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COMPARISON OF BIOELECTRICAL ACTIVITY CHANGES IN THE COURSE OF PHYSIOLOGICAL AND PATHOLOGICAL AGING

PORÓWNANIE ZMIAN AKTYWNOŚCI BIOELEKTRYCZNEJ MÓZGU W PRZEBIEGU FIZJOLOGICZNEGO I PATOLOGICZNEGO PROCESU STARZENIA

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ABSTRACT: Introduction. *Aging of the central nervous system manifests itself by impairment of function and changes in brain structure. Main structural changes is the brain tissue atrophy. The functional changes are impairment of cognitive function, memory, sensation and consciousness. Evaluation of this process required advanced methods for structural and functional examinations. The technical support of diagnostic methods has provided ad-*

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vanced methods of neuroimaging and electroneurophysiological examinations. The essential issue in the evaluation of the progress of physiological aging process in nervous system is to detect the symptoms at the very early stage. This is especially important in the occupation medicine i.e. in case of air crew members. ***Material and Methods.*** *Our studies focus on the developing of neurophysiological methods for evaluation of changes in the reactivity of central nervous system due to the aging process and differentiation between various types of senescence processes and evaluation of their severity. The study was performed in a group of healthy subjects and a group of patients with dementia.* ***Results.*** *In the group of healthy subjects a decrease in alpha band power has been found. Increasing amount of slow waves in EEG recordings was characteristic in the patients group, only. In both groups latency of P_{max} component was prolonged. Evoked potentials in the patient group presented variable shape.* ***Conclusion.*** *The electroneurometric coefficients enable getting inside and are useful in differentiation between physiological and pathological aging of nervous system and prognosis of the progress of functional deficits*
KEY WORDS: *Aging, neurophysiology, aviation medicine, neurodegenerative processes, senescence*

STRESZCZENIE: Wstęp. *Starzenie centralnego układu nerwowego objawia się zmianami zarówno struktury jak i funkcji mózgu. Zmiany strukturalne dotyczą przede wszystkim zaniku i destrukcji zwyrodnieniowej, natomiast zmiany funkcjonalne dotyczą ubytku funkcji poznawczych i percepcji zmysłowej oraz pamięci. Ocena tych procesów wymaga zaawansowanych metod badań struktury i czynności w zakresie neuroobrazowania i badań elektroneurofizjologicznych. Najbardziej istotnym zagadnieniem oceny procesu starzenia jest wykrycie jego najwcześniejszych objawów. Jest to szczególnie znaczące w dziedzinie medycyny pracy i lotniczej.* ***Metody.*** *Badania koncentrowały się na opracowaniu metod elektroneurofizjologicznych oceny zmian reaktywności centralnego układu nerwowego związanych z wiekiem i różnicowania różnych postaci procesu starzenia i stopnia zaawansowania. Badania były prowadzone w grupie osób zdrowych i chorych z objawami demencji.* ***Wyniki.*** *W grupie osób zdrowych stwierdzono obniżenie mocy sygnału w paśmie alfa, natomiast w grupie chorych zwiększony udział fal wolnych w paśmie delta i theta. W obu grupach czas latencji komponenty P_{max} w potencjałach wywołanych był wydłużony. W grupie chorych potencjały wywołane charakteryzowały się zróżnicowaniem kształtów.* ***Wnioski.*** *Ocena metodami elektroneurometrycznymi wspomaga rozpoznanie procesu starzenia a także różnicowanie między procesem fizjologicznym i patologicznym oraz prognozowanie postępu deficytu czynnościowego*

SŁOWA KLUCZOWE: *starzenie, neurofizjologia, medycyna lotnicza, procesy neurodegeneracyjne, starość*

Introduction

The continuous extension of the human life-span to an average 75 years today, up from 47 years in 1900 carries a significant increase in the requirement of medical problems of aging diagnosis and treatment of aging. In the physiological course of aging the effectiveness of the homeostatic processes decreases due to the impairment of all organs functioning. In circulation, it is decreasing vessel elasticity, in lung is the limitation of respiration volume, etc. The term senescence means the property characteristic of old age, the organic process of growing older and showing the effects of increasing age, i.e. loss of the functional efficiency. The theories of the senescence are addressed to the two main concepts. One of them assumes the genetic determination of the programmed apoptotic processes. Another one point the external damages, such as the impairment of the mitochondrial mechanisms by the free radicals, the distortion of the hormonal regulation by released stress corticosteroids that damage hypothalamic neurons, etc. These lead to the age-related malfunction in healthy subjects. Recently, these processes assigned with the physiological aging turned out to pave the way for the pathological processes. Therefore, prolonged human life, work in extreme conditions brought also the onset of the symptoms of slowly developing degenerative processes in which an old age is the most important risk factor. The physiological aging without any symptoms of diseases is called successful aging and may be found in the 10% of population only. In most cases, there are coexisting diseases and therefore the most important and difficult task is to differentiate the physiological and pathological processes associated with aging [22,23].

Hallmarks of aging of the nervous system are of particular importance since they implicate difficulties in the social activity and therefore cause deterioration of the quality of life. The essential issue in the evaluation of the progress of physiological aging process in nervous system is to detect the symptoms of the nervous system aging at the very early stage. This is especially important in the occupation medicine i.e. in case of air crew members.

The aging of the central nervous system manifests itself by impairment of cognitive function, memory, sensation, consciousness and structural changes that are mainly the brain tissue atrophy. However, that are the biochemical changes in synaptic composition and function that underlined the aging process in nervous system rather than a significant loss of neurons or synapses. The available data suggest that these changes are the critical underlying factors for aging-related cognitive decline [4,5,8,10,23].

Changes in neurons and neurotransmitters affect communication between neurons. In certain brain regions, communication between neurons can be reduced because white matter (myelin-covered axons) is degraded or lost. Atrophic changes in the prefrontal cortex and the hippocampus affect complex mental activities such as learning, memory, planning. Changes in the brain's blood vessels reduce blood flow due to the narrowing of the arteries and less growth of new capillaries [9].

In the course of aging amounts of structures called plaques and tangles increases outside of and inside neurons. This process is considered as a significant indicator of the aging process. Plenty of these structures are found in brains of patients suffering from Alzheimer disease being the hallmark of this degenerative process [21].

The current thinking about the evolution from healthy aging to the neurodegenerative process assumes that the gradual aging process results with the stage of MCI (mild cognitive impartment at age 50-60 yrs). The combination of the biological, genetic, environmental, and lifestyle factors over a lifetime decide on the further course of aging. Some people continue on a course of healthy cognitive aging or reveal the neurodegenerative process. Therefore, it is extremely important to recognize the symptoms of this stage and to find methods that allow to evaluate the progression of senescence process [19].

The screening method used for that task is the Mini Mental State Examination (MMSE) or Folstein test (1975) [6]. This is brief a 30-point questionnaire test that is used to screen for cognitive impairment. It samples various functions including arithmetic, memory and orientation. The results between 25 and 30 scores indicate physiological aging while these between 19 and 24 – the MCI state. Lower results mean moderate or severe cognitive function impartment.

Since the first descriptions of patients with a loss of memory, fundamental knowledge of the clinical course, pathogenesis, pathomorphology, neurochemical basis, diagnostic methods and therapy of different types of dementia has greatly progressed. These enable the great step forward in developing diagnostic methods and treatment procedures.

Evaluation of the physiological changes underpinning the senescence process required advanced methods for structural and functional examinations. The technical support of diagnostic methods has provided advanced methods of neuroimaging: CT, MRI, PET SPECT enabled visualization of nervous system structure with high resolution.

Electroencephalography is a more precise noninvasive method useful for recognition the functional impairment and also monitoring progress in the aging process. The trend of the developing in this field is high spatial and time resolution of 3D mapping of brain electrical activity and localization of its sources. Significant progress has been also made in the fields such as neuropsychology that evaluate behavior and intellectual function or neuroinformatics that develops advanced theories of nervous system function using experimental data and computational models [20].

The trend in the central nervous system investigation is to combine structural and functional examinations. The idea of this development is the comprehensive analysis of neuroimages and brain electrical activity maps i.e. fMRI. This methodology enables the topolocalization of brain electrical activity sources and therefore to study the relationships between structure and function.

Our studies focus on the development of neurophysiological methods for evaluation of changes in the reactivity of the central nervous system due to the aging process [4,12,13]. In our Interinstitute Neurophysiology Laboratory at the Military Institute of Aviation Medicine, we deal with the longitudinal elektroneurophysiological examinations of healthy subjects, the air crew. Our previous study suggested that the alpha index decreases in a course of aging.

Physiological aging and its influence on the function of nervous system and also on the behavior is a crucial problem in the occupation medicine. It is particularly important in transportation and aviation medicine in the aspect of emergency and public safety.

In collaboration with the Department of Neurology of Warsaw Medical University we are developing methods for differentiation of various types of senescence with comparative this processes and evaluation of their severity in mild and old gender health persons [7].

Methods

The EEG was recorded using NeuroScan 4.3 system from up to 64 electrodes. Signals were recorded in the frequency band 0.1-200 Hz and sampled with the frequency 1kHz. Using STIM 2 stimulator, the multimodal stimulation was applied. STIM 2 provides also perceptual, attention, memory and cognitive tests such as: Stroop, taping, spatial memory, naming or sorting cards. During examination the patient's behaviour was continuously recorded, using an audio video system synchronized with the signal sampling.

The spectral analysis of EEG signals, comprehensive analysis of resting EEG. before and after each stimuli have been performed. The changes of energetic value spontaneous EEG due to stimulus were evaluated separately in frontal, temporal and occipital regions and the connectivity between different brain specific modules have been analyzed.

The results of both visual and quantitative EEG (QEEG) have been compared in cases of physiological senescence, various types of Alzheimer's disease (AD versus subcortical vascular dementia SVD) and aging matched control group.

The material consisted of EEG data recorded during a longitudinal observation in 112 health air crew members (mean age of 40 yrs). The comparative study was performed in a group of 92 patients, 61 patients with probable Alzheimer's disease (the mean age 73.6 yrs; M 49%) and 31 patients with probable SVD (mean age 72,3; M-43%, F-57%), and 14 old healthy subjects as comparative group (mean age 72,3, M-57%, F-43%). The patients were selected according to NINCDS-ADRDA and NINCDS- AIREN and Erkinjuntii's criteria. According to Mini Mental Scale Examination (MMSE) [Folstein, Folstein, Mc Hugh, (1975)], AD and SVD group was divided into 2 subgroups with mild and moderate dementia. The alpha/slow waves power ratios, mean waves frequency in all and selected derivations were calculated.

The study on evoked potentials were performed in the patient group comprised of 12 patients with probable Alzheimer's disease and the control group comprised of 8 healthy volunteers (mean age 61yrs). The patients with Alzheimer's disease were divided into subgroups with mild (8 patients, 74 yrs), and marked dementia (4 patients, 72 yrs).

Photo-stimulation with the frequency of 0.5 Hz was used in the examination of visual evoked potentials. The evoked potentials were extracted by averaging and the analysis of evoked potentials and EEG signal before and after each stimuli was performed. In Fig.1 the time scale of the stimulation is shown. The periods of the EEG signal selected for analysis are marked.

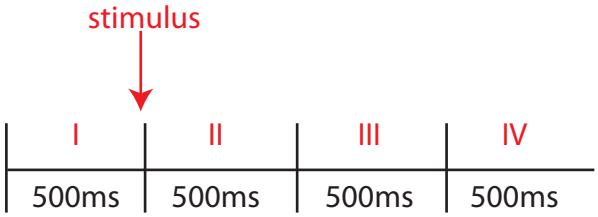

Fig.1. The periods of the EEG signal before and after stimuli. These periods have been labeled as: I – 500 ms before, II – 500 ms after, III – from 500 ms to 1000 ms, and IV – from 1000 ms to 1500 ms.

Ryc. 1. Wybrane do analizy odcinki sygnału przed i po bodźcach. Oznaczenia: I – 500 ms przed, II – 500 ms po, III – od 500 ms do 1000 ms i IV – od 1000 ms do 1500 ms.

The dynamic of the EEG activity was evaluated by coefficients defined as the ratio of EEG power in one of the periods after stimulus to the EEG power in the period 500 ms before stimulus. The coefficients were calculated for each frequency bands, i.e. delta (2-4 Hz), theta (4-7 Hz), alpha (7-13 Hz), beta (13-30 Hz).

The latency and inter-hemispheric symmetry of the evoked potentials were analyzed. The parameters of evoked potentials and EEG signals during stimulation were compared between age matching control groups and patients suffering from dementia.

Results

EEG recordings in the group of healthy subjects presented no abnormalities. However, the tendency to the disorganization of rhythms was observed that manifests itself by changes in the signal power in particular frequency bands. In the group of patients with dementia the increasing amounts of the low frequency activity in delta and theta bands was indicated. These changes have been proved statistically.

Following some examples illustrating the noticed changes in EEG characteristic are presented. The EEG signals recorded in a subject from the control group shown in Fig. 2 contains rhythms and discrete elements of disorganized activity. In example of the EEG of a patient with the middle stage of AD dementia shown in Fig. 3 the alpha rhythm is preserved in the occipital region in right hemisphere and increased amount of slow activity is evident. In case of severe AD disease shown in Fig. 4 the activity in delta and theta band dominates.

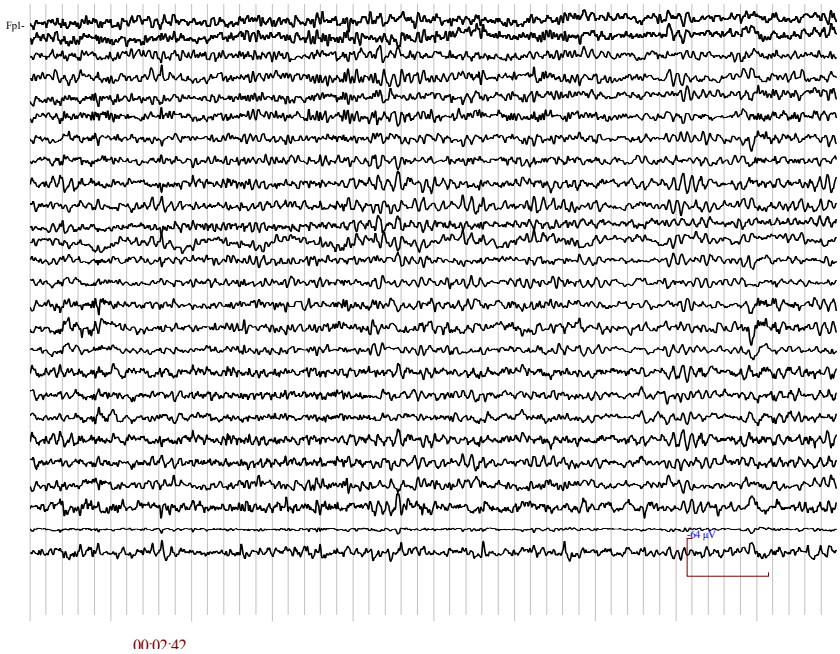

Fig. 2. EEG record of subject from the control group.
Ryc. 2. Zapis EEG osoby z grupy kontrolnej.

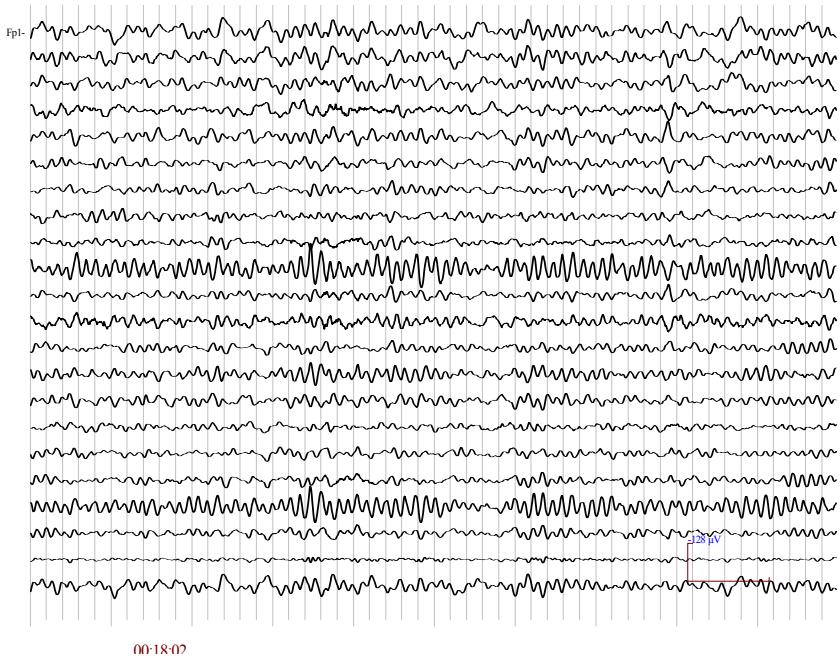

Fig. 3. EEG record of AD patient with mild stage.
Ryc. 3. Zapis EEG pacjenta z zespołem AD w stopniu umiarkowanym.

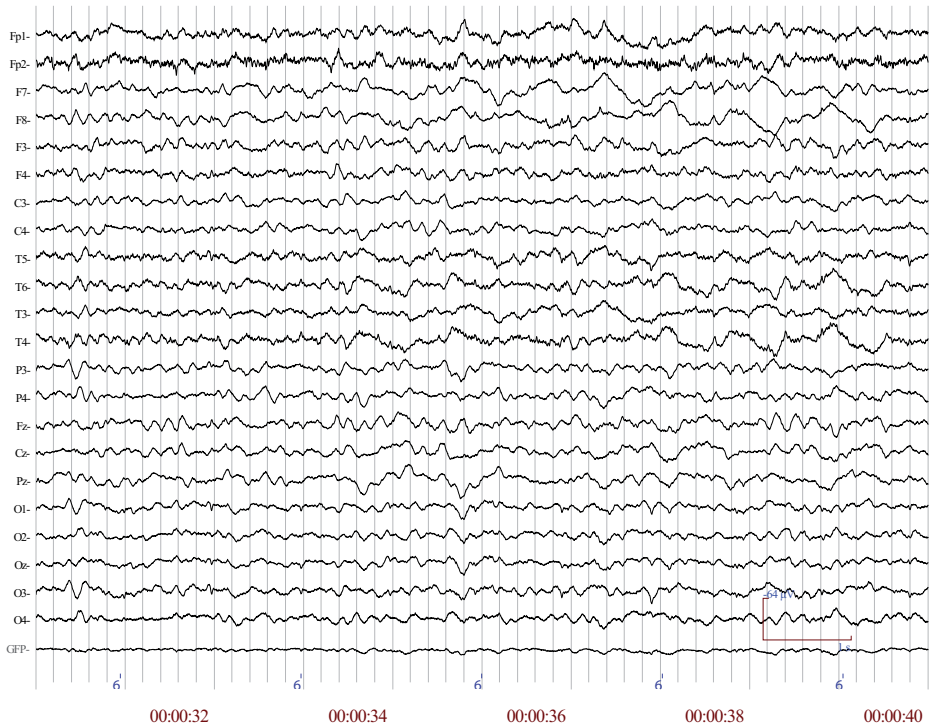

Fig. 4. EEG record of AD patient with severe stage.
Ryc. 4. Zapis EEG pacjenta z zespołem AD w stopniu zaawansowanym.

Results of signal power comparison calculated using MGFP method is presented in Fig. 5. Results indicate no inter-hemispherical difference in any group. In the AD patients group increased power of bioelectrical activity in the frontal region can be noticed.

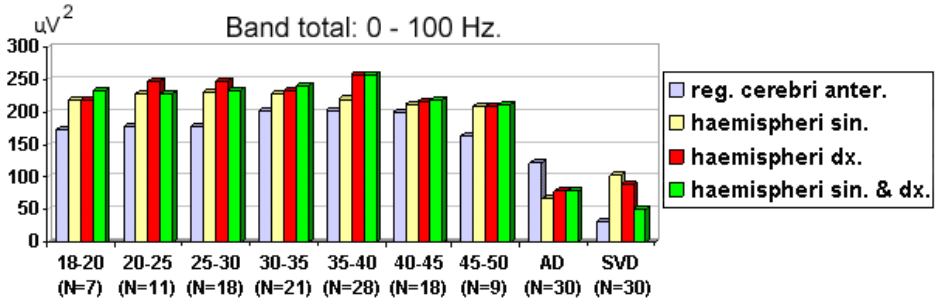

Fig. 5. Power of EEG activity in control and patients group.
Ryc. 5. Wykres mocy sygnału EEG w grupie kontrolnej i w grupie pacjentów.

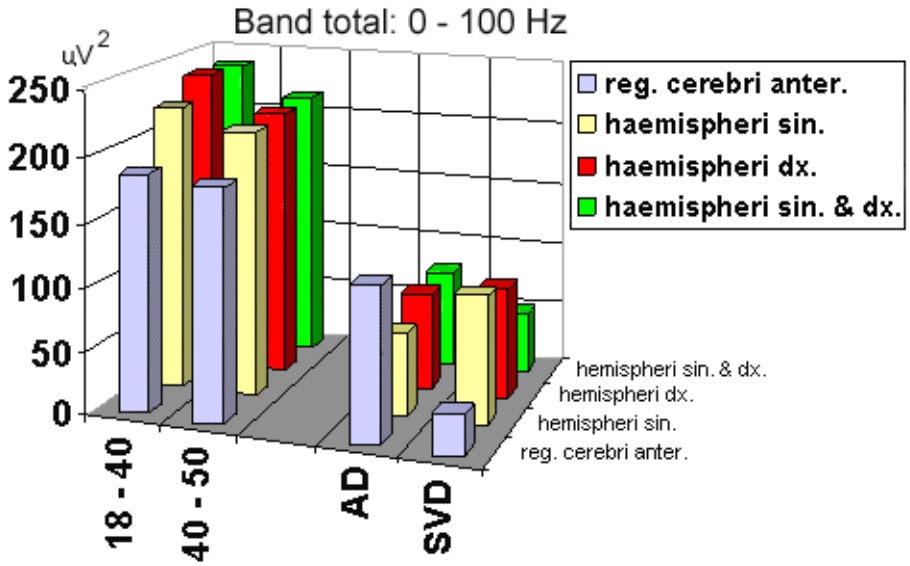

Fig. 5a. Power of EEG activity in control and patients group.
Ryc. 5a. Wykres mocy sygnału EEG w grupie kontrolnej i w grupie pacjentów.

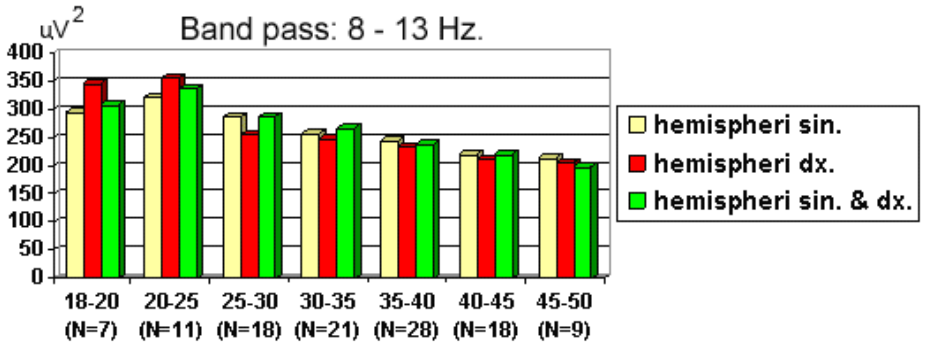

Fig. 6. Power of activity in alpha band decreases in a course of aging.
Ryc. 6. Wykres mocy sygnału EEG w paśmie alfa.

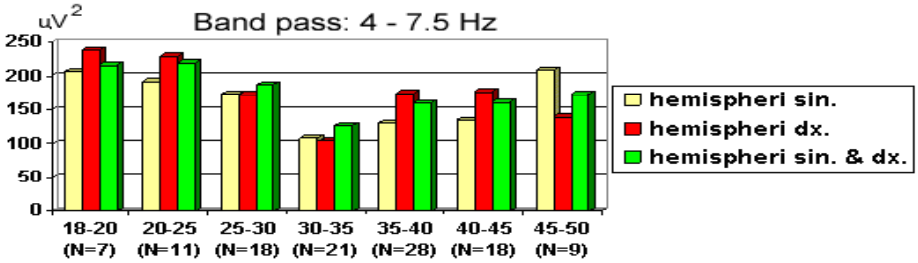

Fig. 7. EEG power in the theta band in particular aging groups.
Ryc. 7. Wykres mocy sygnału w pasmie theta w poszczególnych grupach wiekowych.

The power of alpha rhythm (8-13Hz) decreases with age. Fig. 6 shows results the total alpha power together with hemispheric one in selected aging groups. The EEG activity in theta band (4.5-7Hz) presents different contribution to the total power as shown in Fig. 7. This relationship shows decreased values at age between 30-40 yrs that increases, however, in age over 40 yrs.

A significant correlation was found between cognitive impairment in Alzheimer's disease, MMSE scale and the degree of abnormalities in visual EEGs evaluation ($r=0.77$, $p<0.001$). A similar dependency was not found in subcortical vascular dementia. QEEGs analysis revealed significantly lower values of alpha/slow wave power ratios ($p<0.05$) and the mean frequency of waves from all EEG derivations ($p<0.001$) in the whole group of patients with Alzheimer's disease (AD) compared with the whole group with subcortical vascular dementia (SVD) and with the control group ($p<0.001$). Mean frequency in signal from temporal derivations T3, T4 (decreased in Alzheimer's disease) was found to be a differentiating parameter between the subgroups with Alzheimer's disease and those with subcortical vascular dementia with mild cognitive impairment. Similar differences were detected when comparing subgroups with Alzheimer's disease and subcortical vascular dementia with moderate dementia (AD II and SVD II) ($p<0.05$). Alpha/delta wave power ratio (lower in Alzheimer's disease) ($p<0.05$) was found to be another differentiating parameter between subgroups with Alzheimer's disease and those with subcortical vascular dementia with a moderate degree of dementia (AD II and SVD II) [7].

In the study of visual evoked potentials the delay of the P_{max} component was observed in both control and patients' groups. In Fig. 8a, the pattern of the evoked potentials in healthy subject (58 yrs) is presented. In Fig. 8b, a plot of MGFP function shows the evident increase in power at time of P_{max} and the similar level before and after this response. In case of older subject (72 yrs), the occipital potentials are delayed up to 180 ms (Fig.9). As shown on the map, the hemispheric symmetry is preserved. However, there are no such evident changes in the power as in Fig.8.

The evoked responses is case of asymmetric EEG activity (see Fig. 3) revealed the asymmetry as well. That is shown in Fig.10 together with map. In case of patient with the severe AD disease with the dominant slow activity (see Fig. 4) the evoked responses are not evidently extracted as shown in Fig.11.

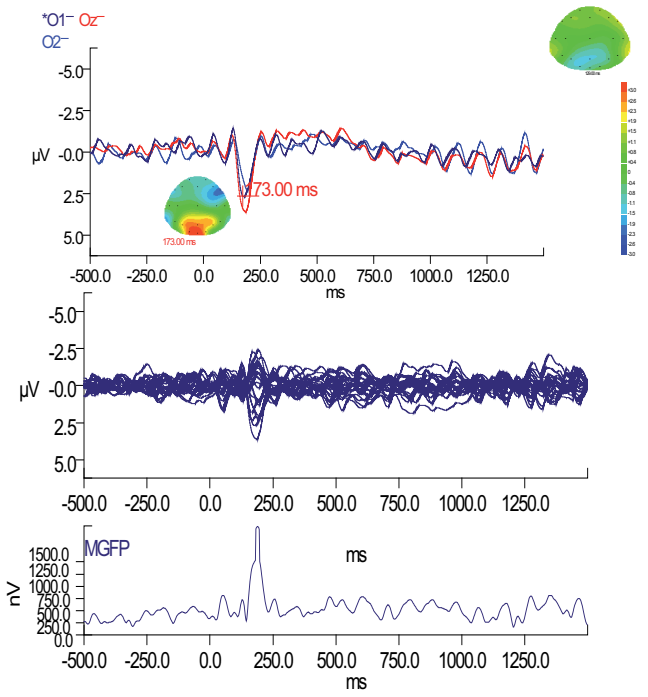

Fig. 8. Evoked potentials recorded in healthy subject (58 yrs).
Ryc. 8. Potencjały wywołane u osoby zdrowej (58 l.).

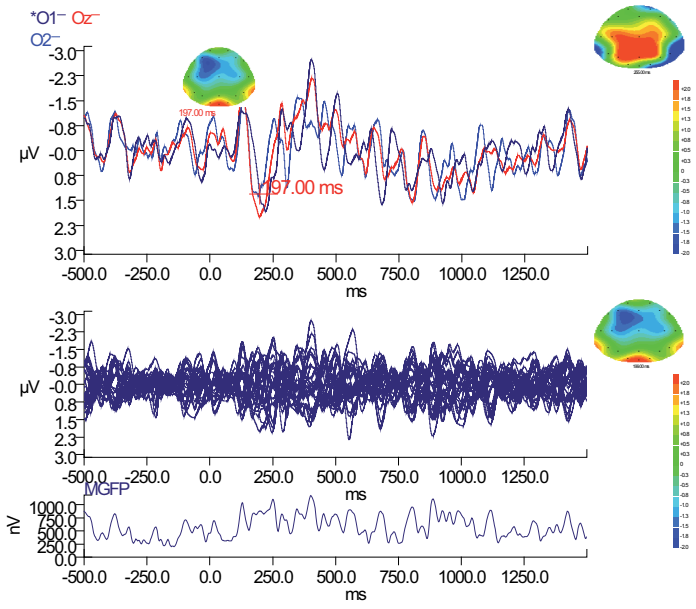

Fig.9. Evoked potentials recorded in healthy subject (72 yrs).
Ryc. 9. Potencjały wywołane u osoby zdrowej (72 l.).

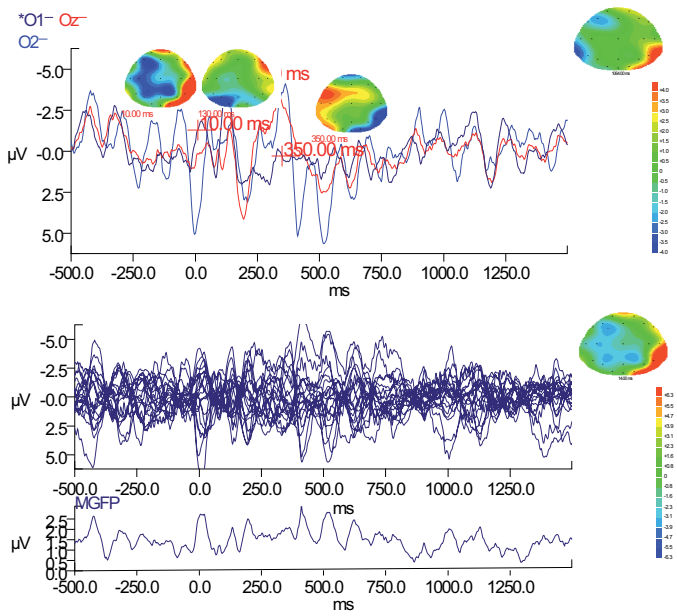

Fig. 10. Evoked potentials recorded in patient with mild stage of dementia.
Ryc. 10. Potencjały wywołane u pacjenta z zespołem AD w stopniu umiarkowanym.

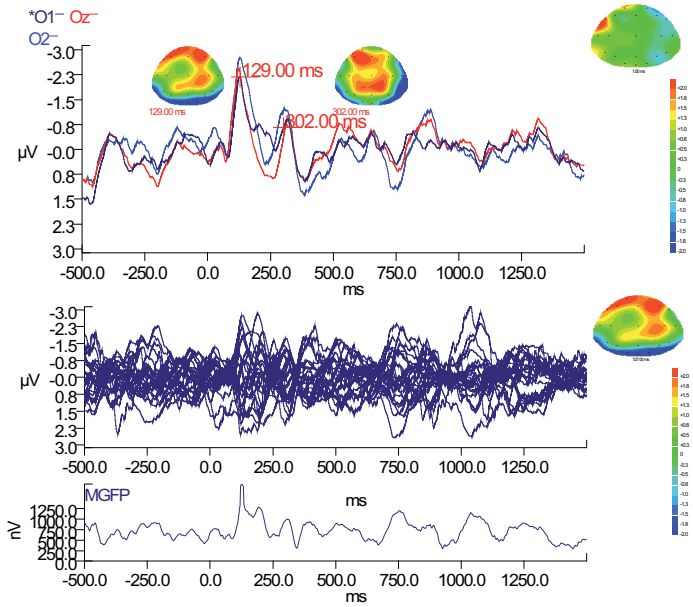

Fig. 11. Visual evoked potentials in cases of severe AD disease. Component P_{max} shows an opposite polarization to normal. The distribution of P_{max} amplitude shows the positive/negative phase.
Ryc. 11. Potencjały wywołane u pacjenta z zespołem AD w stopniu zaawansowanym. Dipolowy charakter rozkładu potencjału P_{max}.

In the study on evoked potentials, the statistically significant delay of LPC components and differences in parameters of EEG before and after stimuli in patients and control groups as well as between patients with mild and severe dementia were found. The changes were significantly larger in frontal than occipital region.

The dynamics of spontaneous EEG during stimulation was evaluated, using spectral analysis in standard frequency bands. This analysis indicates significant differences between control group and patients. The power of EEG signals in particular frequency bands was calculated for each period marked in Fig. 1 as I to IV and the coefficients being a ratio of power in II, III or IV in relation to power in period I were calculated. For example $S1(A)=P_{alpha}(II)/P_{alpha}(I)$, $S2(A)=P_{alpha}(III)/P_{alpha}(I)$, $S1(A)=P_{alpha}(IV)/P_{alpha}(I)$.

The results are shown in figs. 12 and 13, where the mean values in groups together with the mean errors are given.

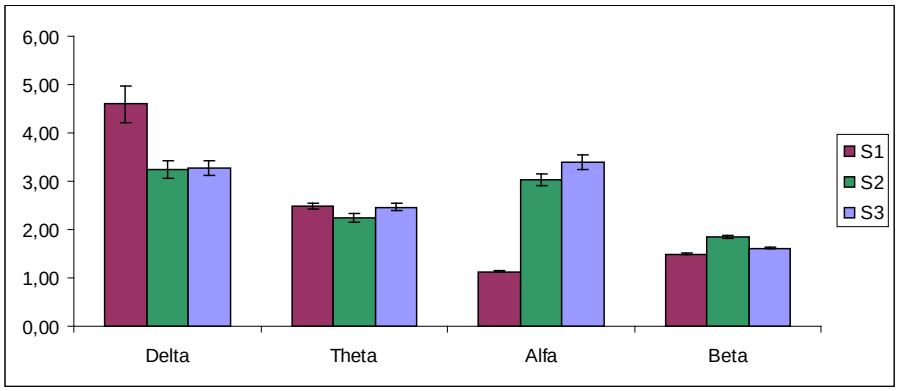

Fig. 12. Mean values and mean errors of the coefficients characterizing the changes of the EEG signals during stimulation in the occipital region. Control group.

Ryc. 12. Średnie wartości i błędy współczynników charakteryzujących zmiany sygnału EEG w czasie stymulacji w grupie kontrolnej.

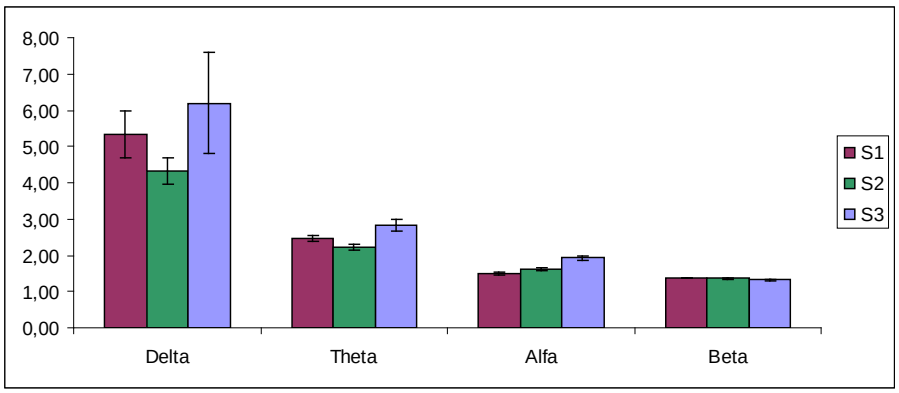

Fig. 13. Mean values and mean errors of the coefficients characterizing the changes of the EEG signals during stimulation in the occipital region. Patients group.

Ryc. 13. Średnie wartości i błędy współczynników charakteryzujących zmiany sygnału EEG w czasie stymulacji w grupie pacjentów.

The results indicate that in controls the changes of EEG during stimulation manifest themselves by a decrease in alpha and delta power whereas in the patients there is not that case. Activity in alpha band does not change evidently but it significantly increases in delta band.

In summary, both spontaneous EEG and evoked potentials reveal characteristic changes that seems to be related to the stage of dementia. These changes manifest by increasing in the amount of low frequency activity and delay of P_{max} component in evoked potentials.

Discussion

In the course of aging the changes in EEG manifest themselves as decreasing in the rhythmicity [1]. In our study, decreasing of alpha rhythm power was noticed in case of the physiological aging, whereas in dementia group increasing in delta and theta rhythm power dominated [7,14]. In evoked potentials tests the similar changes of spontaneous activity during stimulation were observed. Additionally, latency of P_{max} component was prolonged in the control group with preserved normal shape, whereas in dementia Pmax presented variable shapes. Changes detected in evoked activity in controls reflect impairment of the sensory functions due to the slower synaptic processes that not related, however, to the mind dysfunction. This is the somatic aging process that may be compensated. This process is also called as „successful aging". Spectral changes were also described earlier. Decreasing overall EEG power as subject age increased and EEG slowing is those aging adults who were experiencing some decline in mental function were reported [15]. These changes were especially seen in areas over the temporal lobe, an important brain area for memory. Decreasing amplitude and frequency of alpha rhythm has been observed in subjects showing age related cognitive decline [16].

Cognitive impairment with aging is strongly associated with reduced connectivity in the brain. The relationship between increasingly impaired connectivity and synchronization in the brain and increasing degree of cognitive decline was found, especially in the alpha and beta bands [11].

The hypothesis of a functional disconnection of neuro-cognitive networks in patients with mild cognitive impairment (MCI) and Alzheimer Dementia was verified in the study on global amount of phase-locked activity at a given frequency [11]. The authors have shown decreased synchronization in alpha, beta, and gamma frequency bands, and increased in the delta band, confirming the hypothesized disconnection syndrome.

In case of neurodegenerative process, the pathological brain activity in the form of slow waves reflects probably the deficit of acetylcholine that is responsible for disturbances of the synchronization synaptic potentials. Significantly lower frequencies in temporal lobes were noted in the group of patient [17,22]. This could be the result of degeneration of Meynert's nucleus, affecting the activity of functions of the thalamo-cortical connections. An exceptionally notable influence of Meynert's nucleus is apparent in the anterior parts of the brain hemispheres i.e. in the temporal and frontal cortex.

One of the early symptoms of the physiological aging in our observations were

the decreasing reactivity during the day as well as changes in the sleep pattern. This may probably reflect the cortico-subcortical disconnections in the activation process. Brief arousals are an integral component of the sleep process. They increase with other electroencephalographic markers as a function of age. They are highly correlated with traditional sleep-stage amounts and are related to major demographic variables. Age-related norms may make identification of pathologic arousal easier [2].

We have used electroneurometric methods to evaluate different indicators of senescence in physiological and pathological aging. These electrophysiological parameters allowed to identify different changes in particular brain regions and frequency bands [3,12,22]. In evaluation of physiological aging process in contrary to the dementia processes the methods of multimodal evoked potentials are most effective. Degree of EEG abnormalities correlates with the cognitive impairment in AD and quantitative EEG analysis may be helpful in differentiating between various dementia process and evaluation of their severity [7].

Conclusion

The electroneurometric coefficients might be useful in the evaluation of physiological and pathological aging of nervous system and prognosis of the progress of functional deficits.

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