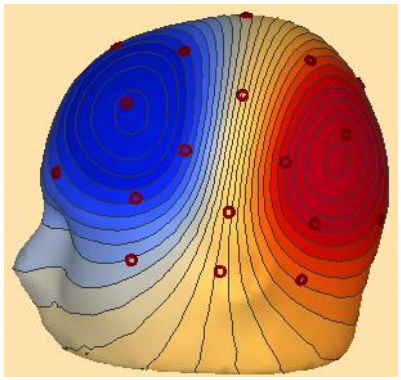
4. The transient is followed by an associated slow after-wave.

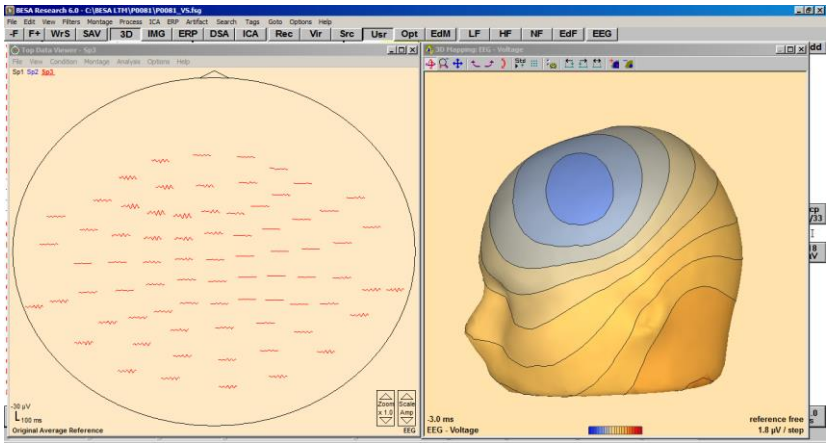
5. The background activity surrounding epileptiform discharges is disrupted by the presence of the epileptiform discharges.

6. Distribution of the negative and positive potentials on the scalp suggests a source of the signal in the brain, corresponding to a radial, oblique or tangential orientation of the source (see dipole). This is best assessed by inspecting voltage maps constructed using common-average reference.

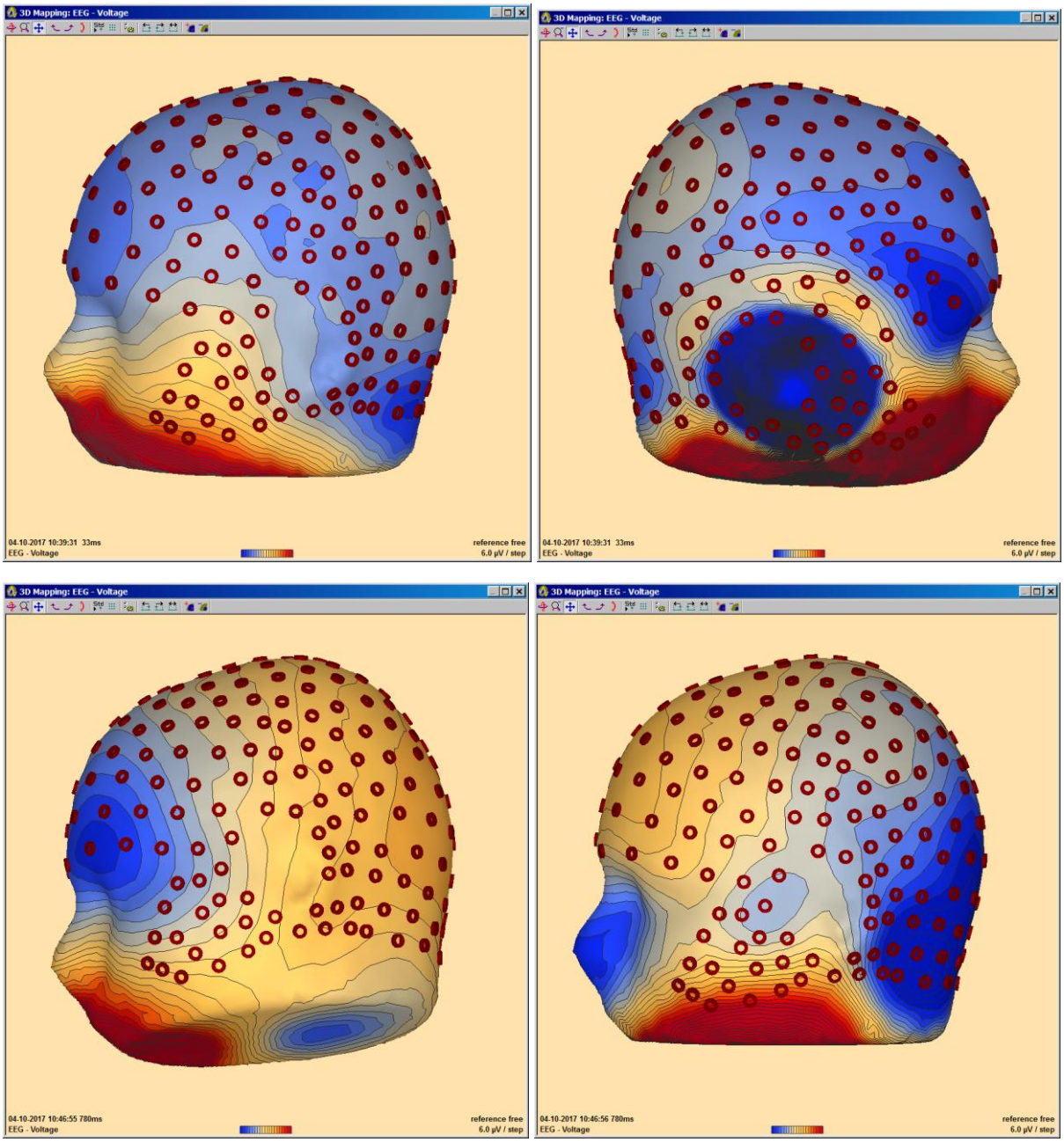
Examples of voltage-maps that fulfill criterion-6:







Examples of voltage maps that do not correspond to a source in the brain, and that do not fulfill criterion-6:



Analysis of EEG samples in source space.

In the second round, you will use the source montage 25s to evaluate the 100 files S01.foc to S100.foc. For some basics on this new source space, please read the document 1-New-Source-Space-25.pdf.

At the end of this documents, 5 spike examples (IntroEpilepsy1…5) and 5 non-spike examples (Intro…6-10) are depicted. Please, open these training samples first and inspect using **F2**, then **F5** to map the peak at annotation before scoring S01 to S100.

1. Installation

Extract the folder BESA CIED to the basis of your C-Drive C:\. Right click onto BESA.exe in C:\BESA CIED\BESA\Program and select Pin to Taskbar (after deleting the previous BESA SIDS icon). Then, everything will work automatically and the program will run with your dongle (hardlock) or with the VPN connection using SoftEther as before.

2. Program start:

If you have pinned the BESA CIED icon to the taskbar you can start easily by clicking on this icon. Alternatively, double click onto BESA.exe in C:\BESA CIED\BESA\Program to start. The program will open as BESA Research 6.

3. Overview and Guideline:

You will find a reference guideline in C:\BESA CIED\Documents\BESA - Guideline for Mapping and Localization in LTM.pdf. Please consult chapters 3 and 9 (in the short guide), if needed. Note that the function keys in BESA CIED are associated with different, special batches (see description of function keys below).

Operational definition of epileptiform discharges, identified in source space:

Epileptiform discharges are abnormal sharp transients, with characteristic (1) changes in time and (2) distribution in space, (3) excluding artifacts and normal variants.

- **In time:** the sharp transient is clearly distinguishable from the ongoing (background) activity, based on its amplitude, duration and morphology. (Check this in the source channel(s) where the discharge is visible).
- **In space**: the location of the signal should make sense anatomically.

  Check this across all channels: Regions with the same polarity should be close together. Opposite polarity may be observed in the other hemisphere or more remote regions.
  Caveat 1: temporal lobe traces may show opposite polarities!
  Caveat 2: Tangential spikes is fissures can show polarity reversal between neighboring regions.
  If unclear, compare time-lag between the peaks in different channels to observe presence of propagation as an additional indicator of epileptiform transients. Presence of propagation is optional. i.e. not compulsory for all spikes.

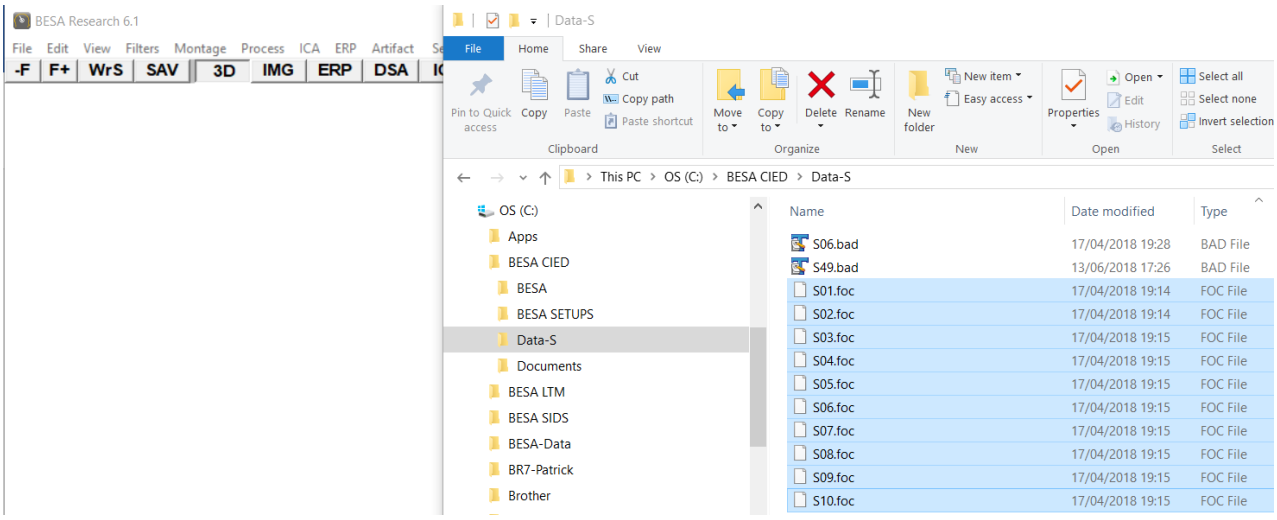
Please see the attached PowerPoint file with the “visual” presentation of this definition. (We inserted some animations, so “play” the slide in projection mode).

After watching the PPT presentation and before evaluating the 100 samples, please go through the 10 **“open label” examples** (5 with epileptiform discharges, and 5 with non-epileptiform sharp transients).

To get familiar with the regions of interest corresponding to each source-channel, after opening the first “open label” example, right-click on the head-icon, which replaces the electrode names. This will pop up a window in which you can see in detail the region´s location. Do this for all channels (regions of interest), to learn the brain regions that each channel represents.

4. Open Files:

Select File Open or CTRL+O to open the files to be rated. It is recommended to CloseAll after opening about 10 files. A fast way to open a series of files for evaluation is to drag them from FileExplorer onto the BESA screen (search for *.foc). The order may not be sequential. Please, check the filename when entering your rating results. The compressed files (*.foc in BESA format) are located in C:\BESA CIED\Data-S:



5. Scaling:

The files are pre-set with a time scale of 10 s / page and individual adjusted amplitude with filters switched Off (data has been pre-filtered from 1-70 Hz).

Gain: You MUST use the arrow up / down keys for fast amplitude scaling or the scaling button on the right (see chapter 9). This is even more important than in sensor-space! Note that the gain is not scaled automatically, thus you need to scale it yourself.

6. Set montages and filters by batches:

The data have been pre-set with the source space montage 25s.

If you press function key **F2,** the montage is reset to source montage 25s (also available under the **Src** button) and filters are switched off.

The function keys **F3-F5** set specific filters. For mapping, key **F5** (5 forward to 40Hz zero-phase) is recommended. Press **F2** to switch filters off again and reset to montage 25s. Please note that F2 (25s without filters) can be used to assess slow-waves following the spike. These are reduced when setting a low zero-phase-shift filter of 2 Hz by selecting **F3**.

If you press **F6**, the montage 25r is set showing the regional source under each of the 25 electrodes with the orientation optimized to pick up the largest activity of this region. Note that orientation is decided by the activity over the whole 10s page. Thus, you might want to enlarge scale to about 2-3 s / page and advance the screen around the annotated event using the 1s arrows at the right and left of the time bar, or N and B keys.

In most cases, you can already make a decision based on inspecting the sample in the 25s montage after pressing **F2** (=unfiltered) and **F3** (=filtered). Next, you should proceed to voltage mapping after pressing **F5** (5 Hz forward filter which advances a spike peak more towards its onset phase). If you are still in doubt press **F6** to set the oriented regional source montage 25r (for details see above and the document on 25s).

Important: You **MUST NOT** inspect the samples in sensor space this time.
ONLY SOURCE MONTAGES THIS TIME!!!

7. 3D-mapping:

To map, click onto the event to be rated near the marker ‘Annotation’ or ‘OBS’. Use the mouse scroll wheel to adjust latency (or right / left arrows). If the sharp transient is riding on slower activity or a noisy

EEG, it is recommended to press **F5** to filter such that the sharp onset transient is not biased by the overlap. Prese **F2** to switch filters off again.

8. Summary of function keys:

The function keys F2-F6 are associated with the following batch functions:

F2:	F2_Spike-Epoch_Filter-Off_25s.bbat	Set montage 25s
F3:	F3_Filter 2-40Hz_25s.bbat	Set 2 Hz – 40 Hz (both zero-phase, typical spike filter)
F4:	F4_Filter 4-30Hz_25s.bbat	Set 4 Hz – 30 Hz (both zero-phase, in more noisy data)
F5:	F5_Filter 5-40Hz_25s.bbat	Set 5 Hz forward – 30 Hz zero-phase, to map onset
F6:	F6_Spike-Epoch_Filter-Off_25r.bbat	Set regional source montage 25r (**Opt** button: Oriented).

The function keys F9-F12 are associated with the following montages:

F9: 25s

F10: 25r

F11: CA25

F12: Original recording

9. Quick-guide to your tasks / Summary of what to do, when scoring the samples:

- Ctr+O: open foc-file
- Inspect the sample by pressing function keys F2 (unfiltered, 1-70) to set source montage 25s
- If you need more narrow filtering for spike review, press F3 (filtered)
- Adjust gain (arrows up and arrows down, or scaling window on lower right for finer adjustment)
- Decide whether epileptiform discharge (score=1) or not (score 0)
    - Scan the screen horizontally (characteristic changes in time)
    - Scan the screen vertically (spatial distribution – reconstruct anatomy and propagation – if any)
    - Exclude artifacts and normal variants
- If not clear, use voltage maps in addition.
- If still undecided / in doubt: use function key F6 to switch to montage 25r (**Opt** button should be set to Regional source oriented). Note that orientation is decided by the activity over the whole 10s page. Thus, you might want to enlarge scale to about 2-3 s an advance the screen around the annotated event using the 1s arrows at the right and left of the time bar, or N and B keys. Using montage 25r, spikes with non-radial orientation in the depth of fissures can become better visible.
- Note the score (0 or 1) into the Excel file
- Go to next EEG file.

Statistical analysis plan

Based on the sensitivities and specificities obtained at cut-off values of 2-6 IFCN-criteria in sensor-space, we will calculate the estimated receiver operating characteristic (ROC) curve. We will calculate 95% CIs for sensitivity, specificity and accuracy using Wilson's method, and we will compare them between the ED-identification methods using McNemar´s test.

We will calculate IRA using Gwet's agreement coefficient AC1 to avoid the "paradoxes of kappa". Inter-rater agreement will be interpreted according to the conventional groups: poor (<0·02), fair (0·2–0·4), moderate (0·4–0·6), substantial (0·6–0·8), and almost perfect agreement (>0·8).