Stereoelectroencephalographic 3-D mapping of epileptogenicity using responses to single-pulse electrical stimulation

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Purpose

We aim at delineating the epileptogenic networks using cortico-cortical evoked potentials (CCEP) (Iwasaki et al, 2010) as a result of single-pulse electrical stimulation (SPES) 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 epilepsy were investigated using stereoelectroencephalographic (SEEG) method (table 1).

Patient	Sex	Age	Localization	Lateralization	Nr. of electrodes	MRI Lesion
1	F	35	Amygdala	R	12	Negative
2	F	24	Rolandic	R	15	Type II cortical dysplasia
3	M	24	Occipito-temporal basal	R	14	MCD
4	F	25	Temporal pole	R	10	Negative
5	F	46	Temporal pole	R	9	Type II cortical dysplasia
6	M	33	Mesial Prefrontal	L	17	Type I cortical dysplasia

Table 1. Patients participating in our study

For each patient, 64 contacts were connected to a Nicolet Wireless64 Amplifier (Natus Medical Inc.). Systematically, we have applied single pulse bipolar stimulation on n=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 (Guideline 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. 1b. We mapped the propagation of the stimulus through the epileptogenic network by analyzing CCEPs. We looked for specific evoked responses that are known to represent a biomarker of the epileptogenicity, like high-frequency oscillations (HFO) (Van't Klooster, 2011) and delayed responses (DR) (Valentin et al, 2002, 2005) . Resecting 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 right) are defined as responses resembling spikes or sharp waves occurring between 100 milliseconds and 1 second after stimulation (Valentin & Alarcon, 2008).

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 based time frequency maps (Benar et al, 2010) to identify HFOs and measure their amplitude. A stimulation trial is considered to have evoked HFOs on a certain contact if the following selection criteria are met:

- a stimulation pulse evokes an oscillation in 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 window placed 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 two times higher than the mean amplitude of the coefficients found at two half-widths around the peak.
- at least 5 pulses per stimulation trial evoked oscillations that match the 3 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 DICOM series and loaded in the surgical planning software to be visualized along with patient's anatomy, as seen on the standard MRI scans.

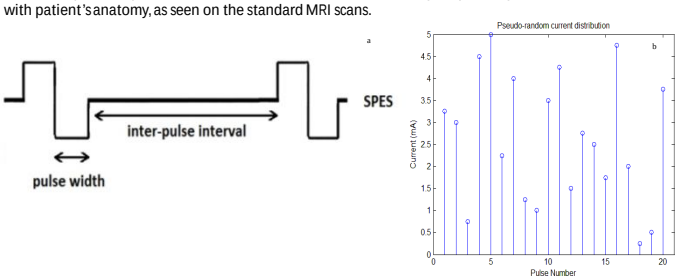

Figure 1. Pulse parameters for single pulse biphasic electrical stimulation: (a) – pulse train example for SPES ; (b) – pseudo-random current distribution for SPES protocol

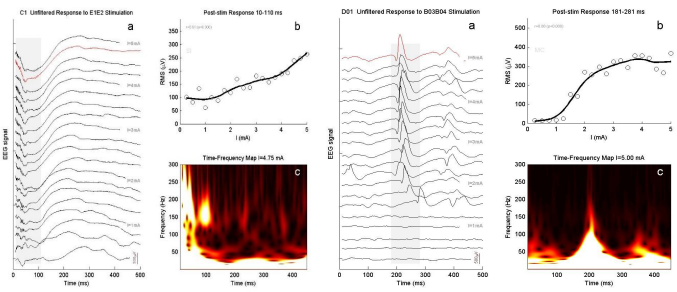

Figure 2. SPES responses. Left - HFOs on Posterior Hippocampus (contact C1) while stimulating the Entorhinal Cortex (contacts E1-E2). Right - DRs on Retrosplenial Cortex (contact D01) while stimulating the Anterior Hippocampus (contacts B03-B04) (a) SEEG traces, sorted by current intensity; (b) - stimulus response curve; (c) - Time-frequency map

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 3-6, superimposed on a slice of the patient's MRI in three different views (AX, SAG, COR), together with the electrode trajectories. The contacts included in the recording montage are highlighted in green. The number of specific responses (DR, HFO) evoked by all stimulations on each contact (Inbound Maps) are shown in figures 3, 5 or 7 using color maps. The response count evoked on all contacts by stimulating each pair (Outbound Maps) are shown in figure 4,6 and 8.

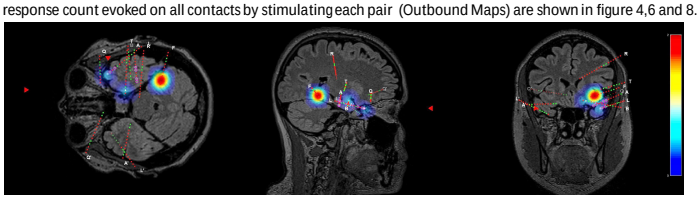

Figure 3. Inbound DR Maps. The following results were obtained: Sensitivity 14.3 %, Specificity 92.5 %, Accuracy 80.9 % (table 2)

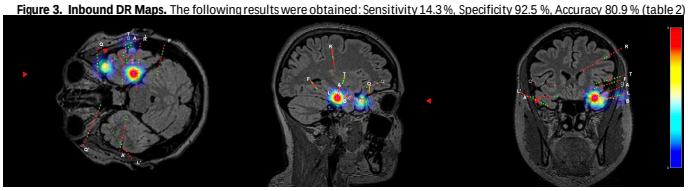

Figure 4. Outbound DR Maps. The following results were obtained: Sensitivity 57.1 %, Specificity 95.0 %, Accuracy 89.4 % (table 3)

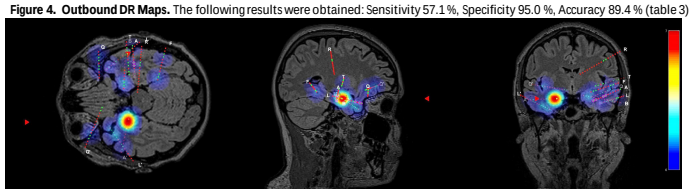

Figure 5. Inbound HFO Maps. The following results were obtained: Sensitivity 42.9 %, Specificity 52.5 %, Accuracy 51.1 % (table 2)

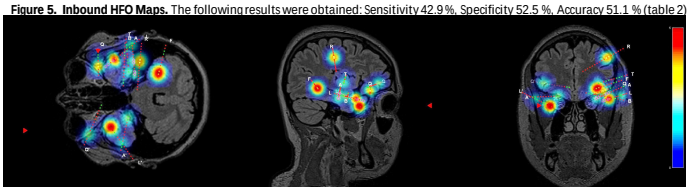

Figure 6. Outbound HFO Maps. The following results were obtained: Sensitivity 100 %, Specificity 22.5 %, Accuracy 34.0 % (table 3)

2. Statistic Results for all 6 patients

Patient	1	2	3	4	5	6	MEAN	SD
Inbound Sensitivity DR	100.0%	26.3%	37.5%	14.3%	25.0%	90.0%	48.9%	36.6%
Inbound Sensitivity HFO	100.0%	31.6%	62.5%	42.9%	31.3%	40.0%	51.4%	26.4%
Inbound Sensitivity DR or HFO	100.0%	52.6%	87.5%	57.1%	50.0%	95.0%	**73.7%**	22.9%
Inbound Sensitivity DR and HFO	100.0%	5.3%	12.5%	0.0%	6.3%	35.0%	26.5%	38.0%
Inbound Specificity DR	25.0%	96.0%	83.3%	92.5%	60.6%	38.6%	66.0%	29.5%
Inbound Specificity HFO	70.0%	86.0%	77.1%	52.5%	18.2%	47.7%	58.6%	24.5%
Inbound Specificity DR or HFO	16.7%	82.0%	64.6%	50.0%	15.2%	20.5%	41.5%	28.3%
Inbound Specificity DR and HFO	78.3%	100.0%	95.8%	95.0%	63.6%	65.9%	**83.1%**	16.0%
Inbound Accuracy DR	29.7%	76.8%	71.9%	80.9%	49.0%	54.7%	60.5%	19.6%
Inbound Accuracy HFO	71.9%	71.0%	73.4%	51.1%	22.4%	45.3%	55.9%	20.2%
Inbound Accuracy DR or HFO	21.9%	73.9%	70.3%	51.1%	26.5%	43.8%	47.9%	21.6%
Inbound Accuracy DR and HFO	79.7%	73.9%	75.0%	80.9%	44.9%	56.3%	**68.4%**	14.5%

Table 2. Sensitivity, Specificity and Accuracy Results for Inbound Response Maps

Patient	1	2	3	4	5	6	MEAN	SD
Outbound Sensitivity DR	100.0%	10.5%	0.0%	57.1%	37.5%	20.0%	37.5%	36.7%
Outbound Sensitivity HFO	100.0%	52.6%	75.0%	100.0%	37.5%	80.0%	74.2%	25.2%
Outbound Sensitivity DR or HFO	100.0%	63.2%	75.0%	100.0%	37.5%	80.0%	**75.9%**	23.7%
Outbound Sensitivity DR and HFO	100.0%	0.0%	0.0%	57.1%	37.5%	20.0%	35.8%	38.5%
Outbound Specificity DR	70.0%	92.0%	87.5%	95.0%	87.9%	77.3%	84.9%	9.5%
Outbound Specificity HFO	20.0%	60.0%	25.0%	22.5%	63.6%	22.7%	35.6%	20.4%
Outbound Specificity DR or HFO	20.0%	60.0%	25.0%	22.5%	63.6%	18.2%	34.9%	21.0%
Outbound Specificity DR and HFO	70.0%	92.0%	87.5%	95.0%	87.9%	81.8%	**85.7%**	8.9%
Outbound Accuracy DR	71.9%	69.6%	65.6%	89.4%	71.4%	59.4%	**71.2%**	10.0%
Outbound Accuracy HFO	25.0%	58.0%	37.5%	34.0%	55.1%	40.6%	41.7%	12.7%
Outbound Accuracy DR or HFO	25.0%	60.9%	37.5%	34.0%	55.1%	37.5%	41.7%	13.6%
Outbound Accuracy DR and HFO	71.9%	66.7%	65.6%	89.4%	71.4%	62.5%	**71.2%**	9.6%

Table 3. Sensitivity, Specificity and Accuracy Results for Outbound Response Maps

Tables 2 and 3 show inbound and outbound sensitivity, specificity and accuracy for DR, HFO and combined responses obtained using logical operators "or" and "and".

- The **highest sensitivity** is obtained for both inbound and outbound response maps by combining DR and HFO responses using logical operator "or".
- The **highest specificity** and **the highest accuracy** 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.

Acknowledgements: Supported by Romanian government UEFISCDI research grant PN-II-ID-PCE-2011-3-0240

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