Chapter

Cellular and EEG Patterns of the Reorganization of Cortical Activity in Animal Experimental Models of Epilepsy (in Cats)

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Abstract

The aim of this chapter is to present the results of experiments performed in attempt of receiving precise information concerning compositions of the patterns of functional states of the structures of cerebral neocortex, reflected in distributions of intracortical electrical fields including patterns reflecting cellular activity. The data were received in conditions of wakefulness and sleep in cats with permanently implanted cortical electrodes—without necessity of using any pharmacological treatment or in conditions of pharmacological alterations of the functional state of cortical tissue—qualified as ionic (IME) and penicillin (PME) models of epilepsy.

Keywords: HFOs—High frequency oscillations, IcEEG—intracortical electroencephalogram, IME—Ionic model of epilepsy, PME—Penicillin model of epilepsy, GSSM—Gyrus suprasylvian medialis, GSP—Gyrus sigmoideus posterior, FFT—Fast Fourier transfer, HPF—High pass filter, LPF—Low pass filter, NF—Notch filter

1. Introduction

The intention of this research was to gather informations that provide an explanation for various findings. Among others, such as the occurrence of phenomena like ripples and high frequency oscillations (HFOs) in EEG records. These oscillations are widely recognized and accepted as biomarkers indicating the reorganization of cortical activity in epilepsy (For example, see [1–3]). The study was performed in a group of cats with permanently implanted cortical electrodes and, in addition, with implanted subdural cannulae enabling transfer of artificial cerebrospinal fluid with increased concentration of potassium ions in arachnoid space and/or application of appropriate pharmacological substances: IME and PME—experimental models of epilepsy (For example, see [4]). In three cats, intracortical electroencephalogram (IcEEG) was recorded using multicontact

concentric electrode: 16 contacts about 40 micrometers each with distance between contacts of 200 micrometers. The experiments were performed with respect to the animals participating in this research, in conditions of quiet wakefulness and sleep. Effects of subdural or intraperitoneal application of penicillin were studied in conditions of general anesthesia, after application of pentobarbital in case of probability of appearance of the clinical epileptic seizures. The first information concerning results of this study was presented during 17th European Congress of Clinical Neurophysiology, Warszawa, 2019 [5].

2. Methods

Figure 1 illustrates the size of the semi-microelectrode in relation to the fragment of cerebral cortex (Nissl stain), localization of implanted electrodes illustrated on the map of cat's brain, and examples of the patterns of cellular discharges. The multi-channel electrode was implanted in the median suprasylvian gyrus (GSSM – gyrus suprasylvianus medialis): number 1 on the map. This is the region of association cortex. Number 2 indicates localization of the second source of information, which is important in this case during evaluation of the functional state of the brain: transcortical macroelectrode (surface electrode versus deep electrode—distance about 3 mm across the cortex)—placed in the somatosensory cortex, close to the motor cortex (GSP – posterior sigmoid gyrus).

The recording of the brain electrical activity in the animals was performed while they were placed in a screened cage. This setup aimed to avoid any alteration of the IcEEG signal caused by electromagnetic fields. The amplifier with a sampling rate of 4 kHz was utilized during the recording process. IcEEG patterns and results of their frequency analysis were presented using equipment offered by ELMIKO—producer of the EEG recording systems.

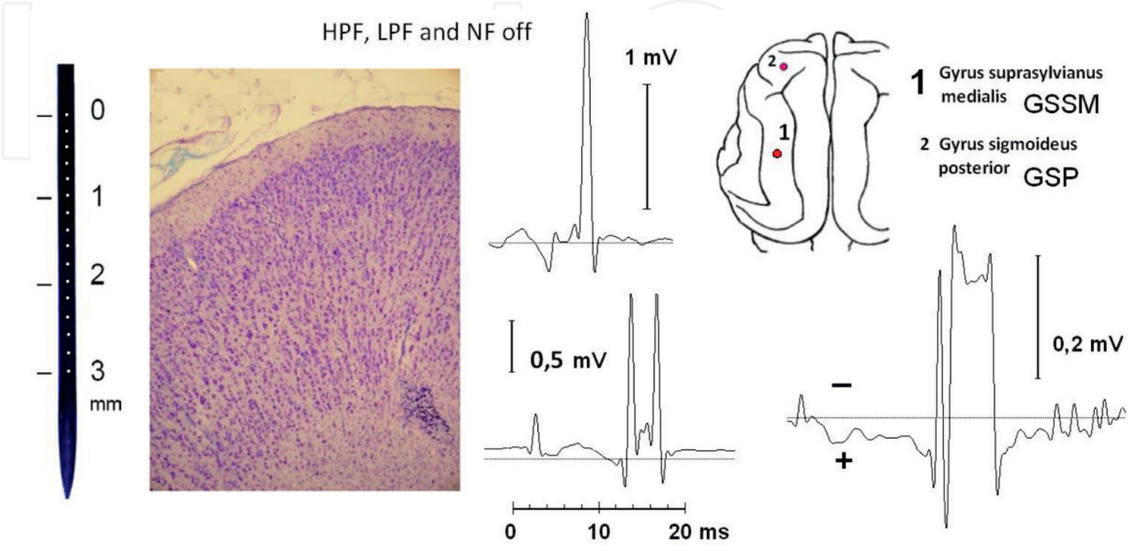

Figure 1.
Illustration of the recording electrode, patterns of cellular discharges and cortical localizations of the implanted electrodes used in this study for evaluation of the functional states of the cerebral cortex. Full description in text.

3. Results

Figure 2(**A**, **B**) illustrates the same fragment of IcEEG record: before (**Figure 2A**) and after modification of the EEG pattern (**Figure 2B**) by using different filters: high pass filter (HPF), low pass filter (LPF) and notch filter (NF). This is the fragment of EEG recorded about half a year after implantation of electrodes and on early stage of subdural transfer of artificial cerebrospinal fluid with increased concentration of potassium ions (IME).

Figure 2A illustrates pattern of cortical activity in sleepy animal, presented without using any filtering of the IcEEG record. These are unipolar derivations, with respect to ground. During the experiment, there were instances of scattered spikes within the cortex. These spikes occurred in various locations and sometimes traveled between different layers. The spikes were most frequently observed in cortical layers L3 and L4, specifically in derivations at depths of 0.6 and 0.8 mm. The results of frequency analysis (FFT with analytical window 256 ms) of the EEG fragment

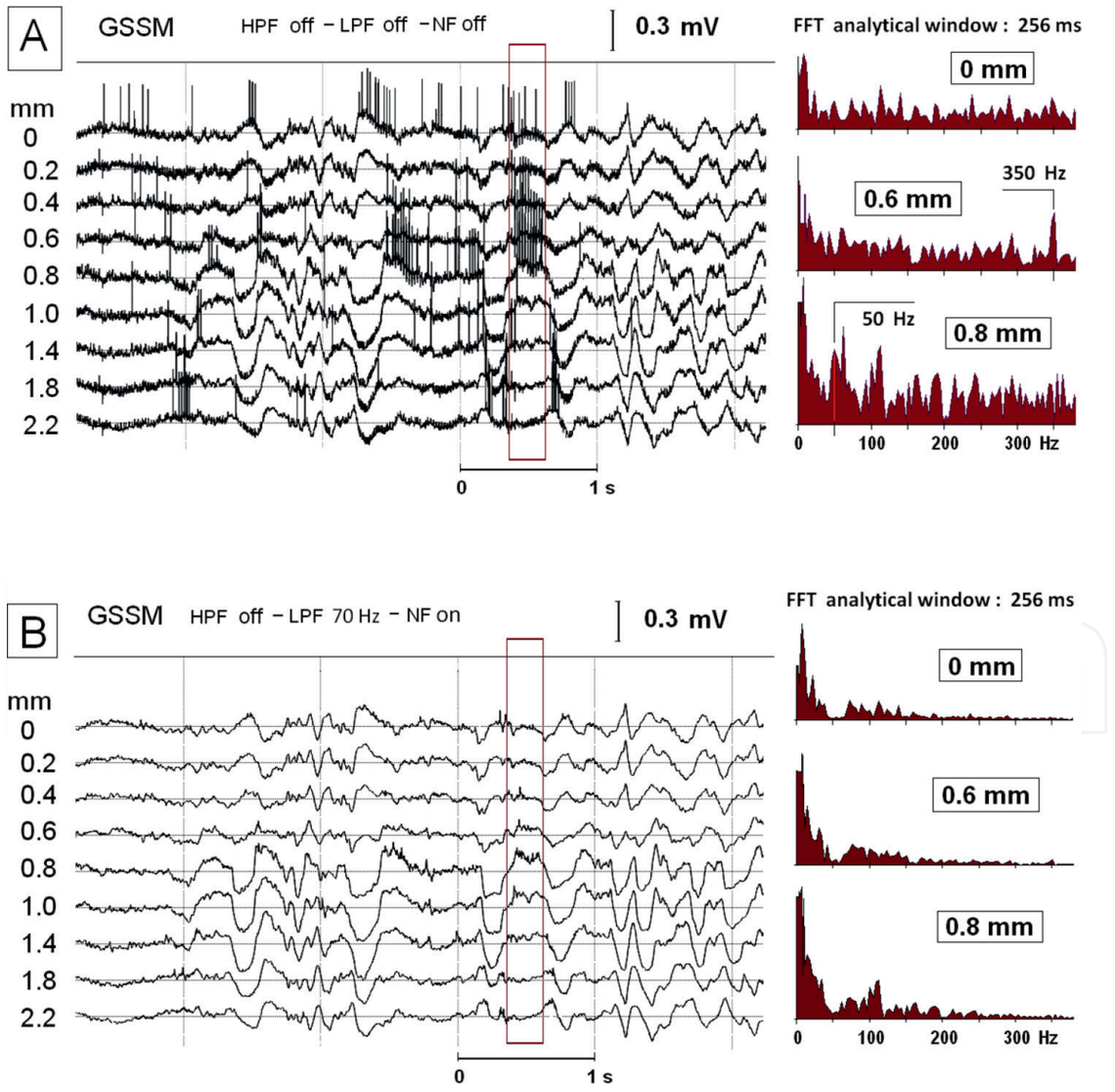

Figure 2.
(A, B). Patterns of the same fragment of IcEEG record: (A) - recorded with all filters switched off, and (B) - presented after filtering using low pass filter (LPF) 70 Hz and notch filter (NF) 50 Hz. Results of frequency analysis (FFT) of selected derivations refer to the IEEG fragment s of 256 ms duration, indictated on the records.

indicated on the IcEEG record illustrate increased activity within the frequency range of 50–60 Hz and 100–120 Hz in derivation from the depth of 0.8 mm and, surprisingly, at about 350 Hz in the derivation at the level of 0.6 mm. This type of information would be unavailable during visual evaluation of this EEG record.

Figure 2B, illustrates effects of using switched on filters: LPF 70 Hz and NF. It confirms appearance of the pattern of Slow Wave Sleep (SWS) during EEG recording with low amplitude ripples in localizations of previously appearing multiple discharges or lack of any signs reflecting existence of the cellular discharges. In **Figure 2B**, due to usage of NF there is a gap in the frequency spectrum around 50 Hz.

Figure 3A, B illustrates similar pattern of widespread, frequent intracortical cellular discharges recorded in the same experiment as illustrated in **Figure 2**(**A**,**B**). This pattern may give impression of existence of the cellular paroxysmal activity. Frequency spectrum of the IcEEG fragment, as shown in **Figure 3A**, illustrates the

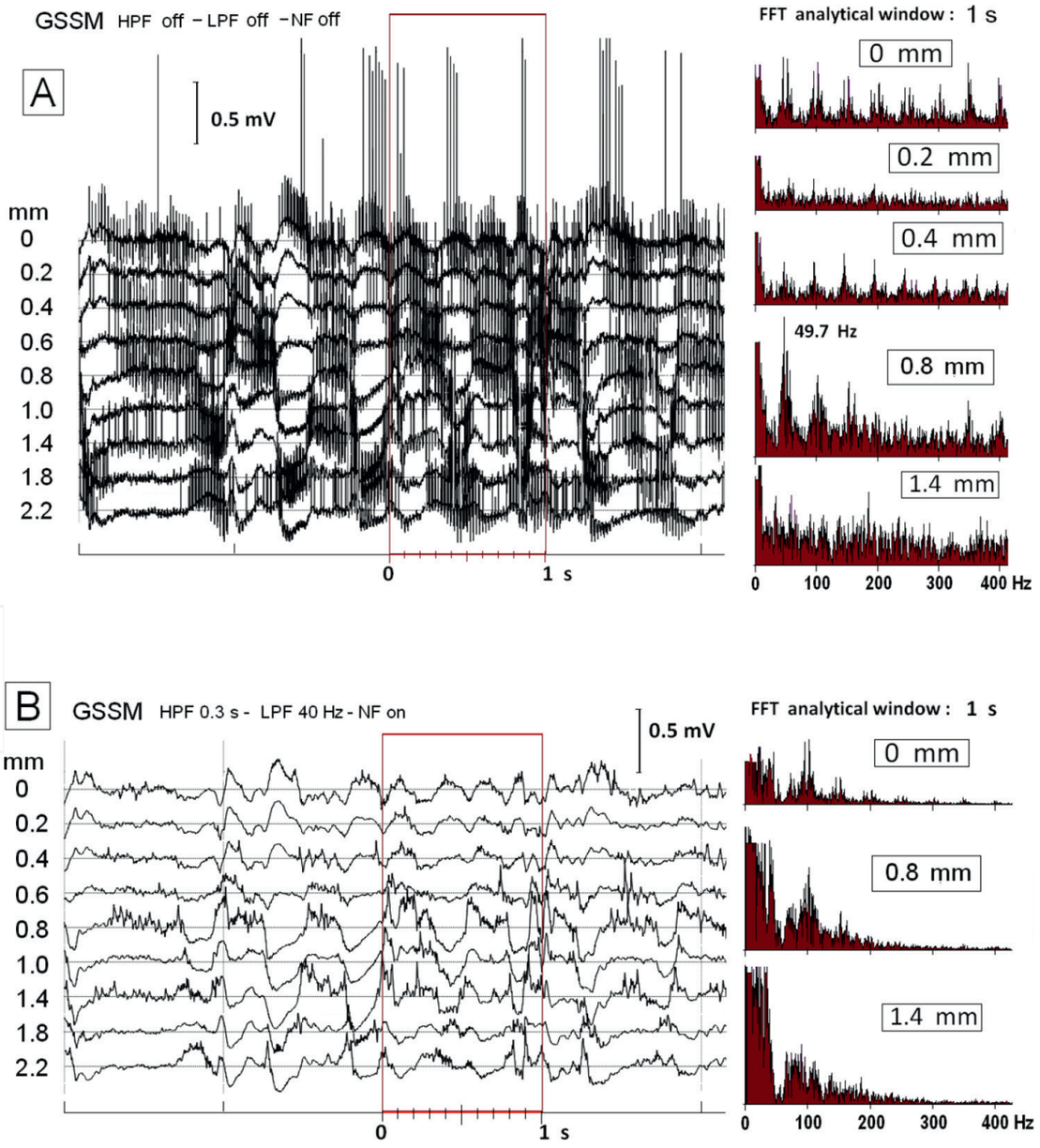

Figure 3.
(A, B). Pattern of IcEEG with greatly intensified appearance of the cellular discharges.

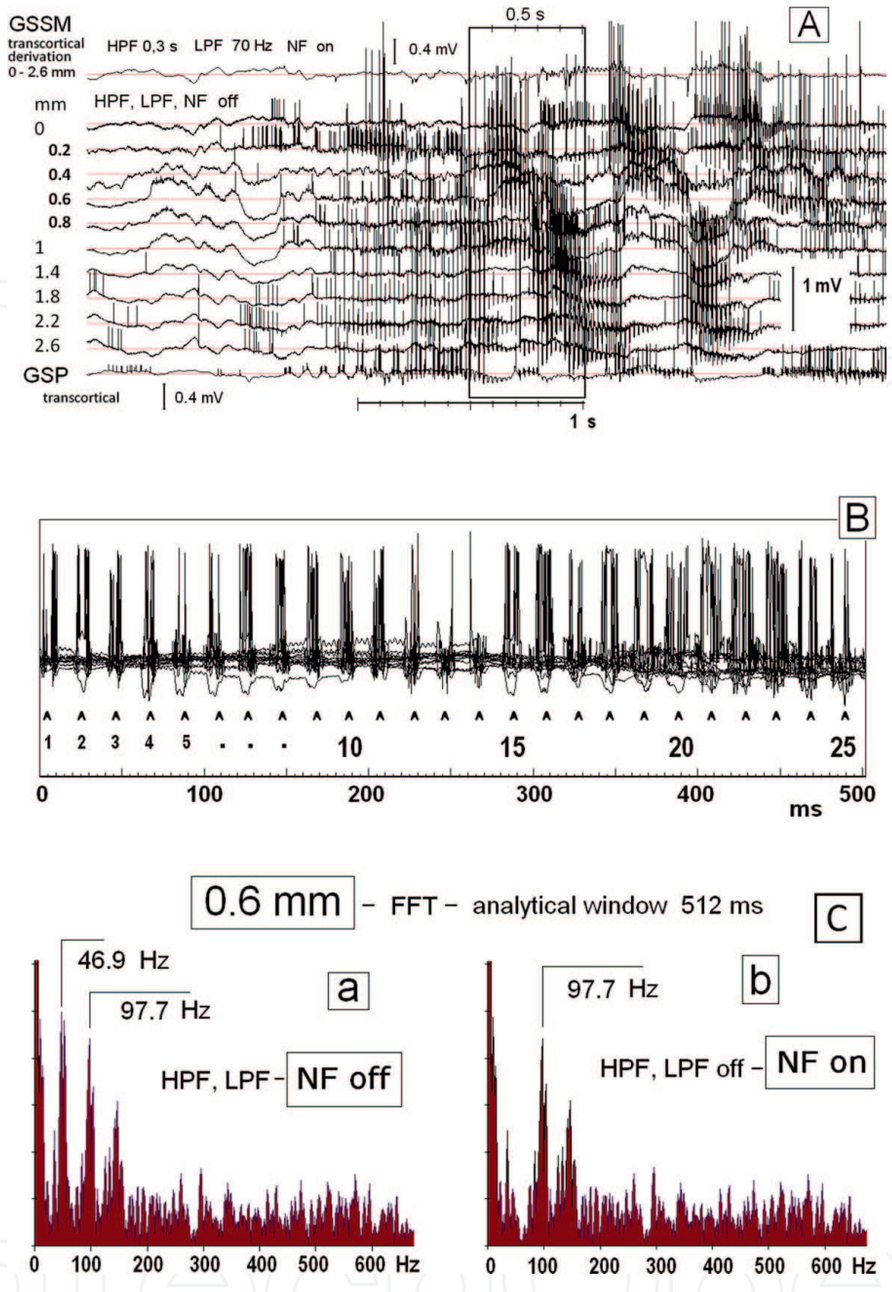

Figure 4.
(A, B, C). Results of visual evaluation of the organization of activity of the cortical generators of the cellular dischages: (A) - IcEEG record with indicated selected fragment illustrating great intensity of spreading cellular dischages (analytical window of 512 ms duration). (B) - after superimposition of all records from the GSSM presented in analytical window - existence of the pattern of rhythmical appearance of the groups of discharges. (C) - results of frequency analysis of the EEG record (in the window) from the depth of 0.6 mm.

existence of great rhythmicity of cellular discharges. There is a prominent peak around 50 Hz, especially evident at the depth of 0.8 mm (49.7 Hz). This indicates a strong rhythmic pattern in the cellular activity within that frequency range.

Figure 3B clearly indicates that the discharges were superimposed on IcEEG patterns of slow wave sleep (SWS). Ripples are very evident, even in conditions of using LPF at the level of 40 Hz. Although the first peak is cut off in the frequency spectrum, the second peak at about 100 Hz is present.

Existence of rhythmicity of the cellular discharges is apparent also during visual evaluation of the EEG record.

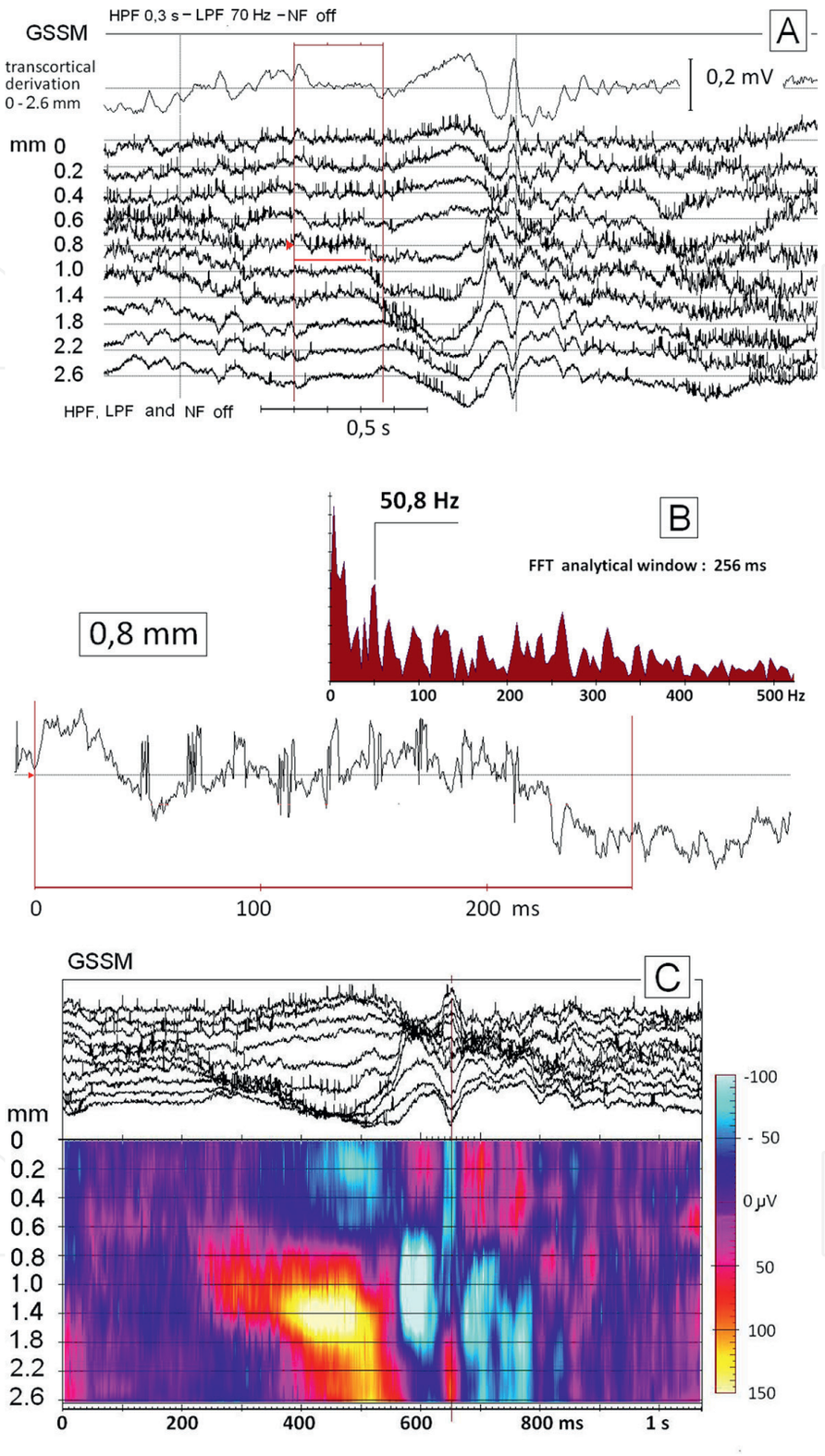

Figure 5.
(A,B,C). Intracortical composition of the bioelectrical patterns coexisting during appearance of the spontaneous discharge of the complex of slow wave and spike, appearing in conditions of IME.

Figure 4(**A**-**C**) illustrates results of evaluation of the selected fragment of the IcEEG recorded 3 weeks after electrode implantation. This fragment represents pattern of cortical activity at the stage of slow wave sleep with a tendency of transferring to REM sleep.

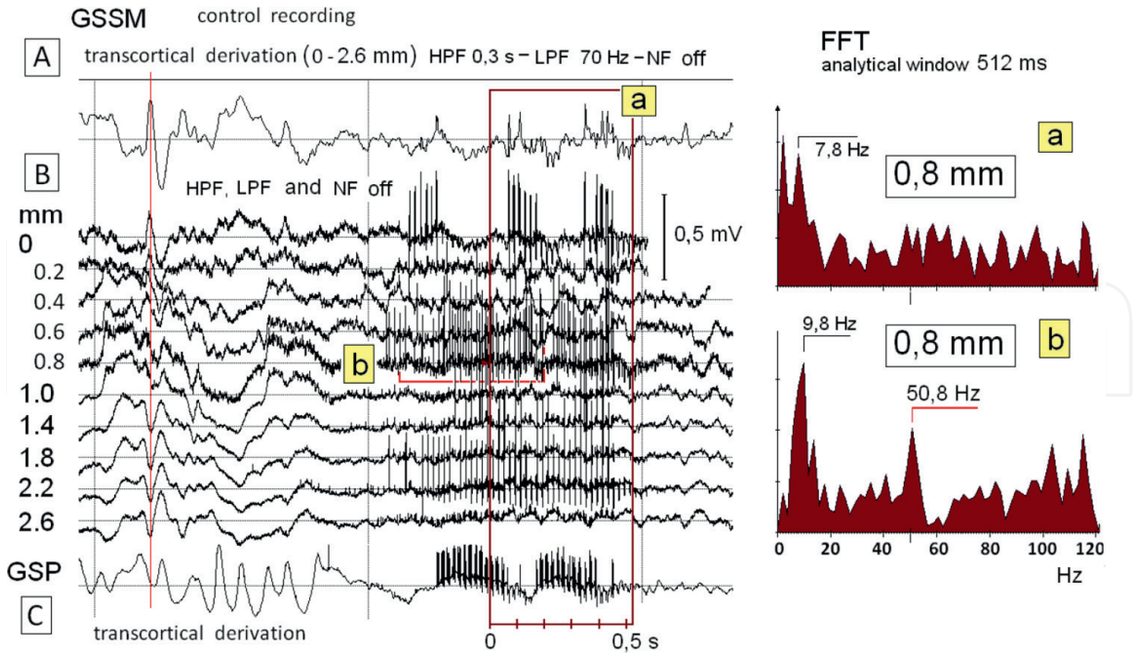

Figure 6.
Illustration of independency of appearance of the EEG spike and cellutar discharges and generalization of discharges in different cortical areas: dischages are present in GSSM as well as GSP records.

Figure 4A illustrates existence of cellular discharges not only in the association cortex (GSSM) but also in somatosensory cortex (GSP). Interestingly, the distribution of these discharges in the somatosensory cortex appears to be independent of the pattern of activity observed in the GSSM. The first channel: transcortical derivation (between the surface and deep electrode: 0–2.6 mm) presents cortical ripples appearing with the intensity much lower in comparison to the deep cortical layers. **Figure 4B** presents the global pattern of the cortical discharges seen after superimposition of all patterns of the cortical activity of EEG fragment indicated on the EEG record. The number of complex structures of the bursts of discharges is about 25 during the period of 512 msec. This is in agreement with the presence of frequency peak seen in the results of FFT evaluation of the EEG record—at the frequency of 46.9 Hz (**Figure 4C**). This peak is absent in conditions of using notch filter (NF on) during EEG recording.

Figure 5(**A**-**C**) illustrates appearance of the spontaneous spike following slow wave recorded in conditions of IME. Both, slow wave and spike are with phase reversal between surface and deep structures of neocortex—negative on the surface. Numerous scattered cellutar spikes can be observed across all cortical layers, indicating cortical activity. Although, there are no high amplitude discharges present in the recorded data. However, transient 50 Hz rhythmic activity is present, especially at the level of 0.8 mm (**Figure 5B**), spreading in deeper and more superficial derivations during development of deep intracortical positivity of the slow wave. Exact evaluation of the intracortical localization of the functional elements appearing during development of the surface negative spike is possible during presentation of this IcEEG fragment as a spatio-temporal map (**Figure 5C**). Presence of the surface negative spike appears to be a consequence of previously appearing intracortical negativity, mainly at the depth of 0.8–1.4 mm.

Figure 6 illustrates transient appearance of the 50 Hz rhythm in frequency spectrum of the burst of high amplitude discharges appearing, during control recording after testing brain activity in conditions of PME. During the burst, there is a tendency

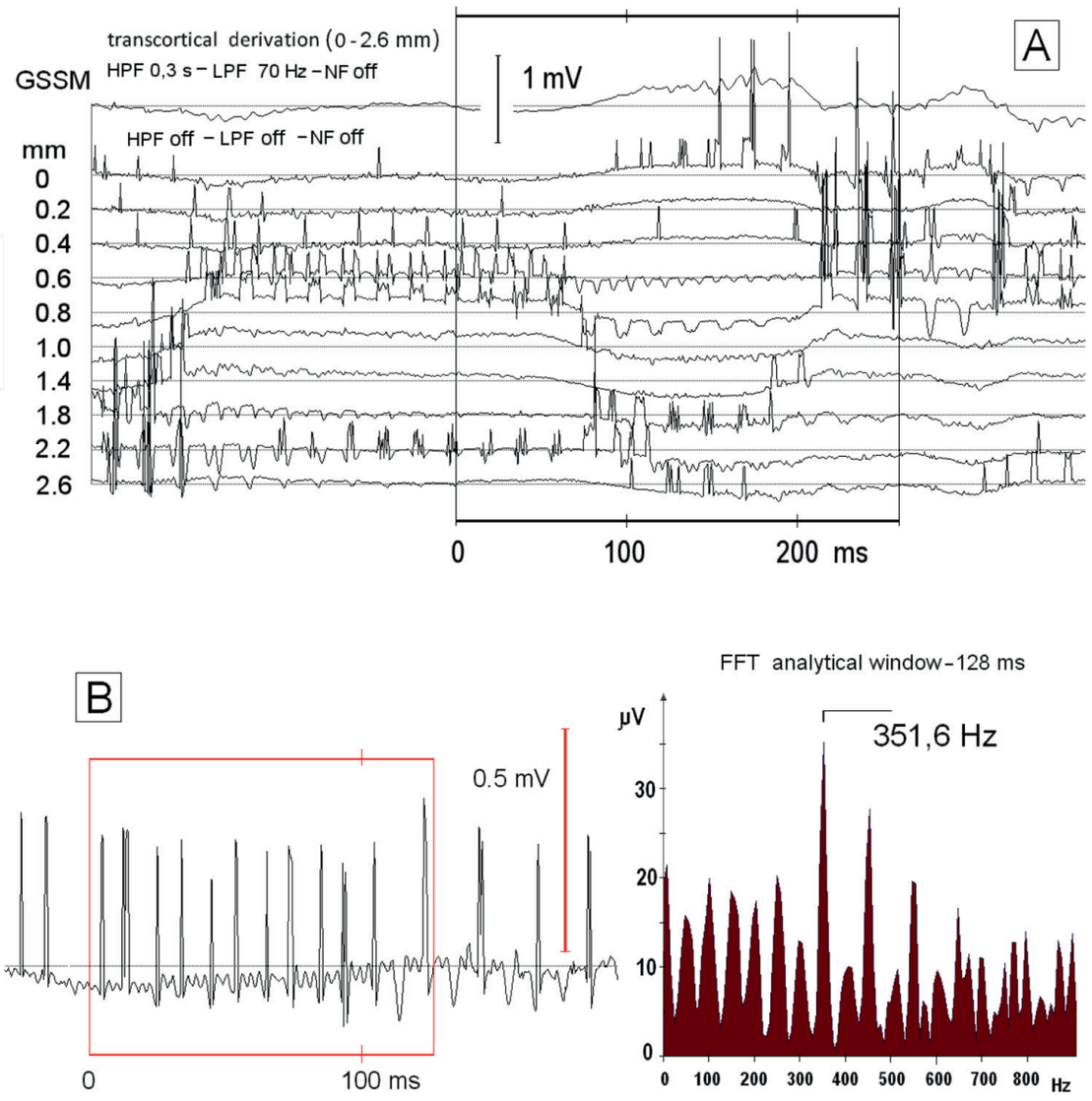

Figure 7.
(A,B). Patterns of the components of selected IcEEG samples, participating in formation of groups of the cortical cellular discharges. (B) illustrates possibility of identification of the origin of high frequency oscillations - frequency about 350 Hz - during visual evaluation of EEG records.

for the pattern of IcEEG to become desynchronized. The burst is preceded by single EEG spike.

Figure 7(A, B) illustrates composition of the bioelectrical patterns that reflect the functional states of the elements within the intracortical cellular network engaged in producing HFOs. These patterns exhibit various frequencies, with a basic rhythm of approximately 50/s of the complexes of one or two groups of spikes of low and high amplitudes, lasting about 10 ms. The highest frequencies observed in the low amplitude rhythmic activity are about 300/s.

Figure 7B illustrates a selected sample of EEG with rhythmic high amplitude spikes. The spikes, or groups of spikes, are spaced approximately 10 ms apart, creating a regular pattern. Additionally, there is a presence of fast, low amplitude waves (about three waves in a period of 10 msec.). The analytical system identifies two rhythmic patterns in the EEG data. The first pattern has leading frequencies at about 50, 100, 150, 200, 250 Hz, and so on. The second pattern shows the first peak at

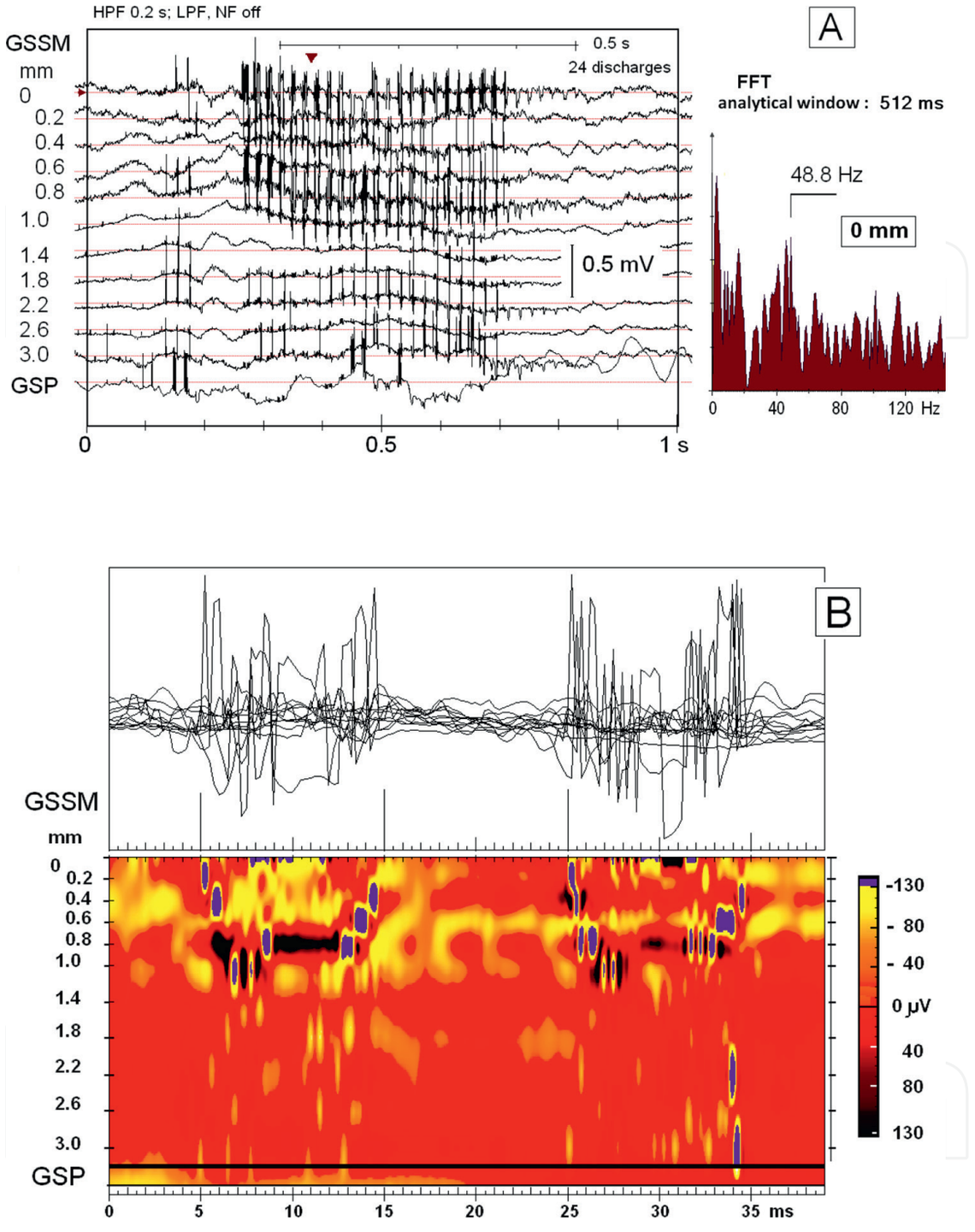

Figure 8.
(A,B). Results of analysis of the spatio-temporal organization of the composition of the elements creating group of cellutar discharges. Selected fragment is indicated on the IcEEG record illustrated in **Figure 8**(**A**).

351.6 Hz. These frequency components represent the recurring rhythms observed in the recorded EEG signal. The compositions of these elements are more precisely presented in **Figure 8**(**A**, **B**).

Figure 8(A, B) illustrates presence of the group of complexes of spikes (about 24 groups in a period of 500 msec.), appearing especially in superficial cortical layers. The leading frequency of the components in the frequency spectrum is 48.8 Hz

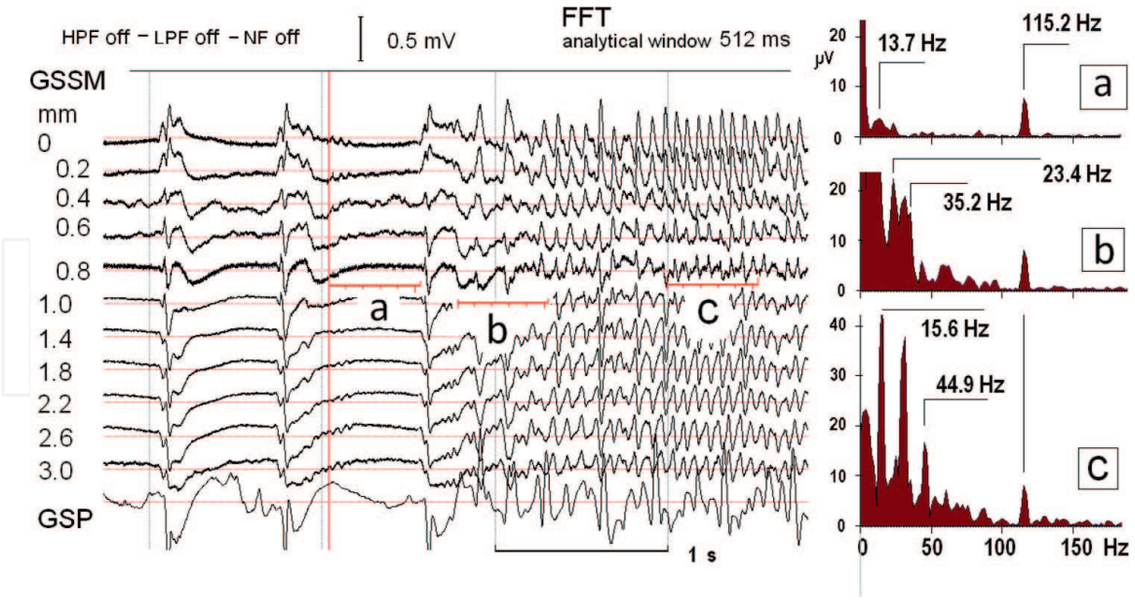

Figure 9.
Transition of the IcEEG pattern to bioelectrical seizure after epicortical injection of penicillin in conditions of general anaesthesia (PME).

(in derivation 0 mm), cohesive with the number of the group of spikes detected during visual evaluation of the EEG record.

Figure 8B presents spatio-temporal composition of the elements within the circuits of the two groups of spikes and existence of low amplitude fast oscillation (between groups of spikes).

Figure 9 illustrates onset of a bioelectrical seizure in the cortical structure of the same animal. The seizure is recorded after the epicortical administration of penicillin, while the animal is under general anesthesia caused by pentobarbital. There are no signs of high amplitude discharges. It may be suspected, that the electrical noise dominating in channels 0 to 0.8 mm reflects 50 Hz artifacts caused by the widespread electrical field or muscular (EMG-electromyographic) artifact. However, the results obtained from the frequency analysis (FFT) clearly illustrate the organization of the observed pattern. In fragment (b), frequency ranges correspond to the frequencies of waves observed in the EEG record (low amplitude waves seen at the beginning of the seizure (20–30 Hz). Surprisingly, fast oscillations (peak frequency 115.2 Hz) are detected at all stages (a, b, c) of analysis.

Figure 10(**A**-**C**) illustrates fragment of the EEG record confirming existence of the complex, basically 50 Hz pattern of cellular activity recorded in another animal, after epicortical injection of penicillin. The effects of this procedure were tested in conditions of deep anesthesia, after administration of pentobarbital.

Figure 10A illustrates fragment of the IcEEG record, typical for EEG patterns existing between bioelectrical seizures: existence of single, high amplitude surface negative sharp waves, with suppression of EEG rhythmic activity between their discharges. Comparison of intracortical, vertical distribution of the patterns of discharges illustrates existence of phase reversal of the main, surface negative component (negativity dominates in two superficial derivations – from the depth 0 and 0.2 mm, with clear positivity, especially at the levels of 1.4, 1.8, and 2.2 mm). This findings confirm the probability that localization of this electrode reflects activity of the cortical cells with localizations at the supra-granular (L3), granular L4, and

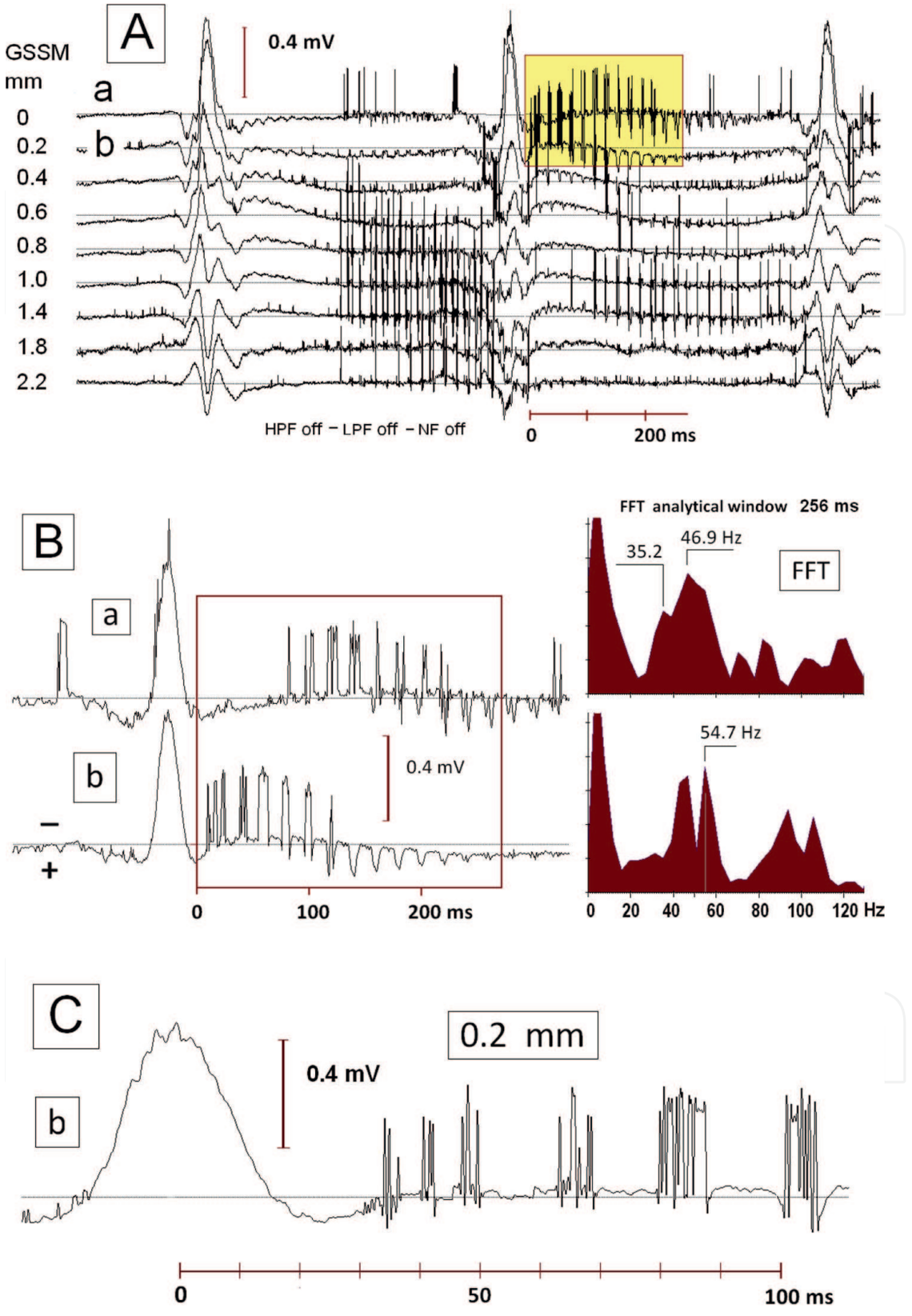

Figure 10.
(A,B,C). Cellular and EEG patterns recorded between consecutive epileptiform seizures in anaesthetized animal (PME).

infra-granular (L5 and L6) layers of the cerebral cortex. Groups of cellular discharges are present between discharges of sharp waves.

Figure 10B illustrates more accurately compositions of the EEG fragment indicated on the record presented in **Figure 10A**: derivations 0 mm (a) and 0.2 mm (b). The main frequencies reflecting cellular activity are between 40 and 60 Hz. **Figure 10C** [b] illustrates existence of groups of numerous spikes reflected as single waves in records presented in **Figure 10B** [b].

4. Conclusion

The presented results of this investigation illustrate complexity of the process of epileptogenic functional reorganization of the cortical activity. Presented illustrations suggest possibility of existence of the EEG pattern reflecting functional state of the intracortical cellular network, relatively independent from the cellular activity of the neuronal systems engaged in formation of the conventional, normal, and abnormal EEG patterns. Functional patterns reflecting activation of this system are presented in wide frequency spectrum of the cortical electrical activity: within the range of gamma and higher frequencies (HFOs), with the basic frequency of activity in gamma frequency range (40–60 Hz). Interdisciplinary approach is necessary in explaining the background and significance of demonstrated phenomenon.

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