Purpose
We aim at delineating the epileptogenic networks using cortico-cortical evoked potentials (CECP) [Iwasaki et al., 2010] as a result of single-pulse electrical stimulation (SPE) on stereotactically implanted depth electrodes for presurgical evaluation of patients with drug-resistant epilepsy. We illustrate the simultaneous activation maps for specific biomarkers (delayed responses - DR and high-frequency oscillations - HFO) in a neuroimaging framework that combines the intracranial electrode stereotactic coordinates with the MRI, providing an exact spatial representation of the brain activation. Sensitivity, specificity and accuracy for the seizure onset zone (SOZ) of each response type are calculated.

Methods
Six patients with focal temporal and frontal epileptiform were investigated using stereoelectroencephalographic (SEEG) method (Table 1).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Localization</th>
<th>Lateralization</th>
<th>Nr. of Electrodes</th>
<th>MRI lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>35</td>
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<td>R</td>
<td>12</td>
<td>Negative</td>
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<tr>
<td>2</td>
<td>F</td>
<td>24</td>
<td>Rolandic</td>
<td>L</td>
<td>15</td>
<td>Type II cortical dysplasia</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>24</td>
<td>Occipito-temporal beal</td>
<td>R</td>
<td>14</td>
<td>MCD</td>
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<tr>
<td>4</td>
<td>F</td>
<td>25</td>
<td>Temporal pole</td>
<td>R</td>
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<tr>
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<td>F</td>
<td>46</td>
<td>Temporal pole</td>
<td>L</td>
<td>9</td>
<td>Type II cortical dysplasia</td>
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<tr>
<td>6</td>
<td>M</td>
<td>33</td>
<td>Motor Prefrontal</td>
<td>L</td>
<td>17</td>
<td>Type II cortical dysplasia</td>
</tr>
</tbody>
</table>

Table 1. Patients participating in study

For each patient, 64 contacts were connected to a Nizol Wireless Amplifier (Natus Medical Inc.). Systematically, we have applied single pulse bipolar stimulation on ≥155 pairs of adjacent contacts and recorded the raw responses on the other 62 contacts at 4096 Hz sampling rate. The constant current biphasic pulses having variable amplitude in the range 1 to 5 mA from pulse to pulse were applied in a pseudo-random sequence using a programmable stimulator (Guldine LP+, FHC Inc, Bowdoin, ME). Each stimulation trial consisted of 20 biphasic pulses having 3 milliseconds pulse width, 15 seconds inter-pulse interval (fig. 1a) and current distribution as shown in fig. 2b. We mapped the propagation of the stimulus through the epileptogenic network by analyzing CECPs. We looked for specific evoked responses that are known to represent a biomarker of the epileptogenicity, like high-frequency oscillations (HFO) [van Kooten, 2011] and delayed responses (DR) [Valentin et al., 2002, 2005]. Reselecting the areas with high density of DR and HFO significantly increase the chances of becoming seizure free [Valentin & Alarcon, 2008; Jacobs et al., 2010].

DRs (fig. 2) are defined as responses resembling spikes or sharp waves occurring between 100 milliseconds and 1 second after stimulation [van Alarcon, 2010]. We considered HFOs (fig. 2 left) in the 100-250 Hz frequency range, that occurred during the first 500 milliseconds after stimulation. We used Morlet wavelet coefficients, and the peak of the evoked oscillation's frequency. The peak's amplitude should be at least two times higher than the mean amplitude of the coefficients found at both half-widths around the peak.

6 stimulation pulses for each of the 100-250 Hz range that has at least 4 oscillation periods (Jacobs et al., 2010)

- the RMS power of the evoked oscillation is higher than the mean RMS power calculated for each contact and each stimulation pulse in a 300 milliseconds time windowed 30 milliseconds after the stimulation pulse
- the Morlet wavelet coefficients exhibit a peak at the evoked oscillation's frequency. The peak's amplitude at half-width should be at least two times higher than the mean amplitude of the coefficients found at both half-widths around the peak.
- at least 5 pulses per stimulation trial evoked oscillations that match the criteria described above and are time locked to a 100 milliseconds window

3D maps of the responses have been created by representing the number of DR/HFO occurrences at the selected contact on the MRI, using the actual coordinates of the contact. For visualization purposes, the responses were spatially smoothed by a Gaussian and normalized by the contact density. Two types of 3D maps were created: Inbound Response Maps show the responses recorded on one contact location while stimulating on all other contact pairs, while the Outbound Response Maps show the responses evoked on all contacts while stimulating on one contact pair. Sensitivity, specificity and accuracy are calculated for each response type.

The 3D maps are exported as DCOM series and loaded in the surgical planning software to be visualized along with patient's anatomy, as seen on the standard MRI scans.

Results

1. Single-patient 3D Maps

Patient 4 featured a bilateral implantation of 10 electrodes. Our neurologist identified the Seizure Onset Zone by visual analysis of the SEEG traces as being located in the right Temporal pole (contacts L01, L02, L04, A01, A02, A05, A06). After a temporal lobectomy, the patient is seizure free.

The Maximum Intensity Projection (MIP) Response Maps are shown in figures 4, 5, 6 and 7 using color maps. The response count evoked on all contacts by stimulating each pair (Outbound Maps) are shown in figure 4-6 and B.

2. Statistical Results for all 6 patients

Patient 2, 3, 4, 5, 6 were found to be Sensitive 100%, Specificity 95% ± 4%. Table 3 shows the Sensitivity, Specificity and Accuracy for Outbound Response Maps. For each stimulus type, the highest sensitivity is obtained for both inbound and outbound response maps by combining DR and HFO responses using logical operator “and”.

Conclusions

- The four types of 3D maps in stereotactic coordinates of the responses to single pulse stimulation can provide complementary valuable information that helps to delineate SOZ and reveal the spatial extent of the epileptogenic networks.
- Combining the information provided by different biomarkers (DR, HFO) may result in better accuracy for SOZ localization than using individual biomarkers. There is a tradeoff between sensitivity, specificity and accuracy when using different ways of combining the biomarkers.

Acknowledgments:
Supported by Romanian government UEFISCDI grant PN-II-RU-TE-2011-3-0240

References