# Identification of the Long-Term Effects of Mild to Moderate Neonatal Cerebral Hypoxia Based on EEG Signals Analysis

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**Abstract.** AbstractHypoxic-ischemic encephalopathy (HIE) during perinatal period is the most common cause of neonatal seizures and is associated with an increased risk of epilepsy in later life. Among newborns affected by perinatal brain injury 20-50% die during the newborn period, and 25-60% of the survivors suffer from permanent neurodevelopmental handicap, including cerebral palsy, seizures, mental retardation, and learning disabilities. In the present study EEG data from 11 patients were analysed with power spectra analysis of the principal components of the EEG signals, fractal dimension estimation and sample entropy estimation. The preliminiary results show that the power density properties in the alpha frequency range correlate with learning difficulties of the subjects.

## Introduction

Hypoxic-ischemic encephalopathy (HIE) during perinatal period is the most common cause of neonatal seizures and is associated with an increased risk of epilepsy in the later life. Long-term neurological sequellae in children after HIE can be attributed to both disturbed brain development and functioning as well as tisue loss after hypoxic-ischemic insult. Although delivery can be a critical point, since it presents a shock to a child's organism that can be accompanied with several complications, hypoxia can occur also prior the delivery due to many causes such as: prolapsed or compressed cord, ruptured uterus, incidents during delivery, etc. Despite the improved pre- and perinatal health care, neonatal encephalopathy still occurs with the incidence of 1-6/1000 [11]. Hypoxia is a situation where oxygen supply to the body is severely reduced and can cause several problems of which the most serious are related to the brain development [10]; [2]; [6]; [7]; [5]. One of the causes for hypoxia is ishemia which is reduced blood flow through the organs. However, as this is still an early stage of life, the affected tissues can recover and the quality of life is not seriously affected. As brain is a very complex organ there are no models to predict the long term effects of perinatal hypoxia on the basis of the hypoxia durantion and severity. In our study we analysed data from the long-term observations of children with mild to moderate HIE.

The subjects were examined at the age of 21 and the following tests were performed: Magnetic resonance imaging (MRI), electroencephalogaphy (EEG), and psychological evaluation. The analysis of the test results showed that there is a wide spectrum of possible outcomes that included significantly reduced brain structures, epileptic labillity, cerebral paralysis, reduced mental capacity, etc. In most of the subjects EEG analysis showed normal EEG or some epileptic outbreaks. Therefore, the question was raised, how does the EEG correlate with the observed reduced volumes of brain structures, psychological evaluation and HIE grade. HIE grade was performed by Sarnat and Sarnat criterium [9]. The criterium was developed in 1976 and combines clinical and EEG findings of the newborn babies, when only clinical findigs are used, it is called modified Sarnat criterium.

The criterium score has three stages: I - mild, II - moderate and III - severe. The following characteristics define the stages:

- I - mild stage:
  - hyper-alert,
  - eyes wide open,
  - does not sleep,
  - irritable,
  - no seizures, and
  - the effect usually last less than 24.
- II - moderate stage:
  - lethargy (difficult to rouse),
  - reduced tone of the extremities and/or trunk,
  - diminished brainstem reflexes (pupil/gag/-suck), and
  - possible clinical seizures.
- III - severe stage:
  - coma (cannot be roused),
  - weak or absent respiratory drive,
  - no response to stimuli (may have spinal reflex to painful stimuli),
  - flaccid tone of the extremities and trunk (floppy),
  - diminished or absent brainstem reflexes (pupil/gag/suck),
  - diminshed tendon reflexes, and
  - EEG severely abnormal.

In order to analyse the EEG spectral properties as well as complexity of the EEG patterns, principal component analysis, fractal dimension estimation, and sample entropy were used, while the results were compared with HIE score, learning difficulties, and reduced volumes of the brain structures.

## 1 Origins and Measurements of the EEG Signals

EEG signals are measurements of electrical activity of brain obtained by using electrodes on the scalp surface. The magnitude of the measured EEG signal varies with the position of the electrodes and their distance from the electrical source [8]. The measured activity represents the sum of the repetitive and periodic electrical activity, and most likely originates from the sum of the excitatory and/or inhibitory postsynaptic potentials in large populations of pyramidal cells in the neocortex [8]. Local postsynaptic potentials along the pyramidal cell membranes cause an electrical gradient, and the sum of all the gradients results in an electrical current, which is reflected in an electrical potential that can be measured on the surface of a human scalp [8]. Brain is a large interconnected system of neurons that fire when sufficient level of the signal is sent to their inputs. In order to sense the neuronal activity on the scalp, we need a large group of synchronised neurons that fire simulatneously.

As brain activity is always divided among groups of neurons, the EEG is a sum of all the neuronal groups' activities in the neocortex and some underlying structures. The depth from which EEG can receive signals is limited by the conductive properties of the brain, liquor, bones and scalp. The values of the potentials are in the range of microvolts and need to be attenuated to obtain measurable values. Usually, the measurements are performed in electrially shielded room that filters electromagnetic noise (Farady cage); however, it is practically impossible to filter out the frequencies of the power lines (50 Hz in EU and most of the world); therefore, notch filters are used to reduce the disturbance.

In parallel to brain signals, muscle artefacts can also be found in the EEG measurements. Most often these artefacts are eye-blinking, swallowing, head motions, and in some cases even breathing and heart rate. All potential must be measured as voltages, meaning that we measure a difference between two potentials. Therefore, a reference electrode must be mounted in the scalp as well and all the potentials are then measured against the reference electrode. Reference electrodes are usually placed on ear lobes, center of the forehead or centrally between the mid forehead and central electrode of the EEG cap. Later on, the values of the electrodes are recalculated on the average value of the electrodes to reject the disturbances that are picked up by all the electrodes. Electrodes are mounted on the cap to ensure secure spatial positioning of the electrodes on the scalp.

There are several standardised systems of electrode mountings, such as international 10-20 system that defines the positions of 32 electrodes as well as its modifications with intermediate electrodes that use 64 or 128 electrodes. Equal stress as for the measuring equipment must be put on the measurement protocol. Measurement protocol must ensure that subject activity is focused on the processes that are under investigation. As brain parallelly processes large amounts of the information, it is essential that investigated processes are stimulated and the rest of the processes are attenuated by the measurement protocol. Only carefully performed measeurements of EEG are useful for more detailed numerical analysis.

In the presented case the measurements were performed on Nicolet One, version 5.7.1., standard EEG apparatus (CareFusion Corporation, San Diego, California, USA). Standard 19 EEG electrode sites and ear lobes were recorded at 256Hz sampling rate, using a bipolar longitudinal montage. We used a set of recording conditions after whole night sleep deprivation using: eye movements and alpha blocking followed by eyes closed resting; eyes open resting; hyperventilation; and photic stimulation. Data were exported and further analysed. An average reference was used for the signals, and the signals were filtered with the 50Hz notch filter and band-pass filter between 0.1Hz and 70Hz. Numerical analysis was performed in Matlab 2009b (The Mathworks inc., Natick, Massachusetts, USA) Eleven subjects were enroled in the study with mild or moderate HIE.

## 2 Principal Components and EEG

Principal componenet analysis [3] is frequently used when high-dimensional data is analysed. By high-dimensional data a matrix of signal values that describe the state of the system is meant. There are two important aspects that can be analysed by PCA: dimensionality of the signals, linear dependency of the signals. When the result are reviewed in the context of the observed system, the dimensionality and linear dependence can be interpreted in the frame of system's properties. The dimenisonality od the EEG signals is directly linked with the number of most active synchronous groups of neurons which are considered as signal sources. The source identification in the brain is however a lenghty procedure that involves sloving inverse problem of electric field computation form dipole sources.

However, the inverse problem does not have a unique solution so some prior asumptions must be made considering the number of sources and their approximate locations before it can be calculated. PCA provides the number of active sources while the activity inditcates the approximate location of dipoles that represent the synchronised groups of neurons. There is, however, one thing that must be mentioned at this stage. Computational activity of the brain usually desynchronises the active regions; therefore, what is expected is tha PCA would in fact identify idle regions rather than active ones. However, linear coupling of the inactive regions reduces the effect and PCA is quite effective in finding the number and also some general location of the active regions. If the measurement protocol is well prepared, then PCA can produce significant results. In our case we had several sections of the measured activity as described above. We performed PCA within the sections and on the whole signal. Regardless of the signal or the subject selection there were three most significant components (PC) while the rest can be considered as measurement or background noise.

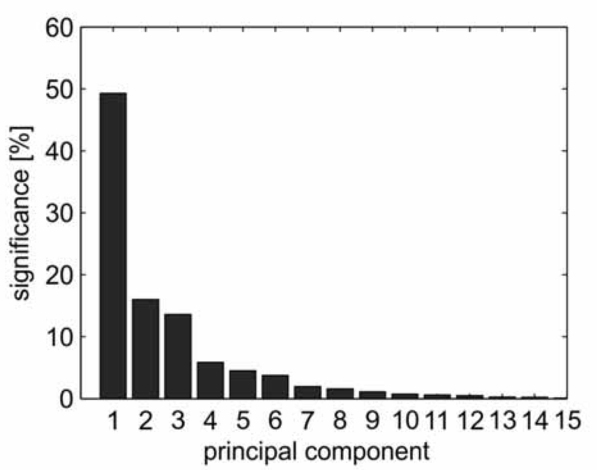


**Figure 1:** A typical significance composition of principal componenets of the measured EEG signals.

The significance composition of the components is presented in Figure 1. In Figure 1 it can be seen that there is one very significant principal component and two almost equally significant ones. To see, how the three most significant components are composed of the electrode signals, an interpolated plot of the eigenvectors was performed. Each eigenvector componenet is associated with the contribution of the corresponding signal to the component.

The typical principal component compositions are shown in Figure 2. From the compositions of the PC one can see that first principal component is oriented from frontal to occipital electrodes, suggesting that it originates in the occipital region that receives visual signals from eyes.

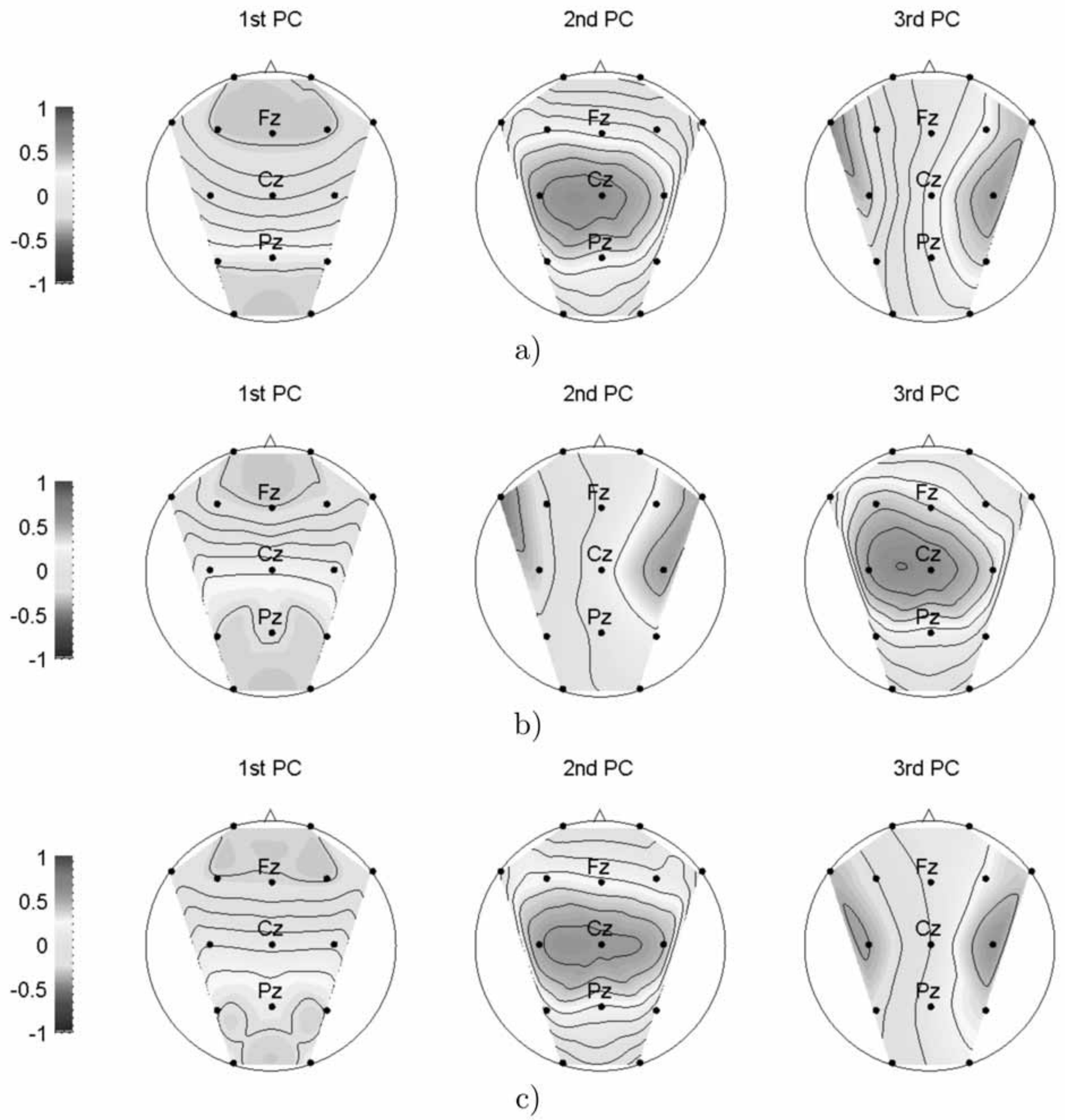


**Figure 2:** A typical compositions of the three most important principal components of the measured EEG signals: a) resting, hyperventilation, b) photic stimulation, c) whole signal.

The assumpition is further backed up by the fact that the significance of the first PC rasises up to 80% during photic stimulation while it becomes even more polar (see Figure 2 b). The second principal component is oriented upwards with its more or less symetrical origin in the central region which suggests diaphargm activation during breathing. The interpretation of the third principal componenet is not clear and would be discarded, however, its significance is almost the same as for the second componenet and in some subjects it even positioined as the second componenet. The compositions of the rest of the compoenents is quite unstable (data not shown).

## 3 Spectral Analysis of the EEG Signals

Spectral analysis of the raw EEG signals showed no significant pattern. The spectral power density showed the usual high power-density values for low frequency signals and approximately exponential decay towards higher frequencies for all subjects. However, spectral analysis of the principal components was more informative. Spectral analysis of the first subject's EEG PC's is shown in Figure 3. In Figure 3 one can see a significant rebound in the alpha rhythm frequency range (8 - 10 Hz). Considering the fact that during measuerements the eyes were closed, the rebound was expected in the component that respresents the activity of the visual region of the brain. Alpha rhythms are associated with resting and become more dominant when we close the eyes and are known to spread from occipital areas to the front.

## 4 PC Spectral Analysis Relation to Clinical Data

Comparison of spectral analysis of principal components and clinical data showed some interesting relations. Closer inspection of power spectrums of first principal component of the subjects showed, that they can be grouped into two groups regarding the rebound of the spectrum in the alpha frequency range. In one group there were subjects that had an obvious local maximum of the power spectrum located in the alpha range. The next group had no apparent visible local maximum in the alpha range. A power spectra of twins that were included in the study and belonged to different groups are shown in Figure 4. Interstingly, when inspectin clinical data, we could observe that the two groups correlate with learning difficulties of the subjects. All the subjets that had no learning difficulties also had obvious rebounds in the alpha range. Subjects with learing problems had typically no rebound in alpha range, except for one subjet; however the subject had additional psy- chological problems that might have affected the learning abilities.

## 5 EEG Pattern Complexitiy Estimation

To further characteris the properties of the EEG signals, we calculated fractal dimension of the signals from O1 and O2 electrodes, as this seemed to be above the source of the main alpha activity. Higuchi dimension was calculated [1]. However, no correlation with clinical data could be found. In all cases very high values of Higuchi dimension around 2 were obtained, which suggest highly random character od the signals. Next, we calculated sample entropy [4]. Again signals from O1 and O2 were selected for the analysis, however, the results again showed no correlation with clinical findings. The values of the sample entropy were similar for the two electrode signals and ranged from 0.6 to 1.5. More systematic analysis is planned in this field in the future.

## 6 Discussion

The interesting correlation between power spectrum of the first principal components of the EEG signals and learning difficulties of the subjects was an important finding. Altough alpha spectrum brain waves are associated with resting, their function, although sometimes controversal, is not irrelevant for the higher functions of the brain. It is known that our memories consolidate during resting, since severe disruption of resting cycle, such as prolonged sleep deprivation, can cause memory problems. Alpha waves are also associated with the long range synchronisations of brain areas that requires good connectivity between several brain regions. Considering hypoxic-ischemic encephalopathy it would be reasonable to expect that HIE can cause connectivity problems in brain that can have different effects on the brain functioning. The size of the brain structures seems to have no direct effect on the connectivity, however, systemic analysis of the brain rhythms can show reduced connectivity through reduced power densities at the frequencies of the major brain rhythms. Surprisingly, the connectivity does not seem to correlate with any of the complexity measures used in this study.

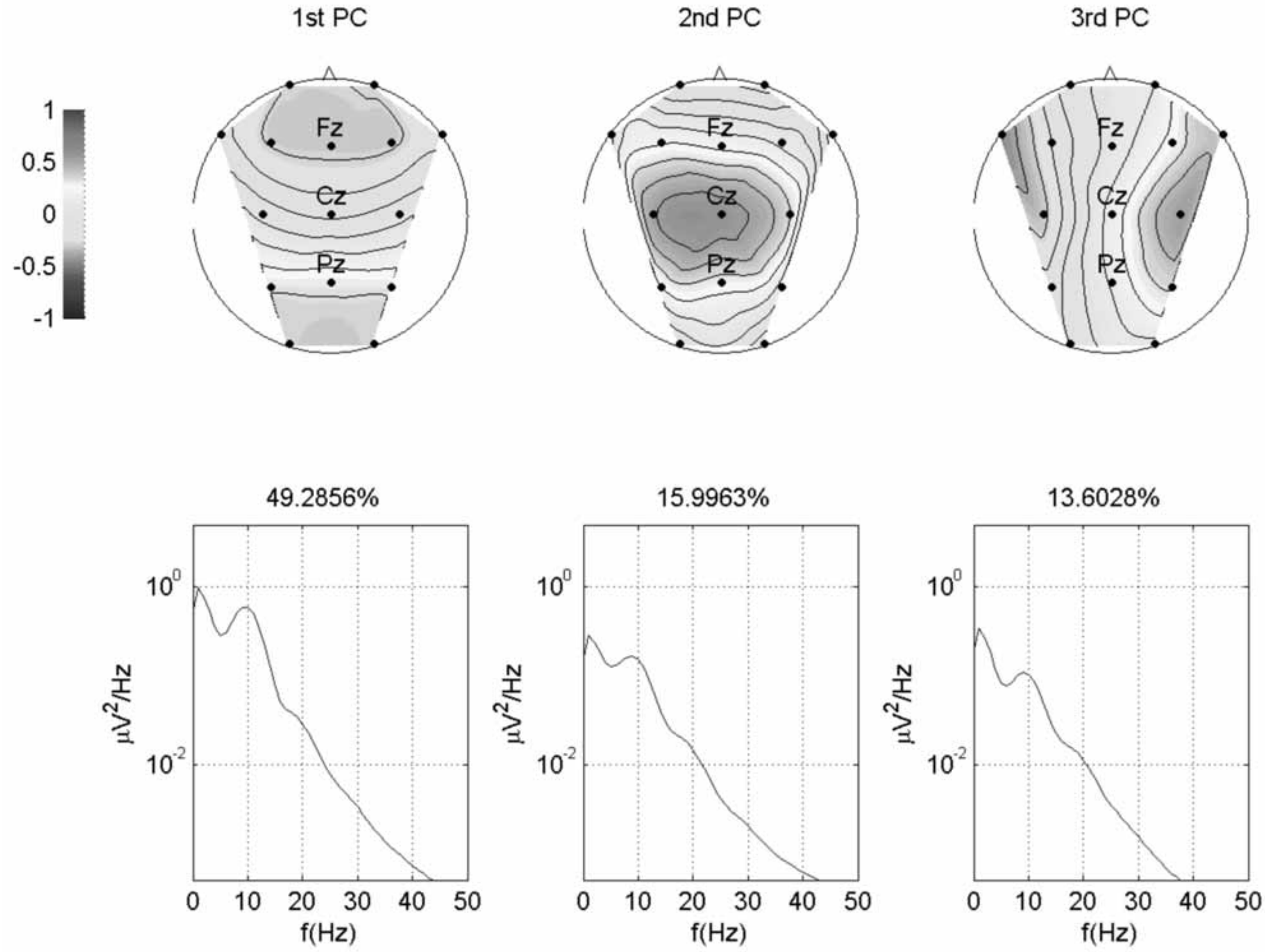


**Figure 3:** A spectra of the principal components of the measured EEG signals of the first subject.

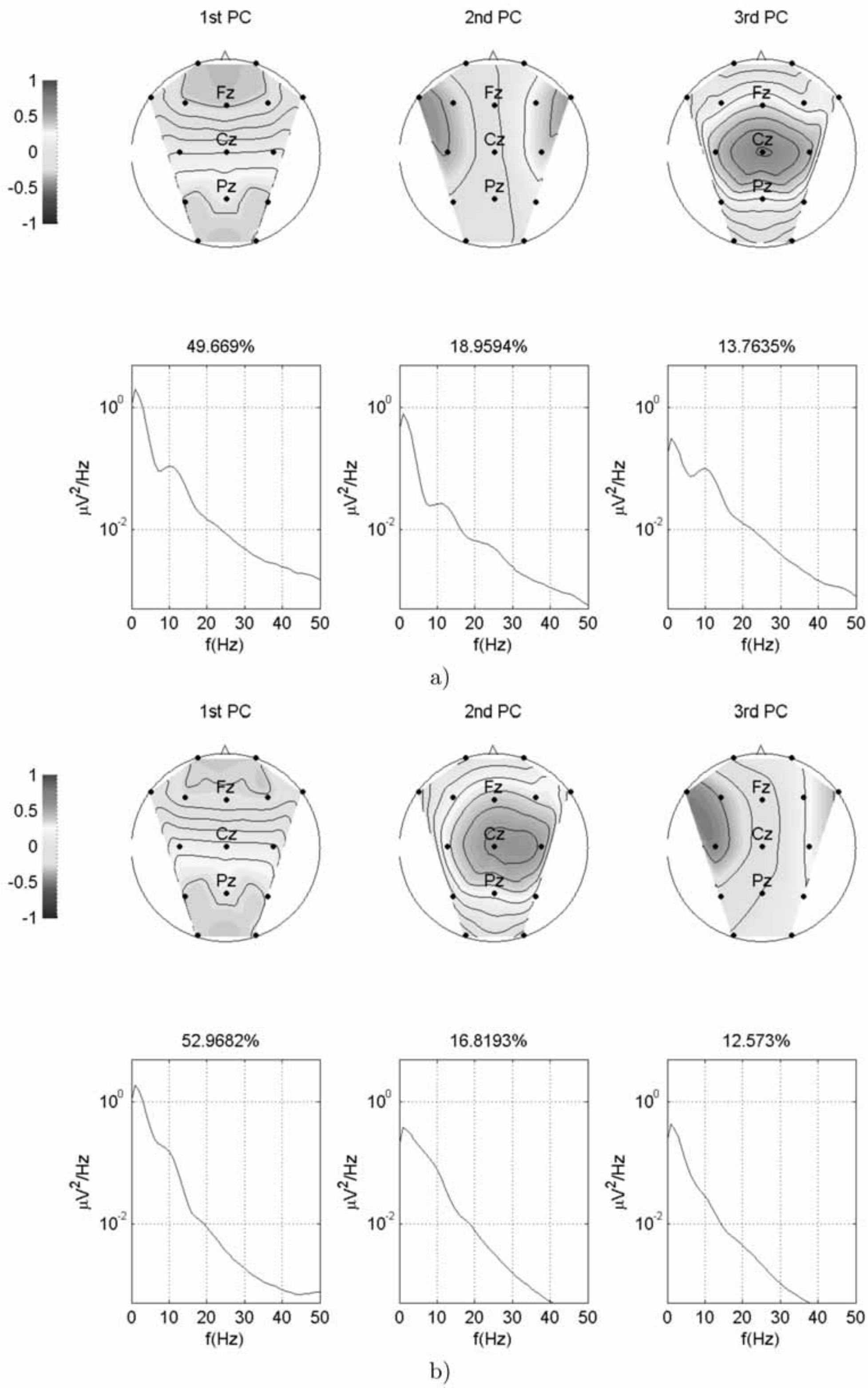


**Figure 4:** A power spectra of twins from different groups according to the alpha range rebound in the spectrum: a) the twin without learning difficulties, b) the twin with learning difficulties.

## References


[1] Higuchi T. Approach to an irregular time series on the basis of fractal theory. *Physica D: Nonlinear Phenomena*. 1998; 31(2): 277-283. doi:10.1016/0167-2789(88)90081-4.

[2] Inder TE, Volpe JJ. Mechanisms of perinatal brain injury. *Seminar in Neonatology*. 2000; 5(1): 3–16. doi:10.1053/siny.1999.0112.

[3] Jackson JE. *A User Guide to Principal Components*. 4th Edition. New York: John Wiley & Sons, inc; 1991. 575p.

[4] Lake DE, Richman JS, Griffin MP, Moorman JR. Sample entropy analysis of neonatal heart rate variability. *Am J Physiol*. 2002; 283(3): 789-797. doi:10.1152/ajpregu.00069.2002.

[5] Marlow N, Rose AS,Ranads CE, Drapper ES. Neuropsychological and educational problems at school age associated with neonatal encephalopathy. Marlow N, Rose AS, Rands CE, Draper ES. Neuropsychological and educational problems at school age associated with neonatal encephalopathy. *Archives of Disease in Childhood-Fetal and Neonatal*. 2005; 90(5): F380-F387. doi:10.1136/adc.2004.067520.

[6] Mercuri, E, Anker S, Guzzetta A, Barnett A, Haataja L, Rutherford M. Early prognostic indicators in infants with neonatal cerebral infarction: a clinical, eeg and mri study. *Pediatrics*. 1999; 103(1): 39-46. PMID:9917437.

[7] Mercuri, E, Guzzetta A, Haataja L, Cowan F, Rutherford M, Counsell S, Papadimitriou M, Cioni C, Dubowitz L. Neonatal neurological examination in infants with hypoxic ischaemic encephalopathy: Correlation with mri findings. *Neuropediatrics*. 1999; 30(2): 83-89. PMID:10401690.

[8] Nuñez PL, Srinivasan R. *TElectric Fields of the Brain: The Neurophysics of EEG*. 2nd Edition. Oxford: Oxford University Press; 2006. 611p.

[9] Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress - clinical and electroencephalographic study. *Archives of Neurology*. 1976; 33(10): 696–705. doi:10.1001/archneur.1976.00500100030012.

[10] Vannucci RC. Hypoxic-ischemic encephalopathy. *American Journal of Perinatology*. 2000; 17: 113–120.

[11] Volpe JJ. *Neurology of the newborn*. 4th Edition. Philadelphia: W.B. Saunders Company; 2001. 912p.