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MULTI-CHANNEL ACTIVITY CORRELATION ANALYSIS – A METHOD TO DETECT CEREBRAL ISCHEMIA BY THE EEG

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Abstract

The occlusion of the middle cerebral and the common carotid artery was used as model of ischemia. We analysed the electroencephalogram to search for features which were sensitive to the changes caused by reduced blood supply of the brain. Bipolar lead combinations were derived for neighboring electrodes, and the total activity was calculated as the mean square value of the time domain signal. A moving correlation window was applied to them to produce mean correlation as a function of time. All cases showed significant increase of the correlation coefficients following the event of the occlusion. It was concluded that multi-channel EEG activity correlation analysis may indicate the simultaneous drop of activity or the drop-increase-drop sequence on most of the channels due to ischemia. This method represented a further step towards the development of a universally applicable real-time ischemia monitor which could be used under intraoperative circumstances and for long-term monitoring to help to reduce neurological risks related to the instability of the cerebral perfusion.

Keywords: EEG, cerebral ischemia, activity correlation.

1. Introduction

This paper describes an analysis method developed to extract information from the electroencephalogram (EEG). Since the electrical activity of the brain is in strong relation with the metabolic state of the cortical cells, and the metabolism is in interaction with the blood flow, the EEG in fact delivers signs of acute cerebrovascular events, which can be recognized this way [1]. There are two important fields of application of EEG analysis: intraoperative and long-term monitoring. During carotid endarterectomy and cardiac operations with bypass the cerebral oxygen supply may be disturbed severely increasing the risk of neurological and psychological defects [2]. These operations are usually performed on elderly patients with atherosclerotic vascular system. This is an important factor in the etiology of the neurological and psychological defects. Long-term monitoring can be used in the diagnosis of epileptic seizures and in the analysis of drug effects. A new goal of long term monitoring could be the usage of processed EEG data to analyse the effectiveness of the current ongoing therapy in intensive care units. It is usual to perform visual analysis in the operating room by a qualified neurologist, or neurophysiologist. This is a monotonous, boring activity which includes the possibility of several mistakes. However, the recording of the electroencephalogram is widely used because it is a non-invasive diagnostic tool of low price. Imaging techniques which are quite popular nowadays are much more expensive (like CT and MRI), and it is generally accepted that they do not provide immediate information about the acute cerebral ischemia, since those histological changes which can be detected by these methods follow the ischemic event several hours later. The EEG recording device combined with a recent powerful computer can be a very efficient, but also cost saving tool to detect patterns in the signals which reveal cerebral accidents.

Thus, our goal is to develop a monitoring device based on an EEG recording machine connected with a computer which is able to detect ischemic changes in the electrical signals on the surface of the brain resulted from acute cerebrovascular events. The method must be applicable on-line with a short (smaller than 1 minute) delay, and it should possess a very good sensitivity not to produce false alarms which undermine the trust in the device and negatively contribute to the initially tensed atmosphere of the operating room.

The main problem of the analysis of electrical signals of the brain is to find features of the EEG, which are sensitive to ischemic changes. There are several cases mentioned in previous studies which show that no single descriptor can be completely reliable. Multivariate methods included monitoring of several features of a single lead. Total power (or activity) and the spectral edge frequency (SEF) are the most commonly used parameters along with the absolute and relative power in the delta, theta, alpha and beta bands. Some methods extended their observation to more (16 to 32) points of the spectra [3]. Their weakness lies in the variance of the periodogram calculated by the Fourier transform.

Another form of using multivariate analysis can be the multi-channel analysis. Its natural advantage is the reduction of the variance of a parameter at a certain time by averaging it over the space, if its expected value is believed to be constant over the scalp. Moreover, disturbances in the blood flow of one of the major supplying arteries may affect a whole hemisphere, therefore the task of recognizing a certain pattern of the signals, or a state of the system (in this case it is the brain) can be converted into detecting similarities over a large portion of the skull. In contrast to previous systems, which are based on a small number of channels, we use 16 electrodes for monitoring.

The middle cerebral artery (MCA) occlusion and the clipping of the common carotid artery (CCA) were used as models of cerebral ischemia in cats [4].

We aimed to compare activity changes in the case of an MCA occlusion which can be regarded as the model of the human stroke; and uni- and bilateral carotid occlusion which reveals the human transitory ischemic attack (TIA). Altogether we carried out 23 occlusions of the carotid in three cats, and 16 occlusions of the left MCA in cats.

We showed that the clipping of the MCA and the CCA causing ischemia was accompanied by changes of total power on every channel at the same time. The MCA occlusion resulted in a better localized disturbance, meaning that the two hemispheres showed a different reaction. In the case of the closure of a carotid artery, ischemic patterns appeared over the whole head. Our goal was to derive EEG features, which distinguished the post occlusion period from other parts of the recordings.

2. Methods

2.1 Experiments

Altogether 20 experiments were carried out with male cats, weighing 2.5 kg ($\pm$0.5 kg), mean age: 2 years. For the MCA occlusion (17 cases) we induced intraperitoneal barbiturate anesthesia (Nembutal 40 mg/kg) and we used the O'Brian-Waltz transorbital approach to reach to the artery. In other 3 experiments when the common carotid arteries were prepared we applied intraperitoneal chloralose anesthesia. During the experiments the important physiological parameters (blood pressure, temperature, blood gases and pH) were kept constant.

The EEG data were recorded using a standard EEG device and a PC with analog/digital conversion board (*Fig. 1*).

The signal was detected by 16 stainless steel screw electrodes which were fixed in the skull after removing the skin and the muscles from the head. We used the broadly accepted 10-20 system for the spatial location of the electrodes with necessary changes due to the anatomy of the animal (*Fig. 2*). The sampling frequency was chosen to be 128 Hz, which was adequate for getting the necessary information from the signals using analog anti-aliasing filters. The EEG was registered referentially, using the average of all channels as reference. The reason is that we failed to find a fixed point on the head of the cat, which could have been suitable for reference,

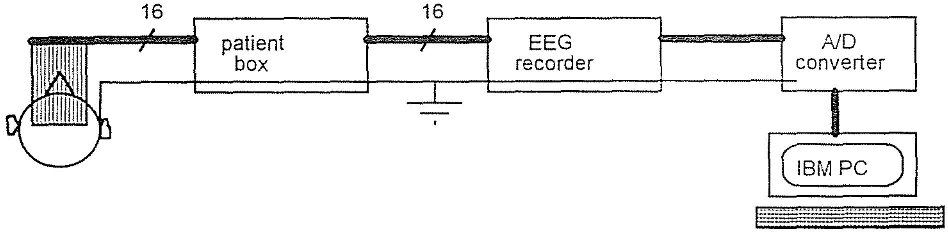

Fig. 1. The experimental setup

because the ears and the surrounding muscles were on a high impedance, and their potential was not constant at all. Therefore we chose the virtual reference as the average of the potential of all 16 channels.

The recording protocol for the MCA cases was the following: 5 minutes of pre-operative control section before opening the way to the artery; 5 minutes of pre-occlusion and 25 minutes after the occlusion. Since we kept the clip on the artery for 2 hours we could evaluate the long term effect of the ischemia as well. During the experiments with repeated CCA occlusion the electroencephalogram was recorded continuously for approximately an hour. In these cases we expected ischemic changes to be present shortly after the clipping so we could regard the sections between two successive closings of the artery as control periods. Thanks to the above mentioned structure of the protocol we were able to record: 1) the long lasting distortion of the EEG signal due to the lack of blood supply compared with the intact period for the MCA cases; 2) the mild changes related to the closing of the CCA as they appear surrounded by normal background activity.

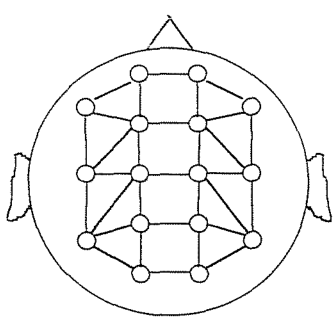

Fig. 2. Placement of electrodes and the bipolar channels. The triangles and squares formed this way are the regions

2.2 Data Analysis

We analysed the data off-line after the experiments. First unipolar and bipolar channels had to be evaluated in regard of the visually observable distortions related to the ischemia. We had a priori information in favour of both methods. Brain mapping techniques based on unipolar channels were used by many researchers to detect cerebral infarction. A clear advantage of the bipolar leads lies in the building of the difference between the electric potentials of two neighboring electrodes. This type of signal is the least sensitive to external disturbances which occur on all channels with the same amplitude at the same time. However, recording referentially involves the possibility of calculating bipolar channels. This way, arbitrary combinations of electrodes can be used to create bipolar leads off-line.

Visual analysis trying to describe ischemic changes of the EEG mentions the following characteristics the most often: depression of the amplitude, short periods where the signal is almost isoelectric, relative poverty of waves meaning the loss of high frequency components [5]. Looking at both uni- and bipolar leads, the latter were definitively more similar to the above mentioned description. Regarding the ratio of the amplitude depression for MCA cases, unipolar recordings showed a decrease of $0.8 + / - 0.3$, whereas the same value for bipolar channels was $0.4 + / - 0.3$ (post-occlusion period divided by pre-occlusion value). For these reasons bipolar channels were taken as the basis of the further calculation.

To extract proper features from the 31 bipolar channels with 128 samples per second, an efficient data reduction method had to be found. We had to consider the following: 1) bipolar channels are originated from 16 recorded leads and these are correlated due to the small distance among the electrodes, therefore, the spatial resolution could be decreased [6]; 2) we aimed to detect events which are present for several seconds, therefore quick changes (high frequency components) could be eliminated; 3) it is useful to calculate a feature which carries physiological meaning, this way the description of the signal by a human observer could be approximated in a more exact way; 4) the data reduction procedure should not be too complex, since an on-line application is proposed.

Considering the above mentioned criteria we choose the activity calculation as the data reduction procedure. Within the terminology of the electroencephalography, total activity (or power) is the sum of the power on all frequencies of the power spectra. According to the law of Parseval, this is equal to the mean square value of the original signal in the time domain over the same period for which the spectrum is calculated (*Fig. 3*).

$$A = \frac{1}{N} \sum_{i=0}^{N-1} |X(i\Delta f)|^2 = \frac{1}{N} \sum_{i=0}^{N-1} x_i^2 \; ,$$

$$X(f) = \mathrm{FFT}\{x_i\} \; .$$

As for the physiological content, the total power can be interpreted as a measure for metabolic activity, furthermore, as a parameter to characterize the difference between the isoelectric signal (brain death, zero activity) and the real EEG. Later in this paper we use the word activity for the mean square value of the signal over a certain period of time which is called epoch.

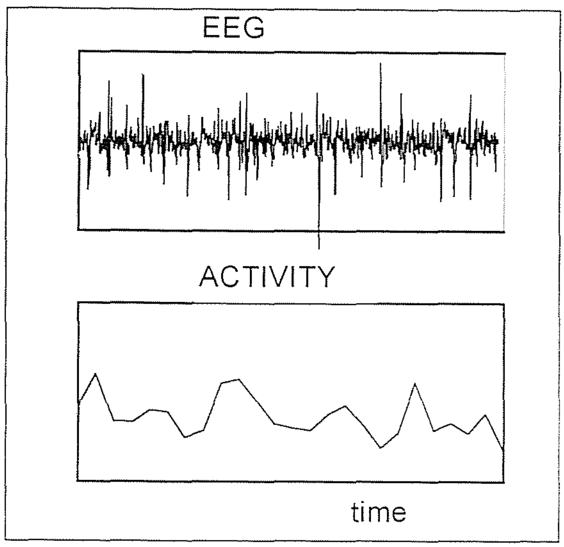

Fig. 3. A segment of normal EEG and the corresponding activity (mean square value by epochs)

A clear advantage of the calculation is that the assessed estimation of the activity has a low variance. Let x be the EEG signal, C_x^2 be the covariance function, μ_x the expected mean of x.

$$\mathrm{var}\,\{\overline{x^2}\} = \frac{1}{N} \sum_{i=0}^{N-1} \left[1 - \frac{i}{N}\right] \left[C_x^2(i) + 2\mu_x^2 C_x(i)\right] \; .$$

If we consider the EEG to be a Gaussian signal with σ_x^2 variance, the following estimation is valid:

$$\text{var}\ \{\overline{x^2}\} = \frac{1}{N}(\sigma_x^4 + 2\mu_x^2\sigma_x^2) \quad \mu_x = 0\ .$$

For real EEG signals $\sigma_x^2 \approx 200$, therefore, the variance is approximately 312, this is less than 1% of the typical activity value.

The determination of the epoch length deserved special attention. We investigated the variance of activity within an epoch as a function of the epoch length. It was concluded that epochs with a length of 1 second provided satisfying approximation of the original squared signal, the activity array contained the necessary information to detect changes of 5 to 10 seconds and the calculation time remained in a range which enables on-line performance.

By these means we get the time function of the power which is the activity array. Since the original EEG contains frequency components between 0 and 32 Hz, the squared signal will extend up to 64 Hz. This can be understood if we regard the signal as a sum of sine waves:

$$\sin^2(x) = \frac{1 - \cos(2x)}{2}\ .$$

The application of averaging causes the spectra to be multiplied by the well known sine function. The sampling frequency drops to $128/N$; where N is the number of samples per epoch because we only retain one value for each epoch. For this reason the spectrum of the activity array is close to a constant value over all frequencies, therefore, the array looks very similar to noise.

Furthermore, visual observation of the EEG revealed some artifacts expressed by large amplitudes over 2-3 seconds. For biological signals where the data set might contain extreme values the application of median filtering could be useful. So we used a moving median window of 7 points to eliminate extremely large power values. Since the output of such a filter could show a rather cornered pattern, another moving average filter was applied, with coefficients corresponding to the 5 point Hanning window (lifted cosine function). The coefficients were the following:

$$h_1 = \frac{1}{12}\ ; \quad h_2 = \frac{1}{4}\ ; \quad h_3 = \frac{1}{3}\ ; \quad h_4 = \frac{1}{4}\ ; \quad h_5 = \frac{1}{12}\ .$$

The final result, the smoothed activity array delivered information about the slow (below 1 Hz) changes of the mean square value of the EEG in the time domain (*Fig. 4*).

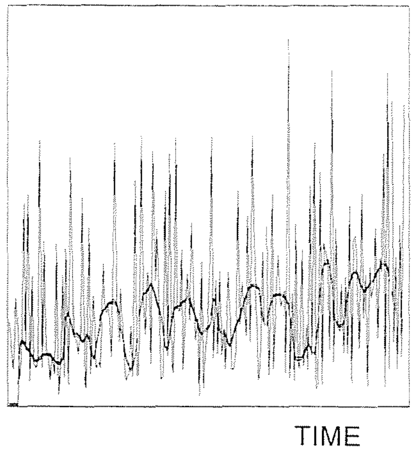

Fig. 4. Effect of smoothing filters. Extreme values are discarded and high frequency changes are also neglected

After this we examined the activity arrays and searched for features of the ischemia occurring shortly after the occlusions. In most cases of MCA clipping the event was followed by drastic drop of the activity on all ipsilateral channels. The CCA cases showed a typical pattern of a drop-increase-drop sequence on several (8 or more) channels. To detect similar trends (drastic drop for the MCA, drop-increase-drop sequence for the CCA cases) on most of the channels, we monitored the cross-correlation coefficients (*Figs. 5,6*).

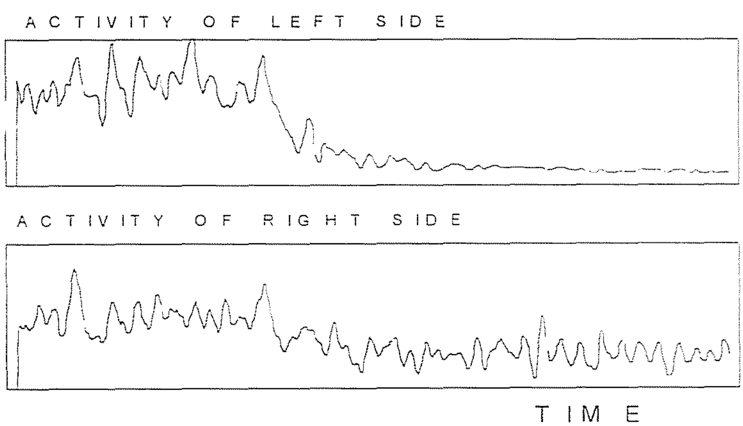

Fig. 5. Drastic drop of activity in the case of left (upper curve) MCA occlusion

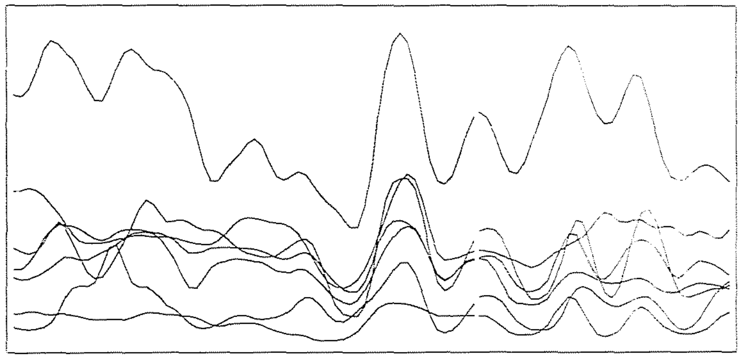

Fig. 6. Activity drop-increase-drop sequence following bilateral carotis clipping. The curves are only demonstrating the pattern, not all channels are shown

The calculated value was the normalized cross-correlation coefficient according to Pearson. We regarded a certain length of data (the activity arrays within a so called correlation window) and calculated Pearson's coefficient for given pairs of channels. The following calculation was performed (x is the signal of a channel, y is the signal of another):

$$r_{xy} = \frac{1}{N}\frac{\sum(x-\overline{x})(y-\overline{y})}{\sqrt{\sigma_x^2\sigma_y^2}} \ ,$$

$$\sigma_x^2 = \frac{1}{N}\sum(x-\overline{x})^2 \quad \sigma_y^2 = \frac{1}{N}\sum(y-\overline{y})^2 \ .$$

The denominator is the square root of the multiplication of the variances, and the numerator is the covariance of the two corresponding arrays. The length of the window must be set in accordance with the size of the pattern that we aim to recognize. After the visual observation of several EEG sections after the occlusion, we decided to apply a window length of 12 points, which means in this case 12 seconds, because the activity vectors contain data at every second. As mentioned, the target pattern is different for the MCA and the CCA cases: the middle cerebral artery occlusion caused a drastic drop of the activity over 20–40 seconds, whereas the carotis clipping resulted in a mild drop, followed by an increase and a repeated drop of the activity. Since these trends occurred simultaneously on all channels, the cross-correlation between them was supposed to increase at this moment.

To obtain adequate results the significance of the coefficients should be tested as well. The hypothesis that the cross-correlation is not a result of coincidence can be evaluated using Student's t-test for the following value:

$$t = r\sqrt{\frac{N-2}{1-r^2}} .$$

If the above calculation for t results in a greater value than the t-distribution at the proper degree of freedom, then we can state that the probability for the correlation coefficient being not significant is smaller than the given p. Since the window length determines the value of N, we can calculate r for a desired t_0 level of significance

$$r = \sqrt{\frac{t_0^2}{N-2+t_0^2}} .$$

If this is 0.5%, and $N = 12$, then r equals 0.7. This means that two sets of data containing 12 samples each are significantly correlated (so the probability of the hypothesis of being uncorrelated is less than 0.5%) if Pearson's correlation coefficient is greater than 0.7.

The second factor to be considered is the combination of the channels to be tested for correlation. It is obvious that 31 leads offer $31 \times 30/2$ possible combinations. For the reasons cited in the introduction we have selected those pairs which may contain physiological meaning. These are neighboring channels. The pattern has the advantage that it divides the scalp into 16 regions, so it is reasonable to pair the channels for correlation within one region. Therefore, the model is useful to observe regional changes of similarity and similar changes over all the regions.

The next question is how to get the correlation value for a region. The algorithm described in this paper uses the simple arithmetic mean of the coefficients calculated by pairs. ($r(ch1, ch2)$ is the correlation between channel 1 and channel 2). This is a simple approach, but it is quick and provides good result in our case.

$$r_1 = \frac{r(ch1,ch2) + r(ch2,ch3) + r(ch1,ch3)}{3} .$$

According to the analysis method presented so far, we have 16 regional average correlation values ($r_1 \ldots r_{16}$) in each second, and we have to determine the ischemic state of the patient from these data. We observed that every occlusion was followed by an increase of all these values. Randomly one or more of them tend to increase as well, but not all of them. This property is very well reflected if we multiply all regional correlation coefficients: the product will be great when all the numbers are close to 1. In other cases the product will be close to zero.

We applied eigenvalue analysis to determine how many percent of the information content of the original 31 bipolar activity vectors can be expressed by 16 values. The correlation matrix **R** was assessed from 200 seconds of data from 31 channels. The eigenvalues (λ) of this matrix were ordered into descending row, and then summed.

$$\mathbf{R}(i,j) = r(ch_i, ch_j) \ ,$$

$$R\Lambda = v\lambda_i \ , \quad \lambda_1 > \lambda_2 > \ldots > \lambda_{31} \ ,$$

$$L_i = \sum_{j=1}^{i} \lambda_j \ .$$

After performing the calculations for more than one hour of control EEG recordings, we concluded that 98% of the information is kept, this means that $L > 0.98$ if $i > 16$. Therefore, we expect the 16 regional correlation coefficients from all over the scalp to deliver enough information, as if the analysis was made from the 31 bipolar activity arrays.

3. Results

The presented results come from 17 experiments when the middle cerebral artery was occluded, and 3 with carotid occlusion. Due to the well-known fact that cats show different severity of ischemia after MCA occlusion, the activity arrays showed a great variety. Nine of them had long lasting depression and in these cases it was possible to detect the ischemia simply by observing one channel only (*Fig. 5*). These were the cases of severe stroke. On the other hand, in the case of mild strokes observation of one channel had no informative value because of the inherent changes being in the same magnitude as the drop due to the occlusion.

According to the observation of the activity vectors, the clipping of the common carotid artery never caused such a solid and drastic suppression of EEG power as the occlusion of the MCA. However, an initial drop signalized the time when the blood flow was stopped, followed by an increase in power which lasted for about 5 seconds. Finally a repeated drop closed the pattern. The event had a total period of 12 seconds and it appeared on all channels (*Fig. 6*).

Fig. 7 is an illustration of this method. We show only 3 channels instead of 31 for better understanding. As the signal (the normal EEG) becomes more dense with larger amplitudes, the mean square value (the activity) increases. Since the ascending tendency in the time functions of the activity is appearing simultaneously, the correlation coefficients between

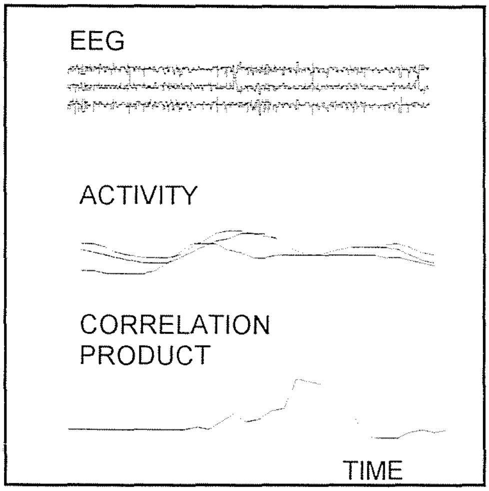

Fig. 7. Synchronized drop-increase-drop sequence and its effect on the correlation product (below). Here 3 channels are shown to demonstrate the method, the actual calculation regards all bipolar channels according to the scheme in *Fig. 2*

pairs of channels begin to increase after a certain time (the time functions of individual correlation coefficients are not shown). This is reflected in the increase of the product. Note that all correlation values must increase since it is true that the product is smaller than the smallest of the coefficients (because they are below one).

Complete experiments are illustrated in *Figs. 8* and *9*. We can see the increased product related to the clipping of the corresponding artery. Visual observation revealed that there were artifacts in the recordings, and they were connected with extremely large correlation products. Their presence is more obvious in *Fig. 9*, during MCA occlusion. After analysing the products of all experiences, we were able to draw a limit, which served as a separating level. If the product reached above the limit the ischemic event was signalized.

Using the above mentioned method, 19 events (the onset of the ischemia) could be detected (82.6%) in the case of carotis occlusions, and 14 (87.5%) in the case of clipping the MCA. Therefore, the combined sensitivity was 84.6%. As for the long lasting ischemia of the MCA cases, this state was characterized by the increased frequency of correlation product peaks above the defined level.

False alarms appeared in the control recording of 8 cats, demonstrating that further refinement of the criteria is necessary. We took those alarms into consideration as well, which were obviously related to external

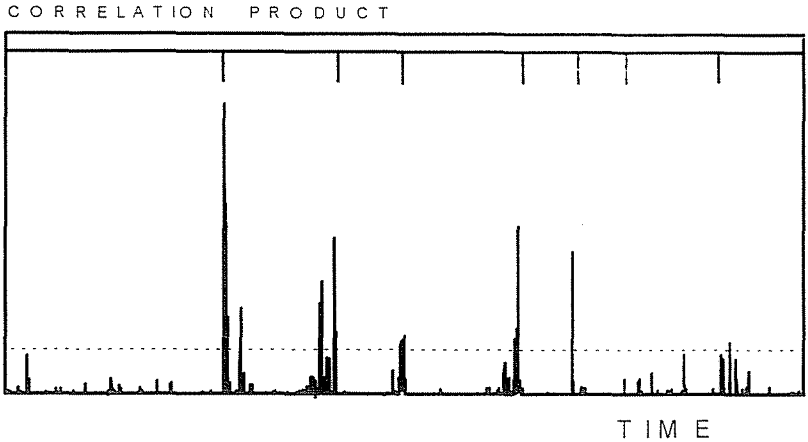

Fig. 8. Repeated carotid occlusions and the increase in the correlation product. The ticks on the upper line are indicating the time of occlusion. The 6th occlusion is not detected because the correlation product did not reach the predefined limit

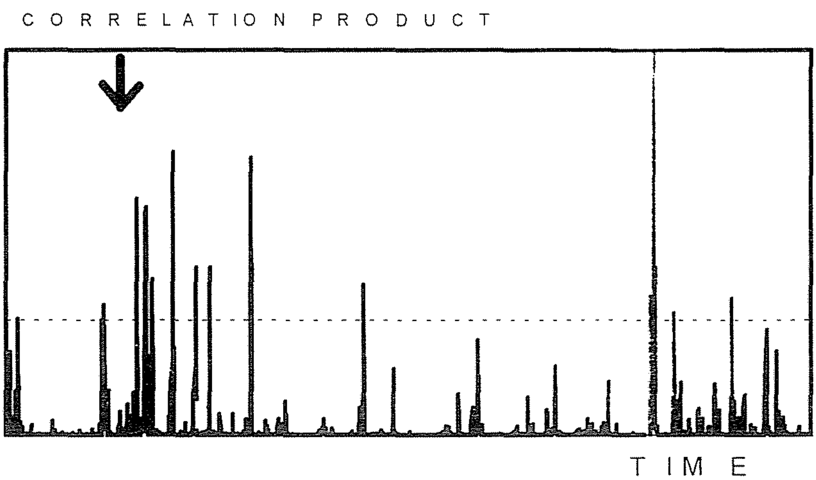

Fig. 9. Clipping of the left MCA at the moment of the arrow. Increase of the correlation product can be observed immediately after the onset of ischemia. As the frequency of correlation product peaks above the defined limit decreases, the animal is recreating blood flow by collateral arteries

electrical interference because such an effect may occur in the operating environment, too.

4. Discussion

The algorithm is based on the spatially synchronously occurring activity changes of the EEG all over the surface of the skull. The calculation of the activity is fast, it has a low variance, and it means a powerful information reduction. The calculation of the cross-correlation using Pearson's coefficient gives a good indication for the similar trend of the activity vectors originated from different areas of the cortex. The eigenvalue analysis of the activities assumes that 16 values at one time contain the majority of the information content of the original signal. Therefore, the 16 regional correlation values are believed to reflect truly the changes all over the whole scalp.

This version of the multi-channel activity array analysis calculates and follows the product of the regional correlation coefficients. It is possible to define ranges of the product in which the value stayed during the onset of ischemia. As expected during a long lasting severe ischemia the monitor signaled several times. We interpreted this as an indication of the impaired condition of the brain, where the frequency of the indication is roughly proportional to the severity of the stroke. We can state that the analysis method found a good way to uniformize the EEG changes related to ischemia and detected them with a high sensitivity, which is comparable with the performance of a human observer. To eliminate false alarms, which are characterized by the relatively low specificity, is still a problem to solve. Comparing to earlier methods developed to detect ischemic changes caused by the occlusion of the MCA, this latest algorithm uses a much shorter window, and this seems to be the reason of more false alarms. However, we should not forget that the detection of the mild changes caused by the clipping of the carotid arteries makes it inevitable to apply a short window.

Further evaluation of the experimental data gained so far can give ideas for a better algorithm with increased specificity which is a high demand for a device in order to maintain trust and belief in the results. We think that this algorithm can be realized and it can be the basis of a monitoring device. The instrument can be connected to an EEG recorder through the analog signal output.

As for the physiological meaning of the presented analysis method we have to remark 3 main points: 1) we observed slow changes (0.5 Hz or below) of the activity expressed as a difference from the isoelectric line (zero mean square value), this is a factor of organized nerve function; 2) regional values are assessed to deliver information from a certain part of the scalp, these regions actually cover the whole surface; 3) we searched for a global change or tendency, which occurs on the majority of the regions believing that ischemic changes show up on most of the channels; this is an important characteristic of the ischemic phenomena.

Fast diagnosis is a precondition of effective therapy in cerebrovascular accidents. Multi-channel activity correlation analysis is not only a quick diagnostic tool, but it is a reliable method because data are collected from the entire scull.

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