

**BASIC CHARACTERISTICS OF EPILEPTIFORM
DISCHARGES TRIGGERED BY LINDANE IN RATS****OSNOVNE KARAKTERISTIKE EPILEPTIFORMNIH
PRAŽNJENJA IZAZVANIH LINDANOM KOD PACOVA**

Nemanja Useinović¹, Marko Vorkapić¹, Aleksa Leković¹, Anida Ademović¹, Nikola Šutulović¹, Željko Grubač¹,
Aleksandra Rašić Marković¹, Dragan Hrnčić¹, Olivera Stanojlović¹

¹University of Belgrade, Faculty of Medicine, Institute for Medical Physiology "Richard Burian", Laboratory for Neurophysiology, Belgrade, Serbia

Correspondence: solja@afrodita.rcub.bg.ac.rs

Abstract

Introduction: EEG is a widely used method of epilepsy examination. In order to quantitatively inspect ictal EEG findings, a number of mathematical models have been developed over the years, one of them being the Fast Fourier Transform (FFT). It transforms the signal from time domain into frequency domain, giving information about their power spectral densities (PSD). Lindane is a well-established neurotoxic agent often used in experimental studies as a model of generalized epilepsy. This study aims to quantitatively examine the characteristics of ictal EEG activity in rats on model of generalized epilepsy induced by lindane.

Materials and Methods: Wistar albino rats were used for the study. Electrodes were surgically implanted over the frontal, parietal and occipital cortices of each animal for EEG recording purposes prior to lindane administration in convulsive dose. An 8-channel EEG apparatus was used, combined with a software developed in the Laboratory (NeuroSciLaBG). Ictal EEG epochs were extracted from the original signal and FFT analysis performed to obtain information considering PSD in predefined frequency bands. Amplitude histogram feature of the software was used to differentiate ictal spikes based on their voltage.

Results: FFT analysis has yielded important information regarding spectral powers in frequency domain. Ictal EEG showed considerable stratification, theta frequency band (4-7 Hz) being markedly dominant. Amplitude histogram showed the majority of spikes to be in the voltage ranges up to 250 μ V, while higher voltage spikes were rarely observed.

Conclusion: FFT is capable of giving important information about ictal period characteristics. Ictal periods induced by lindane are characterized by dominance of theta rhythm and spiking activity mostly in amplitude bins up to 250 μ V. FFT and amplitude histograms can be of critical importance in the future pharmacological and toxicity studies.

Keywords:

seizures,
EEG,
FFT,
lindane,
rats



Sažetak

Uvod: EEG se široko primenjuje prilikom ispitivanja epilepsija. U cilju kvantitativnog ispitivanja iktalnih EEG nalaza, veliki broj matematičkih modela je razvijen tokom godina, među kojima je i Brza Furijeova Transformacija (engl. *Fast Fourier Transform – FFT*). Ona transformiše signal iz vremenskog domena u frekventni domen, dajući informacije o gustini spektralne snage (engl. *Power Spectral Densities – PSD*). Lindan je dobro poznat neurotoksični agens koji se često koristi u studijama kao model generalizovane epilepsije. Cilj ove studije je da se kvantitativno ispituju karakteristike iktalne EEG aktivnosti kod pacova na modelu generalizovane epilepsije indukovane lindanom.

Materijal i metode: Albino pacovi soja Wistar su korišćeni u studiji. Elektrode su hirurški implantirane nad frontalnim, parijetalnim i okcipitalnim korteksima svake životinje u cilju registrovanja EEG-a pre administracije lindana u konvulzivnoj dozi. EEG aparat sa 8 kanala je korišćen, kombinovan sa softverom razvijenim u laboratoriji (NeuroSciLaBG). Iktalne EEG epohe su izdvojene iz originalnog signala i FFT analiza primenjena da bi se dobile informacije o PSD u definisanim frekventnim opsezima. Amplitudni histogram je korišćena da razdvoji iktalne šiljke na osnovu napona.

Rezultati: FFT analiza je dala važne informacije kada je reč o spektralnim snagama u domenu frekventnosti. Iktalni EEG je pokazao primetno raslojavanje, sa dominantnošću teta frekventnog opsega. Amplitudni histogram je pokazao da je većina šiljaka u naponskim opsezima do 250 μ V, dok su šiljci višeg napona retko opservirani.

Zaključak: FFT je sposobna da pruži bitne informacije o karakteristikama iktalnih perioda. Iktalne periode izazvane lindanom karakteriše dominacija teta ritma i šiljate aktivnosti u amplitudnim opsezima do 250 μ V. FFT i amplitudni histogrami bi mogli biti od kritičnog značaja u budućim farmakološkim i toksikološkim studijama.

Ključne reči:

epilepsija,
EEG,
FFT,
lindan,
pacovi

Introduction

About 0.5-1% of general population suffer from epilepsy, chronic neurological condition (1). While recurrent seizures are considered to be the hallmark of epilepsy, seizures are also commonly caused by a wide array of nervous system pathology, such as: cerebrovascular diseases, tumors, neurodegenerative conditions, infections and trauma (2,3). Stigmatizing as it may be, it has a serious impact on somatic and psychological well-being of both the sufferers and the caregivers (4). It bestows a great deal of financial burden upon the families of the patients, up to the point of social isolation (5).

Electroencephalography (EEG) is a convenient and most widely used tool for diagnosis, classification, localization of epileptogenic zone, as well as obtaining data of prognostic value (6,7). During seizures, the brain produces activity patterns recognizable on EEG, which markedly differ from those of a normal brain (8,9). Despite its popularity, EEG recording has a number of pitfalls: the recorded electrical activity represents the summation of excitatory and inhibitory postsynaptic potential waves rather than individual neuronal currents, thus requiring large areas of cortex to be simultaneously active to produce detectable amount of current (10), it does not preclude the diagnosis of epilepsy, nor does it exclude the possibility of one's suffering from it (11). Unless viewed in light of clinical findings, EEG findings are of questionable value in prognosis and guiding the therapy.

Having in mind the aforementioned limitations of simple visual EEG recording inspection, numerous of mathematical methods for EEG evaluation have been

developed over the years. The oldest decomposition method is the Fourier analysis. Fast Fourier Transform (FFT) converts an EEG signal from time domain into a frequency domain. It is a rather popular analysis in computational neuroscience because of the information about EEG tracings it provides, namely the frequency specters and the power spectral densities of EEG signals, making it of paramount importance in modern era of signal processing brought about by technical revolution.

γ -hexachlorocyclohexane, also known by the name lindane, is a well established human carcinogen (12). By its chemical structure, lindane is an organochloride, compounds commonly used as insecticides, notorious for their capability of causing severe toxicity in humans alike (13). Since the 1950s, it has been used in clinical practice for the treatment of scabies and pediculosis, and these still remain the only medical indications for lindane (14,15). The first described case of lindane toxicity and death emerged in 1953 (16). Lindane is neurotoxic agent, and the proposed mechanism by which it exerts its deleterious effects on human brain is by interaction with GABA A receptors (17,18) as well as via NO-mediated signaling (19). Experimental model of general epilepsies caused by lindane is a well established one (20). In lindane model of epilepsy, lindane is administered intraperitoneally in dose of 8 mg/kg. For purposes of describing behavioral changes, a descriptive scale has been developed, which goes as follows: 1. Head nodding, lower jaw twitching; 2. Myoclonic body jerks, bilateral forelimb clonus; 3. Generalized tonic-clonic convulsions; 4. Status epilepticus (21). This scale has proven to be a convenient one and easy to use.

The aim of this study was to quantitatively examine the characteristics of ictal EEG activity in rats on model of epilepsy induced by lindane.

Materials and Methods

Animals

Adult Wistar albino male rats were used in the experiment (body weight 220-250 g). The animals were purchased from local certified supplier (Military-Medical Academy Breeding Laboratories, Belgrade, Serbia). Animals were kept in plexiglass cages (55 x 35 x 30 cm). They were allowed food and tap water ad libitum throughout the experiment. Rats were caged under controlled laboratory conditions (ambiental temperature 22-24 °C, air humidity 50 ± 5%, 12/12 light-dark cycle, with light starting at 8 am till 8 pm). Animals had one week prior to the experiment to adapt to laboratory conditions. Each animal was used only once in course of experiment.

All the experimental procedures were in full compliance with Ethical Guidelines for Work with Animals of Belgrade University Faculty of Medicine.

Surgery and EEG records

In order to implant EEG electrodes, rats were anesthetized with pentobarbital sodium (50 mg/kg, i.p.). Rats were placed in stereotaxic apparatus and three gold-plated electrodes were implanted over the frontal, parietal and occipital cortex and fixed using dental cement. Recovery period lasted for one week. Animals were connected to EEG device via flexible cables. Output signals were directly recorded on computer hard disc with corresponding software (NeuroSciLaBG, Belgrade, Serbia) and installed chip card for EEG monitoring.

Experimental design

The experimental group comprised 6 animals. The animals were placed in separate transparent plexiglass cages (55 x 35 x 15 cm) and EEG tracings were obtained over a 30 minutes observational period following the administration of lindane (8 mg/kg intraperitoneally, Sigma-Aldrich Chemical Co, U.S.A.) dissolved in dimethylsulfoxide (DMSO, Sigma-Aldrich Chemical Co, U.S.A.) and injected in a volume of 0.5 ml/kg body weight.

An 8-channel EEG apparatus (RIZ, Zagreb, Croatia) was used. The signals were digitized using a SCB-68 data acquisition card (National Instruments Co, Austin, TX, USA). A sampling frequency of 512 Hz/channel and 16-bit A/D conversion were used for the EEG signals. The cutoff

frequencies for the EEG recordings were set at 0.3 and 100 Hz for the high-pass and low-pass filters, respectively. Ambient noise was eliminated using a 50 Hz notch filter. Data acquisition and signal processing were performed with the LabVIEW platform software developed in our Laboratory of Neurophysiology (NeuroSciLaBG).

The recordings were examined and ictal activity epochs extracted, ictal activity being defined as having the duration of > 1 sec and amplitude at least twice the background EEG activity. Each of the extracted epochs were thereafter analyzed using the Fast Fourier Transform (FFT) to obtain information regarding their total spectral power, as well as spectral power in delta, theta, alpha and beta frequency domains in relation to total power. The domains were defined as follows: 0.5-4 Hz delta, 4-7 Hz theta, 7-15 Hz alpha and 15-30 Hz beta. Duration of each ictal period was also measured and analyzed.

EEG spikes were differentiated based upon their respective voltages and distributed into one of the 22, 50 µV-bean-size interval groups (ranging between -550 and +550 µV) by the Amplitude Histogram Feature Function of NeuroSciLaBG program.

Data analysis

In order to determine the statistical significance of our results, one-way ANOVA test followed by Fischer's LSD post hoc test was performed for multiple comparisons. The duration of epochs, peak frequencies and power spectral densities obtained via FFT analysis were expressed as mean value, standard error and min-max range. Fractions of total power spectral densities corresponding to individual frequency bands were expressed on a percentage scale as Mean ± SE in a 95% confidence interval. As criteria for statistical significance *p < 0.05 and **p < 0.01 were applied.

Results

Basic features of ictal EEG epochs has been presented in **Table 1**. The mean duration of the ictal period was 7.34 ± 1.56 s, and peak frequency 5.12 ± 0.18 Hz. Total power spectral density of these epochs was 6042.41 + 674.42 µV²/Hz.

The results of the FFT analysis have shown that, at times of ictal EEG activities, the dominant activity was in the range of theta rhythm (p < 0.01, **Figure 1**). Furthermore, comparing each of the four standard frequency bands (delta, theta, alpha, beta), statistical significance was obtained between each of them compared to any other rhythm pattern, reflecting the significant stratification of EEG activity during the ictal periods (see also statistical report

Table 1. Features of EEG ictal periods induced by lindane in rats. For each of the extracted ictal EEG epochs, duration was noted and Fast Fourier Transform (FFT) analysis performed.

Parameter	Mean	Standard Error	Min-Max
Duration (s)	7.34	1.56	1.14-72.80
Peak Frequency (Hz)	5.12	0.18	0.06-7.52
Total Power Spectral Density (µV ² /Hz)	6042.41	674.42	890.53 - 30832.50

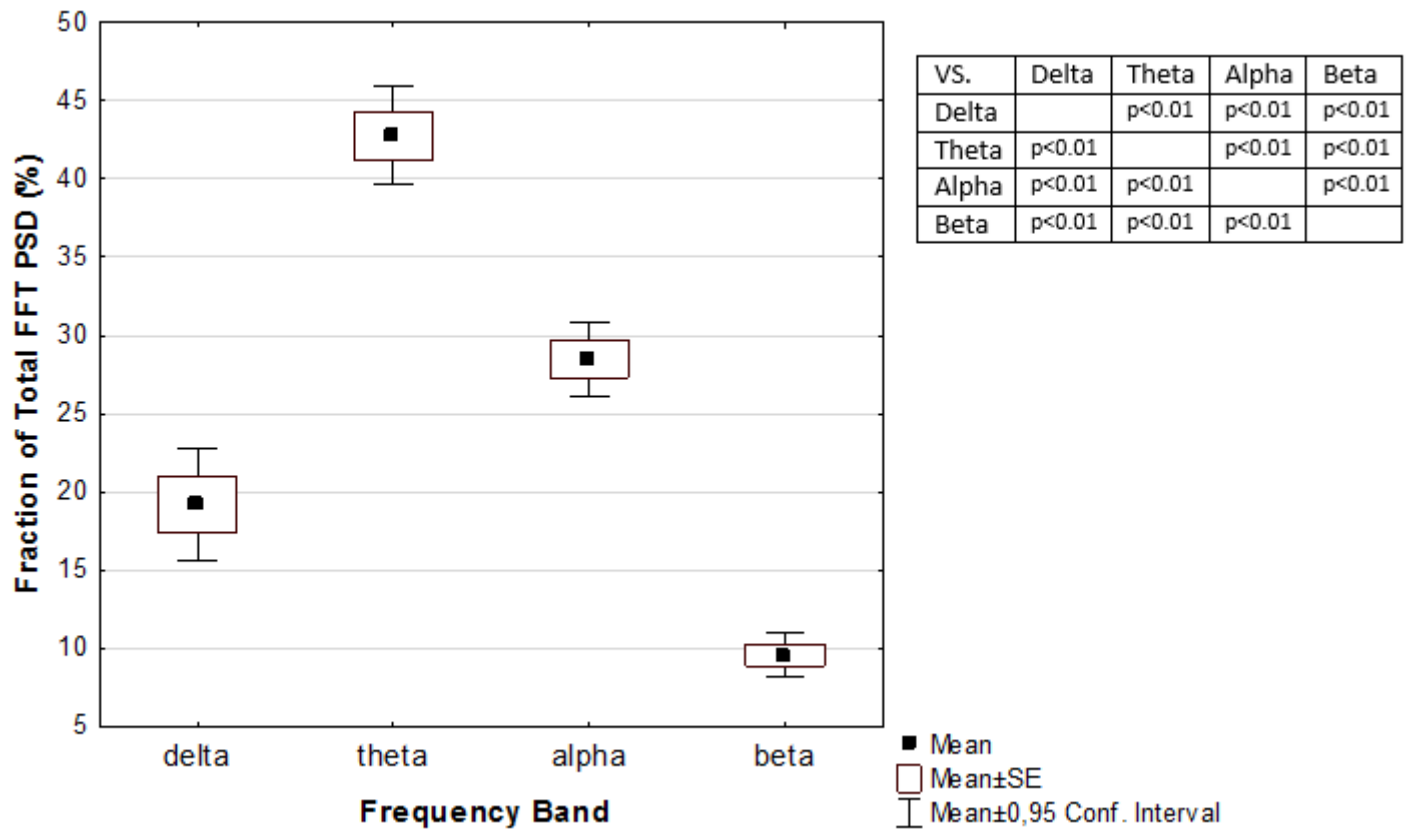


Figure 1. Relative power spectral densities (PSD, %) of individual frequency bands of ictal periods induced by lindane, as a percent of total. (Table to Figure 1).

matrix table to **Figure 1**).

Significances of differences in PSD were determined by one-way ANOVA followed by Fischer’s LSD test and results are presented in statistical matrix table to figure panel.

Analysis of the 50 μ V-bean intervals between 100 and 500 μ V has been shown in the form of amplitude histogram in **Figure 2**. It appeared that a vast majority of the spikes were in lower amplitude ranges (notably 100-150 and 150-200 intervals), whereas 350-400 μ V interval and above were infrequently observed. Statistical analysis and comparison between individual intervals is also shown in statistical report matrix table to **Figure 2**.

Statistical significance of difference in the number of separate 50 μ V-bin intervals was obtained using one-way ANOVA followed by Fischer’s LSD test and the results are shown in statistical matrix table to figure panel.

Discussion

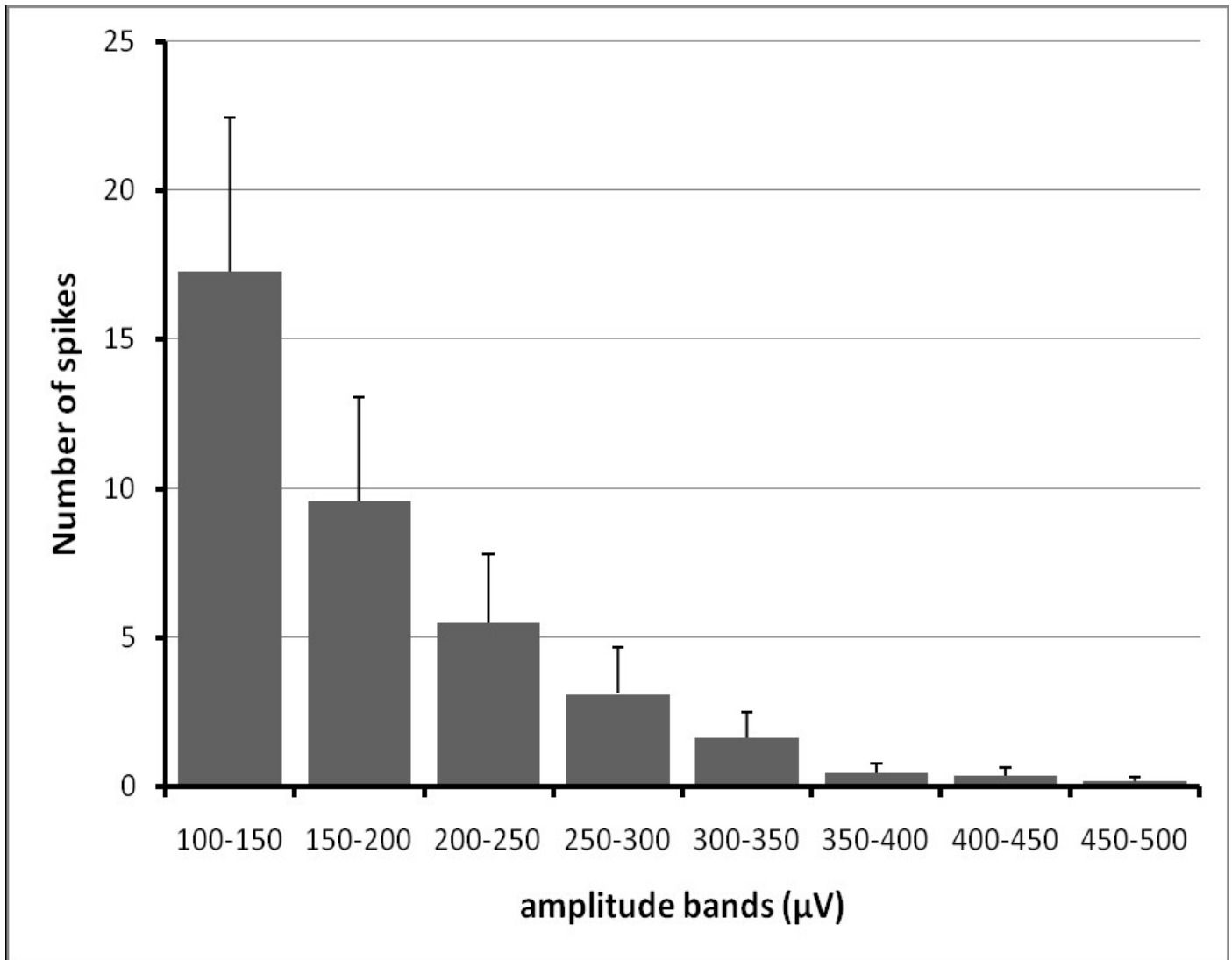
Quantitative electroencephalography is a rapidly evolving field, FFT being just one of many analysis used to study signals. It transforms EEG signal from time to frequency domain and gives information regarding spectral powers of individual frequency bands. Considering the fact that higher spectral densities are correlated with higher energy, spectral density values could give important information about the severity and the extent of abnormal brain functioning, the pathophysiological basis of seizures. The main downside of FFT is its complete lack of temporal

distinction; while providing much detail about signal frequencies, the inability to infer the exact moment when a particular sequence has happened underlines the necessity to develop other algorithms for quantitative EEG analysis.

One important point that merits brief discussion is the fact that performing FFT analysis, which assumes the stationarity of signal being analyzed, is in collision with the brain EEG waves, which do not comply to the stationarity principle. Nevertheless, this point is mostly overcome by the design of this study in two ways: first, FFT can be regarded as a bidirectional analysis, which means that the original signal form can be readily restored, as there is no data loss in the process itself, and second, the mean ictal epoch duration of 7.34 ± 1.56 s, which were used in this research (see **Table 1**), brings the signal close enough to enable FFT to be applied, as also holds true for signals of progressively shorter duration (22,23).

According to the results of this study, during the ictal periods there is a marked slowing of the EEG patterns, reflected by the predominance of theta and delta waves compared to alpha and beta. Power spectral densities of individual frequency bands calculated using the FFT concluded that the dominant frequency band was theta, while beta had the least power (as shown in **Figure 1**).

Previous studies of epileptic spasms have managed to describe three different patterns of ictal EEG: 1) high frequency oscillations preceding spasms, 2) slow activity waves and 3) desynchronization of electrical activity (24). This is in keeping with the results of our study, which



vs.	100-150	150-200	200-250	250-300	300-350	350-400	400-450	450-500
100-150		p = 0.02	*p = 0.04	**p < 0.01	**p < 0.01	**p < 0.01	**p < 0.01	**p < 0.01
150-200	p = 0.21		p = 0.33	p = 0.09	*p = 0.03	**p = 0.01	**p < 0.01	**p < 0.01
200-250	*p = 0.04	p = 0.33		p = 0.4	p = 0.12	*p = 0.03	*p = 0.03	*p = 0.03
250-300	**p < 0.01	p = 0.09	p = 0.4		p = 0.41	p = 0.1	p = 0.09	p = 0.07
300-350	**p < 0.01	*p = 0.03	p = 0.13	p = 0.41		p = 0.19	p = 0.15	p = 0.09
350-400	**p < 0.01	**p = 0.01	*p = 0.04	p = 0.1	p = 0.19		p = 0.85	p = 0.43
400-450	**p < 0.01	**p < 0.01	*p = 0.03	p = 0.09	p = 0.15	p = 0.85		p = 0.51
450-500	**p < 0.01	**p < 0.01	*p = 0.03	p = 0.07	p = 0.09	p = 0.43	p = 0.51	

Figure 2. Number of spikes in ictal period induced by lindane in 50 μV-size amplitude bins. Spikes from the extracted EEG epochs were differentiated into 50 μV-bin intervals using the Amplitude Histogram Feature Function of NeuroSciLaBG program. Only those of voltage 100 μV and higher were analyzed.

discovered a large proportion of slow activity waves during ictal periods. Of what importance it might be when it comes to clinical practice, remains a challenging question.

When it comes to the delta waves, those have long been interpreted as a reflection of brain plasticity and memory consolidation during the NREM phase of sleep (25,26). Brain plasticity is a process often present in the background of an organic brain damage. Delta wave activity is correlated to both the size of organic lesion, as well as the chance for recovery (27,28). The spectral power of

delta waves elucidated by the FFT in this study could be a predictor of extent and severity of epileptogenic activity, although definite conclusions are difficult to make at this point.

Theta waves are normally present in human brain in two locations: one is a hippocampal oscillatory rhythm, and the second one can be recorded from cortex, named cortical theta rhythm. Theta waves function is not fully understood, although it is often said to play important role in arousal (29) and memory formation (30). As the latter

study claims, decrease in theta power is the single most consistent finding at times of memory formation. Since theta waves were consistently the dominant fraction for most, if not all the ictal periods we analyzed for this study, it could be argued that the rise in power of theta waves is the EEG representation of impairment of consciousness and a degree of amnesia regarding the time of seizure itself, as is generally noticed while dealing with the patients suffering from seizures. Relatively low power of high-frequency bands might also contribute to memory issues (31).

Studies regarding EEG total power spectral densities, as well as spectral densities of individual frequency bands is a concept not strictly confined to epilepsy, but also widely applicable to studies of Alzheimer's disease and generalized anxiety disorder (32,33). The study about Alzheimer's disease has noted reduction in high-frequency and increase in low-frequency bands, much like the results this study yielded.

The reason for observed power spectral changes is not clear. A possible explanation might be that lower high-frequency power is a result of transient loss of connections between different parts of cortex, while high low-frequency power has its origins in loss of subcortical cholinergic input, much like what has already been hypothesized in patients with Alzheimer's disease (34, 35). The importance of characterization of ictal periods in frequency domain lies in the possibility of using such parameters in advance-level biosignal analysis and development of software capable of automatic detection and prediction of seizures by setting a starting point for such innovative creations and establishing baseline values.

In this study we also differentiated EEG spikes based on their respective voltage. Most of the positive-end voltage spikes were in the range from 100 to 200 μV , those from 200 to 350 μV were moderately present, whereas those from 350 to 500 μV were noted only occasionally. Whether the distribution of spikes according to their voltage such as this one can be used to estimate the severity of seizure, or could it be considered an important parameter in terms of diagnosis and treatment of seizures, is a question yet to be answered. It has a great potential of finding its place in both the antiepileptic therapy studies, should it reveal the decrease in high-voltage spikes in treated group compared to controls, as well as toxicology studies, if the potentiation of high-voltage spikes is the observed phenomenon.

Conclusion

Fast Fourier Transform is a pioneering mathematical analysis in the era of computational neuroscience, developed in response to the ever-growing need of more sophisticated methods of EEG analysis. It can provide important data required in order to investigate seizures and diagnose epilepsy. Prompt and accurate diagnosis of epilepsy will aid significant portion of mankind in their combat with this vile malady. In this study we have defined the features of ictal periods induced by lindane in rats.

Acknowledgement

This work was supported by the Ministry of Education, Science and Technological Development of Serbia (grant #175032).

References

1. Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. *Lancet* 2006;367:1087–100.
2. Stephen LJ, Brodie MJ. Epilepsy in elderly people. *Lancet*. 2000; 355:1441–6.
3. Singhi P. Infectious causes of seizures and epilepsy in the developing world. *Dev Med Child Neurol*. 2011;53(7):600-9
4. Saada F, Wang ZS, Bautista RE. In focus: The everyday lives of families of adult individuals with epilepsy. *Epilepsy Behav*. 2015;50:10-3.
5. Thompson R, Kerr M, Glynn M, Linehan C. Caring for a family member with intellectual disability and epilepsy: practical, social and emotional perspectives. *Seizure* 2014;23:856–63.
6. Noachtar S, Rémi J. The role of EEG in epilepsy: a critical review. *Epilepsy Behav*. 2009;15(1):22-33.
7. Steinhoff BJ, Scholly J, Dentel C, Staack AM. Is routine electroencephalography (EEG) a useful biomarker for pharmaco-resistant epilepsy? *Epilepsia*. 2013;54 Suppl 2:63-6.
8. Bassett L, Troncy E, Pouliot M, Paquette D, Ascah A, Authier S. Telemetry video-electroencephalography (EEG) in rats, dogs and non-human primates: methods in follow-up safety pharmacology seizure liability assessments. *J Pharmacol Toxicol Methods*. 2014;70(3):230-40.
9. Frost JD Jr, Lee CL, Hrachovy RA, Swann JW. High frequency EEG activity associated with ictal events in an animal model of infantile spasms. *Epilepsia*. 2011;52(1):53-62.
10. Smith SJ. EEG in the diagnosis, classification, and management of patients with epilepsy. *J Neurol Neurosurg Psychiatry*. 2005;76 Suppl 2:ii2-7.
11. Cascino GD. Electroencephalography and epilepsy. *Journal of Epilepsy*. 1996;10:16-23.
12. National Toxicology Program.. Lindane, hexachlorocyclohexane (technical grade), and other hexachlorocyclohexane isomers. *Rep Carcinog*. 2011;12:256-8.
13. Lal R, Saxena DM. Accumulation, metabolism, and effects of organochlorine insecticides on microorganisms. *Microbiol Rev*. 1982;46(1):95-127.
14. Solomon LM, Fahrner L, West DP. Gamma benzene hexachloride toxicity: a review. *Arch Dermatol* 1977;113:353–357.
15. Wilkinson C. Is the treatment of scabies hazardous? *J R Coll Gen Pract*. 1988;38(315):468-9.
16. Danopoulos E, Melissinos K, Katsas G. Serious poisoning by hexachlorocyclohexane. *Arch Ind Hyg Chicago* 1953;8:582–7.

17. Portig J, Schnorr C. The potency of gamma-1,2,3,4,5,6-hexachlorohexane(lindane). *Toxicology* 1988;52:309-21.
18. Aspinwall LS, Bermudez I, King LA, Wafford KA. The interactions of hexachlorocyclohexane isomers with human gamma-aminobutyric acid(A) receptors expressed in *Xenopus* oocytes. *J Pharmacol Exp Ther*. 1997;282(3):1557-64.
19. Hrnčić D, Rašić-Marković A, Djuric D, Šušić V, Stanojlović O. The role of nitric oxide in convulsions induced by lindane in rats. *Food and Chemical Toxicology* 2011; 49: 947-54.
20. Vučević D, Hrnčić D, Radosavljević T, et al. Correlation between electrocorticographic and motor phenomena in lindane-induced experimental epilepsy in rats. *Can J Physiol Pharmacol*. 2008;86(4):173-9.
21. Stanojlović O, Nikolić T, Hrnčić D, Radonjić N, Rašić-Marković A, Mladenović D, Petronijević N. Ontogenetic influence on rat susceptibility to lindane seizure after pretreatment with phencyclidine. *Environ Toxicol Pharmacol*. 2013;35(2):161-70.
22. Stam CJ. Nonlinear dynamical analysis of EEG and MEG: review of an emerging field. *Clin Neurophysiol*. 2005; 116(10):2266-301.
23. Campbell IG. EEG recording and analysis for sleep research. *Curr Protoc Neurosci*. 2009; 49(1):10-2.
24. Honda R, Saito Y, Okumura A, et al. Characterization of ictal slow waves in epileptic spasms. *Epileptic Disord*. 2015;17(4):425-35.
25. Tononi G, Cirelli C. Time to be SHY? Some comments on sleep and synaptic homeostasis. *Neural Plast*. 2012;2012:415250.
26. Assenza G, Di Lazzaro V. A useful electroencephalography (EEG) marker of brain plasticity: delta waves. *Neural Regen Res*. 2015;10(8):1216-7.
27. Assenza G, Zappasodi F, Squitti R, et al. Neuronal functionality assessed by magnetoencephalography is related to oxidative stress system in acute ischemic stroke. *Neuroimage* 2009;44:1267-73.
28. Finnigan SP, Rose SE, Chalk JB. Contralateral hemisphere delta EEG in acute stroke precedes worsening of symptoms and death. *Clin Neurophysiol* 2008;119:1690-4.
29. Green JD, Arduini A. Hippocampal activity in arousal. *J Neurophysiol*. 1954;17(6): 533-57.
30. Greenberg JA, Burke JF, Haque R, Kahana MJ, Zaghoul KA. Decreases in theta and increases in high frequency activity underlie associative memory encoding. *Neuroimage*. 2015;114:257-63.
31. Scholz S, Schneider SL, Rose M. Differential effects of ongoing EEG beta and theta power on memory formation. *PLoS One*. 2017;12(2):e0171913
32. Dadashi M, Birashk B, Taremian F, Asgarnejad AA, Momtazi S. Effects of Increase in Amplitude of Occipital Alpha & Theta Brain Waves on Global Functioning Level of Patients with GAD. *Basic Clin Neurosci*. 2015;6(1):14-20.
33. Wang R, Wang J, Yu H, Wei X, Yang C, Deng B. Power spectral density and coherence analysis of Alzheimer's EEG. *Cogn Neurodyn*. 2015;9(3):291-304.
34. Jeong J. EEG dynamics in patients with Alzheimer's disease. *Clin Neurophysiol* 2004;115:1490-505.
35. Moretti DV, Fracassi C, Pievani M, et al. Increase of theta/ gamma ratio is associated with memory impairment. *Clin Neurophysiol* 2009 ;120:295-303.