SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

Quantitative EEG studies in drug-free and treated states of patients with epilepsy

by Palma Piros

Supervisor: Bela Clemens

UNIVERSITY OF DEBRECEN
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By Palma Piros, MD

Supervisor: Bela Clemens, MD, PhD

Doctoral School of Neurosciences,
University of Debrecen

Head of the **Examination Committee**:	Miklos Antal, MD, PhD, DSc
Members of the Examination Committee:	Anita Kamondi, MD, PhD, DSc
	Csilla Gyimesi, MD, PhD

The Examination takes place at the Library of Department of Anatomy, Histology and Embryology, Faculty of Medicine, University of Debrecen, at 11:00 a.m., 4th of September, 2015.

Head of the **Defense Committee**:	Miklos Antal, MD, PhD, DSc
Reviewers:	Peter Halasz MD, PhD, DSc
	Tamas Jardanhazy, MD, PhD
Members of the Defense Committee:	Anita Kamondi, MD, PhD, DSc
	Csilla Gyimesi, PhD

The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, at 1:00 p.m., 4th of September, 2015.

1. Introduction

Epilepsy is the second most common neurological disease. Its prevalence is 0,4-1,0% in the whole population. Epilepsy research has been limited to the spectacular elements, the seizures and interictal epileptiform EEG anomalies of the disease for a long time. However, epilepsy disease also exists between seizures, so the examination of the state between seizures is reasonable. EEG background activity recorded in waking state with closed eyes is electrically equal to the recently much studied "resting state". Over the past 15 years, our research group examined the EEG background activity in untreated idiopathic generalized epilepsy (IGE) patients, using computerized EEG analysis (quantitative EEG, QEEG). In several IGE groups consistently higher absolute spectral power was found in the delta and theta frequency bands, while the alpha and beta power deviated from the matched healthy control groups in a smaller and non-consistent manner. Increased neuronal synchronization found in the delta and theta bands is characteristic for IGE. It is the expression of increased seizure liability. The significant and consistent changes have motivated the extension of the studies, and the addition of source localization method in the untreated state of IGE. The introduction of source localization method is justified, because -against the old idea- focal or regional, structural or functional abnormalities were found in patients with IGE. Focal or regional abnormalities are assumed to appear also in the electrical activity.

1.1. Status epilepticus

Status epilepticus is a seizure activity lasting more than 30 minutes or a series of seizures without recovery of the baseline level of consciousness between attacks. In the so called non-convulsive status epilepticus (NCSE) ictal EEG activity without clinical motor features is observed with deranged higher cerebral functions. NCSE with generalized spike-wave pattern is usually called absence status (AS). Absence status may be an independent entity, may associate with idiopathic generalized epilepsies or appear as a complication of

symptomatic generalized or focal epilepsies. Absence status may be precipitated by acute cerebral disorders (hemorrhage, sinus thrombosis, subdural hematoma, brain tumor), metabolic-toxic conditions, neuroactive drugs or their sudden withdrawal, a few antibiotics (e.g. ciprofloxacin, gentamicin, ampicillin), fever and sleep deprivation, with or without epileptic medical history. Absence status seems to be an etiologically heterogeneous group, but considering the traditional EEG image it is rather homogeneous. The cortical sources of pathological neuronal synchronization generated absence status are not known, and the large-scale network disturbance occurring during absence status has not been investigated yet.

1.2. Pharmacological treatment of epilepsies

About 60-70 % of the epileptic patients become seizure-free with one antiepileptic drug or with combination therapy. However, 30-40% of the patients do not become seizure-free, and this rate barely declined in the last two or three decades. According to leading pharmacologists, the development of antiepileptic drugs is slower than it should be. There is hardly any "rational" drug development, which is based on neurophysiological facts. One reason is that, in general, little is known about the cerebral effect of these drugs. Traditional pharmacology investigates the mechanism of action of antiepileptic drugs at neuronal level (cell membrane, ion channel, receptor, neuronal signaling), and in a short time interval. System biology revealed that the investigation of micro-dimensions alone is not suitable to describe the overall performances of the brain. The overall performances are the long lasting, pathologically increased seizure liability, and its decrease by pharmacological methods. EEG, magneto-encephalography, and transcranial magnetic stimulation are such methods that can detect the summation of all known and unknown effects of drugs in bigger parts of the brain or at the level of the whole brain.

By computer analysis of EEG background activity, information reflecting the function of the cortex directly, and of the whole central nervous system indirectly, could be obtained. This approach has proved to be successful in case of the highly effective valproate in IGE. Valproate decreases the spectral power in the delta and theta frequency bands in successfully treated IGE patients, so it normalizes the EEG synchronization. Previously, our group demonstrated that valproate causes statistically significant changes in the anterior, frontotemporal areas of the cortex. The results suggest that the effect of other antiepileptic drugs should be investigated at whole brain level, using quantitative EEG.

1.3. Electroencephalography, quantitative electroencephalography

The physics of electroencephalography (EEG) is broadly known, and the creditable method of its registration was developed long ago. EEG activity refers the synchronous voltage fluctuations resulting from the dendrites of large neuron populations (at least 10-20 cm^2 contiguous cortical area). EEG activity is derived from the cortical afferent synaptic activity, but in a barely understood way, non-synaptic mechanisms and glial cells joined to the neurons may contribute to it. If the electrical changes in the cortex are strong enough in a physical manner, they could be recorded also on the scalp. Technical development has established better and better electroencephalographs, whose latest stage is the "digital EEG". This is now a clinically used method. It means, that the EEG signal recorded from the scalp is immediately digitized in the analog-to-digital converter, in other words, it is converted into matrices of numbers and stored in these forms. Its previously mechanical or electronic solutions are replaced by computer control. However, the waveform produced by digital EEG equipment, its analysis and interpretation are exactly the same. They are already well known from traditional EEG. The excess lies in the storage of the digitized information that allows the simultaneous or follow-up processing of it using various software programs. Quantitative EEG is a new

tool for approaching the information content of EEG. QEEG is not a single method, but a multitude of methods that study the EEG activity in selected aspects, and the results are given in numbers.

1.4. Spectral analysis

The spectral power in each individual frequency band (in our studies: delta, theta, alpha, beta) can be calculated with this method known and developed more than 50 years. This is not a physical quantity, but an abstraction of mathematical decomposition (e.g. fast Fourier transformation) that shows the degree of EEG oscillation in each frequency band evolved at the thalamo-cortical level of the brain. Nowadays the range of the examinable electromagnetic frequency bands of the brain extends from 0,1 Hz up to 1000 Hz, but only a part of the spectrum is investigated due to technical reasons. In the EEG literature mainly the "classical" frequency bands have been investigated so far (delta: 1-3 Hz, theta: 4-7 Hz, alpha: 8-12 Hz, beta: 13-20 Hz). The boundaries of these frequency bands were designated based on decades of experience. Delta, theta and alpha rhythms (at least the lower alpha band, 8-10 Hz) reflect the thalamo-cortical integration, to which the connection with the diffuse projection system arising from the septal-hippocampal structures has been added recently.

1.5. Source localization

From the origin of the electrical activity to the surface electrodes, the potentials significantly distort due to the various conductive properties of different layers (cerebrospinal fluid, dura, skull, scalp). The local activity originated from the cortex propagates in all directions by volume conduction, and crosses the good conductive layers. It does not cross the inner border of the skull, but in the layers of the dura and skull capacitive charge distribution occurs on both sides of the layers. The weak localization capability of the scalp EEG is due to these conditions. The recognition of weak localization capability claimed the concrete

EEG localization, the three-dimensional localization of cortical generators of EEG activity. Mathematically it means the solution of the inverse problem, whose essence is the following. The cortical EEG generators should be determined from the field potential (charge distribution) measured on the scalp. The so-called distributed source localization methods (such as the Low Resolution Electromagnetic Tomography, LORETA we used) are suitable for the mapping of the entire cortex. For the sake of brevity, the current source density (CSD, Amper/m^2) is called "activity" in the LORETA literature. LORETA computes the inverse solution within 2394 voxels, which allows a spatial resolution of 7 mm. The calculated values of activity were color-coded and displayed on a T1-weighted MRI brain template digitized at Montreal Neurological Institute. During the tomographic display any voxel, its CSD value and its precise anatomical localization can be found with the help of a cursor.

1.6. Brain connectome and its analysis

Recently "connectome" has been referred to the entire network of the brain which covers many orders of magnitude in time and space. In neurosciences, also in neurology more and more is said about the fact that brain functions do not originate from "brain centers", but from different scale brain networks. It was intuitively suspected before, but was not emphasized due to the lack of mathematical methods necessary for the investigation of network performance. Generally anatomical, functional and effective connectivity are distinguished. EEG functional connectivity (EEGfC) investigated in the dissertation is achieved through short and long association fibers and other unknown mechanisms. Originally EEGfC was defined as temporal correlation of values of voltage differences (two time series) measured at both parts of an electrode pair (against reference electrode). Recently the two electrodes are replaced by the activities of two cortical areas (regions of interest, ROI) or their changes computed by source localization. If the calculation is repeated between each ROI pair, and in many frequency bands, a correlation pattern (matrix) covering

the entire cortex is obtained in all frequency bands. In the matrix the correlation coefficients are color-coded, but many display forms exist. The relationship between two time series is calculated by several methods, out of them coherence and correlation are the best known. At the interpretation of the result, EEGfC has to be known that it is no more than a statistical correlation between two time series and cannot be assigned directly to anatomical or specific neurophysiological processes.

2. Aims of the studies

Effective treatment of epilepsy is a clinical issue, which is not solved in many patients due to aforementioned reasons (1.2. subsection). One reason that should be highlighted is that the effects of antiepileptic drugs on the whole brain, especially on large-scale cerebral electric processes have not been studied, however the traditional pharmacological approach at ion channel or receptor level does not explain the disappearance or remanence of seizures. In pursuance of system biology that our goals rely on, the changes occurred at lower levels of organization, for example at ion channel or receptor level, do not necessarily explain the changes happened in higher units of brain (e.g. thalamo-cortical level) at the level of higher complexity.

In our study large-scale and highly complex organization mean seizure-free and not seizure-free states, and the corresponding global cerebral electrical states, as they appear in the EEG.

1. Our goal is to explore the change of global cerebral state underlying the lamotrigine-induced successful treatment by EEG methods unused for this purpose. Electrical processes of the brain can be investigated at large spatial scale by these methods. In the first study the assumed reduction of abnormal EEG synchronization at thalamo-cortical level caused by lamotrigine in idiopathic generalized epilepsy is approached by spectral analysis of EEG background activity. In the second study we want to demonstrate the changes of

cortical transmembrane currents occurring to drug effect and their anatomical distribution with calculation of current source density derived from EEG in idiopathic generalized epileptic patients. Both studies are based on comparison of results received before and during successful treatment.

2. The recognition of brain network organization underlying ictal and interictal states is also a clinical neurophysiological issue. Hopefully this knowledge may contribute to the development of methods for effective anti-seizure or causal treatment, and prevention of epilepsy. Our factual objective is directed at a typical electro-clinical state, the absence status associated with generalized spike-wave EEG pattern. Neuronal synchronization and its anatomical distribution underlying the ictal EEG pattern are investigated by quantitative EEG and LORETA source localization method, whereas the abnormal interplay between larger cortical areas is revealed by LORETA Source Correlation method.

3. Patient groups

3.1. Study on the effect of lamotrigine on EEG synchronization by spectral analysis of EEG background activity

Newly diagnosed, untreated IGE patients with epilepsy onset after the age of eighth were included.

Exclusion criteria were: permanent medication except oral contraceptives, alcohol or drug abuse, any medical condition that is known to influence EEG activity, and generalized tonic-clonic seizure in the 5 days before EEG registration. The diagnoses of IGE syndromes were made according to generally accepted guidelines. Neurological and EEG investigations were done at the first visit, with treatment started the next day. The initial daily dose of lamotrigine was 25 mg and progressively increased until the seizures stopped. The date of seizures and the incidental adverse events were entered into the seizure diaries. Nineteen patients were enrolled in the study (12 females, 7 males, age: 10-29

years, average: 16,2 years). At the end of the titration the patients took 100-300 mg lamotrigine daily. The daily dose of 14 patients was 200 mg. No patient experienced symptoms or complaints indicating adverse effect of the drug. The first EEG was recorded in drug-free state. The second EEG was done 3 months later when the patients were seizure free.

3.2. Study on the anatomical localization of the cortical effect of lamotrigine

EEG records of untreated and treated IGE patients described in the previous study were analyzed with LORETA source localization method. In both studies the same EEG records were included.

3.3. Source localization and study on EEG functional connectivity in absence status

In our retrospective study seven patients with late-onset absence status were investigated. Relevant events of the patients' medical history, clinical, laboratory and cranial CT findings, neuroactive medication and observed neuropsychiatric symptoms were recorded. Their recent history was very diverse, including the followings: cerebral lesion, upper airway infection, elevated blood glucose level, changes in neuroactive medication, convulsive epileptic seizures. During AS motionlessness, unresponsiveness, lack of verbal and nonverbal communication were observed, but some degree of arousability was preserved. One patient had psychomotor slowing and decreased responsiveness, while the other showed fluctuating somnolence and confusion. The patients were admitted to the neurological department due to these symptoms. AS was suspected because of this state, and that was the reason for EEG examination.

4. Methods and samples

In all three studies, 19-channel EEG samples recorded with standard technique (Ag/AgCl electrodes placed according to the international 10-20 system, physical reference at Fpz, impedances ≤ 5 kΩ, filters were set at 0,1 and 33,6 Hz, sampling frequency was 128/sec, 12-bit on-line digitization) were analyzed using quantitative EEG methods. In the first two studies total of 60x2 second artifact-free EEG epochs reflecting relaxed-waking state were selected for QEEG from all EEG samples. These epochs did not contain any epileptiform potentials.

In the first study the total of 120 seconds EEG background activity was edited by the Neurometric Analysis System software, developed by E. Roy John. Raw absolute power (RAP), raw relative power (RRP), and raw mean frequency (RMF) were calculated for each of the four frequency bands (delta: 1,5-3,5 Hz; theta: 3,5-7,5 Hz; alpha: 7,5-12,5 Hz; beta: 12,5-25,0 Hz). Brand-related coherence was also calculated from auto- and cross-correlation power spectra of the two times series, for the electrode pairs Fp1-Fp2, F3-F4, C3-C4, P3-P4, O1-O2, F7-F8, T3-T4, and T5-T6 (interhemispheric coherence, RCO) and for Fp1-F3, Fp2-F4, T3-T5, T4-T6, C3-P3, C4-P4, F3-O1, and F4-O2 (intrahemispheric coherence, RIC). Scalp-averages for all mentioned variables were computed to reduce the huge amount of numerical data. Group comparison was performed by using scalp-averages. Group averages for the treated (LTG) and untreated (NAE) conditions were compared by Wilcoxon's matched pairs test. Multiple comparisons were done by Friedman and post hoc Dunn test, and corrected *p*-values were presented. Correlation was computed according to the Spearman rank correlation method. Differences with corrected $p \leq 0{,}05$ values were accepted as statistically significant.

In the second study the epochs were analyzed using NeuroGuide Deluxe (version 2.7.1.0) and LORETA software. LORETA activities were computed in

four frequency bands separately (delta: 0,5-3,5 Hz, theta: 3,5-7,5 Hz, alpha: 7,5-12,5 Hz, beta: 12,5-25,0 Hz), for 2394 voxels. The computed activities in all voxels were compared in the untreated and treated condition. *t*-tests were performed for statistical analysis. The uncorrected $p<0,01$results were accepted as statistically significant.

In the third study sixty, consecutive, two-second epochs of the individual ictal patterns were selected and processed to a software package including NeuroGuide Deluxe (version 2.7.1.0), LORETA and LORETA Source Correlation (LSC). Fast Fourier transform-derived data of the selected epochs were used to compute absolute and Z-scored spectral power values for very narrow bands (VNB) of 1 Hz bandwidth across the 1-25 Hz frequency range. LORETA analysis in two frequency bands (1-6 Hz and 12-14 Hz) at the maximum of the spectrum abnormality was performed for all patients. Age-adjusted and Z-scored values were obtained by using LORETA Normative Database.

Intrahemispheric EEGfC was investigated by LSC method. During LSC analysis the temporal correlations (correlation coefficient, *r*) of current source density (CSD) values defined 128 per second were computed between two cortical areas, ROIs. Age-adjusted and Z-scored *r* values for ROIs in each hemisphere were calculated with the remaining (total of 23) ROIs using LSC Normative Database reference values. Using BrainCON software, the EEGfC data were plotted on a "glass brain", on which the dots indicate the Talairach coordinates corresponding the geometric centroids of ROIs, while the lines indicate the values of abnormal connectivity connecting the individual ROIs.

5. Results

5.1. Study on the effect of lamotrigine on EEG synchronization by spectral analysis of EEG background activity

The delta and theta raw absolute power (RAP), the theta raw relative power (RRP), the theta mean frequency (RMF), and the alpha raw mean frequency (RMF) decreased in the treated group compared to the untreated group. Coherence was not significantly influenced by lamotrigine.

The initial RAP_{NAE} values compared to the drug dependent changes (RAP_{LTG}-RAP_{NAE}) showed; the greater the initial value, the greater the degree of the decrease. This phenomenon was observed over the entire scalp in the delta, theta, and alpha frequency bands but only seldom in the beta frequency band.

5.2. Study on the anatomical localization of the cortical effect of lamotrigine

Lamotrigine decreased LORETA activity in all frequency bands to a variable degree. The overwhelming majority of the voxels showing statistically significant changes were crowded in a large, topographically contiguous cluster that included parts of the temporal, parietal, occipital cortex and insula. Lamotrigine primarily decreased activity in those areas where pathologically increased activity had been reported in untreated IGE patients in our previous study. However, statistically non-significant decrease of activity is also observed in the remaining cortical area.

Alpha activity also decreased all over the cortex. However, statistically significant changes occurred only in a limited part of the right hemisphere, temporo-parietally.

5.3. Source localization and study on EEG functional connectivity in absence status

In absence status generalized, spike-multiple spike and wave EEG activity was found in all patients. The greatest Z-scored spectral power was in the 1-6 Hz and 12-14 Hz frequency bands, in all cases. LORETA solutions were generated for the averaged 1-6 Hz and averaged 12-14 Hz bands for each patient. The localization of the four greatest Z-values in the aforementioned frequency bands was analyzed.

The greatest Z-values in the 1-6 Hz frequency band were localized to medial temporal structures (parahippocampal gyrus, hippocampus), medial frontal cortex (the very rostral part of the anterior cingulate), the subcallosal area, and the insula. Additional areas of increased LORETA activity were also observed, but the topography changed from patient to patient. The findings did not show any correspondence with the focal CT abnormalities. In five patients, maximum scores in the 12-14 Hz frequency bands were localized to the anterior cingulate bilaterally. LSC analysis resulted in very dissimilar topographical EEGfC patterns. Three patients displayed a lot of increased EEGfC values among several frontal, temporal, parietal and occipital ROIs. These findings seemed to be random-like ("statistical noise") and did not outline a network. Two patients did not display abnormal Z-scores at all. No topographical relationship was found between the LSC results and the clinical and imaging findings.

6. Discussion

6.1. Study on the effect of lamotrigine on EEG synchronization by spectral analysis of EEG background activity

The core neurophysiological concept of idiopathic generalized epilepsy is the pathologically increased thalamo-cortical oscillation, which can be revealed also in the interictal state. In our patients the effect of lamotrigine was the decrease of oscillation in the delta and theta bands. Decreased EEG synchronization is interpreted as partial normalization of background activity. The decrease of delta, theta synchronization was not accompanied by meaningful changes in RRP, indicating that the percentage of power in the frequency bands did not changed significantly compared with the untreated state. The possible neurophysiological explanation for this is that lamotrigine does not disturb the balance of the underlying, band-specific, selectively distributed neuronal networks.

Our study demonstrated that the effect of lamotrigine is use-dependent. Lamotrigine significantly reduced synchronization in those frequency bands that showed particularly increased synchronization in the untreated condition. The correspondence highlights the correlation between the degree of initial abnormality and lamotrigine induced RAP decrease.

Our results raise the possibility that the QEEG change indicating EEG normalization might be a biological marker of seizure control. Despite this fact, RAP normalization should not be interpreted as a marker of good therapeutic response, even that our patients became seizure-free. In addition to the cortical EEG synchronization, there are other factors that also influence seizure liability, such as activity of several subcortical sites. The changes of RAP in patients not responding to lamotrigine treatment are unknown. The predictable value of EEG indicating therapeutic response can only be determined by examining larger group of patients prospectively.

6.2. Study on the anatomical localization of the cortical effect of lamotrigine

In this study the effect of lamotrigine decreasing neuronal synchronization was confirmed in the theta frequency band. The topographic distribution of this effect is a novel, previously unknown finding. However, it is unclear what relationship between the robust effect of lamotrigine in the posterior part of the brain and the neurophysiology of IGE exists. It is clear that the change of the posterior part of the cortex does not affect the mediobasal frontal site from where the absence and myoclonic seizures may originate. The explanation is probably that the effective treatment can be achieved by pharmacological manipulation not only at the site of seizure onset, but at other cortical areas as well. Previously it has been shown in absence epilepsy that the network also has abnormally functioning elements in the posterior cortical areas. Besides the frontal increased activity, medial parieto-occipital increased activity was observed at the beginning of absence seizures by using brain mapping. Recently it has been confirmed that the events of the immediate preictal period and seizure onset are not limited to the frontal lobe. Network type activity, that is topographically different from absence, was described in juvenile myoclonic epilepsy as well. Based on these findings, it is certain that the medial parietal cortex is a cardinal part of the ictogenic network. It is possible that lamotrigine inhibits seizures by decreasing the local activity of this area.

6.3. Source localization and study on EEG functional connectivity in absence status

Absence status was caused by multiple structural and biochemical cerebral anomalies in our patients, which is common in neurological practice. In this respect, our patients and their EEG anomalies during AS were similar. Our results indicate that absence status is very similar to absence seizures where the generators of the spike and slow wave components are topographically separated.

In the 1-6 Hz frequency band LORETA localized the sources of abnormally synchronized activity to frontal, temporal, parietal areas in all of the patients, and also to occipital areas in four of them. The greatest anomalies were found in the medial temporal structures, anterior cingulate, subcallosal area and the insula. These areas belong to the cortical compartment of the limbic system, and form a strongly interconnected network in healthy persons and epileptic patients. Epileptic synchronization within the limbic system may give rise to focal non-convulsive seizures starting from frontal or temporal sites. The stereotyped LORETA findings suggest that the cortical compartments of the limbic system respond as a whole to ictogenic influences.

In the 12-14 Hz frequency band the greatest LORETA abnormality occurred in the medial frontal cortex (anterior cingulate). Electrical stimulation in this area may elicit generalized spike-wave paroxysms and absence seizures, and this area may be important in generating generalized spike-wave pattern in absence status, too. In our patients the increased activity in the 12-14 Hz frequency band may refer to the area of seizure onset while the wave components (1-6 Hz) correspond to the clinical symptoms.

EEGfC has not been analyzed in long-lasting seizure states with generalized spike-wave, so our results are entirely new. It is surprising and unexplainable that very similar AS symptoms were associated with abnormal network dynamics in some patients, while with normal network dynamics in the others. From EEG aspect AS seems to be characterized by the localization of the sources generating abnormal activities rather than the disturbance of remote connections.

7. Summary

Quantitative EEG studies sensitively indicate the degree of the changes of EEG synchronization, therefore they are suitable for characterization of the interictal state and for examining the effect of EEG synchronization-modifying drugs. All of the studies for the thesis revealed until recently unknown neurophysiological phenomena.

1. Our studies demonstrated that the pathological cortical synchronization in the untreated state was decreased by lamotrigine in seizure-free patients.

2. The effect of lamotrigine was use-dependent (activity-dependent) on the abnormal synchronization.

3. Source localization method confirmed that lamotrigine has normalizing effect mainly in the posterior cortical areas. The results establish the study of the effect of lamotrigine at system level (frequency band and topography).

4. In absence status of severely ill adult patients, the uppermost increased activity of the ictal activity was demonstrated within the 1-6 Hz and 12-14 Hz frequency bands. The main generators of the 1-6 Hz frequency bands were localized in frontal and temporal cortical areas of the two hemispheres that are parts of the limbic system. In the 12-14 frequency band the abnormally synchronized generators were found in the antero-medial frontal cortex. The results suggest that despite the predisposing and seizure-provoking factors, the cortical components of the limbic system respond stereotypically as a whole to ictogenic influences.

8. Keywords

epilepsy, EEG, quantitative EEG, lamotrigine, source localization, LORETA, absence status

9. Publications

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Registry number: DEENK/26/2015.PL
Subject: Ph.D. List of Publications

Candidate: Pálma Piros
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List of publications related to the dissertation

1. **Piros, P.**, Puskás, S., Emri, M., Opposits, G., Spisák, T., Fekete, I., Clemens, B.: Uppermost synchronized generators of spike-wave activity are localized in limbic cortical areas in late-onset absence status epilepticus.
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2. Clemens, B., **Piros, P.**, Bessenyei, M., Tóth, M., Hollódy, K., Kondákor, I.: Imaging the cortical effect of lamotrigine in patients with idiopathic generalized epilepsy: A low-resolution electromagnetic tomography (LORETA) study.
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   DOI: http://dx.doi.org/10.1016/j.clinph.2006.11.016
   IF:2.468

Address: 1 Egyetem tér, Debrecen 4032, Hungary Postal address: Pf. 39, Debrecen 4010, Hungary
Tel.: +36 52 410 443 Fax: +36 52 512 900/63847 E-mail: publikaciok@lib.unideb.hu, Web: www.lib.unideb.hu

List of other publications

4. Clemens, B., **Piros, P.**, Bessenyei, M., Varga, E., Puskás, S., Fekete, I.: The electrophysiological "delayed effect" of focal interictal epileptiform discharges: A low resolution electromagnetic tomography (LORETA) study.
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Epilepsy Res. 70 (2-3), 190-199, 2006.
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Address: 1 Egyetem tér, Debrecen 4032, Hungary Postal address: Pf. 39. Debrecen 4010, Hungary
Tel.: +36 52 410 443 Fax: +36 52 512 900/63847 E-mail: publikaciok@lib.unideb.hu, ▫ Web: www.lib.unideb.hu

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