Clinical Neurophysiology 128 (2017) 1053–1060

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

# High frequency spectral changes induced by single-pulse electric stimulation: Comparison between physiologic and pathologic networks

Mihai Dragos Mălîia [a,b,1], Cristian Donos [c,d,1], Andrei Barborica [c,e], Ioana Mindruta [a,f], Irina Popa [a], Mirela Ene [c], Sándor Beniczky [b,g,*]

[a] University Emergency Hospital, Department of Neurology, Bucharest, Romania
[b] Danish Epilepsy Centre, Department of Clinical Neurophysiology, Dianalund, Denmark
[c] University of Bucharest, Physics Department, Bucharest, Romania
[d] University of Texas Health Science Center at Houston, Houston, TX, United States
[e] FHC Inc., Bowdoin, ME, United States
[f] University of Medicine and Pharmacy 'Carol Davila', Department of Neurology, Bucharest, Romania
[g] Aarhus University Hospital, Department of Clinical Neurophysiology, Aarhus, Denmark

See Editorial, pages 1026–1027

ARTICLE INFO

*Article history:*
Accepted 15 December 2016
Available online 28 December 2016

*Keywords:*
Cortico-cortical connectivity
Epileptic networks
Default mode network
Spectral changes
Single-pulse electric stimulation

HIGHLIGHTS

- Physiologic and pathologic interactions in brain networks are tested with single-pulse electric stimulation (SPES).
- We found a global early excitation of fast rhythms and a delayed inhibition.
- Specific effects were detected, depending on the type of stimulated network.

ABSTRACT

*Objective:* To investigate functional coupling between brain networks using spectral changes induced by single-pulse electric stimulation (SPES).
*Method:* We analyzed 20 patients with focal epilepsy, implanted with depth electrodes. SPES was applied to each pair of adjacent contacts, and responses were recorded from all other contacts. The mean response amplitude value was quantified in three time-periods after stimulation (10–60, 60–255, 255–500 ms) for three frequency-ranges (Gamma, Ripples, Fast-Ripples), and compared to baseline. A total of 30,755 responses were analyzed, taking into consideration three dichotomous pairs: stimulating in primary sensory areas (S1-V1) vs. outside them, to test the interaction in physiologic networks; stimulating in seizure onset zone (SOZ) vs. non-SOZ, to test pathologic interactions; recording in default mode network (DMN) vs. non-DMN.
*Results:* Overall, we observed an early excitation (10–60 ms) and a delayed inhibition (60–500 ms). More specifically, in the delayed period, stimulation in S1-V1 produced a higher gamma-inhibition in the DMN, while stimulation in the SOZ induced a higher inhibition in the epilepsy-related higher frequencies (Ripples and Fast-Ripples).
*Conclusion:* Physiologic and pathologic interactions can be assessed using spectral changes induced by SPES.
*Significance:* This is a promising method for connectivity studies in patients with drug-resistant focal epilepsy.


## 1. Introduction

Brain networks have drawn increased interest in the last years, further expanding on the localizationist-lesional model. This has

* Corresponding author at: Department of Clinical Neurophysiology, Aarhus University Hospital & Danish Epilepsy Centre, Visby Allé 5, 4293-Dianalund, Denmark.
*E-mail address:* sbz@filadelfia.dk (S. Beniczky).
[1] These authors have contributed equally to this work.

http://dx.doi.org/10.1016/j.clinph.2016.12.016
1388-2457/

been especially relevant for epilepsy, as brain networks best account for the pathophysiology of this condition (Spencer, 2002), with profound therapeutic implications (Jiruska et al., 2014).

The majority of the literature on brain networks derives from functional imaging studies and particularly resting state functional MRI (RS-fMRI). However this methodology suffers from limited temporal resolution. Furthermore, the hemodynamic response is only an indirect measure of neuronal activity (Yuan et al., 2016). On the other hand, surface electro-magnetic imaging has limited spatial resolution and a low sensitivity for the deep sources (Gallen et al., 1995; Ding and Yuan, 2011). Single pulse electrical stimulation (SPES) (<0.2 Hz) (Valentin et al., 2002) and cortico-cortical evoked potentials (CCEP) (0.2–1 Hz) (Matsumoto et al., 2004) applied to implanted electrodes in epilepsy surgery candidates, overcome these constraints, and have become the gold-standard for probing in vivo physiological (Guye et al., 2008) and pathological effective connectivity (Iwasaki et al., 2010; Alarcón and Valentín, 2012; Yaffe et al., 2015). Although they induce a modulation of the networks, the evoked responses have been demonstrated to replicate the spontaneous cortical response to epileptiform discharges, both at a macroscopic (Nayak et al., 2014) as well as a microscopic scale (Alarcón et al., 2012).

The study that introduced the SPES method (Valentin et al., 2002), described two types of responses. The first was ubiquitous in the early post-stimulation period, and thus considered as physiological cortical excitability. The second type appeared in the delay period, preferentially on contacts belonging to the seizure onset zone (SOZ) and thus thought as representing pathological, epilepsy-related, hyperexcitability. However, these are low frequency waves readily visible on the raw traces. Van 't Klooster et al, (2011), demonstrated that higher frequencies, in particular ripples (R) and fast ripples (FR) are also modulated by SPES. These are especially relevant for epileptic pathophysiology as they represent biomarkers for the epileptogenic focus (van 't Klooster et al., 2011) and they are more useful in understanding abnormal epilepsy-related neuronal bursting than single-unit recording on micro-electrodes. (Colder et al., 1996).

The default mode network (DMN) is the first resting-state network described in fMRI (Fox et al., 2005) and thought to be preferentially deactivated during loss of consciousness in epileptic seizures (Blumenfeld et al., 2009; Moeller et al., 2010). Being a "task-negative" network serving introspection and meta-consciousness, it is deactivated by salient sensory stimuli, which switch the cingular-opercular network via the primary sensory areas (Sridharan et al., 2008).

There are controversial results on how the epileptogenic networks engage these physiological networks. Although the majority of functional connectivity studies succeed in proving a significant distinction between the SOZ and the control brain areas (Yaffe et al., 2015), the direction varies widely. For example, in the archetypical focal epilepsy, hippocampal sclerosis – mesial temporal lobe epilepsy, analyzing the alterations between the lesioned hippocampus and the DMN, Zhang et al. (2010) found increased connectivity with the posterior cingulate and decreased connectivity with dorsal mesial prefrontal, inferior temporal cortex and medial temporal lobe. However, McCormick et al. (2013) found decreased connectivity between the posterior cingulate and the epileptogenic hippocampus, that was correlated with impaired presurgical memory, and predicted postsurgical cognitive decline.

In this context, the main objective of our study was to investigate cortico-cortical connectivity using spectral changes induced by direct electrical stimulation, which represents a controlled and task-independent method. Furthermore, we assessed whether SOZ engaged in these connections differently than the physiologic neuronal networks. We hypothesized that SPES would, in general, induce a significant spectral change compared to the baseline. Based on the fMRI literature we hypothesized that the DMN would be inhibited by the SPES applied to contacts in the sensory cortex more than by SPES applied to contacts outside these sensory areas. The third hypothesis was that SOZ had a specific effect on the induced spectral changes, especially in the frequency domains related to epileptogenic pathophysiology (R and FR).

## 2. Methods

### 2.1. Patients

The study enrolled 20 patients suffering from drug-resistant epilepsy, who were explored with intracranial electrodes via the SEEG technique, between 2012 and 2015 (Table 1). An average of 13 electrodes (Dixi, Besancon, FR) were implanted in each patient (range 9–17) uni-or bilaterally, having a mean of 165 platinum, 2.5 mm contacts (range 104–219) (Balanescu et al., 2014). Post-implantation CT was registered with preimplantation MRI to determine the coordinates of each contact in the patients' anatomical space, referenced to AC and PC. Up to 64 contacts located in the grey matter were selected for recording by the expert epileptologist (I.M.) after careful review. The selected contacts were connected to a Care Fusion Nicolet EEG 64 Amplifier (Natus Medical Inc., Middleton, WI) for long-term monitoring. The sampling rate was 4096 Hz, with open filters (i.e. only using the anti-aliasing filters). Patients gave their informed consent, and the study was approved by the ethics committee (approval No. 2621/03.02.2012).

### 2.2. Seizure onset zone

The SOZ was determined by a trained epileptologist (I.M.) according to the SEEG principles (Kahane et al., 2003), namely the first contacts displaying relevant ictal onset patterns, as described by Perucca et al. (2014). All contacts located in SOZ were included in the montage used for SPES. Thus 196 (on average 9.8 contacts/patient) of the total recorded 1261 (15%) contacts were considered to be located in the cortical structures generating seizures. Based on these recordings, 18 patients were operated upon, and 13 (72%) had a favorable, Engel I outcome (Engel et al., 1993). We investigated the effect of stimulating in SOZ vs. stimulating in non-SOZ contacts. We chose to include in the analysis all the patients, irrespective of the surgical outcome because the electrophysiological definition of SOZ contacts was consistent throughout our study group, and because the electrodes implanted in the non-seizure free patients were important for the S1-V1 analysis. Furthermore, in spite of correct identification of SOZ, modest surgical outcome was expected in these five patients, due to bihemispheric pathology or superposition between epileptogenic areas and primary motor or language cortex.

### 2.3. SPES protocol

In our epilepsy center, we use SPES according to the clinical standards (Munari et al., 1993; Valentin et al., 2002) to assess epilepsy biomarkers and to reveal physiological and pathological effective connectivity (Donos et al., 2016a; Popa et al., 2016). The stimulation protocol has been extensively described in these studies, as well as its effects on cerebral tissue compared with other low-frequency protocols from the literature (Donos et al., 2016b). Briefly, we use a programmable clinical stimulator (Guideline LP +, FHC Inc, Bowdoin, ME) to generate a sequence of 20 square biphasic pulses having variable amplitude (3 ms pulse duration, stimulation currents varied in the 0.25–5 mA range in steps of 0.25 mA) (Fig. 1). These are arranged in a pseudo-random order and are separated by a 15 s interval (0.067 Hz), allowing the tissue