

Progress Report 2013

Single-unit dynamics in the epileptic foci in
patients with temporal lobe epilepsy

EPIIDYN

PN-II-ID-PCE-2011-3-0240

Contract 153/2011

Stimulus amplitude effect in time and frequency on responses to single pulse electrical stimulation in stereoelectroencephalographic studies.

Cristian Donos¹, Ioana Mindruta^{2,3}, Jean Ciurea⁴, Alin Rasina⁴, Bogdan Balanescu^{1,4}, Andrei Barborica^{1,5}

¹Physics Department, University of Bucharest, Bucharest, Romania, ²Neurology Department, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, ³Neurology Department, University Emergency Hospital, Bucharest, Romania, ⁴Neurosurgery Department, Bagdasar-Arseni Hospital, Bucharest, Romania, ⁵FHC Inc, Bowdoin ME, USA

Introduction

Intracranial Direct Electrical Stimulation (iDES) is a powerful method for exploring excitability of relevant structures in patients with refractory epilepsy. Stereoelectroencephalography (SEEG), in particular, allows a 3D exploration of the epileptogenic network based on a working hypothesis.

- Our first aim is to perform a systematic investigation of the differences between effects of different pulse parameters (monophasic/biphasic, pulse duration, pulse amplitude), in order to find the common denominator of the various different protocols reported in the literature. (Valentin et al, 2002, 2005; Enatsu et al 2012)
- Second, we studied stimulus-response characteristic for single pulse (SPES) to investigate the differences in the excitability of seizure onset zones (SOZ) versus non-SOZ. (Iwasaki et al 2010)

Patients and Methods

We recorded responses to iDES in 8 subjects (table 1) undergoing presurgical evaluation for temporal lobe epilepsy using SEEG.

Patient	Sex	Age	Localization	Lateralization	Nr. of electrodes	Pathology
1	M	38	Occipital	R	8	Calcification
2	F	30	Temporo-parietal Junction	R	10	Dysembryoplastic neuroepithelial tumour (DNET)
3	F	38	Temporal	L	11	-
4	F	33	Temporal, Mesial	L	7	Tumor, Astrocytoma Mesial Structures
5	M	28	Temporal, Neocortex - Middle Temporal Gyrus	L	10	Dysplasia
6	M	46	Temporal, Mesial	L	16	-
7	F	41	Temporal, Mesial	R	11	Hippocampal Sclerosis
8	F	17	Frontal	L	11	Cortical Dysplasia

Table 1. Patients participating in the study

Methods

We first compared the responses not only to different stimulation protocols currently used in clinical practice, but systematically explored the role of various pulse parameters (Figure 2a) in evoking responses. Effects of monophasic versus biphasic pulses of 0.25-3ms pulse width as well as stimulus-response curves in the interval 0 to 5 mA (0.25 mA step) were studied. To decouple time and stimulus amplitude factors, we used trains of pseudo-random amplitude pulses (Figure 2b). This was possible by using a programmable clinical stimulator (Guideline LP+, FHC Inc), that allows the definition of complex and even arbitrary waveforms. The interpulse interval was 15 seconds (0.067 Hz), long enough to allow a resetting of the brain networks in the interval between successive pulses.

We compared the effects of the following stimulation protocols:

- Single Pulse Electric Stimulation, Biphasic (SPESB) – 20 biphasic pulses having 3ms pulse width, 15s interpulse interval and current distribution as shown in fig. 2b
- Single Pulse Electric Stimulation, Monophasic (SPESM) – 40 monophasic pulses having 3ms pulse width, 15s interpulse interval and current distribution as shown in fig. 2b
- Variable Pulse Electric Stimulation (VPDES) – 12 biphasic pulses having pulse width varied in the 0.25 – 3ms range (with 0.25ms step), 15s interpulse interval and constant current value (1 , 2.5 or 5 mA)

We analyzed fast responses and delayed responses to electrical stimulation (Valentin et al, 2002, 2005). The data was sampled at 4096 Hz and recorded using Nicolet 64-channel wireless amplifier. The response was calculated as the RMS value over a 100ms window (typically) starting as early as 10msec after the stimulus application, in order to exclude the stimulation artifacts. Whenever delayed responses were encountered, the analysis window was centered on the peak delayed response.

Whenever High-Frequency Oscillations (HFO) were evoked by electrical stimulation (van 't Klooster 2011), a filtering in the appropriate ripples (100-250Hz) or fast-ripples (250-1000Hz) band was performed. We used the method described by Benar et al 2010 based on time-frequency maps to discriminate filtering artifacts from physiological responses. We calculated for the responses on each contact a time-frequency map using continuous-time wavelet transform (CWTFT) based on Morlet wavelets.

Using biphasic SPES as our base protocol, we tested the excitability of brain areas part of the epileptogenic network by looking at the stimulus-response curves.

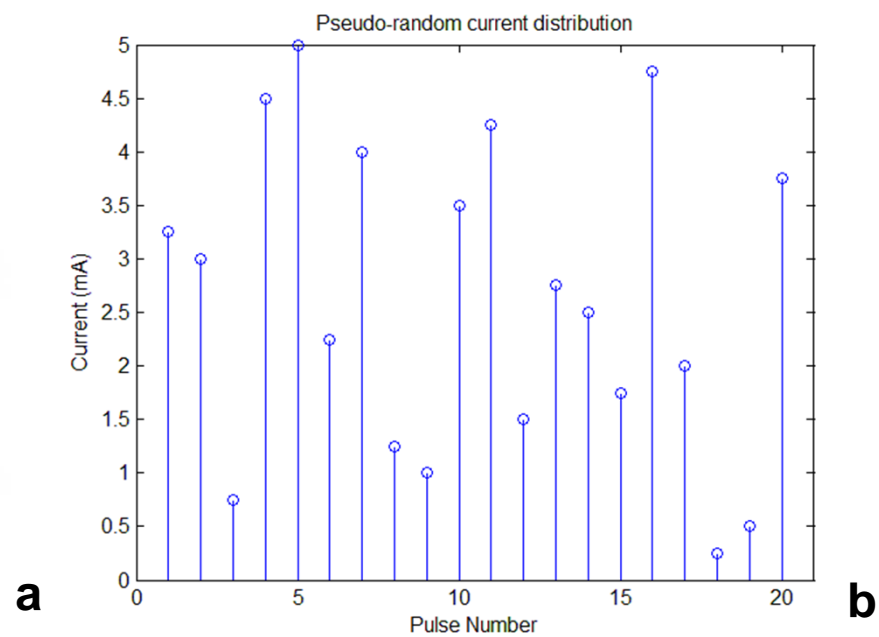
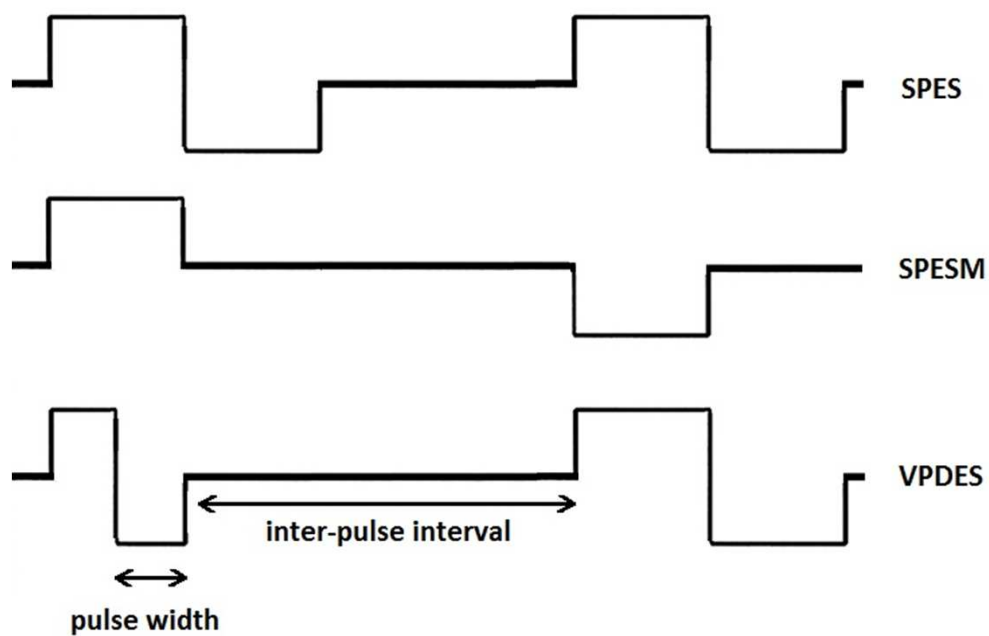


Figure 2. Pulse parameters that were systematically studied: (a) – pulse train example for SPES, SPESM and VPDES ; (b) – pseudo-random current distribution for SPES and SPESM protocol

Results

1. Comparative analysis of the responses to different stimulation protocols

9114 (147 stimulations x 64 contacts) responses to the three different protocols (SPESB, SPESM and VPDES) were recorded in the 8 patients. In 2 of the 8 patients, we were able to apply all three protocols simultaneously. In the 2 out of 8 we applied 2 protocols, and in 5 patients we applied only the biphasic SPES (SPESB) protocol, which is our base protocol.

All three protocols usually showed stimulus-response curves having typical appearances as in figure 3, top-left panels (b).

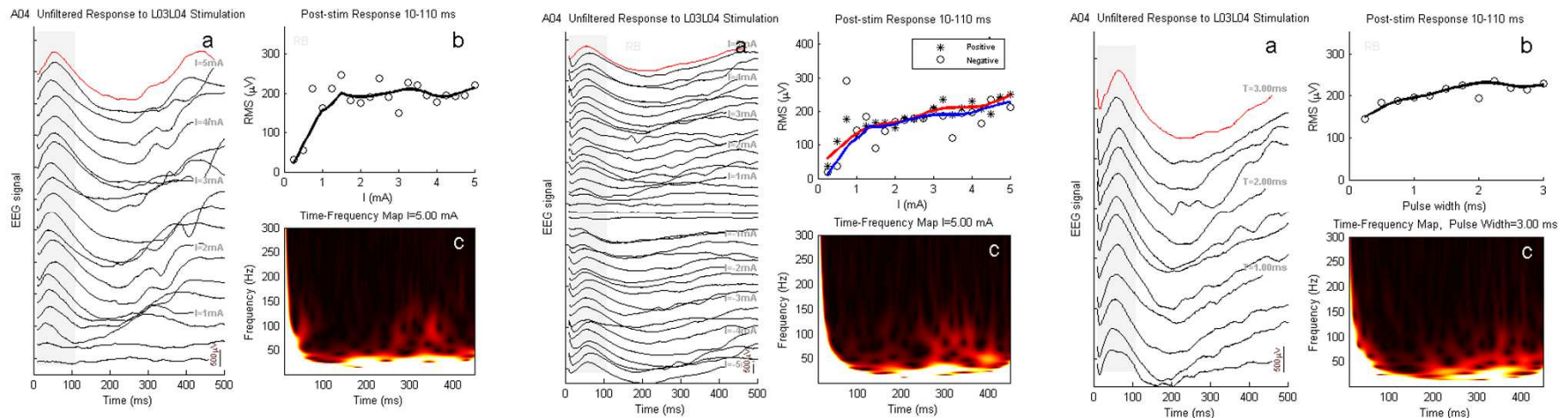


Figure 3. Stimulation-evoked responses on contact A04 (supplementary sensorimotor area) in patient 8 to SPESB (left), SPESM (middle) and VPDES (right) applied to contacts L03-L04 (premotor area). The electrode location for patient 8 is shown in fig 5; (a) – a raster of EEG traces aligned to the stimulation pulses, sorted in ascending order of the parameter varied during stimulation (current, pulse width or inter-pulse interval), from bottom to top; (b) – stimulus-response curve; (c) – time-frequency (TF) map for the selected trace (highlighted in red)

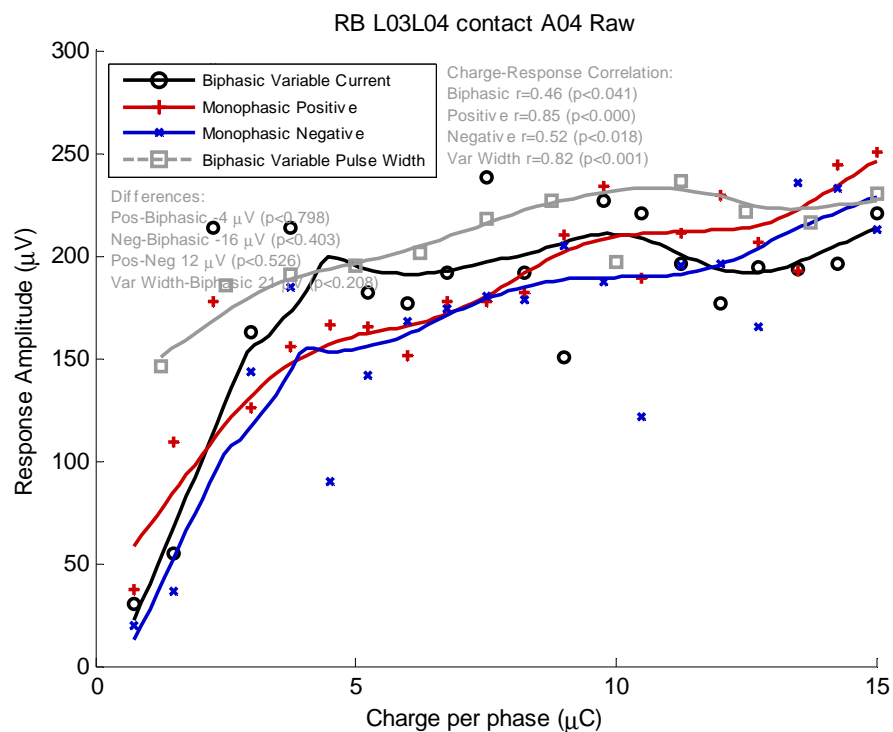


Figure 4. SPESB , SPESM and VPDES effects comparison in contact A04 (supplementary sensorimotor area) , while stimulating L03-L04 (premotor area) in patient 8

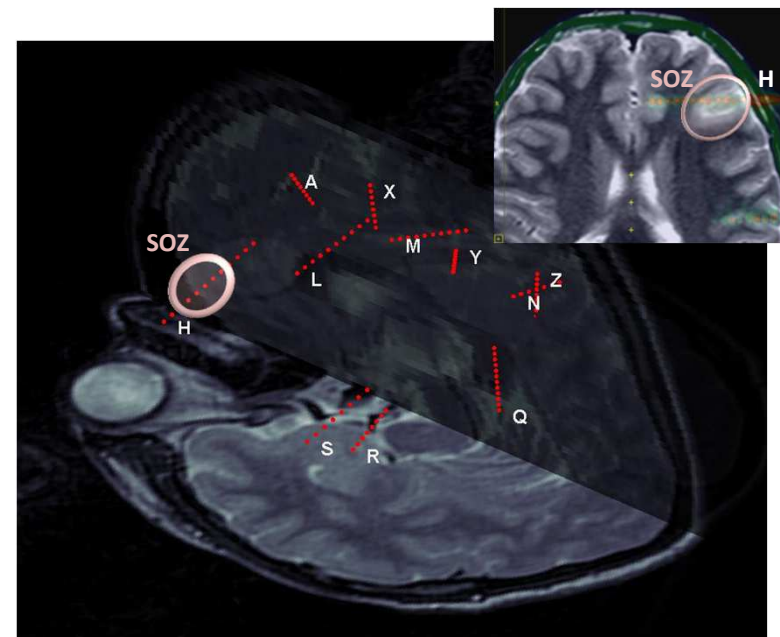


Figure 5. 3D view of the SEEG electrode implantation pattern for patient 8 (type II focal cortical dysplasia in the dorsolateral prefrontal cortex) and postoperative CT detail of the H electrode.

To compare the stimulus-response curves to protocols where different pulse properties were varied (current amplitude, pulse duration, phase), we calculated the charge per phase for each pulse as the common property across protocols. In most situations (Table 2), all protocols resulted in similar evoked responses, for the same injected charge per phase, regardless of the differences in the pulse properties. Figure 4 illustrates such a situation, where differences between responses to SPESB, SPESM and VPDES are non-significant (paired t-test, $p > 0.05$).

On occasions, a brain structure can respond differently to these protocols. Figure 6 shows an example, where patient 8 was stimulated on contacts H06-H07, which are found inside the dysplasia . SPESB and VPDES stimulus – response curves are similar, but SPESM stimulation showed increased excitability for the monophasic positive pulses. Figure 5 is the implantation scheme for patient 8 and shows the anatomic location of the electrodes.

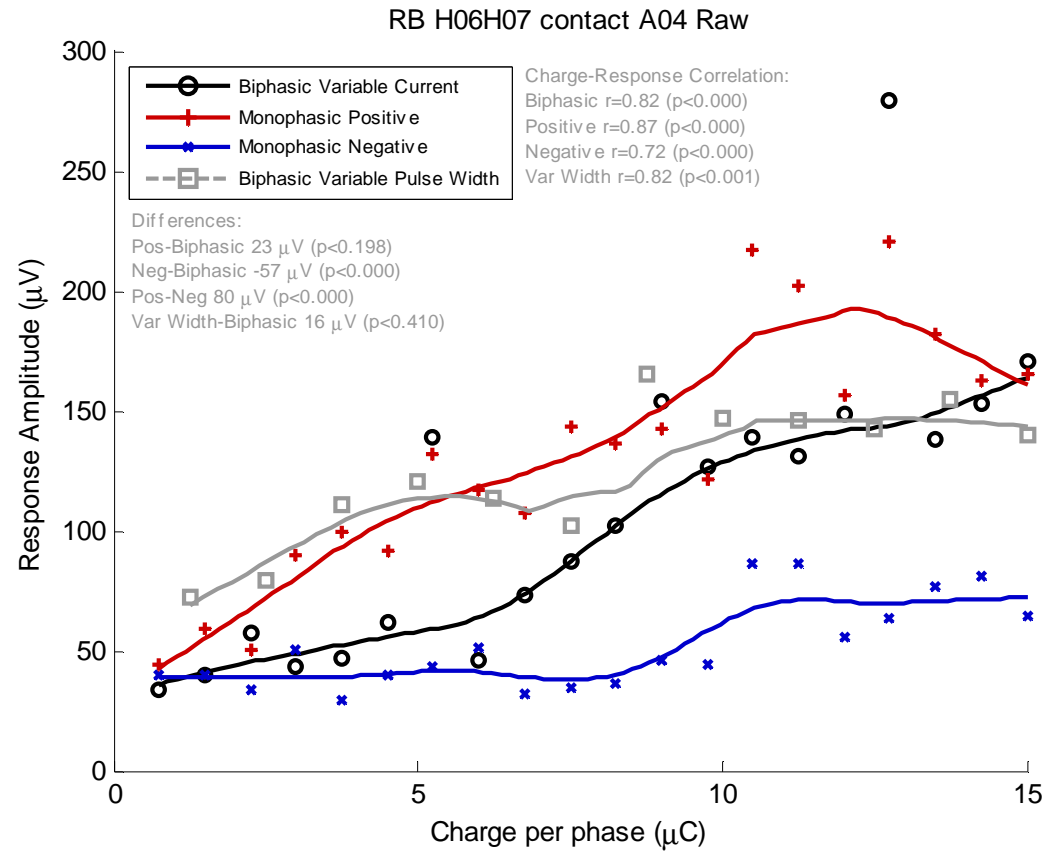


Figure 6. SPESB , SPESM and VPDES effects comparison on contact A04 (SSMA), obtained while stimulating contacts H06-H07 (DLPFC, type II FCD) in patient 8

We used the third quartile (Q_3) value of pooled responses to SPESB recorded on all contacts in each patient, as a threshold for calculating the individual contact activation.

For patient 8, on which we ran all three protocols, 603 activated contacts resulted from 33 stimulations on 6 electrodes (H, L, M, X, Y, Z) (Figure 5).

On the stimulus-response curves we ran a paired t-test ($p < 0.05$) (table 5) for each pair for stimulation protocols, in order to see the correlation between them.

- nSPESB - number of contacts activated during biphasic pulses stimulation
- nPOS - contacts activated using positive monophasic pulses that were not correlated with biphasic pulses stimulation
- nNEG - contacts activated using negative monophasic pulses that were not correlated with biphasic pulses stimulation
- nPOSNEG - contacts activated using positive and negative monophasic pulses were not correlated with each other
- nVPDES - contacts activated using variable pulse duration were not correlated with biphasic pulses stimulation

Patient	Stimulation protocols	Total nr. of stimulations	Nr. of stimulated contacts	Nr. of activated contacts ($>Q_3$)	nSPESB	nPOSNEG	Contacts with responses different from SPESB		
							nPOS	nNEG	nVPDES
5	SPESB, SPESM	22	8	352	176	8(5%)	60(34%)	68(39%)	0
6	SPESB, VPDES	15	7	214	124	0	0	0	48(39%)
8	SPESB, SPESM, VPDES	33	6	603	208	128(62%)	87(42%)	115(55%)	92(44%)

Table 2. Results of the application of at least two different stimulation protocols in the three patients on which at least two protocols were applied. **Statistically significant differences were assessed using paired Student's t-test, $p < 0.05$.**

SEEG Implantation

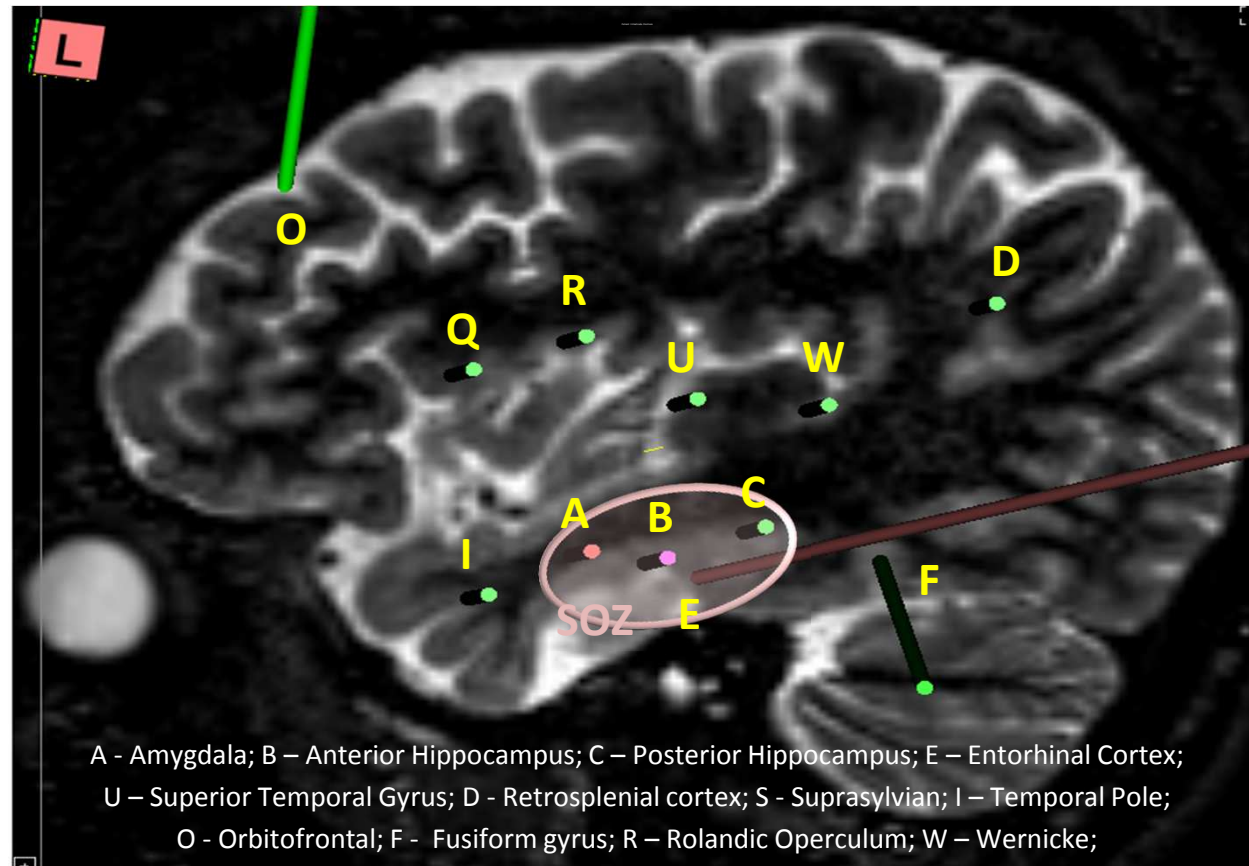


Figure 7. SEEG electrode implantation pattern in patient 3. A - Amygdala; B – Anterior Hippocampus; C – Posterior Hippocampus; E – Entorhinal Cortex; U – Superior Temporal Gyrus; D - Retrosplenial cortex; S - Suprasylvian; I – Temporal Pole; O - Orbitofrontal; F - Fusiform gyrus; R – Rolandic Operculum; W – Wernicke.

2. Stimulus-response curves and effects of SPES stimulation

Stimulation-evoked responses included early responses (figures 3, 8 and 9) and delayed responses (figure 11) having oscillatory components in various frequency bands, including HFO (figures 8,9) and fast-ripples were observed. Early responses (ER), shown in figure 8, and HFO's, shown in figure 9, were evoked in posterior hippocampus (contact C1), which is part of SOZ for patient 3 (figure 7) when stimulating the entorhinal cortex (contacts E1-E2). Stimulating the fusiform gyrus, which is posterior to the SOZ for patient 3, did not evoke any responses in hippocampus, as shown in figure 10.

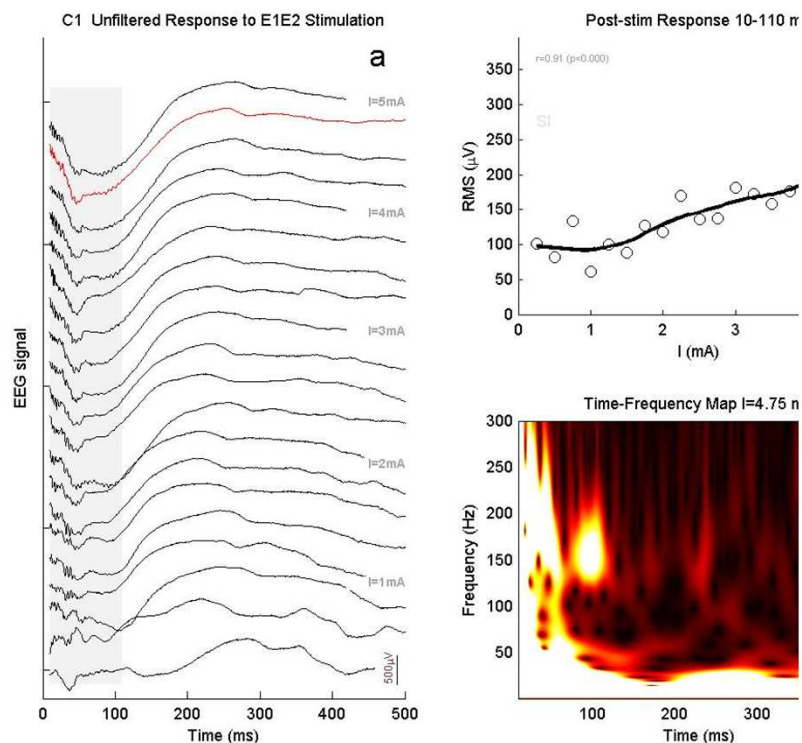


Figure 8. SPESB effects (ER) on posterior hippocampus (contact C1) while stimulating the entorhinal Cortex (contacts E1-E2). (a) EEG traces; (b) - stimulus response curve; (c) – Time-frequency map

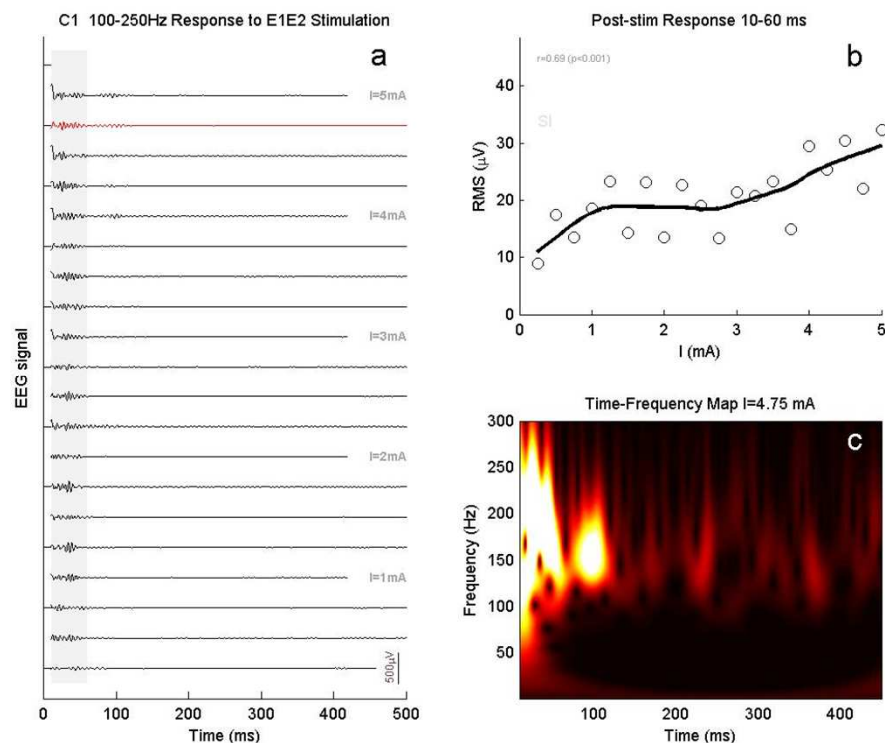


Figure 9. SPESB effects (HFOs) on C1 Hippocampus while stimulating the Entorhinal Cortex (E1E2). (a) – EEG traces filtered in the 100-250 Hz range; (b) - stimulus response curve; (c) – Time-frequency map

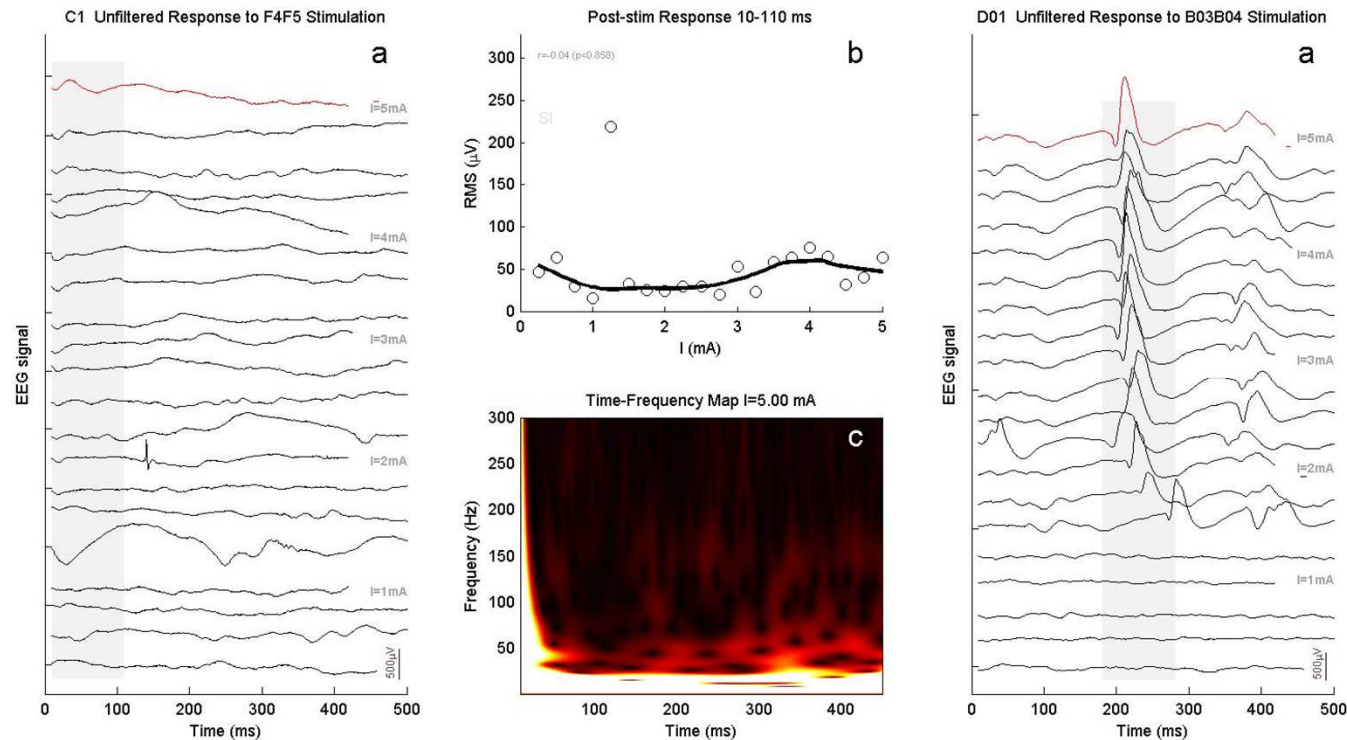


Figure 10. Non-significant SPESB effects evoked in posterior hippocampus (C1, SOZ) of patient 6 while stimulating the Fusiform Gyrus (F4-F5, non-SOZ) (a) – EEG traces, sorted by current; (b) - stimulus-response curve; (c) – TF map

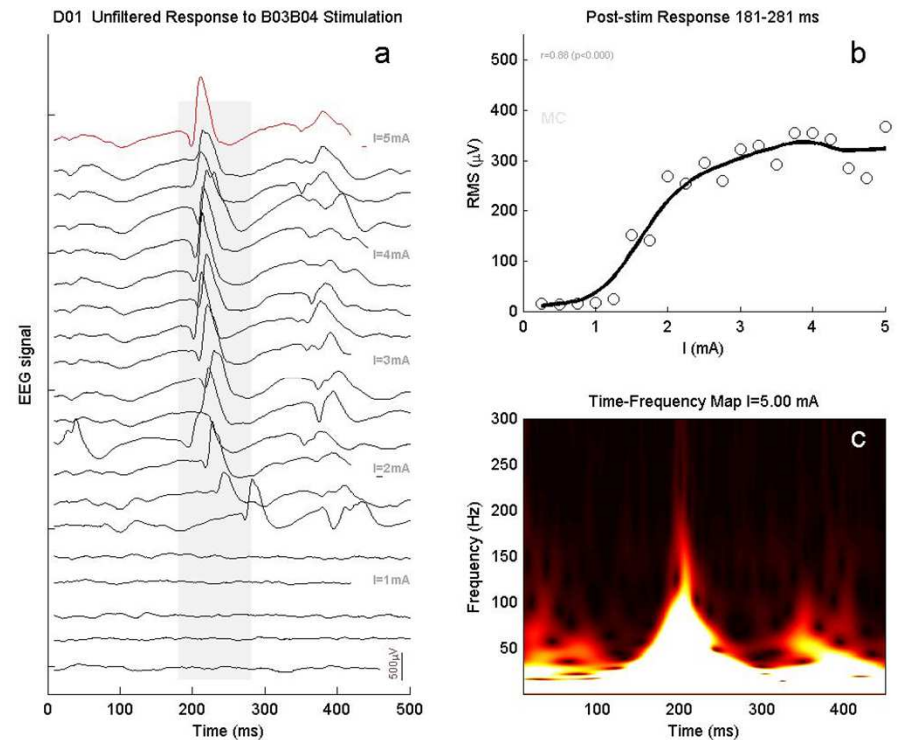


Figure 11. Delayed responses (DR) on contact D01 (retrosplenial cortex) while stimulating contacts B03-B04 (anterior hippocampus) of patient 6; (a) – EEG traces, sorted by current; (b) – stimulus-response curve; (c) – TF map

Delayed responses (DR) (Valentin et al, 2002, 2005) occurring 170 or 400ms post-stimulus were also observed in patients 5 and 6 during SPES stimulation of the anterior hippocampus (patient 5) and the amygdala (patient 6) (figure 11).

Conclusions

The first conclusion is that, in most situations, regardless of the combination of different stimulation currents, pulse widths, phases and polarity used, it is the underlying ***charge per phase*** parameter that determines the magnitude of the response to single-pulse electrical stimulation. This finding provides a method to unify the evaluation of the strength of various stimulation protocols used in literature.

Second, evaluation of quantitative and qualitative effects triggered by SPES in both time and frequency domain can provide important information regarding the seizure initiation and propagation in the epileptic brain. SPES can contribute to the identification of the epileptogenic networks without depending on the spontaneous ictal and inter-ictal events. It provides complementary information resulting in a faster and more accurate invasive monitoring phase.

Acknowledgements

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

References

- Valentin A, Alarcon G, Garcia-Seoane JJ, Lacruz ME, Nayak SD, Honavar M, et al. Single-pulse electrical stimulation identifies epileptogenic frontal cortex in the human brain. *Neurology* 2005 65:426–35.
- Valentin A, Anderson M, Alarcon G, Seoane JJ G, Selway R, Binnie CD, et al. Responses to single pulse electrical stimulation identify epileptogenesis in the human brain in vivo. *Brain* 2002; 125:1709–18.
- Enatsu, R., Piao, Z., O'Connor, T., Horning, K., Mosher, J., Burgess, R., Bingaman, W., Nair, D. Cortical excitability varies upon ictal onset patterns in neocortical epilepsy: a cortico-cortical evoked potential study. *Clin. Neurophysiol.* 2012 123:252—260.
- Iwasaki, M., Enatsu, R., Matsumoto, R., Novak, E., Thankappen, B., Piao, Z., O'Connor, T., Horning, K., Bingaman, W., Nair, D. Accentuated cortico-cortical evoked potentials in neocortical epilepsy in areas of ictal onset. *Epileptic Disord.* 2010 12:292—302.
- van 't Klooster MA, Zijlmans M, Leijten FS, Ferrier CH, van Putten MJ, Huiskamp GJ. Time-frequency analysis of single pulse electrical stimulation to assist delineation of epileptogenic cortex. *Brain* 2011 134(Pt 10):2855-66.
- Bénar CG, Chauvière L, Bartolomei F, Wendling F, Pitfalls of high-pass filtering for detecting epileptic oscillations: a technical note on "false" ripples., *Clin Neurophysiol.* 2010 121(3):301-10.